Prepare Early...Score Higher

Pathology

10th edition

- 500 USMLE-type questions, answers, & explanations
- High-yield facts reinforce key concepts
- Targets what you really need to know
- Student-tested and reviewed

Earl J. Brown

Pathology

PreTest® Self-Assessment and Review

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Pathology

PreTest® Self-Assessment and Review

Tenth Edition

Earl J. Brown, M.D.
Associate Professor
Department of Pathology
Quillen College of Medicine
Johnson City, Tennessee

Student Reviewers

Sara M. Nesler
University of Iowa College of Medicine
Iowa City, Iowa
Class of 2002

Misha F. Haque
Baylor College of Medicine
Houston, Texas
Class of 2001

Joseph Cummings
University of Iowa College of Medicine
Iowa City, Iowa
Class of 2002

Harvey Castro
University of Texas—Galveston School of Medicine
Galveston, Texas
Class of 2002

McGraw-Hill
Medical Publishing Division
New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

McGraw-Hill

A Division of The McGraw-Hill Companies

0-07-138975-X

The material in this eBook also appears in the print version of this title: 0-07-137223-7.

DOI: 10.1036/007138975X

Contents

Preface

The study of pathology, a science so basic to clinical medicine, has been abbreviated sadly in many medical schools in recent years, and at a time when explosive growth is occurring in the science. Recent advances in immunopathology, diagnosis of bacterial and viral diseases including AIDS, and detection of infectious agents such as papillomavirus in cervical dysplasia are proceeding at a tremendous rate. The tenth edition of *Pathology: PreTest® Self-Assessment and Review* includes such new subject areas as predictive values in the interpretation of laboratory data, the importance of cytokines, the molecular basis of genetic and other disease processes, and molecular biology techniques as these apply to lymphoproliferative disorders and other tumors.

The medical student must feel submerged at times in the flood of information—occasionally instructors may have similar feelings. This edition is not intended to cover all new knowledge in addition to including older anatomic and clinical pathology. It is, rather, a serious attempt to present important facts about many disease processes in hopes that the student will read much further in major textbooks and journals and will receive some assistance in passing medical school, licensure, or board examinations.

This page intentionally left blank.

Introduction

Each *PreTest® Self-Assessment and Review* allows medical students to comprehensively and conveniently assess and review their knowledge of a particular basic science, in this instance pathology. The 500 questions parallel the format and degree of difficulty of the questions found in the United States Medical Licensing Examination (USMLE) Step 1. Practicing physicians who want to hone their skills before USMLE Step 3 or recertification may find this to be a good beginning in their review process.

Each question is accompanied by an answer, a paragraph explanation, and a specific page reference to an appropriate textbook or journal article. A bibliography listing sources can be found following the last chapter of this text.

An effective way to use this PreTest® is to allow yourself one minute to answer each question in a given chapter. As you proceed, indicate your answer beside each question. By following this suggestion, you approximate the time limits imposed by the Step 1 exam.

After you finish going through the questions in the section, spend as much time as you need verifying your answers and carefully reading the explanations provided. Pay special attention to the explanations for the questions you answered incorrectly—but read *every* explanation. The author of this material has designed the explanations to reinforce and supplement the information tested by the questions. If you feel you need further information about the material covered, consult and study the references indicated.

The High-Yield Facts added for this edition are provided to facilitate rapid review of pathology topics. It is anticipated that the reader will use the High-Yield Facts as a "memory jog" before proceeding through the questions.

This page intentionally left blank.

Laboratory Values		
Substance	**Source**	**Normal**
Albumin	Serum	3.2–4.5 g/dL
Alkaline phosphatase	Serum	20–130 IU/L
Bicarbonate	Plasma	21–28 mM
Bilirubin, direct (conjugated)	Serum	<0.3 mg/dL
Bilirubin, indirect (unconjugated)	Serum	0.1–1.0 mg/dL
Bilirubin, total	Serum	0.1–1.2 mg/dL
BUN	Serum	8–23 mg/dL
Calcium	Serum	9.2–11.0 mg/dL (4.6–5.5 meq/L)
Chloride	Serum	95–103 meq/L
Cholesterol	Serum	150–250 mg/dL
Creatinine	Serum	0.6–1.2 mg/dL
GGT (γ-glutamyltransferase)	Serum	5–40 IU/L
Glucose (fasting)	Serum	70–110 mg/dL
Insulin	Plasma	4–24 μIU/mL
Iron	Serum	60–150 μg/dL
Iron saturation	Serum	20–55%
Osmolality	Serum	280–295 mosm/L
Phosphorus	Serum	2.3–4.7 mg/dL
Potassium	Plasma	3.8–5.0 meq/L
Protein	Serum	6.0–7.8 g/dL
Sodium	Plasma	136–142 meq/L
T_3 resin uptake	Serum	25–38 relative % uptake
Thyrotropin (TSH)	Serum	0.5–5 μIU/mL
Thyroxine, free (FT_4)	Serum	0.9–2.3 ng/dL
Thyroxine, total (T_4)	Serum	5.5–12.5 μg/dL
Triiodothyronine (T_3)	Serum	80–200 mg/dL
	Hematology	
Platelet count		150,000–450,000/μL
White cell count		4,440–11,000/μL
Lymphocyte count		1,000–4,800/μL (about 34%)
Mean corpuscular volume (MCV)		80–96 μm^3
Mean corpuscular hemoglobin (MCH)		27.5–33.2 pg
Mean corpuscular hemoglobin concentration (MCHC)		33.4–35.5%
Hemoglobin	Whole blood	Female 12–16 g/dL Male 13.5–18 g/dL

High-Yield Facts in Pathology

1. CELL INJURY

Reversible Cell Injury

- swelling of cell organelles and entire cell
- dissociation of ribosomes from endoplasmic reticulum
- decreased energy production by mitochondria
- increased glycolysis → decreased pH → nuclear chromatin clumping

Irreversible Cell Injury

- dense bodies within mitochondria (flocculent densities in heart)
- release of cellular enzymes (e.g., SGOT, LDH, and CPK after MI)
- nuclear degeneration (pyknosis, karyolysis, karyorrhexis)
- cell death

2. FATTY CHANGE OF THE LIVER

Mechanisms

1. Increased delivery of free fatty acids to liver
   - starvation
   - corticosteroids
   - diabetes mellitus
2. Increased formation of triglycerides
   - alcohol (note: NADH > NAD)
3. Decreased formation of apoproteins
   - carbon tetrachloride
   - protein malnutrition (kwashiorkor)

3. CELL DEATH

Apoptosis

- "programmed" cell death
- single cells (not large groups of cells)
- cells shrink → form apoptotic bodies
- gene activation → forms endonucleases
- peripheral condensation of chromatin with DNA ladder
- no inflammatory response

Examples of apoptosis:

1. Physiologic
   - involution of thymus
   - cell death within germinal centers of lymph nodes
   - fragmentation of endometrium during menses
   - lactating breast during weaning
2. Pathologic
   - viral hepatitis
   - cytotoxic T cell–mediated immune destruction (type IV hypersensitivity)

Necrosis

- cause → hypoxia or toxins (irreversible injury)
- many cells or clusters of cells
- cells swell
- inflammation present

Examples of necrosis:

- coagulative necrosis → ischemia (except the brain)
- liquefactive necrosis → bacterial infection (and brain infarction)
- fat necrosis → pancreatitis and trauma to the breast
- caseous necrosis → tuberculosis
- fibrinoid necrosis → autoimmune disease (type III hypersensitivity reaction)
- gangrene → ischemia to extremities → dry (mainly coagulative necrosis) or wet (mainly liquefactive necrosis due to bacterial infection)

4. TERMS

Adaptation

- hypertrophy → increase in the size of cells
- hyperplasia → increase in the number of cells
- atrophy → decrease in the size of an organ
- aplasia → failure of cell production
- hypoplasia → decrease in the number of cells
- metaplasia → replacement of one cell type by another
- dysplasia → abnormal cell growth

Abnormal Organ Development

- anlage → primitive mass of cells
- aplasia → complete failure of an organ to develop (anlage present)

- agenesis → complete failure of an organ to develop (no anlage present)
- hypoplasia → reduction in the size of an organ due to a decrease in the number of cells
- atrophy → decrease in the size of an organ due to a decrease in the number of preexisting cells

5. CARDINAL SIGNS OF INFLAMMATION

- rubor → red
- calor → hot
- tumor → swollen
- dolor → pain

6. COMPLEMENT CASCADE

Products

- C3b → opsonin
- C5a → chemotaxis and leukocyte activation
- C3a, C4a, C5a → anaphylatoxins
- C5–9 → membrane attack complex

Deficiencies

- deficiency of C3 and C5 → recurrent pyogenic bacterial infections
- deficiency of C6, C7, and C8 → recurrent infections with *Neisseria* species
- deficiency of C1 esterase inhibitor → hereditary angioedema
- deficiency of decay-accelerating factor → paroxysmal nocturnal hemoglobinuria

7. THROMBOXANE VS. PROSTACYCLIN

Thromboxane

- produced by platelets
- causes vasoconstriction
- stimulates platelet aggregation

Prostacyclin

- produced by endothelial cells
- causes vasodilation
- inhibits platelet aggregation

8. GRANULOMATOUS INFLAMMATION

Caseating Granulomas

- aggregates of activated macrophages (epitheloid cells)
- tuberculosis

Noncaseating Granulomas
- sarcoidosis
- fungal infections
- foreign-body reaction

9. COLLAGEN TYPES

Fibrillar Collagens
- type I → skin, bones, tendons, mature scars
- type II → cartilage
- type III → embryonic tissue, blood vessels, pliable organs, immature scars

Amorphous Collagens
- type IV → basement membranes
- type VI → connective tissue

10. EDEMA

Exudates
1. Composition
   - increased protein
   - increased cells
   - specific gravity greater than 1.020
2. Cause
   - inflammation
   - increased blood vessel permeability

Transudates
1. Composition
   - no increased protein
   - no increased cells
   - specific gravity less than 1.012
2. Cause → abnormality of Starling forces
   a. increased hydrostatic (venous) pressure
      - congestive heart failure
      - portal hypertension
   b. decreased oncotic pressure → due to decreased albumin
      - liver disease
      - renal disease (nephrotic syndrome)

c. lymphatic obstruction
   - tumors or surgery
   - filaria

11. CARCINOMAS

Squamous Cell Carcinoma
- skin cancer
- lung cancer
- esophageal cancer
- cervical cancer

Adenocarcinoma
- lung cancer
- colon cancer
- stomach cancer
- prostate cancer
- endometrial cancer

Transitional Cell Carcinoma
- urinary bladder cancer
- renal cancer (renal pelvis)

Clear Cell Carcinoma
- renal cortex
- vaginal cancer (associated with DES)

12. NEOPLASMS

Benign
- grow slowly
- remain localized
- may have well-developed fibrous capsule
- do not metastasize
- well differentiated histologically

Malignant
- grow rapidly
- locally invasive
- irregular growth; no capsule
- capable of metastasis
- variable degrees of differentiation (well differentiated, moderately differentiated, poorly differentiated)

13. ONCOGENE EXPRESSION

Growth Factors

1. *c-sis*
   - β chain of platelet-derived growth factor
   - astrocytomas and osteogenic sarcomas

Growth Factor Receptors

1. *c-erb B1*
   - receptor for epidermal growth factor
   - breast cancer and squamous cell carcinoma of the lung
2. *c-neu*
   - receptor for epidermal growth factor
   - breast cancer
3. *c-fms*
   - receptor for colony-stimulating factor (CSF)
   - leukemia

Abnormal Membrane Protein Kinase

1. *c-abl*
   - membrane tyrosine kinase
   - chronic myelocytic leukemia (CML)

GTP-Binding Proteins

1. *c-ras*
   - product is p21 (protein)
   - adenocarcinomas

Nuclear Regulatory Proteins

1. *c-myc* → Burkitt's lymphoma
2. *N-myc* → neuroblastoma
3. *L-myc* → small cell carcinoma of the lung
4. *c-jun*
5. *c-fos*

14. CHROMOSOMES AND CANCER

Point Mutations

- *c-ras* → adenocarcinomas

Translocations
- *c-abl* on chromosome 9 → CML
- *c-myc* on chromosome 8 → Burkitt's lymphoma
- *bcl-2* on chromosome 18 → nodular lymphoma

Gene Amplification
- *N-myc* → neuroblastoma
- *c-neu* → breast cancer
- *c-erb B2* → breast cancer

15. ANTIONCOGENES

Tumor Suppressor Genes
- Rb → retinoblastoma and osteogenic sarcoma
- p53 → many tumors and the Li-Fraumeni syndrome
- WT1 → Wilms' tumor and aniridia
- NF1 → neurofibromatosis type 1

16. CHEMICAL CARCINOGENS

Initiators
- tobacco smoke → many tumors
- benzene → leukemias
- vinyl chloride → angiosarcomas of the liver
- β-naphthylamine → cancer of the urinary bladder
- azo dyes → tumors of the liver
- aflatoxin → hepatoma
- asbestos → mesotheliomas and lung tumors
- arsenic → skin cancer

Promoters
- saccharin → bladder cancer in rats
- hormones (estrogen)

17. VIRUSES AND CANCER

RNA Viruses
- acute-transforming viruses
- slow-transforming viruses
- HTLV-1 → adult T cell leukemia/lymphoma

DNA Viruses

1. HPV (different subtypes)
   - cervical neoplasia
   - condyloma
   - verruca vulgaris
2. EBV
   - African Burkitt's lymphoma
   - carcinoma of the nasopharynx
   - B cell immunoblastic lymphoma
3. Hepatitis B and hepatitis C
   - liver cancer

18. PARANEOPLASTIC SYNDROMES

- Cushing's syndrome (increased cortisol) → lung cancer
- carcinoid syndrome (increased serotonin) → lung cancer or carcinoid tumor of the small intestine
- syndrome of inappropriate ADH secretion (SIADH) → lung cancer and intracranial neoplasms
- hypercalcemia → lung cancer or multiple myeloma
- hypocalcemia → medullary carcinoma of the thyroid (secretes procalcitonin; stains as amyloid)
- hypoglycemia → liver cancer and tumors of the mesothelium (mesotheliomas)
- polycythemia (erythropoietin) → kidney tumors, liver tumors, and cerebellar vascular tumors

19. TUMOR MARKERS

β-HCG (Human Chorionic Gonadodotropin)

- gestational trophoblastic disease (e.g., choriocarcinoma, hydatidiform mole)
- dysgerminoma
- seminoma (10% of cases)

α-Fetoprotein (AFP)

- liver cancer
- germ cell tumors (e.g., yolk sac tumors, embryonal carcinoma, NOT seminoma)

Prostate-Specific Antigen (PSA) and Prostatic Acid Phosphatase (PAP)
- adenocarcinoma of prostate

Carcinoembryonic Antigen (CEA)
- adenocarcinomas of colon, pancreas, stomach, and breast (nonspecific marker)

CA-125
- ovarian cancer

S-100
- melanoma
- neural tumors

20. PROTEIN-ENERGY MALNUTRITION (PEM)

Kwashiorkor
- dietary protein deficiency (without calorie deficiency)
- anasarca (generalized edema)
- fatty liver (due to decreased apoproteins and decreased VLDL synthesis)
- abnormal skin and hair
- defective enzyme formation → malabsorption (hard to treat)

Marasmus
- dietary calorie deficiency (without protein deficiency)
- generalized wasting ("skin and bones")

21. NUTRITIONAL DEFICIENCIES

Vitamin A
- night blindness
- dry eyes and dry skin
- recurrent infections

Vitamin D
- decreased calcium
- bone → decreased calcification, increased osteoid
- children → rickets
- adults → osteomalacia

Vitamin E
- degeneration of posterior columns of spinal cord

Vitamin K
- decreased vitamin K–dependent factors → II, VII, IX, X, and proteins C and S
- increased bleeding
- increased PT and PTT

Vitamin B_1 (Thiamine)
- beriberi → wet (cardiac) or dry (neurologic)
- Wernicke-Korsakoff syndrome (lesions of mamillary bodies)

Vitamin B_3 (Niacin)
- pellagra → **3Ds** = **d**ermatitis, **d**ementia, **d**iarrhea (and death)

Vitamin B_{12} (Cobalamin)
- megaloblastic (macrocytic) anemia
- hypersegmented neutrophils (> 5 lobes)
- subacute combined degeneration of the spinal cord

Vitamin C (Ascorbic Acid)
- scurvy
- defective collagen formation → poor wound healing (wounds reopen)
- bone → decreased osteoid
- perifollicular hemorrhages ("corkscrew" hair)
- bleeding gums and loose teeth

Folate
- megaloblastic (macrocytic) anemia
- hypersegmented neutrophils
- associated with neural tube defects in utero

Iron
- microcytic hypochromic anemia (with increased TIBC)

22. INHERITANCE PATTERNS

Autosomal Dominant (AD)
- disease produced in heterozygous state
- no skipped generations → parents affected (unless new mutation or reduced penetrance)

- father-to-son transmission possible
- males and females affected equally
- recurrence risk is 50%

Autosomal Recessive (AR)
- disease produced in homozygous state
- heterozygous individuals are carriers
- skipped generations
- father-to-son transmission possible
- males and females affected equally
- recurrence risk is 25%

X-Linked Dominant (XD)
- no skipped generations
- no male-to-male transmission
- females affected twice as often as males

X-Linked Recessive (XR)
- skipped generations
- no male-to-male transmission
- males affected more frequently than females

Y Inheritance
- only males affected
- only male-to-male transmission
- all males affected

Mitochondrial
- males and females affected
- only females transmit the disease

23. EXAMPLES OF XR

Hematology Diseases
- glucose-6-phosphate dehydrogenase (G6PD) deficiency
- hemophilia A (deficiency of factor VIII)
- hemophilia B (deficiency of factor IX)

Immunodeficiency Diseases
- Bruton's agammaglobulinemia
- chronic granulomatous disease
- Wiskott-Aldrich syndrome

Storage Diseases
- Fabry's disease
- Hunter's syndrome

Muscle Diseases
1. Duchenne muscular dystrophy
   - defective dystrophin gene (muscle breakdown)
   - pseudohypertrophy of calf muscles
   - Gower maneuver (using hands to rise from floor)
2. Becker muscular dystrophy

Metabolic Diseases
- diabetes insipidus
- Lesch-Nyhan syndrome

Other Diseases
- red-green color blindness
- fragile X syndrome

24. CHROMOSOMES

Terms
- haploid → number of chromosomes in germ cells (23)
- diploid → number of chromosomes found in nongerm cells (46)
- euploid → any exact multiple of the haploid number
- aneuploid → any nonmultiple of the haploid number
- triploid → three times the haploid number (69)
- tetraploid → four times the haploid number (92)
- trisomy → three copies of the same chromosome

25. AUTOSOMAL TRISOMIES

Trisomy 13 (Patau's Syndrome)
- mental retardation
- microcephaly and microphthalmia
- holoprosencephaly (fused forebrain)
- fused central face ("cyclops")
- cleft lip and palate
- heart defects

Trisomy 18 (Edwards' Syndrome)
- mental retardation
- micrognathia
- heart defects
- rocker-bottom feet
- clenched fist with overlapping fingers

Trisomy 21 (Down's Syndrome)
- most cases due to maternal nondisjunction during meiosis I (associated with increased maternal age)
- minority of cases due to Robertsonian (balanced) translocation
- mental retardation (most common familial cause)
- oblique palpebral fissures with epicanthal folds
- horizontal palmar crease
- heart defects (endocardial cushion defect is most common)
- acute lymphoblastic leukemia (first 2 years of life)
- Alzheimer's disease (almost 100% incidence after age 35)
- duodenal atresia ("double-bubble" sign on x-ray)

26. CHROMOSOMAL DELETIONS

5p– (Cri du Chat)
- high-pitched cry
- mental retardation
- heart defects and microcephaly

11p–
- Wilms tumor
- absence of iris

13q–
- retinoblastoma

15q–
1. Maternal deletion → Angelman's syndrome
   - stiff, ataxic gait with jerky movements
   - inappropriate laughter ("happy puppets")
   - may be due to two copies of paternal 15 chromosome (paternal uniparental disomy)

2. Paternal deletion → Prader-Willi syndrome
   - mental retardation
   - short stature and obesity
   - small hands and feet
   - hypogonadism
   - may be due to two copies of maternal 15 chromosome (paternal uniparental disomy)

27. HYPOGONADISM

Klinefelter's Syndrome

- most common genotype is 47,XXY
- male hypogonadism
- testicular dysgenesis → small, firm, atrophic testes
- decreased testosterone
- increased FSH, LH, estradiol
- decreased secondary male characteristics
- tallness, gynecomastia, and female distribution of hair
- infertility

Turner's Syndrome

- most common genotype is 45,XO
- female hypogonadism
- ovarian dysgenesis → streak ovaries
- decreased estrogen
- increased LH, FSH
- primary amenorrhea
- decreased secondary female characteristics
- skeletal abnormalities → short stature
- web neck (cystic hygroma)

28. AMBIGUOUS SEXUAL DEVELOPMENT

True Hermaphrodite

- ovaries and testes both present

Female Pseudohermaphrodite (XX Individual)

- ovaries
- male or ambiguous external genitalia
- due to excess androgens (e.g., congenital adrenal hyperplasia)

Male Pseudohermaphrodite (XY Individual)
- testes
- female external genitalia
- due to decreased androgen effects (most common → testicular feminization)

Androgen Insensitivity Syndrome (XY Individual)
- testicular feminization
- Müllerian duct regression (due to MIF)
- Wolffian duct regression (due to lack of testosterone receptors)
- phenotypic female (due to lack of receptors for DHT)

Decreased 5-α-Reductase (XY Individual)
- formation of testes (due to presence of Y chromosome)
- Müllerian duct regression (due to MIF)
- Wolffian duct development (due to testosterone)
- decreased DHT (due to lack of 5-α-reductase)
- variable external genitalia (due to decreased DHT)

Turner's Syndrome (XO Individual)
- streak gonads (due to lack of two X chromosomes)
- Müllerian duct development (due to lack of MIF)
- Wolffian duct regression (due to lack of testosterone)
- external female (due to lack of DHT)
- decreased secondary female characteristics (due to decreased estrogen)

Congenital Adrenal Hyperplasia (XX Individual)
- development of ovaries (due to two X chromosomes)
- Müllerian duct development (due to lack of MIF)
- Wolffian duct regression (due to lack of local testosterone production)
- external male (due to excess systemic formation of DHT)

29. DISORDERS OF TRINUCLEOTIDE REPEATS

1. Fragile X syndrome → CGG repeats
   - mental retardation (second most common familial cause; trisomy 21 is first)
   - long face with large ears
   - large testes (macroorchidism)
   - trinucleotide sequence expanded in females, not males

2. Huntington's syndrome → CAG repeats
3. Myotonic dystrophy → GCT repeats
4. Spinal-bulbar muscular atrophy → CAG repeats

30. LYMPHOCYTES

B Cells

- form plasma cells that secrete immunoglobulin
- surface antigen receptor composed of immunoglobulin
- rearrange immunoglobulin genes from germ line configuration
- CD19 → pan–B cell marker
- CD20 → pan–B cell marker, also called L26
- CD21 → pan–B cell marker, receptor for EBV
- CD22 → pan–B cell marker

T Cells

- secrete lymphokines
- surface antigen receptor (TCR) is attached to CD3
- rearrange genes for T cell receptor
- CD2 → receptor for sheep erythrocyte (E rosette)
- CD3 → attached to T cell receptor
- CD4 → helper T cells, bind with MHC class II antigens
- CD5 → pan–T cell marker
- CD7 → pan–T cell marker
- CD8 → cytotoxic T cells, bind with MHC class I antigens

Natural Killer Cells

- large granular lymphocytes
- do not need previous sensitization
- CD16 → receptor for Fc portion of IgG

31. IMMUNOGLOBULINS

IgM

- large molecule (pentamer)
- secreted early in immune response (primary response)
- cannot cross the placenta
- can activate complement
- contains a J chain

IgG

- most abundant immunoglobulin in serum
- secreted during second antigen exposure (secondary or amnestic response)
- can cross the placenta
- can activate complement
- can function as opsonin

IgE

- allergies, asthma, parasitic infection
- found attached to the surface of basophils and mast cells
- participates in type I hypersensitivity reactions

IgA

- usually a dimer with a J chain and a secretory component
- found along GI tract and respiratory tract
- secretory immunoglobulin
- can activate alternate complement pathway

IgD

- receptor for B cells
- found on the surface of mature B cells

32. T LYMPHOCYTES

CD4+ Cells

- helper T lymphocytes
- respond to MHC class II antigens

Subtypes:

1. T helper-1 (T_H1) cells
   - secrete → IL-2, IL-3, GM-CSF, γ-interferon, and lymphotoxin (β-TNF)
   - stimulate cell-mediated immune reactions → fight intracellular organisms
2. T helper-2 (T_H2) cells
   - secrete → IL-3, IL-4, IL-5, IL-6, IL-10, and GM-CSF
   - stimulate antibody production → fight extracellular organisms

CD8+ Cells
- cytotoxic T lymphocytes
- respond to MHC class I antigens

33. MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

Class I Antigens
- found on all nucleated cells
- transmembrane α glycoprotein chain with β_2-microglobulin
- react with antibodies and CD8-positive lymphocytes
- fight virus-infected cells and transplants

Class II Antigens
- found on antigen-presenting cells, B cells, and T cells
- transmembrane α chain and β chain
- react with CD4-positive lymphocytes
- fight exogenous antigens that have been processed by antigen-presenting cells

34. DISEASES ASSOCIATED WITH HLA TYPES
- ankylosing spondylitis → HLA-B27
- primary hemochromatosis → HLA-A3
- 21-hydroxylase deficiency → HLA-BW47
- rheumatoid arthritis → HLA-DR4
- insulin-dependent (type I) diabetes mellitus → HLA-DR3/DR4
- systemic lupus erythematosus → HLA-DR2/DR3

35. HYPERSENSITIVITY REACTIONS

Type I
- binding of antigen to previously formed IgE bound to mast cells and basophils
- release of histamine and leukotrienes C_4 and D_4
- urticaria (hives)
- anaphylaxis

Type II
- antibody (IgG or IgM) binds to antigens in situ
- cells destroyed by complement or cytotoxic cells (antibody-dependent cell-mediated cytotoxicity)

- linear immunofluorescence (IF)
- transfusion reactions

Type III

- antibody (IgG or IgM) binds to antigens forming immune complexes
- granular IF
- systemic → serum sickness
- local reaction → Arthus reaction

Type IV

1. Delayed type hypersensitivity
   - CD4 lymphocytes
   - extrinsic antigen associated with class II MHC
   - formation of activated macrophages (epitheloid cells) → granulomas
   - PPD skin test
   - contact dermatitis (poison ivy, poison oak)
2. Cell-mediated immunity
   - CD8 lymphocytes
   - intrinsic antigen associated with class I MHC
   - viral infections and transplant rejection

36. AUTOANTIBODIES

Nuclear

- diffuse (homogenous) → DNA (many diseases), histones (drug-induced SLE)
- rim (peripheral) → double-stranded DNA (SLE)
- speckled (non-DNA extractable nuclear proteins) → Smith (SLE), SS-A and SS-B (Sjögren's syndrome), Scl-70 (progressive systemic sclerosis)
- nucleolar (RNA) → many (e.g., progressive systemic sclerosis)
- centromere → CREST syndrome

Cytoplasmic

- mitochondria → primary biliary cirrhosis

Cells

- smooth muscle → lupoid hepatitis (autoimmune chronic active hepatitis)
- neutrophils → Wegener's granulomatosis and microscopic polyarteritis
- parietal cell and intrinsic factor → pernicious anemia
- microvasculature of muscle → dermatomyositis

Proteins
- immunoglobulin → rheumatoid arthritis
- thyroglobulin → Hashimoto's thyroiditis

Structural Antigens
- lung and glomerular basement membranes → Goodpasture's disease
- intercellular space of epidermis → pemphigus vulgaris
- epidermal basement membrane → bullous pemphigoid

Receptors
- acetylcholine receptor → myasthenia gravis
- thyroid hormone receptor → Graves' disease
- insulin receptor → diabetes mellitus

37. ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCAs)

1. C-ANCAs (cytoplasmic)
   - proteinase 3 → Wegener's granulomatosis
2. P-ANCAs (perinuclear)
   - myeloperoxidase → microscopic polyarteritis

38. AMYLOIDOSIS

Amyloid
- any protein having β-pleated sheet tertiary configuration
- apple-green birefringence with Congo red stain

Systemic Deposition
- multiple myeloma → deposits of amyloid light protein
- chronic inflammatory diseases → deposits of amyloid-associated protein
- hemodialysis → deposits of β_2-microglobulin

Localized Deposition
- senile cardiac disease → deposits of amyloid transthyretin
- Alzheimer's disease → deposits of β_2-amyloid protein
- medullary carcinoma of thyroid → deposits of procalcitonin
- non-insulin-dependent diabetes mellitus (type II) → amyloid deposits in islets of Langerhans of pancreas

39. DEFECTS IN INFLAMMATION OR IMMUNITY

Chédiak-Higashi Syndrome

- autosomal recessive
- defective polymerization of microtubules
- giant lysosomes in leukocytes
- recurrent infections
- albinism (abnormal formation of melanin)

Chronic Granulomatous Disease

- defective NADPH oxidase (enzyme on membrane of lysosomes)
- recurrent infections with catalase-positive organisms
- abnormal nitroblue tetrazolium dye test

Severe Combined Immunodeficiency (SCID)

1. X-linked form
   - defect in IL-2 receptor
2. Autosomal recessive form (Swiss type)
   - lack of adenosine deaminase
   - prenatal diagnosis and gene therapy possible

X-Linked Agammaglobulinemia of Bruton

- defective maturation of B lymphocytes past the pre-B stage
- absence of germinal centers and plasma cells
- bacterial infections begin at the age of 9 months (loss of maternal antibody)
- therapy with immunoglobulin injections

Common Variable Immunodeficiency (CVID)

- variable clinical presentation
- recurrent infections → especially bacteria and *Giardia*
- hyperplastic B cell areas
- therapy with immunoglobulin injections

Isolated Deficiency of IgA

- most patients are asymptomatic
- may develop anti-IgA antibodies
- risk of anaphylaxis with transfusion

DiGeorge's Syndrome
- defective development of pharyngeal pouches 3 and 4
- deletion of chromosome 22
- lack of thymus → no T cells (recurrent viral and fungal infections)
- lack of parathyroid glands → hypocalcemia and tetany
- congenital heart defects

Acquired Immunodeficiency Syndrome (AIDS)
- cause → HIV infection
- infection of CD4+ T lymphocytes
- inversion of CD4/CD8 ratio (normal is 2:1)
- decreased humoral and cell-mediated immunity → recurrent infections
- increased incidence of malignancy (Kaposi's sarcoma and immunoblastic lymphoma)

40. VIRAL CHANGES

Giant Cells
- herpes simplex virus (HSV)
- cytomegalovirus (CMV)
- measles (Warthin-Finkeldey giant cells)
- respiratory syncytial virus

Inclusions
- herpes simplex virus (Cowdry A bodies)
- smallpox virus (Guarnieri bodies)
- rabies virus (Negri bodies)
- molluscum contagiosum (molluscum bodies)

Ground-Glass Change
- nucleus = herpes simplex virus
- cytoplasm (of hepatocytes) = hepatitis B

Atypical Cells
- atypical lymphocytes → Epstein-Barr virus
- smudge cells → adenovirus (respiratory epithelial cells)
- koilocytosis → human papillomavirus (HPV)

41. SYSTEMIC MYCOSES

Candidiasis
- *Candida albicans*
- pseudohyphae
- white plaques (thrush)

Histoplasmosis
- *Histoplasma capsulatum*
- found within the cytoplasm of macrophages
- bird droppings; bat guano in caves
- Ohio and Mississippi valleys

Aspergillosis
- *Aspergillus* species
- septate hyphae with acute-angle branching
- fruiting bodies (when exposed to air → fungus ball in lung cavity)

Blastomycosis
- *Blastomyces dermatitidis*
- broad-based budding
- eastern United States

Coccidioidomyocosis
- *Coccidioides immitis*
- large spherules filled with many small endospores
- southwestern United States (San Joaquin Valley)

Cryptococcosis
- *Cryptococcus neoformans*
- CNS infection in immunosuppressed patients
- mucicarmine-positive capsule
- india ink stain of CSF

Mucormycosis
- nasal infection in diabetic patients
- broad, nonseptate hyphae with right-angle branching

42. FAMILIAL HYPERLIPIDEMIA

Type I Hyperlipoproteinemia
- familial hyperchylomicronemia
- mutation in lipoprotein lipase gene
- increased serum chylomicrons

Type II Hyperlipoproteinemia
- familial hypercholesterolemia
- mutation involving LDL receptor
- increased serum LDL
- increased serum cholesterol

Type III Hyperlipidemia
- floating or broad β disease
- mutation in apolipoprotein E
- increased chylomicron remnants and IDL
- increased serum triglycerides and cholesterol

Type IV Hyperlipidemia
- familial hypertriglyceridemia
- unknown mutation
- increased serum VLDL
- increased serum triglycerides and cholesterol

Type V Hyperlipidemia
- mutation in apolipoprotein CII
- increased serum chylomicrons and VLDL
- increased serum triglycerides and cholesterol

43. ANEURYSMS

Atherosclerotic Aneurysms
- cause → atherosclerosis
- location → abdominal aorta (between renal arteries and bifurcation of the aorta)
- pulsatile mass
- may rupture → sudden, severe abdominal pain in male older than 55
- treat with surgery when diameter is > 5 cm

Luetic Aneurysms
- cause → syphilis (treponema) infection
- obliterative endarteritis (plasma cells around small blood vessels)
- location → ascending (thoracic) aorta
- may produce aortic regurgitation or rupture

Dissecting Aneurysms
1. Due to cystic medial necrosis of aorta
   - hypertension
   - Marfan's syndrome → due to defect in fibrillin gene
2. "Double-barrel" aorta on x-ray

Berry Aneurysms

- location → bifurcation of arteries in circle of Willis
- most commonly bifurcation of anterior communicating artery
- subarachnoid hemorrhage
- associated with polycystic renal disease

44. CARDIAC HYPERTROPHY

Concentric Hypertrophy

- response to pressure overload (e.g., hypertension or aortic stenosis)
- sarcomeres proliferate in parallel
- increased ventricular thickness
- no change in size of ventricular cavity

Eccentric Hypertrophy

- response to volume overload
- sarcomeres proliferate in series
- no increase in ventricle thickness
- increase in size of ventricular cavity

45. CONGENITAL HEART DEFECTS

Left-to-Right Shunts

1. Ventricular septal defect (VSD) → most common congenital cardiac anomaly
2. Atrial septal defect (ASD)
3. Patent ductus arteriosus (PDA)
   - "machine-like" heart murmur
   - indomethacin closes PDA

Right-to-Left Shunts

1. Tetralogy of Fallot (TOF) → most common cause of congenital cyanotic heart disease
   - pulmonary stenosis
   - ventricular septal defect
   - dextropositioned (overriding) aorta
   - right ventricular hypertrophy

No Shunts

1. Coarctation of the aorta
   - infantile type (preductal)
   - adult type (postductal) → rib notching, increased BP in upper extremities, decreased BP in lower extremities
2. Transposition of the great vessels
   - need shunt to be present in order to survive (e.g., PDA)
   - PGE keeps ductus open

46. ATROPHY OF THE STOMACH

Type A → Autoimmune Gastritis

- autoantibodies to parietal cells and intrinsic factor → pernicious anemia
- decreased vitamin B_{12} → megaloblastic anemia
- increased serum gastrin levels
- histologic changes found in fundus of stomach

Type B → Environmental

- no autoantibodies present
- associated with *Helicobacter pylori* (urease breath test is positive)
- decreased serum gastrin levels
- histologic changes found in antrum of stomach

47. INFLAMMATORY BOWEL DISEASE (IBD)

Ulcerative Colitis

- crypt abscesses (microabscesses) and crypt distortion
- disease begins in rectum and extends proximally (no skip lesions)
- does not involve small intestines
- superficial mucosal involvement (not transmural)
- increased risk of colon cancer and toxic megacolon

Crohn's Disease

- granulomas
- segmental involvement (skip lesions)
- may involve small intestines (regional enteritis or ileitis)
- transmural involvement → fissures, fistulas, and obstruction

48. GALLSTONES

Cholesterol Stones

- yellow stones
- risk factors → **Fs** = **f**at, **f**emale, **f**ertile, **f**orty, **f**ifty
- increased incidence in Native Americans

Bilirubin (Pigment) Stones

- black stones
- risk factors → chronic hemolysis and infections of biliary tract
- increased incidence in Asians

49. CONGENITAL ADRENAL HYPERPLASIA (CAH)

21-Hydroxylase Deficiency

- decreased cortisol → increased ACTH
- decreased aldosterone
- sodium loss in the urine → salt-wasting form of CAH
- hyperkalemic acidosis
- virilism in females

11-Hydroxylase Deficiency

- decreased cortisol → increased ACTH
- decreased aldosterone
- increased DOC and 11-deoxycortisol → increased mineralocorticoid effects
- sodium retention → hypertensive form of CAH
- hypokalemic alkalosis
- virilism in females

17-Hydroxylase Deficiency

- decreased cortisol → increased ACTH
- no decreased aldosterone
- decreased sex hormones
- females → primary amenorrhea
- males → pseudohermaphrodites

50. MULTIPLE ENDOCRINE NEOPLASIA

Type 1 (Wermer's Syndrome)

- parathyroid
- pituitary
- pancreas

Type 2 (Sipple's Syndrome)

- parathyroid
- medullary carcinoma of thyroid
- pheochromocytoma

Type 3 (MEN 2B)

- medullary carcinoma of thyroid
- pheochromocytoma
- mucosal neuromas

51. RENAL (GLOMERULAR) SYNDROMES

Nephrotic Syndrome

- marked proteinuria → hypoalbuminemia and edema
- increased cholesterol → oval fat bodies in the urine

Examples (nonproliferative glomerular disease):

1. Minimal change disease (lipoid nephrosis)
   - normal light microscopy
   - EM reveals fusion of foot processes of podocytes
2. Focal segmental glomerulosclerosis (FSGS)
3. Membranous glomerulonephropathy (MGN)
   - thickening of basement membrane ("spikes and domes")
   - uniform subepithelial deposits
4. Diabetes mellitus

Nephritic Syndrome

- hematuria (red blood cells and red blood cell casts in urine)
- variable proteinuria and oliguria
- retention of salt and water (hypertension and edema)

Examples (proliferative glomerular disease):

1. Focal segmental glomerulonephritis (FSGN)
   - mesangial deposits of IgA
   - Berger's disease
2. Acute (diffuse) proliferative glomerulonephritis (DPGN)
   - post-streptococcal glomerulonephritis
   - large, irregular subepithelial deposits
3. Membranoproliferative glomerulonephritis (MPGN)
   - subendothelial deposits → type I MPGN
   - intramembranous deposits → type II MPGN (dense deposit disease)
   - splitting of basement membrane by mesangium → "tram-track" appearance
4. Rapidly progressive glomerulonephritis (RPGN)

52. GLOMERULAR DEPOSITS

Subepithelial
- diffuse proliferative glomerulonephritis (DPGN) → irregular and large
- membranous glomerulonephropathy (MGN) → uniform and small

Intramembranous (Basement Membrane)
- membranoproliferative glomerulonephritis (MPGN), type II

Subendothelial
- membranoproliferative glomerulonephritis, type I
- SLE

Mesangial
- focal segmental glomerulonephritis (FSGN)
- Henoch-Schönlein purpura

53. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

Linear Immunofluorescence
- antimembrane antibody
- Goodpasture's disease

Granular Immunofluorescence
- immune complexes
- other glomerular or systemic disease

Minimal or Negative Immunofluorescence
- pauci-immune disease
- Wegener's granulomatosis
- microscopic polyarteritis nodosa

54. CEREBRAL HEMORRHAGE

Epidural Hematoma
- severe trauma
- arterial bleeding (middle meningeal artery)
- symptoms occur rapidly

Subdural Hematoma
- minimal trauma in elderly
- venous bleeding (bridging veins)
- symptoms occur slowly

Subarachnoid Hemorrhage
- rupture of berry aneurysm
- "worst headache ever"
- bloody or xanthochromic spinal tap

55. INFECTIONS OF THE MENINGES

Bacterial Infections
- increased neutrophils and protein in CSF
- decreased glucose in CSF
- life-threatening

Age	Organism
Neonates	*Escherichia coli*
6 months to 6 years	*Streptococcus pneumoniae*
6 years to 16 years	*Neisseria meningitidis* (meningococcus)
Older than 16 years	*Streptococcus pneumoniae*
Epidemics	*Neisseria meningitidis*

Viral Infections
- increased lymphocytes in CSF
- normal glucose in CSF
- mild and self-limited

56. ATROPHY OF THE NERVOUS SYSTEM

Alzheimer's Disease
- diffuse atrophy of cerebral cortex
- dementia (most common cause in elderly)
- senile plaques (with β-amyloid core)
- neurofibrillary tangles (with abnormal τ protein)

Pick's Disease
- unilateral frontal or temporal lobe atrophy

Huntington's Disease
- trinucleotide repeat disorder
- atrophy of caudate and putamen → decreased GABA and acetylcholine
- progressive dementia
- choreiform movements

Parkinson's Disease
- substantia nigra (depigmentation)
- decreased dopamine in corpus striatum
- cogwheel rigidity and akinesia
- tremor
- treatment → dopamine agonists

57. JOINTS

Rheumatoid Arthritis
- rheumatoid factor (IgM antibody against antibody)
- pannus formation in synovium (hyperplastic synovium with lymphocytes and plasma cells)
- ulnar deviation of fingers
- subcutaneous rheumatoid nodules (at pressure points)
- pain worse in morning ("morning stiffness"); pain decreases with activity

Osteoarthritis
- degenerative joint disease ("wear and tear")
- loss of articular cartilage → smooth subchondral bone (eburnation)
- osteophyte formation (DIP → Heberden's nodes, PIP → Bouchard's nodes)
- pain worse in evening; pain increases with activity

Gout
- hyperuricemia → precipitation of monosodium urate crystals (needle-shaped, negatively birefringent crystals)
- first MTP joint (big toe)
- tophus formation
- increased production of uric acid → Lesch-Nyhan syndrome
- increased turnover of nucleic acid → leukemias and lymphomas
- decreased excretion of uric acid → chronic renal disease, ethanol intake, diabetes

58. STAINS

Routine (H&E)
1. Hematoxylin
   - blue and basic
   - stains negatively charged structures → DNA and RNA
2. Eosin
   - pink and acidophilic
   - stains positively charged structures → mitochondria

Special Stains
- fats → oil red O
- glycogen → PAS-positive, diastase-sensitive
- iron → Prussian blue
- hemosiderin → Prussian blue
- amyloid → Congo red
- α_1 antitrypsin → PAS-positive, diastase-resistant
- calcium → von Kossa

59. ENZYMES

Aminotransferases (AST, ALT)
- myocardial infarction (AST)

- alcoholic hepatitis (AST > ALT)
- viral hepatitis (ALT > AST)

Creatine Kinase (CK or CPK)
- myocardial infarction (CPK-MB)
- muscle diseases (DMD)

Lactate Dehydrogenase (LDH)
- myocardial infarction (LDH1, LDH2)

Amylase or Lipase
- acute pancreatitis

60. HISTOLOGIC "BODIES"

1. Psammoma body:
   - papillary carcinoma of the thyroid
   - papillary tumors of the ovary
   - meningioma
2. Immunoglobulin
   - Russell body → cytoplasmic or extracellular
   - Dutcher body → nucleus (Waldenstrom's)
3. Councilman body → viral hepatitis
4. Mallory body → alcoholic hyaline
5. Cowdry A body → herpes
6. Aschoff body → rheumatoid fever
7. Ferruginous body → asbestos
8. Negri body → rabies
9. Lewy body → Parkinson's
10. Heinz body (denatured hemoglobin) → G6PD deficiency
11. Barr body → number of X chromosomes minus one

61. HEALING OF THE MYOCARDIUM AFTER A MYOCARDIAL INFARCTION

	Gross	Microscopy
0–12 h	None	Usually none (?wavy fibers)
12–24 h	Pallor	Coagulative necrosis
1–3 days	Hyperemic (red) border	Above + neutrophils
4–7 days	Pale yellow	Above + macrophages
7–14 days	Red-purple border	Above + granulation tissue
>2 weeks	Gray-white scar	Fibrosis (scar)

62. FAMILIAL STORAGE DISORDERS

Storage Disease	Enzyme Deficiency	Substance Accumulating
Pompe's disease	α-1,4-glucosidase (acid maltase)	Glycogen
Hurler's syndrome	α-*L*-iduronidase	Heparan sulfate, dermatan sulfate
Hunter's syndrome	sc-l-iduronosulfate sulfatase	Heparan sulfate, dermatan sulfate
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Tay-Sachs disease	Hexosaminidase A	G_{M2} ganglioside
Sandhoff's disease	Hexosaminidase A and B	G_{M2} ganglioside and globoside
Gaucher's disease	Glucocerebrosidase	Glucocerebroside
Fabry's disease	α-galactosidase A	Ceramide trihexosidase

General Pathology

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

1. Increased lipolysis of fat stores, which can result from starvation, diabetes mellitus, or corticosteroid use, is most likely to cause steatosis (fatty liver) through which one of the listed mechanisms?

a. Decreased free fatty acid excretion from the liver leads to free fatty acid accumulation in hepatocytes
b. Excess NADH (high NADH/NAD ratio) causes excess production of lactate from pyruvate, which accumulates in hepatocytes
c. Increased free fatty acid delivery to the liver leads to triglyceride accumulation in hepatocytes
d. Inhibition of apoprotein synthesis by the liver leads to phospholipid accumulation in hepatocytes
e. Inhibition of HMG-CoA reductase activity leads to cholesterol accumulation in hepatocytes

2. An adult patient presents with the sudden onset of massive diarrhea. Grossly, this individual's stool has the appearance of "rice-water" because of the presence of flecks of mucus. Cultures of this patient's stool grow *Vibrio cholerae,* a curved, gram-negative rod that secretes an enterotoxin consisting of a toxic A subunit and a binding B subunit. The cholera enterotoxin causes massive diarrhea by

a. Inhibiting the conversion of Gi-GDP to Gi-GTP
b. Inhibiting the conversion of Gs-GTP to Gs-GDP
c. Stimulating the conversion of Gi-GDP to Gi-GTP
d. Stimulating the conversion of Gs-GDP to Gs-GTP
e. Stimulating the conversion of Gs-GTP to Gs-GDP

3. In an evaluation of an 8-year-old boy who has had recurrent infections since the first year of life, findings include enlargement of the liver and spleen, lymph node inflammation, and a superficial dermatitis resembling eczema. Microscopic examination of a series of peripheral blood smears taken during the course of a staphylococcal infection indicates that the bactericidal capacity of the boy's neutrophils is impaired or absent. What is the most likely cause of this child's illness?

a. Defect in the enzyme NADPH oxidase
b. Defect in the enzyme adenosine deaminase (ADA)
c. Defect in the IL-2 receptor
d. Developmental defect at the pre-B stage
e. Developmental failure of pharyngeal pouches 3 and 4

4. A 24-year-old female presents with severe pain during menses (dysmenorrhea). To treat her symptoms, you advise her to take indomethacin in the hopes that it will reduce her pain by interfering with the production of

a. Bradykinin
b. Histamine
c. Leukotrienes
d. Phospholipase A_2
e. Prostaglandin F_2

5. Which one of the listed statements is the best histologic definition of an abscess?

a. A circumscribed collection of neutrophils with necrotic cellular debris
b. A localized defect that results from the sloughing of necrotic inflammatory tissue from the surface of an organ
c. A localized proliferation of fibroblasts and small blood vessels
d. An aggregate of two or more activated macrophages
e. The excessive secretion of mucus from a mucosal surface

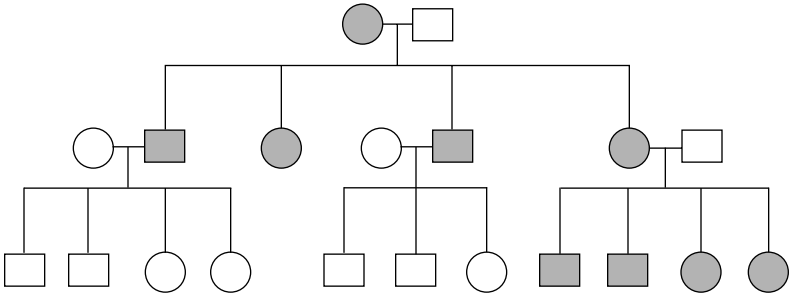
6. A 25-year-old female presents with a history of losing four pregnancies in the past 5 years. She also has a history of recurrent pains in her legs secondary to recurrent thrombosis. Her symptoms are most likely due to a deficiency of

a. PA inhibitors
b. Protein C
c. Plasmin
d. Thrombin
e. C′1 inactivator

7. Evaluation of a pedigree for a certain abnormality reveals the following information: there are skipped generations with male-to-male transmission; females are affected at the same rate as are males; and the disease is produced in the homozygous state, while heterozygous individuals are carriers. What is the inheritance pattern for this disorder?

a. Autosomal dominant
b. Autosomal recessive
c. X-linked dominant
d. X-linked recessive
e. Mitochondrial

8. A 23-year-old female presents with progressive bilateral loss of central vision. You obtain a detailed family history from this patient and produce the associated pedigree (dark circles or squares indicate affected individuals). Which of the following transmission patterns is most consistent with this patient's family history?



a. Autosomal recessive
b. Autosomal dominant
c. X-linked recessive
d. X-linked dominant
e. Mitochondrial

9. A 10-month-old baby is being evaluated for visual problems and motor incoordination. Examination of the child's fundus reveals a bright "cherry red spot" at the macula. Talking to the family of this visually impaired 10-month-old infant, you find that they are Jewish and their family is from the eastern portion of Europe (Ashkenazi Jews). Based on this specific family history, which one of the following enzymes is most likely to be deficient in this infant?

a. Aryl sulfatase
b. β-glucocerebrosidase
c. Hexosaminidase A
d. Hexosaminidase B
e. Sphingomyelinase

10. A 4-year-old male with mental retardation, self-mutilation, and hyperuricemia is likely to have a deficiency of an enzyme involved in the

a. Conversion of homogentisic acid to methylacetoacetate
b. Degradation of galactocerebroside
c. Breakdown of branched-chain amino acids
d. Recycling of guanine and hypoxanthine
e. Synthesis of UMP and CTP

11. Adult individuals with the karyotype 47,XXY would most likely have which one of the following sets of laboratory serum values?

	Testosterone	Follicle-Stimulating Hormone (FSH)	Luteinizing Hormone (LH)	Estradiol
a.	Increased	Increased	Increased	Increased
b.	Increased	Decreased	Decreased	Decreased
c.	Decreased	Increased	Increased	Decreased
d.	Decreased	Increased	Increased	Increased
e.	Decreased	Decreased	Decreased	Decreased

12. A young boy is being evaluated for developmental delay, mild autism, and mental retardation. Physical examination reveals the boy to have large, everted ears and a long face with a large mandible. He is also found to have macroorchidism (large testes), and extensive workup reveals multiple tandem repeats of the nucleotide sequence CGG in his DNA. Which one of the following is the correct diagnosis for this patient?

a. Fragile X syndrome
b. Huntington's chorea
c. Myotonic dystrophy
d. Spinal-bulbar muscular atrophy
e. Ataxia-telangiectasia

13. A biopsy of an enlarged salivary gland from an individual with Sjögren's syndrome is most likely to histologically reveal an extensive infiltrate of

a. Basophils
b. Eosinophils
c. Epithelioid cells
d. Lymphocytes
e. Neutrophils

14. An 8-month-old male infant is admitted to the hospital because of a bacterial respiratory infection. The infant responds to appropriate antibiotic therapy, but is readmitted several weeks later because of severe otitis media. Over the next several months, the infant is admitted to the hospital multiple times for recurrent bacterial infections. Workup reveals extremely low serum antibody levels. The infant has no previous history of viral or fungal infections. The most likely diagnosis for this infant is

a. Isolated IgA deficiency
b. Chronic granulomatous disease
c. DiGeorge's syndrome
d. Wiskott-Aldrich syndrome
e. X-linked agammaglobulinemia of Bruton

15. During a routine physical examination, a 45-year-old male is found to have microscopic hematuria. Further workup reveals a 4.5-cm mass in the upper pole of his right kidney. This mass is resected and reveals a tumor composed of a uniform population of cells with clear cytoplasm. Mitoses are not found. Further workup fails to reveal the presence of any metastatic disease. Based on all of these findings, which of the following best characterizes this tumor? (*Note:* assume that a low stage has a better prognosis than a high stage, and a low grade has a better prognosis than a high grade. Also assume that renal tumors composed of cells with clear cytoplasm that are larger than 2.0 cm in diameter are malignant.)

	Tumor Aggressiveness	Grade	Stage
a.	Benign	Not applicable	Not applicable
b.	Malignant	Low	Low
c.	Malignant	Low	High
d.	Malignant	High	Low
e.	Malignant	High	High

16. A 35-year-old male living in a southern region of Africa presents with increasing abdominal pain and jaundice. He has worked as a farmer for many years, and sometimes his grain has become moldy. Physical examination reveals a large mass involving the right side of his liver, and a biopsy specimen from this mass confirms the diagnosis of liver cancer (hepatocellular carcinoma). The pathogenesis of this tumor involves which of the following substances?

a. Aflatoxin B1
b. Direct-acting alkylating agents
c. Vinyl chloride
d. Azo dyes
e. β-naphthylamine

17. A 59-year-old male is found to have a 3.5-cm mass in the right upper lobe of his lung. A biopsy of this mass is diagnosed as a moderately differentiated squamous cell carcinoma. Workup reveals that no bone metastases are present, but laboratory examination reveals that the man's serum calcium levels are 11.5 mg/dL. This patient's paraneoplastic syndrome is most likely the result of ectopic production of

a. Parathyroid hormone
b. Parathyroid hormone–related peptide
c. Calcitonin
d. Calcitonin-related peptide
e. Erythropoietin

18. A 22-year-old female presents with the sudden onset of a high fever, a diffuse erythematous skin rash, and shock. She started menstruating at age 13 and for several years has used tampons. Which one of the following is the most likely diagnosis for this individual's illness?

a. Erysipelas caused by *Streptococcus pyogenes*
b. Fifth disease caused by human parvovirus B19
c. Scarlet fever caused by *S. pyogenes*
d. Secondary syphilis caused by *Treponema pallidum*
e. Toxic shock syndrome caused by *Staphylococcus aureus*

19. Several days after exploring a cave in eastern Kentucky, a 39-year-old female develops shortness of breath and a low-grade fever. Chest x-rays reveal several irregular areas in both upper lung fields along with enlarged hilar and mediastinal lymph nodes. A biopsy of one of these lymph nodes reveals granulomatous inflammation. Multiple small yeasts surrounded by clear zones are seen within macrophages. Which one of the following organisms is most likely responsible for this individual's disease?

a. *Aspergillus* species
b. *Blastomyces dermatitidis*
c. *C. albicans*
d. *Histoplasma capsulatum*
e. *Mucor*

20. The use of broad-spectrum antibiotics can produce a bleeding diathesis characterized by hematomas, hematuria, melena, and bleeding from the gums by decreasing the normal gut flora and inducing a deficiency of

a. Vitamin A
b. Vitamin B_1
c. Vitamin B_6
d. Vitamin C
e. Vitamin K

21. Hypoxia decreases cellular levels of ATP and inhibits the normal function of the plasma membrane ouabain-sensitive Na-K-ATPase pump. Which one of the listed changes will result from decreased function of this membrane ion pump?

	Sodium Ion Changes	Potassium Ion Changes
a.	Decreased sodium ions inside the cell	Decreased potassium ions outside the cell
b.	Decreased sodium ions inside the cell	Increased potassium ions outside the cell
c.	Increased sodium ions inside the cell	Increased potassium ions outside the cell
d.	Increased sodium ions outside the cell	Increased potassium ions inside the cell
e.	Increased sodium ions outside the cell	Decreased potassium ions inside the cell

22. A 54-year-old male develops a thrombus in his left anterior descending coronary artery. The area of myocardium supplied by this vessel is irreversibly injured. The thrombus is destroyed by the infusion of streptokinase, which is a plasminogen activator, and the injured area is reperfused. The patient, however, develops an arrhythmia and dies. An electron microscopic (EM) picture taken of the irreversibly injured myocardium reveals the presence of large, dark, irregular amorphic densities within mitochondria, which are referred to as

a. Apoptotic bodies
b. Flocculent densities
c. Myelin figures
d. Psammoma bodies
e. Russell bodies

23. Which one of the following microscopic associations concerning hepatocytes is correct?

a. Clear cytoplasmic material that is oil red O–negative but PAS-positive is most likely to be cholesterol
b. Clear cytoplasmic material that is oil red O–positive but PAS-negative is most likely to be lipofuscin
c. Clear nuclear material that is Prussian blue–positive is most likely to be hemosiderin
d. Yellow-brown granular cytoplasmic material that is Prussian blue–negative is most likely to be bile
e. Yellow-brown granular cytoplasmic material that is Prussian blue–positive is most likely to be melanin

24. A 48-year-old male who has a long history of excessive drinking presents with signs of alcoholic hepatitis. Microscopic examination of a biopsy of this patient's liver reveals irregular eosinophilic hyaline inclusions within the cytoplasm of the hepatocytes. These eosinophilic inclusions are composed of

a. Immunoglobulin
b. Excess plasma proteins
c. Prekeratin intermediate filaments
d. Basement membrane material
e. Lipofuscin

25. A 38-year-old female presents with intermittent pelvic pain. Physical examination reveals a 3-cm mass in the area of her right ovary. Histologic sections from this ovarian mass reveal a papillary tumor with multiple, scattered small, round, laminated calcifications. These structures are most likely the result of

a. Apoptosis
b. Dystrophic calcification
c. Enzymatic necrosis
d. Hyperparathyroidism
e. Metastatic calcification

26. After binding to Fas ligand (CD95L), Fas (CD95) self-associates and activates Fas-associated death domain protein (FADD), which in turn induces apoptosis by stimulating

a. *bcl-2*
b. Caspase 8
c. Cytochrome a_3
d. Cytochrome p_{450}
e. Elastase 6

27. A 49-year-old man develops an acute myocardial infarction because of the sudden occlusion of the left anterior descending coronary artery. The areas of myocardial necrosis within the ventricle can best be described as

a. Coagulative necrosis
b. Liquefactive necrosis
c. Fat necrosis
d. Caseous necrosis
e. Fibrinoid necrosis

28. The degradation of intracellular organelles through the process in which autosomes combine with primary lysosomes to form autophagolysosomes is called

a. Autophagy
b. Heterophagy
c. Heteroplasmy
d. Homophagy
e. Endocytosis

29. Histologic sections of an enlarged tonsil from a 9-year-old female reveal an increased number of reactive follicles containing germinal centers with proliferating B lymphocytes. Which one of the listed terms best describes this pathologic process?

a. B lymphocyte hypertrophy
b. Follicular dysplasia
c. Follicular hyperplasia
d. Germinal center atrophy
e. Germinal center metaplasia

30. A patient presents with a large wound to his right forearm that is the result of a chain saw accident. You treat his wound appropriately and follow him in your surgery clinic at routine intervals. Initially his wound is filled with granulation tissue, which is composed of proliferating fibroblasts and proliferating new blood vessels (angiogenesis). A growth factor that is capable of inducing all the steps necessary for angiogenesis is

a. Epidermal growth factor (EGF)
b. Transforming growth factor α (TGF-α)
c. Platelet-derived growth factor (PDGF)
d. Basic fibroblast growth factor (FGF)
e. Transforming growth factor β (TGF-β)

31. The cardinal sign of inflammation called rubor is mainly the result of

a. Decreased interstitial hydrostatic pressure
b. Decreased vascular permeability of capillaries
c. Increased vascular permeability of venules
d. Vasoconstriction of muscular arteries
e. Vasodilation of arterioles

32. During the early stages of the inflammatory response, histamine-induced increased vascular permeability is most likely to occur in

a. Arteries
b. Precapillary arterioles
c. Capillaries
d. Postcapillary venules
e. Veins

33. Which one of the listed statements best describes the process called chemotaxis?

a. Abnormal fusion of phagosomes to primary lysosomes
b. Attachment of chemicals to extracellular material to increase phagocytosis
c. Dilation of blood vessels by chemotherapeutic drugs
d. Movement of cells toward a certain site or source
e. Transmigration of cells from blood vessels into tissue

34. A 3-year-old boy presents with recurrent bacterial and fungal infections primarily involving his skin and respiratory tract. Physical examination reveals the presence of oculocutaneous albinism. Examination of a peripheral blood smear reveals large granules within neutrophils, lymphocytes, and monocytes. The total neutrophil count is found to be decreased. Further workup reveals ineffective bactericidal capabilities of neutrophils due to defective fusion of phagosomes with lysosomes. What is the correct diagnosis?

a. Ataxia-telangiectasia
b. Chédiak-Higashi syndrome
c. Chronic granulomatous disease
d. Ehlers-Danlos syndrome
e. Sturge-Weber syndrome

35. Which of the following laboratory findings is most suggestive of activation of the alternate complement system rather than the classic complement system?

	Serum C2	**Serum C3**	**Serum C4**
a.	Decreased	Normal	Normal
b.	Normal	Decreased	Normal
c.	Normal	Normal	Decreased
d.	Decreased	Normal	Decreased
e.	Decreased	Decreased	Decreased

36. A 19-year-old female is being evaluated for recurrent facial edema, especially around her lips. She also has recurrent bouts of intense abdominal pain and cramps, sometimes associated with vomiting. Laboratory examination finds decreased C4, while levels of C3, decay-accelerating factor, and IgE are within normal limits. These findings are most likely to be associated with a deficiency of

a. β_2-integrins
b. C1 esterase inhibitor
c. Decay-accelerating factor
d. Complement components C3 and C5
e. NADPH oxidase

37. Which one of the listed substances is produced by the action of lipoxygenase on arachidonic acid, is a potent chemotactic factor for neutrophils, and causes aggregation and adhesion of leukocytes?

a. C5a
b. Prostacyclin
c. IL-8
d. Thromboxane A_2
e. Leukotriene B_4

38. During acute inflammation, histamine-induced increased vascular permeability causes the formation of exudates (inflammatory edema). Which one of the listed cell types is the most likely source of the histamine that causes the increased vascular permeability?

a. Endothelial cells
b. Fibroblasts
c. Lymphocytes
d. Mast cells
e. Neutrophils

39. What type of leukocyte actively participates in acute inflammatory processes and contains myeloperoxidase within its primary (azurophilic) granules and alkaline phosphatase in its secondary (specific) granules?

a. Neutrophils
b. Eosinophils
c. Monocytes
d. Lymphocytes
e. Plasma cells

40. Histologic sections of lung tissue from a 68-year-old female with congestive heart failure and progressive breathing problems reveal numerous hemosiderin-laden cells within the alveoli. Theses "heart failure cells" originate from alveolar

a. Endothelial cells
b. Eosinophils
c. Lymphocytes
d. Macrophages
e. Pneumocytes

41. By definition, granulomas are composed of

a. Cholesterol clefts
b. Collagen
c. Endothelial cells and fibroblasts
d. Epithelioid cells
e. Hemosiderin-laden macrophages

42. A 47-year-old male presents with pain in the midportion of his chest. The pain is associated with eating and swallowing food. Endoscopic examination reveals an ulcerated area in the lower portion of his esophagus. Histologic sections of tissue taken from this area reveal an ulceration of the esophageal mucosa that is filled with blood, fibrin, proliferating blood vessels, and proliferating fibroblasts. Mitoses are easily found, and most of the cells have prominent nucleoli. Which one of the following correctly describes this ulcerated area?

a. Caseating granulomatous inflammation
b. Dysplastic epithelium
c. Granulation tissue
d. Squamous cell carcinoma
e. Noncaseating granulomatous inflammation

43. A routine H&E histologic section from an irregular white area within the anterior wall of the heart of a 71-year-old male who died secondary to ischemic heart disease reveals the myocytes to be replaced by diffuse red material. This material stains blue with a trichrome stain. Which one of the listed statements correctly describes this material?

a. It is secreted by endothelial cells and links macromolecules to integrins
b. It is secreted by fibroblasts and has a high content of glycine and hydroxyproline
c. It is secreted by hepatocytes and is mainly responsible for intravascular oncotic pressure
d. It is secreted by monocytes and contains a core protein that is linked to mucopolysaccharides
e. It is secreted by plasma cells and is important in mediating humoral immunity

44. A 27-year-old female presents because of trouble with her vision. Physical examination reveals a very tall, thin female with long, thin fingers. Examining her eyes reveals the lens of her left eye to be in the anterior chamber. Her blood levels of methionine and cystathionine are within normal levels. This patient's signs and symptoms are primarily due to

a. Abnormal copper metabolism
b. Decreased levels of vitamin D
c. Decreased lysyl hydroxylation of collagen
d. Defective synthesis of fibrillin
e. Defective synthesis of type I collagen

45. Which one of the listed changes correctly describes the pathophysiology involved in the production of pulmonary edema in patients with congestive heart failure?

a. Decreased plasma oncotic pressure
b. Endothelial damage
c. Increased hydrostatic pressure
d. Increased vascular permeability
e. Lymphatic obstruction

46. Which one of the listed clinical scenarios best illustrates the concept of active hyperemia?

a. A 22-year-old second-year medical student who develops a red face after being asked a question during a lecture
b. A 37-year-old male who develops massive swelling of the scrotum due to infection with *Wucheria bancrofti*
c. A 69-year-old male who dies secondary to progressive heart failure and at autopsy is found to have a "nutmeg" liver
d. A 6-year-old boy who develops the sudden onset of intense scrotal pain due to testicular torsion
e. A 71-year-old female who develops perifollicular hemorrhages due to a deficiency of vitamin C

47. Procoagulant factors produced by endothelial cells include

a. Thrombomodulin
b. Prostacyclin
c. von Willebrand factor
d. Thromboxane A_2
e. Fibrinogen

48. Which one of the listed laboratory findings is most consistent with an individual who is not taking any medication but has a familial deficiency of coagulation factor VII, assuming all other coagulation factors to be within normal limits?

	Prothrombin Time (PT)	**Partial Thromboplastin Time (PTT)**
a.	Prolonged	Normal
b.	Normal	Prolonged
c.	Shortened	Normal
d.	Normal	Shortened
e.	Shortened	Prolonged

49. A postmortem clot is most likely to

a. Grossly display features of recanalization
b. Grossly have lines of Zahn
c. Grossly have the appearance of "chicken fat" overlying "currant jelly"
d. Microscopically appear attached to the wall of the blood vessel
e. Microscopically have alternating layers of cells and platelets

50. What is the most common site of origin of thrombotic pulmonary emboli?

a. Deep leg veins
b. Lumen of left ventricle
c. Lumen of right ventricle
d. Mesenteric veins
e. Superficial leg veins

51. A 9-year-old boy suddenly develops severe testicular pain. He is taken to the emergency room, where he is evaluated and immediately taken to surgery. There his left testis is found to be markedly hemorrhagic due to testicular torsion. This abnormality caused a hemorrhagic testicular infarction because of

a. Arterial occlusion
b. Septic infarction
c. The collateral blood supply of the testis
d. The dual blood supply of the testis
e. Venous occlusion

52. A young child who presents with megaloblastic anemia is found to have increased orotate in the urine due to a deficiency of orotate phosphoribosyl transferase. This enzyme deficiency decreases the synthesis of

a. Glycogen
b. Purines
c. Pyrimidines
d. Sphingomyelin
e. Tyrosine

53. The combination of a primary defect, such as bilateral renal agenesis, along with its secondary structural change is best referred to by which one of the listed terms?

a. Association
b. Deformation
c. Disruption
d. Sequence
e. Syndrome

54. As a general rule, familial disorders that involve abnormalities of structural proteins (rather than deficiencies of enzymes) and present during adulthood (rather than childhood) have what type of inheritance pattern?

a. Autosomal dominant
b. Autosomal recessive
c. Mitochondrial
d. X-linked dominant
e. X-linked recessive

55. A sex-linked recessive mode of inheritance exists in

a. Myotonic dystrophy
b. Limb-girdle dystrophy
c. Facioscapulohumeral dystrophy
d. Duchenne muscular dystrophy
e. Polymyositis

56. Assume that both parents are carriers for the abnormal gene that causes cystic fibrosis. If they have three children, what is the probability that ALL of their children will develop cystic fibrosis?

a. $\frac{1}{4} \times \frac{1}{4} \times \frac{1}{4}$
b. $\frac{1}{4} + \frac{1}{4} + \frac{1}{4}$
c. $\frac{3}{4} \times \frac{3}{4} \times \frac{3}{4}$
d. $\frac{3}{4} + \frac{3}{4} + \frac{3}{4}$
e. $1 - (\frac{3}{4} + \frac{3}{4} + \frac{3}{4})$

57. The Hardy-Weinberg principle states that, given a frequency of a certain allele A of p and a frequency q of another allele a at the same locus on the same autosomal chromosome in a population with random mating (panmixia), then the number of heterozygous carriers is equal to

a. $p \times p$
b. $q \times q$
c. $p \times q$
d. $2 \times p \times q$
e. $(p \times p) + (p \times q)$

58. A 6-year-old female is being evaluated for recurrent episodes of lightheadedness and sweating due to hypoglycemia. These symptoms are not improved by subcutaneous injection of epinephrine. Physical examination reveals an enlarged liver and a single subcutaneous xanthoma. An abdominal CT scan reveals enlargement of the liver along with bilateral enlargement of the kidneys. Laboratory examination reveals increased serum uric acid and cholesterol with decreased serum glucose levels. Following oral administration of fructose, there is no increase in blood glucose levels. A liver biopsy specimen reveals increased amounts of glycogen in hepatocytes, which also have decreased levels of glucose-6-phosphatase. What is the correct diagnosis?

a. Andersen's syndrome (type IV glycogen storage disease)
b. Cori's disease (type III glycogen storage disease)
c. McArdle's syndrome (type V glycogen storage disease)
d. Pompe's disease (type II glycogen storage disease)
e. von Gierke's disease (type I glycogen storage disease)

59. In tissues affected by the predominant form of Niemann-Pick disease, which one of the following is found at abnormally high levels?

a. Sphingomyelin
b. Sphingomyelinase
c. Kerasin
d. Acetyl coenzyme A
e. Ganglioside

60. A 9-year-old boy is being evaluated for deafness. Physical examination reveals a child with short stature, coarse facial features (low, flat nose, thick lips, widely spaced teeth, facial fullness), a large tongue, and clear corneas. Laboratory examination reveals increased urinary levels of heparan sulfate and dermatan sulfate. Metachromatic granules (Reilly bodies) are found in leukocytes from a bone marrow biopsy. These leukocytes are also found to be deficient in iduronosulfate sulfatase. What is the correct diagnosis?

a. Hunter's disease
b. Hurler's disease
c. I cell disease
d. Metachromatic leukodystrophy
e. Wolman's disease

61. A 45-year-old male presents with severe pain in both knee joints. At the time of surgery, his cartilage is found to have a dark blue-black color. Further evaluation reveals that the patient's urine has darkened rapidly with time. The most likely diagnosis for this abnormality is

a. Hyperphenylalaninemia
b. Tyrosinemia
c. Tyrosinase-positive oculocutaneous albinism
d. Alkaptonuria
e. Maple syrup urine disease

62. Which one of the listed processes is the most likely cause of an aneuploid karyotype?

a. A reciprocal translocation between two acrocentric chromosomes
b. Deletion of both ends of a chromosome with fusion of the damaged ends
c. Division of the centromere along a transverse plane
d. Failure of homologous chromosomes or paired chromatids to separate
e. Two breaks within a single chromosome with reincorporating of the inverted segment

63. The first child of a couple has trisomy 21 (not the result of mosaicism), and they come to you wanting to know the risk of having another child with Down's syndrome. The mother's age is 23, and the father's age is 25. Both appear normal and neither have had any unusual diseases. You analyze their karyotypes and find that the father's karyotype is normal, but the mother has a Robertsonian translocation involving chromosome 21 (21q21q). Which one of the listed percentages is the best estimate of the chance that the next living child of this couple will have Down's syndrome?

a. 0%
b. 15%
c. 33%
d. 50%
e. 100%

64. A male infant dies 1 day after birth. Gross examination at the time of autopsy reveals polydactyly, a cleft lip and palate, and a single, central eye ("cyclops"). Further examination reveals holoprosencephaly, consisting of fused frontal lobes with a single ventricle. Which of the listed chromosomal abnormalities is most consistent with these findings?

a. Deletion 21
b. Deletion 22
c. Trisomy 13
d. Trisomy 18
e. Trisomy 21

65. A 2-month-old girl presents with a soft, high-pitched, mewing cry and is found to have microcephaly, low-set ears and hypertelorism, and several congenital heart defects. The chromosomal abnormality that is most likely to produce these symptoms is

a. 46,XX,$4p^-$
b. 46,XX,$5p^-$
c. 46,XX,$13q^-$
d. 46,XX,$15q^-$
e. 46,XX,$17p^-$

66. A 6-year-old female with a fair complexion is being evaluated for severe mental retardation and seizures. She is found to have a stiff, ataxic gait characterized by jerky movements. She also displays laughter at inappropriate times. What is the correct diagnosis?

a. Beckwith-Wiedemann syndrome
b. Prader-Willi syndrome
c. Angelman's syndrome
d. Smith-Margens syndrome
e. Wolf-Hirschhorn syndrome

67. A 19-year-old female of average intelligence and short stature is being evaluated for amenorrhea. Taking a history, you discover that she has never menstruated. Physical examination reveals that she has a shield-shaped chest and her elbows turn outward when her arms are at her sides. She has a "thick neck" and you notice the absence of secondary female characteristics. Serum estrogen levels are found to be decreased, while both FSH and LH levels are increased. What is the correct diagnosis?

a. Fragile X syndrome
b. Klinefelter's syndrome
c. Multi-X syndrome
d. Turner's syndrome
e. XYY syndrome

68. A 17-year-old individual who is phenotypically female presents for workup of primary amenorrhea and is found to have an XY karyotype. The most likely diagnosis is

a. Androgen insensitivity syndrome
b. Deficiency of 5-α-reductase
c. Kallmann's syndrome
d. Mixed gonadal dysgenesis
e. Turner's syndrome

69. Which immunoglobulins are characteristically present on mature (virgin) B cells, which are B lymphocytes that have not yet been exposed to the appropriate antigen?

a. IgA and IgE
b. IgD and IgA
c. IgE and IgG
d. IgG and IgM
e. IgM and IgD

70. What type of antibody is produced first against a bacterial infection, is very effective at activating complement, and is too large to cross the placenta?

a. IgG
b. IgM
c. IgD
d. IgE
e. IgA

71. Which one of the following sequences correctly describes the usual temporal sequence of T-lymphocyte maturation within the cortex and medulla of the thymus?

a. Double negative → double positive → single positive
b. Double negative → single positive → double positive
c. Double positive → double negative → single positive
d. Double positive → single positive → double negative
e. Single positive → double positive → double negative

72. Which cytokine is produced mainly by T_H1 cells and stimulates cell-mediated immunity by stimulating cytokine-driven proliferation of CD8+ cytotoxic T cells?

a. α-interferon
b. γ-interferon
c. Interleukin 1
d. Interleukin 2
e. Interleukin 3

73. In antigen recognition by cytotoxic T lymphocytes, the T cell receptor recognizes antigens bound to

a. Class I antigens
b. Class II antigens
c. Class III antigens
d. C3b
e. Fc portion of IgG

74. There is a strong association between ankylosing spondylitis and

a. HLA-B27
b. HLA-DR3
c. HLA-DR4
d. HLA-A3
e. HLA-BW47

75. Ten minutes after being stung by a wasp, a 30-year-old male develops multiple patches of red, irregular skin lesions over his entire body. These lesions (urticaria) are pruritic, and new crops of lesions occur every day. This response is primarily the result of liberation of specific vasoactive substances by the action of

a. Activated T lymphocytes on smooth muscle cells
b. IgA on basophils and mast cells
c. IgA on lymphocytes and eosinophils
d. IgE on basophils and mast cells
e. IgE on lymphocytes and eosinophils

76. After receiving incompatible blood, a patient develops a transfusion reaction in the form of back pain, fever, shortness of breath, and hematuria. This type of immunologic reaction is classified as a

a. Systemic anaphylactic reaction
b. Systemic immune complex reaction
c. Delayed type hypersensitivity reaction
d. Complement-mediated cytotoxicity reaction
e. T cell–mediated cytotoxicity reaction

77. Which one of the following histologic or immunofluorescent findings is most indicative of a delayed type hypersensitivity reaction?

a. A linear immunofluorescence pattern in the wall of the esophagus
b. Caseating granulomas in hilar lymph nodes
c. Councilman (apoptotic) bodies in the liver
d. Fibrinoid necrosis around dermal blood vessels
e. Numerous eosinophils in a nasal polyp

78. An allograft is a graft between

a. A human and an animal
b. Two individuals of different species
c. Two individuals of the same species
d. Two individuals of the same inbred strain
e. Identical twins

79. Minutes after a donor kidney is connected to the recipient's blood vessels, the transplanted kidney turns blue, becomes flaccid, excretes a few drops of bloody urine, and has to be removed. Histologic examination of the kidney reveals neutrophils within arterioles, glomeruli, and peritubular capillaries. Immunoglobulin and complement are found to be deposited in blood vessel walls. This type of transplant rejection is due primarily to

a. Donor cytotoxic T lymphocytes that are directed against host antigens
b. Host cytotoxic T lymphocytes that are directed against donor antigens
c. Donor natural killer cells that are directed against host antigens
d. Preformed donor antibodies that are directed against host antigens
e. Preformed host antibodies that are directed against donor antigens

80. An autoantibody that reacts to immunoglobulin (e.g., an anti-IgG autoantibody) is most characteristic of

a. Bullous pemphigoid
b. Diabetes mellitus
c. Goodpasture's disease
d. Pemphigus vulgaris
e. Rheumatoid arthritis

81. Anti-double-stranded DNA antibodies are most likely to be found in which one of the listed individuals?

a. A 28-year-old female with arthritis and a bimalar photosensitive, erythematous rash on her face
b. A 65-year-old female who develops Congo red–positive extracellular deposits in her liver
c. A 29-year-old female who presents with trouble swallowing and sclerodactyly
d. A 35-year-old female who presents with dry eyes, a dry mouth, and enlarged salivary glands
e. A 47-year-old female who presents with periorbital lilac discoloration and erythema on the dorsal portions of her hands

82. A 36-year-old female presents with increased trouble swallowing. Physical examination finds hypertension and sclerodactyly. A skin biopsy reveals dermal fibrosis with an absence of adnexal structures, while laboratory examination finds an autoantibody against DNA topoisomerase (anti-Scl-70). What is the best diagnosis for this individual?

a. Dermatomyositis
b. Mixed connective tissue disorder
c. Progressive systemic sclerosis
d. Sjögren's syndrome
e. Systemic lupus erythematosus

83. An 87-year-old male develops worsening heart failure. Workup reveals decreased left ventricular filling due to decreased compliance of the left ventricle. Two months later the patient dies, and postmortem sections reveal deposits of eosinophilic, Congo red–positive material in the interstitium of his heart. When viewed under polarized light, this material displays an apple-green birefringence. What is the correct diagnosis?

a. Amyloidosis
b. Glycogenosis
c. Hemochromatosis
d. Sarcoidosis
e. Senile atrophy

84. A 28-year-old woman's first son dies at 7 months of age due to severe combined immunodeficiency disease (SCID). Subsequent workup reveals a mutation in the gene for the common γ chain of the interleukin 2 receptor (IL2RG). Lymphocyte and red cell adenosine deaminase (ADA) levels are within normal limits. Workup during the woman's second pregnancy reveals that the fetus has the same abnormality found in her first son. Bone marrow is obtained from the 29-year-old father and is enriched with CD34+ cells (hematopoietic cell progenitors). It is then injected intraperitoneally by percutaneous, ultrasound-guided injection at 16, 17.5, and 18.5 weeks of gestation. At 11 months of life, the second child is found to be clinically normal. What is the mode of inheritance of this patient's disease?

a. Autosomal dominant
b. Autosomal recessive
c. Mitochondrial
d. X-linked dominant
e. X-linked recessive

85. Individuals homozygous for defective CCR5 are resistant to infection by

a. CMV
b. EBV
c. HHV-6
d. HHV-8
e. HIV

86. A 52-year-old male presents with symptoms of gastric pain after eating. During workup, a 3-cm mass is found in the wall of the stomach. This mass is resected and histologic examination reveals a tumor composed of cells having elongated, spindle-shaped nuclei. The tumor does not connect to the overlying epithelium and is found only in the wall of the stomach. This tumor most likely originated from

a. Adipocytes
b. Endothelial cells
c. Glandular epithelial cells
d. Smooth muscle cells
e. Squamous epithelial cells

87. A 64-year-old male presents with symptoms of anemia. On workup, you discover that the patient has been losing blood from the GI tract secondary to a tumor mass in his colon. The pathology report from a biopsy specimen indicates that this mass is an invasive adenocarcinoma. Which one of the listed descriptions best describes the most likely histologic appearance of this tumor?

a. A uniform proliferation of fibrous tissue
b. A disorganized mass of proliferating fibroblasts and blood vessels
c. A disorganized mass of cells forming keratin
d. A uniform proliferation of glandular structures
e. A disorganized mass of cells forming glandular structures

88. A 35-year-old male presents with the new onset of a "bulge" in his left inguinal area. After performing a physical examination, you diagnose the bulge to be an inguinal hernia. You refer the patient to a surgeon, who repairs the hernia and sends the resected hernia sac to the pathology laboratory along with some adipose tissue, which he calls a "lipoma of the cord." The pathology resident examines the tissue grossly and microscopically and decides that it is not a neoplastic lipoma, but instead is nonneoplastic normal adipose tissue. Which one of the following features would have been present had the lesion been a lipoma rather than normal adipose tissue?

a. Anaplasia
b. Fibrous capsule
c. Numerous mitoses
d. Prominent nucleoli
e. Uniform population of cells

89. Which one of the listed numbered sequences best illustrates the postulated sequence of events that precedes the formation of an infiltrating squamous cell carcinoma of the cervix?

1 = Carcinoma in situ
2 = Invasive carcinoma
3 = Mild dysplasia
4 = Moderate dysplasia
5 = Severe dysplasia
6 = Squamous metaplasia

a. 3, then 4, then 5, then 1, then 6, then 2
b. 3, then 4, then 5, then 6, then 1, then 2
c. 5, then 4, then 3, then 1, then 6, then 2
d. 6, then 3, then 4, then 5, then 1, then 2
e. 6, then 4, then 3, then 5, then 2, then 1

90. During a routine physical examination, a 49-year-old male is found to have a 2.5-cm "coin lesion" in the upper lobe of his left lung. The lesion is removed surgically, and histologic sections reveal sheets of malignant cells with clear cytoplasm (clear cell carcinoma). This lung lesion is most likely a metastasis from the

a. Appendix
b. Breast
c. Kidney
d. Pancreas
e. Stomach

91. v-oncs are a type of oncogene that are most characteristically found within

a. Acute-transforming viruses
b. Fungi and parasites
c. Gram-negative bacteria
d. Gram-positive bacteria
e. Slow-transforming viruses

92. Point mutations of the oncogene *c-ras* can result in the inability of the product of this oncogene to bind with

a. GAP
b. p210
c. p53
d. pRb
e. WT1

93. A 4-year-old African boy develops a rapidly enlarging mass that involves the right side of his face. Biopsies of this lesion reveal a prominent "starry sky" pattern produced by proliferating small, noncleaved malignant lymphocytes. Based on this microscopic appearance, the diagnosis of Burkitt's lymphoma is made. This neoplasm is associated with chromosomal translocations that involve

a. *bcl-2*
b. *c-abl*
c. *c-myc*
d. *erb-B*
e. *N-myc*

94. The product of the p53 antioncogene is a nuclear protein that regulates DNA replication and prevents the proliferation of cells with damaged DNA by stopping their cell cycle

a. Between G1 and S
b. Between G2 and M
c. Between M and G1
d. Between S and G2
e. During G3

95. A 76-year-old male farmer presents with a 2-cm mass on the left side of his forehead. A biopsy reveals squamous cell carcinoma. Which one of the following causes the formation of pyrimidine dimers in DNA and is associated with the formation of squamous cell carcinoma?

a. Aflatoxin B1
b. Vinyl chloride
c. UVC
d. UVB
e. Epstein-Barr virus

96. A 17-year-old male presents with a lesion on his face that measures approximately 1.5 cm in its greatest dimension. He has a history of numerous similar skin lesions that have occurred mainly in sun-exposed areas. The present lesion is biopsied and reveals an invasive squamous cell carcinoma. This patient most probably has one type of a group of inherited diseases associated with unstable DNA and increased incidence of carcinoma. What is the diagnosis for this patient?

a. Xeroderma pigmentosa
b. Wiskott-Aldrich syndrome
c. Familial polyposis
d. Sturge-Weber syndrome
e. Multiple endocrine neoplasia type I (MEN I)

97. Gastric carcinoma is most common in which one of the listed geographic locations?

a. Canada
b. France
c. Japan
d. United Kingdom
e. United States

98. A 57-year-old male presents with signs of fatigue that are the result of anemia. Workup reveals that his anemia is the result of bleeding from a colon cancer located in the sigmoid colon. The lesion is resected and at the time of surgery no metastatic disease is found. Which of the listed markers would be most useful for future follow-up of this patient for the evaluation of possible metastatic disease from his colon cancer?

a. α fetoprotein (AFP)
b. Carcinoembryonic antigen (CEA)
c. Chloroacetate esterase (CAE)
d. Human chorionic gonadotropin (hCG)
e. Prostate-specific antigen (PSA)

99. A 23-year-old female presents with the recent onset of vaginal discharge. Physical examination reveals multiple clear vesicles on her vulva and vagina. A smear of material obtained from one of these vesicles reveals several multinucleated giant cells with intranuclear inclusions and ground-glass nuclei. These vesicles are most likely the result of an infection with

a. Cytomegalovirus (CMV)
b. Herpes simplex virus (HSV)
c. Human papillomavirus (HPV)
d. *Candida albicans*
e. *Trichomonas vaginalis*

100. A 19-year-old man living in New Mexico presents to a local clinic after a 1-day history of fever, myalgia, chills, headache, and malaise. He complains of vomiting, diarrhea, abdominal pain, tachypnea, and a productive cough. His white cell count is elevated with an increase in the number of bands. Atypical lymphocytes are also found in the peripheral blood. He is treated with antibiotics, but the next day he develops acute respiratory failure with cardiopulmonary arrest and dies. Postmortem examination of the lungs reveals intraalveolar edema, rare hyaline membranes, and a few interstitial lymphoid aggregates. The most likely cause of this patient's illness is infection with

a. Ebola virus
b. Dengue fever virus
c. Hantavirus
d. Yellow fever virus
e. Alphavirus

101. A 6-year-old boy develops a facial rash that has the appearance of a slap to the face. The rash, which is composed of small red spots, subsequently involves the upper and lower extremities. This boy also has arthralgia and suddenly develops a life-threatening aplastic crisis of the bone marrow. The most likely infectious agent causing these symptoms is

a. Rhinovirus
b. Parainfluenza virus
c. Parvovirus
d. Measles virus
e. Rubella virus

102. Lobar pneumonia is caused predominantly by

a. *Klebsiella pneumoniae*
b. *Staphylococcus pyogenes*
c. *Haemophilus influenzae*
d. *Streptococcus pneumoniae*
e. *Legionella pneumophila*

103. A 33-year-old male in an underdeveloped country presents with a markedly edematous right foot that has multiple draining sinuses. A Gram stain from one of these draining sinuses reveals gram-positive filamentous bacteria that are partially acid-fast. The organism causing this abnormality is

a. *Actinomyces israelii*
b. *Corynebacterium diphtheriae*
c. *Listeria monocytogenes*
d. *Nocardia asteroides*
e. *Pneumocystis carinii*

104. A 38-year-old male presents with right lower quadrant abdominal pain, fever, and a peripheral neutrophilia. An emergency appendectomy is performed, but the appendix is found to be grossly unremarkable. Instead, the lymph nodes surrounding the appendix are found to be enlarged, inflamed, and matted together. Which one of the listed organisms is the most likely cause of these abnormalities?

a. Enteropathic *Escherichia coli*
b. *Enterobius vermicularis*
c. *Trichomonas hominis*
d. *Yersinia enterocolitica*
e. *Bacillus anthracis*

105. A 30-year-old male presents with multiple soft, raised, beefy-red superficial ulcers in his left groin. Physical examination reveals several enlarged left inguinal lymph nodes. A histologic section from an enlarged lymph node that is stained with a silver stain reveals characteristic Donovan bodies within macrophages. What is the most likely diagnosis?

a. Chancroid
b. Gonorrhea
c. Granuloma inguinale
d. Lymphogranuloma venereum
e. Syphilis

106. A 44-year-old female diabetic living on Martha's Vineyard develops the sudden onset of chills and fever. Her symptoms result from destruction of erythrocytes by a particular organism, which was transmitted by the hard-shell tick (ixodid). What is this organism?

a. *Plasmodia vivax*
b. *Plasmodia ovale*
c. *Leishmania donovani*
d. *Leishmania chagasi*
e. *Babesia microti*

107. A 32-year-old male presents with arthritis and conjunctivitis. No rheumatoid factor is found in his serum (i.e., seronegative spondyloarthropathy). A detailed history reveals that he also has severe pain with urination (nongonococcal urethritis). The combination in this patient of arthritis, urethritis, and conjunctivitis is consistent with a diagnosis of Reiter's syndrome, a disorder that is associated with HLA-B27 and infection of the genitourinary tract with

a. *Shigella*
b. *Salmonella*
c. *Yersinia*
d. *Campylobacter*
e. *Chlamydia*

108. A 35-year-old female who lives in the southeastern portion of the United States and likes to hike in the Great Smoky Mountains presents with a spotted rash that started on her extremities and spread to her trunk and face. A biopsy of one of these lesions reveals necrosis and reactive hyperplasia of blood vessels. What is the most likely causative agent of her disease?

a. *Bartonella henselae*
b. *Bartonella quintana*
c. *Coxiella burnetii*
d. *Rickettsia prowazekii*
e. *Rickettsia rickettsii*

109. Finding acid-fast bacilli within peripheral nerves is most suggestive of

a. Relapsing fever
b. Syphilis
c. Leprosy
d. Tuberculosis
e. Weil's disease

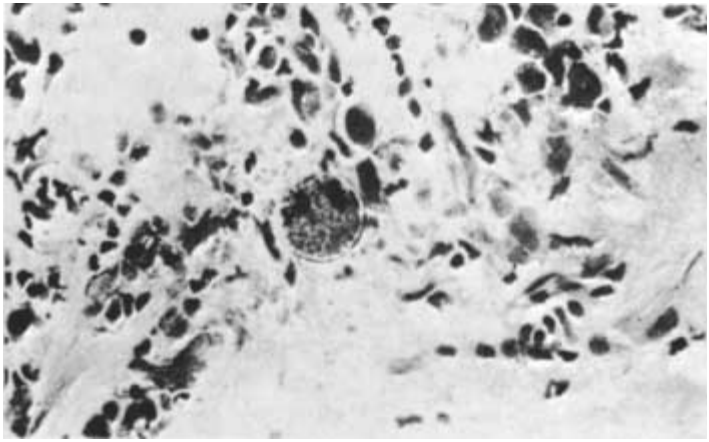
110. A 21-year-old college athlete presents with a nagging cough and a 20-lb weight loss. In addition to the chronic cough and weight loss, his main symptoms consist of fever, night sweats, and chest pains. Examination of his sputum reveals the presence of rare acid-fast organisms. His symptoms are most likely due to an infection with

a. *K. pneumoniae*
b. *L. pneumophila*
c. *Mycobacterium avium-intracellulare*
d. *Mycobacterium tuberculosis*
e. *Mycoplasma pneumoniae*

111. A 21-year-old HIV-positive male presents with malaise, fever, and increasing lymph nodes in his right cervical region. A microscopic section from one of the enlarged lymph nodes that is stained with an acid-fast stain reveals the presence of numerous ("too many to count") acid-fast organisms. Granulomas are not found. What organism is most likely the cause of this patient's acute illness?

a. *M. avium-intracellulare*
b. *M. marinum*
c. *M. leprae*
d. *M. tuberculosis*
e. *M. kansasii*

112. An adult migrant farm worker in the San Joaquin Valley of California has been hospitalized for 2 weeks with progressive lassitude, fever of unknown origin, and skin nodules on the lower extremities. A biopsy of one of the deep dermal nodules shown in the photomicrograph below reveals the presence of



a. Russell bodies
b. Malignant lymphoma
c. *Coccidioides* spherule
d. Lymphomatoid granulomatosis
e. Erythema nodosum

113. Sections of tissue infected with *Blastomyces* would be expected to show organisms with

a. Nonbranching pseudohyphae and blastocysts
b. Acute angle–branching, septate hyphae
c. Wide angle–branching, nonseptate hyphae
d. Broad-based budding
e. Large spheres with external budding

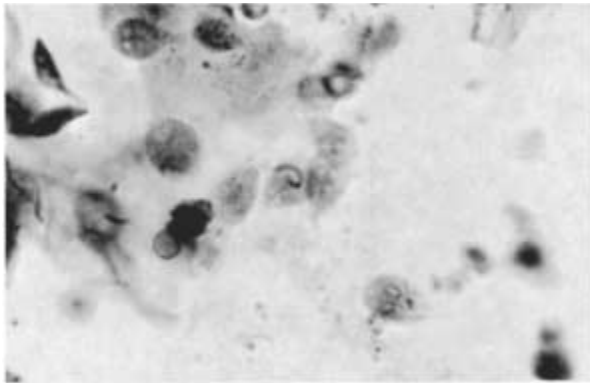
114. A 38-year-old male with AIDS presents with decreasing mental status. The workup at this time includes a spinal tap. Cerebrospinal fluid (CSF) is stained with a mucicarmine stain and india ink. The mucicarmine stain reveals numerous yeasts that stain bright red. The india ink prep reveals through negative staining that these yeasts have a capsule. What is your diagnosis?

a. Chromomycosis
b. Coccidioidomycosis
c. Cryptococcosis
d. Cryptosporidiosis
e. Paracoccidioidomycosis

115. A patient who presents to the hospital with severe headaches develops convulsions and dies. At autopsy the brain grossly has a "Swiss cheese" appearance due to the presence of numerous small cysts containing milky fluid. Microscopically, a scolex with hooklets is found within one of these cysts. What is the causative agent for this disease?

a. *Taenia saginata*
b. *Taenia solium*
c. *Diphyllobothrium latum*
d. *Echinococcus granulosa*
e. *Toxocara canis*

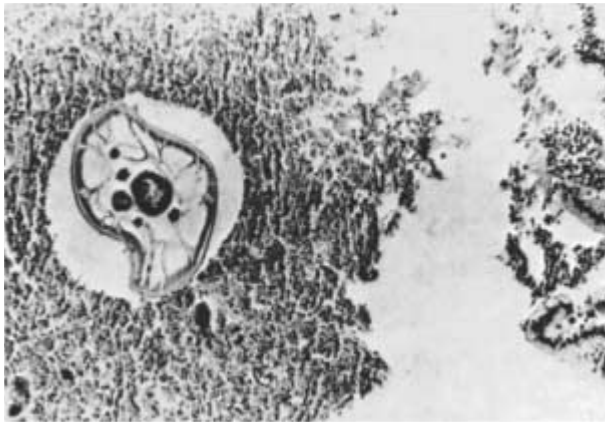
116. A 27-year-old male develops acute diarrhea consisting of foul-smelling, watery stools, along with severe abdominal cramps and flatulence, after returning from a trip to the Caribbean. The associated photomicrograph is from a duodenal aspiration smear. These signs and symptoms are caused by infection with



a. *Acanthamoeba*
b. *Entamoeba histolytica*
c. *E. vermicularis*
d. *Giardia lamblia*
e. *Sporothrix*

117. The most common sign or symptom produced by the organism seen in the associated photomicrograph of a distal colonic biopsy is

a. Aplastic anemia in children
b. Anal pruritus in children
c. Blood loss in adults
d. Centrifugal rash in adults
e. Vitamin B_{12} deficiency in adults



118. Soon after returning from a trip to Costa Rica, a 41-year-old female develops recurrent chills and high fever that recur every 48 h. Examination of her peripheral blood reveals red granules (Schüffner's dots) in enlarged, young erythrocytes. Which one of the listed organisms is most likely to have produced her signs and symptoms?

a. *Afipia felis*
b. *Ancyclostoma duodenale*
c. *B. microti*
d. *P. ovale*
e. *Toxoplasma gondii*

119. An apathetic male infant in an underdeveloped country is found to have peripheral edema, a "moon" face, and an enlarged, fatty liver. Which one of the listed mechanisms is involved in the pathogenesis of this child's abnormalities?

a. Decreased protein intake leads to decreased lipoproteins
b. Decreased caloric intake leads to hypoalbuminemia
c. Decreased carbohydrate intake leads to hypoglycemia
d. Decreased fluid intake leads to hypernatremia
e. Decreased fat absorption leads to hypovitaminosis

120. A patient with malabsorption who develops a deficiency of vitamin A is most likely to subsequently develop

a. Acute leukemia
b. Intestinal metaplasia
c. Megaloblastic anemia
d. Night blindness
e. Soft bones

121. A significant deficiency in vitamin D might be expected to lead to

a. Hyperostosis
b. Relative excess of osteoid
c. Increased absorption of calcium
d. Decreased production of bone matrix
e. Adequate serum phosphorus

122. Which one of the following individuals is most likely to have a deficiency of vitamin E?

a. A premature male infant with skeletal muscle weakness and a hemolytic anemia
b. A 36-year-old male with progressive night blindness
c. A 45-year-old female with bleeding and a prolonged PT and PTT
d. A 48-year-old female with chronic atrophic gastritis and anemia
e. A 67-year-old female with osteopenia and bone pain

123. A 62-year-old male alcoholic is brought into the emergency room acting very confused. Physical examination reveals a thin and emaciated male who has problems with memory, ataxia, and paralysis of his extraocular muscles. Extensive workup reveals atrophy and small hemorrhages in the periventricular region of his brain and around the mamillary bodies. These signs and symptoms are most consistent with a deficiency of

a. Biotin
b. Riboflavin
c. Selenium
d. Pyridoxine
e. Thiamine

124. The clinical combination of dermatitis, diarrhea, and dementia resulting from a deficiency of niacin is referred to as

a. Beriberi
b. Marasmus
c. Pellagra
d. Rickets
e. Scurvy

125. A 70-year-old female is brought to the emergency room by her granddaughter because she has developed ecchymosis covering many areas of her body. Her granddaughter states that her grandmother lives alone at home and has not been eating well. Her diet has consisted of mainly tea and toast, as she does not drink milk or eat fruits or vegetables. Your physical examination reveals small hemorrhages around hair follicles, some of these follicles having an unusual "corkscrew" appearance. You also notice swelling and hemorrhages of the gingiva. The signs and symptoms in this individual are most likely caused by a deficiency of

a. Thiamine
b. Pyridoxine
c. Niacin
d. Vitamin D
e. Vitamin C

126. Histologic sections of skin from an area of sunburn would most likely reveal

a. Epidermal edema
b. Intraepidermal vesicles
c. Full-thickness epithelial necrosis
d. Partial dermal necrosis
e. Necrosis of adnexal structures

127. δ-aminolevulinic acid is excreted in increased amounts in the urine of patients with

a. Lead poisoning
b. Carcinoma of the pancreas
c. Chronic pyelonephritis
d. Vitamin C intoxication
e. Ulcerative colitis

128. Laboratory examination of a 46-year-old male who presents with decreasing vision and photophobia finds a high anion–gap metabolic acidosis. These findings are most consistent with this individual having ingested

a. Cadmium
b. Nickel
c. Mercury
d. Cobalt
e. Methanol

129. A comatose 27-year-old woman is brought to the emergency room by paramedics, and the strong odor of bitter almonds is present. The differential diagnosis must include the possibility of poisoning by

a. Ethylene glycol
b. Carbon monoxide
c. Carbon tetrachloride
d. Cyanide
e. Arsenic

130. Which one of the following sets of serum levels is most likely to be seen in a young female as a result of self-induced starvation (anorexia nervosa)?

	Gonadotropin-Releasing Hormone (GnRH)	Luteinizing Hormone (LH)	Follicle-Stimulating Hormone (FSH)	Estrogen
a.	Increased	Increased	Increased	Increased
b.	Increased	Increased	Increased	Decreased
c.	Increased	Increased	Decreased	Decreased
d.	Increased	Decreased	Decreased	Decreased
e.	Decreased	Decreased	Decreased	Decreased

131. Mutations involving homeobox genes (HOX genes) are most likely to be associated with

a. Abnormal limbs and phocomelia
b. Arachnodactyly and dissecting aortic aneurysm
c. Congenital goiter and hypothyroidism
d. Congenital pigment abnormalities and deafness
e. Synpolydactyly and brachydactyly

132. An 8-year-old boy is found to have progressive corneal vascularization, deafness, notched incisors, and a flattened nose. The most likely cause of these changes is congenital infection by

a. *Toxoplasma*
b. Rubella
c. Cytomegalovirus
d. Herpes simplex virus
e. *T. pallidum*

133. A newborn female infant develops edema, jaundice, and trouble breathing. The blood type of the mother is AB negative, while the baby and the father are both B positive. The mother's only other pregnancy was unremarkable, and she has never received any blood or blood products. Laboratory examination reveals a positive Coombs (DAT) test. What is the best diagnosis?

a. ABO hemolytic disease of the newborn
b. Hemoglobin H disease
c. Hyaline membrane disease of the newborn
d. Hydrops fetalis
e. Rh hemolytic disease of the newborn

134. Artificial surfactant is most likely to be used in the treatment of an infant with

a. Hemolytic disease of the newborn
b. Hyaline membrane disease
c. Physiologic jaundice of the newborn
d. Retrolental fibroplasia
e. Transposition of the great vessels

135. A male infant is born markedly prematurely at 25 weeks of gestation. Due to the immaturity of his lungs, therapy with oxygen is used. Because of extensive medical intervention, this premature infant survives, but unfortunately he is found to be blind resulting from the use of oxygen. Which one of the listed pathologic abnormalities correctly describes the pathology that caused this infant's blindness?

a. Accumulation of abnormal material in the ganglion cells of the retina
b. Fibrous obliteration of the canal of Schlemm
c. Formation of a fibrovascular mass behind the lens
d. Lipid accumulation at the periphery of the cornea
e. Severe degeneration of the macula

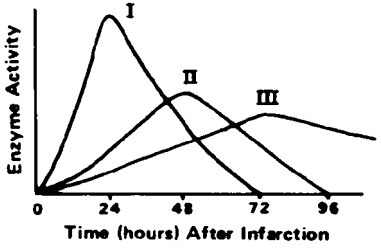
136. Which one of the listed clinical scenarios is most consistent with a diagnosis of SIDS?

a. A 2-year-old female dies suddenly and no autopsy is performed
b. A 3-month-old female dies during sleep and the cause of death is unknown after autopsy
c. A 4-week-old female dies from respiratory complications after being born 10 weeks prematurely
d. A 9-month-old male dies and an autopsy finds evidence of repeated bone fractures and bilateral retinal hemorrhages
e. A male is stillborn at 29 weeks of gestation to a mother with obstetrical complications

137. A 14-month-old male infant presents with an enlarging abdominal mass. Laboratory examination reveals increased urinary levels of metanephrine and VMA (vanillylmandelic acid). A histologic section from the mass reveals a tumor composed of small, primitive-appearing cells with hyperchromatic nuclei and little to no cytoplasm. Occasional focal groups of tumor cells are arranged in a ring around a central space. What is the correct diagnosis for this tumor?

a. Adrenal cortical carcinoma
b. Ganglioneuroma
c. Nephroblastoma
d. Neuroblastoma
e. Pheochromocytoma

138. The enzyme activity curve labeled II in the figure below best represents the pattern for which of the following serum enzymes after an uncomplicated acute myocardial infarction?



a. Aspartate aminotransferase
b. Creatine phosphokinase
c. Lactic dehydrogenase
d. Alkaline phosphatase
e. 59-nucleotidase

139. The table below shows the normal serum values for the five isoenzymes of lactic dehydrogenase (LDH) and the values obtained for one patient. The diagnosis most compatible with the patient's values is

Isoenzyme	Normal percent activity	Patient's percent activity
LDH_1	20–35	18
LDH_2	30–40	24
LDH_3	20–30	13
LDH_4	5–15	26

a. Acute hepatitis
b. Pernicious anemia
c. Pulmonary infarct
d. Myocardial infarct
e. Cerebrovascular accident

140. Specificity of a test is defined by which one of the following expressions?

a. True negatives/(true negatives + false negatives)
b. True negatives/(true negatives + false positives)
c. True positives/(true positives + false negatives)
d. True positives/(true positives + false positives)
e. (True positives + false negatives)/(true negatives + false positives)

General Pathology

Answers

1. The answer is c. *(Cotran, pp 39–40, 859. Chandrasoma, 3/e, pp 8–10.)* Free fatty acids are normally taken up by the liver and esterified to triglyceride, converted to cholesterol, oxidized into ketone bodies, or incorporated into phospholipids that can be excreted from the liver as very-low-density lipoproteins (VLDLs). Abnormalities involving any of these normal metabolic pathways may lead to the accumulation of triglycerides within the hepatocytes. This accumulation of triglycerides is called fatty change or steatosis. Examples of abnormalities that produce hepatic steatosis include diseases that cause excess delivery of free fatty acids to the liver or diseases that cause impaired lipoprotein synthesis. Excess delivery of free fatty acids occurs in conditions that increase lipolysis of adipose tissue, such as starvation, diabetes mellitus, and corticosteroid use. Increased formation of triglycerides can result from alcohol use, as alcohol causes excess NADH formation (high NADH/NAD ratio), increases fatty acid synthesis, and decreases fatty acid oxidation. Impaired apoprotein synthesis occurs with carbon tetrachloride poisoning, phosphorous poisoning, and protein malnutrition. Inhibition of HMG-CoA reductase activity is the mechanism of lovastatin, which indirectly increases liver LDL receptors and increases LDL clearance from the blood.

2. The answer is b. *(Alberts, pp 734–749. Cotran, pp 92–93, 343–344.)* Many extracellular substances cause intracellular actions via second-messenger systems. These second messengers may bind to receptors that are located either on the surface of the cell or within the cell itself. Substances that react with intracellular receptors are lipid-soluble (lipophilic) molecules that can pass through the lipid plasma membrane. Examples of these lipophilic substances include thyroid hormones, steroid hormones, and the fat-soluble vitamins A and D. Once inside the cell these substances generally travel to the nucleus and bind to the hormone response element (HRE) of DNA.

Some substances that react with cell surface receptors bind to guanine-nucleotide regulatory proteins. These proteins, called G proteins, may be classified into four categories, namely Gs, Gi, Gt, and Gq. Two of these receptors, Gs and Gi, regulate the intracellular concentration of cyclic adenosine 5′-monophosphate (cAMP). In contrast, Gt regulates the intracytoplasmic levels of cyclic guanosine 5′-monophosphate (cGMP), and Gq regulates the intracytoplasmic levels of calcium ions. Gs and Gi regulate intracellular cAMP levels by their actions on adenyl cyclase, an enzyme located on the inner surface of the plasma membrane that catalyzes the formation of cAMP from ATP. The adenylate cyclase G protein complex is composed of the following components: the receptor, the catalytic enzyme (i.e., adenyl cyclase), and a coupling unit. The coupling unit consists of GTP-dependent regulatory proteins (G proteins), which may either be stimulatory (Gs) or inhibitory (Gi). When bound to GTP and active, Gs stimulates adenyl cyclase and increases cAMP levels. (Gs can be thought of as the "on switch.") In contrast, when bound to GTP and active, Gi inhibits adenyl cyclase and decreases cAMP levels. (Gi can be thought of as the "off switch.") It is important to note that cholera toxin and pertussis toxin both act by altering this adenyl cyclase pathway. Cholera toxin inhibits the conversion of Gs-GTP to Gs-GDP. In contrast, pertussis toxin inhibits the activation of Gi-GDP to Gi-GTP. Therefore, both cholera toxin and pertussis toxin prolong the functioning of adenyl cyclase and therefore increase intracellular cAMP, but their mechanisms are different. Cholera toxin keeps the "on switch" in the "on" position, while pertussis toxin keeps the "off switch" in the "off" position.

3. The answer is a. *(Cotran, pp 65, 231–236. Rubin, pp 67, 1088.)* Patients with chronic granulomatous disease have defective functioning of phagocytic neutrophils and monocytes due to an inability to produce hydrogen peroxide. That is, their phagocytic cells have a decreased oxidative or respiratory burst. The most common cause of chronic granulomatous disease is defective NADPH oxidase, which is an enzyme on the membrane of lysosomes that converts O_2 to superoxide and stimulates oxygen burst. This deficiency results in recurrent infections with catalase-positive organisms, such as *S. aureus.* The classic form of chronic granulomatous disease usually affects boys and causes death before the age of 10. Key findings in chronic granulomatous disease include lymphadenitis,

hepatosplenomegaly, eczematoid dermatitis, pulmonary infiltrates that are associated with hypergammaglobulinemia, and defective ability of neutrophils to kill bacteria.

A defect in the enzyme adenosine deaminase (ADA) is seen in the autosomal recessive (Swiss) form of severe combined immunodeficiency disease (SCID), while a defect in the IL-2 receptor is seen in the X-linked recessive form of SCID. A developmental defect at the pre-B stage is seen in X-linked agammaglobulinemia of Bruton, while developmental failure of pharyngeal pouches 3 and 4 is characteristic of DiGeorge's syndrome.

4. The answer is e. *(Cotran, 6/e, pp 70–72.)* Certain drugs are important in the control of acute inflammation because they inhibit portions of the metabolic pathways involving arachidonic acid. For example, corticosteroids induce the synthesis of lipocortins, a family of proteins that are inhibitors of phospholipase A_2. They decrease the formation of arachidonic acid and its metabolites, prostaglandins and leukotrienes. Aspirin, indomethacin, and other nonsteroidal anti-inflammatory drugs (NSAIDs), in contrast, inhibit cyclooxygenase and therefore inhibit the synthesis of prostaglandins and thromboxanes. The prostaglandins have several important functions. For example, prostaglandin E_2 (PGE_2), produced within the anterior hypothalamus in response to interleukin 1 secretion from leukocytes, results in fever. Therefore aspirin can be used to treat fever by inhibiting PGE_2 production. PGE_2 is also a vasodilator that can keep a ductus arteriosus open. At birth, breathing decreases pulmonary resistance and reverses the flow of blood through the ductus arteriosus. The oxygenated blood flowing from the aorta into the ductus inhibits prostaglandin production and closes the ductus arteriosus. Therefore prostaglandin E_2 can be given clinically to keep the ductus arteriosus open, while indomethacin can be used to close a patent ductus. Prostaglandin F_2 (PGF_2) causes uterine contractions, which can result in dysmenorrhea. Indomethacin can be used to treat dysmenorrhea by inhibiting the production of PGF_2. Bradykinin is a nonapeptide that increases vascular permeability, contracts smooth muscle, dilates blood vessels, and causes pain. It is part of the kinin system and is formed from high-molecular-weight kininogen (HMWK). Histamine, a vasoactive amine that is stored in mast cells, basophils, and platelets, acts on H_1 receptors to cause dilation of arterioles and increased vascular permeability of venules.

5. The answer is a. *(Cotran, pp 84–87.)* An abscess is a localized collection of neutrophils and necrotic debris. It is basically a localized form of suppurative (purulent) inflammation, which is associated with pyogenic bacteria and is characterized by edema fluid admixed with neutrophils and necrotic cells (liquefactive necrosis or pus). *S. aureus* classically produces abscesses, because it is coagulase-positive and coagulase helps to produce fibrinous material that localizes the infection. Other morphologic patterns of inflammation include serous inflammation, fibrinous inflammation, and pseudomembranous inflammation. Fibrinous inflammation is associated with the deposition of fibrin in body cavities, which subsequently stimulates coagulation. Histologically, fibrin is seen as amorphic eosinophilic material. Fibrinous inflammation within the pericardial cavity (fibrinous pericarditis) produces a characteristic "bread-and-butter" appearance grossly. Serous inflammation produces a thin fluid, such as is present in skin blisters or body cavities. In contrast to fibrinous inflammation, there is not enough fibrinogen present in serous inflammation to form fibrin. Pseudomembranous inflammation refers to the formation of necrotic membranes on mucosal surfaces. Two infections classically associated with pseudomembrane formation are *Clostridium difficile,* which produces a characteristic "mushroom-shaped" pseudomembrane in the colon of people taking broad-spectrum antibiotics, and *C. diphtheriae,* which produces a pseudomembrane in the larynx.

In contrast to an abscess, an ulcer is a defect of epithelium in which the epithelial lining is sloughed and is replaced by inflammatory necrotic material. A localized proliferation of fibroblasts and small blood vessels describes granulation tissue, while an aggregate of two of more activated macrophages refers to a granuloma. The excessive secretion of mucus from a mucosal surface refers to catarrhal (phlegmonous or coryzal) inflammation, such as seen with a runny nose.

6. The answer is b. *(Henry, pp 726–727. Cotran, pp 122–126. Ayala, p 208.)* Two important control points of the coagulation cascade are the fibrinolytic system and certain plasma protease inhibitors. The main component of the fibrinolytic system is plasmin, which is converted from plasminogen by either factor XII or a plasminogen activator (PA). Examples of PAs include tissue plasminogen activator (tPA), urokinase plasminogen activator, and streptokinase. Once formed, plasmin splits fibrin and also

degrades both fibrinogen and coagulation factors VIII and V. Plasma protease inhibitors include antithrombin III and protein C. Antithrombin III in the presence of heparin inhibits thrombin, XIIa, XIa, Xa, and IXa, while protein C inhibits Va and VIIIa. The significance of these control mechanisms is illustrated by the fact that abnormalities of these systems, such as deficiencies of antithrombin III, protein C, or protein S, are associated with hypercoagulable states and increased risk of thrombosis, as the main factors leading to thrombosis include injury to endothelium, alterations in blood flow, and hypercoagulability of the blood. Hypercoagulability may be a primary (genetic) or secondary abnormality. Primary hypercoagulable states include the previously mentioned deficiencies of antithrombin III, protein C, or protein S. These deficiencies are associated with recurrent thromboembolism in early adult life and recurrent spontaneous abortions in women. The causes of secondary hypercoagulable states are numerous and include severe trauma, burns, disseminated cancer, and pregnancy. Lower risk factors for the development of secondary hypercoagulable states include age, smoking, and obesity. Some patients with high titers of autoantibodies against anionic phospholipids such as cardiolipin (the antibody being called a lupus anticoagulant) have a high frequency of arterial and venous thrombosis. To summarize, it is important to remember that the differential diagnosis of recurrent spontaneous abortions in women includes deficiencies of protein C and protein S, and the presence of the lupus anticoagulant, which is part of the anti-phospholipid syndrome.

7. The answer is b. *(Cotran, pp 143–146.)* Inheritance of single abnormal genes generally follows one of the following patterns of inheritance: autosomal dominant, autosomal recessive, or X-linked. Characteristics of autosomal dominant (AD) inheritance include symptoms manifested in the heterozygous state, males and females affected equally, and vertical transmission. The latter term refers to the finding of successive generations affected. Also with autosomal dominant inheritance, children with one affected parent have one chance in two of having the disease (50%). This is also the recurrence risk. Note that unaffected family members cannot transmit the disease. Characteristics of autosomal recessive (AR) inheritance include manifestations in the homozygous state, horizontal transmission, males and females affected equally, and common occurrence of complete penetrance and consanguineous relations. Horizontal transmission refers to finding the disease in siblings but not parents. That is, with

autosomal recessive disorders, parents are usually heterozygous and are clinically normal, while symptoms occur in one-fourth of siblings. Also note that one-half of siblings are carriers (heterozygous) for the trait.

X-linked patterns of inheritance are seen with disorders involving genes located on the X chromosome. The key point about X-linked disorders is that there is no male-to-male transmission. Note that in males the terms dominant and recessive do not apply (since they have only one X chromosome). Also note that X-linked inheritance is different from sex-influenced autosomal dominant inheritance, an example of which is baldness. Characteristics of X-linked dominant disorders, which are quite rare, include no skipped generations (dominant inheritance) and no male-to-male transmission (x-linked inheritance). A key point is to note that females are affected twice as often as males. Affected females transmit the disease to 50% of their daughters and 50% of their sons. Affected males transmit the disease to all of their daughters and none of their sons. A subtype of X-linked dominant disease is seen when the condition is lethal in utero in hemizygous males. Therefore the condition is seen clinically in heterozygous females, who also have an increase in the number of abortions. Characteristics of X-linked recessive disorders include: an affected male does not transmit the disease to his sons, but all daughters are carriers, sons of carrier females have a one in two chance of the disorder, but all daughters are asymptomatic, and the trait occurs in maternal uncles and in male cousins descended from the mother's sisters (oblique transmission). Affected females are rare and may be homozygous for the disease or may have an unfavorable lyonization.

8. The answer is e. *(Cotran, pp 164–165, 1287. Damjanov, pp 298–299.)* Almost all genes occur on chromosomes within the nucleus. There are a few genes, however, that are located within the mitochondria. These mitochondrial genes are found on mitochondrial DNA (mtDNA). These genes are all of maternal origin, possibly because ova have mitochondria within the large amount of cytoplasm while sperm do not. This maternal origin means that mothers transmit all of the mtDNA to both male and female offspring, but only the daughters transmit it further. No transmission occurs through males. This mtDNA contains genes that mainly code for oxidative phosphorylation enzymes, such as NADH dehydrogenase, cytochrome c oxidase, and ATP synthase. Symptoms of deficiencies of these enzymes occur in organs that require large amounts of ATP, such as the brain, mus-

cle, liver, and kidneys. The mtDNA of these patients may be composed of either a mixture of mutant and normal DNA (heteroplasm) or of mutant DNA entirely (homoplasmy). The severity of these diseases correlates with the amount of mutant mtDNA that is present. One disease associated with mitochondrial inheritance is Leber hereditary optic neuropathy (LHON), which is characterized by progressive bilateral loss of central vision and usually occurs between 15 and 35 years of age. Other examples of mitochondrial inheritance include mitochondrial myopathies, which are characterized by the presence in muscle of mitochondria having abnormal sizes and shapes. These abnormal mitochondria may result in the histologic appearance of the muscle as ragged red fibers. Electron microscopy reveals the presence within large mitochondria of rectangular crystals that have a "parking lot" appearance.

9. The answer is c. *(Cotran, pp 153–159.)* One group of lysosomal storage diseases is characterized by the abnormal accumulation of sphingolipids (SLs). Some types of sphingolipids are typically found within the central nervous system, and therefore abnormal accumulation of these substances produces neurologic signs and symptoms. For example, ganglion cells within the retina, particularly at the periphery of the macula, may become swollen with excess sphingolipids. The affected area of the retina appears pale when viewed through an ophthalmoscope. In contrast, the normal color of the macula, which does not have accumulated substances, appears more red than normal. This is referred to as a cherry red spot or a cherry red macula. Substances that may produce this cherry red spot include sphingomyelin, which is increased in individuals with Niemann-Pick disease, and gangliosides, which may be increased in individuals with Tay-Sachs disease, Sandhoff's disease, or G_{M1} gangliosidosis.

Autosomal recessive disorders tend to be more common in areas in which inbreeding is more common. An example of this is the increased frequency of several autosomal recessive genes in Ashkenazi Jews. *Ashkenazi* denotes an ethnic group, mostly of the Jewish faith, from Eastern Europe. People of this faith tend to marry other members of the faith. Two storage diseases that have a higher incidence in Ashkenazi Jews are Tay-Sachs disease and type I Gaucher disease. Tay-Sachs disease is due to a deficiency of hexosaminidase A. This same enzyme is decreased in patients with Sandhoff's disease. Hexosaminidase A is composed of an α subunit and a β subunit. In contrast, hexosaminidase B is composed of two β subunits.

Patients with Tay-Sachs disease have a deficiency of the α subunit. Therefore, they have a deficiency of hexosaminidase A, but not hexosaminidase B. In contrast, patients with Sandhoff's disease have a deficiency of the β subunit, and thus they have a deficiency of both hexosaminidase A and hexosaminidase B. In patients with Tay-Sachs disease, accumulation of G_{M2} ganglioside occurs within many tissues, including the heart, liver, spleen, and brain. Electron microscopy reveals cytoplasmic whorled lamellar bodies within lysosomes. There are several clinical forms of Tay-Sachs disease, but the most severe is the infantile type. Patients develop mental retardation, seizures, motor incoordination, and blindness (amaurosis), and usually die by the age of 3 years.

Type I Gaucher's disease is due to a deficiency of β-glucocerebrosidase. Patients may have increased serum levels of acid phosphatase (an enzyme that is typically found in the prostate), erythrocytes, and platelets. Patients with Gaucher's disease have accumulation of excess glucocerebrosides within phagocytic cells, not ganglion cells. Sphingomyelinase is decreased in patients with Niemann-Pick disease, while aryl-sulfatase is decreased in patients with metachromatic leukodystrophy (MLD).

10. The answer is d. *(Cotran, pp 148, 1254–1255. Champe, 348–349.)* Purine synthesis involves adding carbons and nitrogens to ribose 5-phosphate (R5P), which is a product of the hexose monophosphate (HMP) shunt. R5P is then converted to ribose phosphate pyrophosphate (RPPP), which is subsequently converted to 5′-phosphoribosylamine, the latter step being the committed step in purine nucleotide biosynthesis. Through a series of steps RPPP is converted to inosine 5′-monophosphate (IMP). Several of these biochemical steps involve transferring methyl groups from folate. This is important because folate analogues, such as methotrexate, inhibit DNA synthesis, especially in rapidly growing tumor cells, by inhibiting purine synthesis. Finally IMP is converted into either AMP or GMP. These last biochemical steps are also connected to biochemical reactions that involve adenosine deaminase, an enzyme that is deficient in individuals with the autosomal recessive form of SCID, and hypoxanthine-guanine phosphoribosyl transferase (HGPRT), an enzyme of the purine salvage pathway for recycling guanine and hypoxanthine that is deficient in individuals with the X-linked recessive disorder Lesch-Nyhan syndrome. This disorder is characterized by excess uric acid production, which may produce symptoms of gout, mental retardation, spasticity, self-mutilation, and aggressive behavior.

In contrast, a deficiency of homogentisic oxidase, which is involved in the conversion of homogentisic acid to methylacetoacetate, is associated with alkaptonuria. Abnormal degradation of galactocerebroside is seen in Krabbe's disease, while abnormal breakdown of branched-chain amino acids is seen in maple syrup urine disease.

11. The answer is d. *(Damjanov, p 252. Cotran, p 174.)* Klinefelter's syndrome—male hypogonadism or testicular dysgenesis—is associated with two or more X chromosomes and one or more Y chromosomes, the classic karyotype being 47,XXY. The extra X is from the mother in most cases, and therefore this disorder is associated with increased maternal age. The hypogonadism causes decreased testosterone levels, which leads to eunuchoidism, lack of secondary male characteristics, and a female distribution of hair. Patients are tall due to delayed fusion of the epiphysis from a lack of testosterone. Patients also develop a high voice and gynecomastia, and they have an increased incidence of breast cancer. Blood levels of plasma follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol are all increased. Patients have small, firm, atrophic testes, histologic sections of which reveal atrophy, Leydig cell hyperplasia, sclerosis of the tubules, and lack of sperm production. As a result of these changes, individuals with Klinefelter's syndrome are infertile (Klinefelter's syndrome is the principle cause of male infertility). Patients have a slight decrease in IQ, but they are not severely mentally retarded.

12. The answer is a. *(Cotran, pp 177–179.)* Fragile X syndrome is one of four diseases that are characterized by long repeating sequences of three nucleotides. The other diseases are Huntington's disease, myotonic dystrophy, and spinal and bulbar muscular atrophy. The fragile X syndrome, which is more common in males than females, is one of the most common causes of familial mental retardation. Additional clinical features of this disorder include developmental delay, a long face with a large mandible, large everted ears, and large testicles (macroorchidism). Examination of the DNA from patients with fragile X syndrome reveals multiple tandem repeats of the nucleotide sequence CGG on the X chromosome. Normally these repeats average up to 50 in number, but in patients with fragile X syndrome there are more than 230 repeats. This number of repeats is called a full mutation. Normal transmitting males (NTMs) and carrier females have between 50 and 230 CGG repeats. This number of repeats is called a pre-

mutation. During oogenesis, but not spermatogenesis, premutations can be converted to mutations by amplification of the triplet repeats. This explains the much higher incidence of mental retardation in grandsons rather than brothers of normal transmitting males (Sherman's paradox), as the premutation is amplified in females but not in males. Since the premutation is not amplified in males, no daughters of NTMs are affected. An additional finding associated with these repeat units is anticipation, which refers to the fact that the disease is worse in subsequent generations.

13. The answer is d. *(Cotran, pp 225–226.)* Sjögren's syndrome is characterized by dryness of the mouth (xerostomia) and eyes (keratoconjunctivitis sicca). Secondary Sjögren's syndrome is associated with rheumatoid arthritis (RA), SLE, or systemic sclerosis. The primary form shows increased frequency of HLA-DR3, while association with RA shows a positive correlation with HLA-DR4. Anti-SSB antibodies are fairly specific, anti-SSA less so, and both may occur in SLE; rheumatoid factor is often present. Glomerular lesions are very rare, but a mild tubulointerstitial nephritis is quite common and may result in renal tubular acidosis. In addition to the usual dense, lymphoplasmacytic infiltrate of salivary glands, the lymph nodes may show a "pseudolymphomatous" appearance. True B cell lymphomas have developed with increased frequency in Sjögren's syndrome.

14. The answer is e. *(Cotran, pp 231–236.)* In X-linked agammaglobulinemia of Bruton, B cells are absent but numbers and function of T cells are normal. This abnormality results from defective maturation of B lymphocytes beyond the pre-B stage. This maturation defect leads to decreased or absent numbers of plasma cells, and therefore immunoglobulin levels are markedly decreased. Male infants with Bruton's disease begin having trouble with recurrent bacterial infections at about the age of 9 months, which is when maternal antibodies are no longer present in the affected infant. Therapy for Bruton's disease consists primarily of IV gamma globulin.

Isolated deficiency of IgA is probably the most common form of immunodeficiency. It is due to a block in the terminal differentiation of B lymphocytes. Most patients are asymptomatic, but some develop chronic sinopulmonary infections. Patients are prone to developing diarrhea (*Giardia* infection) and also have an increased incidence of autoimmune disease, such as Hashimoto's thyroiditis. In patients with chronic granulomatous disease (CGD), the neutrophils and macrophages have deficient H_2O_2 pro-

duction due to abnormalities involving the enzyme NADPH oxidase. These individuals have frequent infections that are caused by catalase-positive organisms, such as *S. aureus,* because the catalase produced by these organisms destroys the little hydrogen peroxide that is produced. DiGeorge's syndrome is a T cell–deficiency disorder that results from hypoplasia of the thymus due to abnormal development of the third and fourth pharyngeal pouches. The parathyroid glands are also abnormal, and these individuals develop hypocalcemia and tetany. Congenital heart defects are also present. Wiskott-Aldrich syndrome is also an X-linked recessive disorder, but it is characterized by thrombocytopenia, eczema, and immune deficiency. The immune abnormalities are characterized by progressive loss of T cell function and decreased IgM. The other immunoglobulin levels are normal or increased. There are decreased numbers of lymphocytes in the peripheral blood and paracortical (T cell) areas of lymph nodes. Both cellular and humoral immunity are affected, and, because patients fail to produce antibodies to polysaccharides, they are vulnerable to infections with encapsulated organisms.

15. The answer is b. *(Cotran, pp 321–322. Chandrasoma, pp 307–308.)* It is important to understand the difference between the grading and staging of a tumor. First of all, these terms are applied to malignant neoplasms and not to benign neoplasms. Basically, grading is done histologically, while staging is done clinically. Grading of a malignant tumor is based on the histologic degree of differentiation of the tumor cells and on the number of mitoses that are present. These histologic features are thought to be indicators of the aggressiveness of the malignant neoplasm. Cancers are generally classified as grades I through IV. Lower grades, such as grades I and II, are less aggressive and have a better prognosis, while higher grades, such as grades III and IV, are more aggressive and have a worse prognosis. In contrast to grading, the staging of cancers is based on the size of the primary lesion, the presence of lymph node metastases, and the presence of blood-borne metastases. These characteristics are determined by clinical means. One of the common staging classifications is the TNM classification. Here, the T refers to the tumor size, the N refers to the presence of lymph node metastases, and the M refers to the presence of non–lymph node metastases. The location of the tumor is also important, as the TNM classification uses different staging systems depending upon the location of the primary tumor. Lower stages are smaller, are localized, and have a better prognosis,

while higher stages are larger, are widespread, and have a worse prognosis. Staging has proved to be of greater clinical value than grading.

16. The answer is a. *(Cotran, pp 273, 306–309.)* Many chemicals are associated with an increased incidence of malignancy. These substances are called chemical carcinogens. Although there are direct-acting chemical carcinogens, such as the direct-acting alkylating agents that are used in chemotherapy, most organic carcinogens first require conversion to a more reactive compound. Polycyclic aromatic hydrocarbons, aromatic amines, and azo dyes must be metabolized by cytochrome P450–dependent mixed-function oxidases to active metabolites. Vinyl chloride is metabolized to an epoxide and is associated with angiosarcoma of the liver, not hepatocellular carcinoma. Azo dyes, such as butter yellow and scarlet red, are metabolized to active compounds that have induced hepatocellular cancer in rats, but no human cases have been reported. β-naphthylamine is an exception to the general rule involving cytochrome P450, as the hydrolysis of the nontoxic conjugate occurs in the urinary bladder by the urinary enzyme glucuronidase. In the past there has been an increase in bladder cancer in workers in the aniline dye and rubber industries who have been exposed to these compounds. Aflatoxin B1, a natural product of the fungus *Aspergillus flavus,* is metabolized to an epoxide. The fungus can grow on improperly stored peanuts and grains and is associated with the high incidence of hepatocellular carcinoma in some areas of Africa and the Far East. Hepatitis B virus is also highly associated with liver cancer in these regions.

17. The answer is b. *(Cotran, pp 320–321. Chandrasoma, p 858.)* Symptoms not caused by either local or metastatic effects of tumors are called paraneoplastic syndromes. Bronchogenic carcinomas are associated with the development of many different types of paraneoplastic syndromes. These syndromes are usually associated with the secretion of certain substances by the tumor cells. For example, ectopic secretion of ACTH may produce Cushing's syndrome, while ectopic secretion of antidiuretic hormone (syndrome of inappropriate ADH secretion) may produce hyponatremia. Hypocalcemia may result from the production of calcitonin, while hypercalcemia may result from the production of parathyroid hormone–related peptide (PTHrP), which is a normal substance produced locally by many different types of tissue. PTHrP is distinct from parathyroid hormone (PTH). Therefore, patients with this type of paraneoplastic syndrome have increased calcium levels and

decreased PTH levels. As a result of decreased PTH production, all of the parathyroid glands in these patients are atrophic. Other tumors associated with the production of PTHrP include clear cell carcinomas of the kidney, endometrial adenocarcinomas, and transitional carcinomas of the urinary bladder.

Lung cancers are also associated with multiple, migratory venous thromboses. This migratory thrombophlebitis is called Trousseau's sign and is more classically associated with carcinoma of the pancreas. Hypertrophic osteoarthropathy is a syndrome consisting of periosteal new bone formation with or without digital clubbing and joint effusion. It is most commonly found in association with lung carcinoma, but it also occurs with other types of pulmonary disease. Erythrocytosis is associated with increased erythropoietin levels and some tumors, particularly renal cell carcinomas, hepatocellular carcinomas, and cerebellar hemangioblastomas. It is not particularly associated with bronchogenic carcinomas.

18. The answer is e. *(Cotran, pp 136, 365–366. Ayala, p 148.)* Toxic shock syndrome is caused by infection with certain types of *S. aureus* that secrete the toxin toxic shock syndrome toxin 1 (TSST-1). This toxin is a type of superantigen that binds both class II MHC and TCR outside of the normal antigen-binding groove. As such, this toxin can react with up to 10% of peripheral T cells, which leads to massive T cell activation and shock. Clinically, toxic shock syndrome is most often seen in women who use certain tampons that have been colonized with *Staphylococcus*.

19. The answer is d. *(Cotran, pp 336, 352–353, 354–357. Rubin, pp 432–440.) H. capsulatum,* a dimorphic fungus, causes one of the three major fungal infections in the United States that may result in systemic infection (*Blastomyces* and *Coccidioides* are the other two). Although *H. capsulatum* commonly produces asymptomatic primary disease, it can result in granulomatous inflammation, especially granulomatous lung disease. Multiple small yeasts surrounded by clear zones may be found within the cytoplasm of macrophages. The source for histoplasma is soil contaminated by the excreta of birds (starlings and chickens) and bats. The typical location for individuals to develop histoplasmosis is the Ohio and Mississippi Valley areas. *Aspergillus* species produce several clinical disease states, including allergic aspergillosis, systemic aspergillosis, and aspergilloma. Typically *Aspergillus* species are seen in tissue as acute angle–branching septate

hyphae; however, they may form fruiting bodies in cavities, such as within cystic cavities of the lungs. There they may form a large mass called a fungus ball or aspergilloma. Blastomycosis is a chronic granulomatosis disease caused by a dimorphic fungus, *B. dermatitidis*. In tissues this fungus is seen as a thick-walled yeast having broad-based budding. Without the budding, *Blastomyces* may be mistaken for *Cryptococcus*. The infection, also known as Gilchrist's disease, is seen in individuals living in the Ohio and Mississippi Valley areas and is usually confined to the lungs. *Candida* species, which frequently cause human infections, grow as yeasts, elongated chains of yeast without hyphae (pseudohyphae), or septate hyphae. Mucocutaneous candidal infections can produce white plaques called thrush. Mucormycosis (zygomycosis) is a disease caused by "bread mold fungi" such as *Rhizopus, Mucor,* and *Absidia* species. These infections typically occur in neutropenic patients or diabetics. One form of the disease, typically found in diabetics, is called rhinocerebral mucormycosis and is characterized by facial pain, headache, changing mental status, and a blood-tinged nasal discharge. Tissue sections reveal characteristic broad, nonseptate, right angle–branching hyphae.

20. The answer is e. *(Cotran, pp 446–447.)* Vitamin K compounds include phylloquinone (K_1), which is the major form of vitamin K in plants, and menaquinone (K_2), which is produced by bacteria. Up to 50% of the vitamin K needed by the body is provided by the normal bacteria of the GI tract. Vitamin K is required for the posttranslational conversion of glutamyl residues in some proteins into γ-carboxylates. It participates in the hepatic carboxylation of four procoagulants (factors II, VII, IX, and X) and plasma proteins C and S. For these four proclotting factors, this γ-carboxylation provides the calcium-binding sites necessary for the calcium-dependent interaction with a phospholipid surface. A deficiency of vitamin K, which can result from fat malabsorption, broad-spectrum antibiotics, or diffuse liver disease, produces a bleeding diathesis characterized by hematomas, ecchymoses, hematuria, melena, and bleeding from the gums. Laboratory tests reveal an increased bleeding with prolonged PT and PTT and normal bleeding time

21. The answer is c. *(Cotran, pp 4–15.)* Damage to cells may result in reversible or irreversible injury. Common mediators of cell injury include chemicals, toxins, free radicals, and decreased oxygen delivery by the

blood. Decreased blood flow (ischemia) decreases ATP production by aerobic cellular processes because of the deficiency of oxygen. This results in decreased oxidative phosphorylation by mitochondria, which decreases the functioning of the ATP-dependent sodium pump of the plasma membrane. This decreases the efflux of sodium ions outside the cell and decreases the influx of potassium out of the cell, which increases the sodium ions inside the cell and increases the potassium ions outside the cell. The resultant net gain of intracellular ions causes isosmotic water accumulation and hydropic swelling (cloudy swelling) of the cell and the organelles of the cell. Decreased aerobic respiration by mitochondria also increases anaerobic glycolysis, which decreases intracellular pH by increasing lactic acid production (lactic acidosis). The decreased pH causes chromatin clumping and may activate lysosomal enzymes. Additionally, ribosomes can dissociate from the endoplasmic reticulum (RER), which decreases protein production by cell. All of these changes that result from hypoxia are characteristic of reversible cellular injury, as they are reversible if blood flow and oxygen supply are restored.

22. The answer is b. *(Cotran, pp 5–11.)* With prolonged ischemia, certain cellular events occur that are not reversible, even with restoration of oxygen supply. These cellular changes are referred to as irreversible cellular injury. This type of injury is characterized by severe damage to mitochondria (vacuole formation), extensive damage to plasma membranes and nuclei, and rupture of lysosomes. Severe damage to mitochondria is characterized by the influx of calcium ions into the mitochondria and the subsequent formation of large, flocculent densities within the mitochondria. These flocculent densities are characteristically seen in irreversibly injured myocardial cells that undergo reperfusion soon after injury. Less severe changes in mitochondria, such as mitochondrial swelling, are seen with reversible injury. Cytochrome c released from damaged mitochondria can induce apoptosis, a process through which irreversibly injured cells can shrink and increase the eosinophilia of their cytoplasm. These shrunken apoptotic cells (apoptotic bodies) may be engulfed by adjacent cells or macrophages. Myelin figures are derived from plasma membranes and organelle membranes and can be seen with either reversible or irreversible injury. Psammoma bodies are small, laminated calcifications, while Russell bodies are round, eosinophilic aggregates of immunoglobulin.

23. The answer is d. *(Cotran, pp 39–40, 42–43.)* The differential of brown (or yellow-brown) granules in hepatocytes seen with routine hematoxylin and eosin (H&E) stain includes hemosiderin, bile, and lipofuscin. The special histologic stain for hemosiderin, which contains iron, is Prussian blue. Causes of excess iron deposition in the liver include hemosiderosis, which can result from excessive blood transfusions, and familial hemochromatosis, which results from excessive iron absorption from the gut. Excess bile in the liver can be seen with jaundice, while lipofuscin deposition is seen with aging, cachexia, and severe malnutrition. Lipofuscin is a "wear-and-tear" pigment composed of lipids and phospholipids from lipid peroxidation by free radicals of lipids of subcellular membranes. It does not stain with Prussian blue stain, trichrome stain, oil red O stain, or periodic acid–Schiff (PAS) stain, but is seen best with electron microscopy. The differential of clear spaces in cytoplasm of cells as seen with light microscopy includes glycogen, lipid, and water. Glycogen is a PAS-positive material that is diastase-sensitive, while lipid is oil red O–positive. Accumulation of water is called hydropic change. There is no special stain for water.

24. The answer is c. *(Cotran, pp 45, 869–873.) Hyalin* is a nonspecific term that is used to describe any material, inside or outside the cell, that stains a red homogenous color with the routine hematoxylin and eosin (H&E) stain. There are many different substances that have the appearance of hyalin. Alcoholic hyaline inclusions (Mallory bodies) are irregular eosinophilic hyaline inclusions that are found within the cytoplasm of hepatocytes. Mallory bodies are composed of prekeratin intermediate filaments. They are a nonspecific finding and can be found in patients with several diseases other than alcoholic hepatitis, such as Wilson's disease, and in patients who have undergone bypass operations for morbid obesity. Immunoglobulins may form intracytoplasmic or extracellular oval hyaline bodies called Russell bodies. Excess plasma proteins may form hyaline droplets in proximal renal tubular epithelial cells or hyaline membranes in the alveoli of the lungs (hyaline membrane disease). The hyalin found in the walls of arterioles of kidneys in patients with benign nephrosclerosis is composed of basement membranes and precipitated plasma proteins. Lipofuscin is an intracytoplasmic aging pigment that has a yellow-brown, finely granular appearance with H&E stains. Its appearance does not resemble that of hyaline material.

25. The answer is b. *(Cotran, pp 43–45. Henry, pp 178–187.)* Calcification within tissue can be classified as being dystrophic or metastatic. Dystrophic calcification is characterized by calcification in abnormal (dystrophic) tissue, while metastatic calcification is characterized by calcification in normal tissue. Examples of dystrophic calcification include calcification within severe atherosclerosis, calcification of damaged or abnormal heart valves, and calcification within tumors. Small (microscopic) laminated calcifications within tumors are called psammoma bodies and are due to single-cell necrosis. Psammoma bodies are characteristically found in papillary tumors, such as papillary carcinomas of the thyroid and papillary tumors of the ovary (especially papillary serous cystadenocarcinomas), but they can also be found in meningiomas or mesotheliomas. Dystrophic calcification within tumors of the central nervous system (CNS), which can be seen with x-rays, is useful in the differential diagnosis of these CNS tumors. For example, calcification of a tumor of the cortex in an adult is suggestive of an oligodendroglioma, while calcification of a hypothalamus tumor is suggestive of a craniopharyngioma. Additional periventricular calcification in children is most commonly caused by infection with cytomegalovirus (CMV) or toxoplasmosis. With dystrophic calcification the serum calcium levels are normal, while with metastatic calcification the serum calcium levels are elevated (hypercalcemia). Causes of hypercalcemia include certain paraneoplastic syndromes, such as secretion of parathyroid hormone–related peptide, hyperparathyroidism, iatrogenic causes (drugs), immobilization, multiple myeloma, increased milk consumption (milk-alkali syndrome), and sarcoidosis.

26. The answer is b. *(Cotran, pp 18–25. Rubin, pp 25–27.)* Apoptosis is a distinctive pattern of cell death that is described as a "programmed suicide" process of cells through which stimulation of endogenous endonucleases causes cleavage of nuclear chromatin. Apoptosis as originally defined is a purely morphologic process that differs from necrosis in several respects. Apoptosis involves single cells, not large groups of cells, and with apoptosis the cells shrink and there is increased eosinophilia of cytoplasm. The shrunken apoptotic cells form apoptotic bodies, which may be engulfed by adjacent cells or macrophages. With apoptosis there is no inflammatory response, the cell membranes do not rupture, and there is no release of macromolecules. Importantly, apoptosis is an active process in which acti-

vation of endonucleases causes peripheral condensation of chromatin (the most characteristic feature) and formation of multiples of DNA base pair fragments (called a DNA "ladder").

There are several mechanisms involved in apoptosis of cells. Several of these mechanisms involve substances found in either the *bcl-2* oncogene family or the tumor necrosis family; the latter includes Fas and tumor necrosis factor (TNF). One mechanism of apoptosis involves cytochrome c being released into the cytoplasm from mitochondria via bax channels, which are upregulated by p53. Cytochrome c then binds to and activates apoptosis activating factor 1 (Apaf-1), which then stimulates a caspase cascade. The product of *bcl-2* is normally located on the outer mitochondrial membrane, endoplasmic reticulum, and nuclear envelope. This product inhibits apoptosis by blocking bax channels and by binding to and sequestering Apaf-1. In a different mechanism, Fas ligand (FasL) is produced by immune cells and binds to Fas (CD95), which activates Fas-associated death domain protein (FADD), which in turn activates caspase 8. Cytotoxic T lymphocytes stimulate apoptosis by expressing FasL or secreting substances like perforin (which forms pores) or granzyme B. In one final example, TNF binds to TNF receptor 1 (TNFR-1) and the complex activates TNF-receptor-adaptor protein with a death domain (TRADD), which activates FADD.

Apoptosis is the type of cell death seen with embryonic development, death of immune cells, hormone-induced atrophy, and some bacterial toxins or viral infections. Examples of apoptosis of immune cells include the involution of the thymus with aging and the destruction of proliferating B cells in germinal centers of lymph nodes. Examples of apoptosis resulting from hormone-induced atrophy exclude the death of endometrial cells during menses, ovarian follicular atresia after menopause, and regression of the lactating breast after weaning. An example of a viral infection causing apoptosis is the formation of Councilman bodies in the livers of patients with viral hepatitis. It is important to note that abnormalities of genes involved in apoptosis may contribute to the formation of some malignancies; for example, activation of *bcl-2* is associated with nodular B cell non-Hodgkin's lymphomas.

27. The answer is a. *(Cotran, pp 15–18.)* The cause of cell injury and death may sometimes be inferred from the type of necrosis present. Coagulative necrosis, characterized by loss of the cell nucleus, acidophilic change

of the cytoplasm, and preservation of the outline of the cell, is seen in sudden, severe ischemia of many organs. It is not present, however, in acute ischemic necrosis of the brain. Myocardial infarction resulting from the sudden occlusion of the coronary artery is a classic example of coagulative necrosis. In contrast, with liquefactive necrosis the dead cells are completely dissolved by hydrolytic enzymes. This type of necrosis can be seen in ischemic necrosis of the brain, but classically it is associated with acute bacterial infections. Fat necrosis, seen with acute pancreatic necrosis, is fat cell death caused by lipases. Fibrinoid necrosis is an abnormality seen sometimes in injured blood vessels where plasma proteins abnormally accumulate within the vessel walls. Caseous necrosis is a combination of coagulative and liquefactive necrosis, but the necrotic cells are not totally dissolved and remain as amorphic, coarsely granular, eosinophilic debris. This type of necrosis grossly has the appearance of clumped cheese. It is classically seen in tuberculous infections. Gangrenous necrosis of extremities is also a combination of coagulative and liquefactive necrosis. In dry gangrene the coagulative pattern is predominate, while in wet gangrene the liquefactive pattern is predominate.

28. The answer is a. *(Cotran, pp 25–26.)* The primary function of lysosomes is to degrade macromolecules derived from either intracellular organelles (autophagy) or extracellular products (heterophagy). Primary lysosomes are cytoplasmic vacuoles that contain numerous acid hydrolases produced by the Golgi. These vacuoles combine either with vacuoles containing cellular components (autosomes) or with clathrin-coated endocytic vesicles that contain extracellular material (phagosomes). This fusion forms the secondary lysosome (multivesicular body, or phagolysosome) in which the macromolecules are degraded. If the extracellular material is a ligand coupled to a receptor, then the clathrin-coated endocytic vesicle is called a compartment of uncoupling of receptor and ligand (CURL), and the receptors are then recycled to the plasma membrane. The products of the normal lysosomal function are usually reutilized by the cell, but if the material is not digestible (e.g., lipofuscin or hemosiderin), the end result may be production of residual bodies, which may be removed from the cell by exocytosis.

29. The answer is c. *(Cotran, pp 31–38, 649–650.)* There are many adaptive mechanisms of cells to persistent stimuli. Hypertrophy is an increase in

the size of cells. Examples of hypertrophy include enlarged skeletal muscle in response to repeated exercise or anabolic steroid use and enlarged cardiac muscle in response to volume overload or hypertension. In contrast to hypertrophy, hyperplasia is an increase in the number of cells. Hyperplasia may be the result of a physiologic response or a pathologic process. Examples of physiologic hyperplasia include the increased size of the female breast or uterus in response to hormones. Pathologic hyperplasia may be compensatory to some abnormal process, or it may be a purely abnormal process. Examples of compensatory pathologic hyperplasia include the regenerating liver, increased numbers of erythrocytes in response to chronic hypoxia, and increased numbers of lymphocytes within lymph nodes in response to bacterial infections [follicular (nodular) hyperplasia]. Examples of purely pathologic hyperplasia include abnormal enlargement of the endometrium (endometrial hyperplasia) and the prostate (benign prostatic hyperplasia). Atrophy is a decrease in the size and function of cells. Examples of atrophy include decreased size of limbs immobilized by a plaster cast or paralysis, or decreased size of organs affected by endocrine insufficiencies or decreased blood flow. Metaplasia is a term that describes the conversion of one histologic cell type to another. Examples of metaplasia include respiratory epithelium changing to stratified squamous epithelium (squamous metaplasia) in response to prolonged smoking, the normal glandular epithelium of the endocervix changing to stratified squamous epithelium (squamous metaplasia) in response to chronic inflammation, or the normal stratified squamous epithelium of the lower esophagus changing to gastric-type mucosa in response to chronic reflux. In contrast to metaplasia, dysplasia refers to disorganized growth and is characterized by the presence of atypical or dysplastic cells. Dysplasia can be seen in many organs, such as within the epidermis in response to sun damage (actinic keratosis), the respiratory tract, or the cervix (cervical dysplasia).

30. The answer is d. *(Cotran, pp 97–98, 104–106.)* Growth factors are chemicals that are associated with cell growth. For example, fibroblast growth factor (FGF) can induce the growth and proliferation of fibroblasts. Additionally, one type of FGF, basic FGF, is capable of inducing all of the stages of angiogenesis (basement membrane and extracellular matrix degradation, endothelial migration, endothelial proliferation, and endothelial differentiation). The epidermal growth factor family includes epidermal growth factor (EGF) and transforming growth factor α (TGF-α). These

substances can cause proliferation of many types of epithelial cells and fibroblasts. The EGF receptor is *c-erb B1*. Platelet-derived growth factor (PDGF), which is found in platelets, activated macrophages, endothelial cells, and smooth muscle cells, can cause migration and proliferation of fibroblasts, smooth muscle cells, and monocytes. TGF-β, produced by platelets, endothelial cells, T cells, and macrophages, is associated with fibrosis. In low concentrations it causes the synthesis and secretion of PDGF, but in high concentrations it inhibits growth due to inhibition of the expression of PDGF receptors.

31. The answer is e. *(Cotran, pp 51–55.)* Inflammation can be defined as the reaction of vascularized living tissue to local injury. Celsus originally described four cardinal signs of inflammation: rubor (redness), tumor (swelling), calor (heat), and dolor (pain). Virchow later added a fifth sign, loss of function (functio laesa). Redness (rubor) and heat (calor) are primarily the result of increased blood flow secondary to vasodilation of arterioles. This vasodilation is mainly the result of prostaglandins (prostacyclin) and nitric oxide, but histamine and bradykinin also participate in this response. Swelling (tumor) results from fluid leaking into the interstitium, while pain (dolor) results from the secretion of bradykinin. Loss of function (functio laesa) results from the swelling and pain.

32. The answer is d. *(Cotran, pp 53–55.)* Acute inflammation causes fluid and cells to leak out of blood vessels into the interstitial tissue because of increased permeability of postcapillary venules. This increased vascular permeability results from either direct endothelial injury or contraction of endothelial cells. Substances that cause the latter include histamine (secreted from mast cells, basophils, and platelets), bradykinin, complement components (C3a and C5a), and leukotrienes (C_4, D_4, and E_4). The result of this increased vascular permeability is that large amounts of fluid and cells from the blood can leak into the interstitial tissue. This inflammatory edema fluid, called an exudate, is characterized by a high protein content, numerous inflammatory cells (mainly neutrophils), abundant cellular debris, and a specific gravity greater than 1.020. In contrast to exudates, transudates result from either increased intravascular hydrostatic pressure or decreased osmotic pressure and are characterized by a low protein content, few cells, and a specific gravity less than 1.012.

33. The answer is d. *(Cotran, pp 61–62.)* Chemotaxis is the unidirectional migration of cells toward a certain site or source. The most significant chemotactic agents for neutrophils include bacterial products, complement components (particularly C5a), products of the lipoxygenase pathway (mainly leukotriene B_4), and cytokines (particularly interleukin 8). These chemotactic factors bind to Gq receptors on the surface of neutrophils and activate phospholipase C, leading to the hydrolysis of phosphatidylinositol-4,5-biphosphate (PIP2) in the plasma membrane to inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 releases calcium from endoplasmic reticulum stores. DAG is the principal activator of protein kinase C, which phosphorylates many cytoplasmic proteins. These reactions result in increased calcium levels in the cytoplasm of neutrophils, which then stimulates the assembly of contractile elements in the cytoplasm of leukocytes (actin and myosin), causing movement. These same chemotactic factors activate leukocytes, which results in increased production of arachidonic acid metabolites, activation of the respiratory (oxidative) burst, degranulation and secretion of lysosomal enzymes, and modulation of the leukocyte adhesion molecules.

In contrast, abnormal fusion of phagosomes to primary lysosomes is the principal defect in Chédiak-Higashi syndrome; attachment of chemicals to extracellular material to increase phagocytosis describes opsonins; and transmigration of cells from blood vessels into tissue refers to diapedesis.

34. The answer is b. *(Cotran, pp 64–65. Rubin, pp 1089, 1106.)* Chédiak-Higashi syndrome is an autosomal recessive disorder characterized by the abnormal fusion of phagosomes with lysosomes, which results in ineffective bactericidal capabilities of neutrophils and monocytes. These abnormal leukocytes develop giant intracytoplasmic lysosomes. Abnormal formation of melanosomes in these individuals results in oculocutaneous albinism. Most of these patients eventually develop an "accelerated phase" in which an aggressive lymphoproliferative disease, possibly the result of an Epstein-Barr viral infection, results in pancytopenia and death.

Ataxia-telangiectasia is a chromosome instability syndrome that is characterized by increased sensitivity to x-rays (causing a markedly increased risk of lymphoid malignancies), recurrent infections, oculocutaneous telangiectasias (dilated blood vessels), and cerebellar ataxia. Chronic

granulomatous disease is an X-linked recessive disorder characterized by recurrent bacterial infections due to deficient NADPH oxidase. Ehlers-Danlos syndrome results from many different defects in formation of collagen and is generally characterized by fragile skin and hypermobile joints. Sturge-Weber syndrome is characterized by capillary-venous malformation of leptomeninges and superficial cortex of one cerebral hemisphere with ipsilateral port-wine stains (nevus flammeus) in the trigeminal region of the face.

35. The answer is b. *(Cotran, pp 67–69.)* The complement system is a cascade of plasma proteins whose basic function is the direct lysis of cells, attraction of leukocytes to sites of inflammation (chemotaxis), and activation of leukocytes. The complement system can be activated by one of two basic pathways. The classic pathway is initiated by antigen-antibody (immune) complexes binding to C1. The antibodies that are involved in forming these complement-activating immune complexes are IgM and IgG (subtypes 1, 2, and 3). There are also some non-immunologic activators of the classic complement pathway, such as urate crystals, which may be part of the pathophysiologic process of gout. In the alternate pathway, the early complement components (C1, C4, and C2) are bypassed and C3 is activated directly by such things as bacterial endotoxins, cobra venom factor, lipopolysaccharide, and aggregated immunoglobulin (mainly IgA, but also IgE). C3 nephritic factor is an unusual substance capable of activating the alternate complement system within the glomerulus, producing glomerular injury.

Complement assays can be used clinically to help determine the causes and pathomechanisms of certain diseases. For example, activation of the complement cascade can produce local deposition of C3, which can be seen with special histologic techniques. If a patient has widespread activation of the complement system, then serum assays of C3 levels might be decreased. In particular, activation of the classic complement pathway decreases levels of the early complement components, namely C1, C4, and C2. In contrast, activation of the alternate complement pathway, which bypasses these early complement components, decreases levels of C3, but the levels of the early factors (C2 and C4) are normal.

36. The answer is b. *(Cotran, pp 69, 236.)* Deficiencies of components of the complement system are associated with specific abnormalities.

Patients with congenital deficiencies in the early components of the complement cascade have recurrent symptoms resembling those of systemic lupus erythematosus due to the deposition of immune complexes. Patients with deficiencies of the middle complement components (C3 and C5) are at risk for recurrent pyogenic infections, while those lacking terminal complement components (C6, C7, or C8, but not C9) are prone to developing recurrent infections with *Neisseria* species. A deficiency of decay-accelerating factor (DAF), which breaks down the C3 convertase complex, is seen in paroxysmal nocturnal hemoglobinuria (PNH), a disorder that is characterized by recurrent episodes of hemolysis of red cells because of the excessive intravascular activation of complement. Deficiencies of C1 esterase inhibitor result in recurrent angioedema, which refers to episodic nonpitting edema of soft tissue, such as the face. Severe abdominal pain and cramps, occasionally accompanied by vomiting, may be caused by edema of the gastrointestinal tract. To understand how a deficiency of C1 inhibitor can cause vascularly produced edema (angioedema), note that not only does C1 inhibitor inactivate C1, but it also inhibits other pathways, such as the conversion of prekallikrein to kallikrein and kininogen to bradykinin. A deficiency of C1 inhibitor also leads to excess production of C2, a product of C2 called C2 kinin, and bradykinin. It is the uncontrolled activation of bradykinin that produces the angioedema, as bradykinin increases vascular permeability, stimulates smooth muscle contraction, dilates blood vessels, and causes pain. In contrast, a defect involving β_2-integrins is seen with leukocyte adhesion deficiency, while defects involving NADPH of leukocytes are characteristic of chronic granulomatous disease.

37. The answer is e. *(Cotran, 6/e, pp 70–72, 77.)* Products of arachidonic acid (AA) metabolism are involved extensively in inflammation. In this pathway, arachidonic acid is broken down into leukotrienes (vasoconstrictors) and prostaglandins (vasodilators). Arachidonic acid is a polyunsaturated fatty acid that is normally found esterified in plasma membrane phospholipids. It is released by the activation of phospholipases, such as phospholipase A_2. Cyclooxygenase transforms AA into the prostaglandin endoperoxide PGG_2, which is then converted into PGH_2 and subsequently into three products: thromboxane A_2 (TxA_2), prostacyclin (PGI_2), and the more stable prostaglandins PGE_2, PGF_2, and PGD_2. Thromboxane, found in platelets, is a potent platelet aggregator and blood vessel constrictor.

In contrast, prostacyclin, which is found in the walls of blood vessels, is a potent inhibitor of platelet aggregation and is also a vasodilator. Prostaglandin E and prostacyclin probably account for most of the vasodilation that is seen in inflammation. The prostaglandins are also involved in producing pain and fever in inflammation. In contrast to cyclooxygenase, lipoxygenase converts AA into hydroperoxyl derivatives, namely 12-HPETE in platelets and 15-HPETE in leukocytes. 5-HPETE gives rise to HETE and the leukotrienes (Lts). While many substances can be chemotactic, few are known to be as potent as several of the leukotrienes. Leukotriene B_4 is a potent chemotactic agent that also causes aggregation and adhesion of leukocytes. Additionally, leukotrienes C_4, D_4, and E_4 cause increased vascular permeability, bronchoconstriction, and vasoconstriction. Other chemotactic factors for neutrophils include C5a and IL-8, but these substances are not formed from arachidonic acid.

38. The answer is d. *(Cotran, pp 66, 197.)* Vasoactive amines are important mediators of the early signs and symptoms of acute inflammation. Two important vasoactive amines are histamine and serotonin. Histamine is found in mast cells, basophils, and platelets, and is primarily responsible for the initial swelling found in acute inflammation. This swelling results from histamine binding to H_1 receptors and increasing the permeability of venules. Histamine release is induced by temperature changes (both hot and cold), antibodies (a type I hypersensitivity reaction), anaphylatoxins, IL-1, and IL-8. Neuropeptides, such as substance P, can cause vasodilation and increased vascular permeability directly and by stimulating histamine release by mast cells. Serotonin (5-hydroxytryptamine) is found in platelets and enterochromaffin cells and has actions similar to those of histamine, although these may not be physiologically significant in humans.

39. The answer is a. *(Cotran, pp 76, 79–83.)* There are several types of leukocytes; all have specific structures that enable them to participate in specific types of inflammatory reactions. Acute inflammatory processes, such as pyogenic bacterial infections and tissue necrosis, are associated with infiltrates of neutrophils into tissue and increased numbers of neutrophils in the blood; hence neutrophils are thought of as acute inflammatory cells. Neutrophils are also called polymorphonuclear leukocytes (PMNs or "polys") because they characteristically have nuclei with three to five lobes. Myeloperoxidase is an enzyme within the primary (azurophilic)

granules of neutrophils, while alkaline phosphatase is an enzyme in their secondary (specific) granules. Neutrophils have a short life span and do not divide. IL-1 causes an increased number of neutrophils to be released from the bone marrow. In contrast, chronic inflammatory processes are associated with increased numbers of monocytes and lymphocytes. Monocytes are mononuclear leukocytes with a "bean-shaped" or "horseshoe-shaped" nucleus. Their tissue form is called a macrophage or histiocyte. The activated form of macrophages have abundant eosinophilic cytoplasm and are called epithelioid cells. They secrete many different types of products and may fuse to form giant cells. Lymphocytes are smaller mononuclear leukocytes that have a round to oval nucleus and little cytoplasm. There are two types of lymphocytes, B lymphocytes and T lymphocytes. These types of lymphocytes look histologically identical. B lymphocytes (B cells) mature into plasma cells, which have an eccentric nucleus with a "clock-face" appearance of their chromatin. Plasma cells secrete immunoglobulin, while certain T lymphocytes (T cells) secrete lymphokines. Numbers of lymphocytes are increased in acute viral infections or chronic disease.

Eosinophils are bilobed leukocytes that contain abundant eosinophilic granules within their cytoplasm. These granules contain many different types of substances, such as major basic protein (which is toxic to helminthic parasites), arylsulfatase (which neutralizes leukotrienes), and histaminase (which neutralizes histamine). They participate in specific types of inflammatory processes, such as allergic disorders, parasitic infections, and some diseases of the skin. Basophils are a type of leukocyte that have numerous deeply basophilic granules within their cytoplasm that completely hide the nucleus. Basophils participate in certain specific types of immune reactions because they have surface receptors for IgE. When activated they release vasoactive substances, such as histamine. Mast cells, although not exactly the same as basophils, are found in tissue and are very similar to basophils.

40. The answer is d. *(Cotran, pp 79–82, 549. Henry, p 607.)* Most tissue macrophages originate from a committed bone marrow stem cell that differentiates into a monoblast and then a promonocyte, and then finally matures into a monocyte in the circulating peripheral blood. When called upon, the circulating monocyte can enter into an organ or tissue bed as a tissue macrophage (sometimes called a histiocyte). Examples of tissue macrophages are Kupffer cells (liver), alveolar macrophages (lung), osteo-

clasts (bone), Langerhans cells (skin), microglial cells (central nervous system), and possibly the dendritic immunocytes of the dermis, spleen, and lymph nodes. The entire system, including the peripheral blood monocytes, constitutes the mononuclear phagocyte system. In the lung, alveolar macrophages can phagocytize the red blood cells that accumulate in alveoli in individuals with congestive heart failure. These cells contain hemosiderin and are referred to as "heart failure cells."

41. The answer is d. *(Cotran, pp 83–84, 350–351.)* Granulomatous inflammation is characterized by the presence of granulomas, which by definition are aggregates of activated macrophages (epithelioid cells). These cells may be surrounded by mononuclear cells, mainly lymphocytes, and multinucleated giant cells, which result from the fusion of several epithelioid cells together, may be present. Granulomatous inflammation is a type of chronic inflammation initiated by a variety of infectious and noninfectious agents. Indigestible organisms or particles, or T cell–mediated immunity to the inciting agent, or both, appear essential for formation of granulomas. Although tuberculosis is the classic infectious granulomatous disease, several other infectious disorders are characterized by formation of granulomas, including deep fungal infections (coccidioidomycosis and histoplasmosis), schistosomiasis, syphilis, brucellosis, lymphogranuloma venereum, and cat-scratch disease. In sarcoidosis, a disease of unknown cause, the granulomas are noncaseating, which may assist in histologic differentiation from tuberculosis. No organisms are found in the noncaseating granulomas of sarcoidosis.

42. The answer is c. *(Cotran, pp 106–110.)* Tissue repair occurs through the regeneration of damaged cells and the replacement of tissue by connective tissue. Tissue repair involves the formation of granulation tissue, which histologically is characterized by a combination of proliferating fibroblasts and proliferating blood vessels. Proliferating cells are cells that are rapidly dividing and usually have prominent nucleoli. This histologic feature should not be taken as a sign of dysplasia or malignancy. It is important not to confuse the term *granulation tissue* with the similar-sounding term *granuloma.* The latter refers to a special type of inflammation that is characterized by the presence of activated macrophages (epithelioid cells).

43. The answer is b. *(Cotran, pp 98–103. Rubin, pp 78–84.)* The extracellular matrix (ECM) is composed of fibrous structural proteins and interstitial matrix, the latter being composed of adhesive glycoproteins embedded within a ground substance. The structural proteins of the ECM include collagen fibers, reticular fibers, and elastic fibers. Collagen is a triple helix of three polypeptide α chains that is secreted by fibroblasts and has a high content of glycine and hydroxyproline. Collagens may be either fibrillar or nonfibrillar. The fibrillar (interstitial) types of collagen (types I, III, and V) are found within the ECM (interstitial tissue), while the nonfibrillar type IV collagen is found within the basement membranes, which are special organizations of the interstitial matrix found around epithelial, endothelial, and smooth-muscle cells. Type I collagen is found in skin, tendon, bone, dentin, and fascia; type II collagen is found only in cartilage; and type III collagen (reticulin) appears in the skin, blood vessels, uterus, and embryonic dermis.

The adhesive glycoproteins include fibronectin and laminin. Laminin, the most abundant glycoprotein in basement membranes, is a cross-shaped glycoprotein that is capable of binding multiple matrix components, such as type IV collagen and heparan sulfate. It also binds to specific receptors on the surface of some cells. Fibronectin, secreted by fibroblasts, monocytes, and endothelial cells, is also capable of binding many substances, such as collagen, fibrin, proteoglycans, and integrins. Basically, fibronectin links extracellular matrix component and macromolecules to integrins and is chemotactic for fibroblasts and endothelial cells. Instead of being cross-shaped like laminin, fibronectin is a large glycoprotein composed of two chains held together by disulfide bonds. Albumin is secreted by hepatocytes and is mainly responsible for intravascular oncotic pressure, while immunoglobulins are secreted by plasma cells and are important in mediating humoral immunity.

44. The answer is d. *(Cotran, pp 148–150. Ayala, p 192.)* Several diseases result from abnormalities involving defects in structural proteins. Marfan's syndrome is an autosomal dominant disorder that results from defective synthesis of fibrillin causing connective tissue abnormalities. It is characterized by specific changes involving the skeleton, the eyes, and the cardiovascular system. Skeletal changes seen in individuals with Marfan's syndrome include arachnodactyly (spider fingers) and a large skeleton

causing increase in height. Eyes in patients with Marfan's syndrome typically have a subluxed lens (ectopia lentis) in which the lens is found in the anterior chamber. The lens dislocation in Marfan's syndrome is usually upward, in contrast to the downward dislocation seen with homocystinuria. Cardiovascular lesions associated with Marfan's syndrome include MV prolapse and cystic medial necrosis of the aorta.

Ehlers-Danlos syndrome (EDS) refers to a group of related disorders characterized by defects in collagen synthesis or structure. These defects produce abnormalities of the skin and joints. The skin in these patients is fragile and hyperextensible, while the joints are hypermobile. There are at least 10 variants or subtypes of EDS. Type IV EDS is related to abnormal type III collagen, and as such is associated with ruptured intestinal organs and blood vessels. Type IX EDS involves abnormalities of copper metabolism. There is increased copper in cells, but a decreased copper level in the blood. Type VI EDS is characterized by decreased lysyl hydroxylation of collagen, which causes decreased cross-linking of collagen. Only collagen types I and III are affected. Osteogenesis imperfecta (OI) also results from defective synthesis of type I collagen. These patients have "brittle bones" and also typically develop blue scleras and hearing loss. Decreased levels of vitamin D can produce rickets in children or osteomalacia in adults.

45. The answer is c. *(Cotran, pp 113–116.)* Edema is the accumulation of excess fluid in the interstitial tissue or body cavities. It may be caused by inflammation (inflammatory edema) or it may be due to abnormalities involving the Starling forces acting at the capillary level (noninflammatory edema or hemodynamic edema). Inflammatory edema is caused by increased capillary permeability, which is the result of vasoactive mediators of acute inflammation. An exudate is inflammatory edema fluid resulting from increased capillary permeability. It is characterized by a high protein content, much cellular debris, and a specific gravity greater than 1.020. Pus is an inflammatory exudate containing numerous leukocytes and cellular debris. In contrast, transudates result either from increased intravascular hydrostatic pressure or from decreased osmotic pressure. They are characterized by a low protein content and a specific gravity of <1.012. Noninflammatory edema is the result of abnormalities of the hemodynamic (Starling) forces acting at the level of the capillaries. Increased hydrostatic pressure may be caused by arteriolar dilation, hypervolemia, or increased venous pressure. Hypervolemia may be caused by sodium retention seen in

renal disease, and increased venous hydrostatic pressure can be seen in venous thrombosis, congestive heart failure, or cirrhosis. Decreased plasma oncotic pressure is caused by decreased plasma protein, the majority of which is albumin. Decreased albumin levels may be caused by loss of albumin in the urine, which occurs in the nephrotic syndrome, or by reduced synthesis, which occurs in chronic liver disease. Lymphatic obstruction may be caused by tumors, surgical resection, or infections (for example, infection with filarial worms and consequent elephantiasis).

46. The answer is a. *(Cotran, pp 116–118.)* Hyperemia refers to excess amounts of blood within an organ. It may be caused by increased arterial supply (active hyperemia) or impaired venous drainage (passive hyperemia). Examples of active hyperemia include increased blood flow during exercise, blushing (such as embarrassment associated with being asked a question during a lecture), or inflammation. Examples of passive hyperemia, or congestion, include the changes produced by chronic heart failure. These changes include chronic passive congestion of the lung or the liver. The lung changes are characterized by intraalveolar, hemosiderin-laden macrophages, called "heart failure cells." Congestion in the liver is characterized by centrilobular congestion, which is seen grossly as a "nutmeg" appearance of the liver. In contrast to hyperemia, hemorrhage refers to the leakage of blood from a blood vessel. Blood may escape into the tissue, producing a hematoma, or it may escape into spaces, producing a hemothorax, hemopericardium, or hemarthrosis. Superficial hemorrhages into the skin or mucosa are classified as petechiae (small, pinpoint capillary hemorrhages), purpura (diffuse, multiple superficial hemorrhages), or ecchymoses (larger, confluent areas of hemorrhages).

47. The answer is c. *(Cotran, pp 119–124.)* The three main components of hemostasis include endothelial cells, platelets, and the coagulation system. Endothelial cells exhibit both procoagulant and anticoagulant properties. Their procoagulant activities involve activation of the extrinsic coagulation cascade by their production of tissue factor (thromboplastin) and stimulation of platelet aggregation by their production of von Willebrand factor and platelet-activating factor. Their anticoagulant activities involve the production of prostacyclin (PGI_2), thrombomodulin, and plasminogen activator. The contrasting actions of the arachidonic acid metabolites prostacyclin and thromboxane A_2 (TxA_2) produce a fine-tuned balance

for the regulation of clotting. TxA_2, a product of the cyclooxygenase pathway of arachidonic acid metabolism, is synthesized in platelets and is a powerful platelet aggregator and vasoconstrictor. The prostaglandin PGI_2, also a product of the cyclooxygenase pathway but produced by endothelial cells, inhibits platelet aggregation and causes vasodilation. Aspirin, a cyclooxygenase inhibitor, blocks the synthesis of both TxA_2 and PGI_2 and is used in the treatment of coronary artery disease. Fibrinogen, which is produced by the liver and not endothelial cells, is cleaved by thrombin to form fibrin.

48. The answer is a. *(Cotran, pp 121–124. Henry, pp 725–726, 742–743.)* The coagulation cascade involves the formation of fibrin through the intrinsic, extrinsic, and common pathways. The intrinsic pathway is initiated by contact of factor XII with several types of biologic surfaces. Activated XII (XIIa) initiates the formation of XIa and IXa. The extrinsic pathway is initiated by contact of tissue factor with factor VII. Activated factor VII acts together with IXa, VIIIa, and platelet factor 3 (PF-3), which is a phospholipid complex located on the surface of platelets, to produce activated factor X. This begins the common pathway, which continues with the interaction of Xa, Va, PF-3, and Ca^{++} to cleave prothrombin, forming thrombin, which in turn cleaves fibrinogen to form fibrin.

Two laboratory tests that are used to evaluate the functioning of the coagulation cascade are prothrombin time (PT) and partial thromboplastin time (PTT). Abnormalities of the extrinsic pathway prolong (not shorten) the PT, while abnormalities of the intrinsic pathway prolong (not shorten) the PTT. Note that abnormalities of the common pathway prolong both the PT and the PTT. To illustrate, deficiencies of factor VII produce an abnormal (prolonged) PT with a normal PTT. Compare these results to each of the following: a normal PT with an abnormal PTT can be seen with deficiencies of factors XII, XI, IX, or VIII, while abnormal PT and PTT are seen with deficiencies of X, V, prothrombin, or fibrinogen.

49. The answer is c. *(Cotran, pp 126–129.)* Thrombi may form within the heart, the arteries, or the veins. When formed within the heart or the arteries, thrombi may have laminations, called the lines of Zahn, formed by alternating layers of platelets admixed with fibrin, separated by layers with more cells. Mural thrombi within the heart are associated with myocardial infarcts and arrhythmias, while thrombi in the aorta are associated with

atherosclerosis or aneurysmal dilatations. Arterial thrombi are usually occlusive; however, in the larger vessels they are not. Venous thrombi, which are almost invariably occlusive, are found most often in the legs, in superficial varicose veins or deep veins. Those of the larger outflow veins of the leg may embolize. It is important to be able to tell postmortem clots from venous thrombi. The postmortem clot is usually rubbery, gelatinous, and lacks fibrin strands and attachments to the vessel wall. Large postmortem clots may have a "chicken fat" appearance overlying a dark "currant jelly" base.

50. The answer is a. *(Cotran, pp 129–132.)* An embolus is a detached intravascular mass that has been carried by the blood to a site other than where it was formed. Emboli basically can be thrombotic or embolic, but most originate from thrombi. These thromboemboli, most of which originate in the deep veins of the lower extremities, may embolize to the lungs. The majority of small pulmonary emboli do no harm, but, if they are large enough, they may occlude the bifurcation of the pulmonary arteries (saddle embolus), causing sudden death. Arterial emboli most commonly originate within the heart on abnormal valves (vegetations) or mural thrombi following myocardial infarctions. If there is a patent foramen ovale, a venous embolus may cross over through the heart to the arterial circulation, producing an arterial (paradoxical) embolus.

Types of nonthrombotic emboli include fat emboli, air emboli, and amniotic fluid emboli. Fat emboli, which result from severe trauma and fractures of long bones, can be fatal as they can damage the endothelial cells and pneumocytes within the lungs. Air emboli are seen in decompression sickness, called caisson disease or the bends, while amniotic fluid emboli are related to the rupture of uterine venous sinuses as a complication of childbirth. Amniotic fluid emboli can also lead to a fatal disease, disseminated intravascular coagulopathy (DIC), which is marked by the combination of intravascular coagulation and hemorrhages. In this setting DIC results from the high thromboplastin activity of amniotic fluid.

51. The answer is e. *(Cotran, pp 132–133, 1017–1018.)* Infarcts are localized areas of ischemic coagulative necrosis. They can be classified on the basis of their color into either red or white infarcts, or by the presence or absence of bacterial contamination into either septic or bland infarcts. White infarcts, also referred to as pale or anemic infarcts, are usually the

result of arterial occlusion. They are found in solid organs such as the heart, spleen, and kidneys. Red or hemorrhagic infarcts, in contrast, may result from either arterial or venous occlusion. They occur in organs with a dual blood supply, such as the lung, or in organs with extensive collateral circulation, such as the small intestine and brain. These infarcts are hemorrhagic because there is bleeding into the necrotic area from the adjacent arteries and veins that remain patent. Hemorrhagic infarcts also occur in organs in which the venous outflow is obstructed (venous occlusion). Examples of this include torsion of the ovary or testis. In the latter, twisting of the spermatic cord occludes the venous outflow, but the arterial inflow remains patent because these arterial blood vessels have much thicker walls. This results in venous infarction. Testicular torsion is usually the result of physical trauma in an individual with a predisposing abnormality, such as abnormal development of the gubernaculum testis.

52. The answer is c. *(Champe, pp 352–353.)* The synthesis of pyrimidines begins with the conversion of glutamine to carbamoyl phosphate. This step, which is the committed step in pyrimidine synthesis, is catalyzed by the enzyme carbamoyl phosphate synthetase II (CPSII) and requires 2ATP and CO_2. After several biochemical steps orotate is formed; orotate is then converted to orotidine 5′-monophosphate (OMP) by the enzyme orotate phosphoribosyl transferase. Subsequently OMP is converted to uridine 5′-monophosphate (UMP) by the enzyme OMP decarboxylase. A deficiency of either of these two enzymes leads to a disorder called orotic aciduria, which is characterized by orotate in the urine, abnormal growth, and megaloblastic anemia. Next UMP is converted to CTP, while dUMP is converted by thymidylate synthase to dTMP. This latter step also involves folate and is inhibited by the folate analogue methotrexate, while thymidylate synthase is inhibited by the thymine analogue 5-flurouracil (5-FU). Finally, the ribonucleoside diphosphates (ADP, GDP, CDP, and UDP) are converted to deoxyribonucleoside diphosphates by ribonucleotide reductase, an enzyme that is inhibited by increased levels of dATP, as seen in individuals with the autosomal recessive (Swiss type) form of SCID, which is due to a deficiency of adenosine deaminase (ADA).

53. The answer is d. *(Cotran, pp 464–466. Jorde, pp 319–331.)* There are several similar clinical terms that are used to describe various types of abnormal physical development. An association is a pattern of nonrandom

anomalies with an unknown mechanism (e.g., VATER association). A deformation is an alteration of a normally formed body part by mechanical forces (e.g., oligohydramnios sequence). A disruption is a defect that results from interference in a normally developing process. Dysraphia refers to defects caused by failure of apposed structures to fuse (e.g., spina bifida). Dystopia refers to retention of an organ at a site during development (e.g., dystopic testes remaining in the inguinal canal, called cryptorchidism). A malformation is a morphologic defect that results from an intrinsically abnormal developmental process (e.g., cleft lip or polydactyly). A sequence is a recognized pattern that results from a single preexisting abnormality (e.g., oligohydramnios sequence). *Syndrome* refers to multiple anomalies having a recognizable pattern and known pathogenesis (e.g., Down's syndrome).

54. The answer is a. *(Cotran, pp 143–145.)* There are several general clinical differences between autosomal dominant (AD) disorders and autosomal recessive (AR) disorders. In general, AD mutations usually involve complex structural proteins or regulatory proteins, while AR disorders are more likely to result from abnormalities of proteins that function as enzymes. Examples of AD disorders involving abnormalities of structural proteins include Marfan's syndrome (fibrillin), Ehlers-Danlos syndrome (collagen), osteogenesis imperfecta (collagen), and hereditary spherocytosis (spectrin). Examples of AD disorders involving abnormalities of regulatory proteins include familial hyperlipidemia (LDL receptor), von Willebrand's disease (von Willebrand factor), and hereditary angioedema (C1 esterase inhibitor). Enzyme deficiencies are usually not associated with AD inheritance, because decreased levels of enzymes can usually be compensated for. Examples of AR disorders involving enzyme deficiencies include storage diseases and several amino acid diseases. Also note that, when compared with AD diseases, AR disorders tend to be more uniform in expression and the age of onset is frequently early in life. Examples of this latter fact include diseases of the blood (sickle cell anemia and thalassemia) and the infantile form of polycystic renal disease, which has an AR inheritance. In contrast, the adult form of polycystic renal disease has an AD pattern of inheritance.

55. The answer is d. *(Cotran, pp 1281–1283.)* Classification of the muscular dystrophies is based on the mode of inheritance and clinical features.

Inheritance of the Duchenne type is by an X-linked recessive trait, with the gene located on the short arm of the X chromosome, although spontaneous mutations are fairly common. Autosomal dominant inheritance characterizes both myotonic dystrophy and the facioscapulohumeral type, while limb-girdle dystrophy is autosomal recessive. In Duchenne muscular dystrophy, males are affected and symptoms begin before the age of 4. Pelvic girdle muscles are affected, with resultant difficulty in walking, and this is followed by shoulder girdle weakness and eventual involvement of respiratory and cardiac muscles with death from respiratory failure before age 20. Histologic changes include rounded, atrophic fibers; hypertrophied fibers; degenerative and regenerative changes in adjacent myocytes; and necrotic fibers invaded by histiocytes. Elevation of serum creatine kinase is marked.

56. The answer is a. *(Jorde, pp 58–60.)* The probability that a child will inherit a particular gene found on only one chromosome of a chromosome pair from one parent is 1 in 2 (e.g., 50%). Therefore, the probability that a child will inherit the cystic fibrosis (CF) gene from both parents and develop cystic fibrosis is 1 in 4 (e.g., $\frac{1}{2} \times \frac{1}{2}$). To calculate the probability that two or more events that are independent of each other will all occur, you must multiply the probabilities for each of these events together. Therefore, the probability that three out of three children will each inherit two CF genes is $\frac{1}{4} \times \frac{1}{4} \times \frac{1}{4}$.

57. The answer is d. *(Jorde, pp 60–63.)* The Hardy-Weinberg principle predicts population genotype frequencies based on gene frequencies. The principle, which assumes random mating, states that given gene frequencies p (for an allele A) and q (for another allele a), then the aa genotype (homozygous) = $q \times q$ and the Aa genotype (heterozygous carriers) = $2pq$. The latter can also be written as $(p \times q) + (p \times q)$.

58. The answer is e. *(Cotran, pp 160–163. Rubin, pp 255–257.)* The glycogen storage diseases are due to defective metabolism of glycogen, and at least 11 syndromes stemming from genetic defects in the responsible enzymes have been described. Most of these glycogenoses are inherited as autosomal recessive disorders. von Gierke's disease (type I) results from deficiency of glucose-6-phosphatase, the hepatic enzyme needed for conversion of G6P to glucose, with glycogen accumulation particularly in the enlarged liver and kidney and hypoglycemia. Diagnosis requires

biopsy demonstration of excess liver glycogen plus either absent or low liver glucose-6-phosphatase activity, or a diabetic glucose tolerance curve, or hyperuricemia. von Gierke's disease is the major hepatic or hepatorenal type of glycogenosis. Lysosomal glucosidase deficiency causes Pompe's disease (type II). Glycogen storage is widespread but most prominent in the heart (cardiomegaly). In brancher glycogenosis (type IV) there is accumulation of amylopectin or abnormal glycogen in the liver, heart, skeletal muscle, and brain. The major myopathic form, McArdle's disease (type V), is due to lack of muscle phosphorylase.

59. The answer is a. *(Cotran, pp 156–158.)* Sphingomyelin, a lipid composed of phosphocholine and a ceramide, is characteristically found in abnormally high concentrations throughout the body tissues of patients who have any one of the forms of Niemann-Pick disease. Division of this disease into five categories is generally accepted: type A, the acute neuronopathic form, is the one that has the highest incidence. The lack of sphingomyelinase in type A is the metabolic defect that prevents the hydrolytic cleavage of sphingomyelin, which then accumulates in the brain. Patients who have the type A form usually show hepatosplenomegaly at 6 months of age, progressively lose motor functions and mental capabilities, and die during the third year of life.

60. The answer is a. *(Cotran, pp 159–160. Damjanov, pp 293–294. Jorde, p 149.)* The mucopolysaccharidoses (MPSs) result from deficiencies of specific enzymes involved in the breakdown of glycosaminoglycans (GAGs), which are also called mucopolysaccharides. The seven major types of GAGs are hyaluronic acid, chondroitin sulfate, keratin sulfate, dermatan sulfate, heparan sulfate, and heparin. The MPSs are characterized by accumulation of partially degraded GAGs in multiple organs, including the liver, spleen, heart, and blood vessels. Accumulations of GAGs within leukocytes produce Alder-Reilly bodies, while accumulations within neurons can produce zebra bodies. The MPSs are also characterized by the excretion of excess acid mucopolysaccharides in the urine, a finding that helps to differentiate the MPSs from the mucolipidoses. Most of the MPSs are associated with coarse facial features, clouding of corneas, joint stiffness, and mental retardation. The characteristic appearance of patients with type IH MPS (Hurler's syndrome), which results from a deficiency of alpha-L-iduronidase, has been described as "gargoylism." These patients

excrete excess dermatan sulfate and heparan sulfate, both of which are mucopolysaccharides, in the urine. Type II MPS (Hunter's syndrome) is the only MPS that has an X-linked recessive type of inheritance. These patients have a much milder disease than Hurler's syndrome patients, but they also secrete dermatan sulfate and heparan sulfate in the urine. Type IV MPS, known as Morquio's syndrome, is characterized by short stature, aortic valvular disease, and normal intelligence. These patients are prone to development of subluxation of the spine, which can produce quadriplegia. They secrete keratan sulfate in the urine.

In contrast to the MPSs, the mucolipidoses (MLs) are characterized by abnormalities affecting both the mucopolysaccharidoses (MPSs) and the sphingolipidoses (SLs). Similar to the MPSs, the MLs involve abnormal bone development (dysostosis), while similar to some of the SLs, cherry red maculae and peripheral demyelination are also seen. The MLs, however, unlike the MPSs, do not involve excessive urinary excretion of acid mucopolysaccharides. The metabolism of the carbohydrates in glycoproteins and glycolipids is abnormal in the MLs and results in excess accumulation of oligosaccharides. There are three main types of MLs: type I is sialidosis, type II is inclusion cell (I cell) disease, and type III is pseudo-Hurler's disease. Patients with type II ML lack the enzyme *N*-acetylglucosamine phosphotransferase, which catalyzes the first step in the formation of mannose-6-phosphate. Many lysosomal enzymes in these patients, such as acid hydrolases (which includes glycoprotein and ganglioside sialidases), do not reach the cellular lysosomes and are instead secreted into the plasma. The name I cell originated from the finding of cytoplasmic granular inclusions in affected patients' fibroblasts when cultured in vitro and observed under a phase-contrast microscope. These cytoplasmic inclusions are lysosomes that are swollen with many different types of contents. I cell disease is a slowly progressive disease that starts at birth and is fatal in childhood. Treatment is symptomatic only.

61. The answer is d. *(Rubin, pp 257–260. Cotran, pp 475–476.)* Several autosomal recessive disorders involve inborn errors of amino acid metabolism. Alkaptonuria (ochronosis) is caused by the excess accumulation of homogentisic acid. This results from a block in the metabolism of the phenylalanine-tyrosine pathway, which is caused by a deficiency of homogentisic oxidase. Excess homogentisic acid causes the urine to turn dark upon standing after a period of time. It also causes a dark coloration

of the scleras, tendons, and cartilage. After years, many patients develop a degenerative arthritis. Phenylketonuria (PKU), also called hyperphenylalaninemia, results from a deficiency of phenylalanine hydroxylase, an enzyme that oxidizes phenylalanine to tyrosine in the liver. Infants are normal at birth, but rising phenylalanine levels (hyperphenylalaninemia) result in irreversible brain damage. The excess phenylacetic acid in the urine results in a "mousy" odor. A lack of the enzyme fumarylacetoacetate hydrolase results in increased levels of tyrosine (tyrosinemia). Chronic forms of the disease are associated with cirrhosis of the liver, kidney dysfunction, and a high risk of developing hepatocellular carcinoma. Maple syrup urine disease is associated with an enzyme defect that causes the accumulation of branched-chain α-keto acid derivatives of isoleucine, leucine, and valine. Albinism refers to a group of disorders characterized by an abnormality of the synthesis of melanin. Two forms of oculocutaneous albinism are classified by the presence or absence of tyrosinase, which is the first enzyme in the conversion of tyrosine to melanin. Albinos are at a greatly increased risk for the development of squamous cell carcinomas in sun-exposed skin.

62. The answer is d. *(Cotran, pp 165–171.)* The normal human karyotype consists of 23 pairs of chromosomes, of which 22 are homologous pairs of autosomes and one pair is the sex chromosome. The number of chromosomes found in germ cells (23) is called the haploid number (n), while the number of chromosomes found in all of the remaining cells in the body (46) is called the diploid number ($2n$). Any exact multiple of the haploid number (n) is called euploid. Note that both haploid and diploid cells are euploid. Any number that is not an exact multiple of n is called aneuploid. Aneuploidy can result from nondisjunction (more commonly) or anaphase lag. Nondisjunction is the failure of paired chromosomes or chromatids to separate at anaphase, either during mitosis or meiosis. Nondisjunction during the first meiotic division is the mechanism responsible for the majority of cases of trisomy 21. In contrast, chromosome numbers such as $3n$ and $4n$ are called polypoid. $3n$ is called triploid, while $4n$ is called tetraploid. Do not confuse triploid with trisomy; the latter refers to the presence of three copies of one chromosome, which results in 47 chromosomes. Triploid karyotypes (69 chromosomes) are found in about 7% of miscarriages. Interestingly, they are also associated with abnormalities of the placenta, including cystic villi and partial hydatidiform moles. Both

abnormalities can produce large placentas. Triploid karyotypes are usually due to double fertilization of a haploid ovum by two haploid sperm, that is, there is a total of 69 chromosomes, 46 of which are from the father.

A reciprocal translocation between two acrocentric chromosomes is characteristic of the Robertsonian translocation (centric fusion), which results in the formation of one large metacentric chromosome and a small chromosomal fragment, which is usually lost. Deletion of both ends of a chromosome with fusion of the damaged ends produces a ring chromosome, while abnormal division of the centromere along a transverse plane forms an isochromosome. Turner's syndrome can result from an isochromosome of the X chromosome. Two breaks within a single chromosome with reincorporation of the inverted segment produces an inversion.

63. The answer is e. *(Cotran, pp 152–156. Rubin, pp 228–233.)* Nondisjunction during the first meiotic division is responsible for trisomy 21 in about 93% of patients with Down's syndrome. Nondisjunction during mitosis of a somatic cell early during embryogenesis results in mosaicism in about 2% of patients with Down's syndrome. Translocation of an extra long arm of chromosome 21 causes about 5% of Down's syndrome cases. An important type of translocation, the Robertsonian translocation (centric fusion), involves two nonhomologous acrocentric chromosomes with the resultant formation of one large metacentric chromosome. Carriers of this type of translocation may also produce children with Down's syndrome.

It is important to understand these different causes of Down's syndrome in order to estimate the chance of recurrence if parents already have one child with Down's syndrome. Overall, the risk of recurrence of trisomy 21 after one such child has been born to a family is about 1%. If the karyotypes of the parents are normal, then the recurrence rate is dependent upon the age of the mother. For mothers under the age of 30, the risk is about 1.4%. For mothers over the age of 30, the risk is the same as the age-related maternal risk, which at age 30 is 1/900, at age 35 is 1/350, at age 40 is 1/100, and at age 40 and over is 1/25. The recurrence risk is different for a translocation Down's syndrome, which may be either a 14q21q Robertsonian translocation or a 21q21q translocation. A carrier of a Robertsonian translocation involving chromosomes 14 and 21 has only 45 chromosomes and can theoretically produce six possible types of gametes. Of these, only three are potentially viable: one that is normal, one that is balanced, and one that is unbalanced, having both the translocated chromosome and a

normal chromosome 21. The latter, when combined with a normal gamete, could produce a child with Down's syndrome. Therefore, theoretically, the risk of a carrier of this type of Robertsonian translocation producing a child with Down's syndrome would be 1 in 3. In practice, about 15% of the progeny of mothers with this type of translocation, and very few of the progeny of fathers with this type of translocation, develop Down's syndrome. In contrast, carriers of a 21q21q translocation produce gametes that either have the translocated chromosome or lack any 21 chromosome. Progeny then can have either trisomy 21 or monosomy 21, but, since the latter is rarely viable, approximately 100% of progeny will have Down's syndrome.

64. The answer is c. *(Cotran, pp 170–173.)* The three most common trisomies causing human disease are trisomies 13, 18, and 21. Trisomy 13 (Patau's syndrome) is characterized by forebrain and midline facial abnormalities. Patients can develop holoprosencephaly, which is characterized by fused frontal lobes and a single ventricle. Olfactory bulbs are also absent. The midline facial abnormalities that are seen with trisomy 13 include cleft lip, cleft palate, nasal defects, and a single central eye ("cyclops"). Other defects associated with Patau's syndrome include polydactyly, rocker-bottom feet, and congenital heart diseases. Trisomy 18 (Edwards' syndrome) is characterized by mental retardation, micrognathia (tiny jaw), low-set ears, rocker-bottom feet, and congenital heart diseases. Perhaps most characteristic is a clenched fist with overlapping fingers: the index finger overlying the third and fourth fingers, while the fifth finger overlaps the fourth. Edwards' syndrome is also associated with polyhydramnios and a single umbilical artery.

Trisomy 21 (Down's syndrome) is the most common chromosomal abnormality and is an important cause of mental retardation. Children with Down's syndrome invariably have severe mental retardation, which progressively declines with advancing age. Patients have characteristic facial features that include a flat facial profile, oblique palpebral fissures, and epicanthal folds; a horizontal palmar crease; and a decreased muscle tone at birth that leads to a "floppy baby." About one-third of these children also have congenital heart defects, most commonly ventricular septal defects and AV canal defects. There is also a marked increase in the incidence of acute leukemia, usually acute lymphoblastic leukemia, in children with Down's syndrome who are younger than 3 years of age. There is almost a 100% incidence of Alzheimer's disease in patients with Down's syndrome

by the age of 35. Changes in the brains of patients with Down's syndrome similar to those seen in the brains of patients with Alzheimer's disease include senile plaques and neurofibrillary tangles. Patients with Down's syndrome also have an increased incidence of infections, GI obstruction, and duodenal ulcers.

Deletions involving chromosome 22 (e.g., 22q11) are associated with both DiGeorge's syndrome and the velocardiofacial (VCF) syndrome. DiGeorge's syndrome is associated with absence of the thymus, which leads to cell-mediated immune deficiencies, and absence of the parathyroids, which leads to hypocalcemia. VCF syndrome is associated with palate (velum) abnormalities and dysfunction of the T cells. DiGeorge's syndrome and VCF syndrome may represent spectrums of the same abnormality. In fact, the acronym CATCH-22 refers to the signs of the 22q11 deletion syndrome: cardiac abnormality, abnormal face, T cell defect secondary to thymic hypoplasia, cleft palate, and hypocalcemia secondary to hypoparathyroidism.

65. The answer is b. *(Cotran, pp 180–181. Rubin, pp 227, 234.)* Several genetic diseases are characterized by a deletion of part of an autosomal chromosome. The $5p^-$ syndrome is also called the cri-du-chat syndrome, as affected infants characteristically have a high-pitched cry similar to that of a kitten. Additional findings in this disorder include severe mental retardation, microcephaly, and congenital heart disease. $4p^-$, also called Wolf-Hirschhorn syndrome, is characterized by pre- and postnatal growth retardation and severe hypotonia. Affected infants have many defects including micrognathia and a prominent forehead. The $11p^-$ syndrome is characterized by the congenital absence of the iris (aniridia) and is often accompanied by Wilms tumor of the kidney. The $13q^-$ syndrome is associated with the loss of the Rb suppressor gene and the development of retinoblastoma. Deletions involving chromosome 15 ($15q^-$) may result in either Prader-Willi syndrome or Angelman's syndrome depending on whether the defect involves the paternal or the maternal chromosome (genetic imprinting). $17p^-$, also known as Smith-Margens syndrome, is associated with self-destructive behavior.

66. The answer is c. *(Cotran, pp 180–181.)* Genetic imprinting refers to the fact that different diseases may result from the same chromosomal dele-

tion depending on whether that deletion specifically involves either the maternal chromosome or the paternal chromosome. This finding is in sharp contrast to the classic concept of Mendelian inheritance, which states that the phenotype of a certain allele is independent of whether the chromosome is the maternal or the paternal chromosome. The best example of genetic imprinting involves deletions involving chromosome 15 ($15q^-$). If the deletion involves the maternal chromosome, then Angelman's syndrome results, while deletions involving the paternal chromosome result in Prader-Willi syndrome. Angelman's syndrome is characterized by severe mental retardation, seizures, a stiff ataxic gait with jerky movements, inappropriate laughter, and occasional oculocutaneous albinism. Because of the combination of ataxic gait and inappropriate laughter, these patients are sometimes referred to as "happy puppets." Prader-Willi syndrome is characterized by short stature, obesity, mild to moderate mental retardation, small hands and feet, and hypogonadism, which is characterized in males by cryptorchidism and micropenis and in females by hypoplastic labia.

The cause of genetic imprinting is not known, but it may relate to the degree of methylation of genes. Genes that are more highly methylated are less likely to be transcribed into messenger RNA. Note that a loss of chromosome 15 can also occur if two parental chromosomes of the same type are derived from the same parent. This condition is called uniparental disomy, whereas the normal condition is called biparental disomy. Inheritance of the same (duplicated) chromosome is called isodisomy, while inheritance of homologues from the same parent is called heterodisomy. To illustrate this concept, consider paternal uniparental disomy of chromosome 15. This refers to inheriting two copies of paternal chromosome 15 and no maternal chromosome 15. Therefore, this is essentially the same as a deletion of maternal chromosome 15, which produces Angelman's syndrome.

Inheriting two copies of paternal chromosome 11 results in Beckwith-Wiedemann syndrome. This is not a trisomy, as the maternal chromosome is lost, and therefore this would be a paternal uniparental disomy for chromosome 11. This syndrome is characterized by exomphalos, macroglossia, and gigantism (EMG). Patients also develop hypoglycemia because the genes for insulin and insulinlike growth factors are located in this region. Smith-Margens syndrome ($17p^-$) is associated with self-destructive behavior, while Wolf-Hirschhorn syndrome ($4p^-$) is characterized by growth retardation, severe hypotonia, and micrognathia.

67. The answer is d. *(Cotran, pp 174–176.)* Turner's syndrome (hypogonadism in phenotypic females) is an important cause of primary amenorrhea. Characteristics of this syndrome include small stature due to a lack of a growth spurt during adolescence, a webbed neck, and multiple skeletal abnormalities that include a wide carrying angle of the arms where the elbow is out (cubitus valgus), a "shield-shaped" chest, and a high-arched palate. Individuals with Turner's syndrome are phenotypic females, but they fail to develop secondary characteristics at puberty. Patients have streak gonads, histologic sections of which reveal atrophic, fibrous strands and are devoid of ova and follicles. These hypermaturing ovaries produce decreased estrogen levels, resulting in primary amenorrhea with no menarche. About one-half of patients develop hypothyroidism due to autoantibodies against thyroid hormone. Mental retardation is not associated with Turner's syndrome. Most cases of Turner's syndrome are associated with a 45,XO karyotype, which has no Barr body, but other causes of Turner's syndrome include isochromosome X and mosaicism.

An XYY karyotype, which most often results from nondisjunction at the second meiosis during spermatogenesis, produces individuals who are phenotypically normal except that they may be tall and have severe acne (cystic acne). The relationship of the extra Y to behavior is controversial, but these individuals do have problems with motor and language development. Multi-X females are normal, except there is an increased tendency toward mental retardation that is proportional to the number of X chromosomes that are present.

68. The answer is a. *(Cotran, 6/e, p 176.)* Sexual ambiguity arises when there is disagreement between the various ways of determining sex. Genetic sex is determined by the presence or absence of a Y chromosome. Gonadal sex is based upon the histologic appearance of the gonads. Ductal sex depends on the presence of derivatives of the Müllerian or Wolffian ducts. Phenotypic or genital sex is based on the appearance of the external genitalia. True hermaphroditism refers to the presence of both ovarian and testicular tissue. Pseudohermaphroditism is a disagreement between the phenotypic and gonadal sex. A female pseudohermaphrodite has ovaries but external male genitalia, while a male pseudohermaphrodite has testicular tissue, resulting from an XY genital sex karyotype, but female external genitalia. Female pseudohermaphroditism results from excessive exposure

to androgens during early gestation; most often this is the result of congenital adrenal hyperplasia. Male pseudohermaphroditism results from defective virilization of the male embryo, most commonly caused by complete androgen insensitivity syndrome, also called testicular feminization.

Kallmann's syndrome results from a lack of embryonic migration of cells from the olfactory bulb to the hypothalamus and is characterized by primary amenorrhea, lack of secondary sex characteristics, and decreased sense of smell (hyposmia). Laboratory findings include decreased GnRH, LH, and FSH. Mixed gonadal dysgenesis consists of one well-defined testis and a contralateral streak ovary. It is a cause of ambiguous genitalia in the newborn. Turner's syndrome, which has a 45,XO karyotype, is characterized by a female phenotype and bilateral streak ovaries.

69. The answer is e. *(Cotran, pp 190–191. Isselbacher, pp 1550–1551.)* Both B lymphocytes and T lymphocytes have definite sequences of maturation that are characterized by gene rearrangement and the acquisition of surface markers. These cells originate from a common lymphoid stem cell that is characterized by the intranuclear enzyme terminal deoxynucleotidyl transferase (TdT) and the surface antigens CD34 and CD38. The first definable stage of B cell maturation occurs as the cell begins the process of producing immunoglobulin (Ig). The heavy chain genes, which are located on chromosome 14, are first rearranged, but because this occurs before the rearrangement of the light chain genes, complete immunoglobulin is not yet expressed on the cell surface. Instead μ heavy chain genes are rearranged first, and are found within the cytoplasm. This defines these developing cells as being pre-B cells. These cells also demonstrate surface CD10 (CALLA) and the pan–B cell markers CD19, CD20, and CD22. Next these developing B cells begin to synthesize light chains. κ light chain genes are found on chromosome 2 and are rearranged first. If something goes wrong in this process, then the λ light chain genes on chromosome 22 are rearranged; otherwise they stay in their germline configuration. The synthesized light chains then combine with the intracytoplasmic μ heavy chains to form complete IgM, which is then transported to the surface, forming surface IgM (sIgM). These cells, which have also acquired CD21 but have lost TdT and CD10, are called immature B cells. Next these developing B cells produce IgD, which is also expressed on the cell surface (sIgD). These cells with surface IgM and IgD are called mature B cells. They

are also called "virgin" B cells because these cells have not encountered any foreign antigen. (Note that all of the preceding steps occur in the bone marrow of the developing fetus.)

Later in life, binding of foreign antigen to membrane bound surface Ig results in activation of the B cell, which then becomes either a memory cell or a plasma cell. Before B cells become plasma cells, there may be a class switch (isotype switch) to a particular surface immunoglobulin that the plasma cell will then secrete. This activation occurs within germinal centers, where morphologically B cells are classified as being small cleaved lymphocytes, large cleaved lymphocytes, small noncleaved lymphocytes (with prominent nucleoli), or large noncleaved lymphocytes (with prominent nucleoli). Prior to forming plasma cells, these activated B lymphocytes are called B immunoblasts. Plasma cells are characterized by cytoplasmic immunoglobulin and surface plasma cell antigen 1 (PCA-1). In contrast, memory B lymphocytes, which histologically look like unremarkable small lymphocytes, have surface immunoglobulin of the IgG, IgA, or IgE type. They are found within lymphoid follicles.

70. The answer is b. *(Henry, pp 913–927. Chandrasoma, pp 59–63.)* Immunoglobulins (Igs) are the product of plasma cells, the effector cells of B lymphocyte activation. Igs are composed of light chains and heavy chains, each of which are composed of a variable region and a constant region. The variable regions of both of these chains form the antigen-binding region of Ig, which is called the Fab portion. The portion of Ig that binds complement is called the Fc portion. Not only can the Fc portion of Ig bind to complement, but it can bind to cells that have Fc receptors. There are two types of light chains and five types of heavy chains. The two light chains are the κ chain, the genes of which are located on chromosome 2, and the λ chain, the genes of which are located on chromosome 22. The heavy chains are M, D, A, E, and G, the genes of all of these being on chromosome 14. The combination of one type of light chain with a particular heavy chain forms each of the five types of immunoglobulin.

The most abundant Ig in the serum (80%) is IgG. It is secreted in the second response to certain antigens, but it does not predominate early during the first response. IgG can cross the placenta, and it is the major protective immunoglobulin in the neonate. IgG can also activate complement, participate in antibody-dependent cell-mediated cytotoxicity (ADCC), neutralize toxins or viruses, and function as an opsonin. IgM, which con-

stitutes about 5 to 10% of the Ig in the serum, is secreted in the first exposure to antigen (primary immune response). The monomeric form of IgM is found on the surface of some B cells, while the pentameric form is found in the serum and cannot cross the placenta. IgM is very effective at activating complement. IgD, which forms less than 1% of serum Ig, is found on the cell surface of some B cells and functions in the activation of these B cells. IgE, also known as reaginic antibody, is found on the plasma membrane of mast cells and basophils and participates in type I hypersensitivity reactions, such as allergies, asthma, and anaphylaxis. IgE is used to fight parasitic infections. IgA, which constitutes about 10 to 15% of serum Ig, exists as a monomer in the serum and a dimer in glandular secretions. IgA is synthesized by mucosal plasma cells of the GI tract, lung, and urinary tract—thus making it the immunoglobulin of "secretory immunity"—and is found in saliva, sweat, nasal secretion, and tears. It is secreted as a dimer bound to a secretory piece that stabilizes the molecule against proteolysis.

71. The answer is a. *(Cotran, pp 189–190. Isselbacher, pp 1545, 1549.)* T cells arise from precursor cells in the bone marrow that migrate to the thymus and mature. Like B cells, T cells originate from a common lymphoid stem cell that includes intranuclear terminal deoxynucleotidyl transferase (TdT) and surface antigens CD34 and CD38. This stage of development occurs prior to the migration of the developing cell to the thymus and is called the prethymus stage. There are three stages of maturation within the thymus. Stage I occurs in the outer cortex of the thymus, where the developing T lymphocytes (thymocytes) obtain the surface antigen CD7 followed by CD2 and CD5. These stage I (or early) thymocytes lack both CD4 or CD8 and are called double-negative cells. These cells make up about 10% of the thymocytes in the thymus. The next step in development, which starts in the cortex and continues into the medulla, involves generation of an intact T cell receptor (TCR) on the cell surface. The TCR is a heterodimer, usually made up of an α and a β chain, each having a variable (antigen-binding) region and a constant region, analogous to the immunoglobulin molecule. Early in the formation of TCR, called stage II, the intermediate (common) thymocytes acquire both CD4 and CD8 molecules and are called double-positive T cells. They are the majority of thymocytes in the thymus (80%). Stage III occurs in the medulla, where the T cells lose either the CD4 or the CD8 antigen. These mature thymocytes, which are single-positive cells, make up about 15% of the thymus thymo-

cytes. Post-thymus T cells are either CD4+ or CD8+. CD4+ cells function as helper cells, while CD8+ cells function as cytotoxic cells. In normal, healthy individuals, the helper/suppressor ratio (e.g., CD4/CD8 ratio) in the peripheral blood is about 2:1. That is, about 40% of peripheral lymphocytes are helper cells and 20% of peripheral lymphocytes are cytotoxic T cells.

72. The answer is d. *(Cotran, pp 191–192. Damjanov, pp 400–401.)* The cytokines are soluble mediators of immune reactions that are released from immune cells. Products of lymphocytes are called lymphokines, while products of monocytes or macrophages are called monokines. Two of the more important cells that secrete cytokines are two subsets of T helper lymphocytes, namely T_H1 cells and T_H2 cells. T_H1 cells secrete several types of cytokines, including interleukin 2 (IL-2), γ-IFN, and lymphotoxin (β-TNF). IL-2, secreted by CD4+ T_H1 cells, has autocrine effects to increase IL-2 receptors. It also stimulates NK cells (antibody-dependent cell-mediated immunity) and CD8+ T cells (cell-mediated immunity). T_H2 cells also secrete several types of cytokines, including IL-4, IL-5, IL-6, and IL-10. IL-4 simulates T_H2 cells while at the same time inhibiting T_H1 cells. This combination inhibits cell-mediated immunity and favors humoral immunity. In addition, IL-4 regulates heavy chain class switch to IgE. IL-5 increases the numbers and function of eosinophils. IL-6 is the most potent stimulator for acute-phase reactant production by the liver. Additionally, it stimulates B cells, and synergistically with IL-1 it stimulates T cells. IL-10 inhibits T_H1 cells (cell-mediated immunity), NK cells, and macrophages.

In contrast, IL-1 is produced by many types of cells, including macrophages, antigen-presenting cells (APCs), and other somatic cells. The functions of IL-1 include autocrine effects on the APCs and paracrine effects on T cells. Effects of IL-1 on the APCs include increased expression of adhesion molecules, γ-IFN receptors, and class II antigens. Effects of IL-1 on T cells include increased IL-2 secretion and increased expression of receptors for IL-2 and γ-IFN. Other effects of IL-1 are important in acute inflammation and include stimulation of neutrophils and B cells, production of fever, and increased production of acute-phase reactants. IL-3, also known as multi-CSF, stimulates pluripotential stem cells. Interferon α is an antiviral interferon, while interferon γ is an immune interferon. Interferon γ is the most potent activator of macrophages. These activated macrophages (epithelioid cells) produce granulomas. Effects of interferon γ also include increased class

I antigen expression on all somatic cells, increased class II antigen expression on APCs, and induction of high endothelial venules.

73. The answer is a. *(Cotran, pp 193–194.)* CD8+ cytotoxic T lymphocytes can recognize a foreign antigen only if that antigen is complexed to self-class I antigens. In general these class I molecules bind to proteins synthesized within the cell; one example is the cellular production of viral antigens. The CD8 molecule of the cytotoxic T cell binds to the nonpolymorphic portion of the class I molecule, while the T cell receptor on the surface of the T lymphocyte binds to a complex formed by the peptide fragment of the antigen and the class I antigen. In contrast, CD4+ helper T lymphocytes can recognize a foreign antigen only if that antigen is complexed to self-class II antigens. In general, class II antigens present foreign antigens that have been processed within the cell in endosomes or lysosomes; one example is bacteria. Macrophages and neutrophils are active phagocytes and have receptors for the Fc portion of IgG and C3b; both of these substances are important opsonins. Macrophages also ingest and present antigens to T cells in conjunction with surface class II antigens.

74. The answer is a. *(Cotran, pp 195, 1252–1253.)* A variety of different diseases have an association with certain HLA types. The exact mechanism of this association is unknown. These diseases can be grouped into three broad categories: inflammatory diseases, such as ankylosing spondylitis (associated with HLA-B27); inherited errors of metabolism, such as hemochromatosis (associated with HLA-A3); and autoimmune diseases, which are usually associated with the DR locus. Two examples of the latter are the associations of rheumatoid arthritis with DR4 and of insulin-dependent diabetes with DR3/DR4. Ankylosing spondylitis is one type of spondyloarthropathy that lacks the rheumatoid factor found in rheumatoid arthritis. Other seronegative spondyloarthropathies include Reiter's syndrome, psoriatic arthritis, and enteropathic arthritis. All of these are associated with an increased incidence of HLA-B27. Ankylosing spondylitis, also known as rheumatoid spondylitis or Marie-Strümpell disease, is a chronic inflammatory disease that primarily affects the sacroiliac joints of adult males.

75. The answer is d. *(Cotran, pp 196–199.)* Hypersensitivity diseases are caused by immune mechanisms. They are classified into four different cat-

egories based on the immune mechanisms involved. Type I hypersensitivity reactions involve IgE (reaginic) antibodies that have been bound to the surface of mast cells and basophils. These IgE antibodies are formed by a T cell–dependent process. An allergen initially binds to antigen-presenting cells, which then stimulate T_H2 cells to secrete interleukin 4 (IL-4), IL-5, and IL-6. IL-5 stimulates the production of eosinophils, while IL-4 stimulates B cells to transform into plasma cells and produce IgE. This IgE then attaches to mast cells and basophils, because these cells have cell surface receptors for the Fc portion of IgE. When these "armed" mast cells or basophils are reexposed to the allergen, the antigen bridges two IgE molecules and causes mast cells to release preformed (primary) mediators. This antigen-to-antibody binding also causes these cells to synthesize secondary mediators.

The reactions that occur as a result of the primary mediators of type I hypersensitivity are rapidly occurring, since the mediators have already been made and are present within the granules of mast cells. These substances include biogenic amines, such as histamine, chemotactic factors, enzymes, and proteoglycans. Histamine causes increased vascular permeability, vasodilation, and bronchial smooth muscle contraction. The chemotactic factors are chemotactic for eosinophils and neutrophils. Mast cells also produce new products (secondary mediators) via a series of reactions within the cell membrane that lead to the generation of lipid mediators and cytokines. The lipid mediators are generated from arachidonic acid. Membrane receptors bound to IgE activate phospholipase A_2, which then cleaves membrane phospholipids into arachidonic acid. Lipoxygenase produces leukotrienes, including LTB_4 and leukotrienes C_4, D_4, and E_4. These last three leukotrienes are the most potent vasoactive and spasmogenic agents known. They used to be called slow reactive substance of anaphylaxis (SRS-A). Prostaglandin D_2, which is produced via the enzyme cyclooxygenase, is abundant in lung mast cells. It causes bronchospasm and increased mucus production.

Type I reactions may be either local or systemic. Local reactions include urticaria (hives), angioedema, allergic rhinitis (hay fever), conjunctivitis, food allergies, and allergic bronchial asthma. Systemic reactions usually follow parenteral administration of antigen, such as with drug reactions (penicillin) or insect stings. The amount of antigen may be very small. Symptoms include vomiting, cramps, diarrhea, itching, wheezing, and shortness of breath, and death may occur within minutes. The main treatment is epinephrine.

76. The answer is d. *(Cotran, pp 199–201.)* A blood transfusion reaction is a type II hypersensitivity reaction that is mediated by antibodies reacting against antigens present on the surface of blood group antigens or irregular antigens present on the donor's red blood cells. Type II hypersensitivity reactions result from attachment of antibodies to changed cell surface antigens or to normal cell surface antigens. Complement-mediated cytotoxicity occurs when IgM or IgG binds to a cell surface antigen with complement activation and consequent cell membrane damage or lysis. Blood transfusion reactions and autoimmune hemolytic anemia are examples of this form. Systemic anaphylaxis is a type I hypersensitivity reaction in which mast cells or basophils that are bound to IgE antibodies are reexposed to an allergen, which leads to a release of vasoactive amines that causes edema and broncho- and vasoconstriction. Sudden death can occur. Systemic immune complex reactions are found in type III reactions and are due to circulating antibodies that form complexes upon reexposure to an antigen (such as foreign serum), which then activates complement. This process is followed by chemotaxis and aggregation of neutrophils, which leads to release of lysosomal enzymes and eventual necrosis of tissue and cells. Serum sickness and Arthus reactions are examples of type III reactions. Delayed type hypersensitivity is type IV and is due to previously sensitized T lymphocytes, which release lymphokines upon reexposure to the antigen. This takes time—perhaps up to several days following exposure. The tuberculin reaction is the best-known example. T cell–mediated cytotoxicity leads to lysis of cells by cytotoxic T cells in response to tumor cells, allogenic tissue, and virus-infected cells. These cells have CD8 antigens on their surfaces.

77. The answer is b. *(Cotran, pp 201–206.)* Type IV hypersensitivity reactions do not involve antibody formation, and instead are mediated by T cells (cell-mediated hypersensitivity). There are two subtypes of type IV hypersensitivity reactions, one of which involves CD4+ cells [delayed type hypersensitivity (DTH)] and the other of which involves CD8+ cells (cell-mediated cytotoxicity). Upon first exposure to the antigen in DTH reactions, macrophages ingest the antigen and process it in association with class II antigens (HLA-D) to these helper cells (CD4). Upon reexposure to the antigen, these CD4+ cells are activated and secrete biologically active factors (the lymphokines). Specifically, CD4 T_H1 cells are activated and secrete interferon γ, interleukin 2, and TNF-α. Interferon γ activates macrophages (epithelioid cells) and forms granulomas (caseating or non-

caseating). Interleukin 2 activates other CD4 cells, while TNF-α causes endothelial cells to increase production of prostacyclin and ELAM-1. The classic example of a DTH reaction is the tuberculin skin test (Mantoux reaction). A local area of erythema and induration peaks at about 48 h following intracutaneous injection of tuberculin. Granulomatous inflammation (with epithelioid cells), poison ivy reactions, and contact dermatitis are types of delayed type hypersensitivity. Contact dermatitis is often the result of sensitivity to nickel, which can be found in some watchbands. With T cell–mediated cytotoxicity, sensitized T cells (CD8) by themselves kill antigen-bearing target cells. These cells are called cytotoxic T lymphocytes (CTLs). These CTLs, directed against modified surface HLA antigens, play a role in viral infections, tumors, and graft rejection.

A linear immunofluorescence pattern is consistent with a type II hypersensitivity reaction, while a granular pattern is seen with a type III hypersensitivity reaction. The latter may also reveal fibrinoid necrosis around blood vessels, while eosinophils in an allergic nasal polyp are an example of a type I hypersensitivity reaction.

78. The answer is c. *(Damjanov, pp 655–658.)* An allograft is also called a homograft and refers to a graft between members of the same species. An autograft is a tissue graft taken from one site and placed in a different site in the same individual. Isografts are grafts between individuals from an inbred strain of animals. A graft between individuals of two different species is a xenograft or heterograft.

79. The answer is e. *(Cotran, pp 206–211.)* The rejection of organ transplants involves both humoral and cell-mediated immunologic reactions. Hyperacute rejection, due to preformed host antibodies that are directed against antigens of the graft, occurs within minutes after transplantation. Histologically, neutrophils are found within the glomerulus and peritubular capillaries. These changes illustrate an antigen-antibody reaction at the vascular endothelium, similar to the Arthus reaction. Acute rejection may occur within days or much longer after transplantation. It is called acute because once it begins, the changes progress rapidly. Acute rejection can result from vasculitis or interstitial lymphocytic infiltration. The vasculitis is the result of humoral rejection (acute rejection vasculitis), while the interstitial mononuclear infiltrate is the result of cellular rejection (acute cellular rejection). Acute cellular rejection is responsive to immunosup-

pressive therapy, but acute rejection vasculitis is not. Subacute rejection vasculitis occurs during the first few months after transplantation and is characterized by the proliferation of fibroblasts and macrophages in the tunica intima of arteries. In chronic rejection, tubular atrophy, mononuclear interstitial infiltration, and vascular changes are found. The vascular changes are probably the result of the proliferative arteritis seen in acute and subacute stages. The vascular obliteration leads to interstitial fibrosis and tubular atrophy, resulting in loss of renal function.

In contrast, graft-versus-host (GVH) disease occurs when immunocompetent lymphocytes from the donor, usually from bone marrow or liver, attack the recipient's tissue. GVH may be acute or chronic. Acute GVH is manifested by changes in the skin (dermatitis), the intestines (diarrhea, malabsorption), and the liver (jaundice). Chronic GVH produces changes in the skin (fibrosis) that are similar to the skin changes seen in patients with progressive systemic sclerosis.

80. The answer is e. *(Cotran, pp 211–218.)* Autoantibodies can be directed against antigens in the nucleus or cytoplasm, or they can be directed against certain cells, proteins, structural antigens, or receptors. Autoantibodies against nuclear antigens (antinuclear antibodies or ANAs) are can be grouped into several categories. Antibodies may be directed against DNA, histones, nonhistone proteins bound to RNA, or nucleolar antigens. Antibodies to double-stranded DNA are specific for patients with SLE. Non-DNA nuclear components, called extractable nuclear antigens, include Sm antigen, ribonucleoprotein, SS-A and SS-B reactive antigens, and Scl-70. Autoantibodies to Smith antigen are specific for patients with SLE, antibodies to Scl-70 are specific for patients with progressive systemic sclerosis, and antibodies to either SS-A or SS-B or specific for patients with Sjögren's syndrome. Anticentromere antibodies are found in patients with systemic sclerosis, especially in a subset of patients with the CREST syndrome.

Antimitochondrial antibodies are found in the majority of patients with primary biliary cirrhosis. Anti-smooth-muscle antibodies are characteristic of lupoid autoimmune hepatitis. Antineutrophil cytoplasmic antibodies (ANCAs) may be directed against myeloperoxidase or proteinase 3. The former produces a perinuclear pattern (P-ANCAs) and is seen in some patients with Wegener's granulomatosis, but more often is associated with microscopic polyarteritis nodosa. The latter type of ANCA produces a cyto-

plasmic pattern (C-ANCAs) and is seen mainly in patients with Wegener's granulomatosis. Antibodies to parietal cells of the stomach and intrinsic factor are seen in pernicious anemia, while antibodies to the microvasculature of muscle are seen in dermatomyositis. Autoantibodies to IgG (called rheumatoid factor) are present in patients with rheumatoid arthritis. This type of antibody may also be seen in patients with other types of autoimmune diseases. Antibodies to thyroglobulin are seen in Hashimoto's thyroiditis, while antibodies against type IV collagen, which is found in the basement membranes of the lung and glomerulus, are seen in Goodpasture's disease. Antibodies to antigens found in the intercellular space of the epidermis are seen with pemphigus vulgaris, while antibodies to antigens found in the epidermal basement membrane are seen with bullous pemphigoid. Acetylcholine receptor antibodies are seen with myasthenia gravis, thyroid hormone receptor antibodies are seen with Grave's disease, and insulin receptor antibodies are seen with diabetes mellitus.

81. The answer is a. *(Cotran, pp 216–225.)* Systemic lupus erythematosus (SLE) is a chronic, remitting and relapsing, often febrile multisystem disorder that predominantly affects the skin, kidneys, serosal membranes, and joints. Histologic sections of affected areas reveal vascular lesions with fibrinoid deposits consisting of accumulations of pink-staining homogeneous masses of fibrin, immunoglobulins, and other plasma proteins. SLE has a strong female predominance (10:1), and the disease usually arises in the second and third decades. There is a positive association between SLE and HLA-DR2 and DR3. Some drugs, especially procainamide and hydralazine, cause an SLE-like syndrome. Patients with hereditary C2 or C4 deficiencies also develop a lupuslike syndrome. Patients with SLE have marked B cell hyperactivity. This leads to a polyclonal production of antibodies to self and nonself antigens. Several autoantibodies to both nuclear and cytoplasmic cell components have been found, but antinuclear antibodies (ANAs) are the hallmark of SLE. Most of the visceral lesions in SLE result from the deposition of immune complexes; this is an example of a type III hypersensitivity reaction. The classic lesion involving the skin is an erythematous lesion over the bridge of the nose producing a "butterfly" pattern. Sunlight makes the rash worse. Histologically there is liquefactive degeneration of the basal layer of the epidermis with a perivascular lymphoid infiltrate. Deposits of immunoglobulin and complement can be demonstrated at the dermoepidermal junction. Finding immunoglobulin

deposits in uninvolved skin is considered highly specific for SLE; this is called the lupus band test. The most common symptom is caused by involvement of the joints (arthritis), which produces a nonerosive synovitis. The heart may also be involved in patients with SLE. Small vegetations may develop on the heart valves and are called Libman-Sacks endocarditis. The major cause of death in patients with SLE is involvement of the kidneys leading to renal failure. There are deposits of DNA–anti-DNA complexes within the glomeruli. These deposits are found within the mesangium as well as in subendothelial and subepithelial locations. The subendothelial deposits produce wire-loop lesions and are particularly important. Other sites of involvement include the CNS, which may be life-threatening, and serous membranes, which can produce pleuritis and pleural effusions.

In contrast, Congo red–positive extracellular deposits in the liver are diagnostic of amyloidosis; trouble swallowing with sclerodactyly is suggestive of progressive systemic sclerosis; the combination of dry eyes, a dry mouth, and enlarged salivary glands is suggestive of Sjögren's syndrome; and periorbital lilac discoloration with erythema on the dorsal portion of her hands is suggestive of dermatomyositis.

82. The answer is c. *(Cotran, pp 226–229.)* The combination of trouble swallowing, hypertension, and sclerosis of the skin should raise the possibility of progressive systemic sclerosis (scleroderma), a multisystem disease that involves the cardiovascular, gastrointestinal, cutaneous, musculoskeletal, pulmonary, and renal systems through progressive interstitial fibrosis. Small arterioles in the aforementioned systems show obliteration caused by intimal hyperplasia accompanied by progressive interstitial fibrosis. Evidence implicates a lymphocyte overdrive of fibroblasts to produce an excess of rather normal collagen. Eventually myocardial fibrosis, pulmonary fibrosis, and terminal renal failure ensue. Over half of these patients have dysphagia with solid food caused by distal esophageal narrowing.

83. The answer is a. *(Cotran, pp 251–257.)* Amyloid is a generic term that describes special properties of any protein having a tertiary structure that produces a β-pleated sheet. Amyloid stains brown with iodine ("starchlike"). Histologically, the deposits always begin between or outside of cells. Eventually the amyloid deposits may strangle the cells, leading to

atrophy or cell death. The histologic diagnosis of amyloid is based solely on its special staining characteristics. It stains pink with the routine hematoxylin and eosin stain, but, with Congo red stain, amyloid stains dark red and has an apple-green birefringence when viewed under polarized light. There are many different types of proteins that stain as amyloid, and these are associated with a wide variety of diseases. These diseases may be either systemic, such as with immune dyscrasias, reactive diseases, or hemodialysis, or they may be localized, such as with senile or endocrine disorders. Immune dyscrasias, such as multiple myeloma or B cell lymphomas, secrete amyloid light (AL) chains, while reactive systemic diseases secrete amyloid-associated (AA) protein. This protein is a polypeptide derived from serum amyloid-associated protein, which is produced in the liver. Systemic deposits of AA protein complicate various chronic infections and inflammatory processes, most commonly rheumatoid arthritis, other connective tissue diseases, bronchiectasis, and inflammatory bowel disease. Patients on chronic hemodialysis may develop amyloid deposits consisting of β_2-microglobulin. Patients with senile cardiac disease may develop amyloid deposits in the heart consisting of amyloid transthyretin (ATTR), while patients with senile cerebral disease, such as Alzheimer's disease, may develop amyloid deposits in the brain consisting of β_2-amyloid protein. Do not confuse β_2-amyloid protein with β_2-microglobulin, a component of the MHC class I molecule. Patients with medullary carcinoma of the thyroid, a malignancy of the calcitonin-secreting parafollicular C cells of the thyroid, characteristically have amyloid deposits of procalcitonin within the tumor. Patients with type II diabetes mellitus may have amyloid deposits within pancreatic islets consisting of islet amyloid polypeptide.

84. The answer is e. *(Flake, N Engl J Med 335(24): 1806–1810, 1996. Cotran, pp 235–236.)* Patients with severe combined immunodeficiency disease (SCID) have defects of lymphoid stem cells involving both T cells and B cells. These patients have severe abnormalities of immunologic function with lymphopenia. They are at risk for infection with all types of infectious agents, including bacteria, mycobacteria, fungi, viruses, and parasites. Patients have a skin rash at birth, possibly due to a graft-versus-host reaction from maternal lymphocytes. Patients are particularly prone to chronic diarrhea, due to rotavirus and bacteria, and to oral candidiasis. About 50% of patients with the autosomal recessive form (Swiss type) lack the enzyme adenosine deaminase (ADA) in their red cells and leukocytes. This leads to

accumulation of adenosine triphosphate and deoxyadenosine triphosphate, both of which are toxic to lymphocytes. The other form of SCID is an X-linked form due to a defect in the IL-2 receptor.

85. The answer is e. *(Cotran, pp 236–251, 359–360. Ayala, pp 255–256.)* Acquired immunodeficiency syndrome (AIDS) is caused by infection with the human immunodeficiency virus (HIV), which is an RNA retrovirus. The major genes of HIV are *gag, pol,* and *env. gag* encodes for precursor protein p55, which is processed by viral protease into other components that include p24 (the major core protein) and p7 (nucleocapsid). *pol* encodes viral enzymes including protease, reverse transcriptase, and integrase. Reverse transcriptase is an RNA-dependent DNA polymerase that converts viral RNA to DNA so it can be integrated into the host DNA. *env* encodes for envelope proteins, including gp120 and gp41. Levels of antibodies to gp120 are used to monitor the course of infection, while levels of p24 are used to measure virus load in the blood. HIV enters certain cells by binding to CD4 protein. The molecule on HIV that mediates this attachment is gp120 (a glycoprotein with a molecular weight of 120 kD). An additional ligand that is a cytokine receptor is also necessary for entry into cells. For example, after binding to CD4, new recognition sites on gp120 must bind to CCR5, which is the receptor for β-chemokine. Therefore, individuals homozygous for defective CCR5 are resistant to infection by HIV. After being infected with HIV, the CD4+ lymphocytes die. This results in a characteristic decrease in the peripheral CD4/DC8 cell ratio (which is normally about 2:1). CD4 is also present on other types of cells that may be reservoirs of HIV, including monocytes, macrophages, microglial cell of CNS, follicular dendritic cells of lymph nodes, and Langerhans cells of skin. In contrast to HIV, herpesviruses are large, encapsulated viruses that contain double-stranded DNA. Types of herpesviruses include HSV-1, HSV-2, varicella-zoster virus (VZV), CMV, human herpesvirus 6 (HHV-6, which causes a benign skin rash in infants), HHV-7, EBV, and HHV-8 (which causes Kaposi's sarcoma).

86. The answer is d. *(Cotran, pp 261–264. Chandrasoma, pp 264–268.)* The names given to tumors are based on the parenchymal component of the tumor, which consists of the proliferating neoplastic cells. In general, benign tumors are designated by using the suffix *-oma* attached to a name describing either the cell of origin of the tumor or the gross or micro-

scopic appearance of the tumor. Examples of benign tumors whose names are based on their microscopic appearance include adenomas, which have a uniform proliferation of glandular epithelial cells; papillomas, which are tumors that form finger-like projections; fibromas, which are composed of a uniform proliferation of fibrous tissue; leiomyomas, which originate from smooth muscle cells and have elongated, spindle-shaped nuclei; hemangiomas, which are formed from a uniform proliferation of endothelial cells; and lipomas, which originate from adipocytes. The suffix *-oma* is unfortunately still applied to some tumors that are not benign. Examples of this misnaming include melanomas, lymphomas, and seminomas.

87. The answer is e. *(Cotran, pp 261–264.)* Malignant tumors are generally classified as being either carcinomas or sarcomas. Carcinomas are malignant tumors of epithelial origin, while sarcomas are malignant tumors of mesenchymal tissue. Examples of malignant epithelial tumors (carcinomas) include adenocarcinomas, which consist of a disorganized mass of malignant cells that form glandular structures, and squamous cell carcinomas, which consist of a disorganized mass of malignant cells that produce keratin. Examples of malignant mesenchymal tumors include rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas, and liposarcomas. One clue that a tumor has developed from skeletal muscle, such as a rhabdomyosarcoma, is the presence of cross-striations. These individual cells, seen histologically, are called strap cells. The wall of the stomach consists of smooth muscle, and a tumor that originates from these smooth-muscle cells will consist of proliferating cells with elongated, spindle-shaped nuclei. If a tumor of this type is benign it is called a leiomyoma, while if it is malignant it is called a leiomyosarcoma. This distinction is based on the number of mitoses that are present and the degree of atypia displayed by the neoplastic cells.

88. The answer is b. *(Cotran, pp 264–268. Chandrasoma, pp 260–264.)* Several gross and microscopic features help to differentiate benign neoplasms from malignant neoplasms. Benign neoplasms grow slowly with an expansile growth pattern that often forms a fibrous capsule. This histologic feature can also be useful in distinguishing a benign neoplastic lipoma from normal nonneoplastic adipose tissue. Benign neoplasms characteristically remain localized and do not metastasize. Histologically, benign neoplastic

cells tend to be uniform and well differentiated; that is, they appear similar to their tissue of origin. This histologic feature may not distinguish between benign neoplasms and normal tissue. In contrast to benign tumors, malignant neoplasms grow rapidly in a crablike pattern and are capable of metastasizing. Histologically, the malignant cells are pleomorphic because they differ from one another in size and shape. These cells have hyperchromatic nuclei and an increased nuclear-to-cytoplasmic ratio. Malignant cells tend to have nucleoli, and mitoses may be frequent. These two features only indicate rapidly proliferating cells and can also be seen in reactive or reparative processes. The mitoses in malignancies, however, tend to be atypical, such as tripolar mitoses. Malignant tumors are graded by their degree of differentiation as well differentiated, moderately differentiated, or poorly differentiated. Marked pleomorphism is described as anaplasia. This histologic feature is usually seen in poorly differentiated or undifferentiated malignancies.

89. The answer is d. *(Cotran, pp 1048–1053.)* Some epithelial malignancies (carcinomas) are preceded by disordered growth (dysplasia) of the epithelium. One example of this is the development of squamous cell carcinoma of the uterine cervix. The normal cervix is lined by a stratified layer of squamous epithelium, while the endocervix is composed of mucus-secreting columnar epithelial cells. In response to chronic inflammation, the columnar epithelial cells change to stratified squamous epithelial cells. This change—squamous metaplasia—is characterized histologically by normal-appearing stratified squamous epithelium overlying endocervical glands. Next, infection with human papillomavirus (HPV) causes dysplastic changes within the epithelium. These dysplastic changes are characterized by disorganized stratified squamous epithelium with mitoses located above the basal layers of the epithelium. The cells themselves are pleomorphic and have hyperchromatic nuclei. The intraepithelial dysplasia is divided into three types based on the degree of dysplasia present and the location of mitoses. In mild dysplasia there are mitoses in the basal one-third of the epithelium; in moderate dysplasia mitoses occur in the middle one-third of the epithelium; and in severe dysplasia there are mitoses in the upper one-third of the epithelium. When the dysplastic changes involve the full thickness of the epithelium, it is referred to as carcinoma in situ (CIS). Next, the neoplastic cells start to invade the underlying tissue, forming an invasive squamous cell carcinoma.

90. The answer is c. *(Cotran, pp 263, 293, 1046.)* The most common histologic type of cancer at a given site generally reflects the normal histology of that site. For example, squamous cell carcinomas arise in organs that are normally lined by stratified squamous epithelium. That is, sites associated with the development of squamous cell carcinoma include the skin, lung, esophagus, and cervix. Adenocarcinomas arise from glandular epithelium, and therefore sites associated with the development of adenocarcinoma include the lung, colon, stomach, prostate, and endometrium. Sites for transitional cell carcinoma include the urinary bladder and kidney (renal pelvis). Two types of cancer associated with special sites include clear cell carcinoma and signet cell carcinoma. Sites for clear cell carcinoma include the kidney (renal cortex) and vagina, the latter being associated with previous diethylstilbestrol (DES) exposure, while signet cell carcinoma is seen in the stomach and ovaries. In this malignancy the cells infiltrate individually instead of forming recognizable glandular structures. Each individual cell is filled with a large drop of mucin, which pushes the nucleus to the side, giving it the appearance of a signet ring.

91. The answer is a. *(Cotran, pp 277–279. Rubin, pp 173–183.)* Many cancers originate in association with the abnormal activation of cellular proto-oncogenes (p-oncs), which are cellular genes that promote normal growth and differentiation. The protein product of a proto-oncogene is often a growth factor, a growth factor receptor, or a protein kinase. A cellular proto-oncogene may function as a cellular oncogene (c-onc) if it produces more of its protein product than it normally should. These normal cellular proto-oncogenes may become oncogenic (tumor-forming) by several mechanisms, including gene mutations, translocations, amplification, or interaction with viruses. Increased transcription of proto-oncogenes can result from the integration of viral controller sequences into cellular DNA; this process is associated with retroviruses. These RNA viruses are characterized by having three specific genes: *gag* (which codes for core protein), *pol* (which codes for the polymerase reverse transcriptase), and *env* (which codes for the envelope protein). In addition, these genes are flanked by long terminal repeat units (LTRs), which can turn on genes that are located near to the LTRs. These LTRs can turn on nearby p-oncs (making them c-oncs) by either a slow process of a fast process. The fast way involves first incorporating these proto-oncogenes into the genome of acute-transforming retroviruses by a process called retroviral transduc-

tion. These oncogenes are transduced (captured) by the virus through a chance recombination with the DNA of a normal host cell. These gene sequences within these viruses, now called viral oncogenes (v-oncs), are capable of rapid induction of tumors because, being located within the viral genome, they are always located near the LTRs. This process is called acute transformation. It is important to note also that these acute-transforming viruses do not contain the *pol* gene, so they cannot replicate on their own. Proto-oncogenes may also become oncogenic via slow-transforming viruses, which by chance can be inserted near a proto-oncogene. These viruses may either induce a structural change in the cellular gene (converting it into a cellular oncogene, or c-onc), or the retroviral promoters may turn on the cellular gene (by means of the viral LTRs). This process is called insertional mutagenesis.

92. The answer is a. *(Cotran, pp 280–282. Rubin, pp 173–183.)* Oncoproteins, which are the protein products of oncogenes, are signal-transducing proteins that are located on the inner leaflet of the plasma membrane. They can be grouped into two major categories: guanosine triphosphate (GTP)–binding proteins and non-receptor-associated tyrosine kinases. GTP-binding proteins include the *ras* family and the G proteins. Mutation of the *ras* gene is the single most common abnormality of dominant oncogenes in human tumors and is found in about one-third of all human tumors. Normal *ras* protein (p21) flips back and forth between an activated, signal-transmitting form and an inactive state. In the inactive state, p21 binds GDP, but when cells are stimulated by growth factors, p21 becomes activated by exchanging GDP for GTP, and it can then stimulate MAP kinases and protein kinase C. In normal cells the activated sinal-transmitting stage of *ras* protein bound to GTP is transient because its intrinsic GTPase activity hydrolyzes GTP to GDP, which returns it to its inactive state. The GTPase activity of normal *ras* protein is accelerated by GTPase-activating proteins (GAPs), which function as brakes to prevent uncontrolled ras activity. Mutant *ras* proteins bind GAP, but their GTPase activity is not increased, trapping the mutant proteins in their excited, GTP-bound form.

93. The answer is c. *(Cotran, pp 284–286.)* There are several mechanisms through which proto-oncogenes (p-oncs) can become oncogenic (c-oncs). Normal cellular genes (proto-oncogenes) may become oncogenic by being

incorporated into the viral genome (forming v-oncs), or they may be activated by other processes to form cellular oncogenes (c-oncs). These other processes include gene mutations, chromosomal translocations, and gene amplifications. Gene mutations, such as point mutations, are associated with the formation of cancers by mutant *c-ras* oncogenes. Chromosomal translocations are associated with the development of many types of cancers, one example of which is Burkitt's lymphoma. The most common translocation associated with Burkitt's lymphoma is t(8;14), in which the *c-myc* oncogene on chromosome 8 is brought in contact with the immunoglobulin heavy chain gene on chromosome 14. Two other examples of chromosomal translocations are the association of chronic myelocytic leukemia (CML) with t(9;22), which is the Philadelphia chromosome, and the association of follicular lymphoma with the translocation t(18;14). The former involves the proto-oncogene *c-abl,* which is rearranged in proximity to a break point cluster region (bcr) on chromosome 22. The resultant chimeric *c-abl/bcr* gene encodes a protein with tyrosine kinase activity. The t(18;14) translocation involves the *bcl-2* oncogene on chromosome 18. Expression of the oncogene *bcl-2* is associated with the prevention of apoptosis in germinal centers. Examples of associations that involve gene amplification include *N-myc* and neuroblastoma, *c-neu* and breast cancer, and *erb-B* and breast and ovarian cancer. Gene amplifications can be demonstrated by finding doublet minutes or homogenous staining regions.

94. The answer is a. *(Cotran, pp 286–294.)* In contrast to proto-oncogenes, which are genes that encode for proteins stimulating cell growth, cancer suppressor genes (antioncogenes) encode for proteins that suppress cell growth. Examples of tumor suppressor genes are Rb (associated with retinoblastoma), p53, APC, NF1, DCC, and WT1. In general, these tumor suppressor genes encode proteins that can function as cell surface molecules, regulators of signal transduction, or regulators of nuclear transcription. The DCC gene codes for a cell surface molecule that can transmit negative signals such as contact inhibition. NF1 is associated with regulating signal transduction. It codes for a GAP that binds to a *ras* protein and then increases GTPase activity, which inactivates *ras* product. Loss of normal NF1 functioning causes *ras* to be trapped in an active state. Genes that regulate nuclear transcription include Rb, p53, and WT1. Products of these genes are found within the nucleus and are involved in regulation of the cell cycle. The product of the Rb gene is a nuclear phosphoprotein that reg-

ulates the cell cycle at several points. It exists as an active unphosphorylated form (pRb) and an inactive phosphorylated form (pRb-P). The active unphosphorylated form (pRb) normally stops the cell cycle at G1 going to S. It does this by binding to transcription factors such as the product of *c-myc* and the E2F protein. When pRb is phosphorylated, the cell can enter S and complete the cell cycle. Inactivation of the pRb stop signal causes the cell to continually cycle and undergo repeated mitosis. The product of the p53 gene is also a nuclear protein that regulates DNA replication. The normal p53 prevents the replication of cells with damaged DNA. It does this by pausing cells during G1 (before S), giving the cells time to repair the damaged DNA. The p53 gene, located on chromosome 17, is the single most common target for genetic alterations in human cancers. It is found in many cases of colon, breast, and lung cancers. Mutations in the adenomatous polyposis coli (APC) gene lead to the development of tumors that may progress to adenocarcinomas of the colon, while deletion of WT1, located on chromosome 11, is associated with the development of Wilms tumor, a childhood neoplasm of the kidney.

95. The answer is d. *(Cotran, pp 309–315.)* Ultraviolet rays are associated with the formation of skin cancers, including squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. The ultraviolet portion of the spectrum (ultraviolet rays) is divided into three wavelength ranges: UVA (320 to 400 nm), UVB (280 to 320 nm), and UVC (200 to 280 nm). UVB is the wavelength range that is responsible for the induction of skin cancers. The carcinogenic property of UVB is related to the formation of pyrimidine dimers in DNA. UVC, although a potent mutagen, is not significant because it is filtered out by the ozone layer around the earth.

Some DNA viruses and RNA viruses are associated with the development of dysplasia and malignancy. For example, infection with human papillomavirus (HPV), especially types 16 and 18, is associated with cervical dysplasia; Epstein-Barr virus (EBV) is associated with Burkitt's lymphoma and nasopharyngeal carcinoma; hepatitis B virus (HBV) and hepatitis C virus (HCV) are associated with primary hepatocellular carcinoma; and HHV-8 is associated with Kaposi's sarcoma. HTLV-I is an RNA retrovirus that is associated with the formation of a peculiar type of hematologic malignancy called adult T cell leukemia/lymphoma. These patients have malignant cells in their lymph nodes and blood. This malignancy is endemic in southern Japan and the Caribbean region.

96. The answer is a. *(Cotran, pp 275–276, 296, 310.)* Hereditary factors are important in the development of many types of cancers. They are particularly important in several inherited neoplasia syndromes. The autosomal recessive DNA-chromosomal instability syndromes include ataxia-telangiectasia, Bloom's syndrome, Fanconi's anemia, and xeroderma pigmentosa. These disorders have in common abnormalities involving the normal repair of DNA. Patients with xeroderma pigmentosa have defective endonuclease activity, which normally repairs the pyrimidine dimers found in DNA damaged by ultraviolet (UV) light. These patients have an increased incidence of skin cancers, including basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Wiskott-Aldrich syndrome, characterized by thrombocytopenia and eczema, is an immunodeficiency disease associated with an increased incidence of lymphomas and acute leukemias. Familial polyposis is characterized by the formation of numerous neoplastic adenomatous colon polyps. These individuals have a 100% risk of developing colorectal carcinoma unless surgery is performed. Sturge-Weber syndrome is a rare congenital disorder associated with venous angiomatous masses in the leptomeninges and ipsilateral port-wine nevi of the face. Multiple endocrine neoplasia (MEN) syndrome type 1 (Wermer's syndrome) refers to the combination of adenomas of the pituitary, adenomas or hyperplasia of the parathyroid glands, and islet cell tumors of the pancreas.

97. The answer is c. *(Cotran, pp 271–273, 799. Rubin, pp 207–210.)* There are marked differences in the incidence of various types of cancer in different parts of the world. The highest rates for gastric carcinoma are found in Japan, Chile, China, and Russia, while it is much less common in the United States, the United Kingdom, Canada, and France. The high rates for gastric cancer in Japan might be related to dietary factors, such as eating smoked and salted foods. Other examples of geographic variations in the incidence of neoplasms include nasopharyngeal carcinoma, liver cancer, and trophoblastic disease. Nasopharyngeal carcinoma, associated with the Epstein-Barr virus, is rare in most parts of the world, except for parts of the Far East, especially China. Liver cancer is associated with both hepatitis B infection and high levels of aflatoxin B1. It is endemic in large parts of Africa and Asia. Trophoblastic diseases, including choriocarcinoma, have high rates of occurrence in the Pacific rim areas of Asia. In contrast, Asian populations have a very low incidence of prostate cancer.

98. The answer is b. *(Henry, pp 483–490, 677–679. Cotran, pp 323–325.)* Tumor markers are a diverse group of biochemical substances associated with the presence of some tumors. These tumor markers include hormones, oncofetal antigens, isozymes, proteins, mucins, and glycoproteins. Carcinoembryonic antigen (CEA) is a glycoprotein associated with many cancers including adenocarcinomas of the colon, pancreas, lung, stomach, and breast. It is used clinically to follow up patients with certain malignancies, such as colon cancer, and to evaluate them for recurrence or metastases. Human chorionic gonadotropin (hCG) is a hormone associated with trophoblastic tumors, especially choriocarcinoma. α fetoprotein (AFP) is a glycoprotein synthesized by the yolk sac and the fetal liver and is associated with yolk sac tumors of the testes and liver cell carcinomas. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are associated with cancer of the prostate. Chloroacetate esterase (CAE), not to be confused with CEA, is a histochemical stain used in the differentiation of acute leukemias. It is not considered to be a tumor marker.

99. The answer is b. *(Cotran, pp 359–361, 1038–1039. Rubin, pp 366–373. Chandrasoma, p 805.)* The cytopathic effect of viruses is often a clue to the diagnosis of the type of infection that is present. There are several types of herpesviruses, which are relatively large, double-stranded DNA viruses. Infection by herpes simplex virus (HSV) or varicella-zoster virus (VZV) is recognized by nuclear homogenization (ground-glass nuclei), intranuclear inclusions (Cowdry type A bodies), and the formation of multinucleated cells. Herpes simplex type 2, a sexually transmitted viral disease, results in the formation of vesicles that ulcerate and cause burning, itching, and pain. These lesions heal spontaneously, but the virus remains dormant in the lumbar and sacral ganglia. Recurrent infections may occur, and transmission to the newborn during delivery is a feared complication that may be fatal to the infant. Shingles and chickenpox are caused by herpes zoster, which is identical to varicella. Cytomegalovirus (CMV) causes both the nucleus and the cytoplasm of infected cells to become enlarged. Infected cells have large, purple intranuclear inclusions surrounded by a clear halo and smaller, less prominent basophilic intracytoplasmic inclusions. Adenoviruses can produce similar inclusions, but the infected cells are not enlarged. Adenoviruses also produce characteristic smudge cells in infected respiratory epithelial cells. Human papillomavirus (HPV) infection may produce a characteristic effect that is called koilocytosis. Histologic

examination reveals enlarged squamous epithelial cells that have shrunken nuclei ("raisinoid") within large cytoplasmic vacuoles. Candidiasis is the most common fungal infection of the vagina and is especially common in patients who have diabetes or take oral contraceptives. *Candida* infection causes vulvar itching and produces a white discharge. Microscopic examination of the vaginal discharge reveals yeast and pseudohyphae. *T. vaginalis,* a large, pear-shaped, flagellated protozoan, causes severe vaginal itching with dysuria. It produces a thick yellow-gray discharge.

100. The answer is c. *(Damjanov, pp 886–887, 928–930. Duchin, N Engl J Med 330: 949–955.)* The *Hantavirus* genus belongs to the *Bunyaviridae* family and includes the causative agent of a group of diseases that occur throughout Europe and Asia and are referred to as hemorrhagic fever with renal syndrome. The characteristic features of this syndrome are hematologic abnormalities, renal involvement, and increased vascular permeability. Respiratory involvement is generally minimal in these diseases. Although several species of rodents in the United States are known to be infected with *Hantavirus,* no human cases were reported until an outbreak of severe, often fatal respiratory illness occurred in the United States in May 1993 in the Four Corners area of New Mexico, Arizona, Colorado, and Utah. This illness resulted from a new member of the genus *Hantavirus* that caused a severe disease characterized by a prodromal fever, myalgia, pulmonary edema, and hypotension. The main distinguishing feature of this illness, which is called *Hantavirus* pulmonary syndrome, is noncardiogenic pulmonary edema resulting from increased permeability of the pulmonary capillaries. Laboratory features common to both *Hantavirus* pulmonary syndrome and hemorrhagic fever with renal syndrome include leukocytosis, atypical lymphocytes, thrombocytopenia, coagulopathy, and decreased serum protein concentrations. Abdominal pain, which can mimic an acute abdomen, may be found in both *Hantavirus* pulmonary syndrome and hemorrhagic fever with renal syndrome.

Dengue fever virus is a type of flavivirus; flaviviruses which are similar to alphaviruses. Dengue fever (breakbone fever) is initially similar to influenza but then progresses to a rash, muscle pain, joint pain, and bone pain. It can produce a potentially fatal hemorrhagic disorder. Yellow fever virus, which causes yellow fever, is another flavivirus. It is spread by a mosquito and produces characteristic coagulative necrosis of liver acinar zone 2 (midzonal necrosis). The necrotic hepatocytes produced by the process

of apoptosis in the absence of inflammation result in Councilman bodies. Because of liver failure, patients become jaundiced (hence the term yellow fever) and may vomit clotted blood ("black vomit"). Another flavivirus is the cause of St. Louis encephalitis, which is spread by the *Culex* mosquito. Alphaviruses, a type of togavirus, are similar to flaviviruses. They are the prototypical arboviruses, which are arthropod-born viruses. Clinical diseases include eastern equine encephalitis (EEE), western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE). Ebola virus is a member of the *Filoviridae* family that causes a severe hemorrhagic fever. Outbreaks occur in Africa and typically make the national news.

101. The answer is c. *(Joklik, pp 1060–1063. Rubin, pp 361–364. Cotran, p 333.)* Human parvovirus may cause a serious aplastic crisis in patients with an underlying chronic hemolytic anemia. In children, infection with parvovirus produces a characteristic rash, called erythema infectiosum or fifth disease, which first appears on the face and is described as a "slapped-cheek" appearance. Human parvovirus infection in adults produces a nonspecific syndrome of fever, malaise, headache, myalgia, vomiting, and a transient rash. Arthralgia is more common in adults than in children. In contrast to parvovirus, rhinoviruses are the causative agents of the common cold (coryza). This infection is characterized by rhinorrhea, pharyngitis, cough, and low-grade fever. Parainfluenza viruses, single-stranded RNA viruses that kill ciliated respiratory epithelial cells, are the most common cause of croup, which is a disease of children that is characterized by a barking sound on inspiration. Rubeola virus, an RNA virus, is the cause of measles. After an incubation period of 10 to 21 days, measles is characterized by fever, rhinorrhea, cough, skin lesions, and mucosal lesions (Koplik spots). Rubella virus, another RNA virus, produces a mild, acute febrile illness, but if the infection occurs in the first trimester of pregnancy it can produce developmental abnormalities such as cardiac lesions, ocular abnormalities, deafness, and mental retardation.

102. The answer is d. *(Cotran, pp 717–721.)* Most cases of lobar pneumonia are caused by *S. pneumoniae* (reclassification of the pneumococcus). Streptococcal or pneumococcal pneumonia involves one or more lobes and is often seen in alcoholics or debilitated persons. Type 3 pneumococcus (*S. pneumoniae*) causes a virulent lobar pneumonia characterized by mucoid sputum, which is also seen in *K. pneumoniae*. *K. pneumoniae* (Friedländer's

bacillus) usually produces a bronchopneumonia, rather than lobar pneumonia, but this is clinically indistinguishable from pneumococcal lobar pneumonia. *Legionella* species cause a fibrinopurulent lobular pneumonia that tends to be confluent, almost appearing lobar.

103. The answer is d. *(Cotran, pp 334, 343, 369. Chandrasoma, pp 488, 794, 882–883.) Nocardia* (*N. asteroides*) and *Actinomyces* species are classified as filamentous soil bacteria, although they are often described among the fungi. *A. israelii* is a normal inhabitant of the mouth; it can be seen in the crypts of tonsillectomy specimens. *Actinomyces* is a branched, filamentous gram-positive bacteria. Two forms of disease produced by *Actinomyces* are cervicofacial actinomyces and pelvic actinomyces. The former consists of an indurated (lumpy) jaw with multiple draining fistulas or abscesses. Small yellow colonies called sulfur granules may be seen in the draining material. Histologic section reveals tangled masses of gram-positive filamentous bacteria. Cultures of *Actinomyces* grow as white masses with a domed surface, which is called a "molar tooth" appearance. Another filamentous gram-positive bacteria is *N. asteroides*. A characteristic that helps to differentiate these two is the fact that *Nocardia* is partially acid-fast. "Partial" means using weak mineral acids in the acid-fast stain. Nocardiae are aerobic and acid-fast, in contrast to *Actinomyces* species, which are strict anaerobes and not acid-fast. Inhaled nocardial bacteria produce lung or skin infections. Progressive pneumonia with purulent sputum and abscesses is suggestive of nocardiosis, especially if dissemination to the brain or subcutaneous tissue occurs. *Nocardia* is also one cause of mycetoma, a form of chronic inflammation of the skin that causes indurated abscesses with multiple draining sinuses. Patients who develop nocardiosis are often immunosuppressed, and transplant rejection, steroid therapy, AIDS, or alveolar proteinosis are often antecedent. Organisms in sputum, pus, or bronchial lavage specimens are gram-positive. A modified acid-fast stain should be used for diagnosis.

C. diphtheriae is a small, pleomorphic gram-positive bacillus that may have club-shaped swellings at either pole. These rods tend to arrange themselves at right angles, producing characteristic V or Y configurations described as "Chinese characters." *C. diphtheriae* produces a toxin that blocks protein synthesis by causing irreversible inactivation of elongation factor 2 (EF-2). This toxin can produce a pseudomembrane covering the larynx, which is difficult to peel away without causing bleeding, and heart

damage with fatty change. *L. monocytogenes* is a short, gram-positive, nonspore-forming bacillus that can produce neonatal disease or can result in stillbirth. Characteristics that are unique to *Listeria* include a tumbling motility on hanging drop and an umbrella-shaped motility pattern when a specimen is stabbed into a test tube agar slant.

104. The answer is d. *(Cotran, pp 387–388, 807–809.) Yersinia* (formerly called *Pasteurella*) is an important genus of gram-negative bacilli that causes a wide variety of human and animal disease, ranging from plague (*Y. pestis*) to acute mesenteric lymphadenitis (*Y. enterocolitica*) in older children and young adults. *Y. enterocolitica* infections also occur in the terminal ileum in young adults, causing an ileitis that produces inflammation not unlike that seen in some stages of Crohn's disease (regional enteritis). Since the organisms grow slowly on enrichment media, they may be overgrown by other coliforms at 37°C. The organisms may be isolated by means of cold enhancement at 4°C.

105. The answer is c. *(Chandrasoma, pp 799–806. Cotran, pp 361–364.)* Granuloma inguinale is a rare, sexually transmitted disease that is caused by *Calymmatobacterium donovani,* a small, encapsulated gram-negative bacillus. Infection results in a chronic disease that is characterized by superficial ulcers of the genital region. Regional lymph node involvement produces large nodular masses that develop extensive scarring. Specialized culture medium is available, but its use is not practical. Serologic tests are also not useful. Instead, histologic examination is used to demonstrate Donovan bodies, which are organisms within the cytoplasm of macrophages. They are seen best with silver stains or Giemsa's stain. Chancroid is an acute venereal disease that is characterized by painful genital ulcers with lymphadenopathy. It is caused by *Haemophilus ducreyi,* a small, gram-negative bacillus. Gram stains of the suppurative lesions or cultures on specialized media may be used to make the diagnosis. Serologic tests are not useful. *Neisseria gonorrheae,* a gram-negative diplococcus, causes gonorrhea, an acute suppurative infection of the genital tract. In males it produces a purulent discharge (urethritis) and dysuria. In women, it may be asymptomatic (50%), or it may produce infection of the cervix with accompanying vaginal discharge, dysuria, and abdominal pain. Ascending infections in women can lead to salpingitis, tuboovarian abscess, and pelvic inflammatory disease (PID). Fitz-Hugh–Curtis syndrome refers to perihep-

atitis infection. In newborns, infection acquired during birth can produce a purulent conjunctivitis (ophthalmia neonatorum). This disease has been prevented due to prophylactic therapy to newborn infants. A Gram stain of the urethral or cervical exudate may reveal the intracytoplasmic gram-negative diplococci, or the exudate can be cultured on special media. Serologic tests are not useful. Characteristically, *N. gonorrheae* produces acid from glucose, but not from maltose or lactose. The spirochete *T. pallidum,* the causative agent of syphilis, has not been grown on any culture media; therefore, other means are available to aid in the diagnosis of syphilis. Dark-field or immunofluorescence examination may be used to detect organisms in the genital ulcers of primary syphilis. Antibodies to cardiolipin, a substance in beef heart that is similar to a lipoid released by *T. pallidum,* are used to screen for syphilis. This is the basis of both the VDRL and the rapid plasma reagin (RPR) tests; however, these screening tests are not totally specific. *Chlamydia* species are obligate intracellular parasites that form elementary bodies and reticulate bodies. The former are small, extracellular, and infectious, while the latter are intracellular and noninfectious. Three *Chlamydia* species are *C. psittaci, C. pneumoniae,* and *C. trachomatis.* The last causes several human diseases including trachoma, inclusion conjunctivitis, nongonococcal urethritis, and lymphogranuloma venereum (LGV). Specialized culture media and direct examination procedures are available to aid in the diagnosis of these diseases. The regional lymph nodes in patients with lymphogranuloma venereum have a characteristic histologic appearance typified by necrotizing granulomas forming stellate areas of necrosis. Trachoma is the leading cause of blindness in underdeveloped countries. It is a chronic infection of the conjunctiva that eventually scars the conjunctiva and cornea. Lymphogranuloma venereum is a sexually transmitted disease that is characterized by the formation of a genital ulcer with local necrotizing lymphadenitis. The skin test for LGV is the Frei test, which consists of intradermal injection of LGV antigen. *C. psittaci* is the causative agent of psittacosis (parrot fever). It produces a severe pulmonary disease and should be suspected in patients with a history of bird contact, such as pet shop workers or parrot owners.

106. The answer is e. *(Cotran, pp 388–389, 1253, 1317.)* A localized skin rash in the summertime followed within a period of weeks by arthritis, especially involving less than three joints, should arouse suspicion of Lyme disease. This disorder was first described in the mid-1970s in Connecticut

when small clusters of cases of children who developed an illness resembling juvenile rheumatoid arthritis were first noted. The disease has now been shown to be caused by a spirochete, *Borrelia burgdorferi,* through the bite of a tick belonging to the genus *Ixodes.* The spirochete-infested ticks reside in wooded areas where there are deer and small rodents. The deer act as a wintering reservoir for the ticks. In the spring the tick larval stage emerges and evolves into a nymph, which is infective for humans if they are bitten. Adult ticks are also capable of transmitting the spirochete during questing. The bite is followed by a rash called erythema chronicum migrans, which may resolve spontaneously. However, many patients have a transient phase of spirochetemia, which may allow the spread of the spirochete to the meninges, heart, and synovial tissue. Originally thought to be confined to New England, Lyme disease has now been shown to be present in Europe and Australia as well. The spirochetes are sensitive to penicillin, erythromycin, and tetracycline.

107. The answer is e. *(Cotran, pp 195, 1252–1253.)* Seronegative spondyloarthropathies are spondyloarthropathies that lack the rheumatoid factor found in rheumatoid arthritis. These disorders include Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis, and enteropathic arthritis. All of these are associated with an increased incidence of HLA-B27. Reiter's syndrome refers to the triad of arthritis, nongonococcal urethritis, and conjunctivitis. It may be an autoimmune reaction to previous gastrointestinal or genitourinary infections. Causes of these gastrointestinal infections include *Shigella, Salmonella, Yersinia,* and *Campylobacter.* The organism causing the genitourinary infection is *Chlamydia.*

108. The answer is e. *(Cotran, pp 383–385, 535–537. Damjanov, pp 866–878.)* Rickettsia are obligate intracellular parasites that infect endothelial cells and produce symptoms as a result of vasculitis and formation of microthrombi. Serologic tests for rickettsia include complement fixation tests and the Weil-Felix agglutination reaction. The basis for the latter test is the fact that the sera of infected patients can agglutinate strains of *Proteus vulgaris.* There are numerous types of rickettsia that produce many different diseases. Examples include Rocky Mountain spotted fever (RMSF, caused by *R. rickettsii*), epidemic typhus (caused by *R. prowazekii* and spread by the human body louse *Pediculus humanus*), endemic typhus (caused by *R. typhi* and spread by lice), scrub typhus (caused by *R. tsutsug-*

amushi and spread by mites), ehrlichiosis, and Q fever (caused by *C. burnetii* and spread not by vectors but by inhalation of aerosols). RMSF is found not only in the Rocky Mountains, but also the southeastern and south central United States. The vector in the Rocky Mountains is the wood tick (*Dermacentor andersoni*), while in the southeast it is the dog tick (*Dermacentor variabilis*) and in the south central United States it is the Lone Star tick. The animal reservoirs for RMSF are wild rodents and dogs. The rash of RMSF characteristically begins peripherally and spreads centrally to the trunk and face. The pathology involves infection of blood vessels producing thrombosis. Intracellular bacilli form parallel rows in an end-to-end arrangement ("flotilla at anchor facing the wind"). Patients also develop muscle pain and high fever.

Bartonella infections are also characterized by proliferations of blood vessels. Examples of *Bartonella* include *B. quintana, B. henselae,* and *B. bacilliformis,* the causative agent of Oroya fever. *B. quintana* is spread by the human body louse and is the causative agent of trench fever (seen in the trenches of World War I) and bacillary angiomatosis. This latter term refers to a lesion seen in patients with AIDS consisting of a lobular proliferation of capillaries with abundant leukocytoclastic debris. *B. henselae* is the causative agent of cat-scratch fever. Histologically, this disease is characterized by the formation of stellate microabscesses with necrotizing granulomas.

109. The answer is c. *(Cotran, pp 385–387.)* Lepromatous and tuberculoid leprosy, the major forms of leprosy, are caused by infection with *Mycobacterium leprae*. Nerve involvement is most typical of the lepromatous form. Histologic sections reveal acid-fast bacilli within peripheral nerves. Numerous bacilli in packets within histiocytes (lepra cells) are also found in the lesions of lepromatous leprosy. Polyclonal hypergammaglobulinemia often occurs in lepromatous leprosy, in which patients do not have the adequate cellular immune response of the tuberculoid form. Large amounts of antilepra antibody occur in the lepromatous form with frequent formation of antigen-antibody complexes and resultant disorders such as erythema nodosum. A "clear" zone between infiltrate and overlying epidermis is characteristic of lepromatous leprosy, unlike the encroachment on basal epidermis of the tuberculoid infiltrate.

110. The answer is d. *(Cotran, pp 83–84, 349–352, 722–726.)* Tuberculosis (TB) is caused by infection with *M. tuberculosis*. Mycobacteriaceae are

slow-growing aerobic rods with cell walls rich in glycolipids, true waxes, and long-chain fatty acids called mycolic acids. The lipid-rich mycolic acid–containing cell wall is responsible for the unique staining properties of the mycobacteria, namely their impermeability to most basic dyes and their resistance to acid decolorization (acid-fast staining). Infection with *M. tuberculosis* occurs either as a primary infection or a secondary reactivation or reinfection. The initial infection of primary tuberculosis, the Ghon complex, consists of a subpleural lesion near the fissure between the upper and lower lobes and enlarged caseous lymph nodes that drain the pulmonary lesion. The histologic lesions of TB reveal caseating granulomas with Langerhans giant cells. Although primary pulmonary tuberculosis is usually asymptomatic, systemic and localizing symptoms can occur. These symptoms include malaise, anorexia, weight loss, fever, night sweats, cough, and hemoptysis. The pulmonary lesion of secondary tuberculosis is usually located in the apex of one or both lungs. Progressive pulmonary tuberculosis may result in cavitary fibrocaseous tuberculosis, miliary tuberculosis, or tuberculous bronchopneumonia. Miliary tuberculosis consists of multiple small yellow-white lesions scattered throughout the entire lung. These lesions are the result of erosion of a granulomatous lesion into a blood vessel with subsequent lympho-hematogenous dissemination. While TB is often asymptomatic, the resultant hypersensitivity reaction is a marker for infection in those individuals without clinically apparent disease. The TB skin test is called the Mantoux test and is performed by intradermally injecting purified protein derivative (PPD). An area of induration ½ cm or more in diameter at 48 h is a positive result. The diagnosis of TB depends upon the clinical picture and chest x-ray. Acid-fast stains of sputum are followed with culture, not only to identify the species of mycobacterium but to determine the pattern of antibiotic sensitivity. Treatment is isoniazid (INH) combined with other antibiotics.

K. pneumoniae is a cause of bacterial pneumonia in debilitated and malnourished individuals, such as chronic alcoholics. Patients develop production of thick, gelatinous sputum. This bacterial infection has a greater mortality than pneumococcal pneumonia. Legionnaires' disease is a form of bronchopneumonia that is caused by the gram-negative bacillus *L. pneumophila.* This organism is almost ubiquitous in water and is spread by inhalation of contaminated airborne droplets. Infection results in a patchy bronchopneumonia, and microscopically the alveolar spaces are filled with an inflammatory exudate of neutrophils and macrophages. There may be

multiple small areas of necrosis and abscess. Organisms cannot be visualized by routine stains, so instead a Dieterle silver stain is used.

111. The answer is a. *(Cotran, pp 334, 352. Damjanov, pp 850–854.)* There are several types of mycobacteria that are not *M. tuberculosis.* These organisms are called atypical mycobacteria, or mycobacteria other than tuberculosis (MOTT). They are separated into different classes (Runyon classes) based on several culture characteristics, such as pigment production, colony morphology, and rate of growth. Examples of MOTT include *M. avium-intracellulare, M. marinum,* and *M. leprae,* which is the causative agent of leprosy. *M. avium-intracellulare* is an important cause of infection in patients with AIDS. Histologic sections in these immunosuppressed patients do not reveal granulomas because the cellular immune reactions of these patients are defective. Instead numerous organisms can be seen with special stains. *M. marinum* inhabits marine organisms and grows in water. It can cause superficial disease or skin and subcutaneous disease, and can be obtained from infected aquariums or swimming pools.

112. The answer is c. *(Cotran, pp 352–353.)* In the approximate center of the photomicrograph is the classic refractile, double-walled spherule of the deep fungus *Coccidioides immitis,* which is several times the diameter of the largest inflammatory cell nearby. Coccidioidomycosis is endemic in California, Arizona, New Mexico, and parts of Nevada, Utah, and Texas, where it resides in the arid soils and is contracted by direct inhalation of airborne dust. If inhaled, it produces a primary pulmonary infection that is usually benign and self-limiting in immunologically competent persons, often with several days of fever and upper respiratory flulike symptoms. However, certain ethnic groups, such as some blacks, Asians, and Filipinos, are at risk of developing a potentially lethal disseminated form of the disease that can involve the central nervous system. If the large, double-walled spherule containing numerous endospores can be demonstrated outside the lungs (e.g., in a skin biopsy), this is evidence of dissemination. Antibodies of high titers are detectable by means of complement fixation studies in patients undergoing spontaneous recovery. Amphotericin B is usually reserved for treating high-risk and disseminated infection. The cultured mycelia of the organism on Sabouraud's agar present a hazard for laboratory workers.

113. The answer is d. *(Rubin, pp 336, 434–443. Cotran, p 352–353.)* The deep fungal infections produce characteristic morphologic features in tissue sections. The two basic morphologic types of fungi are yeasts, which are oval cells that reproduce by budding, and molds, which are filamentous colonies consisting of branched tubules called hyphae. Some yeasts produce buds that do not detach. Instead they form long structures that resemble hyphae and are called pseudohyphae. This is characteristic of *Candida* species. *Blastomyces* is a larger, double-contoured yeast that is characterized by broad-based budding. *Aspergillus* is characterized by septate hyphae with acute-angle branching of the filamentous colonies and occasional fruiting bodies. Irregular, broad, nonseptate hyphae with wide-angle branching are seen with mucormycosis (zygomycosis). Large spheres with external budding, referred to as a "ship's wheel," are seen with *Paracoccidioides,* while large spheres with endospores are seen with coccidiomyces infection.

114. The answer is c. *(Cotran, pp 336, 379–380. Rubin, pp 436–438.)* Cryptococcosis is caused by *Cryptococcus neoformans,* an encapsulated yeast (not dimorphic) that infects the central nervous system, primarily in immunocompromised patients. The soil-dwelling yeast is inhaled, but lung involvement tends to be mild in individuals who are not immunodeficient. Diagnosis of cryptococcal meningitis is achieved by finding encapsulated yeasts in CSF preparations. The capsule can be seen with a mucicarmine stain, or it can be negatively stained using india ink. The CSF and serum should also be tested for cryptococcal antigen by the latex cryptococcal agglutination test (LCAT), which is positive in more than 90% of cases. Cryptococcal meningitis varies from a chronic inflammatory and granulomatous infection to a noninflammatory meningitis with numerous yeasts massed, sometimes forming cystic "soap bubble" lesions in the brain. Do not confuse cryptococcus with cryptosporidium. *Cryptosporidium parvum* is a protozoan parasite that may cause a transient diarrhea in immunocompetent individuals or a chronic diarrhea in patients with AIDS (cryptosporidiosis). Histologically, sporozoites may be found attached to the surface of intestinal epithelial cells. They are best seen with an acid-fast stain.

Chromomycosis is a chronic infection of the skin that is produced by an organism that appears as a brown, thick-walled sphere ("copper penny")

in tissue sections. Coccidioidomycosis is a mycotic infection caused by inhalation of the arthrospores of the dimorphic fungus *C. immitis.* Within the lung the spores enlarge to form large spherules (sporangia) that become filled with many small endospores. The cyst ruptures, releasing the endospores. Unruptured spherules incite a granulomatous reaction, while the endospores cause a neutrophilic response. Paracoccidioidomycosis (South American blastomycosis) is a chronic granulomatous infection caused by *Paracoccidioides brasiliensis,* a dimorphic fungus seen in tissues as a large central organism having peripheral oval budding. This histologic appearance is described as being similar to a mariner's wheel.

115. The answer is b. *(Cotran, pp 394–396. Rubin, pp 475–476.)* Intestinal tapeworm (cestode) infections result from eating improperly prepared meat. *T. saginata* is acquired from ingesting contaminated beef, *T. solium* is acquired from contaminated pork, and *D. latum* is obtained from contaminated fish. The life cycles of these tapeworms involve larval stages in animals and worm stages in humans. If the contaminated meat contains the larval forms of these organisms, then they may develop into adult worms in the intestines of infected humans. These individuals generally remain asymptomatic, except that *D. latum* may cause a vitamin B_{12} deficiency. A very different disease results from humans eating the eggs of *T. solium,* which may be found in human feces. In this case, the eggs hatch into larva, which then penetrate the gut wall and disseminate via the bloodstream to lodge in different organs. There they encyst and differentiate into cysticerci. Multiple cysticerci in the brain produce a "Swiss cheese" appearance grossly, and microscopically a scolex (the head of the worm) is found with hooklets. This disease is called cysticercosis. Another cestode, *E. granulosa,* is the cause of hydatid disease in humans. Individuals become infected by eating the tapeworm eggs. Patients are usually sheep herders who get the eggs from their dogs. Larvae released from the eggs disseminate most often to the liver (75%), but they may also travel to the lungs or skeletal muscle. They form large, slowly growing, unilocular cysts that contain multiple scolices. *Toxocara* species, such as *T. canis* and *T. cati,* are one cause of visceral larval migrans. This disease is characterized by infection of visceral organs by helminthic larvae. The typical patient is a young child who develops hypereosinophilia and hypergammaglobulinemia. Ocular manifestations of toxocariasis are common, especially the loss of vision in one eye in a child. Note that this disease is different from cutaneous larva

migrans, which is caused by the larval forms of the hookworms and *Strongyloides stercoralis.*

116. The answer is d. *(Damjanov, pp 987–988.) G. lamblia,* a flagellate protozoan, is the most common cause of outbreaks of waterborne diarrheal disease in the U.S. and is seen frequently in Rocky Mountain areas. Ingestion of cysts from contaminated water results in trophozoites in the duodenum and jejunum. Identification of the trophozoite stage is done by duodenal aspiration or small-bowel biopsy; identification of the cyst stage (intermittent) is done by examination of stool. The trophozoite may appear as a pear-shaped, binucleate organism ("two eyes"). Giardiasis may cause malabsorption but is often asymptomatic. Duodenal aspiration, immunofluorescence, and ELISA testing for *Giardia* antigens are diagnostic and therapy with metronidazole or quinacrine is effective.

117. The answer is b. *(Damjanov, pp 1013–1018.)* The photomicrograph shows a cross-section of an *Enterobius* adult worm. Morphologic features of this nematode include the bilateral crests, the meromyarial type of musculature, and the noncellular cuticle with spines. *E. vermicularis,* the agent responsible for the helminthic infection most common in the United States, usually produces pruritus ani as the outstanding and most disturbing symptom of enterobiasis (pinworm infection). In children with anal pruritus, the "Scotch tape" test can be used to help identify perianal eggs. Enterobius worms often attach themselves to the fecal mucosa and contiguous regions, and they can even be a cause of acute appendicitis. In contrast, blood loss in adults can result from infection with hookworms, while a deficiency of vitamin B_{12} can result from infection with the fish tapeworm *D. latum.* Aplastic anemia in children with chronic hemolytic anemias can result from infection with parvovirus, while a centrifugal rash can result from infection of endothelial cells by *R. prowazekii,* the causative agent of epidemic typhus.

118. The answer is d. *(Cotran, pp 389–391.)* Malaria results from infection with one of four species of plasmodia, namely *P. falciparum, P. vivax, P. ovale,* and *P. malariae.* Malarial organisms (sporozoites) are released into the blood after the bite of an affected *Anopheles* mosquito. These sporozoites then enter the hepatocyte via a hepatocyte receptor for the serum proteins thrombospondin and properdin. In the liver, they multiply asexually to

form numerous merozoites, which are released when the hepatocyte ruptures. These merozoites then infect erythrocytes and form either gametocytes, which are taken up and fertilized in the mosquito, or trophozoites, which become schizonts that develop into merozoites that infect other red cells. In the blood, *P. falciparum* merozoites bind to glycophorin molecules on red blood cells, while *P. vivax* merozoites bind to Duffy antigens on red blood cells. (Note that patients who are Duffy antigen–negative are resistant to *P. vivax* infection.) *P. vivax* infects only young erythrocytes (reticulocytes), while *P. malariae* infects only old erythrocytes. Within the red cells, merozoites mature to form schizonts, which then secrete proteins that form knobs on the surface of the red cells. Sequestrins form on top of these knobs and then bind to endothelial cells via ICAM-1, the thrombospondin receptor, and CD46, causing thrombosis.

Clinically, patients with malaria develop recurrent bouts of chills and high fever (paroxysms) that result from rupture of infected erythrocytes. These symptoms cycle at different time intervals depending upon the type of malaria. For example, infection with *P. malariae* causes symptoms to cycle every 72 h, and thus it is called quartan or malarial malaria. The remaining plasmodia cause symptoms that cycle every 48 h. The disease produced by *P. falciparum,* however, is much more serious and is called malignant tertian malaria. *P. falciparum* malaria is more serious because it alters RBCs, making them more adherent to endothelial cells. This in turn leads to capillary plugging and obstruction. In the brain this is called cerebral malaria, while in the kidney the disease produces acute renal failure (called blackwater fever). In contrast, *P. vivax* malaria is called benign tertian malaria, and the disease caused by *P. ovale* is similar to that caused by *P. vivax.*

Babesiosis is caused by *B. microti.* It is somewhat similar to malaria, except that it is transmitted by the hard-shell tick (ixodid) and it infects individuals living on islands off of the New England coast, such as Martha's Vineyard. Patients develop the sudden onset of chills and fever due to destruction of erythrocytes. The disease is usually self-limited, but patients may develop hemoglobinemia, hemoglobinuria, and renal failure.

119. The answer is a. *(Damjanov, pp 714–716. Cotran, pp 437–439.)* Protein-energy malnutrition (PEM) in underdeveloped countries leads to a spectrum of symptoms from kwashiorkor at one end to marasmus at the other. Marasmus, caused by a lack of caloric intake (i.e., starvation), leads to generalized wasting, stunted growth, atrophy of muscles, and loss of

subcutaneous fat. There is no edema or hepatic enlargement. These children are alert, not apathetic, and are ravenous. In contrast, children with kwashiorkor, which is characterized by a lack of protein despite adequate caloric intake, have peripheral edema, a "moon" face, and an enlarged, fatty liver. The peripheral edema is caused by decreased albumin and sodium retention, while the fatty liver is caused by decreased synthesis of the lipoproteins necessary for the normal mobilization of lipids from liver cells. Additionally, these children have "flaky paint" areas of skin and abnormal pigmented streaks in their hair ("flag sign"). In children with marasmus, the skin is inelastic due to loss of subcutaneous fat. In either severe kwashiorkor or marasmus, thymic atrophy may result in the reduction in number and function of circulating T cells. B cell function (i.e., immunoglobulin production) is also depressed, so that these children are highly vulnerable to infections.

120. The answer is d. *(Cotran, pp 439–441.)* The symptoms of vitamin A deficiency result from abnormalities involving the normal functions of vitamin A. These normal functions include maintaining mucus-secreting epithelium, restoring levels of the visual pigment rhodopsin, increasing immunity to infections, and acting as an antioxidant. Deficiencies of vitamin A result in squamous metaplasia of mucus membranes, not intestinal metaplasia. Squamous metaplasia of the respiratory tract leads to increased numbers of pulmonary infections due to lack of the normal protective mucociliary "elevator." Squamous metaplasia of the urinary tract leads to increased numbers of urinary tract stones, while such metaplasia in sebaceous and sweat glands of dry skin causes follicular hyperkeratosis and predisposes to acne. There are numerous eye changes produced by a vitamin A deficiency. These changes include dry eyes (xerophthalmia), soft cornea (keratomalacia), and elevated white plaques of keratin debris on the conjunctiva (Bitot's spots). Because vitamin A is important in the normal function of rhodopsin, a visual pigment important for vision in dim light, a deficiency of vitamin A is associated with poor vision in dim light. This night blindness is usually the first symptom seen in patients with a vitamin A deficiency. Rather than causing acute leukemia, vitamin A is used with good results in the treatment of acute promyelocytic leukemia. Megaloblastic anemia is associated with a deficiency of either vitamin B_{12} or folate, while a deficiency of vitamin D leads to decreased mineralization of bones (soft bones).

121. The answer is b. *(Cotran, pp 441–446.)* Vitamin D is essential for maintenance of normal bone remodeling in the adult; therefore, a significant deficiency in adults leads to poorly mineralized bone, or osteomalacia. Deficiency also results in decreased intestinal absorption of calcium and inadequate serum calcium and phosphorus, and, therefore, impaired mineralization of osteoid. Defective mineralization of osteoid causes formation of soft, easily deformed bones. Since there is no decreased production of osteoid matrix, a relative excess of woven bone or osteoid with wide osteoid seams results.

122. The answer is a. *(Cotran, p 446.)* Vitamin E (α tocopherol, the most potent form, and tocotrienols) functions primarily as an antioxidant. As such, it protects membranes, especially the membranes of erythrocytes, from peroxidation of polyunsaturated fatty acids. This antioxidation property of vitamin E acts in concert with selenium. Deficiencies of vitamin E may produce spinocerebellar degeneration and skeletal muscle abnormalities. Manifestations of the neuropathologic changes, which affect the posterior columns of the spinal cord, include decreased tendon reflexes, ataxia, and loss of pain, position, and vibration sense. Note that red cells use vitamin E to protect their membranes from oxidation, and a deficiency of vitamin E in newborns can lead to a hemolytic anemia. In contrast, progressive night blindness is associated with a deficiency of vitamin A; bleeding with a prolonged PT and PTT is associated with a deficiency of vitamin K; chronic atrophic gastritis and anemia are associated with a deficiency of vitamin B_{12}; and osteopenia and bone pain are associated with a deficiency of vitamin D.

123. The answer is e. *(Cotran, pp 447–448. Chandrasoma, pp 160–162. Rubin, pp 348–349.)* Vitamin B_1 (thiamine) has three important functions. It participates in oxidative decarboxylation of α-keto acids; participates as a cofactor for transketolase in the pentose phosphate path; and participates in maintaining neural membranes. The causes of thiamine deficiency include poor diet, deficient absorption and storage, and accelerated destruction of thiamine diphosphate. This deficiency may be seen in alcoholics and prisoners of war because of poor nutrition, or it may be seen in individuals who eat large amounts of polished rice. (Polishing rice removes the outer, thiamine-containing portion of the grain.) Thiamine deficiency (called beriberi) mainly affects two organ systems, the heart and the ner-

vous system. If the heart is affected in a patient with beriberi, it may become dilated and flabby. Patients may also develop peripheral vasodilation that leads to a high-output cardiac failure and marked peripheral edema. This combination of vascular abnormalities is called wet beriberi. The peripheral nerves in beriberi may be damaged by focal areas of myelin degeneration, which leads to footdrop, wristdrop, and sensory changes (numbness and tingling) in the feet and lower legs. These symptoms are referred to as dry beriberi. Thiamine deficiency may produce the central nervous system (CNS) symptoms of Wernicke-Korsakoff syndrome. Wernicke's encephalopathy consists mainly of foci of hemorrhages and necrosis in the mammillary bodies and about the ventricular regions of the thalamus and hypothalamus, about the aqueduct in the midbrain, and in the floor of the fourth ventricle. Symptoms of Wernicke's syndrome include progressive dementia (confusion), ataxia, and paralysis of the extraocular muscles—often with bilateral lateral rectus, or sixth nerve, palsies (ophthalmoplegia). Korsakoff psychosis is a thought disorder that produces retrograde memory failure and confabulation.

In contrast to niacin, biotin (vitamin H) is an important cofactor for multisubunit enzymes that catalyze carboxylation reactions, an example of which is the synthesis and oxidation of fatty acids. A deficiency of biotin can lead to multiple symptoms, including depression, hallucinations, muscle pain, and dermatitis. Biotin is present in dietary food and is also produced by intestinal bacteria. Deficiencies of biotin are quite rare, but can occur in people who consume raw eggs. This is because egg white contains a heat-labile protein, avidin, which combines very tightly with biotin and prevents the absorption of biotin. Pyridoxine is a cofactor that participates in transamination reactions, decarboxylation reactions, and transsulfuration reactions. It is important in the synthesis of GABA and d-ALA. Deficiencies of pyridoxine can lead to decreased synthesis of GABA, which can cause convulsions in infants or a polyneuropathy in adults, or decreased ALA, which produces a hypochromic, sideroblastic anemia. Patients also develop cheilosis (inflammation and fissuring of the lips), angular stomatitis (cheilosis occurring at the corners of the mouth), glossitis (atrophy of the mucosa of the tongue), and seborrheic dermatitis. Pyridoxine deficiency may result from pregnancy or therapy with certain drugs, such as isoniazid, methyldopa, or levodopa. A common cause of B_6 deficiency is chronic alcoholism. A deficiency of riboflavin (vitamin B_2) is characterized by changes that occur around the mouth, namely cheilosis, angular stom-

atitis, and glossitis. Additionally, patients may develop seborrheic dermatitis of the face or genitalia, or blindness, which is the result of vascularization of the cornea (interstitial keratitis). Selenium is an antioxidant that is part of glutathione peroxidase, an enzyme that is found in red cells and white cells. As such, it prevents oxidative damage to both red blood cells and white cells. A deficiency of selenium leads to a form of dilated cardiomyopathy in children. This deficiency has been described in China and is called Keshan disease.

124. The answer is c. *(Cotran, pp 448–450. Chandrasoma, pp 160–162. Rubin, pp 349–350.)* Niacin (vitamin B_3) is required for the synthesis of both NAD and NADP, two enzymes that participate in many dehydrogenase enzymes. In general, NAD-linked dehydrogenases catalyze reactions in oxidative pathways like the TCA cycle, while NADP-linked enzymes are found in reductive synthesis pathways such as the pentose phosphate pathway. Deficiencies of niacin produce pellagra, a disease that is characterized by the triad of dementia, dermatitis ("glove" or "necklace" distribution), and diarrhea. Decreased levels of niacin may result from diets that are deficient in niacin, such as diets that depend upon maize (corn) as the main staple, because niacin in maize is bound in a form that is not available. Part of the body's need for niacin is supplied by the conversion of the essential amino acid tryptophan to NAD, and therefore a deficiency of tryptophan can also produce symptoms of pellagra. Deficiencies of tryptophan can be seen in individuals with Hartnup disease, which is caused by the abnormal membrane transport of neutral amino acids and tryptophan in the small intestines and kidneys. Deficiencies of tryptophan can also be found in individuals whose diets are high in leucine (an amino acid that inhibits one of the enzymes necessary to convert tryptophan to NAD), in patients with carcinoid tumors (tumors that can convert tryptophan into serotonin), or in patients with tuberculosis who receive isoniazid therapy (because isoniazid is a pyridoxine antagonist and pyridoxine is also necessary for the conversion of tryptophan to NAD). In contrast to pellagra, beriberi is due to a deficiency of thiamine, marasmus is due to a deficiency of calories, rickets is due to a deficiency of vitamin D in children, and scurvy is due to a deficiency of vitamin C.

125. The answer is e. *(Cotran, pp 449–450, 1227–1228.)* Vitamin C (ascorbic acid) is a water-soluble vitamin that is important in many body

functions, such as the synthesis of collagen, osteoid, certain neurotransmitters, and carnitine. In the synthesis of collagen, vitamin C functions as a cofactor for the hydroxylation of proline and lysine and for the formation of the triple helix of tropocollagen. Patients with decreased vitamin C (scurvy) have abnormal synthesis of connective tissue due to abnormal synthesis of collagen along with abnormal synthesis of osteoid. The former leads to impaired wound healing. In addition, previous wounds may reopen. Because the synthesis of collagen is abnormal, the blood vessels are fragile, leading to bleeding gums, tooth loss, subperiosteal hemorrhage, and petechial perifollicular skin hemorrhages. Abnormal synthesis of osteoid (unmineralized bone) leads to decreased amounts of osteoid in the bone and increased calcification of the cartilage. Vitamin C also functions as an antioxidant and is important in neutrophil function and iron absorption in the gut. These functions are also decreased in patients with scurvy. This syndrome is common in elderly people living on a diet deficient in milk, fruits, and vegetables.

In contrast to scurvy, which is caused by a deficiency of vitamin C, rickets is caused by a deficiency of vitamin D. Rickets is characterized by a lack of calcium. In this abnormality the osteoblasts in bone continue to synthesize osteoid, but this material is not mineralized. This results in increased amounts of osteoid (unmineralized bone) and decreased mineralized bone. In adults this produces osteomalacia and bone pain. Histologically, the bone osteoid seams are markedly increased in thickness. In children this produces rickets, a disease that is characterized by increased osteoid at normal growth centers of bone, which produces wide epiphyses at the wrists and knees and leads to growth retardation. Thiamine deficiency causes beriberi and niacin deficiency causes pellagra.

126. The answer is a. *(Cotran, pp 433–434. Rubin, pp 334–335.)* Burns of the skin, which may involve partial thickness or the full thickness of the epidermis, are classified as being first-degree burns, second-degree burns, or third-degree burns. The first two are partial-thickness burns, while third-degree burns are full-thickness burns. First-degree burns, such as with a sunburn, are mild and heal without scarring. Clinically, erythema is present, which is due to dilation of the capillaries in the dermis. Histologic sections of the skin would show epidermal edema and focal epithelial necrosis. Second-degree burns clinically reveal erythema, edema, and vesiculation (blister formation). These types of burns may heal with dermal

scarring, and histologic sections would reveal full-thickness epidermal necrosis and partial necrosis of the dermis. There is no necrosis of the adnexal structures that are located deeper in the dermis. Third-degree burns are the most severe types of burns and consist of extensive necrosis of the epidermis, dermis, and adnexal structures. These burns, which have a high risk of infection, heal with severe scarring and need skin grafts for treatment.

127. The answer is a. *(Cotran, pp 420–421. Ayala, p 204.)* The major organs affected by lead poisoning are the blood, nervous system, gastrointestinal tract, and kidneys. Many times the early signs and symptoms of lead poisoning are seen only in the blood. These changes include a hypochromic and microcytic anemia with basophilic stippling of the red blood cells. Lead interferes with aminolevulinic acid dehydratase (ALA-D) and ferroketolase (heme synthetase), two enzymes involved in the production of hemoglobin. As a result of decreased activity of both of these enzymes in red cells, iron is displaced from heme, forming increasing blood levels of zinc protoporphyrin and its product, free erythrocyte protoporphyrin (FEP). Also as a result of decreased activity of erythrocyte ALA-D, urinary δ-aminolevulinic acid is increased. Children exposed to lead are vulnerable to CNS damage, which can decrease mental abilities, while adults can develop a peripheral demyelination neuropathy that produces a wrist- and footdrop. GI symptoms include severe, poorly localized abdominal pain, which is called lead colic. In the kidney, damage to the proximal tubular epithelial cells causes Fanconi's syndrome, which consists of the triad of amino aciduria, glycosuria, and hyperphosphaturia. Increased reabsorption of urinary proteins leads to large eosinophilic, acid-fast intranuclear droplets in the tubular epithelial cells. Lead may also be deposited in the gums (forming a blue line along the margins of the gums called Bruton's line) or in the epiphyses of children (which may be seen on x-ray).

128. The answer is e. *(Cotran, pp 421–422.)* Many environmental chemicals are potential causes of quite serious human diseases. Methanol, originally called wood alcohol, is metabolized in the body by the enzyme alcohol dehydrogenase to formaldehyde and formic acid. These metabolites cause necrosis of retinal ganglion cells, which leads to a metabolic acidosis and blindness. It is interesting to note that the treatment for acute

methanol ingestion is IV ethyl alcohol, because it is also metabolized by alcohol dehydrogenase and therefore ties up this enzyme. Cadmium, which can be found in tobacco smoke, has been implicated in producing not only an acute form of pneumonia, but, with chronic exposure to small concentrations of cadmium vapors, diffuse interstitial pulmonary fibrosis and an increased incidence of emphysema as well. Nickel can cause contact dermatitis, which is a type IV hypersensitivity reaction, while mercury toxicity damages the kidneys and the brain. The neurologic symptoms include a tremor due to cerebellar abnormalities, and mental changes. Historically the use of mercury in the hatmaking industry caused these symptoms and resulted in the expression "mad as a hatter." A famous widespread outbreak of mercury poisoning occurred in the Minamata coastal region of Japan (and led to the term Minamata disease). Cobalt poisoning can produce a dilated cardiomyopathy.

129. The answer is d. *(Rubin, pp 326–332. Cotran, pp 421–422.)* Ethylene glycol, commonly used as an antifreeze, is toxic to humans (and cats and dogs) because it causes a metabolic acidosis and acute tubular necrosis in the kidney, as ethylene glycol is metabolized to calcium oxalate (polarizable crystals), which are deposited in the renal tubules. Carbon monoxide is a colorless, odorless gas that is produced by natural gas heaters and is found in car exhaust. It replaces oxygen in hemoglobin, causing the formation of carboxyhemoglobin. This results in extreme cyanosis and anoxia. It produces a characteristic cherry red color of the skin and blood. Carbon tetrachloride can produce liver damage (with steatosis), while cyanide causes cellular damage by binding to cytochrome oxidase and inhibiting cellular respiration. Cyanide is used in industry; an industrial accident in India in 1984 killed more than 2000 people. Cyanide is also a component of amygdalin, which is found in the pits of several fruits, such as apricots and peaches. It is also found in laetrile, a drug that is used outside of the United States. Cyanide poisoning produces a cherry red color of the skin and also produces the odor of bitter almonds on the breath. Acute arsenic toxicity causes central nervous toxicity and renal tubular necrosis, while chronic arsenic exposure causes GI disturbances, peripheral neuropathies, and skin changes (thick areas of skin with increased pigmentation called arsenical keratosis). Arsenic is also associated with cancers of the skin, respiratory tract, and liver (angiosarcomas). Arsenic accumulates in the hair and nails (forming transverse ridges called Mees' lines).

130. The answer is e. *(Cotran, p 439.)* The clinical findings of anorexia nervosa, which refers to self-induced starvation, usually in previously healthy young females, are similar to those in severe protein-energy malnutrition (PEM). Decreased gonadotropin-releasing hormone (GnRH) decreases levels of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which leads to amenorrhea. Decreased thyroid hormone leads to signs and symptoms of hypothyroidism, which include cold intolerance, bradycardia, constipation, and skin and nail changes. Decreased estrogen can produce osteoporosis, while cardiac arrhythmias may result from hypokalemia and may cause sudden death. Compare anorexia nervosa to bulimia, which refers to binge eating followed by induced vomiting, usually in previously healthy young females. This disorder is associated with menstrual irregularities; complications include electrolyte abnormalities (hypokalemia) and aspiration of gastric contents.

131. The answer is e. *(Cotran, pp 466–470.)* Abnormalities of genes that control normal morphogenesis during embryonic development are associated with the development of congenital malformations. Two important types of genes associated with morphogenesis include homeobox (HOX) genes and paired box (PAX) genes. HOX genes act in temporal or spatial combinations and play an important role in the patterning of limbs, vertebrae, and craniofacial structures. Mutations of HOX genes may cause extra digits (synpolydactyly) or short digits (brachydactyly). It is interesting to note that vitamin A is an upstream regulator of HOX genes, and the use of retinoic acid during pregnancy may produce congenital abnormalities. Mutations of certain PAX genes are associated with malformations. Mutations of PAX-3 are seen in Waardenburg syndrome (congenital pigment abnormalities and deafness), while PAX-6 mutations may be seen with aniridia, and PAX-2 may be involved with Wilms syndrome. In contrast, abnormal limbs and phocomelia (underdeveloped limbs that are short stumps without fingers or toes) can result from thalidomide use, while arachnodactyly and dissecting aortic aneurysm in adults are seen in Marfan's syndrome. Congenital goiter or hypothyroidism can result from iodide deficiency.

132. The answer is e. *(Cotran, pp 470–471. Rubin, pp 221–223.)* TORCH is an acronym referring to a group of microorganisms that produce similar

changes during fetal or neonatal infection. The T stands for toxoplasma, the O for others, the R for rubella, the C for cytomegalovirus, and the H for herpes simplex virus. The "others" include syphilis, tuberculosis, and many other microorganisms. Manifestations of the TORCH complex include brain lesions, such as encephalitis and intracranial calcifications; ocular defects, including chorioretinitis; and cardiac abnormalities. Children born with congenital syphilis, caused by maternal infection with *T. pallidum,* initially show changes typical of the TORCH complex, but later they may develop characteristic lesions including flattening of the nose (saddle nose), notched incisors (Hutchinson's teeth), malformed molars (mulberry molars), outward bowing of the anterior tibias (saber shins), and progressive vascularization of the cornea (interstitial keratitis). The combination of deafness, interstitial keratitis, and notched incisors is referred to as Hutchinson's triad.

133. The answer is e. *(Cotran, pp 473–475.)* Hemolytic disease of the newborn (HDN) is a type of isoimmune hemolytic anemia that is caused by maternal antibodies that react against fetal red blood cells. Once the maternal antibodies cross the placenta, the fetal red cells are destroyed, leading to a hemolytic anemia. The breakdown of hemoglobin leads to hyperbilirubinemia (jaundice), which is due to severe unconjugated hyperbilirubinemia, as the released heme is not easily conjugated by the immature newborn liver, which is deficient in glucuronyl transferase. The unconjugated bilirubin is water-insoluble and has an affinity for lipids. In an infant with a poorly developed blood-brain barrier, the bilirubin may bind to the lipids in the brain and produce kernicterus. The severe anemia may result in congestive heart failure, which, together with hypoproteinemia may lead to generalized edema (anasarca), which in its most severe form is called hydrops fetalis. In the peripheral blood of the newborn, many immature red blood cells may be found (nucleated RBCs or normoblasts). This condition is called erythroblastosis and led to another name for HDN being erythroblastosis fetalis.

In order for the mother to make antibodies that are directed against fetal erythrocyte antigens, she must lack the erythrocyte antigens that the child has, which were inherited from the father. The most important erythrocyte antigens involved in HDN are the Rh and the ABO antigens. The most important Rh antigen is the D antigen. Therefore, for Rh incompatibility, the mother must be Rh negative (d), the child Rh positive (D). For

ABO incompatibility, the mother must be type O (lacking the A and B antigens), the child type A or B. ABO incompatibility is the most common cause of hemolytic disease of the newborn. Usually the disease is less severe than HDN due to Rh incompatibility because there is poor expression of blood group antigens A and B on neonatal red cells.

134. The answer is b. *(Damjanov, pp 1473–1483. Cotran, pp 471–473.)* A disorder in newborns that is histologically identical to ARDS is called neonatal respiratory distress syndrome [hyaline membrane disease (HMD)]. HMD, which accounts for 20% of all deaths in the first 28 days of life, is basically a disease of premature infants; most affected infants weigh 1000 to 1500 g. Contributing factors in the development of HMD include diabetes in the mother (maternal diabetes with increased glucose causes increased fetal secretion of insulin, which inhibits the effects of steroids such as lung maturation and production of surfactant) and cesarean section. Infants who develop HMD appear normal at birth, but within minutes to hours their respirations become labored. Grossly the lungs are a mottled, red-purple color, while microscopically there are hyaline membranes in air spaces, similar to those of ARDS. Two defects have been identified in infants with HMD. One is a deficiency of pulmonary surfactant. Surfactant, a lipid consisting of dipalmitoyl phosphatidylcholine, reduces the surface tension in air-fluid interfaces by getting between the molecules in the liquid and reducing their attraction to each other. This reduces the tendency for the alveoli to collapse after birth on expiration. Synthesis of surfactant increases throughout fetal development, but becomes maximal at 34 to 36 weeks. With a deficiency of surfactant, the lungs tend to collapse on expiration (atelectasis) and become stiff. The other defect is increased pulmonary epithelial permeability. This accounts for the protein-rich edema fluid in the alveoli and also for the formation of hyaline membranes. The most reliable test to determine pulmonary maturity is the ratio of lecithin to sphingomyelin (L/S), both of which are phospholipids. The production of lecithin (phosphatidylcholine) begins at 5 months of gestation, but secretion begins at 7 months of gestation, and levels rise sharply at 34 to 36 weeks of gestation. The level of sphingomyelin does not change during this time. An L/S ratio of about 2 indicates fetal maturity, 1.2 indicates a possible risk, and below 1 indicates a definite risk. The treatment for HMD is to give the infant artificial surfactant at birth.

135. The answer is c. *(Cotran, pp 1368–1369. Rubin, pp 1556–1557.)* Retinopathy of prematurity (ROP), also called retrolental fibroplasia (because of the formation of a fibrovascular mass behind the lens), is a cause of blindness in premature infants that is related to the therapeutic use of high concentrations of oxygen. Immature blood vessels in the retina, particularly in the peripheral portion of the temporal retina, are prone to injury with high-dose oxygen, which inhibits the production of vascular endothelial growth factor (VEGF). This inhibition causes apoptosis of vascular endothelial cells with subsequent constriction and obliteration of the retinal blood vessels. This initial stage of ROP is referred to as the vaso-obliterative phase. Withdrawal of oxygen therapy stimulates VEGF production and results in a marked increase in the proliferation of vascular endothelial cells with new blood formation (neovascularization). This phase of ROP is called the vasoproliferative phase. The incidence of this complication has been markedly reduced due to close clinical monitoring of the concentration of administered oxygen. In contrast, accumulation of abnormal material in the ganglion cells of the retina is seen clinically as a "cherry red macula," while fibrous obliteration of the canal of Schlemm is a cause of closed-angle glaucoma. Lipid accumulation at the periphery of the cornea produces corneal arcus, a commonly found aging change. Degeneration of the macula occurs most often due to age-related maculopathy, but it can also be caused by inherited disorders or drugs, such as chloroquine.

136. The answer is b. *(Cotran, pp 481–482.)* Sudden infant death syndrome (SIDS) is a heterogeneous, multifactorial disorder, but by definition it refers to sudden death of infant under 1 year of age that is unexplained after thorough examination. Most cases of SIDS occur between 2 and 4 months of life, and the child usually dies during sleep ("crib death" or "cot death"). A risk factor for SIDS is sleeping in a prone position. Therefore healthy infants should sleep on their back or side. Maternal factors associated with SIDS include age less than 20, being unmarried, low socioeconomic group, smoking, and drug abuse. Infant factors associated with SIDS include prematurity, low birth weight, male sex, and a history of SIDS in a sibling. In contrast to SIDS, death from respiratory complications after being born 10 weeks prematurely is suggestive of hyaline membrane disease, while evidence of repeated bone fractures and bilateral retinal hemorrhages is suggestive of trauma, child abuse, or "shaken baby" syndrome.

137. The answer is d. *(Cotran, pp 286, 484–489.)* Neuroblastomas are malignant tumors of the adrenal medulla that occur in very young patients who present with an abdominal mass. Histologically, these tumors are composed of small cells forming Homer-Wright rosettes, which are groups of cells arranged in a ring around a central mass of pink neural filaments. Electron microscopy reveals neurosecretory granules within the cytoplasm of the tumor cells, while immunohistochemical stains are positive for neuron-specific enolase (NSE). These highly aggressive tumors are unique because some spontaneously regress and some dedifferentiate into benign tumors, such as ganglioneuromas. Three distinct chromosomal abnormalities are associated with neuroblastomas. These abnormalities include near-terminal deletion of part of the short arm of chromosome 1 (partial monosomy 1), homogeneously staining regions (HSRs) of chromosome 2, and multiple double minute chromatin bodies. The latter two are the result of amplification of the oncogene *N-myc*. The number of *N-myc* copies correlates with the aggressiveness of the tumor. Dedifferentiation of a neuroblastoma into a benign ganglioneuroma is associated with a marked reduction in this gene amplification. In contrast, deletion of chromosome 11 is associated with nephroblastoma (Wilms tumor), a malignant tumor of the kidney found in young patients. This chromosome abnormality is associated with deletion of WT1, a tumor suppressor gene.

138. The answer is a. *(Henry, pp 279–285. Cotran, p 561.)* The levels of serum aspartate aminotransferase (AST), which is also called serum glutamic-oxaloacetic transaminase (SGOT) (curve II), become elevated within 12 h after nearly all acute myocardial infarctions; they generally reach a peak level within 48 h and return to normal within 4 to 5 days. After myocardial infarctions, creatine phosphokinase levels (curve I) rise and fall more rapidly than do SGOT levels. Lactic dehydrogenase levels (curve III) also become elevated within 1 day after infarctions, but they remain elevated for about 10 days. Alkaline phosphatase and 59-nucleotidase levels, normal during infarctions, usually show marked increases in patients who have obstructive jaundice.

139. The answer is a. *(Henry, pp 281–284.)* The patient described probably has hepatitis, according to the values given for the five isoenzymes of lactic dehydrogenase (LDH). Liver cells contain higher proportions of LDH4 and LDH5 than do myocardium or red blood cells, both of which

contain greater relative amounts of LDH1 and LDH2. Lung tissue is high in LDH3, and brain tissue contains only small amounts of LDH5. During the LDH increase following a myocardial infarction, levels of LDH1 are usually higher than those of LDH2. This pattern is called a "flipped" LDH.

140. The answer is b. *(Henry, pp 76–77.)* Diagnostic specificity is defined as the probability of a negative diagnostic test (true negatives) in the absence of the disease (true negatives and false positives), or simply, it is the ability of a test to correctly identify a person who is free of the specific disease. Specificity can be calculated using the formula true negatives/(true negatives + false positives). Diagnostic sensitivity is defined as the probability of a positive diagnosis (true positives) in patients with the disease the test is designed to detect (true positives and false negatives). Sensitivity can be calculated using the formula true positives/(true positives + false negatives). The best information from laboratory tests comes from their positive and negative predictive values (PVs) relating the results to the prevalence of the disease in the population being studied. Positive predictive value equals true positives/(true positives + false positives), while predictive negative value equals true negatives/(true negatives + false negatives).

This page intentionally left blank.

Cardiovascular System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

141. Primary type II hyperlipidemia (familial hypercholesterolemia) results from a defect in

a. Lipoprotein lipase
b. Low-density lipoprotein (LDL) receptor
c. Apolipoprotein E
d. Apolipoprotein CII
e. Lipoprotein(a)

142. Which one of the listed statements best explains the pathophysiology involved in the production of a type IV secondary hyperlipidemic pattern because of decreased insulin in an individual with diabetes mellitus?

a. Decreased production of albumin causes increased fatty acid binding to VLDL, which inhibits its degradation to LDL
b. Increased binding of bile salts in the gut decreases the enterohepatic circulation of cholesterol
c. Increased lipolysis causes increased fatty acid delivery to the liver, which increases production of VLDL
d. Stimulation of β-oxidation of acyl-CoA in the liver increases the production of ketone bodies from acetyl-CoA
e. Stimulation of HMG-CoA reductase in the liver increases the production of cholesterol, which decreases the synthesis of hepatic LDL receptors

143. The presence of lipoprotein(a) is associated with an increased risk for the development of coronary and cerebral vascular disease. One possible reason for this relates to the fact that lipoprotein(a) has kringle regions, which are regions that have structural homology with

a. Cardiolipin, and this homology increases the formation of clots on cardiac valves
b. Fibrinogen, and this homology increases the formation of fibrin thrombi
c. Hepatic lipase, and this homology decreases the formation of low-density lipoproteins
d. Lipoprotein lipase, and this homology decreases the ability to metabolize chylomicrons
e. Plasminogen, and this homology decreases the ability to clear thrombi

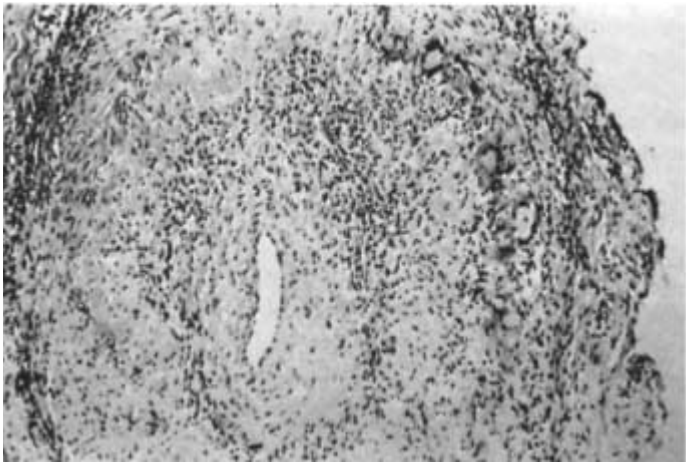
144. A factor that stimulates the proliferation of smooth-muscle cells and also relates to the pathogenesis of atherosclerosis is

a. Platelet-derived growth factor
b. Transforming growth factor β
c. Interleukin 1
d. Interferon α
e. Tumor necrosis factor

145. A 41-year-old female presents with recurrent severe headaches and increasing visual problems. Physical examination reveals her blood pressure to be 220/150. Her symptoms are most likely to be associated with

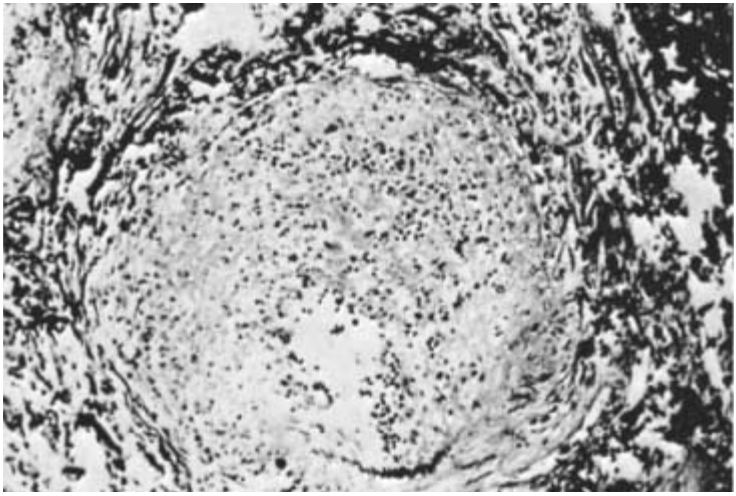
a. Medial calcific sclerosis
b. Arteriosclerosis obliterans
c. Hyperplastic arteriolosclerosis
d. Hyaline arteriolosclerosis
e. Thromboangiitis obliterans

146. An 82-year-old woman presents with headaches, visual disturbances, and muscle pain. A biopsy of the temporal artery is shown in the associated photomicrograph. The next course of action is to



a. Administer corticosteroids
b. Verify with a repeat biopsy
c. Administer anticoagulants
d. Perform angiography
e. Order a test of the erythrocyte sedimentation rate

147. A 27-year-old male presents with fever, abdominal pain, muscle pain, and multiple tender cutaneous nodules. No pulmonary signs are found. A biopsy from one of the skin lesions is seen in the photomicrograph below. Involvement of small vessels by inflammation is not found. Laboratory tests are negative for P-ANCAs and C-ANCAs. Which one of the following is most likely to be present in this patient's serum?



a. CMV antigen
b. Cryptococcus antigen
c. Hepatitis B antigen
d. Histoplasma antigen
e. Pneumocystis antigen

148. In a patient with vasculitis, the finding of serum antineutrophil cytoplasmic autoantibodies (ANCAs) that react by immunofluorescence staining in a perinuclear pattern (P-ANCAs) is most suggestive of

a. Giant cell arteritis
b. Classic polyarteritis nodosa
c. Wegener's granulomatosis
d. Churg-Strauss syndrome
e. Microscopic polyangiitis

149. A 38-year-old female presents with the new onset of multiple purpuric skin lesions. Two years ago she developed late-onset asthma and mild hypertension. Laboratory examination reveals an increase in the number of eosinophils in the peripheral blood (peripheral eosinophilia), and a biopsy from one of the purpuric skin lesions reveals leukocytoclastic vasculitis. No perivascular IgA deposits are found, and no antineutrophil cytoplasm autoantibodies are present. Which one of the listed disorders is the best diagnosis for this individual?

a. Churg-Strauss syndrome
b. Henoch-Schönlein purpura
c. Macroscopic polyarteritis nodosa
d. Microscopic polyangiitis
e. Wegener's granulomatosis

150. A 30-year-old male smoker presents with gangrene of his extremities. Which one of the following histologic findings from a biopsy of the blood vessels supplying this area would be most suggestive of the diagnosis of Buerger's disease?

a. Granulomatous inflammation with giant cells
b. Fibrinoid necrosis with overlying thrombosis
c. Focal aneurysmal dilation
d. Fragmentation of neutrophils
e. Thrombosis with microabscesses

151. During a routine physical examination, a 60-year-old white male is found to have a 5-cm pulsatile mass in his abdomen. Angiography reveals a marked dilation of his aorta distal to his renal arteries. This aneurysm is most likely the result of

a. Atherosclerosis
b. A congenital defect
c. Hypertension
d. A previous syphilitic infection
e. Trauma

152. A 56-year-old male presents with the sudden onset of excruciating pain. He describes the pain as beginning in the anterior chest, radiating to the back, and then moving downward into the abdomen. His blood pressure is found to be 160/115. Your differential diagnosis includes myocardial infarction; however, no changes are seen on ECG, and you consider this to be less of a possibility. You obtain an x-ray of this patient's abdomen and discover a "double-barrel" aorta. This abnormality most likely results from

a. A microbial infection
b. Loss of elastic tissue in the media
c. A congenital defect in the wall of the aorta
d. Atherosclerosis of the abdominal aorta
e. Abnormal collagen synthesis

153. A 2-year-old girl is being evaluated for marked swelling of her neck. During the workup of this patient, a karyotype reveals that she is monosomic for the X chromosome. Which one of the listed abnormalities is most likely responsible for the swelling of this patient's neck?

a. Bacillary angiomatosis
b. Capillary hemangioma
c. Cystic hygroma
d. Nevus flammeus
e. Spider angioma

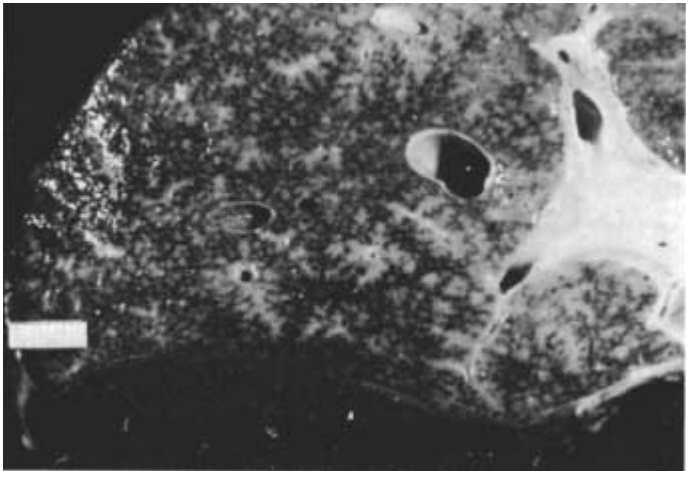
154. Where are glomus tumors most commonly found?

a. Head and neck
b. Axilla and upper arms
c. Fingers and toes
d. Groin and upper thigh
e. Knee and upper calf

155. Histologic sections from an irregular, enlarging brown lesion on the left forearm of a 23-year-old male who is HIV-positive would most likely reveal

a. Irregular vascular spaces lined by nests of uniform cells
b. Multiple dilated endothelial-lined vessels that lack red blood cells
c. Numerous neutrophils, nuclear dust, and purple granules
d. Proliferating blood vessels, endothelial cells, and fibroblasts
e. Proliferating spindle stromal cells with slitlike spaces and extravasation of erythrocytes

156. A 56-year-old woman dies in a hospital where she is being evaluated for shortness of breath, ankle edema, and mild hepatomegaly. Because of the gross appearance of the liver at necropsy in the photograph below, one would also expect to find



a. A pulmonary saddle embolus
b. Right heart failure
c. Portal vein thrombosis
d. Biliary cirrhosis
e. Splenic amyloidosis

157. Which one of the listed disorders is the best example of an abnormality that produces systolic dysfunction primarily because of increased afterload?

a. Anemia
b. Aortic regurgitation
c. Mitral regurgitation
d. Mitral stenosis
e. Systemic hypertension

158. A 64-year-old male presents with recurrent chest pain that develops whenever he attempts to mow his yard. He relates that the pain goes away after a couple of minutes if he stops and rests. He also states that the pain has not increased in frequency or duration in the last several months. What is the correct diagnosis for this patient?

a. Stable angina
b. Unstable angina
c. Atypical angina
d. Prinzmetal's angina
e. Myocardial infarction

159. Which one of the listed substances has the following characteristic serum changes following a myocardial infarction: levels begin to increase 4 to 6 h after the onset of chest pain, reach maximal serum concentration in about 12 to 24 h, and remain elevated for about 3 to 10 days?

a. AST (SGOT)
b. CPK isoenzyme MB
c. LDH (with isotype LDH1 greater than LDH2)
d. ALT (SGPT)
e. Troponin I

160. A 59-year-old male develops intense substernal, crushing chest pain that is not relieved by nitroglycerin. He is admitted to the MICU, but his condition worsens as he develops severe heart failure and dies 2 days later. At autopsy a large necrotic area is found that involves a large portion of the anterior left ventricle. This necrotic area is most likely due to an occlusive thrombus involving the

a. Distal 2 cm of the left anterior descending artery
b. Distal 2 cm of the left circumflex artery
c. Proximal 2 cm of the left anterior descending artery
d. Proximal 2 cm of the left circumflex artery
e. Proximal one-third of the right coronary artery

161. Arrange the following numbered statements in the correct order of the expected sequence of events that normally occur during healing of a myocardial infarction.

1 = Collagen is deposited, forming a fibrous scar
2 = Flocculent densities form within mitochondria
3 = Granulation tissue begins to form
4 = Macrophages begin to arrive at the area of coagulative necrosis
5 = Neutrophils begin to arrive at the area of coagulative necrosis

a. 2, then 3, then 4, then 5, then 1
b. 2, then 4, then 5, then 3, then 1
c. 2, then 5, then 4, then 3, then 1
d. 4, then 5, then 3, then 2, then 1
e. 5, then 4, then 3, then 2, then 1

162. Several days following a myocardial infarction, a 51-year-old male develops the sudden onset of a new pansystolic murmur along with a diastolic flow murmur. Workup reveals increased left atrial pressure that develops late in systole and extends into diastole. These abnormalities in this individual are most likely the result of

a. Aneurysmal dilation of the left ventricle
b. Obstruction of the aortic valve
c. Rupture of the left ventricle wall
d. Rupture of a papillary muscle
e. Thrombosis of the left atrial cavity

163. Three weeks following a myocardial infarction, a 54-year-old male presents with fever, productive cough, and chest pain. The pain is worse with inspiration, better when he is sitting up, and not relieved by nitroglycerin. Physical examination finds a friction rub along with increased jugular venous pressure and pulsus paradoxus (excess blood pressure drop with inspiration). What is the most likely explanation for these findings?

a. Caplan's syndrome
b. Dressler's syndrome
c. Ruptured papillary muscle
d. Ruptured ventricular wall
e. Ventricular aneurysm

164. A 39-year-old female presents with increasing shortness of breath. She states that for the past 6 months she has been taking an unauthorized appetite suppressant to try to lose weight. Physical examination reveals signs of right heart failure. She is admitted to the hospital to work up her symptoms, but she dies suddenly. A section from her heart at the time of autopsy reveals marked thickening of the right ventricle, but the thickness of the left ventricle is within normal limits. The endocardium does not appear to be increased in thickness or fibrotic, and the cardiac valves do not appear abnormal. Neither ventricular cavity is dilated. Which one of the following best describes this cardiac pathology?

a. Carcinoid heart disease
b. Cor pulmonale
c. Eccentric hypertrophy
d. Systemic hypertensive heart disease
e. Volume overload to the heart

165. A 71-year-old female presents with increasing chest pain and occasional syncopal episodes, especially with physical exertion. She has trouble breathing at night and when she lies down. Physical examination reveals a crescendo-decrescendo midsystolic ejection murmur with a paradoxically split second heart sound (S_2). Pressure studies reveal that the left ventricular pressure during systole is markedly greater than the aortic pressure. What is the correct diagnosis?

a. Aortic regurgitation
b. Aortic stenosis
c. Constrictive pericarditis
d. Mitral regurgitation
e. Mitral stenosis

166. The most frequent cause of aortic valve incompetence and regurgitation is

a. Latent syphilis
b. Infective endocarditis
c. Rheumatic fever
d. Aortic dissection
e. Congenital defects

167. Physical examination of an asymptomatic 29-year-old female with a history of rheumatic fever during childhood finds an early diastolic opening snap with a rumbling late diastolic murmur. These findings are most suggestive of

a. Aortic regurgitation
b. Aortic stenosis
c. Mitral regurgitation
d. Mitral stenosis
e. Pulmonic stenosis

168. Acute rheumatic fever classically develops in children 1 to 4 weeks after a group A β-hemolytic streptococcal (*Streptococcus pyogenes*) infection of the

a. Aorta
b. Heart
c. Lungs
d. Pharynx
e. Skin

169. The most characteristic and frequent feature of chronic rheumatic heart disease is the development of

a. Vegetations on the endocardium
b. Aschoff bodies within the myocardium
c. Fibrin deposits within the pericardium
d. Stenosis of the mitral valve
e. Incompetence of the pulmonic valve

170. A 31-year-old female presents with fever, intermittent severe pain in the left upper quadrant of her abdomen, and painful lesions involving her fingers and nail beds. History reveals that she had acute rheumatic fever as a child and that when she was around 20 years of age she developed a new cardiac murmur. At the present time one of three blood cultures submitted to the hospital lab grows out a particular organism. Which one of the following is most likely to be that organism?

a. *Staphylococcus aureus*
b. α-hemolytic viridans streptococci
c. *Candida* species
d. Group A streptococci
e. *Pseudomonas* species

171. A 23-year-old woman develops the sudden onset of congestive heart failure. Her condition rapidly deteriorates and she dies in heart failure. At autopsy, patchy interstitial infiltrates composed mainly of lymphocytes are found, some of which surround individual myocytes. What is the most likely cause of this patient's heart failure?

a. Autoimmune reaction (to group A β-hemolytic streptococci)
b. Bacterial myocarditis (due to *S. aureus* infection)
c. Hypersensitivity myocarditis (due to an allergic reaction)
d. Nutritional deficiency (due to thiamine deficiency)
e. Viral myocarditis (due to coxsackievirus infection)

172. At the time of autopsy of a 39-year-old female who died of complications of systemic lupus erythematosus, several medium-sized vegetations are found on both sides of the mitral valve and tricuspid valve. These cardiac vegetations are most likely the result of

a. Turbulent blood flow through an incompetent mitral valve
b. Abnormal secretion of a vasoactive amine
c. Presence of an anticardiolipin antibody
d. Cachexia produced by a hypercoagulable state
e. Bacterial colonization of an abnormal valve

173. A 37-year-old woman presents with prolonged cramps, nausea, vomiting, diarrhea, and episodic flushing of the skin. Additionally, she develops pearly white, plaquelike deposits on the tricuspid valve leaflets. These cardiac lesions most likely are due to

a. Rheumatic heart disease
b. Amyloidosis
c. Iron overload
d. Hypothyroidism
e. Carcinoid heart disease

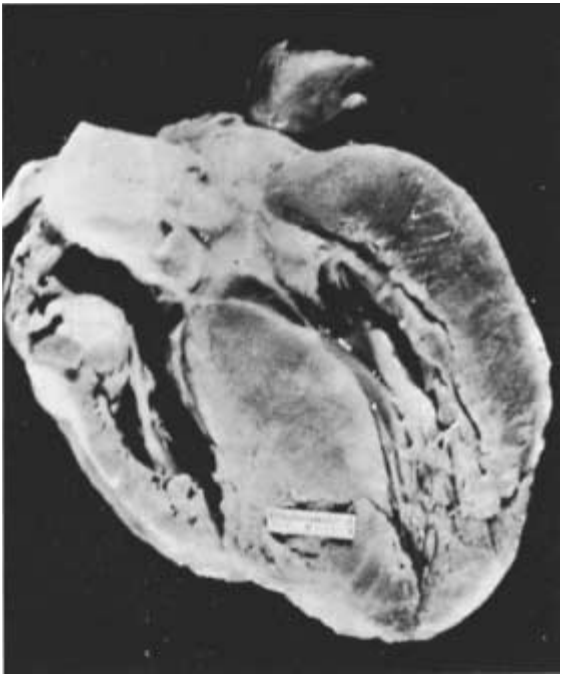
174. A 59-year-old patient receiving chemotherapy with the anthracycline Adriamycin develops severe heart failure. Sections from an endocardial biopsy specimen reveal vacuolization of the endoplasmic reticulum of the myocytes. What type of cardiac damage is Adriamycin most likely to produce?

a. Dilated cardiomyopathy
b. Hyperplastic cardiomyopathy
c. Hypertrophic cardiomyopathy
d. Obliterative cardiomyopathy
e. Restrictive cardiomyopathy

175. A 17-year-old high school student dies suddenly while playing basketball. At autopsy, asymmetric hypertrophy of the interventricular septum is discovered. Histologic sections from this area reveal disorganization of the myofibers, which are thicker than normal and have hyperchromatic nuclei. What is the most likely diagnosis?

a. Hypertrophic cardiomyopathy
b. Dilated cardiomyopathy
c. Constrictive cardiomyopathy
d. Secondary cardiomyopathy
e. Endomyocardial fibrosis

176. The familial form of the abnormality seen in this gross photograph of the heart is



a. An autosomal dominant disorder associated with an abnormal β-myosin gene
b. An autosomal dominant disorder associated with an abnormal fibrillin gene
c. An autosomal recessive disorder associated with decreased acid maltase formation
d. An X-linked recessive disorder associated with an abnormal dystrophin gene
e. An X-linked recessive disorder associated with decreased NADPH oxidase formation

177. An elderly patient who becomes acutely short of breath presents with the combination of hypotension, elevated jugular venous pressure, and muffled heart sounds. This triad of symptoms is most suggestive of

a. Chronic pericarditis
b. Chronic pericardial effusion
c. Cardiac tamponade
d. Dissecting aortic aneurysm
e. Right heart failure

178. The most common primary tumor of the heart in adults is usually located in the left atrium and is called a

a. Chordoma
b. Rhabdomyoma
c. Leiomyoma
d. Myxoma
e. Papillary fibroelastoma

179. The combination of a ventricular septal defect with an aorta that overrides the septal defect, stenosis of the pulmonic valve, and increased thickness of the right ventricle is diagnostic of

a. Chagas' disease
b. Eisenmenger's syndrome
c. Löffler's syndrome
d. Roger's disease
e. Tetralogy of Fallot

180. Which one of the following is the most common congenital heart defect to cause an initial left-to-right shunt?

a. Tetralogy of Fallot
b. Coarctation of the aorta
c. Ventricular septal defect
d. Atrial septal defect
e. Patent ductus arteriosus

181. Which one of the listed statements correctly describes the flow of blood in an individual with an atrial septal defect who develops Eisenmenger's syndrome?

a. Aorta to pulmonary artery to lungs to left atrium to left ventricle to aorta
b. Left atrium to right atrium to right ventricle to lungs to left atrium
c. Left ventricle to right ventricle to lungs to left atrium to right ventricle
d. Right atrium to left atrium to left ventricle to aorta to right atrium
e. Right ventricle to left ventricle to aorta to right atrium to right ventricle

182. Prior to surgery, what is the most appropriate medical therapy for a newborn infant with transposition of the pulmonary artery and aorta?

a. Prostaglandin E_2 should be given to keep the ductus arteriosus open
b. Prostaglandin E_2 should be given to close the ductus arteriosus
c. Oxygen should be given to keep the ductus arteriosus open
d. Indomethacin should be given to keep the ductus arteriosus open
e. Indomethacin should be given to close the ductus arteriosus

Cardiovascular System

Answers

141. The answer is b. *(Cotran, pp 504–506.)* Lipids are transported in the blood complexed to proteins called apolipoproteins. Abnormalities of this lipid transport or metabolism result in hyperlipoproteinemias, which are responsible for most syndromes of premature atherosclerosis. The primary hyperlipidemias are divided into five distinct electrophoretic patterns. Type I hyperlipoproteinemia, caused by a mutation in the lipoprotein lipase gene, results in increased chylomicrons and triglycerides. Type II hyperlipoproteinemia, perhaps the most frequent Mendelian disorder, is caused by a mutation in the low-density lipoprotein (LDL) receptor gene. This results in increased LDL and cholesterol. Homozygotes for this gene defect have markedly increased plasma cholesterol levels and develop severe atherosclerosis at an early age. Mutations in the apolipoprotein E gene result in type III hyperlipoproteinemia, which is characterized by increased intermediate-density lipoproteins (IDLs), triglycerides, and cholesterol. Type IV hyperlipoproteinemia causes increased very-low-density lipoproteins (VLDLs) and triglycerides. The genetic defect causing this abnormality is a mutation in the lipoprotein lipase gene. Type V hyperlipoproteinemia, caused by a mutation in apolipoprotein CII, results in increased VLDLs, chylomicrons, triglycerides, and cholesterol. Lipoprotein(a) is an altered form of LDL that contains the apolipoprotein B100 linked to apolipoprotein(a). Increased levels of lipoprotein(a) are associated with an increased incidence of coronary and cerebral vascular disease independent of the total LDL level.

142. The answer is c. *(Isselbacher, pp 2062–2063, 2068. Ayala, p 123. Cotran, p 872.)* Increased serum lipids (hyperlipidemia) may be a primary genetic defect or may be secondary to another disorder, such as the nephrotic syndrome, alcoholism, hypothyroidism, or diabetes mellitus. Secondary increased cholesterol may be due to diet, hypothyroidism, or nephrotic syndrome, while secondary increased triglycerides may be due to diet or diabetes mellitus and increased cholesterol and triglycerides

together may be due to alcohol ingestion, pregnancy, or decreased albumin due to liver or kidney disease. Secondary hypertriglyceridemia in patients with diabetes mellitus usually occurs secondary to increased blood levels of VLDL. The reason for this is that with decreased levels of insulin with diabetes mellitus there is increased mobilization of free fatty acids from adipose tissue (increased lipolysis). This increases delivery of free fatty acids to the liver, which increases production and secretion of VLDL by the liver. This is a type IV hyperlipidemia pattern. Ethanol can also produce a type IV pattern due to increased VLDL. This is because ethanol also increases lipolysis of adipose tissue, which increases delivery of free fatty acids to the liver. Ethanol also increases the esterification of fatty acid to triglycerides in the liver and inhibits the release of lipoproteins from the liver. With the nephrotic syndrome, increased cholesterol (increased LDL) can result from increased production and decreased catabolism of lipoproteins.

In contrast to the mechanisms involved in producing secondary hyperlipidemia, increased binding of bile salts in the gut to decrease the enterohepatic circulation of cholesterol is the mechanism by which cholestyramine can decrease serum cholesterol levels. Stimulation of HMG-CoA reductase in the liver to increase the production of cholesterol and decrease the synthesis of hepatic LDL receptors is the mechanism of lovastatin, which is used to treat type II hyperlipidemia.

143. The answer is e. *(Cotran, pp 503–507. Damjanov, pp 1405–1406.)* There are various risk factors that predispose individuals to the development of atherosclerosis and ischemic heart disease. These risk factors are either quite significant (major factors) or less significant (minor factors). Major factors include diet and hyperlipidemia (hypercholesterolemia and hypertriglyceridemia), hypertension, cigarette smoking, and diabetes mellitus. Minor risk factors include obesity, lack of physical exercise, male gender, stress, oral contraceptives (birth control pills), and hyperhomocystinemia. Another minor risk factor is the presence in the serum of lipoprotein(a), which is an altered form of LDL that contains the apoprotein B100 linked to apoprotein(a). This special type of apoprotein has structural homology to plasminogen. These similar areas are called kringles because they resemble a type of Danish pastry. It is thought that, because of the similarity of structure, Lp(a) competes with plasminogen in clots and decreases the ability to form plasmin and clear clots.

144. The answer is a. *(Cotran, p 509. Rubin, pp 492–495.)* The pathogenesis of atherosclerosis depends in part on the inflammatory function of macrophages, which involves the release of numerous cytokines. Platelet-derived growth factor (PDGF) is mitogenic and chemotactic for smooth-muscle cells. This may explain the recruitment and proliferation of smooth-muscle cells in atherosclerosis. Other macrophage products participate in the pathophysiology of atherosclerosis by other means. Interleukin 1 (IL-1) and tumor necrosis factor (TNF) transform the normally anticoagulant endothelial surface into a procoagulant surface by stimulating endothelial cells to produce platelet-activating factor (PAF), tissue factor (TF), and plasminogen activator inhibitor (PAI). Interferon α and transforming growth factor β inhibit cell proliferation. This could explain the failure of endothelial cells to repair endothelial defects. These defects could then either provide entry areas for lipoproteins and plasma-derived factors or serve as an area where thrombi are formed.

145. The answer is c. *(Cotran, pp 514–515, 523.)* Malignant hypertension refers to dramatic elevations in systolic and diastolic blood pressure often resulting in early death from cerebral and brainstem hemorrhages. Pathologically, the renal vessels demonstrate a concentric obliteration of arterioles by an increase in smooth-muscle cells, and protein deposition in a laminar configuration that includes fibrin material, which leads to total and subtotal occlusion of the vessels. These changes are called *hyperplastic arteriolosclerosis.* In contrast, hyaline arteriolosclerosis as seen in diabetes mellitus is presumably caused by leakage of plasma components across the endothelium with or without hypertension. Medial calcific sclerosis (Mönckeberg's arteriosclerosis) is characterized by dystrophic calcification in the tunica media of muscular arteries. There is no narrowing of the lumen of the affected vessels. Thromboangiitis obliterans (Buerger's disease) is occlusion by a proliferative inflammatory process in arteries of heavy cigarette smokers and is often associated with HLA-A9,B5 genotypes.

146. The answer is a. *(Cotran, pp 516–518. Rubin, pp 516–517.)* Giant cell arteritis (temporal arteritis), although not a major public health problem, is an important disease to consider in the differential diagnosis of patients of middle to advanced age who present with a constellation of

symptoms that may include migratory muscular and back pains (polymyalgia rheumatica), dizziness, visual disturbances, headaches, weight loss, anorexia, and tenderness over one or both of the temporal arteries. The cause of the arteritis (which may include giant cells, neutrophils, and chronic inflammatory cells) is unknown, but the dramatic response to corticosteroids suggests an immunogenic origin. The disease may involve any artery within the body, but involvement of the ophthalmic artery or arteries may lead to blindness unless steroid therapy is begun. Therefore, if temporal arteritis is suspected, the workup to document it should be expedited and should include a biopsy of the temporal artery. Frequently, the erythrocyte sedimentation rate (ESR) is markedly elevated to values of 90 or greater. Whereas tenderness, nodularity, or skin reddening over the course of one of the scalp arteries, particularly the temporal, may show the ideal portion for a biopsy, it is important to recognize that the temporal artery may be segmentally involved or not involved at all even when the disease is present.

147. The answer is c. *(Damjanov, pp 1429–1431. Cotran, pp 520–521.)* Classic polyarteritis nodosa (PAN) is a systemic disease characterized by necrotizing inflammation of small or medium-sized muscular arteries, typically involving the visceral vessels but sparing the small blood vessels of the lungs and kidneys. Histologically, there is intense localized acute inflammation and necrosis of vessel walls with fibrinoid necrosis, and often thrombosis of the vessel with ischemic infarcts of the affected organ. Healed lesions display fibrosis in the walls of affected blood vessels with focal aneurysmal dilations. Clinically, polyarteritis is a protracted, recurring disease that affects young adults. It is a multisystem disease affecting many organs of the body, and this makes it difficult to diagnose unless the vasculitis is recognized by biopsy. Symptoms include fever, weight loss, malaise, abdominal pain, headache, and myalgia. Skin involvement results in palpable purpura. The etiology is not known, but 30% of patients with classic PAN have circulating hepatitis B antigen in their serum.

148. The answer is e. *(Cotran, pp 516, 521–522. Rubin, pp 515–516. Damjanov, pp 1429–1431.)* Antineutrophil cytoplasmic antibodies (ANCAs) may be found in patients with certain inflammatory vascular diseases or glomerular diseases, and their presence is of clinical importance for diagnosing these diseases. Immunofluorescence reveals ANCAs to have two dif-

ferent patterns. One is directed toward myeloperoxidase of neutrophils and is found in a perinuclear location (P-ANCAs). This pattern is seen in patients with microscopic polyarteritis nodosa (PAN) or idiopathic crescentic glomerulonephritis without systemic disease. Microscopic polyarteritis commonly involves glomerular and pulmonary capillaries and may produce hematuria, hemoptysis, and renal failure. Histologic sections reveal segmental fibrinoid necrosis. The other ANCA pattern reveals the antibodies to be directed against neutral leukocyte protease (proteinase 3) and results in a cytoplasmic staining pattern (C-ANCAs). This pattern is seen in patients with Wegener's granulomatosis or Churg-Strauss syndrome.

149. The answer is a. *(Cotran, pp 516, 521–522. Rubin, pp 515–516. Damjanov, pp 1429–1431.)* Leukocytoclastic angiitis refers to the histologic finding of fragmented neutrophils surrounding small blood vessels. The differential diagnosis of leukocytoclastic vasculitis includes microscopic polyarteritis nodosa and three other disorders: Henoch-Schönlein purpura, Wegener's granulomatosis, and Churg-Strauss syndrome. Henoch-Schönlein purpura is a disorder of children who present with hemorrhagic urticaria and hematuria following an upper respiratory infection. The pathology of this disease involves the deposition of IgA immune complexes in small vessels of the skin. Because the antibody is IgA, the alternate complement pathway is activated in these patients. Wegener's granulomatosis (WG) is characterized by acute necrotizing granulomas of the upper and lower respiratory tract, focal necrotizing vasculitis affecting small to medium-sized vessels, and renal disease. Histologically there is fibrinoid necrosis of small arteries, early infiltration by neutrophils, and granuloma formation with giant cells. The peak incidence is in the fifth decade, and many patients have C-ANCAs. The disease is highly fatal, with death occurring within 1 year, unless recognized and treated with immunosuppressive agents. Churg-Strauss syndrome (allergic vasculitis) is a form of necrotizing vasculitis with granulomas of the respiratory tract and asthma. The disorder is associated with increased serum IgE and peripheral eosinophilia.

150. The answer is e. *(Cotran, p 523. Rubin, pp 519–520.)* Buerger's disease (thromboangiitis obliterans) is characterized by segmental acute and chronic inflammation of intermediate and small arteries. This disorder

almost always occurs in cigarette smokers at a young age (usually below 35 years) and is often associated with HLA-A9,B5 genotypes. It used to be found exclusively in men, but recently there has been an increase in the number of reported cases in women. The vessels primarily affected are in the extremities, and this leads to painful ischemia and gangrene of the legs and arms due to thrombosis. Histologic sections reveal an acute inflammatory infiltrate involving the entire wall of the vessel. In contrast to atherosclerosis, small microabscesses may be seen within thrombi. The inflammation leads to intimal proliferation that obliterates the lumen and causes pain. The disease may regress on cessation of smoking. In contrast, granulomatous inflammation with giant cells involving blood vessels can be seen with temporal arteritis or Takayasu's arteritis. Fragmentation of neutrophils surrounding blood vessels is called leukocytoclastic vasculitis, the differential for which includes microscopic polyarteritis nodosa, Henoch-Schönlein purpura, Wegener's granulomatosis, and Churg-Strauss syndrome.

151. The answer is a. *(Cotran, pp 524–528.)* An aneurysm is an abnormal dilation of any vessel. The causes of aneurysms are many, but the two most important ones are atherosclerosis and cystic medial necrosis. Atherosclerotic aneurysms, the most common type of aortic aneurysms, usually occur distal to the renal arteries and proximal to the bifurcation of the aorta. Many atherosclerotic aneurysms are asymptomatic, but if they rupture they produce sudden, severe abdominal pain, shock, and a risk of death. Prior to rupture, physical examination reveals a pulsatile mass in the abdomen. Cystic medial necrosis refers to the focal loss of elastic and muscle fibers in the media of vessels and is seen in patients with hypertension, dissecting aneurysms, and Marfan's syndrome. Trauma may also lead to the formation of dissecting aneurysms.

Berry aneurysms, found at the bifurcation of arteries in the circle of Willis, are due to congenital defects in the vascular wall. Syphilitic (luetic) aneurysms are caused by obliterative endarteritis of the vasa vasorum of the aorta. These aneurysms are part of the tertiary manifestation of syphilis and become evident 15 to 20 years after persons have contracted the initial infection with *Treponema pallidum*. Elastic tissue and smooth-muscle cells of the media undergo ischemic destruction as a result of the treponemal infection (obliterative endarteritis). As a consequence of ischemia in the media, musculoelastic support is lost and fibrosis occurs. Grossly, the aorta

has a "tree-bark" appearance. Luetic aneurysms almost always occur in the thoracic aorta and may lead to luetic heart disease by producing insufficiency of the aortic valve (aortic regurgitation).

152. The answer is b. *(Cotran, pp 149–150, 526–528, 1310–1313.)* Dissecting aneurysms are usually the result of cystic medial necrosis of the aorta. This abnormality results from loss of elastic tissue in the media and is associated with hypertension and Marfan's syndrome. Most cases of dissecting aneurysms involve a transverse tear in the intima and are located in the ascending aorta, just above the aortic ring. The pain caused by a dissecting aneurysm is similar to the pain caused by a myocardial infarction, but it extends into the abdomen as the dissection progresses. Additionally, the blood pressure is not decreased with a dissecting aneurysm unless the aorta itself has ruptured.

In contrast, berry aneurysms, found at the bifurcation of arteries in the circle of Willis, are due to congenital defects in the vascular wall. Rupture of these aneurysms may produce a fatal subarachnoid hemorrhage. Berry aneurysms have been noted in about one-sixth of patients with adult polycystic renal disease and account for death in about 10% of patients with this type of polycystic renal disease. Syphilitic (luetic) aneurysms occur in the thoracic aorta and may lead to luetic heart disease by producing insufficiency of the aortic valve. Mycotic (infectious) aneurysms result from microbial infection during septicemia, usually secondary to bacterial endocarditis. They are prone to rupture and hemorrhage. The Ehlers-Danlos syndromes (EDSs) are a group of eight syndromes characterized by defects in collagen synthesis. In EDS IV there is deficient synthesis of type III collagen and a tendency to rupture of muscular arteries, including dissecting aneurysms of the aorta.

153. The answer is c. *(Cotran, pp 531–535.)* Benign tumors of vessels may originate from either blood vessels or lymphatics. Hemangiomas are benign tumors of blood vessels that histologically reveal the presence of red blood cells (erythrocytes) within the lumen of the proliferating vessels. Hemangiomas may be subclassified as capillary or cavernous. The juvenile (strawberry) hemangioma is a fast-growing lesion that appears in the first few months of life, but completely regresses by the age of 5 years. In contrast to hemangiomas, lymphangiomas are tumors that are derived from lymphatic vessels. Histologically they reveal dilated vessels lined by

endothelial cells, but they lack red blood cells in their lumen. The absence of red blood cells helps to distinguish these lesions from hemangiomas. Cystic hygromas are cystic lymphangiomas that typically occur in the neck or axilla. They may grow to such a large size that the neck is deformed. These lesions may be found in patients with Turner's syndrome, an abnormality that results from complete or partial monosomy for the X chromosome. Swelling of the neck in these individuals occurs because of dilated lymphatic vessels. With time the swelling decreases, but patients may develop bilateral neck webbing and loose skin on the back of the neck.

In contrast, dilated blood vessels (vascular ectasia) may be congenital or acquired. "Birthmarks" may be caused by congenital vascular ectasia (nevus flammeus) or capillary hemangiomas. "Port-wine stains" are similar lesions that may be caused by vascular ectasia or cavernous hemangiomas of the skin. Spider angiomas are acquired vascular ectasias that are the result of increased estrogen levels. They are associated with pregnancy and liver disease. Bacillary angiomatosis is a nonneoplastic proliferation of blood vessels that is found in immunocompromised patients, particularly patients with AIDS. Histologically, there are proliferating capillaries that are lined by protuberant endothelial cells. Additionally, numerous neutrophils are present along with nuclear dust and purple granules. These latter granules are *Rickettsia*-like bacteria that are the cause of this lesion, which responds to erythromycin.

154. The answer is c. *(Cotran, p 533. Rubin, p 527.)* Glomus tumors (glomangiomas) are very painful tumors that are derived from the glomus body, which is a specialized connection between arteries and veins that is involved with thermoregulation. Glomus tumors are typically found in the distal regions of the fingers and toes, sometimes in a subungual location. Histologically they reveal vascular spaces that are lined by nests of uniform cells.

155. The answer is e. *(Cotran, pp 535–537.)* Kaposi's sarcoma (KS) comprises four distinct forms. The classic, or European, form has been known since 1862. It occurs in older men of Eastern European or Mediterranean origin (predominantly Italian or Jewish) and is characterized by purple maculopapular skin lesions of the lower extremities and visceral involvement in only 10% of cases. The African form occurs in younger people and is more aggressive; it often involves lymph nodes in children. The rare form

in immunosuppressed recipients of renal transplants often regresses when immunosuppression stops. In the epidemic form associated with AIDS, skin lesions may occur anywhere and disseminate to the mucous membranes, GI tract, lymph nodes, and viscera. Histologic determination is difficult, but all four clinical types appear similar. In the early stages, irregular, dilated epidermal vascular spaces, extravasated red cells, and hemosiderin are characteristic. This histologic appearance is very similar to that of granulation tissue or stasis dermatitis. Later in the disease process, more characteristic lesions show spindle cells around slit spaces with extravasation of erythrocytes. In contrast, irregular vascular spaces lined by nests of uniform cells describes the histologic appearance of a glomus tumor, while multiple dilated endothelial-lined vessels that lack red blood cells describes the histologic appearance of lymphangiomas. Numerous neutrophils, nuclear dust, and purple granules characterize bacillary angiomatosis, while proliferating blood vessels, endothelial cells, and fibroblasts suggest granulation tissue.

156. The answer is b. *(Cotran, pp 116–117, 546–550.)* The photograph shows the classic pattern of hepatic congestion around central veins, which leads to necrosis and degeneration of the hepatocytes surrounded by pale peripheral residual parenchyma. This is the pattern arising in the liver from chronic passive congestion as a result of right heart failure ("nutmeg liver"). Mitral stenosis with consequent pulmonary hypertension leads to right heart failure, as does any cause of pulmonary hypertension, such as emphysema (cor pulmonale). Right heart failure also leads to congestion of the spleen and transudation of fluid into the abdomen (ascites) and lower-extremity soft tissues (pitting ankle edema) as a result of venous congestion. Portal vein thrombosis is most often seen in association with hepatic cirrhosis.

157. The answer is e. *(Cotran, pp 546–550.)* There are many causes of congestive heart failure, but basically the heart will fail if it is forced to work in an abnormal state for a prolonged period of time. These abnormal states can cause systolic dysfunction or diastolic dysfunction. Systolic dysfunction may result from increased preload, increased afterload, or decreased contractility. Causes of increased preload (volume overload) include regurgitation (mitral regurgitation and aortic regurgitation), anemia, hyperthyroidism, and beriberi. Note that diseases with increased car-

diac output, such as anemia, hyperthyroidism, and beriberi, are classified as high-output failure diseases. In contrast, diseases that decrease cardiac output are called low-output failure diseases. Causes of increased afterload (pressure overload) include hypertension, aortic stenosis, and hypertrophic cardiomyopathy. Decreased contractility can result from myocardial infarction, myocardial ischemia, drugs, and certain infections. Diastolic dysfunction results from decreased filling of the ventricles during diastole. Examples of this include mitral stenosis, infiltrative diseases such as amyloidosis, and constrictive pericardial diseases.

158. The answer is a. *(Cotran, p 554.)* One of the consequences of myocardial ischemia is chest pain, which is called angina. Angina is caused by a mismatch between the myocardial oxygen demand and the myocardial blood flow. There are three main types of angina. Typical angina (stable angina) is the most common type and is characterized by pain that results from exercise, stress, or excitement. The pain is promptly relieved by rest (which decreases oxygen demand) or nitroglycerin. Nitroglycerin is converted to nitric oxide, which is a vasodilator that increases perfusion to the heart. ECG changes in patients with stable angina are nonspecific and include T wave inversion and ST segment depression, which occurs secondary to ischemia of the subendocardium of the left ventricle. The second type of angina, Prinzmetal's angina (atypical angina), is caused by coronary artery vasospasm and is characterized by pain occurring at rest. This pain may be relieved by calcium channel blockers or nitroglycerin. ECG in these patients reveals ST segment elevation, which is the result of transmural ischemia. The third type of angina is unstable angina, which is characterized by increasing frequency of pain, increased duration of pain, or pain that is produced by less physical exertion. This final type of angina indicates that a myocardial infarction (MI) may be near, most likely due to the formation of a thrombus over an area of coronary artery atherosclerosis. In contrast to an MI, with angina there is no actual necrosis (infarction) of myocardial tissue, and therefore there are no increased cardiac enzymes, such as LDH and CPK, in the serum. Also, the pain of angina is not made worse with deep inspiration, a sign that is suggestive of pleural disease.

159. The answer is e. *(Cotran, p 561. Henry, p 290.)* The clinical diagnosis of myocardial infarction depends upon correlating clinical symptoms,

ECG findings, and serum cardiac enzyme changes. The classic description of the pain produced by an MI is crushing, substernal pain that may radiate down the patient's left arm. This pain may be associated with sweating, nausea, and vomiting. ECG findings associated with MI include ST segment elevation (which may return to normal), inverted T waves, and abnormal Q waves. Serum enzymes that may be elevated after an MI include troponin, CPK, SGOT (AGT), and LDH, which are increased temporally in that order. The troponin complex is made up of three protein subunits: troponin I (Tn-I), troponin T, and troponin C. There are three isoforms of Tn-I: two in skeletal muscle and one in cardiac muscle (cTn-I). cTn-I levels begin to increase 4 to 6 h after the onset of chest pain, reach maximal serum concentration in about 12 to 24 h, and remain elevated for about 3 to 10 days. CPK exists in three isoenzymes, MM, MB, and BB, where M stands for muscle and B stands for brain. Elevation of the CPK MB isoenzyme is seen following an MI. Levels begin to rise at 4 to 8 h, peak at 12 to 24 h, and return to normal in 3 to 4 days. LDH exists in five isoenzyme forms. Normally serum LDH2 is greater than LDH1, but following an MI this ratio is flipped; that is, LDH1 is greater than LDH2. LDH1 levels begin to rise at 10 to 12 h, peak at 2 to 3 days, and return to normal in 7 to 10 days.

160. The answer is c. *(Cotran, pp 555–559. Rubin, pp 556–57.)* The area of necrosis produced by a myocardial infarction depends upon the site of occlusion and the anatomic distribution of the affected vessel. The left anterior descending (LAD) artery supplies the anterior left ventricle, the apex, and the anterior two-thirds of the interventricular septum. The left circumflex artery supplies the lateral and posterior wall of the left ventricle. The right coronary artery supplies the right ventricle and the posterior one-third of the interventricular septum (if there is a right-dominant distribution). Generally, posterior (inferior or diaphragmatic) infarcts result from occlusion of the right coronary artery, anterior infarcts (such as infarction of the anterior left ventricle) from occlusion of the LAD, and posterolateral infarcts from occlusion of the left circumflex artery. It is also important to note that atherosclerosis, which is the main cause of coronary artery occlusion, does not affect the coronary arteries equally. Generally atherosclerosis affects the proximal 2 cm of the LAD and left circumflex artery, and the proximal and distal one-third of the right coronary artery.

161. The answer is c. *(Cotran, pp 556–561.)* Areas of myocardial infarction (MI) undergo a series of changes that consists of typical ischemic coagulative necrosis followed by inflammation and repair. MIs less than 6 to 12 h old are not apparent on gross examination. By 12 to 24 h, there is pallor in the area of infarction, which is due to the trapped blood. On days 1 to 3, grossly the infarct develops a hyperemic (red) border and then becomes pale yellow over the next several days (days 4 to 7). By 7 to 14 days, the area of necrosis is surrounded by a hyperemic red-purple border of highly vascularized granulation tissue. Over the next few weeks, the area of necrosis changes to a gray-white fibrotic scar. Electron microscopic (EM) changes in MI can be seen at 20 to 40 min, but routine histologic changes are first seen at 1 to 3 h. These EM findings consist of signs of reversible injury (mitochondrial swelling and distortion of cristae) and signs of irreversible injury (mitochondrial amorphous densities called flocculent densities). The earliest histologic change is the formation of wavy fibers. These wavy fibers result from the pulling of the noncontractile necrotic fibers by adjacent viable fibers. Histologic features of coagulation necrosis are seen at 12 to 24 h. An acute inflammatory response consisting mainly of neutrophils is most pronounced on days 2 to 3, while macrophages predominate during days 4 to 7. The ingrowth of highly vascularized granulation tissue begins around day 7 and is maximal at 2 to 4 weeks. Note that at about days 4 to 10 the infarcted tissue becomes quite soft, and there is a risk of cardiac rupture. These events within the first few weeks are followed by scarring (fibrosis), which is well developed by the sixth week and is irreversible.

162. The answer is d. *(Cotran, pp 562–563.)* Cardiac rupture, whether of free wall, septum, or papillary muscle, occurs in only 1 to 5% of cases following acute myocardial infarction. It occurs usually within the first week of infarction, when there is maximal necrosis and softening (4 to 5 days) and is very rare after the second week. Rupture of the free wall results in pericardial hemorrhage and cardiac tamponade. Rupture of the interventricular septum causes a left-to-right shunt. Serious mitral valve incompetence results from rupture of anterior or posterior papillary muscles. This valve incompetence can produce signs of mitral regurgitation, including a new pansystolic murmur along with a diastolic flow murmur. Indeed, the onset of a new murmur following a myocardial infarction should raise the possibility of papillary rupture.

Other common complications of myocardial infarction include arrhythmias such as heart block, sinus arrhythmias, or ventricular tachycardia or fibrillation. These occur in 90% of complicated cases. Next in importance, but not in frequency (only 10%), is cardiogenic shock from severe left ventricular contractile incompetence. Milder left ventricular failure with lung edema occurs in 60% of these cases, while mural thrombosis with peripheral emboli may occur in up to 40%. Ventricular aneurysm forms a "bulge" of the left ventricular chamber; it consists of scar tissue and does not rupture, but may contain a thrombus. Sudden cardiac death occurs within 2 h in 20% of patients with acute myocardial infarction.

163. The answer is b. *(Cotran, pp 562–563, 587–589.)* Cardiac rupture is most frequent at 4 to 7 days post-MI, while fibrinous pericarditis usually develops around day 2 to 3. Pericarditis that develops approximately 1 to 3 weeks following an MI is called Dressler's syndrome. This is an autoimmune disorder. Pericarditis refers to inflammation of the pericardium. Patients develop severe retrosternal chest pain that is typically worse with deep inspiration or coughing. Physical examination reveals the characteristic pericardial friction rub. ECG changes and pulsus paradoxus are also present. Pericarditis developing after a myocardial infarct is usually either serous or serofibrinous. Serous pericarditis contains few inflammatory cells and may also result from uremia or autoimmune diseases such as SLE. Serofibrinous pericarditis has a fibrinous exudate mixed with the serous fluid and may result from uremia or viral infections. Other types of pericarditis include purulent (suppurative) pericarditis with many inflammatory cells (seen with bacterial infections) or hemorrhagic pericarditis (seen with carcinoma or tuberculosis).

164. The answer is b. *(Cotran, pp 564–566. Abenhaim, N Engl J Med 335(9):609–616. Connolly, N Engl J Med 337(9):581–588.)* Hypertensive heart disease (HHD) can be divided into systemic HHD and pulmonary HHD. Systemic HHD is the result of systemic hypertension, which causes left ventricular (LV) hypertrophy. There is by definition no other cardiac disease present that could cause LV hypertrophy, such as aortic stenosis. Hypertension is a pressure overload on the heart, and as such it causes concentric LV hypertrophy without dilation. In contrast, eccentric hypertrophy is the result of volume overload on the heart. In systemic HHD the LV is stiff, as there is decreased LV compliance. In a patient with uncontrolled

hypertension, LV dilation would indicate LV failure. Pulmonary HHD indicates right ventricular hypertrophy that is the result of pulmonary disease. By definition, this type of heart disease is called cor pulmonale. Pulmonary diseases that can cause cor pulmonale include diseases of the lung parenchyma, such as chronic obstructive pulmonary disease and interstitial fibrosis, and diseases of the pulmonary vessels, such as multiple pulmonary emboli and pulmonary vascular sclerosis. The latter has been associated with the use of the combination of diet drugs fenfluramine and phentermine. (This combination has been referred to as Fen-Phen.)

165. The answer is b. *(Cotran, pp 567–568.)* Aortic stenosis (AS) is usually the result of a bicuspid aortic valve (AV), degenerative calcification of a bicuspid valve, or rheumatic heart disease. Patients with aortic stenosis may present with angina (chest pain), syncopal episodes with exertion, and heart failure. Angina results from the mismatch between increased oxygen demand of the hypertrophied left ventricle (LV) and decreased blood flow, while syncope results from the inability to increase stroke volume as necessary with a stenotic AV. AS is the most common valvular disease that is associated with angina and syncope. The characteristic heart murmur of AS is a crescendo-decrescendo midsystolic ejection murmur that has a paradoxically split S_2. In order to pump the blood into the aorta across a stenotic AV, the pressure in the LV must be much greater than the resultant pressure in the aorta. In order to produce this increased pressure, the LV undergoes concentric hypertrophy, which increases contractility. This concentric hypertrophy also makes the wall of the LV stiffer (decreased compliance). This stiff LV is unable to dilate until the time the LV starts to fail.

166. The answer is c. *(Damjanov, pp 1257–1272.)* Aortic regurgitation (AR) is rheumatic in origin in approximately 70% of cases. Much less frequently it is due to syphilis, ankylosing spondylitis (rarely), infective endocarditis, aortic dissection, or aortic dilation from cystic medial necrosis. Congenital forms of aortic stenosis occur fairly frequently, but AR is rarely congenital in origin. In chronic AR, patients remain asymptomatic for many years, but clinical manifestations include exertional dyspnea, angina, and left ventricular failure. Owing to the rapidly falling arterial pressure during late systole and diastole, there is often wide pulse pressure, Corrigan's "water-hammer" pulse, capillary pulsations at the nail beds, and a pistol-shot sound over the femoral arteries. A blowing diastolic murmur is heard

along the left sternal border. Volume overload of the heart is the basic defect and results in left ventricular dilation and hypertrophy.

167. The answer is d. *(Cotran, p 568.)* The normal mitral valve (MV) is a bicuspid valve with the anterior cusp approximately twice the area of the posterior cusp. The MV area is normally 5 to 6 cm^2. Clinically significant mitral stenosis (MS) usually results when the valve area decreases to less than 1 cm^2. MS most commonly develops as a consequence of rheumatic heart disease. It may also develop due to congenital abnormalities or calcium deposition. In patients with mitral stenosis there is decreased flow across the MV due to the stenosis of the valve. In order to move the blood into the left ventricle (LV), the left atrial (LA) pressure during diastole is greater than normal and greater than the LV pressure. Instead of producing changes in the LV, mitral stenosis causes the left atrium to hypertrophy and dilate. These changes predispose patients with MS to arrhythmias (which are felt as palpitations) and to the development of LA thrombi (which may lead to systemic emboli). The hypertrophied left atrium may also compress the esophagus (resulting in dysphagia, or problems swallowing food) or irritate the recurrent laryngeal nerve (producing hoarseness). The increased LA pressure also causes a middiastolic murmur and can be reflected back into the lungs and to the right ventricle. In the lungs this produces venous congestion and hemorrhage, which cause dyspnea, fatigue, and hemoptysis.

168. The answer is d. *(Cotran, pp 570–572.)* Rheumatic fever (RF) is a systemic disease with the major findings of migratory polyarthritis of large joints, carditis, erythema marginatum of skin (although skin involvement is not very common), subcutaneous nodules, and Sydenham's chorea, a neurologic disorder with involuntary, purposeless, rapid movements, which is most likely to occur in adolescent females and during pregnancy. There is no relation to Huntington's chorea. Fever is a minor characterization, although quite frequent. Rheumatic nodules may develop over pressure points during the later stages and seldom occur in cases without cardiac involvement. RF usually follows a pharyngeal infection with group A β-hemolytic streptococci because of an autoimmune mechanism based on cross-reactions between cardiac antigens and antibodies evoked by one of the many streptococcal antigens, e.g., streptococcal M protein. Immunofluorescence shows immunoglobulins and complement along sarcolemmal

sheaths of cardiac myofibers, but Aschoff bodies seldom contain immunoglobulins or complement.

169. The answer is d. *(Cotran, pp 570–572.)* Rheumatic fever (RF) produces both acute and chronic manifestations. Acute RF produces a pancarditis of all three layers of the heart. It is manifested by myocarditis, which is characterized histologically by the Aschoff body; pericarditis, which is referred to as "bread-and-butter" pericarditis; and verrucous endocarditis. In contrast to acute RF, chronic RF produces damage to cardiac valves. The mitral valve is most commonly involved, followed by the aortic valve. The stenotic valve has the appearance of a "fish mouth" or "buttonhole." An additional finding in chronic RF is a rough portion of the endocardium of the left atrium, called a MacCallum's patch.

170. The answer is b. *(Cotran, pp 572–576. Chandrasoma, pp 349–353.)* Infective endocarditis is the result of microorganisms growing on any of the heart valves. These organisms may have either high virulence or low virulence. Highly virulent organisms, such as *S. aureus* and group A streptococci, infect previously normal valves and produce severe symptoms within 6 weeks. This abnormality is referred to as acute bacterial endocarditis. In contrast, organisms of low virulence, such as α-hemolytic viridans streptococci and *Staphylococcus epidermidis,* infect previously damaged valves, such as valves damaged by rheumatic fever. These organisms produce symptoms that last longer than 6 weeks. This abnormality is referred to as subacute bacterial endocarditis. Infective endocarditis in IV drug abusers, which normally occurs on the tricuspid valve, is caused by *S. aureus,* group A streptococci, *Candida* species, and gram-negative bacilli such as *Pseudomonas* species. Symptoms in patients with infective endocarditis are the result of bacteremia, emboli from the vegetations, immune complexes, and valvular disease. Bacteremia produces fever, positive blood cultures (several of which may be needed for confirmation), abscesses, and osteomyelitis. Embolization of parts of the large, friable vegetations can produce Roth spots in the retina, splinter hemorrhages in nail beds, and infarcts of the brain, heart, and spleen. Splenic infarcts produce left upper quadrant (LUQ) abdominal pain. Immune complexes can deposit in multiple areas of the body and cause glomerulonephritis, vasculitis, tender nodules in the fingers and toes (Osler's nodes), and red papules in the

palms and soles (Janeway lesions). Valvular disease can also result in perforation and valvular regurgitation.

171. The answer is e. *(Cotran, pp 584–586. Rubin, pp 575–576.)* Inflammation of the myocardium (myocarditis) has numerous causes, but most of the well-documented cases of myocarditis are of viral origin. The most common viral causes are coxsackieviruses A and B, echovirus, and influenza virus. Patients usually develop symptoms a few weeks after a viral infection. Most patients recover from the acute myocarditis, but a few may die from congestive heart failure or arrhythmias. Sections of the heart show patchy or diffuse interstitial infiltrates composed of T lymphocytes and macrophages. There may be focal or patchy acute myocardial necrosis. Bacterial infections of the myocardium produce multiple foci of inflammation composed mainly of neutrophils. Giant cell myocarditis, which was previously called Fiedler's myocarditis, is characterized by granulomatous inflammation with giant cells and is usually rapidly fatal. In hypersensitivity myocarditis, which is caused by hypersensitivity reactions to several drugs, the inflammatory infiltrate includes many eosinophils, and the infiltrate is both interstitial and perivascular. Beriberi, one of the metabolic diseases of the heart, is a cause of high-output failure and is characterized by decreased peripheral vascular resistance and increased cardiac output. Patients have dilated hearts, but the microscopic changes are nonspecific. Hyperthyroid disease and Paget's disease are other causes of high-output failure.

172. The answer is c. *(Cotran, pp 576–577.)* Plaques or vegetations are found in characteristic locations within the heart in several different disorders. Vegetations can occur in acute rheumatic fever as small masses found in a row along the lines of closure of the valves. In contrast, the vegetations of infective endocarditis are large, irregular masses that extend beyond the valves onto the chordae. Nonbacterial thrombotic (marantic) endocarditis, which is associated with prolonged debilitating diseases and cachexia, may produce one or two small, sterile vegetations at the line of valve closure. In patients with systemic lupus erythematosus, medium-sized vegetations (Libman-Sacks endocarditis) may occur on either or both sides of the valve leaflets, typically on the mitral valve and the tricuspid valve. The development of Libman-Sacks endocarditis is associated with the presence of the

lupus anticoagulant (antiphospholipid syndrome), an antibody that makes platelets "sticky" and increases the chance of thrombosis.

173. The answer is e. *(Cotran, pp 577–578, 835–837.)* White plaques involving the right side of the heart are associated with the carcinoid syndrome. This syndrome is characterized by episodic flushing, diarrhea, bronchospasm, and cyanosis. These symptoms are caused by the release of vasoactive amines, such as serotonin, from carcinoid tumors. These substances are inactivated by enzymes such as monoamine oxidase (MAO) in the liver, lung, and brain. MAO-A degrades norepinephrine and serotonin, while MAO-B degrades dopamine. Cardiac symptoms are found in patients with liver metastases, which bypass the inactivation by the liver itself. The cardiac lesions producing carcinoid heart disease are found on the right side of the heart because these active metabolites are inactivated in the lung. The cardiac lesions consist of fibrous plaques found on the tricuspid and pulmonic valves. Microscopic sections of these plaques reveal smooth-muscle cells and sparse collagen fibers in an acid mucopolysaccharide matrix. Similar lesions can develop with the use of certain diet suppressants or with ergotamine therapy for migraine headaches. Diet suppressants associated with these lesions include dexfenfluramine (Redux) and Fen-Phen (fenfluramine and phentermine). Redux increases serotonin levels by increasing release and decreasing uptake of serotonin in the CNS (supposedly this increases satiety). Phentermine decreases the appetite center in the brain by increasing norepinephrine levels by increasing the release and decreasing the uptake of norepinephrine.

In contrast to the case with carcinoid heart disease, plaques in the left atrium are seen in chronic rheumatic heart disease and are called MacCallum's patches. Vegetations also occur in rheumatic heart disease; these are small and are found in a row along the lines of closure of the valves. Amyloid deposits may be found in the heart secondary to multiple myeloma or as an isolated event, such as in senile cardiac amyloidosis. Grossly the walls of the heart may be thickened, and there may be multiple small nodules on the left atrial endocardial surface. Iron overload can affect the heart as a result of hereditary hemochromatosis or hemosiderosis. Grossly the heart is a rust-brown color and resembles the heart in idiopathic dilated cardiomyopathy. In hypothyroidism the heart is characteristically flabby, enlarged, and dilated, which results in decreased cardiac output. This reduced circulation results in a characteristic symptom of

hypothyroidism, cold sensitivity. Histologically there is an interstitial mucopolysaccharide edema fluid within the heart.

174. The answer is a. *(Cotran, pp 578–584.)* The cardiomyopathies (CMPs) may be classified into primary and secondary forms. The primary forms are mainly idiopathic (unknown cause). Most of the secondary cardiomyopathies result in a dilated cardiomyopathy that is characterized by congestion and four-chamber dilation with hypertrophy. The walls are either of normal thickness or they may be thinner than normal. This results in a flabby, globular, banana-shaped heart that is hypocontracting. The microscopic appearance is not distinctive. The ventricles may contain mural thrombi. The causes of secondary dilated CMP are many and include alcoholism (the most common cause in the United States), metabolic disorders, and toxins. Examples of the latter include cobalt, which has been used in beer as a foam stabilizer; anthracyclines; cocaine; and iron, the deposition of which is seen in patients with hemochromatosis. The anthracycline Adriamycin, which is used in chemotherapy, causes lipid peroxidation of myofiber membranes. One final form of DCM develops in the last trimester of pregnancy or the first 6 months after delivery. About half of these patients recover full cardiac function.

Other forms of cardiomyopathies include a hypertrophic form, a restrictive form, and an obliterative form. In hypertrophic CMP the major gross abnormality is within the interventricular septum, which is usually thicker than the left ventricle. Constrictive (restrictive) CMP is associated with amyloidosis, sarcoidosis, endomyocardial disease, or storage diseases. These abnormalities produce a stiff, hypocontracting heart.

175. The answer is a. *(Cotran, pp 578–584.)* Hypertrophic cardiomyopathy is characterized by asymmetric hypertrophy of the interventricular septum, histologic sections of which reveal disorganized, hypertrophied myofibers. These changes produce hypercontractility that predisposes patients to the risk of sudden death. Patients may experience dyspnea, lightheadedness, and chest pain, especially upon physical exertion; however, many patients appear to be asymptomatic, although sudden, unexpected death occurs not infrequently, especially following or during physical exertion. This risk is increased with factors that either increase the contractility of the heart or decrease the volume of the left ventricle (both of which increase the left ventricular outflow obstruction). Treatment for patients

with hypertrophic cardiomyopathy, therefore, is with drugs that decrease contractility. Examples of these types of drugs include β-adrenergic blockers and calcium channel blockers. In individuals with hypertrophic cardiomyopathy, agents that increase contractility are contraindicated. Examples of these types of drugs include glycosides, such as digitalis. Epinephrine and β-adrenergic agonists, which increase cardiac output by increasing stroke volume and heart rate, would also be contraindicated. Diuretics would also be dangerous, as they would decrease intravascular volume, and this would accentuate the bad effects of the septal hypertrophy because of the decreased left ventricular volume.

In contrast, dilated (congestive) cardiomyopathy results in a flabby, hypocontractile heart. Constrictive (restrictive) cardiomyopathy is associated in the United States with amyloidosis and endocardial fibroelastosis. It is so named because of the infiltration and deposition of material in the endomyocardium and the layering of collagen and elastin over the endocardium. This deposition affects the ability of the ventricles to accommodate blood volume during diastole. Endocardial fibroelastosis, which occurs mainly in infants during the first 2 years of life, is associated with a prominent fibroelastic covering over the endocardium of the left ventricle. There may be associated aortic coarctation, ventricular septal defects, mitral valve defects, and other abnormalities. In contrast, endomyocardial fibrosis is a form of restrictive cardiomyopathy that is found mainly in young adults and children in Southeast Asia and Africa. It differs from endocardial fibroelastosis in the United States in that elastic fibers are not present.

176. The answer is a. *(Cotran, pp 578–584.)* The cardiomyopathy shown in the photograph is designated hypertrophic cardiomyopathy with the synonyms of idiopathic hypertrophic subaortic stenosis (IHSS), hypertrophic obstructive cardiomyopathy, and asymmetric septal hypertrophy (ASH). It is characterized by a prominent and hypertrophic interventricular septum that is out of proportion to the thickness of the left ventricle. Histologically the myocardial fibers exhibit disarray, caused by wide fibers with unusual orientation, and prominent hyperchromatic nuclei. There is an increased incidence of hypertrophic cardiomyopathy within families, and there is evidence that it may be an autosomal dominant disorder. The disease is thought to result from a mutation in the cardiac β-myosin heavy chain gene. In contrast, an abnormal fibrillin gene is associated with Marfan's syndrome, decreased acid maltase is associated with Pompe's disease,

an abnormal dystrophin gene is associated with Duchenne muscular dystrophy, and decreased NADPH oxidase is associated with chronic granulomatous disease.

177. The answer is c. *(Cotran, p 587.)* Accumulations of excess fluid within the pericardial cavity are called pericardial effusions. The sudden filling of the pericardial space with fluid is called pericardial tamponade. The three classic signs of pericardial tamponade, called Beck's triad, include hypotension, elevated jugular pressure, and muffled heart sounds. The latter is due to the damping effect of the pericardial fluid on the heart sounds. Some patients may also demonstrate a decrease in systemic pressure with inspiration, which is called paradoxic pulse. The decrease in cardiac output produces dyspnea, shortness of breath, and hypotension. Decreased atrial filling results in elevated jugular venous pressure. There are several types of pericardial effusions. Serous pericardial effusions are caused most often by congestive heart failure, but they can also be caused by renal disease that produces uremia. Serosanguinous effusions are caused by trauma and cardiopulmonary resuscitation (CPR). Chylous effusions are caused by lymphatic obstruction, while cholesterol effusions are seen in patients with myxedema, which is caused by hypothyroidism. Hemopericardium (blood in the pericardial cavity) is most commonly caused by the rupture of a myocardial infarction.

178. The answer is d. *(Cotran, pp 589–591.)* Most tumors involving the heart are secondary to metastases, most commonly from bronchogenic carcinoma or breast carcinoma, and they usually involve the pericardium. Primary tumors of the heart are quite rare; the most common in the adult is the myxoma. These tumors occur most often in the left atrium, and if pedunculated they may interfere with the mitral valve by a "ball valve" effect. Histologically they are composed of stellate cells in a loose myxoid background. Rhabdomyomas are the most common primary cardiac tumors in infants and children and often occur in association with tuberous sclerosis. Histologically, so-called spider cells may be seen. Papillary fibroelastomas usually are incidental lesions found at the time of autopsy and are probably hamartomas rather than true neoplasms.

179. The answer is e. *(Cotran, p 595. Rubin, pp 548–549.)* The tetralogy of Fallot consists of subaortic ventricular septal defect, obstruction to right ventricular outflow, aortic overriding of the ventricular septal defect (aortic

dextroposition), and moderate right ventricular hypertrophy. The obstruction to right ventricular outflow may be caused by infundibular stenosis of the right ventricle or stenosis of the pulmonic valve. A right-sided aorta occurs in about 25% of cases with this tetralogy. Most patients are cyanotic from birth or develop cyanosis by the end of the first year of life, since even mild obstruction of right ventricular outflow is progressive. The tetralogy of Fallot is the most common cause of cyanosis after 1 year of age and causes 10% of all forms of congenital heart disease. Hypoxic attacks and syncope are serious complications, forming the most common mode of death from this disease during infancy and childhood. Other complications include infectious endocarditis, paradoxical embolism, polycythemia, and cerebral infarction or abscess.

180. The answer is c. *(Cotran, pp 591–597. Rubin, pp 543–544.)* Congenital heart defects may or may not involve shunting of blood between the systemic and pulmonary circulations. Examples of defects with no shunts include coarctation of the aorta, Ebstein's malformation (a downward displacement of an abnormal tricuspid valve into an underdeveloped right ventricle), and transposition of the great vessels. Examples of defects that initially involve a left-to-right shunt, from the higher-pressure left side to the lower-pressure right side, include ventricular septal defects (the most common of all heart defects), atrial septal defects, patent ductus arteriosus, and persistent truncus arteriosus. These defects initially do not produce cyanosis, but cyanosis may develop later (tardive cyanosis). A defect that initially involves a right-to-left shunt is the tetralogy of Fallot. This is the most common cyanotic congenital heart disease of older children and adults.

181. The answer is d. *(Cotran, pp 592–595.)* Left-to-right congenital shunts are not initially cyanotic, but cyanosis may develop later (tardive cyanosis) if the shunt shifts to a right-to-left shunt due to increased pulmonary vascular resistance (Eisenmenger's complex). Atrial septal defects (ASDs) illustrate this pathophysiologic effect well. The shunt with an ASD is initially left-to-right: left atrium to right atrium to right ventricle to lungs to left atrium. Cyanosis does not occur until later, when the shunt reverses, becoming right-to-left. This occurs because with time the pulmonary vessels become hyperplastic and irreversible pulmonary hypertension develops because of the volume overload to the lungs. The blood flow with an

ASD that has reversed due to Eisenmenger's complex is: right atrium to left atrium (e.g., right-to-left) to left ventricle to aorta, then back to right atrium. An ASD with elevated pulmonary pressures allows emboli to enter the systemic circulation directly (paradoxical embolus). Note that ASDs are the most common type of congenital heart disease that presents in adults; these individuals develop palpitations, exertional dyspnea, systolic flow murmurs, widely split fixed S_2, and right axis deviation.

182. The answer is a. *(Cotran, pp 595–596.)* As the endocardial cushions join to divide the ventricles, the streams of blood from the right and left ventricles are divided as they flow out of the truncus. A spiral septum develops to physically separate the two streams of blood. The fusion of the spiral ridges results in division of the truncus into the pulmonary and aortic arteries. Occasionally the spiral is reversed, resulting in the aorta arising from the right ventricle and the pulmonary artery from the left. This is a complete transposition of the great vessels and produces two completely separate blood systems. This situation obviously is incompatible with life unless some type of mixing of blood can occur between these separate systems. In utero, mixing of blood occurs across the atrial septum and in connections with the placental circulation. Cases that survive to corrective surgery must have a persistent atrial septal defect or patent ductus arteriosus to allow mixing of blood. Therefore, clinical consideration should be to keep the ductus arteriosus open. Usually, at birth, breathing decreases pulmonary resistance and this then reverses flow through the ductus arteriosus. This oxygenated blood (flowing from the aorta into the ductus) inhibits prostaglandin production, which in turn closes the ductus arteriosus. To keep the ductus arteriosus open, prostaglandin E_2 should be given.

This page intentionally left blank.

Hematology

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

183. Which of the following red cell abnormalities is most indicative of hemolysis?

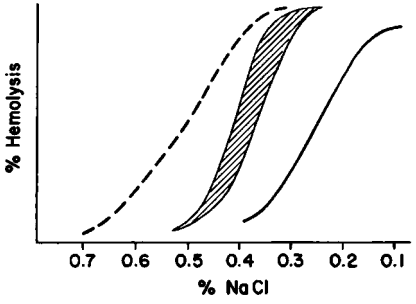
a. Target cells
b. Acanthocytes
c. Schistocytes
d. Basophilic stippling
e. Heinz bodies

184. Markedly decreased blood levels of which one of the listed substances are most characteristic of intravascular hemolysis?

a. Alkaline phosphatase
b. Bilirubin
c. Haptoglobin
d. Lactate dehydrogenase
e. Methemoglobin

185. The graph below depicts the results of a red cell osmotic fragility test. The dashed curve represents which of the following?

a. Glucose-6-phosphate dehydrogenase deficiency
b. Thalassemia
c. Hereditary spherocytosis
d. Drug-induced hemolytic anemia
e. Normal response



186. Two days after receiving the antimalarial drug primaquine, a 27-year-old black man develops sudden intravascular hemolysis resulting in a decreased hematocrit, hemoglobinemia, and hemoglobinuria. Examination of the peripheral blood reveals erythrocytes with a membrane defect forming "bite" cells; when crystal violet stain is applied, many Heinz bodies are seen. The most likely diagnosis is

a. Hereditary spherocytosis
b. Glucose-6-phosphate dehydrogenase deficiency
c. Paroxysmal nocturnal hemoglobinuria
d. Autoimmune hemolytic anemia
e. Microangiopathic hemolytic anemia

187. A single nucleotide change in a codon on chromosome 11 that causes valine to replace glutamic acid at the sixth position of the β chain of hemoglobin is associated with

a. α thalassemia
b. Glucose-6-phosphate dehydrogenase deficiency
c. Hereditary spherocytosis
d. Paroxysmal nocturnal hemoglobinuria
e. Sickle cell anemia

188. A 22-year-old African American male wants to know if he has sickle cell trait. He has no previous history of the signs or symptoms of sickle cell anemia. What laboratory method or test can be used to detect the presence of hemoglobin S?

a. Coombs' test
b. Metabisulfite test
c. Osmotic fragility test
d. Schilling test
e. Sucrose hemolysis test

189. Deletion of all four normal α-globin genes will most likely produce

a. α thalassemia minor
b. β thalassemia minor
c. Cooley's anemia
d. Hemoglobin H disease
e. Hydrops fetalis

190. Hemoglobin electrophoresis of the blood from an individual with Cooley's anemia (β thalassemia major) would most likely show which one of the following combinations of findings?

	Hemoglobin A	Hemoglobin A2	Hemoglobin F
a.	Increased	Increased	Increased
b.	Increased	Increased	Decreased
c.	Increased	Decreased	Increased
d.	Decreased	Increased	Increased
e.	Decreased	Decreased	Decreased

191. A 49-year-old female presents with signs of anemia and states that every morning her urine is dark. Workup reveals that her red blood cells lyse in vitro with acid (positive Ham's test). What is the best diagnosis for this patient?

a. Warm autoimmune hemolytic anemia
b. Paroxysmal nocturnal hemoglobinuria
c. Paroxysmal cold hemoglobinuria
d. Isoimmune hemolytic anemia
e. Cold-agglutinin autoimmune hemolytic anemia

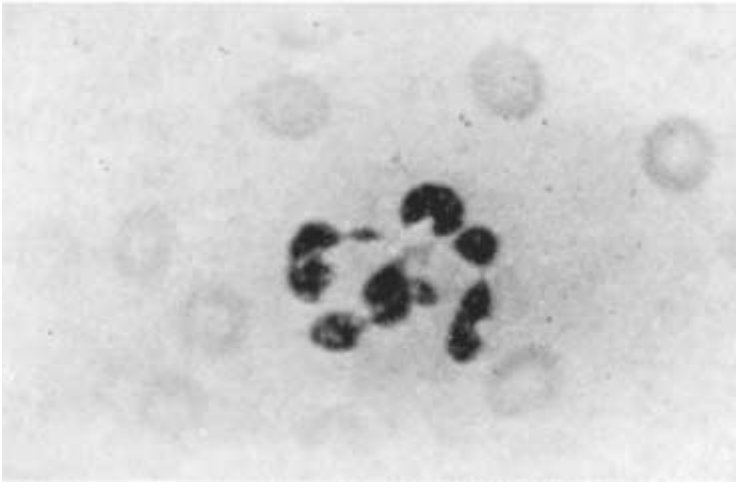
192. Which one of the listed types of antibodies is the best example of a cold agglutinin that is associated with cold autoimmune hemolytic anemia?

a. An anti-AB IgM antibody associated with isoimmune blood transfusion reaction
b. An anti-i IgM antibody associated with infectious mononucleosis
c. An anti-IgG IgG antibody associated with rheumatoid arthritis
d. An anti-P IgG antibody associated with paroxysmal cold hemoglobinuria
e. An anti-Rh IgG antibody associated with hemolytic disease of the newborn

193. A 67-year-old male presents with increasing fatigue and is found to be anemic. Physical examination reveals a hard 1-cm nodule in the left lobe of the prostate. The prostatic-specific antigen (PSA) level is found to be elevated. Examination of the peripheral blood reveals an occasional myelocyte. The erythrocytes are mainly normochromic and normocytic, and teardrop RBCs are not found. There are however, about two nucleated red blood cells per 100 white cells. What is the best diagnosis for this patient's anemia?

a. Fanconi's anemia
b. Microangiopathic hemolytic anemia
c. Myelophthisic anemia
d. Autoimmune hemolytic anemia
e. Aplastic anemia

194. The neutrophil in the photomicrograph shown below was obtained from peripheral blood and is most likely to be found in association with



a. Folic acid deficiency
b. Infection
c. Iron deficiency
d. Malignancy
e. Ingestion of a marrow-toxic agent

195. Megaloblasts result from the impaired synthesis of

a. DNA
b. RNA
c. Glutathione
d. β-globin chains
e. Decay-accelerating factor

196. The serum total iron-binding capacity (TIBC) is inversely proportional to serum levels of

a. Bilirubin
b. Ferritin
c. Haptoglobin
d. Hemopexin
e. Iron

197. An anemic patient has the following red cell indexes: mean corpuscular volume, 70 mm^3; mean corpuscular hemoglobin, 22 pg; and mean corpuscular hemoglobin concentration, 34%. These values are most consistent with a diagnosis of

a. Folic acid–deficiency anemia
b. Iron-deficiency anemia
c. Pernicious anemia
d. Sideroblastic anemia
e. Thalassemia minor

198. An anemic patient is found to have hypochromic, microcytic red cells. Additional tests reveal the serum iron levels, the total iron-binding capacity, and the transferrin saturation to be reduced. A bone marrow biopsy reveals the iron to be present mainly within macrophages. The correct diagnosis is

a. Iron deficiency
b. Thalassemia trait
c. Anemia of chronic disease
d. Sideroblastic anemia
e. Pernicious anemia

199. Porphyrias result from the abnormal synthesis of

a. α-globin
b. β-globin
c. Heme
d. Spectrin
e. Transferrin

200. Which set of laboratory findings in the table below is most likely to be present in an individual with a renal cell carcinoma and secondary polycythemia who is not dehydrated?

	RBC Count	RBC Mass	Erythropoietin Amount
a.	Normal	Normal	Increased
b.	Increased	Increased	Increased
c.	Decreased	Decreased	Normal
d.	Increased	Decreased	Increased
e.	Decreased	Increased	Decreased

201. Physical examination that finds multiple palpable purpuric lesions on the legs of a 7-year-old boy is most suggestive of

a. Bleeding secondary to excess corticosteroids
b. Erythema secondary to active hyperemia
c. Hemorrhage secondary to hypersensitivity vasculitis
d. Telangiectasis secondary to a congenital malformation
e. Thrombosis secondary to viral infection

202. Antibodies made in the spleen that are directed against the cell surface antigens GpIIb/IIIa or GpIb/IX are characteristically seen in individuals with

a. Cold autoimmune hemolytic anemia
b. Felty's syndrome
c. Hashimoto's thyroiditis
d. Immune thrombocytopenic purpura
e. Warm autoimmune hemolytic anemia

203. A 37-year-old woman who has a clinical picture of fever, splenomegaly, varying neurologic manifestations, and purplish ecchymoses of the skin is found to have a hemoglobin level of 10.0 g/dL, a mean corpuscular hemoglobin concentration (MCHC) of 48, peripheral blood polychromasia with stippled macrocytes, and spherocytes, with a blood urea nitrogen level of 68 mg/dL. The findings of coagulation studies and the patient's fibrin-degraded products are not overtly abnormal. Which of the following is most closely identified with these findings?

a. Idiopathic thrombocytopenic purpura
b. Thrombotic thrombocytopenic purpura
c. Disseminated intravascular coagulopathy
d. Submassive hepatic necrosis
e. Waterhouse-Friderichsen syndrome

204. A 5-year-old child develops the sudden onset of bloody diarrhea, vomiting of blood, hematuria, and renal failure following a flulike gastrointestinal illness. The blood urea nitrogen (BUN) level is markedly increased, but fibrin degradation products and blood clotting times are within normal limits. A peripheral blood smear reveals poikilocytes, schistocytes, and a decrease in the number of platelets. No fever or neurologic symptoms are present. What is the best diagnosis for this patient?

a. Autoimmune thrombocytopenic purpura (autoimmune ITP)
b. Disseminated intravascular coagulopathy (DIC)
c. Hemolytic-uremic syndrome (HUS)
d. Isoimmune thrombocytopenic purpura (isoimmune ITP)
e. Thrombotic thrombocytopenic purpura (TTP)

205. von Willebrand's disease is characterized by abnormal platelet aggregation when platelets are exposed to

a. Aspirin
b. Collagen
c. Fibrinogen
d. Ristocetin
e. Streptomycin

206. A 5-year-old boy is being evaluated for recurrent epistaxis and other abnormal bleeding episodes, including excessive bleeding from the umbilical cord at birth. Laboratory studies reveal the following: decreased hemoglobin (with microcytic hypochromic red cell indices), normal platelet count, markedly prolonged prothrombin time (PT) and partial thromboplastin time (PTT), and unmeasurable thrombin time (TT). Platelet aggregation studies reveal a normal platelet response to ristocetin, but with other substances (including collagen, ADP, and epinephrine), this patient's platelets exhibit a primary wave defect. Based on these findings, this patient most likely has

a. Afibrinogenemia
b. Bernard-Soulier syndrome
c. Glanzmann's thrombasthenia
d. Gray platelet syndrome
e. Wiskott-Aldrich syndrome

207. Administration of which one of the following substances would theoretically correct the abnormal bleeding laboratory tests in an individual who is deficient in coagulation factor V?

a. Activated factor VIII
b. Activated factor X
c. Fibrinogen
d. Plasmin
e. Thrombin

208. A 5-year-old boy presents with recurrent hemarthroses and intramuscular hematomas. Laboratory tests reveal normal bleeding time, platelet count, and PT, but the PTT is prolonged. This boy's condition most likely results from an abnormality involving

a. Chromosome 5
b. Chromosome 14
c. Chromosome 21
d. X chromosome
e. Y chromosome

209. A 27-year-old female in the last trimester of her first pregnancy presents with the sudden onset of multiple skin hemorrhages. She states that for the past several days she has not felt the baby move. Workup reveals an increase in PT and PTT, while fibrin degradation products (FDPs) are increased in the patient's blood. Her platelet count is found to be 43,000/μL. What is the most likely diagnosis for this patient?

a. Autoimmune thrombocytopenic purpura (autoimmune ITP)
b. Isoimmune thrombocytopenic purpura (isoimmune ITP)
c. Thrombotic thrombocytopenic purpura (TTP)
d. Hemolytic-uremic syndrome (HUS)
e. Disseminated intravascular coagulopathy (DIC)

210. A 45-year-old male with an artificial heart valve is given oral coumadin (Warfarin) to prevent the formation of thrombi on his artificial valve. Which combination of laboratory tests is most likely to be found in this individual?

	Tourniquet Test	Bleeding Time	Platelet Count	PTT	PT
a.	Positive	Prolonged	Normal	Normal	Normal
b.	Normal	Normal	Normal	Prolonged	Normal
c.	Positive	Prolonged	Decreased	Normal	Normal
d.	Normal	Normal	Normal	Normal	Prolonged
e.	Normal	Prolonged	Normal	Prolonged	Normal

211. An 11-year-old Jamaican boy develops a massive benign enlargement of the cervical lymph nodes associated with fever and leukocytosis. Which of the following lymph node disorders could account for these findings?

a. Toxoplasmosis
b. Histiocytic medullary reticulosis
c. Burkitt's disease
d. Sinus histiocytosis with massive lymphadenopathy
e. Angioimmunoblastic lymphadenopathy with dysproteinemia

212. A person taking an oral sulfonamide is found to have a markedly decreased peripheral blood neutrophil count, but the numbers of platelets and erythrocytes are normal. If the peripheral neutropenia is the result of antineutrophil antibodies being produced in response to taking the sulfonamide, then this patient would be expected to have

a. An atrophic spleen
b. Decreased vitamin B_{12} levels
c. Hypoplasia of the bone marrow myeloid series
d. Hyperplasia of the bone marrow myeloid series
e. A monoclonal large granular lymphocyte proliferation in the peripheral blood

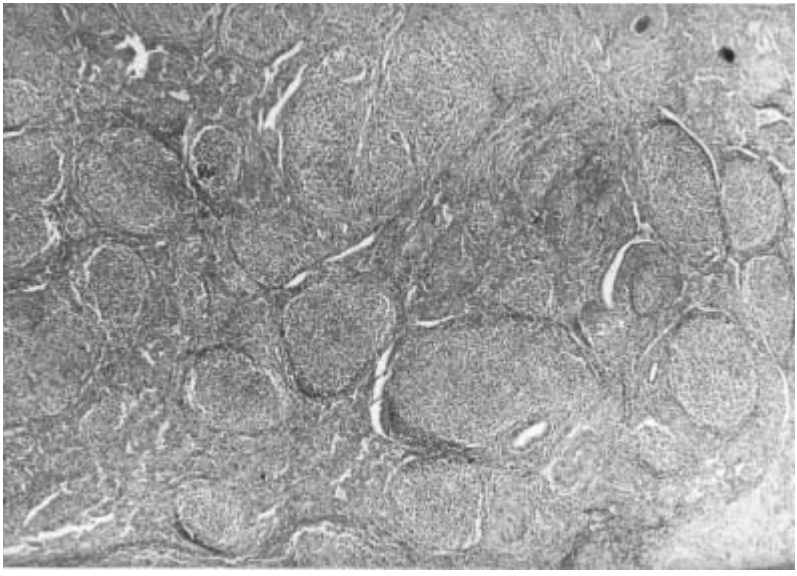
213. Parasitic infections, such as trichinosis, schistosomiasis, and strongyloidiasis, characteristically cause elevated numbers in the peripheral blood of

a. Basophils
b. Eosinophils
c. Macrophages
d. Neutrophils
e. T lymphocytes

214. During a viral infection, a 23-year-old female develops enlarged lymph nodes at multiple sites (lymphadenopathy). A biopsy from one of these enlarged lymph nodes reveals a proliferation of reactive T immunoblasts, cells that have prominent nucleoli. These reactive T cells are most likely to be found in which one of the following regions of the lymph node?

a. Hilum
b. Medullary sinuses
c. Paracortex
d. Primary follicles
e. Secondary follicles

215. The non-Hodgkin's lymphoma pictured in the photomicrograph below may be characterized by which of the following?



a. Increased frequency in adolescents
b. Neoplastic proliferation of T lymphocytes
c. Neoplastic proliferation of B lymphocytes
d. Nonneoplastic proliferation of tingible-body macrophages
e. Well-differentiated lymphocytic lymphoma

216. Which one of the listed types of lymphomas is classified as a low-grade lymphoma in the working classification of Non-Hodgkin's lymphoma and is characterized by malignant cells that are similar to the malignant cells of chronic lymphocytic leukemia?

a. Diffuse large cell lymphoma
b. Follicular large cell lymphoma
c. Immunoblastic lymphoma
d. Small lymphocytic lymphoma
e. Small non–cleaved cell lymphoma

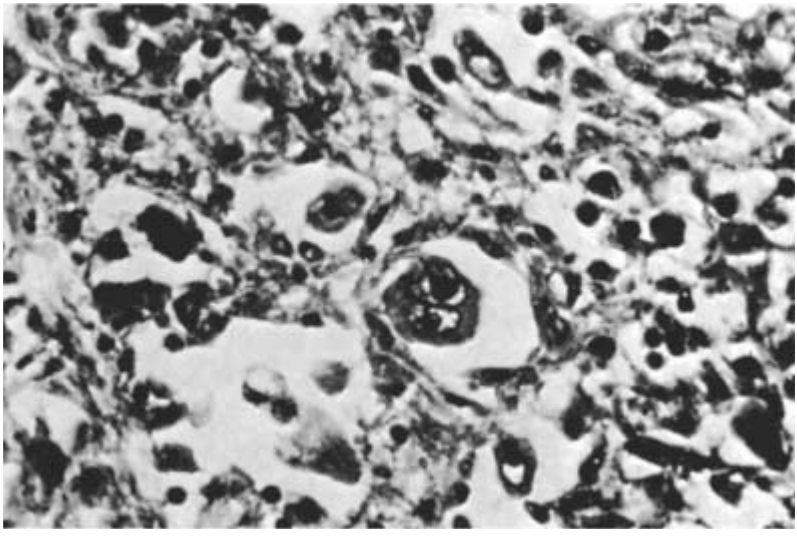
217. Histologic sections from a rapidly enlarged cervical lymph node in a 35-year-old female reveal a diffuse, monotonous proliferation of small, noncleaved lymphocytes, which are forming a "starry sky" appearance because numerous tingible-body macrophages are present. A touch prep reveals that many of these cells have cytoplasmic vacuoles, which would most likely react with

a. Myeloperoxidase
b. Oil red O
c. Nonspecific esterase
d. Chloracetate esterase
e. Periodic acid–Schiff (PAS)

218. A 20-year-old male presents in the emergency room with a lymphoma involving the mediastinum that is producing respiratory distress. The lymphocytes are most likely to have cell surface markers characteristic of which of the following?

a. B lymphocytes
b. T lymphocytes
c. Macrophages
d. Dendritic reticulum cells
e. Langerhans cells

219. A 22-year-old female presents with fever, weight loss, night sweats, and painless enlargement of several supraclavicular lymph nodes. A biopsy from one of the enlarged lymph nodes is shown in the photomicrograph below. The binucleate or bilobed giant cell with prominent acidophilic "owl-eye" nucleoli shown is a



a. Call-Exner cell
b. Hürthle cell
c. Reed-Sternberg cell
d. Sézary cell
e. Strap cell

220. Lacunar cells are variants of Reed-Sternberg cells that are specifically found in

a. Lymphocyte-predominate Hodgkin's disease
b. Lymphocyte-depleted Hodgkin's disease
c. Mixed-cellularity Hodgkin's disease
d. Nodular sclerosis Hodgkin's disease
e. Anaplastic Hodgkin's disease

221. A 28-year-old male presents with widespread ecchymoses and bleeding gums. Physical examination reveals enlargement of his spleen and liver. Laboratory examination of his peripheral blood reveals a normochromic, normocytic anemia, along with a decreased number of platelets and an increased number of white blood cells. Coagulation studies reveal prolonged prothrombin and partial thromboplastin times and increased fibrinogen degradation products. Examination of the patient's bone marrow reveals the presence of numerous granular-appearing blast cells with numerous Auer rods. These immature cells make up about 38% of the nucleated cells in the marrow. The correct diagnosis for this patient is

a. Acute erythroid leukemia
b. Acute lymphoblastic leukemia
c. Acute monocytic leukemia
d. Acute myelomonocytic leukemia
e. Acute promyelocytic leukemia

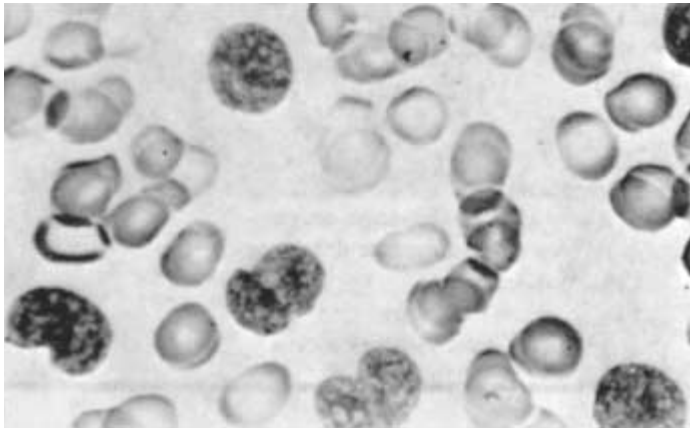
222. A 4-year-old female is being evaluated for the sudden onset of multiple petechiae and bruises. She is found to have a peripheral leukocyte count of 55,000, 86% of which are small, homogeneous cells that have nuclei with immature chromatin. Indistinct nucleoli are also present. Initial tests on these immature cells are as follows: TdT, positive; PAS, positive; acid phosphatase, positive; and myeloperoxidase, negative. Based on these findings, the immature cells most likely originated from

a. Myeloblasts
b. Monoblasts
c. Megakaryoblasts
d. Lymphoblasts
e. Erythroblasts

223. A 38-year-old male presents with increasing weakness and is found to have a markedly elevated peripheral leukocyte count. Laboratory testing on peripheral blood finds a decreased leukocyte alkaline phosphatase (LAP) score, while chromosomal studies on a bone marrow aspirate find the presence of a Philadelphia chromosome. This abnormality refers to a characteristic chromosomal translocation that involves the oncogene

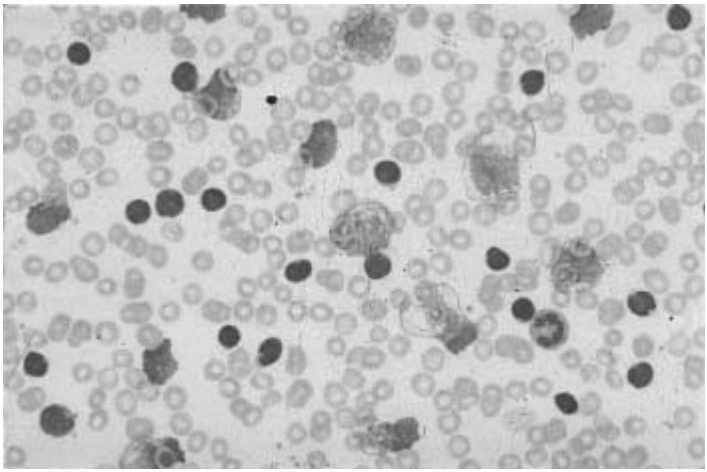
a. *bcl-2*
b. *c-abl*
c. *c-myc*
d. *erb-B*
e. *N-myc*

224. The photomicrograph below is of peripheral blood from a patient with splenomegaly, anemia, and pancytopenia. If hairy cell leukemia is suspected, which of the following would be useful in establishing the diagnosis?



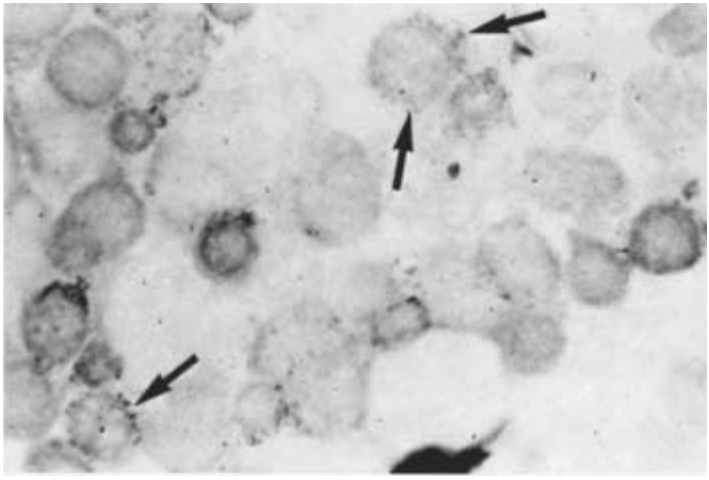
a. Myeloperoxidase stain
b. Sudan black B
c. Acid phosphatase stain
d. Leukocyte alkaline phosphatase
e. Nonspecific esterase

225. A 72-year-old male presents with increasing fatigue. Physical examination reveals an elderly male in no apparent distress (NAD). He is found to have multiple enlarged, nontender lymph nodes along with an enlarged liver and spleen. Laboratory examination of his peripheral blood reveals a normocytic normochromic anemia, a slightly decreased platelet count, and a leukocyte count of 72,000 cells per μL. An example of his peripheral blood is seen in the picture below. What is your diagnosis?



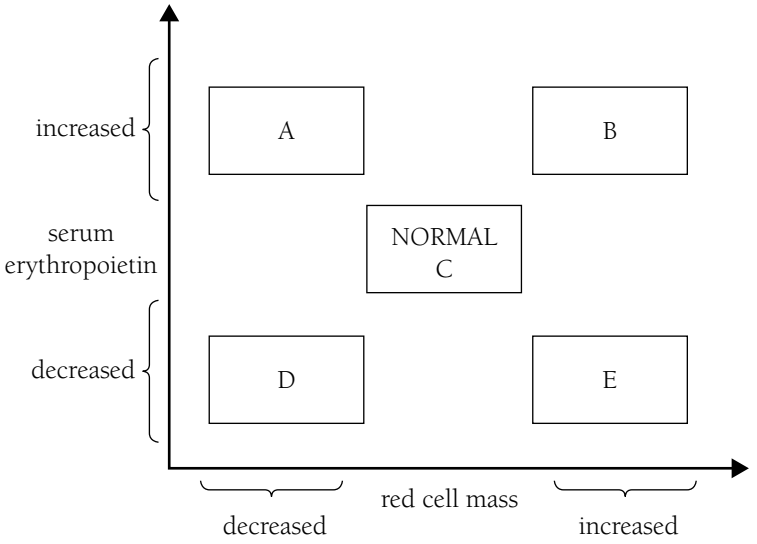
a. Acute lymphoblastic leukemia
b. Atypical lymphocytosis
c. Chronic lymphocytic leukemia
d. Immunoblastic lymphoma
e. Prolymphocytic leukemia

226. The cells seen in the photomicrograph below were removed from an anemic patient and stained with an iron stain. These abnormal cells are most suggestive of



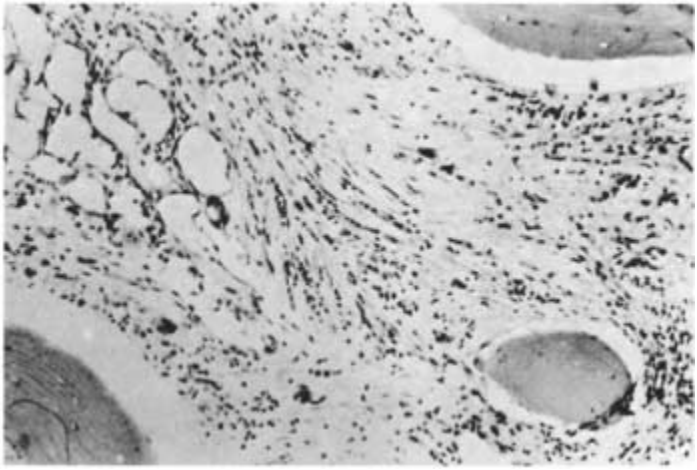
a. Acute blood loss
b. Lead poisoning
c. Iron deficiency
d. Myelodysplasia
e. Vitamin B_{12} deficiency

227. Which one of the labeled boxes in the diagram below is most consistent with the expected findings for an individual with polycythemia rubra vera?



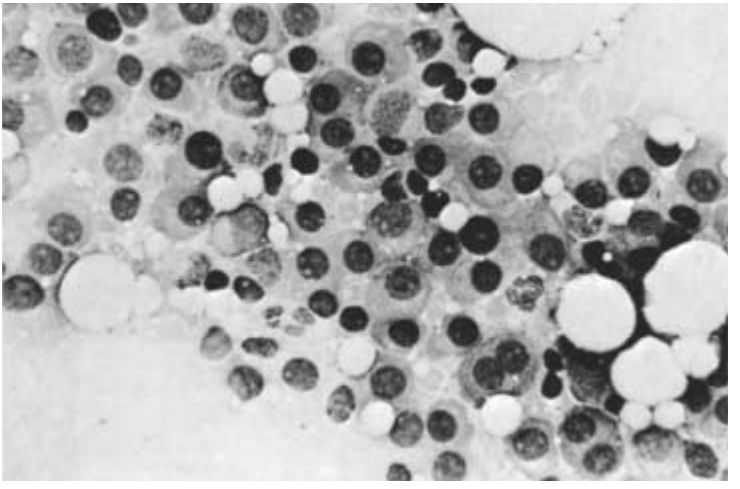
a. Box A
b. Box B
c. Box C
d. Box D
e. Box E

228. The bone marrow biopsy shown in the photomicrograph below was performed because of splenomegaly and anemia in an adult. On the basis of the appearance of the bone marrow core, the most likely diagnosis is



a. Chronic myeloid leukemia (CML)
b. Aplastic anemia
c. Acute leukemia
d. Myeloid metaplasia with myelofibrosis
e. Microangiopathic hemolytic anemia

229. A bone marrow aspirate is obtained from a 70-year-old man whose symptoms include weakness, weight loss, and recurrent infections. Laboratory findings include proteinuria, anemia, and an abnormal component in serum proteins. A photomicrograph of the bone marrow aspirate is shown below. The best diagnosis is



a. Monomyelocytic leukemia
b. Histiocytic leukemia
c. Multiple myeloma
d. Gaucher's disease
e. Leukemic reticuloendotheliosis

230. Which one of the listed substances is secreted by malignant plasma cells in individuals with multiple myeloma and is the osteoclast-activating factor (OAF) that produces the characteristic lytic bone lesions?

a. Interleukin 1
b. Interleukin 6
c. Tumor necrosis factor β
d. Transforming growth factor β
e. Platelet-derived growth factor

231. A 54-year-old female presents with headaches, visual abnormalities, bleeding, and Raynaud's phenomenon. Workup reveals a normal serum calcium, and no lytic lesions are found within the skeleton by x-ray. Serum electrophoresis reveals a single large M spike in the peripheral blood due to a monoclonal proliferation of IgM. Sections from the patient's bone marrow reveal numerous plasma cells, lymphocytes, and plasmacytoid lymphocytes. What is the correct diagnosis for this patient?

a. IgM multiple myeloma
b. Monoclonal gammopathy of undetermined significance
c. μ heavy chain disease
d. Plasmacytoid small cell lymphoma
e. Waldenström's macroglobulinemia

232. A 5-year-old girl is brought to your office by her mother, who states that the girl has been drinking a lot of water lately. Physical examination reveals a young girl whose eyes protrude slightly. Further workup reveals the presence of multiple lytic bone lesions involving her calvarium and the base of her skull. What is the most likely diagnosis for this young girl?

a. Letterer-Siwe disease
b. Hand-Schüller-Christian disease
c. Dermatopathic lymphadenopathy
d. Unifocal Langerhans cell histiocytosis
e. Sarcoidosis

233. A 20-year-old female presents with a 5-day history of fatigue, low-grade fever, and sore throat. Physical examination reveals bilateral enlarged, tender cervical lymph nodes, an exudative tonsillitis, and an enlarged spleen. A complete blood cell count reveals the hemoglobin and platelet counts to be within normal limits. The total white blood cell count is increased to 9200 cells per μL. Examination of the peripheral blood reveals the presence of atypical mononuclear cells with abundant cytoplasm. These cells have peripheral condensation of the cytoplasm, which gives them a "ballerina skirt" appearance. Which one of the listed findings is most likely to be present in this individual?

a. Aggregates of mononuclear cells with cytoplasmic Birbeck granules in the liver
b. Elevated levels of δ-ALA in the urine
c. Group A streptococcus on culture of the tonsillar exudate
d. Heterophil antibodies in the serum
e. M spike in the γ region of a serum protein electrophoresis

Hematology

Answers

183. The answer is c. *(Henry, pp 576–582.)* Abnormalities of red cells can help to identify a disease process. Schistocytes, which are red cell fragments, indicate the presence of hemolysis, and they can occur in hemolytic anemia, megaloblastic anemia, or severe burns. Red cell shapes characteristic of hemolysis include triangular cells and helmet cells. Target cells (red cells with a central dark area) are the result of excess cytoplasmic membrane material and are found in patients with liver disease, such as obstructive jaundice, or in any of the hypochromic anemias. Acanthocytes are irregularly spiculated red cells found in patients with abetalipoproteinemia or liver disease. Echinocytes, in contrast, have regular spicules (undulations) and may either be artifacts (crenated cells) or be found in hyperosmolar diseases such as uremia. Basophilic stippling of red cells (irregular basophilic granules within erythrocytes) varies from fine granules, seen in young reticulocytes (polychromatophilic cells), to coarse granules seen in diseases with impaired hemoglobin synthesis, such as lead poisoning and megaloblastic anemia. Heinz bodies are formed by denatured hemoglobin and are not seen with routine stains. They are found in patients with glucose-6-phosphatase dehydrogenase deficiency and the unstable hemoglobinopathies.

184. The answer is c. *(Cotran, pp 606–607.)* Destruction of red cells (hemolysis) may occur within the vascular compartment (intravascular hemolysis) or within the mononuclear-phagocyte system (extravascular hemolysis). In both cases, the hemolysis leads to anemia, and the breakdown of hemoglobin leads to jaundice due to increased indirect bilirubin. Intravascular hemolysis releases hemoglobin into the blood (hemoglobinemia); this hemoglobin then binds to haptoglobin. When haptoglobin levels are depleted, free hemoglobin is oxidized to methemoglobin, and then both hemoglobin and methemoglobin are secreted into the urine (hemoglobinuria and methemoglobinuria). Within the renal tubular epithelial cells, hemoglobin is reabsorbed and hemosiderin is formed; when these cells are shed into the urine, hemosiderinuria results. Since extravascular hemolysis does not occur within the vascular compartment, hemoglobin-

emia, hemoglobinuria, methemoglobinuria, and hemosiderinuria do not occur. The breakdown of the red cells within the phagocytic cells causes anemia and jaundice, just as with intravascular hemolysis, and, since hemoglobin escapes into the blood from the phagocytic cells, plasma haptoglobin levels are also reduced. Unlike the case with intravascular hemolysis, the erythrophagocytosis causes hypertrophy and hyperplasia of the mononuclear phagocytic system, which in turn may lead to splenomegaly.

185. The answer is c. *(Henry, pp 633–634. Cotran, 607–609.)* Hereditary spherocytosis (HS), an autosomal dominant disorder, is characterized by an abnormality of the skeleton of the red cell membrane that makes the erythrocyte spherical, less deformable, and vulnerable to splenic sequestration and destruction (extravascular hemolysis). This mild to moderate hemolytic anemia can lead to splenomegaly, jaundice, and pigmented gallstones. In HS, the defect in the spectrin molecule results in decreased binding to protein 4.1. This decreases the amount of red blood cell membrane and causes the formation of spherocytes (because of the low surface-to-volume ratio). Spherocytes in a peripheral blood smear show a smaller diameter than normal and an apparent increase in hemoglobin concentration because of a decrease in cell surface, with consequent deeper staining for hemoglobin. The increase in hemoglobin concentration within the red cells can be seen clinically as an increase in the mean cell hemoglobin concentration (MCHC). The osmotic fragility test (the shaded area in the graph reflects a normal response to a hypotonic solution) can be used to document the presence of spherocytes in the peripheral blood. Spherocytes lyse at a higher concentration of sodium chloride than do normal red cells. In contrast, flat hypochromic cells, such as those in thalassemia, have a greater capacity to expand in dilute salt solution and thus lyse at a lower concentration (which is seen in the unbroken curve to the far right). The longer the incubation of the red cells in these salt concentrations, the greater the response to osmotic change. The differential diagnosis of spherocytosis in the peripheral blood includes hereditary spherocytosis and autoimmune hemolytic anemia.

186. The answer is b. *(Cotran, pp 601–611, 619–621.)* Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme of the hexose monophosphate shunt pathway that maintains glutathione in a reduced (active) form. Glutathione normally protects hemoglobin from oxidative injury. If the

erythrocytes are deficient in G6PD, as occurs in G6PD deficiency, exposure to oxidant drugs, such as the antimalarial drug primaquine, denatures hemoglobin, which then precipitates with erythrocytes as Heinz bodies. Macrophages within the spleen remove these bodies, producing characteristic "bite" cells. These red cells then become less deformable and are trapped and destroyed within the spleen (extravascular hemolysis). The gene for G6PD is located on the X chromosome and has considerable pleomorphism at this site. Two variants are the A type, which is found in 10% of African Americans and is characterized by milder hemolysis of younger red cells, and the Mediterranean type, which is characterized by a more severe hemolysis of red cells of all ages.

In contrast, hereditary spherocytosis (HS), an autosomal dominant disorder, is characterized by an abnormality of the skeleton of the red cell membrane that makes the erythrocyte spherical, less deformable, and vulnerable to splenic sequestration and destruction (extravascular hemolysis). In HS, there is a defect in the spectrin molecule, which then is less binding to protein 4.1. This disorder can be diagnosed in the laboratory by the osmotic fragility test. Paroxysmal nocturnal hemoglobinuria (PNH), an acquired clonal stem cell disorder, is characterized by abnormal red cells, granulocytes, and platelets. The red cells are abnormally sensitive to the lytic activity of complement due to a deficiency of glycosyl phosphatidyl inositol (GPI) linked proteins, namely decay-accelerating factor (DAF, or CD55), membrane inhibitor of reactive lysis (CD59), or CD59 (a C8 binding protein). Complement is activated by acidosis, such as with exercise or sleep, which can produce red morning urine. Complications of PNH include the development of frequent thromboses and possibly acute leukemia. Autoimmune hemolytic anemia is caused by anti–red cell antibodies and is diagnosed using the Coombs antiglobulin test. Microangiopathic hemolytic anemia refers to hemolysis of red cells caused by narrowing within the microvasculature and is seen in patients with prosthetic heart valves or those with disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, or hemolytic-uremic syndrome.

187. The answer is e. *(Cotran, pp 611–615.)* Hemoglobin S (Hb S) is formed by the replacement of glutamic acid by valine in the sixth position in the β chain of hemoglobin. On deoxygenation, Hb S polymerizes and the red cells sickle. In patients heterozygous for Hb S (sickle cell trait, Hb AS), there is approximately 45% Hb S and 55% Hb A. Because of the content of

Hb A, erythrocytes only sickle at low oxygen tension and symptoms are much milder than in sickle cell disease. Hb F does not react with hemoglobin S, so that patients who have Hb S and large amounts of Hb F, as occurs in newborns with sickle cell disease, are asymptomatic. Clinically, sickle cell disease is characterized by the triad of chronic hemolytic anemia, vascular occlusion, and vulnerability to infection. The severe chronic hemolytic anemia leads to chronic hyperbilirubinemia (jaundice), which leads to pigmented gallstones. Vascular occlusion results in leg ulcers, renal papillary necrosis, and multiple infarcts, which may cause severe bone pain. Repeated splenic infarcts cause progressive fibrosis and splenic atrophy (autoinfarction). Rather than hypersplenism, most adults have a small, functionless, fibrotic spleen. The lack of splenic function along with defects in the alternate complement pathway predispose to infections such as *Salmonella* osteomyelitis and pneumococcal infections. The vasoocclusive disease also leads to painful crises, hand-foot syndrome in children (consisting of the typical triad of fever, pallor, and symmetric swelling of hands and feet), and infarctive crises. In patients not having yet undergone splenic autoinfarction (usually children), massive splenic sequestration (sequestration crisis) may lead to rapid splenic enlargement, hypovolemia, and shock. Patients with sickle cell disease have a normocytic anemia with a corrected reticulocyte count of greater than 3%. The erythrocyte sedimentation rate (ESR) is zero because the sickled red cells cannot aggregate and settle in the test tube. Hydroxyurea has recently been approved for the treatment of sickle cell disease because it increases the synthesis of hemoglobin F, thus reducing the severity of the disease.

188. The answer is b. *(Cotran, pp 611–615. Henry, pp 623–624, 635, 641–642, 771–772, 1096–1098.)* The metabisulfite test is used to detect the presence of hemoglobin S, but it does not differentiate the heterozygous sickle cell trait from the homozygous sickle cell disease. The test is based on the fact that erythrocytes with a large proportion of hemoglobin S sickle in solutions of low oxygen content. Metabisulfite is a reducing substance that enhances the process of deoxygenation. The osmotic fragility test is a diagnostic test for hereditary spherocytosis. Spherocytes lyse at a higher concentration of salt than do normal cells, thus causing an increased osmotic fragility. The direct antiglobulin test (DAT), or Coombs' test, is used to differentiate autoimmune hemolytic anemia (AIHA) due to the presence of anti–red cell antibodies from other forms of hemolytic anemia.

In this test, antibodies to human immunoglobulin cause the agglutination (clotting) of red cells if these anti–red cell antibodies are present on the surface of the red cells. In patients with paroxysmal nocturnal hemoglobinuria, the erythrocytes are excessively sensitive to complement-mediated lysis in low ionic environments (the basis for the sucrose hemolysis test) or in acidotic conditions, such as sleep, exercise, or the Ham's acid hemolysis test. The Schilling test, which measures intestinal absorption of vitamin B_{12} with and without intrinsic factor, is used to diagnose decreased vitamin B_{12} caused by pernicious anemia, which is characterized by a lack of intrinsic factor.

189. The answer is e. *(Cotran, pp 618–619.)* The thalassemia syndromes are characterized by a decreased or absent synthesis of either the α- or the β-globin chain of hemoglobin A (α2-β2). α thalassemias result from reduced synthesis of α-globin chains, while β thalassemias result from reduced production of β-globin chains. Therefore, α thalassemias are associated with a relative excess production of non-α-globin chains, while β thalassemias are associated with a relative excess production of α-globin chains. Non-α-globin chains are γ-globin chains (which form γ tetramers called hemoglobin Bart's) in the fetus, but are β-globin chains (which form β tetramers called hemoglobin H) in the adult.

Most of the α thalassemias result from deletions of one or more of the total of four α-globin genes, while β thalassemias result from point mutations involving the β-globin gene. There are two α-globin genes on each chromosome 16, and the normal genotype is α,α/. On each chromosome either or both of the α genes can be deleted. Deletion of both genes (– –/) is called α thal 1. This genotype is found in individuals in Southeast Asia and the Mediterranean. In contrast, deletion of only one α gene on a chromosome (– α/) is called α thal 2 and is found in Africans. The severity of α thalassemia depends on the number of α genes deleted. Deletions of only one gene (–α/α,α) results in a silent carrier. These patients are completely asymptomatic and all laboratory tests are normal. This clinical state can only be inferred from examination of a pedigree. Deletion of two α genes results in α thal trait. There are two possibilities for deletion of two α genes: the deletions may be on the same chromosome (– –/α,α, which is called the cis type) or the deletions may be on different chromosomes (–α/–α, which is called the trans type). The former, which is also called heterozygous α thal 1, is more common in Asians, while the latter, which is also called α thal 2, is more common in Africans. Clinically this is quite important because the off-

spring of parents with the trans deletions cannot develop H disease or hydrops. Deletion of three α genes (– –/– α) is called hemoglobin H disease. This name results from the fact that excess β chains postnatally form aggregates of β tetramers, which are called hemoglobin H. These aggregates form Heinz bodies, which can be seen with crystal blue stain. The most severe form of α thalassemia, hydrops fetalis, results from deletion of all four alpha genes (– –/– –). In this disease, which is lethal in utero, no α chains are produced. Staining of the erythrocytes with a supravital stain demonstrates numerous intracytoplasmic inclusions within the red cells, which are aggregates of hemoglobin Bart's (γ4).

190. The answer is d. *(Cotran, pp 615–618. Rubin, pp 1078–1079.)* β thalassemias result from reduced production of β-globin chains, which results in a relative excess production of α-globin chains. Most of the β thalassemias result from point mutations involving the β-globin gene. The amount of β-globin produced depends upon the location of the point mutation. Promoter region mutations result in decreased production of β-globin. This is called β+ thalassemia. Chain terminator mutations generally produce no functional β-globin. This is called β0 thalassemia. Splicing mutations may result in either β0 or β+ thalassemia. In patients with β thalassemia, a deficiency of β-globins causes a deficiency of hemoglobins that have β-globin chains, and at the same time there is an increase in hemoglobins that do not have β-globin chains (due to the excess α chains present). These hemoglobins include hemoglobin A_2 (α2-δ2) and hemoglobin F (α2-δ2). The most severe clinical form of β thalassemia is Cooley's anemia (β thal major), which is characterized by severe, transfusion-dependent anemia. Because of the need for repeated transfusions, over time these patients develop iron accumulation that leads to the formation of hemochromatosis. Indeed, congestive heart failure due to iron deposition within the heart is the major cause of death. Individuals with β thal major have increased reticulocytes, increased hemoglobin A_2, and markedly increased hemoglobin F (90%). In these patients, increased α chains produce intramedullary destruction ("ineffective erythropoiesis"). The resultant increased red marrow produces a "crew-cut" x-ray appearance of the skull and enlarges the maxilla.

191. The answer is b. *(Cotran, pp 619–621.)* Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder that is char-

acterized by abnormal red cells, granulocytes, and platelets. The red blood cells (RBCs) are abnormally sensitive to the lytic activity of complement due to a deficiency of glycosyl phosphatidyl inositol (GPI) linked proteins, namely decay-accelerating factor (DAF, or CD 55), membrane inhibitor of reactive lysis (CD55), or CD59 (a C8 binding protein). Complement is normally activated by acidotic states, such as occur with exercise or sleep. In patients with PNH, the acidotic condition that develops during sleep (which is usually at night) causes hemolysis of red blood cells and results in red urine in the morning. The erythrocytes of these patients lyse in vitro with acid (Ham's test) or sucrose (sucrose lysis test). Complications of PNH include the development of frequent thromboses, particularly of the hepatic, portal, or cerebral veins. Since PNH is a clonal stem cell disorder, patients are at an increased risk of developing aplastic anemia or acute leukemia.

The autoimmune hemolytic anemias are important causes of acute anemia in a wide variety of clinical states and can be separated into two main types: those secondary to "warm" antibodies and those reactive at cold temperatures. Warm-antibody autoimmune hemolytic anemias react at 37°C in vitro, are composed of IgG, and do not fix complement. They are found in patients with malignant tumors, especially leukemia-lymphoma; with use of such drugs as α-methyldopa; and in the autoimmune diseases, especially lupus erythematosus. Cold-antibody autoimmune hemolytic anemia reacts at 4 to 6°C, fixes complement, is of the IgM type, and is classically associated with *Mycoplasma* pneumonitis (pleuropneumonia-like organisms). These antibodies are termed *cold agglutinins* and may reach extremely high titers and cause intravascular red cell agglutination.

192. The answer is b. *(Cotran, pp 620–621.)* Antibody-mediated destruction of red cells results from either autoimmune reactions or isoimmune reactions. The latter are due to antibodies from one person that react with red cells from another person. This isoimmune destruction is seen with blood transfusions and hemolytic disease of the newborn. The autoimmune hemolytic anemias (AIHAs) are hemolytic anemias that are due to the presence of antibodies that destroy red cells. The AIHAs are divided into two main types: those secondary to "warm" antibodies and those secondary to "cold" antibodies. The antibodies seen in warm-antibody autoimmune hemolytic anemias react at 37°C in vitro, are composed of IgG, and do not fix complement. Instead, immunoglobulin-coated red blood cells are

removed by splenic macrophages that recognize the Fc portion of the immunoglobulin. These warm IgG antibodies are found in patients with malignant tumors, especially leukemia-lymphoma; they are associated with the use of such drugs as α-methyldopa; and they are also found in the autoimmune diseases, especially lupus erythematosus. Cold-antibody autoimmune hemolytic anemia (cold AIHA) is subdivided into two clinical categories based on the type of antibodies involved. These two types of cold antibodies are cold agglutinins and cold hemolysins. Cold agglutinins are monoclonal IgM antibodies that react at 4 to 6°C. They are called agglutinins because the IgM can agglutinate red cells due to its large size (pentamer). Additionally, IgM can activate complement, which may result in IV hemolysis. *Mycoplasma* pneumonitis and infectious mononucleosis are classically associated with cold-agglutinin formation. In contrast, cold hemolysins are seen in patients with paroxysmal cold hemoglobinuria (PCH). These cold hemolysins are unique because they are biphasic antierythrocyte autoantibodies. These antibodies are IgG that is directed against the P blood group antigen. They are called biphasic because they attach to red cells and bind complement at low temperatures, but the activation of complement does not occur until the temperature is increased. This antibody, called the Donath-Landsteiner antibody, was previously associated with syphilis, but may follow various infections, such as mycoplasmal pneumonia.

193. The answer is c. *(Cotran, pp 621, 630–633.)* Myelophthisic anemia results from space-occupying lesions of the bone marrow, such as granulomas or metastatic carcinomas. It is characterized by the presence of leukoerythroblastosis in the peripheral blood. This term refers to finding in the peripheral blood immature white cells, such as myelocytes and metamyelocytes, and immature red blood cells, such as nucleated red blood cells. Metastatic disease in the bone can produce localized bone pain and elevation of alkaline phosphatase that is associated with a normal γ-glutamyltransferase (GGT) level.

In contrast, microangiopathic hemolytic anemia refers to mechanical destruction (hemolysis) of red cells caused by narrowing within the microvasculature and is seen in patients with prosthetic heart valves or severe calcific aortic stenosis, or in patients having disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, or hemolytic-uremic syndrome. In addition to microangiopathic HA, other causes of IV mechanical destruction of red cells include march hemoglobinuria and cer-

tain types of infections, such as bartonellosis and malaria. Aplastic anemia is a stem cell disorder of the bone marrow that causes a marked decrease in the production of marrow cells that results in extreme marrow hypoplasia. Patients present with symptoms related to pancytopenia (anemia, agranulocytosis, and thrombocytopenia). Because their bone marrow cannot respond normally, patients with aplastic anemia have no increased reticulocytes in the peripheral blood (no polychromasia). Aplastic anemia may be inherited (Fanconi's anemia) or acquired. The most common cause of aplastic anemia is drugs. Other causes include chemicals (benzene and glue sniffing), radiation, and certain types of infections, such as hepatitis C. There are certain predisposing conditions, such as PNH, that are associated with an increased risk of developing aplastic anemia.

194. The answer is a. *(Cotran, pp 621–627.)* In contrast to a normal, mature neutrophil, which has from two to five nuclear lobes, the neutrophil shown has at least six lobes and is an illustration of neutrophilic hypersegmentation. Granulocytic hypersegmentation is significant and among the first hematologic findings in the peripheral blood of patients who have megaloblastic anemia in its developmental stages. Neutrophilic hypersegmentation is generally considered a sensitive indicator of megaloblastic anemia, which can be caused by a deficiency in vitamin B_{12}, in folate, or in both. Tetrahydrofolate (FH4) acts as an intermediate in the transfer of one-carbon units from compounds such as formiminoglutamic acid (FIGlu), a breakdown product of histidine. Excess urinary levels of FIGlu are a useful clinical indicator of a folate deficiency. Folate deficiency may result from dietary deficiency, impaired absorption, or impaired utilization. Dietary deficiency most often occurs in chronic alcoholics or the elderly. Impaired absorption occurs in malabsorptive states, while impaired utilization can occur with folate antagonists, an example being methotrexate. Increased requirements for B_{12} and folate may be seen in pregnancy, cancer, and chronic hemolytic anemia; if these needs are not met, deficiency states can result. Note that folate deficiency during pregnancy has been associated with the development of open neural tube defects in the fetus. Folate supplements are recommended for all women prior to and after conception.

195. The answer is a. *(Cotran, pp 621–627.)* Deficiency of either vitamin B_{12} or folate results in megaloblastic anemia. Deficiency impairs DNA syn-

thesis and delays mitotic division, which in turn causes the nuclei to be enlarged. The synthesis of RNA and cytoplasmic elements is not affected, however, so there is nuclear-cytoplasmic asynchrony. These cellular changes affect all rapidly proliferating cells in the body, but in the bone marrow they result in enlarged erythroid precursors, which are referred to as megaloblasts. These abnormal cells produce abnormally enlarged red cells, which are called macroovalocytes. These megaloblasts also undergo autohemolysis within the bone marrow, resulting in ineffective erythropoiesis. Granulocyte precursors are also enlarged and are called giant metamyelocytes. These abnormal cells produce enlarged hypersegmented neutrophils. The megakaryocytes are large and have nuclear abnormalities, but, although the platelet count is decreased, the platelets are not enlarged. Abnormalities of glutathione production are seen in patients with glucose-6-phosphate dehydrogenase deficiency, while decreased synthesis of β-globin chains is seen in patients with β thalassemia. Abnormalities of decay-accelerating factor are seen in patients with paroxysmal nocturnal hemoglobinuria.

196. The answer is b. *(Henry, pp 189–190, 243, 246. Cotran, pp 610–613.)* There are multiple forms of iron, including dietary forms and body forms. The latter can be subdivided into functional forms, storage forms, and transport forms. Functional iron is found in hemoglobin, myoglobin, and enzymes (such as catalase and cytochromes). All storage iron is in the form of ferritin or hemosiderin. In the liver, ferritin is found within parenchymal cells, while in the spleen and bone marrow, ferritin is found within macrophages. Very small amounts of ferritin circulate in the plasma, but since it is derived from the storage pool, serum ferritin levels are a good indicator of total body stores. Iron is transported in the plasma by transferrin, normally about 33% saturated with iron. The normal serum iron level is 100 μg/dL, while the normal total iron-binding capacity (TIBC) is about 300 μg/dL. The TIBC indicates the blood transferrin levels and is inversely proportional to the total body stores of iron. That is, iron deficiency (decreased ferritin) is associated with increased TIBC, while iron excess (increased ferritin) is associated with decreased TIBC. Note that TIBC is not necessarily reflective of serum iron levels, as these may not accurately reflect total body iron stores.

197. The answer is e. *(Henry, pp 78–79, 657–659.)* The differential diagnosis of microcytosis includes β thalassemia (due to a defect in globin

chain synthesis) and iron-deficiency anemia. It is important to distinguish between these two disorders because therapy with iron benefits patients with iron-deficiency anemia, but harms patients with thalassemia because these patients are at risk for iron overload. Both thalassemia minor and iron-deficiency anemia are microcytic disorders in which the mean corpuscular hemoglobin is usually found to be reduced. Red blood cell indexes may be useful in differentiating the two disorders because, while the mean corpuscular hemoglobin concentration (MCHC) is often normal or only slightly reduced in association with thalassemia minor, the MCHC is often definitely reduced in association with iron-deficiency anemia. (Both pernicious and folate-deficiency anemias lead to megaloblastic changes in erythrocytes.) The red cell distribution width (RDW) is a measure of variation in the size of the red cells (anisocytosis). The RDW is increased in patients with iron-deficiency anemia, but is normal in patients with β thalassemia. Also unique to the microcytic anemias is the fact that patients with β thalassemia have increased red blood cell counts, while patients with all of the other microcytic anemias have decreased red blood cell counts. This increased red cell count in β thalassemia may be due to the increased hemoglobin F, which shifts the oxygen dissociation curve to the left. This in turn causes an increased release of erythropoietin. Unlike iron-deficiency anemia, β thalassemia begins as a microcytic anemia. In contrast, iron-deficiency anemia progresses through several stages. First there is decreased storage iron, which is followed by decreased circulating iron. At this time patients are still not clinically anemic. Next patients develop a normocytic normochromic anemia that transforms into a microcytic normochromic anemia and finally a microcytic hypochromic anemia.

198. The answer is c. *(Henry, pp 618–620, 626–627, 630–631, 657–659.)* The four main causes of microcytic/hypochromic anemias are iron deficiency, anemia of chronic disease (AOCD), thalassemia, and sideroblastic anemia. Additional laboratory tests can differentiate between these four diseases. The serum iron and percentage of saturation are decreased in both iron-deficiency anemia and AOCD, are increased in sideroblastic anemia, and may be normal or increased in thalassemia. The total iron-binding capacity (TIBC) is increased only in iron-deficiency anemia; it is normal or decreased in the other diseases. An additional differentiating test for these four diagnoses is evaluation of the bone marrow iron stores. In iron deficiency, iron stores are decreased or absent. In AOCD, iron is present, but is

restricted to and increased within macrophages. It is decreased in amount within marrow erythroid precursors. Marrow iron is increased in patients with sideroblastic anemia. Iron levels in patients with thalassemia trait are generally within normal limits. Approximately one-third of the normoblasts in the normal bone marrow contain ferritin granules and are called sideroblasts. In sideroblastic anemia, because of the deficiency of pyridoxine and ferritin, the production of globin or heme is markedly reduced, and ferritin granules accumulate within the mitochondria that rim the nucleus. This produces the characteristic ring sideroblast.

199. The answer is c. *(Lee, pp 1272–1290.)* The porphyrias are inherited or acquired disorders of heme biosynthesis with varied patterns of overproduction, accumulation, and excretion of heme synthesis intermediates. Major characteristics of the porphyrias include intermittent neurologic dysfunction and skin sensitivity to sunlight (unlike the other types, intermittent acute porphyria produces no skin photosensitivity). Porphyria cutanea tarda is the most common type and involves chronic skin lesions (on the face, forehead, and forearms) and frequent hepatic disease. Excess urinary porphobilinogen excretion occurs in variegate porphyria and intermittent acute porphyria. Detection of porphobilinogen in the urine forms the basis for a positive Watson-Schwartz reaction in the diagnosis of variegate and intermittent acute porphyria.

200. The answer is b. *(Cotran, pp 633, 662–663.)* Polycythemia refers to an increased concentration of red blood cells (RBCs) in the peripheral blood. This is manifested by an increase in red blood cell count, hemoglobin concentration, or hematocrit. An increase in red blood cell count, reported clinically as number of cells per μL, is not the same thing as the RBC mass, which is a radioactive test that is reported in mL/kg. The RBC count and the RBC mass do not always parallel each other. For example, a decreased plasma volume increases the RBC count but does not affect the RBC mass. An increased red blood cell concentration may be a relative polycythemia or an absolute polycythemia. A relative polycythemia is due to a decrease in the plasma volume (hemoconcentration), causes of which include prolonged vomiting, diarrhea, or the excessive use of diuretics. An absolute polycythemia is due to an increase in the total red cell mass and may be primary, due to a defect in myeloid stem cells (polycythemia rubra vera), or secondary, due to an increase in the production of erythropoietin

(EPO). In patients with primary polycythemia, a myeloproliferative disorder, the red cell mass is increased but the levels of erythropoietin are normal or decreased. The EPO level is low because the total oxygen content of the blood is increased and there is no stimulus for increasing the secretion of EPO. The marked increased red cell mass in patients with polycythemia vera predisposes them to thrombotic complications and hemorrhages. The high cell turnover from the increase in the red cell mass predisposes these patients to development of hyperuricemia and symptoms of gout. Patients also develop increased numbers of basophils and eosinophils in the peripheral blood. The increased histamine release from these basophils may result in intense pruritus and peptic ulceration. Bleeding from the latter may lead to an iron-deficiency anemia. In patients with secondary polycythemia, the increased erythropoietin may be appropriate or inappropriate. Appropriate causes of increased erythropoietin include lung disease, cyanotic heart disease, living at high altitudes, or abnormal hemoglobins with increased oxygen affinity. Inappropriate causes of increased erythropoietin include erythropoietin-secreting tumors, such as renal cell carcinomas, hepatomas, or cerebellar hemangioblastomas.

201. The answer is c. *(Cotran, pp 517, 633–634. Isselbacher, pp 305–306.)* Hemorrhages into the skin may produce lesions of varying sizes. Petechiae measure less than 2 mm in size, purpuric lesions measure 2 mm to 1 cm, and ecchymoses are larger than 1 cm. Erythema and telangiectasis do not involve hemorrhage outside of blood vessels. They can be differentiated from true hemorrhages into the skin by the fact that they blanch if direct pressure is applied to them. True purpura may be caused by hemostatic or nonhemostatic defects. Hemostatic defects are caused by platelet or coagulation abnormalities, while nonhemostatic defects generally involve the blood vessels. These vascular abnormalities can be separated into palpable and nonpalpable purpura. The latter may be caused by excess corticosteroids (Cushing's syndrome), vitamin C deficiency (scurvy), infectious agents, or abnormal connective tissue diseases (Ehlers-Danlos syndrome). Causes of palpable purpura include diseases that cause cutaneous vasculitis, such as collagen vascular diseases and Henoch-Schönlein purpura. The latter, also known as anaphylactoid purpura, is a type of hypersensitivity vasculitis found in children. It usually develops 1 to 3 weeks following a streptococcal infection, but it may also occur in relation to allergic food reactions. Cross-reacting IgA or immune complexes are deposited on the

endothelium of blood vessels. Patients may develop fever, purpura, abdominal pain, arthralgia, arthritis, and glomerulonephritis.

202. The answer is d. *(Cotran, pp 635–636.)* Idiopathic (immune) thrombocytopenic purpura (ITP) is a major cause of increased peripheral destruction of platelets. Clinically, ITP may be divided into an acute form and a chronic form. The acute form is more commonly seen in children following a viral infection, while the chronic form is more often seen in adult women of childbearing years. Most individuals with ITP are asymptomatic, but if the platelet count drops low enough, they may develop petechial hemorrhages or epistaxis, usually after an upper respiratory infection. Both clinical types of ITP are associated with the development of antiplatelet antibodies, mainly against the platelet antigens GpIIb/IIIa and GpIb/IX. Therefore, ITP is a form of autoimmune destruction of platelets.

There are several therapies for patients with symptomatic ITP. Since the spleen is the major site for the production of the autoimmune antiplatelet antibodies in patients with ITP and since the spleen is the site for the removal of the platelets (antibody-coated platelets bind to the Fc receptors of macrophages within the spleen), splenectomy may be beneficial in symptomatic patients with ITP. Other therapies include corticosteroids, which decrease antibody formation and also inhibit reticuloendothelial function, and high-dose immunoglobulin therapy, which floods the Fc receptors of the splenic macrophages with Ig, making them less likely to bind to antibody-coated platelets.

203. The answer is b. *(Cotran, pp 636–637, 985–986.)* A fulminating septic state should always be considered whenever the constellation of fever, deteriorating mental status, skin hemorrhages, and shock develops. Such conditions can be seen in gram-negative rod septicemia caused by any of the coliforms (gram-negative endotoxic shock) or fulminant meningococcemia (Waterhouse-Friderichsen syndrome). However, a form of nonbacterial vasculitis termed thrombotic thrombocytopenic purpura (TTP) is notorious for producing a clinical syndrome very similar to fulminating infective states. TTP is characterized by arteriole and capillary occlusions by fibrin and platelet microthrombi and is usually unassociated with any of the predisposing states seen in disseminated intravascular coagulopathy (DIC), such as malignancy, infection, retained fetus, and amniotic fluid embolism. Macrocytic hemolytic anemia, variable jaundice, renal fail-

ure, skin hemorrhages, and central nervous system dysfunction are all seen in TTP and are related to the fibrin thrombi, which can be demonstrated with biopsies of skin, bone marrow, and lymph node. There is less coagulopathy in TTP than is found in DIC, and hemolytic anemia is generally not found in idiopathic or autoimmune thrombocytopenic purpura. The condition of patients with TTP may be improved by plasmapheresis, with 80% survival.

204. The answer is c. *(Damjanov, pp 1089, 1716, 1751, 1823. Cotran, pp 636–637, 985–986.)* Hemolytic-uremic syndrome (HUS) is similar to thrombotic thrombocytopenic purpura (TTP) in that it produces a microangiopathic hemolytic anemia, but it is distinguished from TTP by the lack of neurologic symptoms and by the severe acute renal failure, which is manifested clinically by a markedly increased serum BUN. Classic HUS is seen in children and is related to infection, usually acquired from contaminated ground meat, by verocytotoxin-producing *Escherichia coli.* This toxin is similar to *Shigella* toxins, which, together with *E. coli* and viruses, are causes of the adult form of HUS. Multiple microthrombi in glomerular capillaries result in renal failure, while systemically the microthrombi cause microangiopathic hemolytic anemia. Subsequently thrombocytopenia develops and leads to a bleeding diathesis, seen as vomiting of blood and hematuria. Disseminated intravascular coagulopathy (DIC) is separated from these two thrombotic microangiopathic syndromes by its excessive activation of the clotting system, which results in increased fibrin degradation products (FDP or FSP) and prolonged clotting times (PT and PTT) due to depletion of coagulation factors.

205. The answer is d. *(Cotran, pp 638–639. Henry, pp 732–735.)* Platelet aggregation studies are used to evaluate qualitative disorders of platelets. These tests measure the response of platelets to various aggregating agents, such as ADP, epinephrine, collagen, and ristocetin. ADP causes the initial aggregation of platelets (phase I). This is followed by activation of the platelets, which then release their own ADP, which further aggregates the platelets (phase II). Platelet aggregation may be caused by collagen, ADP, or ristocetin. In von Willebrand's disease (vWD), aggregation induced by collagen and ADP is normal, but ristocetin is decreased. In contrast, patients with Glanzmann's thrombasthenia, storage pool disease, aspirin ingestion, or uremia have normal aggregation with ristocetin, but aggregation with

collagen, epinephrine, thrombin, and ADP is decreased. vWD is considered to be adhesion defects of platelets. Platelet adhesion refers to attachment of platelets to sites of endothelial cell injury where collagen is exposed. von Willebrand factor (vWF) is a molecular bridge between the subendothelial collagen and platelets through the platelet receptor GpIb. A deficiency of either vWF (vWD) or GpIb (Bernard-Soulier syndrome) results in defective platelet adhesion to collagen (adhesion defects). Cryoprecipitate, which contains vWF, corrects this defect in patients with vWD, but not in patients with Bernard-Soulier syndrome (since the defect involves the receptor for vWF). Clinically, vWD is characterized by mucocutaneous bleeding, menorrhagia, and epistaxis. Milder forms of the disease may not be diagnosed until the patient is older. Factor VIII is a complex of several components that can be discerned electrophoretically. Of all the factor VIII components, factor VIII:R, or ristocetin cofactor, is most apt to be abnormal in von Willebrand's disease. Prothrombin time, fibrinogen levels, and factors IX and XIII are not affected in this disorder.

206. The answer is a. *(Cotran, p 637. Henry, pp 247, 710–713.)* Platelet aggregation refers to platelets binding to other platelets. One mechanism for this involves fibrinogen, which can act as a molecular bridge between adjacent platelets by binding to GpIIb and GpIIIa receptors on the surface of platelets. Abnormalities of platelet aggregation (aggregation defects or primary wave defects) include Glanzmann's thrombasthenia and afibrinogenemia. Patients with Glanzmann's thrombasthenia have a deficiency of GpIIb-IIIa and defective platelet aggregation. Patients with low or no fibrinogen levels characteristically have prolonged PT, PTT, and TT values: in fact, they are so prolonged they are unmeasurable.

In contrast to platelet aggregation, platelet secretion refers to the secretion of the contents of two types of granules within the platelet cytoplasm. α granules contain fibrinogen, fibronectin, and platelet-derived growth factor, while dense bodies contain ADP, ionized calcium, histamine, epinephrine, and serotonin. Decreased platelet secretion (activation defects) is seen with deficiencies of these granules; these diseases are called storage pool defects. They can involve either α granules (gray platelet syndrome) or dense bodies (Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome, or TAR). Wiskott-Aldrich syndrome is an X-linked disorder that is characterized by eczema, thrombocytopenia (small platelets), and immunodeficiency consisting of decreased levels of IgM and progressive loss of T cell function.

These patients have recurrent infections with bacteria, viruses, and fungi. TAR refers to the combination of thrombocytopenia and absent radii.

207. The answer is e. *(Cotran, pp 121–124. Henry, pp 725–726, 742–743.)* The coagulation cascade ends with the formation of fibrin from fibrinogen, but it begins with the activation of factor XII in the intrinsic pathway, which then activates in turn factors XI and IX. Activated factor IX together with VIIIa and platelet factor 3 (PF-3) activates factor X, which, together with Va, PF-3, and Ca^{++}, cleaves prothrombin to thrombin. Finally, thrombin cleaves fibrinogen to form fibrin. Congenital deficiencies of factor V are quite rare. Laboratory findings with a deficiency of this factor include a prolonged PTT and PT with a normal TT. Since activated factor V is involved in the next-to-last step of the coagulation cascade that forms thrombin, the only way to correct this deficiency (i.e., which substance can activate the coagulation cascade independent of factor V levels) is the addition of thrombin.

208. The answer is d. *(Cotran, pp 638–639. Henry, pp 725–726, 729–731.)* Hemophilia A is an X-linked recessive disorder that results from a deficiency of coagulation factor VIII. Since it is an X-linked disorder, the gene that codes for coagulation factor VIII must be on the X chromosome. Clinically, patients with hemophilia exhibit a wide range of severity of symptoms that depends upon the degree to which factor VII activity is decreased. Petechiae and small ecchymoses are characteristically absent, but large ecchymoses and subcutaneous and intramuscular hematomas are common. Other types of bleeding that are characteristic include massive hemorrhage following trauma or surgery and "spontaneous" hemorrhages in parts of the body that are normally subject to trauma, such as the joints (hemarthroses). Intra-abdominal hemorrhage and intracranial hemorrhage also occur. The latter is a major cause of death for these individuals. Because of the decreased factor VIII activity, patients with hemophilia A have a prolonged PTT, which measures the intrinsic coagulation cascade. Other clinical tests, including bleeding time, tourniquet test, platelet count, and PT, are normal. Treatment is with factor VIII concentrates, but this carries a risk for the transmission of viral hepatitis and AIDS.

209. The answer is e. *(Cotran, pp 640–642.)* Disseminated intravascular coagulopathy (DIC) is a severe thrombohemorrhagic disorder that results

from extensive activation of the coagulation sequence. With DIC there are widespread fibrin deposits in the microcirculation, which leads to hemolysis of the red cells (microangiopathic hemolytic anemia), ischemia, and infarcts in multiple organs. Continued thrombosis leads to consumption of platelets and the coagulation factors, which subsequently leads to a bleeding disorder. The excessive clotting also activates plasminogen and increases plasmin levels, which cleaves fibrin and increases serum levels of fibrin split products. DIC is never a primary disorder, but instead is always secondary to other diseases that activate either the intrinsic or the extrinsic coagulation system. Activation of the intrinsic pathway results from the release of tissue factor into circulation. Examples include obstetric complications (due to release of placental tissue factor) and cancers (due to release of the cytoplasmic granules of the leukemic cells of acute promyelocytic leukemia or to release of mucin from adenocarcinomas). Coagulation may also result from the activation of the extrinsic pathway by widespread injury to endothelial cells, such as with the deposition of antigen-antibody complexes (vasculitis) or endotoxic damage by microorganisms.

210. The answer is d. *(Cotran, pp 637–642. Henry, pp 725–726, 729–736, 740–743.)* Abnormalities of blood vessels (capillary fragility) or platelets can be detected by either the tourniquet test or the bleeding time. These tests do not test the coagulation cascade. In contrast, the platelet count and platelet morphology are both useful in evaluating platelet abnormalities, while the prothrombin time (PT) and the partial thromboplastin time (PTT) measure the coagulation cascade. The PT measures the extrinsic pathway, while the PTT measures the intrinsic coagulation pathway.

An abnormal tourniquet test and bleeding time with a normal PTT and PT may be caused by either blood vessel abnormalities or platelet abnormalities. Blood vessel abnormalities and abnormal platelet function are accompanied by normal platelet counts (choice a in the table). Causes of blood vessel abnormalities include decreased vitamin C (scurvy) and vasculitis, while causes of platelet dysfunction include Bernard-Soulier syndrome and Glanzmann's thrombasthenia. A decrease in the platelet count (choice c in the table) indicates thrombocytopenia and can be seen in patients with ITP. Normal platelet counts with normal bleeding times are suggestive of abnormalities of the coagulation cascade. A prolonged PTT only (choice b in the table) is seen with abnormalities of the intrinsic pathway, such as hemophilia A or B. A prolonged PT only (choice d in the table)

is seen with abnormalities of the extrinsic pathway, such as a deficiency of factor VII. A prolongation of both PTT and PT is seen with liver disease, vitamin K deficiency, and DIC. Deficiencies of the vitamin K–dependent factors, such as induced with coumadin therapy or broad-spectrum antibiotic therapy, are associated with a normal tourniquet test, bleeding time, and platelet count, but there is also a markedly increased PT, and the PTT may be increased or normal (also choice d in the table). Therefore, the PT is used as a screening test to monitor patients taking oral coumadin. A prolonged bleeding time with a normal platelet count, but a prolonged PTT (choice e in table), is highly suggestive of von Willebrand's disease.

211. The answer is d. *(Damjanov, pp 1125–1144. Rubin, p 1091.)* Clinicians and pathologists alike should be familiar with the benign syndrome of lymph node enlargement called sinus histiocytosis with massive lymphadenopathy. This is a self-limiting, invariably benign disorder found classically in young black African and Caribbean patients, but it has been found in others as well. It is characterized clinically by profound enlargement of regional cervical lymph nodes, fever, and leukocytosis. Histologically, the lymph nodes show marked histiocytic proliferation within the sinuses, with engulfment of lymphocytes within the histiocytes. There may be skin involvement, and histiocytes containing phagocytosed lymphocytes may be present in the skin biopsy specimen. The patients predictably revert to normal within a period of months. Histiocytic medullary reticulosis is a disease in which a form of malignant histiocytes is found in lymph node sinuses, with engulfed red cells found within the neoplastic histiocytes (erythrophagocytosis). Primitive, round lymphoblastic tumor cells are found in tissue taken from patients with Burkitt's lymphoma.

212. The answer is d. *(Cotran, pp 646–647.)* Decreased numbers of neutrophils in the peripheral blood (neutropenia) may be due to decreased production of neutrophils in the bone marrow or to increased peripheral destruction of neutrophils. Decreased production may be caused by megaloblastic anemia, certain drugs, or stem cell defects such as aplastic anemia, leukemias, or lymphomas. Drug-induced destruction of neutrophil precursors is the most common cause of peripheral neutropenia. With all of these different causes of decreased neutrophil production, the bone marrow is hypoplastic and there is a decrease in the number of granulocytic precur-

sors. Some causes of neutropenia also cause a decrease in the numbers of platelets and erythrocytes (pancytopenia).

In contrast to decreased production, neutropenia secondary to peripheral destruction causes a hyperplasia of the bone marrow, with an increase in the number of granulocytic precursors. Causes of increased destruction of neutrophils include sequestration in the spleen due to hypersplenism (not splenic atrophy), increased utilization, such as with overwhelming infections, and immunologically mediated destruction (immune destruction). Causes of immune destruction include Felty's syndrome and certain drug reactions, such as to aminopyrine and some sulfonamides. Drugs may cause decreased production or increased destruction of neutrophils. In the latter, antibodies are formed against neutrophils, and then these cells are destroyed peripherally. Felty's syndrome refers to the combination of rheumatoid arthritis, splenomegaly, and neutropenia. A significant number of patients with Felty's syndrome have a monoclonal proliferation of CD8 large granular lymphocytes, unrelated to drug use.

213. The answer is b. *(Cotran, pp 196–199, 647–649. Rubin, pp 74–75, 1089–1090.)* Leukocytosis (increased numbers of leukocytes in the peripheral blood) is a reaction seen in many different disease states. The type of leukocyte that is mainly increased may be an indicator of the type of disease process present. Eosinophilia is associated with cutaneous allergic reactions; allergic disorders, such as bronchial asthma or hay fever; Hodgkin's disease; some skin diseases, such as pemphigus, eczema, and dermatitis herpetiformis; and parasitic infections, such as trichinosis, schistosomiasis, and strongyloidiasis. The most common cause of eosinophilia is probably allergy to drugs such as iodides, aspirin, or sulfonamides, but eosinophilia is also seen in collagen vascular diseases. Marked eosinophilia occurs in hypereosinophilic syndromes (Löffler's syndrome and idiopathic hypereosinophilic syndrome), which may be treated with corticosteroids. Neutrophilic leukocytosis (neutrophilia) may be the result of acute bacterial infections or tissue necrosis, such as is present with myocardial infarction, trauma, or burns. Basophilia is most commonly seen in immediate type (type I) hypersensitivity reactions. Both eosinophils and basophils may be increased in patients with any of the chronic myeloproliferative syndromes. Monocytosis is seen in chronic infections, such as tuberculosis, some collagen vascular diseases, neutropenic states, and some types of

lymphomas. Lymphocytosis may be seen along with monocytosis in chronic inflammatory states or in acute viral infections, such as viral hepatitis or infectious mononucleosis.

214. The answer is c. *(Cotran, pp 649–650. Chandrasoma, pp 433–443.)* Lymph nodes may be enlarged (lymphadenopathy) secondary to reactive processes, which can be either acute or chronic. Acute reaction (acute nonspecific lymphadenitis) can result in focal or generalized lymphadenopathy. Focal lymph node enlargement is usually the result of bacterial infection. Sections from involved lymph nodes reveal infiltration by neutrophils. In contrast, generalized acute lymphadenopathy is usually the result of viral infections and usually produces a proliferation of reactive T lymphocytes called T immunoblasts. These reactive T cells tend to have prominent nucleoli and can be easily mistaken for malignant lymphocytes or malignant Hodgkin cells.

Reactive processes involving lymph nodes typically involve different and specific portions of the lymph nodes depending upon the type of cell that is reacting. For example, reactive B lymphocytes typically result in hyperplasia of the lymphoid follicles and germinal centers (follicular hyperplasia). Examples of diseases that are associated with follicular hyperplasia include chronic inflammation caused by organisms, rheumatoid arthritis, and AIDS. Lymph nodes from patients with AIDS undergo characteristic changes that begin with follicular hyperplasia with loss of mantle zones, intrafollicular hemorrhage ("follicle lysis"), and monocytoid B cell proliferation. Subsequently there is depletion of lymphocytes (CD4+ lymphocytes) in both the follicles and the interfollicular areas. In contrast to reactive B cell processes, reactive T lymphocytes typically result in hyperplasia involving the T cell areas of the lymph node, namely the interfollicular regions and the paracortex. Examples of clinical situations associated with a T lymphocyte response include viral infections, vaccinations, use of some drugs (particularly Dilantin), and systemic lupus erythematosus. The sinusoidal pattern of reaction involves expansion of the sinuses by benign macrophages, as seen in reactive proliferations of the mononuclear-phagocytic system. Stellate microabscesses (irregular areas composed of central necrotic cellular and neutrophil debris surrounded by palisading macrophages) are characteristic of cat-scratch disease, lymphogranuloma venereum, and tularemia.

215. The answer is c. *(Cotran, pp 651–655, 659–661. Rubin, pp 1131–1132. Silverberg, pp 383–384.)* In general, the non-Hodgkin's lymphomas (NHLs) can be divided histologically into nodular forms and diffuse forms. The nodular NHLs, as seen in the picture associated with this question, are characterized by being more common in an older age group (they are rare in those under 20), more often presenting with widespread disease (higher stage), and having a better prognosis but responding less to chemotherapy. All nodular NHLs, one of which is seen in the picture associated with this question, are the result of neoplastic proliferations of B lymphocytes. Histologically these nodules somewhat resemble the germinal centers of lymphoid follicles, but instead they are characterized by increased numbers (crowding) of nodules, their location in both the cortex and the medulla, their uniform size, and their composition (a monotonous proliferation of cells). In contrast to the nodular NHLs, the diffuse NHLs may be derived from either B lymphocytes or T lymphocytes. Two types of NHL that are always diffuse in appearance are small lymphocytic NHL (SLL) and lymphoblastic lymphomas.

216. The answer is d. *(Cotran, pp 658–659.)* The working formulation divides the non-Hodgkin's lymphomas (NHLs) into low grade, intermediate grade, and high grade based on prognostic criteria. The low-grade NHLs include small lymphocytic NHL (well-differentiated lymphocytic NHL), follicular small cleaved NHL, and follicular mixed small cleaved and large cell NHL. The intermediate-grade NHLs include follicular large cell NHL, diffuse small cleaved NHL, diffuse mixed small cleaved and large cell NHL, and diffuse large cell NHL. The high-grade NHLs include immunoblastic lymphoma, lymphoblastic lymphoma, and small noncleaved NHL (Burkitt's lymphoma).

Some of the NHLs are associated with involvement of the peripheral blood (leukemic phase). More than half of the patients with small lymphocytic lymphoma (SLL) have involvement of the bone marrow with spillage of neoplastic cells into the peripheral blood, where they appear as mature lymphocytes, many of which are smudged. The clinical picture is then similar to that of chronic lymphocytic leukemia (CLL). Follicular NHLs commonly involve the bone marrow, but spillage into the peripheral blood is much less common than in SLL. Still, when the malignant small cleaved lymphocytes are found within the peripheral blood, they have a characteristic cleaved

appearance that is described as "buttock cells." Lymphoblastic lymphoma is an aggressive, rapidly progressive malignancy in which lymphoblasts typically involve the bone marrow and peripheral blood. The clinical picture then is similar to that of T cell acute lymphoblastic leukemia (ALL).

217. The answer is b. *(Henry, pp 695–699. Cotran, p 662–663.)* Burkitt's lymphoma, or undifferentiated lymphoma, is characterized by a rapid proliferation of primitive lymphoid cells with thick nuclear membranes, multiple nucleoli, and intensely basophilic cytoplasm when stained with Wright's stain. The cells are often mixed with macrophages in biopsy, giving a starry sky appearance. The cytoplasmic vacuoles of the lymphoma cells contain lipid, and this would be reflected by a positive oil red O reaction. PAS stain is nonspecific but does mark neutrophils and acute lymphoblastic leukemia cells. Nonspecific esterase is found predominantly within monocytes but also in megakaryocytes. Chloracetate esterase and myeloperoxidase are primarily found within the lysosomes of granulocytes, including neutrophils, promyelocytes, and faintly in rare monocytes.

218. The answer is b. *(Cotran, p 654–658, 661–662.)* T cell lymphomas occurring in the thoracic cavity in young patients usually arise in the mediastinum and have a particularly aggressive clinical course with rapid growth in the mediastinum impinging upon the trachea or mainstem bronchi and leading to marked respiratory deficiency, which can in turn lead to death in a relatively short period of time if not treated. These unique lymphomas are characterized by rapid cell growth and spread into the circulation, where they produce elevated total white counts reflected by circulating lymphoma cells. As T cells they have characteristics of rosette formation with sheep blood cells. T cells also have subtypes and subsets, which can be delineated by monoclonal antibodies as CD4 helper and CD8 suppressor (cellular differentiation) T cell surface antigens. The tumor cells also express IL-2 receptor. Fc receptors occur on B cells and macrophages. Class II HLA antigens can be found on macrophages, Langerhans cells, and dendritic reticulum cells.

219. The answer is c. *(Cotran, pp 670–675.)* The diagnosis of Hodgkin's disease depends on the clinical findings added to the total histologic picture, which includes the presence of binucleated or bilobed giant cells with prominent acidophilic "owl-eye" nucleoli known as Reed-Sternberg (RS)

cells. However, cells similar in appearance to RS cells may also be seen in infectious mononucleosis, mycosis fungoides, and other conditions. Thus, while RS cells are necessary for histologic confirmation of the diagnosis of Hodgkin's disease, they must be present in the appropriate histologic setting of lymphocyte predominance, nodular sclerosis, mixed cellularity, or lymphocyte depletion to make the correct diagnosis. In contrast, Call-Exner bodies are seen in granulosa cell tumors of the ovary, Hürthle cells are associated with Hashimoto's thyroiditis, Sézary cells are associated with mycosis fungoides, and strap cells are seen in skeletal muscle tumors, such as rhabdomyomas.

220. The answer is d. *(Cotran, pp 670–675.)* Hodgkin's disease is broadly divided into four histologic subtypes, the most common of which is the nodular sclerosis variant. This type is characterized morphologically by the presence of the lacunar variant of Reed-Sternberg (RS) cells and by bands of fibrous tissue that divide the lymph node into nodules. Unlike the other subtypes of Hodgkin's disease, it is more common in females. Young adults are classically affected and the disease typically involves the cervical, supraclavicular, or mediastinal lymph nodes. Involvement of extranodal lymphoid tissue is unusual. Variant RS cells with a multilobed, puffy nucleus ("popcorn" cells) are seen in the lymphocyte-predominant subtype.

221. The answer is e. *(Cotran, pp 675–678.)* The leukemias are malignant neoplasms of the hematopoietic stem cells that are characterized by diffuse replacement of the bone marrow by neoplastic cells. These malignant cells frequently spill into the peripheral blood. The leukemias are divided into acute and chronic forms, and then further subdivided based on lymphocytic or myelocytic (myelogenous) forms. Thus, the four basic patterns of acute leukemia are acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelocytic leukemia (AML), and chronic myelocytic leukemia (CML).

Acute leukemias are characterized by a decrease in the mature forms of cells and an increase in the immature forms (leukemic blasts). Acute leukemias (both ALL and AML) have an abrupt clinical onset and present with symptoms due to failure of normal marrow function. Symptoms include fever (secondary to infection), easy fatigability (due to anemia), and bleeding (due to thrombocytopenia). The peripheral smear in patients with acute leukemia usually reveals the white cell count to be increased.

The peripheral smear also reveals signs of anemia and thrombocytopenia. More importantly, however, there are blasts in the peripheral smear. The diagnosis of acute leukemia is made by finding more than 30% blasts in the bone marrow.

AML primarily affects adults between the ages of 15 and 39 and is characterized by the neoplastic proliferation of myeloblasts. Myeloblasts, characterized by their delicate nuclear chromatin, may contain three to five nucleoli. Myeloblasts in some cases of AML contain distinct intracytoplasmic rodlike structures that stain red and are called Auer rods. These are abnormal lysosomal structures (primary granules) that are considered pathognomonic of myeloblasts. AML is divided into seven types by the French-American-British (FAB) classification:

M1—myeloblastic leukemia without maturation (cells are mainly blasts)
M2—myeloblastic leukemia with maturation (some promyelocytes are present)
M3—hypergranular promyelocytic leukemia (numerous granules and many Auer rods)
M4—myelomonocytic leukemia (both myeloblasts and monoblasts)
M5—monocytic leukemia (infiltrates in the gingiva are characteristic)
M6—erythroleukemia (Di Guglielmo's disease)
M7—acute megakaryocytic leukemia (associated with myelofibrosis)

Acute promyelocytic leukemia (M3 AML) is characterized by several specific features that are found in no other types of acute leukemia. There are numerous abnormal promyelocytes present that contain numerous cytoplasmic granules and numerous Auer rods. If these numerous granules are released from dying cells, which may occur with treatment, they may activate extensive, uncontrolled intravascular coagulation and cause the development of disseminated intravascular coagulopathy (DIC). This abnormality is characterized by increased fibrin degradation products in the blood. M3 AML is also characterized by the translocation t(15;17), which results in the fusion of the retinoic acid receptor α gene on chromosome 17 to the PML unit on chromosome 15. This produces an abnormal retinoic acid receptor and provides the basis for treatment of these patients with all-trans-retinoic acid.

222. The answer is d. *(Cotran, pp 654–658.)* Acute lymphoblastic leukemia (ALL) is primarily a disease of children and young adults that is

characterized by the presence of numerous lymphoblasts within the bone marrow. These malignant cells may spill over into the blood and other organs. In contrast to myeloblasts, lymphoblasts do not contain myeloperoxidase, but they do stain positively with the PAS stain or acid phosphatase stain and for the enzyme TdT. The French-American-British (FAB) classification of ALL divides ALL into three types based on the morphology of the proliferating lymphoblasts. L1-ALL, seen in about 85% of the cases of ALL, consists of small homogeneous blasts. L2-ALL, seen in only 15% of cases of ALL, but more common in adults, consists of lymphoblasts that are larger and more heterogeneous (pleomorphic) than L1 blasts. These cells may also contain nuclear clefts. The final type of FAB ALL is the L3 type, which is seen in less than 1% of the cases of ALL. This form is essentially the leukemic form of Burkitt's lymphoma. Like the malignant cells of Burkitt's lymphoma, these L3-ALL cells are large blasts with cytoplasmic vacuoles that stain positively with the oil red O lipid stain.

In contrast to the FAB classification of ALL, the immunologic classification of ALL is based on the developmental sequence of maturation of B lymphocytes and T lymphocytes. First it is necessary to determine whether the blasts have B cell or T cell markers. Most cases of ALL are of B cell origin; that is, the lymphoblasts express both CD19 and DR. A few cases of ALL are of T cell origin; the lymphoblasts lack CD19 and DR and instead express T cell antigens CD2, 5, and 7. Many cases of T-ALL involve a mediastinal mass and are clinically similar to cases of lymphoblastic lymphoma. To subclassify B-ALL, first determine if surface immunoglobulin (sIg) is present. Mature B-ALL cells (L3-ALL or Burkitt's lymphoma) have surface immunoglobulin, which is not found in the other types of B-ALL. These mature cells typically lack TdT, which is a marker for more immature cells. Next determine if there is cytoplasmic μ present. Cytoplasmic μ chains are specific for pre-B ALL cells, which have a characteristic translocation t(1;19). The B cell ALL cells that lack both surface Ig and cytoplasmic μ are called early pre-B-ALL and are separated into the CALLA (CD10)-positive and CALLA-negative types.

223. The answer is b. *(Cotran, pp 284–286, 679–682.)* Chronic myeloid leukemia (CML) is one of the four chronic myeloproliferative disorders, but, unlike myeloid metaplasia or polycythemia vera, CML is associated with the Philadelphia chromosome translocation t(9;22) in over 90% of cases. This characteristic translocation, which involves the oncogene *c-abl* on chromo-

some 9 and the breakpoint cluster region on chromosome 22, results in the formation of a new fusion protein (P210) that is a non-receptor tyrosine kinase. [In contrast, the translocation t(8;14) and the *c-myc* oncogene are associated with Burkitt's lymphoma.] In differentiating CML from a leukemoid reaction, several other features are important in addition to the presence of the Philadelphia chromosome: lack of alkaline phosphatase in granulocytes, increased basophils and eosinophils in the peripheral blood, and, often, increased platelets in early stages followed by thrombocytopenia in late or blast stages. Other well-known features of CML include marked splenomegaly, leukocyte counts greater than 50,000/μL, and mild anemia.

224. The answer is c. *(Cotran, pp 668–669.)* Hairy cell leukemia, a type of chronic B cell leukemia, should be suspected in patients with splenomegaly; pancytopenia, including thrombocytopenia; bleeding; fatigue; and leukemic lymphocyte-like cells in the peripheral blood demonstrating cytoplasmic projections at the cell periphery ("hairy" cells). These cells stain for acid phosphatase, and the reaction is refractory to treatment with tartaric acid [tartrate-resistant acid phosphatase (TRAP)]. These hairy cells also express pan–B cell markers (CD19 and CD20), the monocyte marker CD11c, and the plasma cell marker PCA-1. The most common sign in these patients is splenomegaly, which is due to leukemic cells infiltrating the red pulp, which is unusual considering that most leukemias preferentially infiltrate the white pulp. Because these neoplastic cells proliferate in the spleen, splenectomy may be a treatment choice. Another treatment option is interferon α and pentostatin; the latter blocks adenine deaminase. The histologic appearance of the bone marrow is that of "fried eggs," but aspiration of the marrow typically produces a dry tap.

225. The answer is c. *(Cotran, pp 658–659.)* Chronic lymphocytic leukemia (CLL) is the most common leukemia and is similar in many aspects to small lymphocytic lymphoma (SLL). It is typically found in patients older than 60 years of age. Histological examination of the peripheral smear reveals a marked increase in the number of mature-appearing lymphocytes. These neoplastic lymphocytes are fragile and easily damaged. This fragility produces the characteristic finding of numerous smudge cells in the peripheral smears of patients with CLL. About 95% of the cases of CLL are of B cell origin (B-CLL) and are characterized by having pan–B cell markers, such as CD19. These malignant cells characteristically also have

the T cell marker CD5. The remaining 5% of cases of CLL are mainly of T cell origin. Patients with CLL tend to have an indolent course and the disease is associated with long survival in many cases. The few symptoms that may develop are related to anemia and the absolute lymphocytosis of small, mature cells. Splenomegaly may be noted. In a minority of patients, however, the disease may transform into prolymphocytic leukemia or a large cell immunoblastic lymphoma (Richter's syndrome). Prolymphocytic leukemia is characterized by massive splenomegaly and a markedly increased leukocyte count consisting of enlarged lymphocytes having nuclei with mature chromatin and nucleoli.

226. The answer is d. *(Cotran, pp 678–679. Henry, pp 630–631, 685.)* Approximately 35% of normoblasts in normal bone marrow contain ferritin granules and are called sideroblasts. The iron in these normal sideroblasts is not located around the nucleus. The photomicrograph associated with this question instead demonstrates sideroblasts that have distinctive rings of Prussian blue–positive granules around their nuclei. These abnormal cells are called ring sideroblasts. In these cells iron accumulates within mitochondria without any progression into hemoglobin. Ring sideroblasts can be found in patients with alcoholism, selective deficiencies of pyridoxine, sideroblastic anemia, and myelodysplastic syndromes (MDSs). Myelodysplastic syndromes are characterized by peripheral pancytopenia, hypercellular bone marrow, and dysplastic features of blood cells, such as megaloblastoid erythroid precursors, hypogranular or Pelger-Huët white blood cells, and macrothrombocytes. A dimorphic population of red cells may be seen in the peripheral blood of some patients with some types of MDS. Chromosomal abnormalities are commonly associated with the MDSs, especially $5q^-$ and trisomy 8. Except for chronic myelomonocytic leukemia (CMML), which is characterized by a marked increase in the number of monocytes, the MDSs are subclassified by the number of blasts present within the bone marrow. If there are less than 5% blasts present, the MDS is either refractory anemia (RA) or refractory anemia with ring sideroblasts (RARS). Refractory anemia with excess blasts (RAEB, pronounced "rab") has between 5 and 20% blasts, while refractory anemia with excess blasts in transformation (RAEBIT, pronounced "rabbit") has between 20 and 30% blasts in the marrow. Acute leukemia is defined as the presence of more than 30% blasts in the marrow. Usually these blasts are also found in the peripheral blood, but in a minority of cases of acute

leukemia there is a peripheral leukopenia. These cases are referred to as aleukemic leukemia.

227. The answer is e. *(Cotran, pp 682–683.)* Polycythemia rubra vera (PRV) is a myeloproliferative disorder that is characterized by excessive proliferation of erythroid, granulocytic, and megakaryocytic precursors derived from a single stem cell. In PRV the erythroid series dominates, but there is hyperplasia of all elements. There is plethoric congestion of all organs. The liver and spleen are typically moderately enlarged and may show extramedullary hematopoiesis. Thrombotic complications are an important cause of morbidity and mortality, and major and minor hemorrhagic complications are also frequent. The red cell count is elevated with hematocrit >60% (despite the fact that serum erythropoietin levels are decreased). The white cell count and platelet count are also elevated. Leukocyte alkaline phosphatase (LAP) activity is elevated, in contrast to the case with chronic myeloid leukemia, where it is reduced. Pruritus and peptic ulceration are common, possibly in relation to increased histamine release from basophils.

228. The answer is d. *(Cotran, pp 683–685.)* Myeloid metaplasia with myelofibrosis is a myeloproliferative disorder in which the bone marrow is hypocellular and fibrotic and extramedullary hematopoiesis occurs, mainly in the spleen (myeloid metaplasia). Marked splenomegaly with trilineage proliferation of normoblasts, immature myeloid cells, and large megakaryocytes occur. Giant platelets and poikilocytic (teardrop) red cells are seen in the peripheral smear. Clinically, myeloid metaplasia may be preceded by polycythemia vera or chronic myeloid leukemia. Biopsy of the marrow is essential for diagnosis. In contradistinction to chronic myeloid leukemia, levels of leukocyte alkaline phosphatase are elevated or normal in myeloid metaplasia; in CML, levels are low or absent. In 5 to 10% of cases of myeloid metaplasia, acute leukemia occurs. In aplastic anemia the marrow is very hypocellular, but consists largely of fat cells, not fibrosis. There is no splenomegaly. Microangiopathic and other hemolytic anemias that result from trauma to red cells show many erythrocytic abnormalities (helmet and burr cells, triangle cells, and schistocytes) in the peripheral smear.

229. The answer is c. *(Cotran, pp 663–666.)* The bone marrow aspirate exhibits a proliferation of plasma cells that are characterized by well-

defined perinuclear clear zones and by dense cytoplasmic basophilia due to increased RNA accumulations. Weakness, weight loss, recurrent infections, proteinuria, anemia, and abnormal proliferation of plasma cells in the bone marrow are findings that highly suggest the presence of multiple myeloma, a plasma cell dyscrasia. The more definitive diagnostic criteria are findings of M component in the results of serum electrophoresis and plasma cell levels of above 20% in the bone marrow. Multiple myeloma, which occurs more commonly in males than in females, shows an increasing incidence with increasing age, and most patients are in their seventies.

230. The answer is b. *(Cotran, pp 663–666.)* Multiple myeloma is characterized by a triad of marrow plasmacytosis, serum or urine M (monoclonal) protein, and lytic bone lesions. Myeloma is a monoclonal malignancy of the B lymphocyte system, with bone pain the most common symptom. Osteolytic, punched-out bone lesions are characteristic, especially in the skull. Since the process is lytic, alkaline phosphatase is usually not elevated. These osteolytic lesions result from the production of osteoclast-activating factor (OAF) by the myeloma cells. This results in increased serum calcium levels (hypercalcemia). OAF is in fact IL-6, and increased amounts of IL-6 are associated with a worse prognosis because the survival of the myeloma cells is dependent upon IL-6. Myeloma is not associated with lymphadenopathy, but recurrent infections are frequent because of the severe suppression of normal immunoglobulins. In fact, infection is the most common cause of death in these patients and is usually due to encapsulated bacteria. There is no increase in viral infections in these patients because their cell-mediated immunity is normal.

231. The answer is e. *(Cotran, p 666–667. Silverberg, pp 452–453.)* Waldenström's macroglobulinemia (WM), associated with a monoclonal production of IgM, is clinically distinct from multiple myeloma. It is somewhat like a cross between multiple myeloma (MM) and small lymphocytic lymphoma (SLL). As with myeloma, there is a monoclonal production of immunoglobulin (IgM) that produces an M spike. Unlike the case with myeloma, however, there are no lytic bone lesions and no hypercalcemia, and the bone marrow shows proliferation of plasma cells, lymphocytes, and plasmacytoid lymphocytes. Like SLL, WM is associated with infiltration of organs outside of the bone marrow by neoplastic cells. These include the lymph nodes and the spleen. (Involvement of these organs is

unusual in patients with MM.) Because IgM is a large molecule (a pentamer), patients with WM are prone to developing the hyperviscosity syndrome, which consists of visual abnormalities, neurologic signs (headaches and confusion), bleeding, and cryoglobulinemia.

Other monoclonal proliferations of immunoglobulin include monoclonal gammopathy of undetermined significance (MGUS) and heavy chain disease. MGUS may be associated with an M spike and increased marrow plasma cells, but the number of plasma cells will be less than 20%. Note that M proteins are found in 1 to 3% of asymptomatic persons over the age of 50. Heavy chain disease refers to types of plasma cell dyscrasia that are associated with the monoclonal production of immunoglobulin heavy chains only (not light chains). There are basically three types of heavy chain disease: α heavy chain disease, γ heavy chain disease, and μ heavy chain disease. α heavy chain disease is seen primarily in the Mediterranean region, hence its other name, Mediterranean lymphoma. It is characterized by numerous plasma cells infiltrating the lamina propria of the small intestines. This disease is preceded by an abnormality called immunoproliferative small intestinal disease (IPSID), which is characterized by villous atrophy of the small intestines with steatorrhea. Unique patients with this disease are treated with antibiotics. γ heavy chain disease is rare and is similar to non-Hodgkin's lymphoma. μ heavy chain disease is found rarely in some patients with CLL.

232. The answer is b. *(Cotran, pp 685–686. Rubin, pp 1364–1365.)* Langerhans cell histiocytosis, previously known as histiocytosis X, refers to a spectrum of clinical diseases that are associated with the proliferation of Langerhans cells. These cells, not to be confused with the Langerhans-type giant cells found in caseating granulomas of tuberculosis, have Fc receptors and HLA-D/DR antigens and react with CD1 antibodies. These cells contain distinctive granules, seen by electron microscopy, that are rod-shaped organelles resembling tennis rackets. They are called LC (Langerhans cells) granules, pentilaminar bodies, or Birbeck granules. There are three general clinical forms of Langerhans histiocytosis. Acute disseminated Langerhans cell histiocytosis (Letterer-Siwe disease) affects children before the age of 3 years. These children have cutaneous lesions that resemble seborrhea, hepatosplenomegaly, and lymphadenopathy. The Langerhans cells infiltrate the marrow, which leads to anemia, thrombocytopenia, and recurrent infections. The clinical course is usually rapidly fatal; however, with inten-

sive chemotherapy 50% of patients may survive 5 years. Multifocal Langerhans cell histiocytosis (Hand-Schüller-Christian disease) usually begins between the second and sixth years of life. The characteristic triad consists of bone lesions, particularly in the calvarium and the base of the skull; diabetes insipidus; and exophthalmos. These lesions are the result of proliferations of Langerhans cells. Lesions around the hypothalamus lead to decreased ADH production and signs of diabetes insipidus. Unifocal Langerhans cell histiocytosis (eosinophilic granuloma), seen in older patients, is usually a unifocal disease, most often affecting the skeletal system. The lesions are granulomas that contain a mixture of lipid-laden Langerhans cells, macrophages, lymphocytes, and eosinophils.

In contrast, sarcoidosis is characterized by a proliferation of activated macrophages that form granulomas. It is not a proliferation of Langerhans cells. Dermatopathic lymphadenitis refers to a chronic lymphadenitis that affects the lymph nodes draining the sites of chronic dermatologic diseases. The lymph nodes undergo hyperplasia of the germinal follicles and accumulation of melanin and hemosiderin pigment by the phagocytic cells.

233. The answer is d. *(Cotran, pp 371–373.)* Infectious mononucleosis is a benign lymphoproliferative disorder caused by infection with the Epstein-Barr virus (EBV). It typically occurs in young adults and presents with systemic symptoms, lymphadenopathy, and pharyngitis. Hepatosplenomegaly may be present. Peripheral blood shows an absolute lymphocytosis, and many lymphocytes are atypical with irregular nuclei and abundant basophilic vacuolated cytoplasm. These represent CD8+ T killer cells induced by EBV-transformed B lymphocytes. These atypical lymphocytes are usually adequate for diagnosis, along with a positive heterophil or monospot test (increased sheep red cell agglutinin). Administration of ampicillin for a mistaken diagnosis of streptococcal pharyngitis results in a rash in many patients.

This page intentionally left blank.

Respiratory System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

234. Histologic sections (routine H&E stain) of lung reveal the alveoli to be filled with pale, nongranular pink fluid. Neither leukocytes nor erythrocytes are present within this fluid. What is the most likely (i.e., most common) cause of this abnormality?

a. Bacterial pneumonia
b. Congestive heart failure
c. Lymphatic obstruction by tumor
d. Pulmonary embolus
e. Viral pneumonia

235. A 7-year-old boy accidentally inhales a small peanut, which lodges in one of his bronchi. A chest x-ray reveals the mediastinum to be shifted toward the side of the obstruction. The best description for the lung changes that result from this obstruction is

a. Absorptive atelectasis
b. Compression atelectasis
c. Contraction atelectasis
d. Patchy atelectasis
e. Hyaline membrane disease

236. Histologic sections of lung tissue from an individual with adult respiratory distress syndrome (ARDS) are most likely to reveal

a. Angioinvasive infiltrates of pleomorphic lymphoid cells
b. Deposits of needle-like crystals from the membranes of eosinophils
c. Infiltrating groups of malignant cells having intercellular bridges
d. Irregular membranes composed of edema, fibrin, and dead cells lining alveoli
e. Plexiform lesions within pulmonary arterioles

237. While recovering in bed 1 week after an abdominal hysterectomy, a 42-year-old female develops acute shortness of breath with hemoptysis. Physical examination finds the patient to be afebrile with moderate respiratory distress, calf tenderness, and a widely split S_2. What is the correct diagnosis?

a. Atelectasis
b. Bacterial pneumonia
c. Pulmonary embolus
d. Pulmonary hypertension
e. Viral pneumonia

238. A specimen from a lung biopsy reveals occasional plexiform lesions within pulmonary arterioles. This abnormality is most characteristic of

a. Churg-Strauss syndrome
b. Adult respiratory distress syndrome
c. Wegener's granulomatosis
d. Pulmonary hypertension
e. Lymphomatoid granulomatosis

239. A 19-year-old female presents with urticaria that developed after she took aspirin for a headache. She has a history of chronic rhinitis, and physical examination reveals the presence of nasal polyps. This patient is at an increased risk of developing which one of the following pulmonary diseases following the ingestion of aspirin?

a. Asthma
b. Chronic bronchitis
c. Emphysema
d. Interstitial fibrosis
e. Pulmonary hypertension

240. Which one of the following is a correct association concerning the pathogenesis of smoking-induced emphysema?

a. Destruction of distal acinus = centrilobular emphysema
b. Destruction of distal acinus = paraseptal emphysema
c. Destruction of entire acinus = panlobular emphysema
d. Destruction of proximal acinus = centrilobular emphysema
e. Destruction of proximal acinus = paraseptal emphysema

241. An abnormality that inhibits the normal functioning of the ATPase-containing dynein arms of cilia is most likely to produce

a. Asthma
b. Bronchiectasis
c. Cirrhosis
d. Emphysema
e. Steatosis

242. Histologic examination of lung tissue reveals multiple suppurative, neutrophil-rich exudates that fill the bronchi and bronchioles and spill over into the adjacent alveolar spaces only. The majority of lung tissue is not involved in this inflammatory process. Hyaline membranes are not found. This histologic appearance best describes

a. Bronchiectasis
b. Bronchopneumonia
c. Lobar pneumonia
d. Interstitial pneumonitis
e. Pulmonary abscess

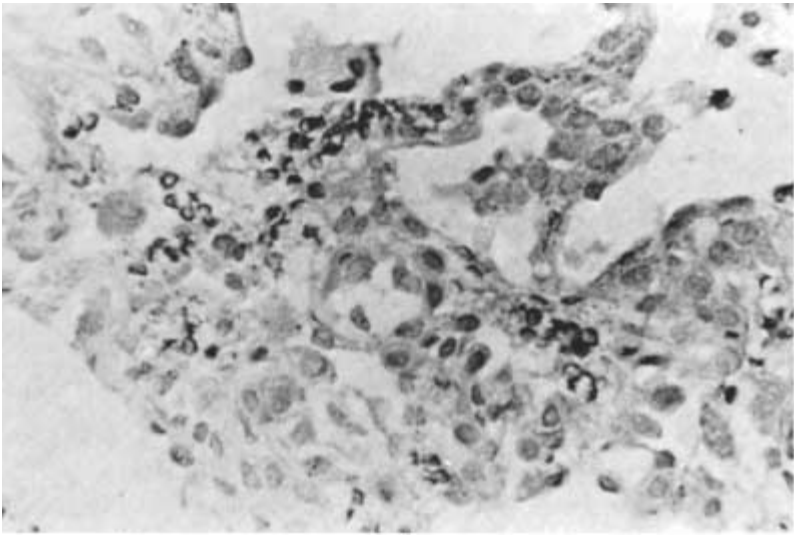
243. A 44-year-old male alcoholic presents with fever and a productive cough with copious amounts of foul-smelling purulent sputum. Physical examination finds that changing the position of this individual produces paroxysms of coughing. Which one of the following is most likely responsible for this patient's signs and symptoms?

a. Esophageal cancer
b. Esophageal reflux
c. Myocardial infarction
d. Pulmonary abscess
e. Pulmonary infarction

244. A 25-year-old female presents with fever, malaise, headaches, and muscle pain (myalgia). A chest x-ray reveals bilateral infiltrates. You draw a tube of blood from the patient (the tube contains anticoagulant) and place the tube in a cup of ice. After the blood has cooled, you notice that the red cells have agglutinated (not clotted). This agglutination goes away after you warm up the tube of blood. This patient's illness is most likely due to infection with

a. Influenza A virus
b. *Mycoplasma pneumoniae*
c. *Streptococcus pneumoniae*
d. *Pneumocystis pneumoniae*
e. *Mycobacterium tuberculosis*

245. A 23-year-old HIV-positive male presents with a cough and increasing shortness of breath. A histologic section from a transbronchial biopsy stained with Gomori's methenamine-silver stain is shown in the photomicrograph below. What is the correct diagnosis?

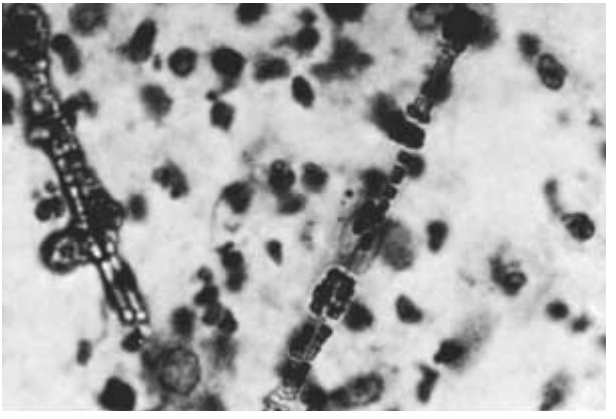


a. *Pseudomonas* pneumonia
b. *Aspergillus* pneumonia
c. *Pneumocystis carinii* pneumonia
d. Cytomegalovirus pneumonia
e. Influenza pneumonia

246. A routine chest x-ray performed on an asymptomatic adult male patient who works at sandblasting reveals a fine nodularity in the upper zones of the lungs and "eggshell" calcification of the hilar lymph nodes. The patient's serum calcium level is 9.8 mg/dL, while his total protein is 7.2 g/dL. He denies any history of drug use or cigarette smoking. A biopsy from his lung reveals birefringent particles within macrophages. This material is most likely to be

a. Asbestos
b. Beryllium
c. Carbon
d. Silica
e. Talc

247. The photomicrograph of the bronchial washing specimen shown below depicts



a. Schaumann bodies
b. Ferruginous bodies
c. Cholesterol crystals
d. *Candida* species
e. Silica particles

248. A 24-year-old African American female presents with nonspecific symptoms including fever and malaise. A chest x-ray reveals enlarged hilar lymph nodes ("potato nodes"), while her serum calcium level is found to be elevated. Biopsies of the enlarged hilar lymph nodes would most likely reveal

a. Caseating granulomas
b. Dense, granular, PAS-positive, eosinophilic material
c. Markedly enlarged epithelial cells with intranuclear inclusions
d. Noncaseating granulomas
e. Numerous neutrophils with fibrin deposition

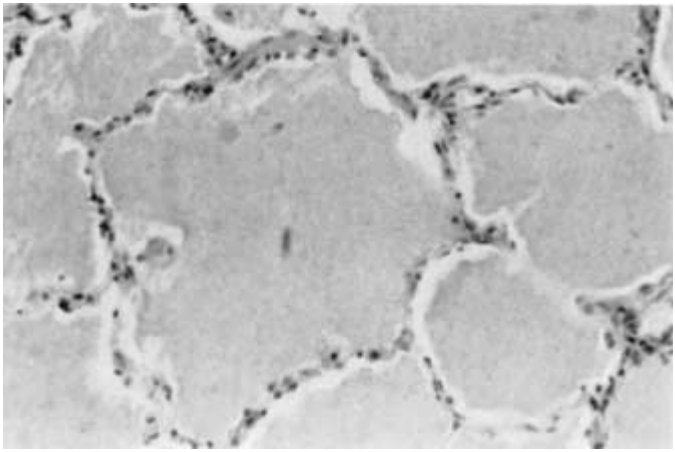
249. A 61-year-old male presents with increasing shortness of breath. A chest x-ray reveals a diffuse pulmonary infiltrate, while a transbronchial biopsy reveals fibrosis of the walls of the alveoli, many of which contain sheets of "desquamated" cells. Which of the following would be the best therapy for this patient?

a. Theophylline
b. Steroids
c. Antibiotics
d. Isoniazid
e. Symptomatic treatment only

250. Sections of the lung from a patient with Wegener's granulomatosis who presents clinically with hemoptysis are most likely to show

a. Atypical lymphocytes invading blood vessels
b. Granulomatous inflammation of blood vessels with numerous eosinophils
c. Granulomatous inflammation of bronchi with *Aspergillus*
d. Large, serpiginous necrosis with peripheral, palisading macrophages
e. Necrotizing hemorrhagic interstitial pneumonitis

251. A 45-year-old man presents with shortness of breath, cough with mucoid sputum, and some weight loss, and has diffuse, bilateral alveolar infiltrates on chest x-ray. Pulmonary function tests reveal decreased diffusing capacity and hypoxia. The patient had worked for several years at grinding aluminum. The photomicrograph below is from a lung biopsy. Your diagnosis is



a. *Pneumocystis carinii* pneumonia
b. Diffuse alveolar damage
c. Pulmonary edema
d. Pulmonary alveolar proteinosis
e. Lipid pneumonia

252. Bronchiolitis obliterans with organizing pneumonia (BOOP) is characterized histologically in the lung by

a. Asteroid bodies in giant cells within bronchioles
b. Loose fibrous tissue within bronchioles and alveoli
c. Multiple rheumatoid nodules within the interstitial tissue
d. Numerous eosinophils within the walls of the alveoli
e. Numerous lymphocytes within the walls of the alveoli

253. A 54-year-old male presents with several problems involving his face and pain in his shoulder. He states that he has smoked 2 packs of cigarettes a day for almost 40 years. Physical examination reveals ptosis of his left upper eyelid, constriction of his left pupil, and lack of sweating (anhidrosis) on the left side of his face. No other neurologic abnormalities are found. This individual most likely has

a. A bronchioloalveolar carcinoma involving the left upper lobe
b. A small cell carcinoma involving the hilum of his left lung
c. A squamous cell carcinoma involving the left mainstem bronchus
d. An adenocarcinoma involving the apex of his left lung
e. An endobronchial carcinoid tumor involving the right mainstem bronchus

254. During a routine physical examination, a 43-year-old male is found to have a 2.5-cm "coin" in the peripheral portion of his right upper lobe (RUL). Several sputum samples sent for cytology are unremarkable, and a bronchoscopic examination is also unremarkable. Surgery is performed and the mass is resected. Histologic examination reveals lobules of connective tissue that contain mature hyaline cartilage. These lobules are separated by clefts that are lined by respiratory epithelium. What is the correct diagnosis?

a. Adenocarcinoma
b. Bronchioloalveolar carcinoma
c. Carcinoid
d. Fibroma
e. Hamartoma

255. A 67-year-old male long-term smoker presents with weight loss, a persistent cough, fever, chest pain, and hemoptysis. Physical examination reveals a cachectic male with clubbing of his fingers and dullness to percussion over his right lower lobe. A chest x-ray reveals a 3.5-cm hilar mass on the right and postobstructive pneumonia of the right lower lobe. Sputum cytology is suspicious for malignant cells. Histologic examination of a transbronchial biopsy specimen reveals infiltrating groups of cells with scant cytoplasm. No glandular structures or keratin production are seen. The nuclei of these cells are about twice the size of normal lymphocytes and do not appear to have nucleoli. What is the correct diagnosis of the lung lesion in this individual?

a. Adenocarcinoma
b. Hamartoma
c. Large cell undifferentiated carcinoma
d. Small cell undifferentiated carcinoma
e. Squamous cell carcinoma

256. A 39-year-old female presents with a cough and increasing shortness of breath. A chest x-ray is interpreted by the radiologist as showing a right lower lobe (RLL) pneumonia. No mass lesions are seen. The woman is treated with antibiotics, but her symptoms do not improve. On her return visit, the area of consolidation appears to be increased. Bronchoscopy is performed. No bronchial masses are seen, but a transbronchial biopsy is obtained in an area of mucosal erythema in the RLL. After the diagnosis is made, the RLL is removed and a section from this specimen reveals well-differentiated mucus-secreting columnar epithelial cells that infiltrate from alveolus to alveolus. What is the correct diagnosis?

a. Bronchioloalveolar carcinoma
b. Carcinoid
c. Large cell carcinoma
d. Small cell carcinoma
e. Squamous cell carcinoma

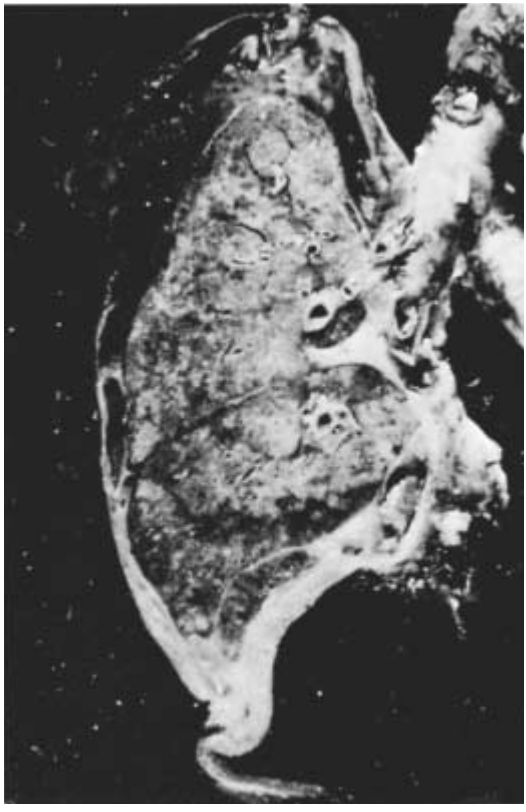
257. Which one of the listed abnormalities is an example of a type of pleural effusion that is better classified as an exudate (inflammatory edema) rather than a transudate?

a. Chylothorax
b. Empyema
c. Hemothorax
d. Hydrothorax
e. Pneumothorax

258. A 19-year-old female presents with sudden, severe right-sided chest pain that developed shortly after she had been placing heavy boxes on shelves in her garage. Physical examination reveals an afebrile female in mild respiratory distress. Breath sounds are markedly decreased on the right, and the right lung is hyperresonant to percussion. Which one of the following is most likely present in this individual?

a. Pneumoconiosis
b. *Pneumocystis* infection
c. Bacterial pneumonia
d. Viral pneumonia
e. Pneumothorax

259. A 57-year-old male presents with a lesion similar to that seen in this gross photograph of a sagittal section of the lung. Which one of the listed characteristics, if present in this lesion, would favor the diagnosis of mesothelioma?



a. Lamellar bodies seen by electron microscopy
b. Long microvilli seen by electron microscopy
c. Peripheral cytoplasmic keratin staining
d. Positive CEA reaction
e. Positive Leu-M_1 staining

Respiratory System

Answers

234. The answer is b. *(Cotran, pp 549–550, 700.)* Pulmonary edema refers to excess accumulation of fluid in the extravascular spaces of the lung. Pulmonary edema can be classified based on the etiology into cardiogenic pulmonary edema and noncardiogenic pulmonary edema. Cardiogenic pulmonary edema results from abnormalities of hemodynamic (Starling) forces, while noncardiogenic pulmonary edema results from cellular injury. Causes of cardiogenic pulmonary edema include increased hydrostatic forces, as seen with congestive heart failure (the most common cause of pulmonary edema); decreased oncotic pressure, such as resulting from decreased albumin levels; and lymphatic obstruction. Noncardiogenic edema may be the result of either endothelial injury (infections, disseminated intravascular coagulopathy, or trauma) or alveolar injury (from inhaled toxins, aspiration, drowning, or near drowning). Microscopically, pulmonary edema reveals the alveoli to be filled with pale pink fluid. Cardiogenic edema may lead to alveolar hemorrhages and hemosiderin-laden macrophages (heart failure cells). Where cardiogenic edema is present, chest x-rays show an increase in the caliber of the blood vessels in the upper lobes, perivascular and peribronchial fluid ("cuffing"), and Kerley B lines (fluid in the interlobular septa). Noncardiogenic edema produces a "whiteout" of the lungs.

235. The answer is a. *(Cotran, pp 699–700.)* Atelectasis refers to lung collapse. It is divided into four types. Absorptive (obstructive) atelectasis results from airway obstruction, such as occurs with mucus, tumors, or foreign bodies. The air within the lungs distal to the obstruction is absorbed, the lung collapses, and the mediastinum then shifts toward the collapsed lung. With compression, atelectasis fluid within the pleural cavity, such as seen with congestive heart failure (CHF), causes increased pleural pressure, which collapses lung tissue. In this instance the mediastinum shifts away from the collapsed lung. In contraction, atelectasis fibrosis causes collapse

of lung tissue. Patchy atelectasis may result from loss of pulmonary surfactant, which is seen in hyaline membrane disease of the newborn.

236. The answer is d. *(Damjanov, pp 1503–1505. Cotran, pp 700–703.)* Adult respiratory distress syndrome (ARDS) is a syndrome characterized clinically by the rapid onset of severe, life-threatening respiratory insufficiency. ARDS has also been called adult respiratory failure, shock lung, traumatic wet lung, pump lung, and diffuse alveolar damage (DAD). The initial and basic lesion in ARDS is diffuse damage to the alveolar wall. Protein-rich edema fluid then leaks into the alveolar spaces and combines with fibrin and dead cells to produce hyaline membranes that line the alveoli and are the characteristic histologic feature of ARDS. In the acute edematous stage, the lungs are congested (pulmonary congestion) and show pulmonary edema with interstitial inflammation. Collapsed, airless pulmonary parenchyma is called atelectasis and can also be seen in ARDS. These other changes, although present in ARDS, are not pathognomonic.

In contrast, angioinvasive infiltrates of pleomorphic lymphoid cells are seen with lymphomatoid granulomatosis, a disease of middle-aged individuals that is characterized by an angiocentric and angioinvasive infiltrate of atypical lymphoid cells. Deposits of needle-like crystals from the membranes of eosinophils, called Charcot-Leyden crystals, can be seen in patients with asthma, while infiltrating groups of malignant cells having intercellular bridges characterize squamous cell carcinoma. Plexiform lesions within pulmonary arterioles are diagnostic of pulmonary hypertension.

237. The answer is c. *(Cotran, pp 130–132, 703–704.)* Pulmonary emboli may be caused by thrombi, air (after surgery), amniotic fluid (complications of labor), fat (associated with trauma causing fractures of long bones), or tumors (renal cell carcinomas invading the vena cava). Pulmonary emboli are common and are found in about 10 to 20% of hospital autopsies. Occlusions of the pulmonary arteries by blood clots are almost always embolic, arising from thrombi in the deep veins of the leg [deep vein thromboses (DVTs)]. Typical settings for the development of deep vein thrombosis include increased venous stasis and hypercoagulable states, such as after surgery. Calf tenderness, associated with DVTs, is a useful clinical sign that points toward pulmonary emboli as the cause of breathing problems after surgery. Pulmonary emboli may produce other clinical

symptoms, such as anxiety, pleuritic chest pain, dyspnea, fever, cough, hemoptysis, or sudden death. Hypoxemia results from increased A-a gradients, the result of increased alveolar dead space. The majority of pulmonary thromboemboli do no harm and eventually organize or lyse; however, depending on the size of the embolus and the hemodynamic status of the patient, a pulmonary infarct may be produced. Pulmonary infarcts grossly have an apex pointing toward the occluded vessel and a pyramidal base extending toward the pleural surface. The histologic hallmark is ischemic necrosis of the lung.

238. The answer is d. *(Cotran, pp 704–706.)* Pulmonary vascular sclerosis refers to the vascular changes associated with pulmonary hypertension. Elevation of the mean pulmonary arterial pressure is the result of endothelial dysfunction and vascular changes. The vascular changes vary with the size of the vessel. The main arteries have atheromas that are similar to systemic atherosclerosis, but are not as severe. Medium-sized arteries show intimal thickening and neomuscularization. Smaller arteries and arterioles show intimal thickening, medial hypertrophy, and reduplication of the internal and external elastic membranes. A distinctive arteriolar change, a plexiform lesion, consists of intraluminal angiomatous tufts that form webs. This pattern is thought to be diagnostic of primary hypertension.

The changes of pulmonary vascular sclerosis may be primary or secondary. Primary pulmonary vascular sclerosis almost always occurs in young women, who develop fatigue, syncope (with exercise), dyspnea on exertion (DOE), and chest pain. Secondary sclerosis may occur at any age, and symptoms depend on the underlying cause. Possible causes include certain types of heart disease, such as mitral valve disease, left ventricular failure, and congenital valvular disease with left-to-right shunt, as well as certain types of pulmonary disease, such as chronic obstructive or interstitial lung disease and recurrent pulmonary emboli. Pulmonary hypertension is also associated with diet pills (Redux and Fen-Phen), while "exotic" causes include *Crotalaria spectabilis* ("bush tea") and adulterated olive oil.

239. The answer is a. *(Cotran, pp 712–716.)* Chronic obstructive pulmonary diseases (COPDs) are characterized by obstruction to airflow somewhere along the airways. These diseases may affect the bronchus, the bronchiole, or the acinus. Asthma, bronchiectasis, and chronic bronchitis affect primarily the bronchus, while emphysema affects primarily the aci-

nus. Asthma is a pulmonary disease that is caused by excessive bronchoconstriction secondary to airways that are hyperreactive to numerous stimuli. Asthma has been divided into extrinsic and intrinsic categories. The extrinsic category includes atopic (allergic) asthma, occupational asthma, and allergic bronchopulmonary aspergillosis. The intrinsic category includes nonreaginic asthma and pharmacologic asthma. The former is related to respiratory tract infections, while the latter is often related to aspirin sensitivity. These aspirin-sensitive patients often have recurrent rhinitis and nasal polyps. In these patients the aspirin initiates an asthmatic attack by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase pathway. This causes the relative excess production of the leukotrienes, which are bronchoconstrictors.

240. The answer is d. *(Cotran, pp 707–711.)* Emphysema (abnormal dilation of the air spaces distal to the terminal bronchioles) may be classified based on the anatomic location of the abnormal dilation within the respiratory lobule. The normal respiratory lobule is composed of three to five terminal bronchioles and their acini, which in turn are composed of a respiratory bronchiole, alveolar ducts, alveolar sacs, and alveoli. Emphysema may affect the proximal acinus (centrilobular emphysema), the distal acinus (paraseptal emphysema), or the entire acinus (panlobular emphysema). It is postulated that emphysema results from an imbalance between elastase, which is produced by neutrophils and macrophages and destroys the walls of airways, and antielastase, which inactivates elastase. There is a well-established association between panacinar emphysema and a hereditary deficiency of α_1 antitrypsin, an enzyme that functions as an antielastase. This enzyme is coded for by proteinase-inhibitor (Pi) genes on chromosome 14. The normal Pi allele is M, and the normal homozygote is MM. The Z allele yields the lowest level of antiproteinase, and the Pi ZZ homozygote is the most deficient in α_1 antitrypsin. Cigarette smoking, which is associated with the production of centrilobular emphysema, increases elastase activity and decreases α_1 antitrypsin activity.

241. The answer is b. *(Cotran, pp 716–717.)* Patients with bronchiectasis have a persistent, productive cough due to abnormally dilated bronchi, which are the result of a chronic necrotizing infection. Patients with Kartagener's syndrome have the triad of bronchiectasis, recurrent sinusitis, and

situs inversus. The respiratory problems associated with this syndrome are caused by abnormal motility of the cilia, which is due to abnormalities of the ATPase-containing dynein arms. Abnormal cilia inhibit the normal functioning of the respiratory epithelium, which is to clear microorganisms and foreign particles within the respiratory mucus. This results in repeated respiratory infections. Males with this condition tend to be sterile because of the ineffective motility of the tails of the sperm. In contrast, patients with asthma develop episodic wheezing due to bronchial smooth-muscle hyperplasia and excess production of mucus. Extrinsic (allergic) asthma may be related to IgE (type I) immune reactions; intrinsic (nonallergic) asthma may be triggered by infections or drugs. Clinically there is an elevated eosinophil count in the peripheral blood, and Curschmann's spirals and Charcot-Leyden crystals may be found in the sputum. Chronic bronchitis is characterized by a productive cough that is present for at least 3 months in at least two consecutive years. There is hyperplasia of mucous glands with hypersecretion, due in large part to tobacco smoke. Emphysema is abnormal dilation of the alveoli due to destruction of the alveolar walls. Steatosis refers to the accumulation of triglyceride within the cytoplasm of hepatocytes.

242. The answer is b. *(Cotran, pp 717–722. Chandrasoma, pp 488, 794, 882–883.)* Pulmonary infections may be caused by bacteria, fungi, viruses, or mycoplasma. Bacterial infections generally result in a polymorphonuclear (neutrophil) response. Bacterial infection of the lung (pneumonia) results in consolidation of the lung, which may be patchy or diffuse. Patchy consolidation of the lung is seen in bronchopneumonia (lobular pneumonia), while diffuse involvement of an entire lobe is seen in lobar pneumonia. Histologically, bronchopneumonia is characterized by multiple, suppurative neutrophil-rich exudates that fill the bronchi and bronchioles and spill over into the adjacent alveolar spaces. In contrast, lobar pneumonia is characterized by four distinct stages: congestion, red hepatization, gray hepatization, and resolution.

243. The answer is d. *(Cotran, p 722.)* A pulmonary abscess is a localized suppurative process within the pulmonary parenchyma that is characterized by tissue necrosis and marked acute inflammation. Possible causes of a lung abscess include aerobic and anaerobic streptococci, *Staphylococcus aureus,* and many gram-negative organisms. Aspiration more often gives a

right-sided single abscess, as the airways on the right side are more vertical. Antecedent pneumonia gives rise to multiple diffuse abscesses. The abscess cavity is filled with necrotic suppurative debris unless it communicates with an air passage. Clinically an individual with a lung abscess will have a prominent cough producing copious amounts of foul-smelling, purulent sputum. Changes in position evoke paroxysms of coughing. There is also fever, malaise, and clubbing of the fingers and toes. With antibiotic therapy 75% of lung abscesses resolve. Complications of a lung abscess include pleural involvement (empyema) and bacteremia, which could result in brain abscesses or meningitis.

244. The answer is b. *(Cotran, pp 721–722.)* Acute interstitial pneumonia refers to inflammation of the interstitium of the lung that is the result of infection, typically with either *M. pneumoniae* or viruses such as influenza A and B. This type of pneumonia is called primary atypical pneumonia because it is atypical when compared to the "typical" bacterial pneumonia, such as produced by *S. pneumoniae*. These bacterial pneumonias are characterized by acute inflammation (neutrophils) within the alveoli. In contrast, acute interstitial pneumonia is characterized by lymphocytes and plasma cells within the interstitium, that is, the alveolar septal walls. Viral cytopathic effects, such as inclusion bodies or multinucleated giant cells, may be seen histologically with certain viral infections. Certain viruses produce pneumonia in certain patient groups, e.g., respiratory syncytial virus in infants and adenovirus in military recruits. Infection with *M. pneumoniae* results in the production of a nonspecific cold IgM antibody, which characteristically reacts with red cells having the I antigen. Since most adult red cells have I antigens, blood from a patient with mycoplasma pneumonia will hemagglutinate when cooled. This type of reaction is not seen with infection by either *P. pneumoniae* or *Mycobacterium tuberculosis*.

245. The answer is c. *(Damjanov, pp 1006–1008. Cotran, p 247, 381–382.)* Infection by the protozoan *P. carinii* is characterized by the presence of oval and helmet-shaped organisms whose capsules are made more visible by use of Gomori's methenamine-silver staining technique. This organism, although it has low virulence, is opportunistic; it is often seen to attack severely ill, immunologically depressed patients. It is frequently the first opportunistic infection to be diagnosed in HIV-1–positive patients, and it is a leading cause of death in patients with AIDS.

246. The answer is d. *(Cotran, pp 727–734.)* The pneumoconioses are pulmonary diseases that are caused by nonneoplastic lung reactions to several types of environmental dusts. Silicosis, seen in sandblasters and mine workers, is characterized by fibrosis. Early in the disease there are multiple, very small nodules in the upper zones of the lung, which produces a fine nodularity on x-ray. These areas histologically show fibrosis and birefringent particles. The fibrotic lesions may also be found in the hilar lymph nodes, which can become calcified and have an "eggshell" pattern on x-ray examination. Asbestos results in larger areas of fibrosis, and histologically asbestos (ferruginous) bodies are found. Reactions to coal (carbon) may result in anthracosis; simple coal worker's pneumoconiosis, which is composed of multiple small nodules; or complicated coal worker's pneumoconiosis, which is composed of fibrotic nodules that are larger than 2 cm (progressive massive fibrosis). In the chronic state, beryllium elicits a cell-mediated immunity response, seen histologically as noncaseating granulomas. Noncaseating granulomas are also seen in patients with sarcoidosis, a disease that may cause enlargement of the hilar lymph nodes ("potato nodes").

247. The answer is b. *(Damjanov, pp 1536–1541. Cotran, pp 732–734.)* The segmented or beaded, often dumbbell-shaped bodies are ferruginous bodies that are probably asbestos fibers coated with iron and protein. The term *ferruginous body* is applied to other inhaled fibers that become iron-coated; however, in a patient with interstitial lung fibrosis or pleural plaques, ferruginous bodies are probably asbestos bodies. The type of asbestos mainly used in America is chrysotile, mined in Canada, and it is much less likely to cause mesothelioma or lung cancer than is crocidolite (blue asbestos), which has limited use and is mined in South Africa. Cigarette smoking potentiates the relatively mild carcinogenic effect of asbestos. Laminated spherical (Schaumann) bodies are found in granulomas of sarcoid and chronic berylliosis.

248. The answer is d. *(Henry, pp 271, 287, 360. Lever, pp 252–256. Cotran, pp 734–735, 1364.)* Sarcoidosis is a systemic disease characterized by noncaseating granulomas in multiple organs. The diagnosis of sarcoidosis depends upon finding these noncaseating granulomas in commonly affected sites. In 90% of cases, bilateral hilar lymphadenopathy ("potato nodes") or lung involvement is present and can be revealed by chest x-ray

or transbronchial biopsy. The eye and skin are the next most commonly affected organs, so that both conjunctival and skin biopsies are clinical possibilities. Noncaseating granulomas may be found in multiple infectious diseases, such as fungal infections, but sarcoidosis is not caused by any known organism. Therefore, before the diagnosis of sarcoidosis can be made, cultures must be taken from affected tissues, and there must be no growth of any organism that may produce granulomas. In patients with sarcoidosis, blood levels of angiotensin-converting enzyme are increased, and this may also be used as a clinical test. In the past, the Kveim skin test was used to assist in the diagnosis of sarcoidosis, but since it involves injecting into patients extracts of material from humans, it is no longer used.

249. The answer is b. *(Cotran, pp 735–737.)* Interstitial pulmonary fibrosis (IF) may be a slowly progressive disease with no recognizable etiology. This disease entity has many names, such as chronic interstitial pneumonitis and diffuse fibrosing alveolitis, but the common name is usual interstitial pneumonitis (UIP). The form of this disease that progresses very rapidly is called Hamman-Rich syndrome. The pathogenesis of UIP involves damage to type I pneumocytes with the subsequent proliferation of type II pneumocytes and secretion of factors by macrophages that cause fibrosis. The end-stage form of IF is characterized by large cysts with intervening fibrosis, which imparts the gross appearance of a "honeycomb lung." There are several subtypes of IF, which are characterized by their histologic appearance. Lymphocytic interstitial pneumonitis (LIP) has numerous lymphocytes, Giant cell interstitial pneumonitis (GIP) has giant cells, and plasma cell interstitial pneumonitis (PIP) has numerous plasma cells. LIP is seen in patients with Sjögren's syndrome or AIDS and is associated with an increased risk of developing lymphoma. An important subtype is desquamative interstitial pneumonitis (DIP), which is characterized histologically by sheets of cells within the alveoli. This type of IF may respond to the use of steroids. UIP, in contrast, does not respond to therapy, and therefore treatment is symptomatic treatment only. Theophylline is used to treat asthma, antibiotics are used to treat bacterial infections, and INH is used in combination with other drugs to treat tuberculosis.

250. The answer is d. *(Cotran, pp 522–523, 738–739.)* The pulmonary hemorrhagic syndromes are characterized by hemorrhage within the alve-

oli, which may be severe enough to produce hemoptysis. Several of these diseases are associated with blood vessel abnormalities, namely inflammation of the vessels (angiitis). Necrotizing granulomatous arteritis affecting the upper and lower respiratory tracts and the kidneys is seen in patients with Wegener's granulomatosis. These areas of necrosis are characteristically large and serpiginous, and exhibit peripheral palisading of macrophages. In patients with Wegener's granulomatosis, the nose, sinus, antrum, and trachea often exhibit ulcerations. Originally the disease was lethal, but the prognosis is now much improved by immunosuppressive drugs. Eosinophilic granulomatous arteritis occurs in some patients with asthma who have eosinophilic pulmonary infiltrates; this abnormality is called Churg-Strauss syndrome. The areas of necrosis are not large and serpiginous as in Wegener's. Granulomatous inflammation centered around bronchi (bronchocentric granulomatosis) is often related to allergic pulmonary aspergillosis. Lymphomatoid granulomatosis is a disease of middle-aged people that is characterized by an angiocentric and angioinvasive infiltrate of atypical lymphoid cells. Goodpasture's syndrome is characterized by the development of a necrotizing hemorrhagic interstitial pneumonitis and rapidly progressing glomerulonephritis because of antibodies directed against the capillary basement membrane in alveolar septa and glomeruli. A linear IgG immunofluorescence pattern is present, which is characteristic of a type II hypersensitivity reaction. The prognosis for Goodpasture's syndrome has been markedly improved by intensive plasma exchange to remove circulating anti–basement membrane antibodies and by immunosuppressive therapy to inhibit further antibody production.

251. The answer is d. *(Cotran, pp 739–740.)* In pulmonary alveolar proteinosis (PAP), the alveolar spaces contain an intensely eosinophilic, proteinaceous, granular substance. Alveolar walls are relatively normal, without inflammatory exudate or fibrosis, although type II pneumocytes may be hyperplastic. The process is often patchy, with groups of normal alveoli alternating with groups of affected alveoli. Acicular (cholesterol) clefts and densely eosinophilic bodies (necrotic cells) are found within the granular material. Distinction from edema fluid may be difficult, but PAP alveolar material stains with periodic acid–Schiff (PAS). At low power, alveolar material seen in *P. carinii* pneumonia may also mimic PAP, but with high power the foamy material seen with *Pneumocystis* is not present in PAP. In PAP the material is surfactant accumulation due either to overproduc-

tion or to failure of macrophage clearance. Causes of PAP include occupational exposure to silica or aluminum dusts. It also occurs in immunosuppressed patients and toxic drug reactions and is often associated with infections by organisms such as nocardia, fungi, and TB (possible impaired macrophage killing). The treatment of choice is bronchoalveolar lavage to remove the proteinaceous debris.

252. The answer is b. *(Cotran, p 738.)* Bronchiolitis obliterans with organizing pneumonia (BOOP) is a nonspecific reaction to multiple infectious or inflammatory lesions of the lungs. Causes of BOOP include infections (viral and bacterial), chemical toxins, drugs, and collagen vascular diseases. The lungs respond to these agents, causing bronchiolar injury by forming loose, fibrous tissue within the bronchioles (bronchiolitis obliterans) and alveoli (organizing pneumonia). Patients present with cough and dyspnea, and chest x-ray reveals interstitial infiltrates. Patients usually improve gradually, but steroid therapy may be needed. In contrast, asteroid bodies in giant cells are a nonspecific finding but can be found in the noncaseating granulomas of sarcoidosis. Multiple rheumatoid nodules within the interstitial tissue can be seen with rheumatoid arthritis, or might be part of Caplan's syndrome. Numerous eosinophils within the walls of the alveoli can be seen in patients with asthma.

253. The answer is d. *(Cotran, pp 742, 744, 747.)* Horner's syndrome occurs with apical (superior sulcus) tumors of any type (Pancoast tumor), but since most peripheral cancers of the lung are adenocarcinomas, most tumors of the apex of the lung are adenocarcinomas. Horner's syndrome is characterized by enophthalmos, ptosis, miosis, and anhidrosis on the same side as the lesion due to invasion of the cervical sympathetic nerves. Involvement of the brachial plexus causes pain and paralysis in the ulnar nerve distribution.

254. The answer is e. *(Damjanov, pp 1541–1545. Cotran, pp 748–749.)* Pulmonary hamartomas, although infrequent, are still the most common of all benign lung tumors. Hamartomas consist of various tissues normally found in the organ where they develop, but in abnormal amounts and arrangements. In the lung they consist of lobules of connective tissue often containing mature cartilage, fat, or fibrous tissue and separated by clefts lined by entrapped respiratory epithelium. The peak incidence is at age 60,

and the tumor is usually found as a well-circumscribed, peripheral "coin" lesion on routine chest x-ray. Unless the radiographic findings are pathognomonic of hamartoma with "popcorn ball" calcifications, the lesion should be excised or at least carefully followed. Conservative excision is curative.

255. The answer is d. *(Cotran, pp 724–745.)* Lung cancers are classified according to their histologic appearance. First they are divided into two groups based on the size of the tumor cells, namely small cell carcinomas and non–small cell carcinomas. Small cell carcinomas, also called "oat cell" carcinomas, contain scant amounts of cytoplasm, and their nuclei are small and round and rarely have nucleoli. These malignancies, which are of neuroendocrine origin and display neurosecretory granules on electron microscopy, may cause a variety of paraneoplastic syndromes, such as from the synthesis and secretion of hormones such as ACTH and serotonin. Other effects not well understood on the neuromuscular system include central encephalopathy and Eaton-Lambert syndrome, a myasthenic syndrome resulting from impaired release of acetylcholine and usually associated with pulmonary oat cell carcinoma. Oat cell carcinomas form 20 to 25% of primary lung tumors, occur most frequently in men of middle age or older, have a strong association with cigarette smoking, and carry a poor prognosis, as they metastasize early (e.g., bone marrow metastases). The non–small cell carcinomas are classified as to the differentiation of the tumor cells. Squamous cell carcinomas are characterized by keratin pearl formation, intracytoplasmic keratin, or the formation of intercellular bridges. Adenocarcinomas are characterized by the formation of glandular structures. They are typically found at the periphery of the lung (peripheral carcinomas) and sometimes may be found in an area of previous scar (scar carcinoma). Non–small cell carcinomas of the lung that do not form glands or show squamous differentiation are called undifferentiated large cell carcinomas.

256. The answer is a. *(Damjanov, pp 1541–1545. Cotran, p 747.)* One type of bronchogenic carcinoma that has unique characteristics is bronchioloalveolar carcinoma (BAC). This tumor is characterized by well-differentiated, mucus-secreting columnar epithelial cells that infiltrate along the alveolar walls and spread from alveolus to alveolus through the pores of Kohn. This pneumonic spread can be mistaken for pneumonia on

chest x-ray. These tumors, which make up about 2 to 5% of bronchogenic carcinomas, do not arise from the major bronchi. Instead they are thought to arise in terminal bronchioles from Clara cells. Even though these tumors may be multiple, they are well differentiated and have a good prognosis.

257. The answer is b. *(Cotran, pp 749–751.)* The causes of pleural effusions may classified as being inflammatory or noninflammatory. The formation of noninflammatory edema is related to abnormalities involving the Starling forces and may result in the formation of noninflammatory pleural effusions. Increased hydrostatic pressure, such as is seen with congestive heart failure, causes hydrothorax, which is a transudate. Decreased oncotic pressure, such as is seen with renal disease associated with albuminuria, also causes hydrothorax. Increased intrapleural negative pressure produced by atelectasis causes hydrothorax, while decreased lymphatic drainage, which can be caused by a tumor obstructing lymphatics, produces chylothorax. Chylothorax is characterized by milky fluid that contains finely emulsified fats. An additional type of noninflammatory pleural effusion is hemothorax, which may be caused by trauma or ruptured aortic aneurysm. Inflammatory edema may be caused by increased vascular permeability. Inflammation in the adjacent lung, such as with collagen vascular diseases, produces a serofibrinous exudate. Suppurative inflammation in the adjacent lung may produce a suppurative pleuritis, which is called an empyema.

258. The answer is e. *(Cotran, p 751.)* Pneumothorax refers to the accumulation of air in the pleural cavity. Types of pneumothorax include spontaneous pneumothorax, traumatic pneumothorax, and therapeutic pneumothorax. Spontaneous pneumothorax is most commonly associated with emphysema, asthma, and tuberculosis. One special type, however, is idiopathic spontaneous pneumothorax, which occurs primarily in young people. This disorder results from rupture of subpleural blebs. These blebs are most often located in the apex of the lung, and rupture is usually related to stretching or raising the arms. Recurrence of idiopathic spontaneous pneumothorax is common.

259. The answer is b. *(Cotran, pp 751–753.)* Malignant mesothelioma and adenocarcinoma are two neoplasms that may involve the pleural surfaces, as seen in the gross photograph. Malignant mesothelioma arises from

the pleural surfaces and develops with significant and chronic exposure to asbestos (usually occupationally incurred). As the malignant mesothelioma spreads, it lines the pleural surfaces, including the fissures through the lobes of the lungs, and results in a tight and constricting encasement. This restricts the excursions of the lungs during ventilation. Adenocarcinoma of the lung also may invade the pleural surfaces and spread in an advancing manner throughout the pleural lining. The differential diagnosis histologically between an epithelial type of malignant mesothelioma and an adenocarcinoma may be difficult and sometimes impossible without special techniques. A characteristic feature seen by electron microscopy is numerous long microvilli on the surface of cells from mesotheliomas. Other histologic characteristics that favor the diagnosis of malignant mesothelioma over adenocarcinoma include positive acid mucopolysaccharide staining that is inhibited by hyaluronidase, perinuclear keratin staining (not peripheral), and negative staining with CEA and Leu-M_1.

This page intentionally left blank.

Head and Neck

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

260. A 48-year-old male living in an underdeveloped country presents with pain in the left side of his face. Physical examination reveals a large, indurated area involving the left side of his jaw with multiple sinuses draining pus. This draining material contains a few scattered small yellow granules. This lesion is most likely caused by an infection with

a. *Streptococcus pyogenes*
b. *Borrelia vincentii*
c. *Corynebacterium diphtheriae*
d. *Klebsiella rhinoscleromatis*
e. *Actinomyces israelii*

261. A 4-year-old boy presents with multiple laryngeal squamous papillomas. Obtaining a history, you discover this boy has had the same types of lesions removed in the past, but they have now recurred. This boy's condition (juvenile papillomatosis) is most likely related to which one of the listed organisms?

a. Cytomegalovirus (CMV)
b. Epstein-Barr virus (EBV)
c. Herpes simplex virus (HSV)
d. Human immunodeficiency virus (HIV)
e. Human papillomavirus (HPV)

262. The most common histologic type of carcinoma of the oral cavity is

a. Adenocarcinoma
b. Clear cell carcinoma
c. Large cell undifferentiated carcinoma
d. Small cell undifferentiated carcinoma
e. Squamous cell carcinoma

263. Histologic sections from a 3-cm mass found in the mandible of a 55-year-old female reveal a tumor consisting of nests of tumor cells that appear dark and crowded at the periphery of the nests and loose in the center (similar to the stellate reticulum of a developing tooth). Grossly, the lesions consist of multiple cysts filled with a thick, "motor oil"–like fluid. What is the correct diagnosis for this tumor?

a. Pleomorphic adenoma
b. Ameloblastoma
c. Mucoepidermoid carcinoma
d. Adenoid cystic carcinoma
e. Acinic cell carcinoma

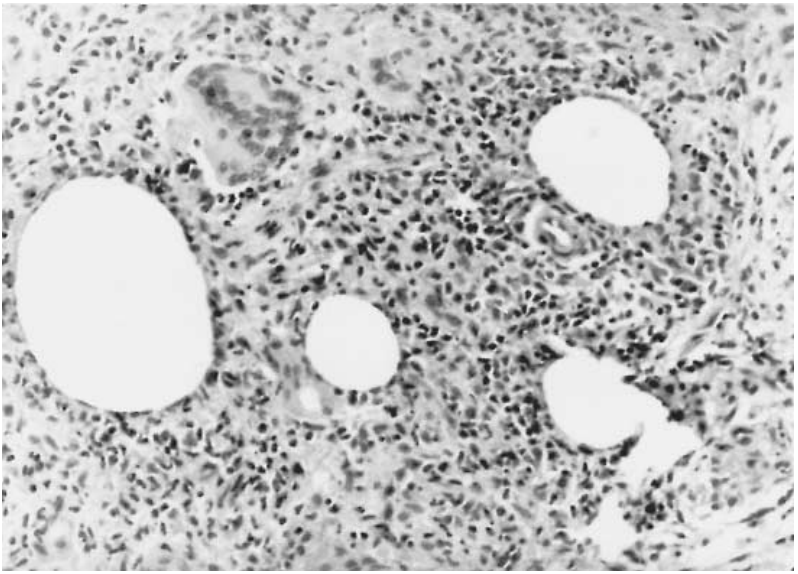
264. A 24-year-old female presents after having several "attacks" that last for about 24 h. She states that during these attacks she develops nausea, vomiting, vertigo, and ringing in her ears. Physical examination reveals a sensorineural hearing loss. The pathology of her condition involves

a. Acute suppurative inflammation
b. Dilation of the cochlear duct and saccule
c. A cyst of the middle ear filled with keratin
d. A tumor of the middle ear composed of lobules of cells in a highly vascular stroma
e. New bone formation around the stapes and the oval window

265. Deletion of both Rb (retinoblastoma) genes in the same developing cell is most characteristically associated with the development of

a. Blue sclera
b. No iris
c. Subluxed lens
d. White pupil
e. Yellow sclera

266. A 37-year-old woman presents with a recurrent swelling in her left upper eyelid. The lesion is biopsied by an ophthalmologist, and a section from that specimen, seen in the photomicrograph below, is characteristic of a

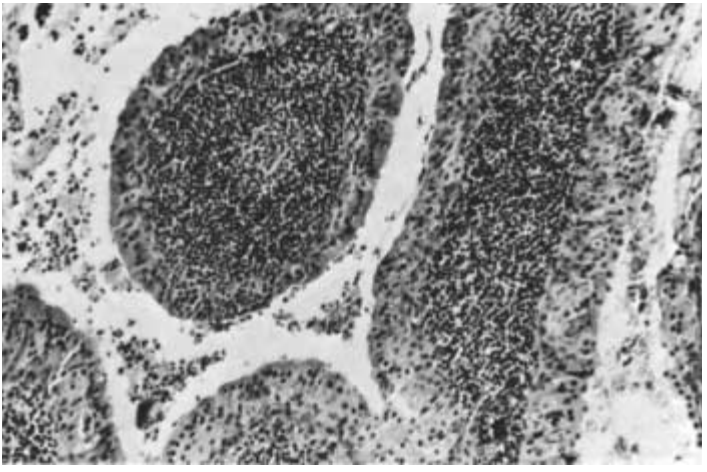


a. Chalazion
b. Hordeolum
c. Xanthelasma
d. Hydrocystoma
e. Sebaceous carcinoma

267. What type of cyst is characteristically located in the lateral (or anterolateral) portion of the neck, is derived from remnants of the pharyngeal apparatus, and does not move with swallowing?

a. Branchial cleft cyst
b. Dentigerous cyst
c. Odontogenic keratocyst
d. Radicular cyst
e. Thyroglossal duct cyst

268. The papillary lesion lined by oncocytic cells seen in the photomicrograph below is referred to as



a. Adenoid cystic carcinoma
b. Lymphoepithelioma
c. Thyroglossal duct neoplasm
d. Warthin's tumor
e. Sebaceous lymphadenoma

269. Histologic sections of a parotid gland tumor that is found to be infiltrating along the facial nerve are most likely to reveal

a. Atypical cells forming tubular and cribriform patterns
b. Infiltrating groups of vacuolated epithelial cells
c. A mixture of epithelial structures and mesenchyme-like stroma
d. A mixture of squamous epithelial cells and mucus-secreting cells
e. Papillary folds composed of a double layer of oncocytic cells

Head and Neck

Answers

260. The answer is e. *(Cotran, pp 334, 369. Rubin, pp 361, 380, 406–407, 1303, 1320.)* Numerous diseases result from bacterial infections of the oral cavity. *A. israelii,* a normal inhabitant of the mouth, is a branched, filamentous gram-positive bacteria that may produce an indurated (lumpy) jaw with multiple draining fistulas or abscesses. Small yellow colonies, called sulfur granules, may be seen in the draining material. Scarlet fever, a disease of children, is caused by several strains of β-hemolytic group A streptococci (*S. pyogenes*). An erythrogenic toxin damages vascular endothelium and produces a rash on the skin and oral mucosa. The tongue in a patient with scarlet fever may be fiery red with prominent papillae (raspberry tongue) or white-coated with hyperemic papillae (strawberry tongue). Acute necrotizing ulcerative gingivitis (Vincent's angina or trench mouth) is caused by two symbiotic organisms, a fusiform bacillus and a spirochete (*B. vincentii*), the combination being termed fusospirochetosis. *C. diphtheriae* causes diphtheria, which is characterized by oral and pharyngeal pseudomembranes and a peripheral lymphocytosis. Rhinoscleroma, a chronic inflammation of the nose, is caused by *K. rhinoscleromatis* and histologically is characterized by numerous foamy macrophages, called Mikulicz cells.

261. The answer is e. *(Cotran, pp 765–766.)* Tumors of the larynx may be reactive proliferations or neoplastic growths. The laryngeal nodule is a common abnormality formed as a reactive process to excessive use; as such it may be found in singers and is called a "singer's nodule." These nodules are solitary, produce hoarseness, and histologically reveal a polyp consisting of fibrosis, dilated vascular spaces, and myxomatous degeneration of the stroma. Laryngeal neoplasms may be either benign or malignant. Squamous papillomas are benign neoplasms that occur in two clinical forms. One form is typically solitary and occurs in adults (solitary squamous papilloma), while the other form is multiple and occurs in children (juvenile papillomatosis). The latter form is associated with human papillo-

mavirus (HPV) and may recur locally after excision. Malignant neoplasms of the larynx are most often squamous cell carcinomas.

262. The answer is e. *(Cotran, pp 759–761.)* Carcinoma of the oral cavity accounts for approximately 5% of all human malignancies. More than 90% of oral carcinomas are of the squamous cell type; precursor lesions include leukoplakia (dysplastic leukoplakia) and erythroplasia, with transformation rates of approximately 15 and 50%, respectively. Oral carcinoma is more common in males. Smoking, tobacco chewing, chronic irritation, heat exposure, and irradiation are all thought to contribute to carcinogenesis. The lower lip is the most common site, followed by the floor of the mouth, the anterior tongue, the palate, and the posterior tongue. Prognosis varies according to site but is best for lesions of the lip and worst for lesions in the floor of the mouth.

263. The answer is b. *(Cotran, p 761.)* A rare tumor of the oral cavity (found most commonly in the mandible) that is similar to the enamel organ of the tooth is the ameloblastoma. This locally aggressive tumor consists of nests of cells that at their periphery are similar to ameloblasts and centrally are similar to the stellate reticulum of the developing tooth. A similar lesion occurs in the sella turcica and is called a craniopharyngioma. In contrast, pleomorphic adenomas, mucoepidermoid carcinomas, adenoid cystic carcinomas, and acinic cell carcinomas are all tumors that originate in salivary glands.

264. The answer is b. *(Cotran, pp 766–767. Rubin, pp 1331–1333.)* Ménière's disease is an abnormality that is characterized by periodic episodes of vertigo that are often accompanied by nausea and vomiting, sensorineural hearing loss, and tinnitus (ringing in the ears). These symptoms are related to hydropic dilation of the endolymphatic system of the cochlea. Inflammation of the middle ear (otitis media), which occurs most often in children, may be acute or chronic. If otitis media is caused by viruses, there may be a serous exudate, but if it is produced by bacteria, there may be a suppurative exudate. Acute suppurative otitis media is characterized by acute suppurative inflammation (neutrophils), while chronic otitis media involves chronic inflammation with granulation tissue. Chronic otitis media may cause perforation of the eardrum or may lead to the formation of a cyst within the middle ear that is filled with keratin,

called a cholesteatoma. The name is somewhat of a misnomer, as cholesterol deposits are not present. Otosclerosis, a common hereditary cause of bilateral conduction hearing loss, is associated with formation of new spongy bone around the stapes and the oval window. Patients present with progressive deafness. Tumors of the middle ear are quite rare, but a neoplasm that arises from the paraganglia of the middle ear (the glomus jugulare or glomus tympanicum) is called a chemodectoma. Other names for this tumor include nonchromaffin paraganglioma and glomus jugulare tumor. This lesion is characterized histologically by lobules of cells in a highly vascular stroma (zellballen). A similar tumor that occurs in the neck is called a carotid body tumor.

265. The answer is d. *(Cotran, pp 286–287, 1372–1373.)* Retinoblastoma is the most common malignant tumor of the eye in children. Clinically, retinoblastoma may produce a white pupil (leucoria). This is seen most often in young children in the familial from of retinoblastoma, which is due to a deletion involving chromosome 13. These familial cases of retinoblastoma are frequently multiple and bilateral, although like all the sporadic, nonheritable tumors they can also be unifocal and unilateral. Histologically, rosettes of various types are frequent (similar to neuroblastoma and medulloblastoma). There is a good prognosis with early detection and treatment; spontaneous regression can occur but is rare. Retinoblastoma belongs to a group of cancers (osteosarcoma, Wilms tumor, meningioma, rhabdomyosarcoma, uveal melanoma) in which the normal cancer suppressor gene (antioncogene) is inactivated or lost, with resultant malignant change. Retinoblastoma and osteosarcoma arise after loss of the same genetic locus—hereditary mutation in the q14 band of chromosome 13. In contrast, a blue sclera can be seen with osteogenesis imperfecta, while a yellow sclera is seen with jaundice. Lack of an iris (aniridia) can sometimes be associated with Wilms tumor of the kidney, while a subluxed lens can be found in individuals with either Marfan's syndrome or homocystinuria.

266. The answer is a. *(Silverberg, pp 2047–2050. Rubin, p 1538.)* Many lesions of the eyelid are submitted for pathologic examination. One of the most common eyelid lesions is the chalazion, a chronic inflammatory reaction to lipid released into the tissue from the eyelid's sebaceous glands of Meibom or Zeis. Characteristic histologic features of this lesion include a chronic inflammatory reaction with giant cells that surround empty spaces

where the lipid vacuoles from the sebaceous glands had been located. Because the major clinical disorder to be differentiated from chalazia is sebaceous carcinoma, ophthalmologists biopsy recurrent lesions suspected of being chalazia to rule out sebaceous carcinoma. Hordeolums (styes) are acute staphylococcal infections of the eyelash follicles (external hordeolum) or the Meibomian glands (internal hordeolum). Xanthelasmas (yellow plaques on the skin) histologically reveal aggregates of foamy macrophages within the dermis. Hydrocystomas are one type of cyst that may affect the eyelid and may be lined by apocrine or eccrine cells.

267. The answer is a. *(Cotran, pp 761, 767–768.)* Two cysts that occur in the neck are the branchial cleft cyst (usually located in the anterolateral part of the neck) and the thyroglossal duct cyst (usually located in the anterior part of the neck). Each of these cysts may histologically reveal a lining composed of squamous epithelium or pseudostratified columnar epithelium. Branchial cleft cysts, which arise from remnants of the branchial (pharyngeal) apparatus, may contain lymphoid tissue, while thyroglossal duct cysts may move up and down as the patient swallows.

There are several types of cysts that occur in and around the oral cavity. The most common type is the radicular cyst. These cysts result from chronic inflammation of the tooth apex. Histologic sections reveal chronic inflammation of the tooth apex with epithelialization of periapical granulation tissue. Other types of oral cysts include follicular cysts (which arise from the epithelium of the tooth follicle), odontogenic keratocysts (which consist of keratinized squamous epithelium), and inclusion (fissural) cysts (which are fluid-filled cysts lined by squamous or respiratory epithelial cells). Follicular cysts are called dentigerous cysts because the associated tooth is unerupted, while odontogenic keratocysts are important because they may recur and act aggressively. These keratocysts may also be associated with basal cell carcinomas of the skin. Mucoceles, which typically occur on or near the lips due to a ruptured minor salivary gland, consist of a cyst filled with mucous material. They lack an epithelial lining.

268. The answer is d. *(Cotran, pp 771–772. Rubin, pp 1314–1315.)* Warthin's tumors occur mainly in the lower regions of the parotid gland, especially near the angle of the mandible, and on rare occasion may be bilateral. They are completely benign neoplasms, although they carry some undesirable synonyms: adenolymphoma, which is a misnomer, and papil-

lary cystadenoma lymphomatosum, a term undesirable both for the lymphomatosum part as well as its length. For these reasons most prefer the term Warthin's tumor. The pattern is highly characteristic of an epithelial surface lining of acidophilic cells that overlay benign lymphoid tissue elements, including germinal centers. The epithelial portion probably arises from early duct cells that become entrapped within developing parotid lymph nodes during embryogenesis. Sebaceous lymphadenomas contain sebaceous cells within the lymphoid tissue. Thyroglossal duct cysts are located in the midline of the neck but may be found extending up to the base of the tongue, and there is a similarity between the lymphoid islands seen in thyroglossal duct cysts and in Warthin's tumors; however, thyroid follicles may lead to the correct diagnosis in the former. Lymphoepithelioma is a tumor that is recognized by hyperplastic duct epithelium surrounded by lymphoid tissue. Myoepithelial islands embedded in lymphoid tissue may be seen in the minor and major salivary glands in Sjögren's syndrome.

269. The answer is a. *(Cotran, pp 769–773.)* The salivary glands give rise to a wide variety of tumors, the majority of which are of epithelial origin and benign. Most tumors occur in adults and have a slight female predominance. Approximately 75 to 85% occur in the parotids, 10 to 20% in the submandibular glands, and the remainder in the minor glands. In the parotid the vast majority are benign, whereas in the minor glands 35 to 50% are malignant. Clinically, most tumors of the salivary glands present as palpable masses, regardless of histologic type. The most common neoplasm of the parotid gland is the pleomorphic adenoma (mixed tumor), which histologically reveals epithelial structures embedded within a mesenchyme-like stroma consisting of mucoid, myxoid, or chondroid tissue. A malignant tumor may develop from a pleomorphic adenoma, in which case it is called a carcinoma ex pleomorphic adenoma. The second most common tumor is Warthin's tumor (papillary cystadenoma lymphomatosum), which histologically reveals cleftlike spaces lined by oncocytic epithelial cells overlying a stroma with a dense lymphocytic infiltrate. The epithelial cells are oncocytic because their pink cytoplasm is packed with mitochondria.

Three malignant tumors of the salivary glands are mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma. Mucoepidermoid carcinomas consist of a mixture of squamous epithelial cells and

mucus-secreting cells. The mucus-secreting cells of a mucoepidermoid carcinoma can demonstrate intracellular mucin with a special mucicarmine stain. Adenoid cystic carcinomas form tubular or cribriform patterns histologically and have a tendency to invade along perineural spaces, especially the facial nerve. Acinic cell carcinomas contain glands with cleared or vacuolated epithelial cells.

Gastrointestinal System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

270. A newborn infant is noted to have coughing and cyanosis during feeding. This infant is also noted to have marked gastric dilation due to "swallowed" air. Workup reveals that this infant has the most common type of esophageal atresia. Which one of the listed statements correctly describes this type of congenital abnormality?

a. Atresia of the esophagus with fistula between both segments and the trachea
b. Atresia of the esophagus with fistula between the trachea and the blind upper segment
c. Atresia of the esophagus with fistula between the trachea and the distal esophageal segment
d. Atresia of the esophagus without tracheoesophageal fistula
e. Fistula between a normal esophagus and the trachea

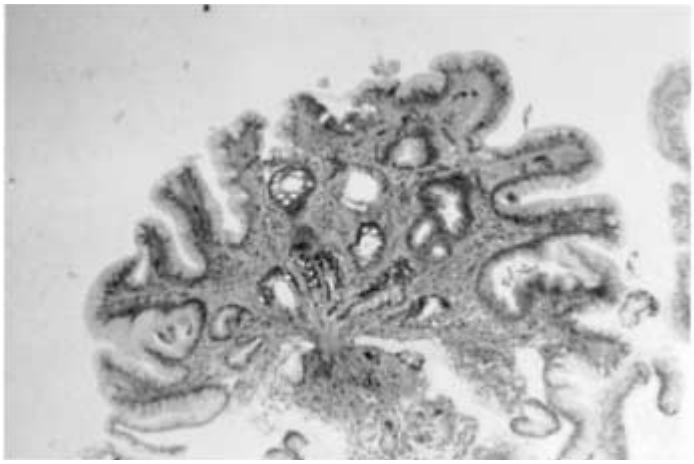
271. A 49-year-old female presents with increasing problems swallowing food (progressive dysphagia). X-ray studies with contrast reveal that she has a markedly dilated esophagus above the level of the lower esophageal sphincter (LES). No lesions are seen within the lumen of the esophagus. This patient's symptoms are most likely caused by

a. Decreased LES resting pressure
b. Absence of myenteric plexus in the body of esophagus
c. Absence of myenteric plexus at the LES
d. Absence of submucosal plexus in the body of esophagus
e. Absence of submucosal plexus at the LES

272. A 45-year-old male alcoholic with a history of portal hypertension presents with vomiting of blood (hematemesis) and hypotension. He denies any history of vomiting nonblood material or retching prior to vomiting blood. During workup he dies suddenly. Based on his history and physical findings, histologic sections from his esophagus would most likely reveal

a. Columnar epithelium in the distal esophagus
b. Decreased ganglion cells in the myenteric plexus
c. Dilated blood vessels in the submucosa
d. Mucosal outpouchings (diverticula) in the distal esophagus
e. Numerous intraepithelial neutrophils with scattered eosinophils

273. The photomicrograph below shows an esophageal biopsy taken 10 cm above the lower esophageal sphincter. This condition is most likely to occur as a result of



a. Destruction of the ganglion cells in Auerbach's plexus
b. Ingestion of lye
c. Long-term gastroesophageal reflux
d. Portal hypertension with portacaval shunting
e. Vomiting against a closed lower esophageal sphincter

274. A 71-year-old male presents with dysphagia and is found to have a 5-cm mass that is located in the middle third of the esophagus and extends into adjacent lung tissue. A biopsy from this mass would most likely reveal

a. A mass composed of benign cartilage
b. A mass composed of benign smooth-muscle cells
c. Infiltrating groups of cells forming glandular structures
d. Infiltrating sheets of cells forming keratin
e. Infiltrating single cells having intracellular mucin

275. A 2-week-old neonate presents with regurgitation and persistent, severe projectile vomiting. An olive-like epigastric mass is felt during physical examination. A chest x-ray does not reveal the presence of bowel gas in the chest cavity. This infant's mother did not have polyhydramnios during this pregnancy. What is the best treatment for this infant's condition?

a. Oral medication with omeprazole and clarithromycin
b. Oral medication with vancomycin or metronidazole
c. Surgery to cut a hypertrophied stenotic band at the pylorus
d. Surgery to remove a mass of the adrenal gland
e. Surgery to resect an aganglionic section of the intestines

276. A 49-year-old female taking ibuprofen for increasing joint pain in her hands presents with increasing pain in her midsternal area. Gastroscopy reveals multiple, scattered, punctate hemorrhagic areas in her gastric mucosa. Biopsies from one of these hemorrhagic lesions reveal mucosal erosions with edema and hemorrhage. No mucosal ulceration is seen. What is the best diagnosis?

a. Active chronic gastritis
b. Acute gastritis
c. Autoimmune gastritis
d. Chronic gastritis
e. Peptic ulcer disease

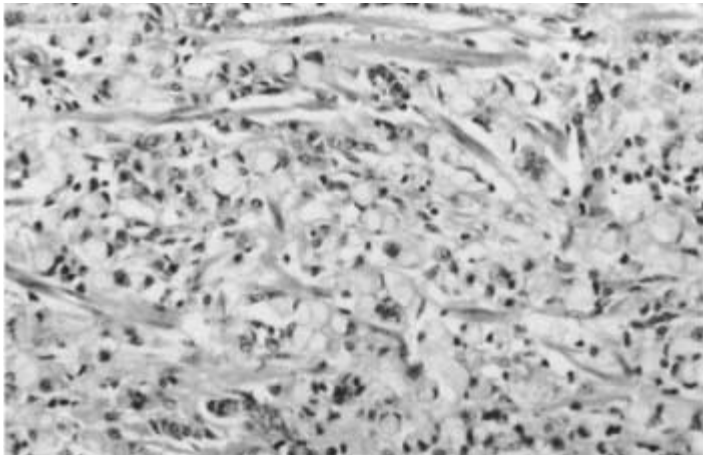
277. A biopsy of the antrum of the stomach of an adult who presents with epigastric pain reveals numerous lymphocytes and plasma cells within the lamina propria, which is of normal thickness. There are also scattered neutrophils within the glandular epithelial cells. A Steiner silver stain from this specimen is positive for a small, curved organism, which is consistent with

a. Enteroinvasive *Escherichia coli*
b. Enterotoxigenic *E. coli*
c. *Helicobacter pylori*
d. *Salmonella typhi*
e. *Shigella* species

278. A 51-year-old male presents with epigastric pain that is lessened whenever he eats. A gastroscopy is performed to evaluate these gastric symptoms and a solitary gastric ulcer is seen. This ulcer is round and has punched-out straight walls. The margins of the ulcer are slightly elevated, and gastric rugae radiate outward from the ulcer. Based on these findings, in order to relieve the epigastric pain this patient should

a. Take indomethacin twice a day
b. Abstain from smoking
c. Eat only two meals per day
d. Drink alcohol with his evening meal
e. Have surgery to resect the ulcer

279. Gastric tumors with the histologic appearance illustrated in the photomicrograph below are likely to have a gross appearance described best by which one of the listed terms?

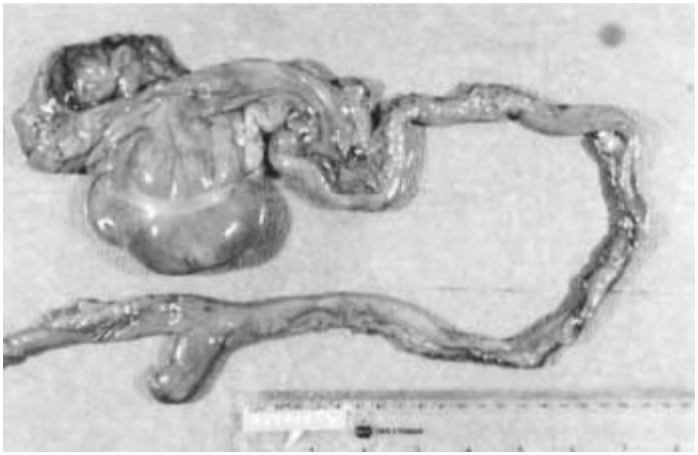


a. Cystosarcoma phyllodes
b. Linitis plastica
c. *Peau d'orange*
d. Rodent ulcer
e. Sarcoma botryoides

280. The overall incidence of malignancies of the stomach in the United States is decreasing primarily due to a decreased incidence of

a. Signet ring carcinoma
b. Primary non-Hodgkin's lymphoma
c. Intestinal-type gastric carcinoma
d. Gastric stromal sarcoma
e. Diffuse gastric carcinoma

281. The congenital abnormality of the ileum illustrated below



a. Is present in approximately 20% of normal persons
b. Is lined by heterotopic gastric mucosa in less than 2% of cases
c. Often shows mucosal ulceration
d. Is related to persistence of the vitellointestinal duct
e. Usually arises from the mesenteric border of the ileum

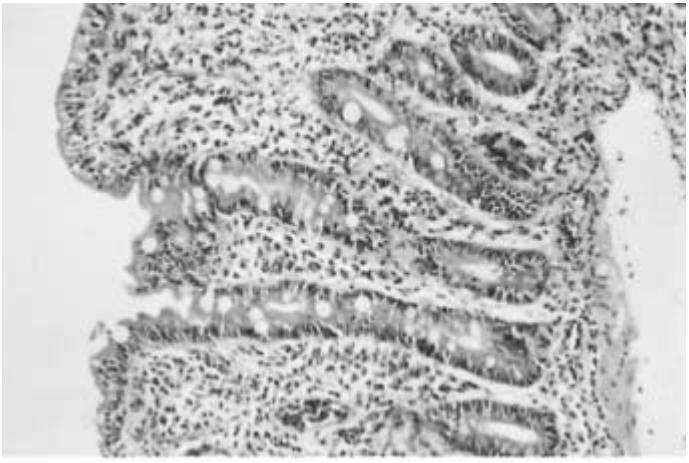
282. The signs and symptoms in which one of the listed individuals are most likely to be due to intussusception of the bowel?

a. An 18-year-old male with fever, leukocytosis, and right lower quadrant abdominal pain
b. A 3-year-old child with the abrupt onset of colicky abdominal pain and bloody, "currant jelly" stools
c. A 55-year-old male with the acute onset of severe abdominal pain
d. A 67-year-old female with fever, leukocytosis, and left lower quadrant abdominal pain
e. A newborn infant with projectile vomiting and midepigastric mass

283. A 10-month-old, previously healthy male infant develops a severe, watery diarrhea 2 days after visiting the pediatrician for a routine checkup. The most likely diagnosis is

a. Rotavirus infection
b. Enterotoxigenic *E. coli* infection
c. *Entamoeba histolytica* infection
d. Lactase deficiency
e. Ulcerative colitis

284. The appearance of the small intestinal mucosa illustrated in the photomicrograph below indicates



a. Small intestinal lymphoma
b. Whipple's disease
c. Celiac disease
d. Crohn's disease
e. *Giardia lamblia* infestation

285. A 45-year-old male presents with fever, chronic diarrhea, and weight loss. He is found to have multiple pain and swelling of his joints (migratory polyarthritis) and generalized lymphadenopathy. Physical examination reveals skin hyperpigmentation. A biopsy from his small intestines reveals the presence of macrophages in the lamina propria that contain PAS-positive cytoplasm. The best diagnosis for this individual is

a. Abetalipoproteinemia
b. Crohn's disease
c. Hartnup disease
d. Nontropical sprue
e. Whipple's disease

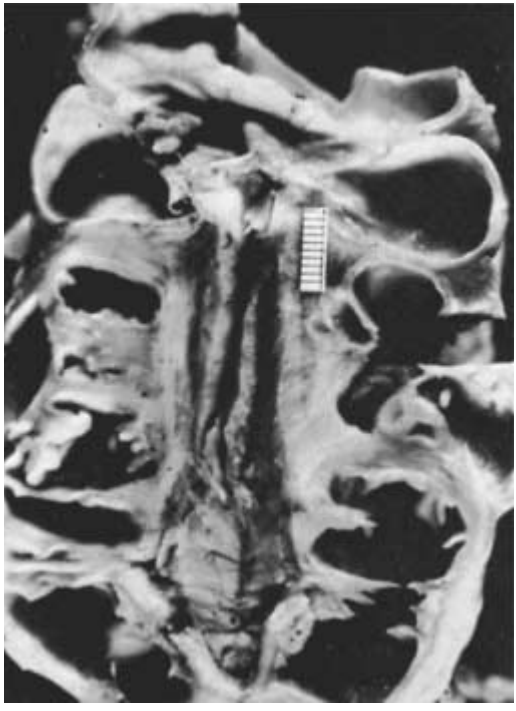
286. Which one of the following statements is more characteristic of ulcerative colitis than of Crohn's disease?

a. Fibrosis may produce a "lead pipe" appearance with "creeping fat" around the outside of the gut
b. Inflammation begins in the rectum and extends proximally without skip lesions
c. Microscopy may reveal transmural inflammation with noncaseating granulomas
d. Sudden abdominal pain may result from intestinal obstruction due to pericolonic abscess
e. Transmural involvement may produce fissures, fistulas, and bowel obstruction

287. A 39-year-old male presents with bloody diarrhea. Multiple stool examinations fail to reveal any ova or parasites. A barium examination of the patient's colon reveals a characteristic "string sign." A colonoscopy reveals the rectum and sigmoid portions of the colon to be unremarkable. A biopsy from the terminal ileum reveals numerous acute and chronic inflammatory cells within the lamina propria. Worsening of the patient's symptoms results in emergency resection of the distal small intestines. Gross examination of this resected bowel reveals deep, long mucosal fissures extending deep into the muscle wall. Several transmural fistulas are also found. What is the best diagnosis for this patient?

a. Ulcerative colitis
b. Lymphocytic colitis
c. Infectious colitis
d. Eosinophilic colitis
e. Crohn's disease

288. Examine the gross picture of a colon below. Which one of the following best describes signs and symptoms that may be produced by this abnormality?

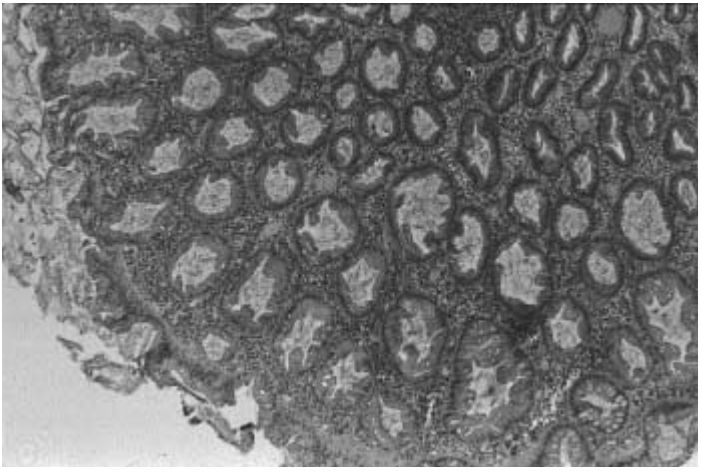


a. Abdominal cramps, diarrhea, and episodic facial flushing
b. Epigastric pain that is relieved by food intake
c. Fever, leukocytosis, and left-sided abdominal pain
d. Fever, leukocytosis, and right-sided abdominal pain
e. Retrosternal pain, especially when lying down

289. A 39-year-old female presents with chronic abdominal cramps, watery diarrhea, and periodic facial flushing. Physical examination reveals wheezing and a slightly enlarged liver. Workup reveals several masses within the liver and a large mass in the small intestine. Which one of the listed substances is most likely to be elevated in the urine of this individual as a result of her disease?

a. 5-hydroxyindoleacetic acid (5-HIAA)
b. Aminolevulinic acid (ALA)
c. *N*-formiminoglutamate (FIGlu)
d. Normetanephrine
e. Vanillylmandelic acid (VMA)

290. During routine colonoscopy of a 65-year-old male, a 2-mm "dewdrop"-like polyp is found in the sigmoid colon. A biopsy of this lesion is seen in the picture below. What is the best diagnosis?



a. Hyperplastic polyp
b. Hamartomatous polyp
c. Inflammatory polyp
d. Adenomatous polyp
e. Lymphoid polyp

291. Familial polyposis coli is characterized by

a. Autosomal recessive pattern of inheritance
b. Multiple hamartomatous polyps throughout the colon
c. 100% risk of carcinoma
d. An association with fibromatosis and multiple osteomas
e. An association with tumors of the central nervous system

292. The Astler-Coller modification of the Dukes classification is used to classify cancers of the

a. Colon
b. Liver
c. Lung
d. Pancreas
e. Stomach

293. An 18-year-old woman presents with abdominal pain localized to the right lower quadrant, nausea and vomiting, mild fever, and an elevation of the peripheral leukocyte count to 17,000/μL. Examination of the surgically resected appendix is most likely to reveal

a. An appendix with a normal appearance
b. Neutrophils within the muscular wall
c. Lymphoid hyperplasia and multinucleated giant cells within the muscular wall
d. A dilated lumen filled with mucus
e. A yellow tumor nodule at the tip of the appendix

294. Postmortem histologic sections taken from the liver of a 19-year-old female who died from an overdose of acetaminophen would most likely reveal

a. Centrilobular necrosis
b. Focal scattered necrosis
c. Geographic necrosis
d. Midzonal necrosis
e. Periportal necrosis

295. The basic abnormality involved in the pathophysiology of Crigler-Najjar syndrome is

a. Excess production of bilirubin
b. Reduced hepatic uptake of bilirubin
c. Impaired conjugation of bilirubin
d. Impaired canalicular transport of bilirubin glucuronide
e. Extrahepatic biliary obstruction

296. *Kernicterus* is a term that refers to the deposition of bilirubin in the

a. Basal ganglia
b. Cornea
c. Myocardium
d. Retina
e. Skin

297. A 62-year-old male with hepatic failure secondary to cirrhosis develops a pungent odor in his breath (fetor hepaticus). He is also noted to have marked ascites, gynecomastia, asterixis, and palmar erythema. His serum ammonia levels are found to be elevated. This patient's gynecomastia is the result of

a. Decreased synthesis of albumin
b. Defective metabolism of the urea cycle
c. Deranged bilirubin metabolism
d. Impaired estrogen metabolism
e. The formation of mercaptans in the gut

298. A 44-year-old male presents with the sudden onset of severe right upper quadrant (RUQ) abdominal pain, ascites, tender hepatomegaly, and hematemesis. These symptoms are suggestive of Budd-Chiari syndrome, a disorder that is caused by

a. Obstruction of the common bile duct
b. Obstruction of the intrahepatic sinusoids
c. Thrombosis of the hepatic artery
d. Thrombosis of the hepatic vein
e. Thrombosis of the portal vein

299. A 27-year-old female presents with headaches, muscle pain (myalgia), anorexia, nausea, and vomiting. She denies any history of drug or alcohol use, but upon further questioning she states that recently she has lost her taste for coffee and cigarettes. Physical examination reveals a slight yellow discoloration of her scleras, while laboratory results indicate a serum bilirubin level of 1.8 mg/dL, and aminotransferases (AST and ALT) levels are increased. These signs and symptoms are most consistent with a diagnosis of

a. Gilbert's syndrome
b. Chronic hepatitis
c. Amebic liver abscess
d. Acute viral hepatitis
e. Acute hepatic failure

300. A 4-year-old boy presents with mild fatigue and malaise. Several other children in the day-care center he attends 5 days a week have developed similar illnesses. Physical examination finds mild liver tenderness, but no lymphadenopathy is noted. Laboratory examination finds mildly elevated serum levels of liver enzymes and bilirubin. The boy recovers from his mild illness without incident. This disorder was most likely caused by infection with

a. Cytomegalovirus (CMV)
b. Epstein-Barr virus (EBV)
c. Group A β-hemolytic streptococcus
d. Hepatitis A virus
e. Hepatitis B virus

301. Which one of the following hepatitis profile patterns is most consistent with an asymptomatic hepatitis B carrier?

	Hepatitis B Surface Antigen (HBsAg)	Hepatitis B e Antigen (HBeAg)	Antibody to Surface Antigen (anti-HBs)	Antibody to Core Antigen (anti-HBc)
a.	Positive	Negative	Negative	Negative
b.	Positive	Positive	Negative	Negative
c.	Positive	Positive	Negative	Positive
d.	Positive	Negative	Negative	Positive
e.	Negative	Negative	Positive	Positive

302. A mononuclear portal inflammatory infiltrate that disrupts the limiting plate and surrounds individual hepatocytes (piecemeal necrosis) is characteristic of

a. Ascending cholangitis
b. Chronic active hepatitis
c. Acute alcoholic hepatitis
d. Cholestatic jaundice
e. Nutritional cirrhosis

303. The combination of episodic elevations in serum transaminase levels along with fatty change in hepatocytes is most suggestive of infection with

a. Hepatitis A virus
b. Hepatitis B virus
c. Hepatitis C virus
d. Hepatitis D virus
e. Hepatitis E virus

304. A 49-year-old female presents with increasing fatigue and is found to have elevated liver enzymes (AST and ALT). You follow her in your clinic and find over the next 9 months that her liver enzymes have remained elevated. All serologic tests for viral markers are within normal limits. A liver biopsy reveals chronic inflammation in the portal triads that focally destroys the limiting plate and "spills over" into the adjacent hepatocytes. There are no granulomas present, and there is no evidence of fibrosis surrounding any of the bile ducts within the portal triads. Anti-smooth-muscle antibodies and antinuclear antibodies are found in the patient's serum. An LE cell test is positive. What is the diagnosis?

a. Autoimmune hepatitis
b. Chronic persistent hepatitis
c. Primary biliary cirrhosis
d. Primary sclerosing cholangitis
e. Systemic lupus erythematosus

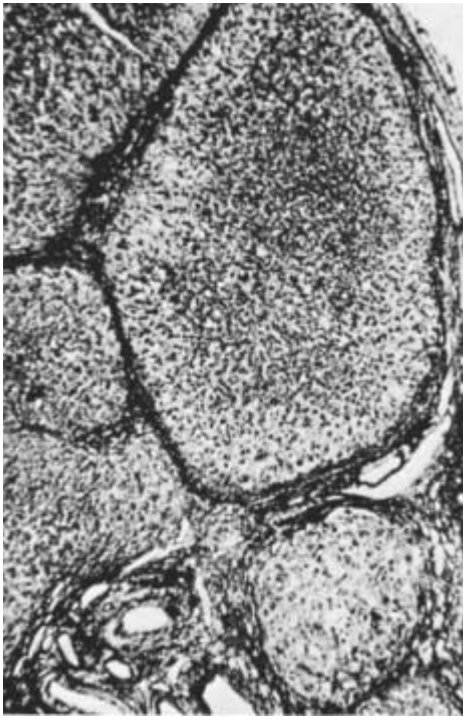
305. Dilated sinusoids and irregular cystic spaces filled with blood within the liver, which may rupture, leading to massive intraabdominal hemorrhage, are most commonly associated with

a. Salicylates
b. Estrogens
c. Anabolic steroids
d. Acetaminophen
e. Vinyl chloride

306. A 49-year-old male presents with symptoms that developed following a long weekend of binge drinking. His serum reveals a γ-glutamyl transferase (GGT) level of 65 IU/L. A liver biopsy reveals fatty change (steatosis) of numerous hepatocytes. This patient's liver abnormality is most likely the result of

a. Decreased free fatty acid delivery to the liver
b. Decreased production of triglycerides
c. Increased mitochondrial oxidation of fatty acids
d. Increased NADH production
e. Increased release of lipoproteins

307. Cirrhosis, as illustrated in the photomicrograph below, is characterized histologically by finding



a. Enlarged hepatocytes with large purple intranuclear inclusions
b. Fibrosis and regenerative nodules of hepatocytes
c. Increased amounts of iron within Kupffer cells and hepatocytes
d. Large red aggregates of PAS-positive, diastase-resistant material within hepatocytes
e. Perivenular fibrosis with Mallory bodies

308. Which of the listed types of cells found within the liver is the major source of the excess collagen deposited in cirrhosis?

a. Hepatocytes
b. Kupffer cells
c. Ito cells
d. Endothelial cells
e. Bile duct epithelial cells

309. A 36-year-old male presents because his skin has been darkening recently. You notice that his skin has a dark, somewhat bronze color. Workup reveals signs of diabetes mellitus. His serum iron is found to be 1150 mg/dL, and his transferrin saturation is 98%. A liver biopsy is performed and reveals extensive deposits of hemosiderin in the hepatocytes and Kupffer cells. The mechanism most likely responsible for this constellation of findings is

a. Defective excretion of copper into the bile
b. Defective synthesis of α_1 antitrypsin
c. Defective synthesis of glycogen
d. Excessive absorption of galactose from the small intestines
e. Excessive reabsorption of iron from the small intestines

310. A 5-year-old girl is brought in with severe vomiting that has developed suddenly 5 days after she has had a viral infection. Upon questioning, her parents indicate that she was given aspirin for several days to treat a fever that occurred with the viral illness. She is hospitalized and quickly develops signs of cerebral edema. Liver tissue reveals marked steatosis. What is the correct diagnosis?

a. α_1 antitrypsin deficiency
b. Dubin-Johnson syndrome
c. Hepatitis D infection
d. Reye's syndrome
e. Wilson's disease

311. Which one of the following tumors is most likely to be associated with primary sclerosing cholangitis?

a. Adenocarcinoma of the gallbladder
b. Adenocarcinoma of the pancreas
c. Cholangiocarcinoma
d. Hepatoblastoma
e. Hepatocellular carcinoma

312. A 26-year-old presents with right upper quadrant abdominal pain and is found to have a large cyst in the right lobe of his liver. X-rays reveal the cyst to have a calcified wall. The cyst is then surgically excised. Examination of this tissue histologically reveals a thick, acellular, laminated eosinophilic wall. The fluid within the cyst is found to be granular and contain numerous small larval capsules with scoleces ("brood capsules"). Which one of the following is the correct diagnosis?

a. Pyogenic liver abscess
b. Amebic liver abscess
c. Hydatid cyst
d. Schistosomiasis
e. Oriental cholangiohepatitis

313. An oval lesion is found in the right lobe of the liver in an otherwise asymptomatic 24-year-old female. Surgical resection finds a single well-demarcated lesion that has a prominent, central, stellate white scar. This gross appearance is most consistent with a diagnosis of

a. Metastatic adenocarcinoma
b. Focal nodular hyperplasia
c. Hemangioma
d. Hepatocellular carcinoma
e. Nodular regenerative hyperplasia

314. A 51-year-old male alcoholic with a history of chronic liver disease presents with increasing weight loss and ascites. Physical examination reveals a slightly enlarged, soft, nontender prostate. Examination of the scrotum is unremarkable, and fecal occult blood tests are negative. A chest x-ray is unremarkable, but a CT scan of the abdomen reveals a single mass in the left lobe of the liver. Workup reveals elevated levels of α-fetoprotein in this patient's blood. At this point the most likely diagnosis for the liver mass is

a. Angiosarcoma
b. Cholangiocarcinoma
c. Hepatoblastoma
d. Hepatocellular carcinoma
e. Metastatic colon cancer

315. A deficiency of which one of the listed enzymes is most likely to be associated with the formation of multiple pale yellow, hard, round stones within the gallbladder?

a. 1-α-hydroxylase
b. 7-α-hydroxylase
c. 11-hydroxylase
d. 17-hydroxylase
e. 21-hydroxylase

316. A 54-year-old male presents with a high fever, jaundice, and colicky abdominal pain in the right upper quadrant. The gallbladder cannot be palpated on physical examination. Workup reveals hemoglobin level of 15.3 g/dL, unconjugated bilirubin level of 0.9 mg/dL, conjugated bilirubin level of 1.1 mg/dL, and alkaline phosphatase level of 180 IU/L. What is the correct diagnosis?

a. Acute cholecystitis
b. Chronic cholecystitis
c. Bile duct obstruction by a stone
d. Carcinoma of the gallbladder
e. Carcinoma of the head of the pancreas

317. An infant is brought in by his mother, who says that his skin tastes salty. With time this patient's pancreas is expected to undergo progressive fibrosis with atrophy of the exocrine glands and cystic dilation of the ducts. The basic abnormality in this infant involves

a. Decreased synthesis of surface receptor
b. Decreased intracellular cAMP
c. Decreased glycosylated chloride channel
d. Increased phosphorylation of chloride channel
e. Increased ductal secretion of water

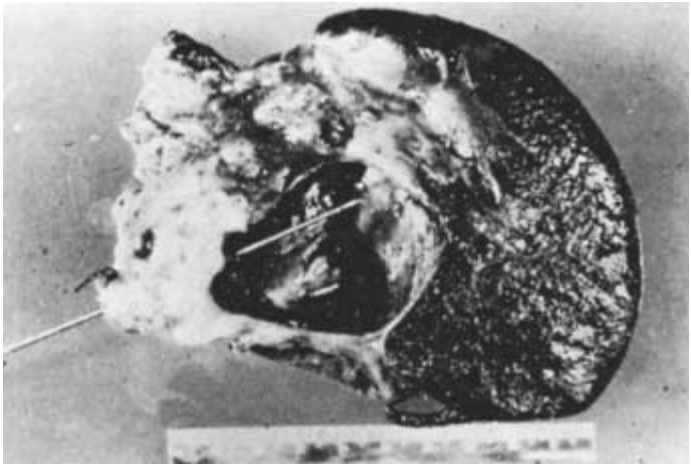
318. A 54-year-old male alcoholic presents with the sudden onset of severe, constant epigastric pain that radiates to his midback. Further evaluation finds fever, steatorrhea, and discoloration around his flank and umbilicus. Laboratory tests find elevated serum levels of amylase and lipase. What is the most likely cause of these findings?

a. Acute appendicitis
b. Acute cholangitis
c. Acute cholecystitis
d. Acute diverticulitis
e. Acute pancreatitis

319. A 45-year-old male presents with weight loss, steatorrhea, and malabsorption. A CT scan of the abdomen reveals a questionable mass in the head of the pancreas. A biopsy specimen microscopically reveals chronic inflammation and atrophy of the pancreatic acini with marked fibrosis. No malignancy is identified. What is the most common cause of this patient's disease in adults in the United States?

a. Abdominal trauma
b. Chronic alcoholism
c. Cystic fibrosis
d. Gallstones
e. Hyperlipidemia

320. A middle-aged male alcoholic has had repeated bouts of pancreatitis following periods of binge drinking. In recent months he has had a low-grade fever, and on examination a mass is palpated in the epigastrium. This mass, removed at celiotomy, is shown in the photograph below. What is the diagnosis?



a. Pancreatic carcinoma
b. Mucinous cystadenoma
c. Perforated ulcer
d. Pancreatic pseudocyst
e. Cystic hepatoma

321. According to Courvoisier's law, a pancreatic cancer located in the head of the pancreas would characteristically produce

a. Migratory thrombophlebitis
b. Obstructive jaundice and a dilated gallbladder
c. Obstructive jaundice and a nonpalpable gallbladder
d. Steatorrhea and a nontender gallbladder
e. Steatorrhea and a tender gallbladder

322. A 55-year-old female with painful chronic diarrhea, multiple recurrent duodenal ulcers, and increased basal gastric acid output is most likely to have

a. A gastrin-secreting tumor of the pancreas
b. A serotonin-secreting tumor of the ileum
c. A somatostatin-secreting tumor of the duodenum
d. An epinephrine-secreting tumor of the adrenal medulla
e. An erythropoietin-secreting tumor of the liver

323. Whipple's triad, seen in patients with a tumor that originates from the β cells of the pancreas, consists of

a. Diabetes mellitus, cholelithiasis, and steatorrhea
b. Hypercalcemia, signs of hypercalcemia, and signs of hypercalcemia relieved by hyperventilation
c. Hypoglycemia, signs of hypoglycemia, and signs of hypoglycemia relieved by glucose
d. Mild diabetes mellitus, necrolytic migratory erythema, and venous thrombi
e. Watery diarrhea, hypochloremia, and achlorhydria

324. An 11-year-old male presents with weight loss and dehydration despite excessive eating (polyphagia) and drinking of fluids (polydipsia). He has also had to go to the bathroom more often recently, and he has even had to wake up during the night to urinate. Laboratory examination reveals fasting hyperglycemia, while urinary examination reveals 4+ glucose (on a scale of 0 to 4+) and trace ketones. Which one of the listed abnormalities is the best diagnosis for this child?

a. Insulin-dependent diabetes mellitus (IDDM)
b. Nonobese non-insulin-dependent diabetes mellitus (NIDDM) due to impaired insulin release
c. Nonobese non-insulin-dependent diabetes mellitus (NIDDM) due to insulin resistance
d. Mature-onset diabetes of the young (MODY)
e. Diabetes insipidus

325. Which one of the listed findings is more characteristic of juvenile diabetes mellitus (type 1 diabetes mellitus) than of adult onset diabetes mellitus (type 2 diabetes mellitus)?

a. Amyloid deposition occurs in islets of Langerhans
b. It is associated with HLA-DR3 and HLA-DR4
c. Numbers of insulin receptors on adipocytes are decreased
d. There is insulin resistance that results from marked obesity
e. Treatment with oral hypoglycemic agents is effective

326. A laboratory test that measures serum levels of Hb A_{1c} (glycosylated hemoglobin) can be used to measure long-term control of an individual with

a. Autoimmune hemolytic anemia
b. Cystic fibrosis
c. Diabetes insipidus
d. Diabetes mellitus
e. Megaloblastic anemia

327. Which one of the listed statements best characterizes the renal abnormality described as Kimmelstiel-Wilson disease?

a. Amyloid nephrosis
b. Capsular drops
c. Glycogen nephrosis
d. Hyaline arteriolosclerosis
e. Nodular glomerulosclerosis

Gastrointestinal System

Answers

270. The answer is c. *(Cotran, p 777.)* The most common congenital anomaly of the esophagus is tracheal-esophageal fistula (TEF). Congenital anomalies of the esophagus are classified into five types, but only four types are associated with esophageal atresia. Type A abnormalities consist of atresia of the esophagus without a connection to the trachea (no fistula). Type B consists of atresia of the esophagus with a fistula between the trachea and the blind upper segment, while type C (the most common type) is characterized by atresia of the esophagus with a fistula between the trachea and the distal esophageal segment. Type D involves esophageal atresia with a fistula between both segments and the trachea, while type E is characterized by a fistula between a normal esophagus and the trachea. This abnormality involves no atresia. To summarize, type A has no fistula, type B connects to the upper segment, type C to the lower segment, and type D to both segments. These defects are dangerous because material that is swallowed may pass into the trachea (aspiration) either directly (types B, D, and E) or indirectly through reflux in that there is a blind upper pouch present (types A and C). Additionally, gastric dilation can occur due to "swallowed" air in those anomalies in which the trachea communicates with the lower esophagus (types C, D, and E). Also important is the fact that any defect that interferes with fetal swallowing in utero will produce polyhydramnios during pregnancy.

271. The answer is b. *(Cotran, pp 778–779.)* Achalasia, which means "un-relaxation," is a term that describes the absence of normal lower esophageal sphincter (LES) relaxation. This condition results from decreased or absent ganglion cells in the myenteric plexus in the body of the esophagus. The etiology of this neuronal loss is unknown in many cases; however, some cases are secondary to other diseases, such as diabetes mellitus, amyloidosis, sarcoidosis, and Chagas' disease, which is caused by *Trypanosoma cruzi*. Because of the increased LES pressure and the absence of peristaltic waves in the lower esophagus, the esophagus in

these patients is dilated and tortuous above the level of the LES. Barium x-ray studies reveal this dilation. The distal esophagus has a characteristic "beaklike" appearance. Patients with achalasia have an increased risk of developing aspiration pneumonia and squamous cell carcinoma.

272. The answer is c. *(Cotran, p 783.)* Most lesions of the esophagus present with similar symptoms, such as heartburn and dysphagia, but the most serious disease, which carries the risk of exsanguination, is bleeding esophageal varices. Varices occur in about two-thirds of all patients with cirrhosis, and in the majority of patients the etiology is alcoholic cirrhosis. The cirrhosis causes portal hypertension, which shunts blood into connecting channels between the portal and caval systems, such as the subepithelial plexus of veins in the lower esophagus. Varices produce no symptoms until they rupture and cause massive bleeding (hematemesis), which may lead to death. Other diseases, such as gastritis, esophageal laceration (Mallory-Weiss tears), or peptic ulcer disease, may cause hematemesis.

In contrast, columnar epithelium in the distal esophagus is seen with Barrett's esophagus; decreased ganglion cells in the myenteric plexus are seen with achalasia, a disorder that is characterized by aperistalsis, incomplete relaxation of the lower esophageal sphincter (LES) with swallowing, and increased resting tone of the LES, all of which lead to esophageal dilation and symptoms of progressive dysphagia.

273. The answer is c. *(Cotran, pp 780–782.)* The presence of columnar epithelium lining part or all of the distal esophagus is known as Barrett's esophagus. It is considered an acquired change resulting from reflux of acidic gastric contents with ulceration of the esophageal squamous epithelium and replacement by metaplastic, acid-resistant, columnar epithelium. Endoscopically it has a velvety-red appearance. Microscopically, intestinal-type epithelium is most common, but gastric-type epithelium is also seen. Varying degrees of dysplasia may be present. The risk of carcinoma is increased 30- to 40-fold. Virtually all of these tumors are of the adenocarcinoma type and they account for up to 10% of all esophageal cancers.

274. The answer is d. *(Cotran, pp 783–787.)* Carcinoma of the esophagus accounts for about 10% of malignancies of the GI tract, but for a disproportionate number of cancer deaths. Predisposing factors include

smoking, esophagitis, and achalasia. Of these carcinomas, 60 to 70% are squamous cell carcinomas that characteristically begin as lesions in situ. Adenocarcinoma occurs mainly in the lower esophagus and may arise in up to 10% of cases of Barrett's esophagus. Anaplastic and small cell variants also occur. Polypoid lesions are most common, followed by malignant ulceration and diffusely infiltrative forms. Tumors tend to spread by direct invasion of adjacent structures, but lymphatic and hematogenous spread may occur. Distant metastases are, however, a late feature. Five-year survival is less than 10%.

275. The answer is c. *(Cotran, pp 788–789, 805.)* Several congenital abnormalities of the gastrointestinal tract present with specific symptoms. Infants with congenital hypertrophic pyloric stenosis present in the 2nd or 3rd week of life with symptoms of regurgitation and persistent severe vomiting. Physical examination reveals a firm mass in the region of the pylorus. Surgical splitting of the muscle in the stenotic region is curative. Diaphragmatic hernias, if large enough, may allow abdominal contents—including portions of the stomach, intestines, or liver—to herniate into the thoracic cavity and cause respiratory compromise. Congenital aganglionic megacolon (Hirschsprung's disease) is caused by failure of the neural crest cells to migrate all the way to the anus, resulting in a portion of distal colon that lacks ganglion cells and both Meissner's submucosal and Auerbach's myenteric plexuses. This results in a functional obstruction and dilation proximal to the affected portion of colon. Symptoms of Hirschsprung's disease include failure to pass meconium soon after birth followed by constipation and possible abdominal distention.

276. The answer is b. *(Cotran, pp 789–790, 796–797.) Gastritis* is a nonspecific term that describes any inflammation of the gastric mucosa. Acute gastritis refers to the clinical situation of gastric mucosal erosions (not mucosal ulcers). Acute gastritis is also known as hemorrhagic gastritis or acute erosive gastritis. Acute gastritis is associated with the use of nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and corticosteroids, and also with alcohol, chemotherapy, ischemia, shock, and even severe stress. Two types of stress ulcers are Curling's ulcers, seen in patients with severe burns, and Cushing's ulcers, seen in patients with intracranial lesions. Grossly acute gastritis appears as multiple, scattered, punctate (less than 1 cm) hemorrhagic areas in the gastric mucosa. This is helpful in dif-

ferentiating acute gastritis from peptic ulcers, which tend to be solitary and larger. Microscopically the gastric mucosa from a patient with acute gastritis is likely to reveal mucosal erosions, scattered neutrophils, edema, and possibly hemorrhage.

277. The answer is c. *(Cotran, pp 790–793.)* Chronic gastritis is histologically characterized by the presence of lymphocytes and plasma cells. It is important to realize that the presence of neutrophils within the glandular epithelium indicates active inflammation and may be the main type of inflammation present (acute gastritis), or may be combined with more numerous chronic inflammations (active chronic gastritis). Chronic gastritis is divided into subgroups based either on etiology (immunologic or infectious), location (antrum or body), histopathology, or clinical features. *H. pylori* gastritis is associated with infection by *H. pylori,* a small, curved, gram-negative rod that is found in approximately 20% of the general population. The organisms are found in the mucus overlying the surface/foveolar epithelium. These changes tend to affect primarily the antral or antral-body-fundic mucosa. This is the type of gastritis normally associated with active chronic gastritis. The therapy for *Helicobacter* is either triple therapy (metronidazole, bismuth salicylate, and either amoxicillin or tetracycline) or double therapy (omeprazole and clarithromycin).

In contrast, autoimmune gastritis, also known as diffuse corporal atrophic gastritis or type A atrophic gastritis, is characterized by the presence of autoimmune antibodies including parietal cell antibodies and intrinsic factor antibodies. This type of gastritis is associated with pernicious anemia and achlorhydria. Pernicious anemia is the result of decreased intrinsic factor, which in turn produces a vitamin B_{12} deficiency. This vitamin deficiency causes megaloblastic anemia and subacute combined disease of the spinal cord. Histologically there is diffuse atrophy (reduced mucosal thickness), gland loss, widespread intestinal metaplasia, and variable chronic and acute inflammation. These changes are found predominately in the body-fundus mucosa (usually absent in the antrum). There is an increased risk for gastric cancer, but these patients do not develop peptic ulcers.

278. The answer is b. *(Cotran, pp 793–796. Rubin, pp 688–694.)* Gastric ulcers may be either acute gastric ulcers, peptic ulcers, or ulcers from malignant cancers. Acute gastric ulcers are stress ulcers that are really ero-

sions and not true ulcers. Certain gross and microscopic characteristics help to differentiate benign peptic ulcers from malignant ulcers. Benign peptic ulcers tend to be round and regular with punched-out straight walls. The margins are only slightly elevated and rugae radiate outward from the ulcer. Histologically, the surface of the ulcer shows acute inflammation and necrotic fibrinoid debris, while the base has active granulation tissue overlying a fibrous scar. Grossly, the floor of the ulcer is smooth. The gastric epithelium adjacent to the ulcer is reactive and is characterized by numerous mitoses and epithelial cells with prominent nucleoli. In contrast, malignant ulcers grossly are irregular with raised irregular margins. *H. pylori* may be seen with either type of ulcer, and its presence is not diagnostic for the type of ulcer. It is also found in 20% of the general population. Peptic ulcers are due to the effects of acid and may occur anywhere in the gastrointestinal tract exposed to acid-peptic activity. Over 98% of cases occur in the stomach or duodenum, with duodenal cases outnumbering gastric cases 4 to 1. Ulcers associated with Zollinger-Ellison syndrome are typically multiple and frequently involve distal duodenum and jejunum. Duodenal ulceration appears to be related to hypersecretion of acid. Gastric ulceration typically occurs in a setting of normo- or hypochlorhydria with abnormality of mucosal defense mechanisms, back-diffusion of acid, and possibly local ischemia. *H. pylori* is present in up to 100% of patients with duodenal ulcers and about 75% of patients with gastric ulcers. The treatment of peptic ulcers involves trying to decrease the effects of gastric acid. There are several types of drugs that can be used to treat peptic ulcers, such as cimetidine and omeprazole. Because food neutralizes acid within the stomach and relieves the typical epigastric pain of peptic ulcer disease, patients are advised to eat frequent small meals. Additional therapeutic measures include abstaining from substances or actions that increase gastric acid production, such as coffee, alcohol, and prostaglandin production inhibitors, which include aspirin, indomethacin, ibuprofen, and smoking.

279. The answer is b. *(Cotran, pp 798–802.)* "Signet ring cell" carcinoma is a morphologic variant of adenocarcinoma most often seen in the stomach. In these tumors, intracellular mucin vacuoles coalesce and distend the cytoplasm of tumor cells, which compresses the nucleus toward the edge of the cell and creates a signet ring appearance. Tumors of this type are usually deeply invasive and fall into the category of advanced gastric carcinoma. There is often a striking desmoplasia with thickening and

rigidity of the gastric wall, which may result in the so-called linitis plastica ("leather bottle") appearance. Advanced gastric carcinoma is usually located in the pyloroantrum, and the prognosis is poor, with 5-year survival of only 5 to 15%.

In contrast, cystosarcoma phyllodes is a type of breast tumor (*phyllodes* refers to its leaflike appearance), and *peau d'orange* refers to breast tumors that cause the overlying skin to have the appearance of an orange. *Rodent ulcer* refers to the clinical appearance of some basal cell carcinomas of the skin, while sarcoma botryoides is a malignant vaginal tumor that has a grapelike gross appearance.

280. The answer is c. *(Cotran, pp 798–802.)* The death rate from gastric carcinoma has been decreasing for decades but still shows marked variations among countries; Japan, Chile, and Iceland have rates up to 6 times higher than the U.S. and Australia. First-generation migrants carry the risk of their country of origin, but subsequent generations assume the risk of their new country. The decreased rate is due to a decrease in the rate of the intestinal type of gastric cancer. The incidence of the other type, diffuse gastric carcinoma, has not changed recently. Early gastric carcinoma (EGC) refers to a local neoplastic lesion limited to the mucosa and submucosa without penetration of the muscularis propria. Metastasis can occur, however, from EGC to local lymph nodes in up to 5% of cases. EGC is usually recognizable on radiographic or endoscopic examination, and so in most cases is potentially curable. It develops very slowly into a frankly invasive lesion and, if detected early and removed, allows a 5-year survival of up to 95% compared with 15% for gastric carcinoma overall. Of all gastric carcinomas, 50 to 60% arise in the pyloroantrum, 10% in the cardia, 10% in the whole organ, and the remainder in other sites. Diffusely infiltrative carcinoma extends widely through the stomach wall, often without producing an intraluminal mass, and incites a marked desmoplastic reaction that results in a thickened, inelastic stomach wall.

281. The answer is d. *(Cotran, pp 804–805.)* Meckel's diverticulum occurs in the ileum, usually within 30 cm of the ileocecal valve, and is present in approximately 2% of normal persons. It represents incomplete involution of the vitellointestinal duct and always arises from the antimesenteric border of the intestine. Heterotopic gastric or pancreatic tissue may be present in about one-half of cases. Peptic ulceration, which occurs as a

result of acid secretion by heterotopic gastric mucosa, is usually located in the adjacent ileum. Complications include perforation, ulceration, intestinal obstruction, intussusception, and neoplasms, including carcinoid tumors.

282. The answer is b. *(Cotran, pp 825–826.) Intussusception* refers to a condition in which one portion of the GI tract is pulled into the lumen of an adjoining portion of the GI tract. The most common location for this is the terminal ileum, and there are two types of patients who are most at risk, namely weaning infants and adults with a polypoid mass. It is thought that in weaning infants, exposure to new antigens causes hypertrophy of the lymphoid follicles in the terminal ileum and this may result in intussusception. Intussusception produces a classic triad of signs that includes sudden colicky abdominal pain, abdominal distention, and a "currant jelly" stool due to the vascular compromise produced by pulling of the mesentery.

In contrast, the combination of fever, leukocytosis, and right lower quadrant abdominal pain is suggestive of acute appendicitis, while fever, leukocytosis, and left lower quadrant abdominal pain is suggestive of acute diverticulitis. A newborn infant with projectile vomiting and mid-epigastric mass probably has hypertrophic pyloric stenosis, while the acute onset of severe abdominal pain in a male older than 55 might be due to a ruptured abdominal aortic aneurysm.

283. The answer is a. *(Cotran, pp 805–811.)* The causes of diarrhea are numerous, and diarrhea may be broadly classified into multiple categories including secretory, osmotic, and exudative. Both secretory and exudative diarrhea may have infectious causes. Several viruses may cause secretory diarrhea. Rotavirus is a major cause of diarrhea in children between the ages of 6 and 24 months. Clinical symptoms consisting of vomiting and watery (secretory) diarrhea begin about 2 days after exposure. Bacterial enterocolitis may be related to either the production of performed toxins, such as with *Vibrio cholerae* and enterotoxigenic *E. coli* (a major cause of "traveler's diarrhea"), or it may be related to bacterial invasion of the colon, as seen with salmonella and shigella. *E. histolytica* is a cause of amebiasis and is endemic in underdeveloped countries. It characteristically produces flask-shaped ulcers in the colon and may embolize to the liver, where it produces amebic liver abscesses. Lactase deficiency, a cause of osmotic

diarrhea, is very rarely a congenital disorder, but much more commonly is an acquired disorder seen in adults that results in malabsorption of milk and milk products. The onset of symptoms from ulcerative colitis is most commonly apparent between the ages of 20 and 25 years.

284. The answer is c. *(Cotran, pp 813–814.)* Celiac disease, or gluten-sensitive enteropathy, is an inflammatory condition of the small intestinal mucosa related to dietary gluten. It is more common in females and shows familial clustering. Histologically it is characterized by villus atrophy with hyperplasia of underlying crypts and increased mitotic activity. The surface epithelium shows disarray of the columnar epithelial cells and increased intraepithelial lymphocytes. There is a chronic inflammatory infiltrate in the lamina propria. Definitive diagnosis in patients with these features on biopsy depends on response to a gluten-free diet and subsequent gluten challenge.

285. The answer is e. *(Cotran, pp 812–815. Rubin, pp 711–717.)* The causes of malabsorption are vast, but in a few cases biopsy specimens of the small intestine may provide clues to a specific diagnosis. Whipple's disease is a systemic disease associated with malabsorption, fever, skin pigmentation, lymphadenopathy, and arthritis. Biopsy of the small intestine typically reveals the lamina propria to be infiltrated by numerous PAS-positive macrophages that contain glycoprotein and rod-shaped bacteria. The organism, *Tropheryma whippelii,* is a gram-positive actinomycete. The disease responds promptly to broad-spectrum antibiotic therapy. Abetalipoproteinemia is a genetic defect in the synthesis of apolipoprotein B that leads to an inability to synthesize prebetalipoproteins (VLDLs), betalipoproteins (LDLs), and chylomicrons. These individuals have no chylomicrons, VLDLs, or LDLs in their blood. A biopsy of the small intestine reveals the mucosal absorptive cells to be vacuolated by lipid (triglyceride) inclusions, and peripheral smear reveals numerous acanthocytes, which are red blood cells that have numerous irregular spikes on their cell surface. The symptoms of malabsorption may be partially reversed by ingestion of medium-chain triglycerides rather than long-chain triglycerides, because these medium-chain triglycerides are absorbed directly into the portal system and are not incorporated into lipoproteins. Tropical and nontropical (celiac) sprue are both characterized by shortened to absent villi in the small intestines (atrophy). Celiac sprue is a disease of malabsorption

related to a sensitivity to gluten, which is found in wheat, oats, barley, and rye. This disease is related to HLA-B8 and to previous infection with type 12 adenovirus. These patients respond to removal of gluten from their diet. Tropical sprue is an acquired disease found in tropical areas, such as the Caribbean, the Far East, and India. It is the result of a chronic bacterial infection. Granulomas in mucosa and submucosa of an intestinal biopsy, if infectious causes have been excluded, are highly suggestive of Crohn's disease. Fibrosis of the lamina propria and submucosa may be seen in patients with systemic sclerosis. Bacterial overgrowth, a result of numerous causes such as the blind loop syndrome, strictures, achlorhydria, or immune deficiencies, may also cause malabsorption. Treatment is with appropriate antibiotics.

286. The answer is b. *(Cotran, pp 815–820.)* The term inflammatory bowel disease (IBD) is used to describe two diseases with many similar features, Crohn's disease and ulcerative colitis. Histologically, both of these diseases produce distorted crypt architecture with crypt destruction and loss. These abnormalities of the colonic crypts help to differentiate IBD from infectious colitis. Both Crohn's disease and ulcerative colitis produce acute and chronic inflammation of the colonic mucosa. Lymphocytes and plasma cells are increased in number in the lamina propria. Neutrophils may be seen within the colonic epithelium, and, if present within the lumens of the crypts, may produce crypt abscesses. This latter change, however, is more commonly associated with ulcerative colitis. One important way to differentiate between these two inflammatory bowel diseases is the location of involved colon. Crohn's disease may affect any portion of the GI tract, but most commonly there is involvement of the terminal ileum (regional enteritis) or the proximal portion (right side) of the colon. GI involvement is segmental with skip areas. In contrast, almost all cases of ulcerative colitis involve the rectum, and involvement extends proximally (left side) without skip lesions (diffuse involvement).

287. The answer is e. *(Cotran, pp 815–820.)* The two inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC), are both chronic, relapsing inflammatory disorders of unknown etiology. They both may show very similar morphologic features and associations, such as mucosal inflammation, malignant transformation, and extragastrointestinal manifestations that include erythema nodosum (especially ulcerative coli-

tis), arthritis, uveitis, pericholangitis (especially with ulcerative colitis, in which sclerosing pericholangitis may produce obstructive jaundice), and ankylosing spondylitis. CD is classically described as being a granulomatous disease, but granulomas are present in only 25 to 75% of cases. Therefore, the absence of granulomas does not rule out the diagnosis of CD. CD may involve any portion of the gastrointestinal tract and is characterized by focal (segmental) involvement with "skip lesions." Involvement of the intestines by CD is typically transmural inflammation, which leads to the formation of fistulas and sinuses. The deep inflammation produces deep longitudinal, serpiginous ulcers, which impart a "cobblestone" appearance to the mucosal surface of the colon. Additionally in Crohn's disease, the mesenteric fat wraps around the bowel surface, producing what is called "creeping fat," and the thickened wall narrows the lumen, producing a characteristic "string sign" on x-ray. This narrowing of the colon, which may produce intestinal obstruction, is grossly described as a "lead pipe" or "garden hose" colon. In contrast to CD, UC affects only the colon, and the disease involvement is continuous. The rectum is involved in all cases, and the inflammation extends proximally. Since UC involves the mucosa and submucosa, but not the wall, fistula formation and wall thickening are absent (but toxic megacolon may occur). Grossly, the mucosa displays diffuse hyperemia with numerous superficial ulcerations. The regenerating, nonulcerated mucosa appears as "pseudopolyps."

288. The answer is c. *(Cotran, pp 823–825.)* One of the most common abnormalities of the colon seen in older patients is diverticulosis (multiple outpouchings of the mucosa into and through the muscular wall). Sometimes GI diverticula are classified as being either true diverticula or false diverticula. True diverticula have all layers of the intestine in the diverticulum, an example being Meckel's diverticulum, while false diverticulum lack the muscle layer, an example being the usual type of colonic diverticula seen in older patients. These false colonic diverticula are found in the sigmoid region (the left side) in a double vertical row along the antimesenteric taenia coli. They are thought to be the result of decreased dietary fiber that increases intraluminal pressure. Most diverticula are asymptomatic, but they may become inflamed, somewhat analogously to inflammation of the appendix (associated with fever, leukocytosis and right-sided abdominal pain). Patients with inflamed diverticula (diverticulitis) present with fever, leukocytosis, and left-sided abdominal pain ("left-sided appendicitis"). In

contrast, abdominal cramps, diarrhea, and episodic facial flushing are characteristic signs of the carcinoid syndrome, while epigastric pain that is relieved by food intake suggests peptic ulcer, and retrosternal pain, especially when lying down, suggests gastric reflux.

289. The answer is a. *(Cotran, pp 835–837. Rubin, pp 720–721.)* The patient shows signs of the carcinoid syndrome, which include flushing, diarrhea, and bronchoconstriction. The syndrome results from elaboration of serotonin (5-hydroxytryptamine) by a primary carcinoid tumor in the lungs or ovary, or from hepatic metastases from a primary carcinoid tumor in the gastrointestinal tract. However, primary appendiceal carcinoid tumors, the most common gastrointestinal carcinoid tumors, very rarely metastasize and are virtually always asymptomatic. Carcinoid tumors arise from cells of the neuroendocrine system, which, as part of the amine precursor uptake and decarboxylation (APUD) system, are capable of secreting many products. Grossly, carcinoid tumors, which tend to be multiple when they occur in the stomach or intestines, are characteristically solid and firm and have a yellow-tan appearance on sectioning. Histologically they are composed of nests of relatively bland-appearing monotonous cells. Diagnosis is based on finding increased urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion from metabolism of excess serotonin. In contrast, increased urinary levels of aminolevulinic acid (ALA) are seen with lead toxicity, increased *N*-formiminoglutamate (FIGlu) with folate deficiency, and increased normetanephrine or vanillylmandelic acid (VMA) with tumors of the adrenal medulla (pheochromocytoma in adults and neuroblastoma in children).

290. The answer is a. *(Cotran, pp 827–831.)* Colonic polyps are either non-neoplastic, which have no malignant potential, or neoplastic, which are precursors of cancer. Most colon polyps are nonneoplastic and are the result of abnormal maturation or inflammation. Hyperplastic polyps histologically have a serrated "sawtooth" appearance, while grossly they tend to be small and have a "dewdrop" appearance. These polyps are thought to be an aging change and are not associated with malignant transformation. Inflammatory polyps or pseudopolyps may be formed by inflamed regenerating epithelium, as seen with Crohn's disease or ulcerative colitis. Juvenile (retention) polyps contain abundant stroma and dilated glands filled with mucus, while lymphoid polyps contain intramucosal lymphoid tissue.

Hamartomatous polyps are similar to juvenile polyps, but they also contain smooth muscle. An interesting fact about juvenile polyps, which are typically found in children or young adults, is that they are prone to self-amputation, and patients may find them floating in the toilet (which can be disturbing for the patient).

In contrast to the nonneoplastic polyps, neoplastic polyps arise from proliferative, dysplastic epithelium, which is characterized by stratification of cells having plump, elongated nuclei. As a group these dysplastic polyps are called adenomatous polyps. Based on their architecture, they are further classified as either tubular adenomas, villous adenomas, or mixed tubulovillous adenomas. The risk for malignancy is dependent upon the size of the polyp and the type and the amount of dysplasia present. The risk for developing a malignancy is greater for large villous polyps that have severe dysplasia.

291. The answer is c. *(Cotran, pp 831–833.)* Although most colonic polyps occur sporadically, there are several conditions in which colonic polyposis is familial and sometimes associated with extraintestinal abnormalities. Familial polyposis coli is usually transmitted as an autosomal dominant condition and is characterized by multiple adenomatous colonic polyps, with a minimum of 100 polyps necessary for diagnosis. As with sporadic adenomatous polyps, there is a risk of malignancy, and this increases to 100% within 30 years of diagnosis. Panproctocolectomy is therefore usually recommended. Gardner's syndrome is the association of colonic polyposis with multiple osteomas, fibromatosis, and cutaneous cysts. The association of colonic polyposis with central nervous system tumors is known as Turcot's syndrome.

292. The answer is a. *(Cotran, pp 833–835.)* Colon cancer is a frequent type of cancer in adults of the United States. It may be found in the left side of the colon (producing a "napkin ring" or "apple core" appearance) or the right side of the colon (producing a polypoid mass). In either location, bleeding may produce an iron-deficiency anemia. Histologically, the vast majority of colon cancers are adenocarcinomas. Currently the most common classification used to stage colon carcinomas is the Astler-Coller modification of the Dukes classification of colon cancer. This classification is as follows: A = mucosa (or submucosa, arbitrary); B1 = into muscularis propria; B2 = through muscularis propria; C1 = into muscularis propria with

lymph node metastasis; C2 = through muscularis propria with lymph node metastasis; D = distant spread.

293. The answer is b. *(Cotran, pp 839–840. Rubin, pp 748–749.)* Acute appendicitis, a disease found predominantly in adolescents and young adults, is characterized histologically by acute inflammatory cells (neutrophils) within the mucosa and muscular wall. Clinically, acute appendicitis causes right lower quadrant pain, nausea, vomiting, a mild fever, and a leukocytosis in the peripheral blood. These symptoms may not occur in the very young or the elderly. The inflamed appendiceal wall may become gangrenous and perforate in 24 to 48 h. Even with classic symptoms, the appendix may be histologically unremarkable in up to 20% of the cases. False-positive diagnoses are to be preferred to the possible severe or fatal complications of a false-negative diagnosis of acute appendicitis that results in rupture. Lymphoid hyperplasia with multinucleated giant cells (Warthin-Finkeldey giant cells) is characteristic of measles (rubeola). These changes can be found in the appendix, but this is quite rare. Dilation of the lumen of the appendix, called a mucocele, may be caused by mucosal hyperplasia, a benign cystadenoma, or a malignant mucinous cystadenocarcinoma. If the latter tumor ruptures, it may seed the entire peritoneal cavity, causing the condition called pseudomyxoma peritonei. The most common tumor of the appendix is the carcinoid tumor. Grossly it is yellow in color and is typically located at the tip of the appendix. Histologically, carcinoids are composed of nests or islands of monotonous cells. Appendiceal carcinoids rarely metastasize.

294. The answer is a. *(Cotran, pp 14–15, 846–848.)* The type and distribution of necrotic hepatocytes is often a clue as to the cause of the hepatic injury. Focal scattered necrosis is characteristic of viral hepatitis, but may also be seen with bacterial infections or other toxic insults. In focal necrosis, there is necrosis of single hepatocytes, or small clusters of hepatocytes, that is randomly located in some, but not all, of the liver lobules. In contrast, zonal necrosis refers to the finding of hepatocellular necrosis in identical areas in all of the liver lobules. There are basically three types of zonal necrosis. Centrilobular (acinar zone 3) necrosis is characteristic of ischemic injury (heart failure or shock), toxic effects (acetaminophen toxicity), carbon tetrachloride exposure, or chloroform ingestion. Drugs such as acetaminophen may be metabolized in zone 1 to toxic compounds that cause necrosis of

zone 3 hepatocytes because they receive the blood from zone 1. Midzonal (zone 2) necrosis is quite rare, but may be seen in yellow fever, while periportal (zone 1) necrosis is seen in phosphorus poisoning or eclampsia. Submassive necrosis refers to liver cell necrosis that crosses the normal lobular boundaries. Classically the necrosis goes from portal areas to central veins (or vice versa) and is called bridging necrosis. If the hepatocellular necrosis is severe, it is called massive necrosis. This type of extensive necrosis is described as acute yellow atrophy, as grossly the liver appears soft, yellow, flabby, and decreased in size with a wrinkled capsule. It may be produced by hepatitis viruses (usually B or C), drugs, or chemicals.

295. The answer is c. *(Henry, pp 87–88, 258–260. Cotran, pp 848–851.)* Jaundice is caused by increased blood levels of bilirubin, which result from abnormalities in bilirubin metabolism. Bilirubin, the end product of heme breakdown, is taken up by the liver, where it is conjugated with glucuronic acid by the enzyme bilirubin UDP-glucuronosyl transferase (UGT) and then secreted into the bile. Unconjugated bilirubin is not soluble in an aqueous solution, is complexed to albumin, and cannot be excreted in the urine. Unconjugated hyperbilirubinemia may result from excessive production of bilirubin, which occurs in hemolytic anemias. It can also result from reduced hepatic uptake of bilirubin, as occurs in Gilbert's syndrome, a mild disease associated with a subclinical hyperbilirubinemia. Unconjugated hyperbilirubinemia may result from impaired conjugation of bilirubin. Examples of diseases resulting from impaired conjugation include physiologic jaundice of the newborn and Crigler-Najjar syndrome, which result from either decreased UGT activity (type II) or absent UGT activity (type I). Conjugated bilirubin is water-soluble, nontoxic, and readily excreted in the urine. Conjugated hyperbilirubinemia may result from either decreased hepatic excretion of conjugates of bilirubin, such as in Dubin-Johnson syndrome, or impaired extrahepatic bile excretion, as occurs with extrahepatic biliary obstruction.

296. The answer is a. *(Cotran, pp 474, 849–850.)* Physiologic jaundice of the newborn refers to mild elevation of the serum bilirubin levels that occurs on days 2 to 4 of life. This abnormality is generally the result of decreased levels of UGT, and therefore the serum bilirubin is mainly unconjugated (indirect) bilirubin. In full-term infants, the maximum bilirubin levels are less than 6 mg/dL (normal is less than 2 mg/dL), while in premature

infants, the maximal levels may rise to 12 mg/dL. It is important to realize that in newborns the blood-brain barrier is not fully developed and unconjugated bilirubin may be deposited in the brain, particularly in the lipid-rich basal ganglia, producing severe neurologic abnormalities. Grossly the brain has a bright yellow pigmentation that is called kernicterus. Note that kernicterus does not result unless serum bilirubin levels are greater than 20 mg/dL. Treatment, if needed, consists of exposing the skin to light (440 to 470 nm), which activates oxygen and converts bilirubin to photobilirubin. This substance is hydrophilic and can be excreted in the urine.

297. The answer is d. *(Cotran, pp 852–853. Chandrasoma, pp 636–637.)* Despite various underlying causes, the clinical features of all types of liver failure are similar. A defective urea cycle results in hyperammonemia, while a foul-smelling breath (fetor hepaticus) is thought to occur due to volatile, sulfur-containing mercaptans being produced in the gut. If liver cell necrosis is present, serum hepatic enzymes, such as LDH, ALT, and AST, will be increased. Impaired estrogen metabolism in males can result in gynecomastia, testicular atrophy, palmar erythema, and spider angiomas of the skin. Additionally, deranged bilirubin metabolism results in jaundice (mainly conjugated hyperbilirubinemia) and a decreased synthesis of albumin (hypoalbuminemia) results in ascites. Symptoms of hepatic encephalopathy, a metabolic disorder of the neuromuscular system, include stupor, hyperreflexia, and asterixis (a peculiar flapping tremor of the hands).

298. The answer is d. *(Cotran, pp 881–884.)* Abnormalities of the hepatic blood flow occur in various disease states and result in characteristic symptoms. Because of their dual blood supply, arterial occlusion of either the hepatic artery or the portal vein rarely results in liver infarcts. However, thrombosis of branches of the hepatic artery may result in a pale (anemic) infarct, or possibly a hemorrhagic infarct due to blood flow from the portal vein. In contrast, occlusion of the portal vein, which may be caused by cirrhosis or malignancy, may result in a wedge-shaped red area called an infarct of Zahn. This is a misnomer, however, since it is not really an infarction but instead is the result of focal sinusoidal congestion. Hepatic vein thrombosis (Budd-Chiari syndrome) is associated with polycythemia vera, pregnancy, and oral contraceptives. Clinically, Budd-Chiari syndrome is characterized by the sudden onset of severe right upper quadrant abdominal pain, ascites, tender hepatomegaly, and hematemesis.

Occlusion of the central veins, called venoocclusive disease, may be rarely seen in Jamaican drinkers of alkaloid-containing bush tea, but is much more commonly found following bone marrow transplantation (up to 25% of allogenic marrow transplants).

299. The answer is d. *(Cotran, pp 864–867. Chandrasoma, pp 643–645.)* Several clinical syndromes may develop after exposure to any of the viruses that cause hepatitis, including asymptomatic hepatitis, acute hepatitis, fulminant hepatitis, chronic hepatitis, and the carrier state. Asymptomatic infection in individuals is documented by serologic abnormalities only. Liver biopsies in patients with acute hepatitis, either the anicteric phase or the icteric phase, reveal focal necrosis of hepatocytes (forming Councilman bodies) and lobular disarray resulting from ballooning degeneration of the hepatocytes. These changes are nonspecific, but the additional finding of fatty change is suggestive of hepatitis C virus (HCV) infection. Clinically, acute viral hepatitis is classified into three phases. During the prodrome phase, patients may develop symptoms that include anorexia, nausea and vomiting, headaches, photophobia, and myalgia. An unusual symptom associated with acute viral hepatitis is altered olfaction and taste, especially the loss of taste for coffee and cigarettes. The next phase, the icteric phase, involves jaundice produced by increased bilirubin. Patients may also develop light stools and dark urine (due to disrupted bile flow) and ecchymoses (due to decreased vitamin K). The final phase is the convalescence phase. Fulminant hepatitis refers to massive necrosis and is seen in about 1% of patients with either hepatitis B or C, but very rarely with hepatitis A infection. The biggest risk for fulminant hepatitis is coinfection with both hepatitis B and D. Chronic hepatitis is defined as elevated serum liver enzymes for longer than 6 months. Patients may be either symptomatic or asymptomatic.

300. The answer is d. *(Cotran, pp 856–864. Chandrasoma, pp 641–643.)* Several types of viruses are implicated as being causative agents of viral hepatitis. Each of these has unique characteristics. Hepatitis A virus, an RNA picornavirus, is transmitted through the fecal-oral route (including shellfish) and is called infectious hepatitis. It is associated with small outbreaks of hepatitis in the United States, especially among young children at day care centers. Hepatitis B virus, which causes "serum hepatitis," is associated with the development of a serum sickness–like syndrome in about

10% of patients. Immune complexes of antibody and HBsAg are present in patients with vasculitis. Hepatitis C virus is characterized by episodic elevations in serum transaminases, and also by fatty change in liver biopsy specimens. Hepatitis D virus is distinct in that it is a defective virus and needs HBsAg to be infective. Hepatitis E virus is characterized by waterborne transmission. It is found in underdeveloped countries and has an unusually high mortality in pregnant females. It is important to remember that the liver may be infected by other viruses, such as yellow fever virus, Epstein-Barr virus (EBV, the causative agent of infectious mononucleosis), CMV, and/or herpes virus. The latter is characterized histologically by intranuclear eosinophilic inclusions (Cowdry bodies) and nuclei that have a ground-glass appearance.

301. The answer is d. *(Cotran, pp 857–859. Rubin, pp 774–777.)* Hepatitis B virus (HBV) is a member of the DNA-containing hepadnaviruses. The mature HBV virion is called the Dane particle. Products of the HBV genome include the nucleocapsid [hepatitis B core antigen (HBcAg)], envelope glycoprotein [hepatitis B surface antigen (HBsAg)], and DNA polymerase. After exposure to HBV, there is a relatively long asymptomatic incubation period, averaging 6 to 8 weeks, followed by an acute disease lasting several weeks to months. HBsAg is the first antigen to appear in the blood. It appears before symptoms begin, peaks during overt disease, and declines to undetectable levels in 3 to 6 months. HBeAg, HBV-DNA, and DNA polymerase appear soon after HBsAg. HBeAg peaks during acute disease and disappears before HBsAg is cleared. The presence of either HBsAg or HBeAg without antibodies to either is seen early in hepatitis B infection. Anti-HBsAg appears at about the time of the disappearance of HBsAg and indicates complete recovery. Anti-HBc first appears much earlier, shortly after the appearance of HBsAg, and levels remain elevated for life. Its presence indicates previous HBV infection, but not necessarily that the hepatitis infection has been cleared. Persistence of HBeAg is an important indicator of continued viral replication with probable progression to chronic hepatitis. With normal recovery from hepatitis B, both HBsAg and HBeAg are absent from the blood, while anti-HBs and anti-HBc are present. If anti-HBs is never produced, then HBsAg may not be cleared. In this case, the patient may remove the HBeAg and be an asymptomatic carrier, or the HBeAg may persist and the patient could be a chronic carrier who has progressed to chronic active hepatitis. In both of these conditions, anti-HBc is still present.

302. The answer is b. *(Cotran, pp 864–867.)* Chronic hepatitis has been defined as an inflammatory process of the liver that lasts longer than 1 year and lacks the nodular regeneration and architectural distortion of cirrhosis. In chronic active hepatitis, an intense inflammatory reaction with numerous plasma cells spreads from portal tracts into periportal areas. The reaction destroys the limiting plate and results in formation of periportal hepatocytic islets. Prognosis is poor, and the majority of patients develop cirrhosis. Chronic persistent hepatitis is usually a sequela of acute viral hepatitis and has a benign course without progression to chronic active hepatitis or cirrhosis. The portal inflammation does not extend into the periportal areas, and this differentiates chronic persistent hepatitis from chronic active hepatitis.

303. The answer is c. *(Cotran, pp 860–861.)* The hepatitis viruses are responsible for most cases of chronic hepatitis, but the chance of developing chronic hepatitis varies considerably depending on which type of hepatitis virus is the infecting agent. Neither hepatitis A nor hepatitis E virus infection is associated with the development of chronic hepatitis. About 5% of adults infected with hepatitis B develop chronic hepatitis, and about one-half of these patients progress to cirrhosis. In contrast to hepatitis B, chronic hepatitis develops in about 50% of patients with hepatitis C. Clinically, chronic hepatitis C is characterized by episodic elevations in serum transaminases, and also by fatty change in liver biopsy specimens. Hepatitis D infection occurs in two clinical settings. There might be acute coinfection by hepatitis D and hepatitis B, which results in chronic hepatitis in less than 5% of cases. If, instead, hepatitis D is superinfected upon a chronic carrier of hepatitis B virus, then about 80% of cases progress to chronic hepatitis.

304. The answer is a. *(Cotran, pp 864–868. Chandrasoma, pp 652–653.)* Chronic hepatitis is defined clinically by the presence of elevated serum liver enzymes for longer than 6 months. Liver biopsies in patients with chronic hepatitis may reveal inflammation that is limited to the portal areas (chronic persistent hepatitis), or the inflammation may extend into the adjacent hepatocytes. This inflammation causes necrosis of the hepatocytes (piecemeal necrosis) and is called chronic active hepatitis. These changes are nonspecific and can be seen with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. The finding of hepatocytes with ground-glass eosinophilic cytoplasm is highly suggestive of HBV infection, while fatty

change (steatosis) is suggestive of HCV. A clinically distinct subtype of chronic hepatitis is called chronic autoimmune ("lupoid") hepatitis. This disease occurs in young females who have no serologic evidence of viral disease. These patients have increased IgG levels and high titers of autoantibodies, such as anti-smooth-muscle antibodies and antinuclear antibodies. They also have test positive for LE, which is the basis for the name lupoid hepatitis, but there is no relationship of this disease to systemic lupus erythematosus. The prognosis for these patients is poor, as many progress to cirrhosis.

In contrast to chronic hepatitis, two disorders that are classified as primary biliary diseases are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Primary biliary cirrhosis is primarily a disease of middle-aged females and is characterized by pruritus, jaundice, and hypercholesterolemia. More than 90% of patients have antimitochondrial autoantibodies, particularly to mitochondrial pyruvate dehydrogenase. A characteristic lesion, called the florid duct lesion, is seen in portal areas and is composed of a marked lymphocytic infiltrate and occasional granulomas. Primary sclerosing cholangitis is characterized by fibrosing cholangitis that produces concentric "onion-skin fibrosis" in portal areas. It is associated with chronic ulcerative colitis, one type of inflammatory bowel disease.

305. The answer is c. *(Cotran, pp 868–869, 883.)* Hepatic injury can result from a wide range of drugs, chemicals, and toxins. Peliosis hepatis is an abnormality of the hepatic blood flow that results in sinusoidal dilation and the formation of irregular blood-filled lakes, which may rupture and produce massive intraabdominal hemorrhage or hepatic failure. Peliosis hepatitis is most often associated with the use of anabolic steroids, but more rarely it may be associated with oral contraceptives. Reye's syndrome, characterized by microvesicular fatty change in the liver and encephalopathy, has been related to the use of salicylates in children with viral illnesses. Acetaminophen toxicity results in centrilobular liver necrosis, while estrogens may be related to thrombosis of the hepatic or portal veins. Several hepatic tumors are related to exposure to vinyl chloride, including angiosarcoma and hepatocellular carcinoma.

306. The answer is d. *(Cotran, pp 39–40, 869–873. Chandrasoma, pp 8–10.)* Alcohol can produce hepatic steatosis via several mechanisms, such as increased fatty acid synthesis, decreased triglyceride utilization, decreased

fatty acid oxidation, decreased lipoprotein excretion, and increased lipolysis. Ethanol is taken up by the liver and is converted into acetaldehyde by either alcohol dehydrogenase (the major pathway), microsomal P-450 oxidase, or peroxisomal catalase. These pathways also convert nicotinamide adenine dinucleotide (NAD) to NADH. This excess production of NADH changes the normal hepatic metabolism away from catabolism of fats and toward anabolism of fats (lipid synthesis), resulting in decreased mitochondrial oxidation of fatty acids and increased hepatic production of triglyceride. Ethanol also increases lipolysis and inhibits the release of lipoproteins. Increased lipolysis increases the amount of free fatty acids that reach the liver.

307. The answer is b. *(Cotran, pp 853–855. Rubin, pp 796–798.)* Cirrhosis refers to fibrosis of the liver that involves both central veins and portal triads. This fibrosis is the result of liver cell necrosis and regenerative hepatic nodules. These nodules consist of hyperplastic hepatocytes with enlarged, atypical nuclei, irregular hepatic plates, and distorted vasculature. There is distortion of the normal lobular architecture. These changes diffusely involve the entire liver; they are not focal. It is thought that the fibrosis is the result of fibril-forming collagens that are released by hepatic lipocytes (cells of Ito). These cells are initiated by unknown factors and then are further stimulated by such factors as platelet-derived growth factor and transforming growth factor β.

Cirrhosis used to be classified as being either micronodular (less than 3-mm nodules) or macronodular (greater than 3-mm nodules), but this classification is now not generally used since it does not correlate with the etiology of the cirrhosis. In fact, in time some macronodular cirrhosis will become micronodular. Instead, cirrhosis is classified according to its etiology, such as alcoholic, viral, immune, or idiopathic (cryptogenic). Alcoholic liver damage, hemochromatosis, and biliary cirrhosis (both primary and secondary) typically result in a micronodular pattern. Postnecrotic cirrhosis is typically macronodular, and a mixed or variable pattern may be seen in the cirrhosis of Wilson's disease and α_1 antitrypsin deficiency.

In contrast, enlarged hepatocytes with large purple intranuclear inclusions are suggestive of viral infection, particularly CMV, while increased amounts of iron within Kupffer cells and hepatocytes are seen with hemochromatosis; large red aggregates of PAS-positive, diastase-resistant material within hepatocytes are seen with α_1 antitrypsin deficiency; and perivenular fibrosis with Mallory bodies is seen with alcoholic hepatitis.

308. The answer is c. *(Fawcett, pp 657–660. Cotran, pp 846–847, 853–855.)* Ito cells are fat-containing lipocytes found within the space of Disse of the liver. They participate in the metabolism and storage of vitamin A and also secrete collagen in the normal and the fibrotic (cirrhotic) liver. In normal livers, types I and III collagens (interstitial types) are found in the portal areas and occasionally in the space of Disse or around central veins. In cirrhosis, types I and III collagens are deposited throughout the hepatic lobule. Endothelial cells normally line the sinusoids and demarcate the extrasinusoidal space of Disse. Attached to the endothelial cells are the phagocytic Kupffer cells, which are part of the monocyte-phagocyte system.

309. The answer is e. *(Cotran, pp 873–875. Chandrasoma, pp 655–658.)* Abnormalities of metabolism are associated with a diverse group of liver diseases. Hemochromatosis (excessive accumulation of body iron) may be primary or secondary. Primary hemochromatosis is a genetic disorder of iron metabolism that is inherited as an autosomal recessive disorder. The classic clinical triad for this disease consists of micronodular pigment cirrhosis, diabetes mellitus, and skin pigmentation. The combination of diabetes and skin pigmentation is called bronze diabetes. In the majority of patients serum iron is above 250 mg/dL, serum ferritin is above 500 ng/dL, and iron (transferrin) saturation approaches 100%. In patients with primary hemochromatosis, the excess iron is deposited in the cytoplasm of parenchymal cells of many organs, including the liver and pancreas. Liver deposition of iron leads to cirrhosis, which in turn increases the risk of hepatocellular carcinoma. Iron deposition in the islets of the pancreas leads to diabetes mellitus. Iron deposition in the heart leads to congestive heart failure, which is the major cause of death in these patients. Deposition of iron in the joints leads to arthritis, while deposition in the testes leads to atrophy. Secondary hemochromatosis, also called systemic hemosiderosis, is most common in patients with hemolytic anemias, such as thalassemia. Excess iron may also be due to an excessive number of transfusions or to increased absorption of dietary iron. In idiopathic (primary) hemochromatosis, iron accumulates in the cytoplasm of parenchymal cells, but in secondary hemochromatosis the iron is deposited in the mononuclear phagocytic system. In both conditions the iron is deposited as hemosiderin, which stains an intense blue color with Prussian blue stain. Since the iron deposition does not usually occur in the parenchymal cells in sec-

ondary hemochromatosis, there usually is no organ dysfunction or injury.

310. The answer is d. *(Cotran, pp 869, 875–876. Chandrasoma, pp 655–658.)* Reye's syndrome (RS) is an acute postviral illness that is seen mainly in children. It is characterized by encephalopathy, microvesicular fatty change of the liver, and widespread mitochondrial injury. Electron microscopy (EM) reveals large budding or branching mitochondria. The mitochondrial injury results in decreased activity of the citric acid cycle and urea cycle and defective β-oxidation of fats, which then leads to the accumulation of serum fatty acids. The typical patient presents several days after a viral illness with pernicious vomiting. RS is associated with hyperammonemia, elevated serum free fatty acids, and salicylate (aspirin) ingestion.

In contrast, Wilson's disease, which is related to excess copper deposition within the liver and basal ganglia of the brain, is characterized by varying liver disease and neurologic symptoms. The liver changes vary from fatty change to jaundice to cirrhosis, while the neurologic symptoms consist of a Parkinson-like movement disorder and behavioral abnormalities. A liver biopsy may reveal steatosis, Mallory bodies, necrotic hepatocytes, or cholestasis. Increased copper can be demonstrated histologically using the rhodamine stain. α_1 antitrypsin deficiency causes both liver disease and lung disease, especially panacinar emphysema. Liver biopsies reveal red blobs within the cytoplasm of hepatocytes that are PAS-positive and diastase-resistant. Dubin-Johnson syndrome is associated with conjugated hyperbilirubinemia that results from decreased hepatic excretion of conjugates of bilirubin.

311. The answer is c. *(Cotran, pp 878–880. Rubin, pp 795–796.)* Diseases of the biliary tract may lead to manifestations of jaundice, and, if prolonged and severe, may lead to cirrhosis. These diseases can be classified as either primary or secondary. Causes of secondary biliary cirrhosis include biliary atresia, gallstones, and carcinoma of the head of the pancreas. Histologic examination of the liver may reveal bile stasis in the interlobular bile ducts and bile duct proliferation in the portal areas. Two primary causes include primary biliary cirrhosis and primary sclerosing cholangitis. Primary sclerosing cholangitis (PSC) is characterized by fibrosing cholangitis that produces concentric "onion-skin" fibrosis in portal areas. It is highly associated with chronic ulcerative colitis. Abnormal development of the biliary tract

may lead to several abnormalities, including von Meyenburg's complex (small bile duct hamartomas near normal portal tracts) and Caroli's disease, which is characterized by segmental dilation of the larger intrahepatic bile ducts. There is an increased risk of developing cholangiocarcinoma, a malignancy of bile ducts, in patients with PSC. Primary biliary cirrhosis (PBC) is primarily a disease of middle-aged women and is characterized by pruritus, jaundice, and hypercholesterolemia. More than 90% of patients have antimitochondrial autoantibodies, particularly the M2 antibody to mitochondrial pyruvate dehydrogenase. A characteristic lesion, called the florid duct lesion, is seen in portal areas and is composed of a marked lymphocytic infiltrate and occasional granulomas.

312. The answer is c. *(Cotran, pp 358–359, 395–397.)* There are numerous organisms other than viruses that can cause infections of the liver and result in liver disease. Bacteria may cause nonsuppurative or suppurative infections. The latter can result in the formation of pyogenic liver abscesses, which clinically cause high fever, right upper quadrant abdominal pain, and hepatomegaly. There are several parasites that can cause hepatic disease. Infection with the ova of *Echinococcus granulosus* may produce a hydatid cyst within the liver, which is characterized by a thick, acellular, laminated eosinophilic wall (seen on x-ray as a calcified wall). The fluid within the cyst is granular and contains numerous small larval capsules with scoleces, called "brood capsules." Spillage of this cyst fluid at the time of surgery may produce anaphylactic shock and be deadly. Amebic trophozoites of *E. histolytica* reach the liver from the colonic submucosa and produce multiple, small amebic liver abscesses that coalesce to form large cysts with thick "anchovy paste" inside. Trophs of *Entamoeba* can be found within the wall of the cyst. Schistosomiasis (*Schistosoma mansoni* in the Middle East and *S. japonicum* in the Far East) can cause liver disease, as the adult worm lives in the intestinal venous plexus and eggs may reach the liver via the portal vein. Acute disease results in granulomas, while chronic infection produces a characteristic "pipe stem" fibrosis. Oriental cholangiohepatitis, seen in eastern Asia, is characterized by infection of bile ducts with *Clonorchis sinensis.*

313. The answer is b. *(Cotran, pp 886–888.)* Neoplasms of the liver, either benign or malignant, have characteristic microscopic or gross appearances. Benign tumors of the liver include hemangiomas (the most com-

mon), focal nodular hyperplasias, nodular regenerative hyperplasias, and adenomas. Hemangiomas are characterized by numerous small endothelial-lined spaces filled with blood. The lack of erythrocytes or blood would raise the possibility of the lesion being a lymphangioma, while pleomorphic or atypical endothelial cells would suggest the possibility of an angiosarcoma. Focal nodular hyperplasia, which has a characteristic gross appearance of a central stellate scar within the tumor, microscopically reveals hepatic nodules surrounded by fibrous bands having numerous proliferating bile ducts. This type of tumor is related to birth-control pills, but has no association with malignancy. In contrast, nodular regenerative hyperplasia involves the entire liver and forms multiple spherical nodules. Histologic sections reveal plump hepatocytes surrounded by rims of atrophic cells. Nodular regenerative hyperplasia is clinically important because it is associated with the subsequent development of portal hypertension. Two types of hepatic adenomas are the liver cell adenoma and the bile duct adenoma. Liver cell adenomas are seen in female patients taking birth-control pills. These adenomas may bleed, but are not associated with malignancy. Histologically, cords of hepatocytes are present, but there is no lobular architecture.

314. The answer is d. *(Cotran, pp 888–891. Chandrasoma, pp 659–662.)* The most common primary malignancy of the liver is the hepatocellular carcinoma (hepatoma). These tumors are associated with certain viral infections (hepatitis B and hepatitis C viruses), aflatoxin (produced by *Aspergillus flavus*), and cirrhosis. Microscopic sections of these tumors reveal pleomorphic tumor cells that form trabecular patterns, which are similar to the normal architecture of the liver. Hepatomas may secrete α fetoprotein (AFP), but this tumor marker may also be seen in yolk sac tumors or fetal neural tube defects. Clinically, hepatocellular carcinomas have a tendency to grow into the portal vein or the inferior vena cava and may be associated with several types of paraneoplastic syndromes, such as polycythemia, hypoglycemia, and hypercalcemia. There is a microscopic fibrolamellar variant of hepatocellular carcinoma that is seen more often in females, is not associated with AFP, is grossly encapsulated, and has a better prognosis. It is important to compare the characteristics of hepatocellular carcinomas with those of another type of primary tumor of the liver, namely cholangiocarcinoma, which is a malignancy of bile ducts. This tumor is associated with Thorotrast and infection with the liver fluke (*C. sinensis*), but it is not associated with cirrhosis. Histologically, the tumor

cells contain cytoplasmic mucin, which is not found in hepatomas. Instead, these malignant cells may contain cytoplasmic bile. Malignant metastatic tumors are the most common tumors found in the liver. Grossly there may be multiple or single nodules, which microscopically usually resemble the primary tumor. For example, metastatic colon cancer to the liver histologically reveals adenocarcinoma. Metastatic disease to the liver usually does not cause functional abnormalities of the liver itself, and the liver enzymes and bilirubin levels in the blood are usually normal. Angiosarcomas are highly aggressive malignant tumors that arise from the endothelial cells of the sinusoids of the liver. Their development is associated with certain chemicals, such as vinyl chloride, arsenic, and Thorotrast. A malignant tumor of the liver that is found in children is the hepatoblastoma. Microscopically, these tumors consist of ribbons and rosettes of fetal embryonal cells.

315. The answer is b. *(Cotran, pp 893–895.)* Gallstones, which affect 10 to 20% of the adult population in developed countries, are divided into two main types. Cholesterol stones are pale yellow, hard, round, radiographically translucent stones that are most often multiple. Their formation is related to multiple factors including female sex hormones (such as with oral contraceptives), obesity, rapid weight reduction, and hyperlipidemic states. Their prevalence approaches 75% in some Native American populations. 7-α-hydroxylase is an enzyme involved in converting cholesterol to bile acids. Decreased functioning of this enzyme, such as with a congenital deficiency or inhibition by clofibrate, causes excess secretion of cholesterol and an increased incidence of cholesterol gallstones. The other main type of gallstones are pigment stones, which are brown or black in color and composed of bilirubin calcium salts. They are found more commonly in Asian populations and are related to chronic hemolytic states, diseases of the small intestines, and bacterial infections of the biliary tree. In contrast to 7-α-hydroxylase and bile acid synthesis, 1-α-hydroxylase is involved in vitamin D synthesis, while 11-hydroxylase, 17-hydroxylase, and 21-hydroxylase are all enzymes found in the adrenal cortex. A deficiency of these enzymes is seen with congenital adrenal hyperplasia.

316. The answer is c. *(Cotran, pp 895–898. Chandrasoma, pp 663, 665–667.)* Patients with obstruction of the common bile duct present clinically with Charcot's triad, which consists of biliary colic, high fever (sec-

ondary to cholangitis), and jaundice. Jaundice secondary to extrahepatic obstruction is associated with normal hemoglobin levels, normal serum indirect bilirubin levels, and increased levels of direct bilirubin and alkaline phosphatase. Common causes of obstruction of the common bile duct include cancer in the head of the pancreas and obstruction by a gallstone. Clinically, these two can be differentiated using Courvoisier's law, which states that in a patient with obstructive jaundice, the presence of a palpable gallbladder is indicative of obstruction due to a cancer of the head of the pancreas. This is because the obstruction causes the gallbladder to dilate. In contrast, most patients with gallstones have cholecystitis, which is associated with a thickened gallbladder wall that prevents the gallbladder from dilating. Therefore, if the obstruction is due to a gallstone, the gallbladder will not dilate and will not be palpable. Cholecystitis (inflammation of the gallbladder) may be either an acute or a chronic response. In acute cholecystitis, which may be associated with a stone (calculous type) or lack a stone (acalculous type), there is an acute inflammatory response that consists mainly of neutrophils. Acute cholecystitis usually presents with right upper quadrant pain and may constitute a surgical emergency. Chronic cholecystitis, which is associated with stones in more than 90% of cases, has a variable histologic appearance, but findings include a thickened muscular wall, scattered chronic inflammatory cells (lymphocytes), and outpouchings of the mucosa (Rokitansky-Aschoff sinuses).

317. The answer is c. *(Cotran, pp 477–481.)* Cystic fibrosis (CF) is one of the most common lethal genetic diseases that affects white populations (1/2000). The primary abnormality in patients with cystic fibrosis involves the epithelial transport of chloride. Normally, binding of a ligand to a membrane surface receptor activates adenyl cyclase, which leads to increased intracellular cAMP. This in turn activates protein kinase A, which phosphorylates the cystic fibrosis transmembrane conductance regulator (CFTR), causing it to open and release chloride ions. Sodium ions and water then follow the chloride ions to maintain the normal viscosity of mucus. The most common abnormality in patients with CF involves decreased glycosylation of the CFTR, which then does not become incorporated into the cell membrane. A lack of chloride channels then causes decreased chloride, sodium, and water secretion, all of which together results in a very thick mucus (the other name of CF is mucoviscidosis). These thick mucus plugs can block the pancreatic ducts, causing fibrosis

and cystic dilation of the ducts (hence the name cystic fibrosis). Decreased excretion of pancreatic lipase leads to malabsorption of fat and steatorrhea, which may lead to deficiency of fat-soluble vitamins. Thick mucus may also cause intestinal obstruction in neonates, a condition called meconium ileus. Abnormal mucus in the pulmonary tree leads to atelectasis, fibrosis, bronchiectasis, and recurrent pulmonary infections, especially with *Staphylococcus aureus* and *Pseudomonas* species. Obstruction of the vas deferens and seminal vesicles in males leads to sterility, while obstruction of the bile duct produces jaundice. This child's skin tasted salty because of increased sweat electrolytes, the result of decreased reabsorption of electrolytes from the lumina of sweat ducts.

318. The answer is e. *(Cotran, pp 904–907.)* Inflammation of the pancreas (pancreatitis) may be either acute or chronic. Patients with acute pancreatitis typically present with abdominal pain that is associated with increased serum levels of pancreatic enzymes (amylase and lipase). Most cases of acute pancreatitis are associated with either alcohol ingestion or biliary tract disease (gallstones). Alcohol ingestion is the most common cause, and pancreatitis usually follows an episode of heavy drinking. Other, less frequent causes include hypercalcemia, hyperlipidemias, shock, infections (CMV and mumps), trauma, and drugs. Acute pancreatitis usually presents as a medical emergency. Symptoms of acute pancreatitis include abdominal pain that is localized to the epigastrium and radiates to the back, vomiting, and shock, the latter being the result of hemorrhage and kinins released into the blood. In severe pancreatitis there may be hemorrhage in the subcutaneous tissue around the umbilicus (Cullen's sign) and in the flanks (Turner's sign). Activation of the plasma coagulation cascade may lead to disseminated intravascular coagulopathy (DIC). Laboratory confirmation of pancreatic disease involves the finding of elevated serum amylase levels in the first 24 h and rising lipase levels over the next several days. Other pancreatic enzymes, such as trypsin, chymotrypsin, and carboxypeptidases, have not been as useful for diagnosis as have amylase and lipase. Complications seen in patients who survive the acute attack include pancreatic abscess formation, pseudocyst formation, or duodenal obstruction. Diabetes mellitus almost never occurs after a single attack of pancreatitis.

319. The answer is b. *(Cotran, pp 907–909.)* Chronic pancreatitis is characterized histologically by chronic inflammation and irregular fibrosis

of the pancreas. The major cause of chronic pancreatitis in adults is chronic alcoholism, while in children the major cause is cystic fibrosis. Recurrent attacks of acute pancreatitis also result in the changes of chronic pancreatitis. Hypercalcemia and hyperlipidemia also predispose to chronic pancreatitis (since they are causes of acute pancreatitis), while in as many as 10% of patients, recurrent pancreatitis is associated with pancreas divisum. This condition refers to the finding of the accessory duct being the major excretory duct of the pancreas. Chronic ductal obstruction may be a cause of chronic pancreatitis and may be associated with gallstones, but it is more appropriate to relate gallstones with acute ductal obstruction and resultant acute pancreatitis. Complications of chronic pancreatitis include pancreatic calcifications, pancreatic cysts and pseudocysts, stones within the pancreatic ducts, diabetes, and fat malabsorption, which results in steatorrhea and decreased vitamin K levels.

320. The answer is d. *(Cotran, p 909.)* Pseudocysts of the pancreas are so named because the cystic structure is essentially unlined by any type of epithelium. True cysts, wherever they are found in the body, are always lined by some type of epithelium, whether columnar cell, glandular, squamous, or flattened cuboidal cell. The pancreatic pseudocyst is most commonly found against a background of repeated episodes of pancreatitis. Eventual mechanical large duct obstruction by an inflammatory process per se, periductal fibrosis, or an abscess along with inspissated duct fluid from secretions and enzymes leads to the expanding mass. The mass lesion may be located between the stomach and liver, between the stomach and the colon or transverse mesocolon, or in the lesser sac. Drainage or excision is necessary for adequate treatment. Acute bacterial infection may complicate the course.

321. The answer is b. *(Cotran, pp 910–911.)* Most carcinomas of the pancreas arise from the ductal epithelium of the pancreas and are adenocarcinomas. Pancreatic cancers are highly malignant tumors that account for about 5% of cancer deaths in the U.S. Their occurrence has increased threefold in the past 40 years, mainly as a result of smoking and exposure to chemical carcinogens. They are more frequent in diabetics than nondiabetics. Most cases are found in the head of the pancreas (70%) and produce symptoms such as obstructive jaundice and migratory thrombophlebitis, usually in the superficial veins of the leg (Trousseau's sign). Courvoisier's

law states that obstructive jaundice in the presence of a dilated gallbladder is most suggestive of cancer of the head of the pancreas. About 20% of pancreatic adenocarcinomas are found in the body and 10% are found in the tail. Tumors located in the tail of the pancreas present late, when therapy is no longer possible. The major symptoms of pancreatic carcinomas in general include weight loss, abdominal pain (usually the first symptom), back pain, and malaise. Surgery for a tumor of the head of the pancreas may involve pancreatoduodenectomy, which is called a Whipple procedure.

322. The answer is a. *(Cotran, pp 926–928.)* Functional islet cell tumors of the pancreas secrete specific substances that result in several syndromes. Pancreatic gastrinomas (tumors of the G cells of the pancreas) secrete gastrin and are a cause of Zollinger-Ellison syndrome. This syndrome consists of intractable gastric hypersecretion, severe peptic ulceration of the duodenum and jejunum, and high serum levels of gastrin. The majority of gastrinomas are malignant. Insulinomas (tumors of β cells) are the most common islet cell neoplasm and are usually benign. Symptoms include low blood sugar, hunger, sweating, and nervousness. Glucagonomas (islet cell tumors of the α cells) secrete glucagon and are characterized by mild diabetes, anemia, venous thrombosis, severe infections, and a migratory, necrotizing, erythematous skin rash. δ cell tumors, which secrete somatostatin, produce a syndrome associated with mild diabetes, gallstones, steatorrhea, and hypochlorhydria. The majority of δ cell tumors are malignant. D1 tumors [also called vasoactive intestinal peptide tumors (VIPomas)] produce Verner-Morrison syndrome, which is characterized by explosive, profuse diarrhea with hypokalemia and hypochlorhydria. This combination of symptoms is referred to as pancreatic cholera.

323. The answer is c. *(Cotran, pp 926–927.)* Insulinomas are tumors that originate from the β cells of the islets of Langerhan in the pancreas. Symptoms that result from the excess and uncontrolled secretion of insulin include low blood sugar (hypoglycemia) with subsequent hunger, sweating, and nervousness. These symptoms are usually produced by fasting, alcohol, or exercise. The classic triad of symptoms associated with insulinomas is called Whipple's triad and consists of hypoglycemia, symptoms of hypoglycemia, and relief of these symptoms with glucose intake. C peptide, a product of insulin synthesis, has no known physiologic function;

however, its levels can be useful in the evaluation of patients who present with decreased serum glucose levels and increased insulin levels. In these patients, increased levels of C peptide indicate endogenous insulin secretion, such as from an insulinoma. In contrast, decreased levels of C peptide indicate that the insulin that is present is exogenous insulin, because in the process of manufacturing insulin the C peptide is removed. Exogenous insulin injection may be fictitious injection, such as with Munchausen syndrome.

324. The answer is a. *(Cotran, pp 913–917.)* Diabetes mellitus (DM) results from the clinical effects of decreased action of insulin, such as increased serum glucose levels (hyperglycemia). DM is divided into several clinical groups. First, diabetes can be classified as being either primary ("idiopathic") or secondary, i.e., secondary to diseases destroying the islets, such as pancreatitis, hemochromatosis, or tumors, or to substances that have antagonistic effects to insulin, such as corticosteroids, growth hormone, or glucagon. Primary DM can be classified as being either dependent upon insulin [type 1 (insulin-dependent DM)] or not dependent upon insulin [type 2 (non-insulin-dependent DM)]. IDDM is also called juvenile-onset DM because it is primarily found in children, the peak incidence being at the time of puberty. These patients usually present with symptoms such as polyuria, polydipsia, polyphagia, weight loss, metabolic acidosis, and/or electrolyte imbalance.

325. The answer is b. *(Cotran, pp 915–926.)* There are many clinical and pathophysiologic differences between type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus (IDDM) occurs most often in children, while NIDDM is found in adults. Type 2 is often associated with obesity, but children with IDDM are of normal weight, even though they have an increased appetite (polyphagia). The defect in IDDM is decreased blood insulin levels due to a decrease in the number of insulin-producing β cells. This destruction is autoimmune-mediated, as the majority of patients with type 1 DM have circulating islet cell antibodies [including anti–glutamic acid decarboxylase (anti-GAD)]. Many patients with type 2 DM, in contrast, have normal or increased blood insulin levels. These patients nonetheless have hyperglycemia because of a decrease in the number of insulin receptors in adipocytes and skeletal muscle cells (insulin resistance). Type 1 DM

is linked to HLA types DR3, DR4, and DR3/4, while type 2 DM is not linked to certain HLA types. Other genetic factors (such as the incidence of the disease in relatives) are strong in type 2 DM and much weaker in type 1 DM. There are also histologic differences between these two groups when the islets of Langerhans are examined. The islets of patients with IDDM reveal atrophy, fibrosis, and possibly a lymphocytic infiltrate (insulitis). The islets of patients with NIDDM lack the inflammation, but may show focal atrophy with amyloid deposition. This amyloid is composed of amylin, a normal product of the β cells. Other factors associated with IDDM and not NIDDM include HLA-D linkage, possible viral cause (there is homology between coxsackievirus and GAD), and ingesting cow's milk early in life. It is important, however, to remember that the chronic, long-term complications found in blood vessels, kidneys, eyes, and nerves occur in both of these types of DM.

326. The answer is d. *(Cotran, pp 919–920. Henry, pp 637–638.)* The major complications of hyperglycemia, as seen in individuals with diabetes mellitus, are related to two mechanisms, nonenzymatic glycosylation of proteins and abnormalities in polyol pathways. Nonenzymatic glycosylation involves the attachment of glucose to proteins forming unstable Schiff bases, which may rearrange to form more stable Amadori-type products that eventually may form irreversible advanced glycosylation end products (AGEs). These end products may then cause cross-linking between collagen molecules. This cross-linking in the BM of endothelial cells can trap LDL in vessel walls, accelerating atherosclerosis. In addition, albumin and IgG may bind to glycosylated basement membranes, causing the increased thickness of basement membranes that is characteristic of diabetic microangiopathy. Binding of AGEs to different receptors may have many different effects, such as stimulation of monocyte emigration, release of cytokines, increased endothelial permeability, and increased proliferation of fibroblasts and smooth-muscle cells. In addition, glycosylation of hemoglobin produces glycosylated hemoglobin (Hb A_{1c}), which can be used to measure long-term control of an individual with diabetes mellitus. In contrast, a lab test for autoimmune hemolytic anemia is the Coombs test (direct antiglobulin test); for cystic fibrosis the sweat chloride test is used; for diabetes insipidus serum osmolality and serum sodium levels are tested; and for megaloblastic anemia serum B_{12} and folate levels are tested.

327. The answer is e. *(Cotran, pp 920–924, 966–968.)* Diabetes may produce abnormalities that affect any part of the kidney, such as the glomerulus, the blood vessels (benign nephrosclerosis), the tubules (Armanni-Ebstein lesions, which refers to vacuolization of the cells of the proximal convoluted tubules), the interstitium, and the pelvis (infection leads to pyelonephritis and acute papillary necrosis). Diabetic lesions of the glomerulus include capillary basement thickening, diffuse glomerulosclerosis (increase in mesangium and mesangial cells), and nodular glomerulosclerosis. The latter refers to oval hyaline masses at the periphery of the glomerulus and is also called Kimmelstiel-Wilson disease. Nodular glomeruloscleroses may resemble amyloid, and, if they are present, amyloid staining should be done. Other characteristic lesions found in the glomerulus include "capsular drops" (round nodules found between Bowman's capsule and the parietal epithelium) and "fibrin caps" (subendothelial accumulations along capillary loops).

Urinary System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

328. The basic abnormality producing metabolic alkalosis is

a. Decreased arterial hydrogen ion concentration with increased arterial bicarbonate causing arterial pH to be greater than 7.4
b. Decreased respirations with increased arterial carbon dioxide and hydrogen ion concentrations causing arterial pH to be less than 7.4
c. Increased arterial hydrogen ion concentration with decreased arterial bicarbonate causing arterial pH to be less than 7.4
d. Increased arterial hydrogen ion concentration with decreased arterial bicarbonate causing arterial pH to be greater than 7.4
e. Increased respirations with decreased arterial carbon dioxide and hydrogen ion concentrations causing arterial pH to be greater than 7.4

329. An anxious 19-year-old female presents with perioral numbness and carpopedal spasm. Laboratory examination reveals decreased P_{CO_2} and decreased bicarbonate. Which one of the listed conditions is most consistent with these findings?

a. Metabolic acidosis due to ketoacidosis
b. Metabolic acidosis due to renal tubular acidosis
c. Metabolic alkalosis due to thiazide diuretic
d. Respiratory acidosis due to hypoventilation
e. Respiratory alkalosis due to hyperventilation

330. In utero bilateral renal agenesis is most likely to produce

a. Anencephaly
b. Gastroschisis
c. Oligohydramnios
d. Polycythemia
e. Retrolental fibroplasia

331. An 8-month-old male infant presents with progressive renal and hepatic failure. Despite intensive medical therapy, the infant dies. At the time of autopsy, the external surfaces of his kidneys are found to be smooth, but cut section reveals numerous cysts that are lined up in a row. What is the mode of inheritance of this renal abnormality?

a. Autosomal dominant
b. Autosomal recessive
c. X-linked dominant
d. X-linked recessive
e. Mitochondrial

332. What is the most likely cause of the combination of generalized edema, hypoalbuminemia, hypercholesterolemia, marked proteinuria, and fatty casts and oval fat bodies in the urine?

a. Nephritic syndrome
b. Nephrotic syndrome
c. Acute renal failure
d. Renal tubular defect
e. Urinary tract infection

333. A 35-year-old female recovering from hepatitis B develops hematuria, proteinuria, and red cell casts in the urine. Which of the following would best describe the changes within the kidney in this patient?

a. Plasma cell interstitial nephritis
b. IgG linear fluorescence along the glomerular basement membrane
c. Granular deposits of antibodies in the glomerular basement membrane
d. Diffuse thickening of the glomerular basement membrane by subepithelial immune deposits
e. Nodular hyaline glomerulosclerosis

334. Treatment with steroids would most likely produce a beneficial response in a young child with

a. Acute cystitis
b. Acute pyelonephritis
c. Focal segmental glomerulosclerosis
d. Minimal change disease
e. X-linked agammaglobulinemia

335. A 28-year-old male with AIDS presents with moderate proteinuria and hypertension. Histologic sections of the kidney reveal the combination of normal-appearing glomeruli and occasional glomeruli that have deposits of hyaline material. No increased cellularity or necrosis is noted in the abnormal glomeruli. Additionally, there is cystic dilation of the renal tubules, some of which are filled with proteinaceous material. Electron microscopy reveals focal fusion of podocytes, and immunofluorescence examination finds granular IgM/C3 deposits. What is the best diagnosis for this renal abnormality?

a. Diffuse proliferative glomerulonephritis (DPGN)
b. Focal segmental glomerulonephritis (FSGN)
c. Focal segmental glomerulosclerosis (FSGS)
d. Membranous glomerulopathy (MGN)
e. Minimal change disease (MCD)

336. A 7-year-old boy presents with bilateral swelling around his eyes. His parents state that the child's eyes have become "puffy" over the past several weeks, and his urine has become cocoa-colored. Physical examination reveals bilateral periorbital edema, but peripheral edema is not found. The boy is afebrile and his blood pressure is slightly elevated. A urinary dipstick reveals mild proteinuria, while microscopic examination of the boy's urine reveals hematuria with red blood cell casts. Laboratory tests reveal increased ASO titers and decreased serum C3 levels, but C2 and C4 levels are normal. A throat swab for streptococci is negative. A microscopic section from the kidney reveals increased numbers of cells within the glomeruli. An electron microscopic section of the kidney reveals large electron-dense deposits in the glomeruli that are located between the basement membrane and the podocytes. The foot processes of the podocytes are otherwise unremarkable. Which one of the following renal diseases most likely produced the abnormalities in this young boy?

a. Acute post-streptococcal glomerulonephritis
b. Focal segmental glomerulonephritis
c. Focal segmental glomerulosclerosis
d. Membranous glomerulonephritis
e. Minimal change disease

337. Immune complexes located within the glomerular basement membrane would most likely be found in a patient with

a. Acute glomerulonephritis (GN)
b. Membranous GN
c. Type I membranoproliferative glomerulonephritis (MPGN)
d. Type II MPGN
e. IgA nephropathy

338. A 21-year-old female presents because her urine has turned a brown color. She states that about 2 months ago her urine turned brown 2 days after a cold and stayed brown for about 3 days. At the current time a urinalysis reveals 2+ blood with red cells and red cell casts. Further laboratory tests include a complete blood count (CBC), serum electrolytes, BUN, creatinine, glucose, antinuclear antibodies (ANAs), and serum complement levels (C3 and C4). All of these tests are within normal limits. Immunofluorescence examination of a renal biopsy from this patient reveals the presence of large, irregular deposits of IgA/C3 in the mesangium. A linear staining pattern is not found. What is the most likely diagnosis for this patient?

a. Berger's disease
b. Focal segmental glomerulosclerosis
c. Goodpasture's disease
d. Lipoid nephrosis
e. Membranoproliferative glomerulonephritis

339. Rapidly progressive glomerulonephritis is characterized histologically by

a. Crescents in the glomeruli
b. Fibrinoid necrosis of the afferent arterioles
c. Fibromuscular hyperplasia of the renal artery
d. Neutrophils in the interstitium
e. Splitting of the basement membrane by mesangial cells

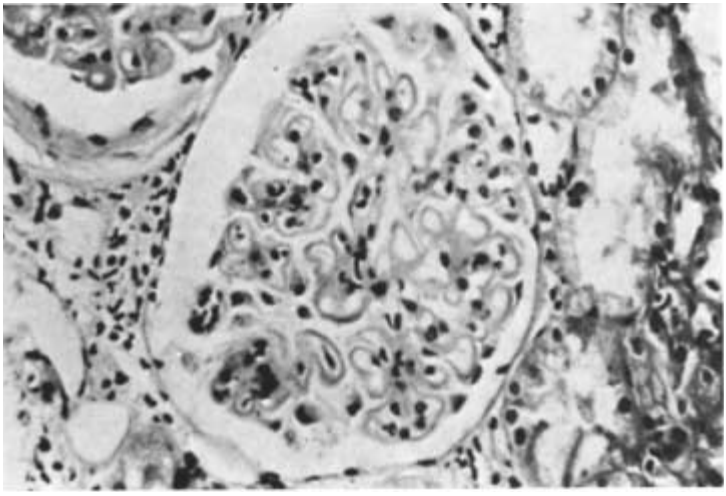
340. A linear pattern of immunoglobulin deposition along the glomerular basement membrane that can be demonstrated by immunofluorescence is typical of

a. Lupus nephritis
b. Diabetic glomerulopathy
c. Goodpasture's syndrome
d. Goldblatt's kidney
e. Renal vein thrombosis

341. A characteristic histologic feature of class IV lupus nephritis is

a. "Holly leaf" mesangial deposits
b. "Spike and dome" appearance of the basement membrane
c. "String of popcorn" immunofluorescence pattern
d. "Tram-track" splitting of the basement membrane
e. "Wire-loop" appearance of the glomerular capillaries

342. Marked thickening of the glomerular basement membrane, as shown in the photomicrograph below, may be seen in

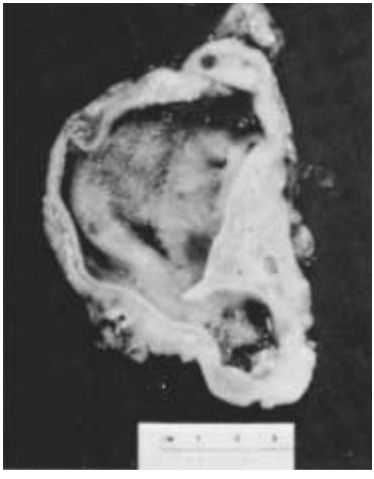


a. Lipoid nephrosis
b. Diabetes mellitus
c. Goodpasture's syndrome
d. Acute pyelonephritis
e. Chronic glomerulonephritis

343. Histologic sections of a kidney reveal patchy necrosis of epithelial cells of both the proximal and distal tubules with flattening of the epithelial cells, rupture of the basement membrane (tubulorrhexis), and marked interstitial edema. Acute inflammatory cells are not seen. What is the best diagnosis?

a. Acute pyelonephritis
b. Acute tubular necrosis
c. Chronic glomerulonephritis
d. Chronic pyelonephritis
e. Diffuse cortical necrosis

344. The gross appearance of the kidney shown below is most compatible with which of the following conditions?



a. Cystic renal dysplasia
b. Acute pyelonephritis
c. Chronic pyelonephritis
d. Acute glomerulonephritis
e. Chronic glomerulonephritis

345. During a routine physical examination, a 42-year-old female is found to have an elevated blood pressure of 150/100 mmHg. Workup reveals a small left kidney and a normal-sized right kidney. Laboratory examination reveals elevated serum renin levels. Further workup reveals that renal vein renin levels are increased on the left but decreased on the right. This patient's hypertension is most likely the result of

a. Atherosclerotic narrowing of the left renal artery
b. Atherosclerotic narrowing of the right renal artery
c. Fibromuscular hyperplasia of the left renal artery
d. Fibromuscular hyperplasia of the right renal artery
e. Hyaline arteriolosclerosis

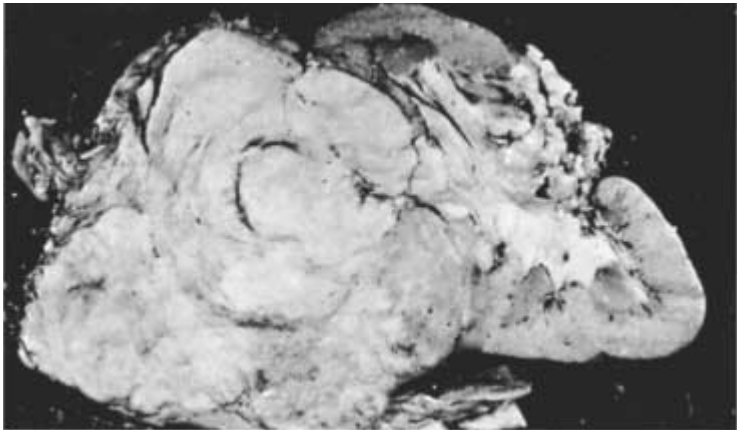
346. Which one of the following gross appearances of a kidney is most characteristic of malignant nephrosclerosis?

a. Broad U-shaped cortical scars overlying dilated calyces in renal poles
b. Depressed cortical areas overlying necrotic papillae of varying stages
c. Multiple small petechial hemorrhages on the surface
d. Multiple small white areas on the surface
e. Wedge-shaped (i.e., V-shaped) pale cortical scars

347. The combination of severe acute flank pain and microscopic hematuria is suggestive of

a. Cholelithiasis
b. Choledocholithiasis
c. Kidney tumor
d. Urinary bladder tumor
e. Urolithiasis

348. The kidney shown in the photomicrograph below exhibits a tumor that originated in the upper pole. Histologic sections from this lesion would most likely reveal



a. Clear cell carcinoma
b. Signet cell carcinoma
c. Small cell carcinoma
d. Squamous cell carcinoma
e. Transitional cell carcinoma

349. Which one of the listed individuals is most likely to have a tumor that has a histologic appearance characterized by undifferentiated mesenchymal cells with immature tubules and abortive glomerular formation?

a. A 2-week-old infant with a midepigastric mass, projectile vomiting, and normal urinary hydroxy-indoleacetic acid (HIAA)
b. An 8-month-old infant with an abdominal mass and normal urinary vanillylmandelic acid (VMA)
c. A 14-month-old infant with an abdominal mass and increased urinary VMA
d. A 13-year-old child with basophilic stippling of erythrocytes and increased urinary aminolevulinic acid (ALA)
e. A 39-year-old female with abdominal cramps, watery diarrhea, periodic facial flushing, wheezing, and increased urinary HIAA

350. Physical examination of a 3-day-old male infant reveals urine leaking from the area of the umbilicus. What is the correct diagnosis?

a. Balanoposthitis
b. Meckel's cyst
c. Meckel's diverticulum
d. Omphalocele
e. Urachal fistula

351. A 19-year-old male presents with dysuria and a yellow-green urethral discharge. No prostatic pain is present. Microscopic examination of the discharge reveals numerous neutrophils, but no bacteria are present. Which one of the following is the best diagnosis for this individual given only this information?

a. Acute cystitis
b. Acute prostatitis
c. Gonococcal urethritis
d. Interstitial cystitis
e. Nongonococcal urethritis

352. A biopsy of the mucosa of the urinary bladder from an individual with acute cystitis due to infection with *Escherichia coli* would most likely reveal

a. An infiltrate of lymphocytes and plasma cells
b. An infiltrate of neutrophils
c. Inflammation with eosinophils
d. Noncaseating granulomas
e. Sheets of macrophages with granular cytoplasm

353. A 49-year-old male who is a long-term smoker presents with frequency and hematuria. Histologic examination of sections taken from an exophytic lesion of the urinary bladder reveal groups of atypical cells with frequent mitoses forming finger-like projections that have thin, fibrovascular cores. These groups of atypical cells do not extend into the lamina propria and muscularis. No glands or keratin production are found. What is the most accurate diagnosis for this bladder tumor?

a. Adenocarcinoma, noninvasive
b. Inverted papilloma
c. Transitional cell carcinoma in situ
d. Papillary transitional cell carcinoma (TCC), noninvasive
e. Squamous cell carcinoma in situ

Urinary System

Answers

328. The answer is a. *(Ayala, pp 132–135. Isselbacher, pp 255–260.)* The uncomplicated acid-base disorders, which may be of metabolic or respiratory origin, are classified as being metabolic acidosis, metabolic alkalosis, respiratory acidosis, or respiratory alkalosis. The pH (normal 7.38 to 7.44) determines whether the primary process is an acidemia (pH < 7.38) or an alkalemia (pH > 7.44). (Note that compensation for an alkalosis is always acidosis, while compensation for acidosis is always alkalosis, but in either case, compensation does not bring the pH into the normal range.) With metabolic disorders, examine the bicarbonate (normal 21 to 28 mM). Bicarbonate levels in metabolic acidosis are <21 mM, while those in metabolic alkalosis are >28 mM. Similarly, with respiratory disorders, examine the Pa_{CO_2} (normal P_{CO_2} is 35 to 40 mmHg arterial, 40 to 45 mmHg venous). In a patient with respiratory alkalosis the Pa_{CO_2} is <35, while with respiratory acidosis the Pa_{CO_2} is 40.

In metabolic acidosis, increased serum acid (increased hydrogen ion concentration) causes a decrease in serum pH and a decrease in serum bicarbonate concentration. The causes of metabolic acidosis are broken down clinically into two groups: those with a normal anion gap and those with an increased anion gap. (The serum anion gap is found by taking the serum sodium concentration and subtracting the concentration of two anions, namely chloride and bicarbonate. Normally, the anion gap is between 10 and 16 meq/L.) Increased anion gaps result from increased unmeasured anions, such as may occur in the following clinical situations: ketoacidosis (increased β-hydroxybutyric acid and acetoacetic acid, seen with diabetic ketoacidosis); lactic acidosis (hypoxic conditions); chronic renal failure (uremia); and ingestion of certain substances such as salicylates, ethylene glycol, methanol, and formaldehyde. A normal anion gap metabolic acidosis may result from either loss of bicarbonate (diarrhea) or loss of renal regeneration of bicarbonate, seen with renal tubular acidosis type 1 (decreased excretion of titratable acid, i.e., NH_4^+) and renal tubular acidosis type 4. In a patient with metabolic acidosis, the body tries to com-

bat the decreased pH by increasing the respiratory rate (tachypnea), which helps to raise the pH by blowing off CO_2 and decreasing the serum CO_2 (hypocapnia). The body also compensates through renal mechanisms that increase H^+ excretion and increase bicarbonate reabsorption.

Patients with metabolic alkalosis lose acid, and this causes an increase in the blood pH and $[HCO_3^-]$. The body compensates for this increased pH by decreasing the respiratory rate, which increases blood CO_2 levels (hypercapnia) and increases the renal excretion of bicarbonate. Causes of metabolic alkalosis include vomiting (losing gastric acid), increased aldosterone secretion (which causes increased $[H^+]$ excretion by the kidneys), and certain diuretics.

329. The answer is e. *(Ayala, pp 132–135. Isselbacher, pp 259–260.)* Respiratory alkalosis results from an increase in the respiratory rate that decreases blood CO_2 (hypocapnia) and results in decreased arterial $[H^+]$ and $[HCO_3^-]$. The body tries to compensate for the increased pH through renal mechanisms, namely decreased H^+ excretion and decreased reabsorption of HCO_3^-. Note that there is also no respiratory compensation for respiratory alkalosis. Causes of respiratory alkalosis include diseases or states that cause hypoxemia (such as living at high altitude), psychogenic causes, and ingestion of salicylates (which can cause a mixed respiratory alkalosis and metabolic acidosis).

Respiratory acidosis is caused by a decrease in the respiratory rate, which increases blood CO_2 (hypercapnia) and results in increased arterial $[H^+]$ and $[HCO_3^-]$. The body tries to compensate for the decreased pH through renal mechanisms, namely increased H^+ excretion (through titratable H^+) and increased reabsorption of HCO_3^-. Note that there is no respiratory compensation for respiratory acidosis. Causes of respiratory acidosis include substances that inhibit the medullary respiratory center (such as opiates, sedatives, and anesthetics), impairment of the respiratory muscles (due to neurologic diseases such as multiple sclerosis), airway obstruction, and other pulmonary diseases, such as ARDS and COPD.

330. The answer is c. *(Cotran, p 465. Rubin, pp 217, 865.)* Failure of the metanephric diverticulum to develop normally leads to bilateral renal agenesis, which in turn leads to a constellation of symptoms called Potter's syndrome (sequence). The kidneys are important for the circulation of amniotic fluid. The fetus swallows amniotic fluid (about 400 mL/day), and

then absorbs it in the respiratory and digestive tracts. Waste products cross the placental membrane and enter maternal blood in the intervillous space. Excess water is excreted by the fetal kidneys into the amniotic fluid. Developmental abnormalities that impair fetal swallowing of amniotic fluid, such as esophageal atresia or severe anomalies of the CNS, lead to polyhydramnios (too much amniotic fluid), while agenesis of the kidneys or urinary obstruction leads to oligohydramnios (too little amniotic fluid). The oligohydramnios leads to characteristic facial features that include wide-set eyes; low-set, floppy ears; and a broad, flat nose.

331. The answer is b. *(Cotran, pp 936–942.)* Cystic diseases of the kidney, which may be congenital, acquired, or inherited, have characteristic gross appearances. In two types of cystic renal disease, the numerous cysts are found in both the cortex and medulla. These two types of polycystic disease of the kidney are the infantile type and the adult type. Adult polycystic kidney disease typically presents in adulthood and has an autosomal dominant inheritance pattern. Histologically, the cysts are lined by tubular epithelium, while the stroma between the cysts is normal. Adult polycystic renal disease is associated with liver cysts and berry aneurysms, which may rupture and cause a subarachnoid hemorrhage. About one-half of patients with adult polycystic renal disease eventually develop uremia. Infantile polycystic kidney disease typically presents in newborns, has an autosomal recessive pattern of inheritance, and is associated with hepatic cysts (microhamartomas) and congenital hepatic fibrosis. Grossly, these renal cysts have a radial spoke arrangement.

In two types of cystic renal disease, the cysts are limited to the medulla. Medullary sponge kidney is usually asymptomatic, is not familial, and is characterized by normal-sized kidneys with small cysts in the renal papillae. In medullary cystic disease complex (nephronophthisis), kidneys are small and sclerotic with multiple cysts at the corticomedullary junction. Individuals with this abnormality present in the first two decades of life with salt-wasting polyuria and progressive renal failure. Most cases are familial and display both recessive and dominant inheritance patterns. Two other types of cysts that are not limited to the medulla are simple cysts and acquired cysts. Simple cortical cysts are single, unilateral cysts, found in adults, that are benign. Patients are usually asymptomatic, but they may present with microscopic hematuria. Acquired polycystic renal disease is

associated with chronic renal dialysis. These kidneys are shrunken and have multiple cysts and an irregular surface.

332. The answer is b. *(Cotran, pp 935–936.)* Glomerular diseases may clinically produce either nephrotic syndrome or nephritic syndrome. Nephrotic syndrome is characterized by marked proteinuria, that is, proteinuria greater than 3.5 g per 24 h. Because of this marked proteinuria, patients lose albumin (hypoalbuminemia), which leads to peripheral edema. Patients also characteristically have increased serum lipid levels (hyperlipidemia) due to increased hepatic synthesis of cholesterol. The cholesterol is carried within LDL and spills into the urine (lipiduria), where it produces microscopic fatty casts and oval fat bodies. The latter are renal tubular epithelial cells or macrophages that have excess cholesterol in the cytoplasm. Polarization of this excess cholesterol produces Maltese crosses. In contrast to nephrotic syndrome, nephritic syndrome is mainly caused by inflammatory glomerular diseases and produces hematuria (blood in the urine). Red blood cell casts may be present. These patients also may have proteinuria, but it is generally less severe than that in patients with nephrotic syndrome and is generally less than 3.5 g/day. Patients also retain salt and water, which leads to hypertension and peripheral edema. In contrast to these two glomerular syndromes, renal tubular defects produce symptoms of polyuria, nocturia, and electrolyte abnormalities (such as metabolic acidosis), while infections of the urinary tract cause bacteriuria and pyuria (bacteria and leukocytes in the urine).

333. The answer is c. *(Cotran, pp 943–948.)* Glomerular injury caused by circulating antigen-antibody complexes is a secondary effect from a nonrenal primary source. Numerous clinical examples exist of a serum sickness–like nephritis as a consequence of systemic infection, with classic clinical models such as syphilis, hepatitis B, malaria, and bacterial endocarditis leading to renal disease. Immune complexes to antigens from any of these sources are circulating within the vascular system and become entrapped within the filtration system of the glomerular basement membranes. This can be seen as granular, bumpy deposits by immunofluorescence within the basement membranes of the glomeruli. Linear fluorescence, on the other hand, is seen in primary antiglomerular basement membrane disease, in which antibodies are directed against the

glomerular basement membrane itself. Plasma cell interstitial nephritis is seen in immunologic rejection of transplanted kidneys. Nodular glomerulosclerosis is an effect of diabetes mellitus. The presence of red blood cell casts in the urine nearly always indicates that there has been glomerular injury but is not specific for any given cause. Thickening of the glomerular basement membrane caused by subepithelial immune deposits is seen in membranous glomerulonephritis. While the morphology of membranous glomerulonephritis is different from that of nephritis caused by circulating antigen-antibody complexes (immune complexes), there are similarities in the pathogenesis in that both disorders may be a consequence of or exist in association with infections such as hepatitis B, syphilis, or malaria. Other causes of membranous glomerulonephritis include reactions to penicillamine and gold, and certain malignancies such as malignant melanoma.

334. The answer is d. *(Damjanov, pp 2089–2090. Cotran, pp 954–956.)* There are numerous causes of nephrotic syndrome (NS), including immune complex diseases, diabetes, amyloidosis, toxemia of pregnancy, and such circulating disturbances as bilateral renal vein thrombosis, but NS in small children (under 3 years of age) should suggest the possibility of the renal disease known as minimal change disease (MCD), which is synonymous with foot process disease or nil disease. This peculiar entity presents clinically as insidious nephrotic syndrome, characteristically occurring in younger children but also seen in adults (rarely), with hypoalbuminemia, edema, hyperlipidemia, massive selective proteinuria, and lipiduria (lipoid nephrosis). MCD is a selective proteinuria because it results from decreased amounts of polyanions (mainly heparan sulfate) in the glomerular basement membrane. These polyanions normally block the filtration of the small but negatively charged albumin molecules. The glomeruli in patients with MCD lack electron-dense deposits, and immunofluorescence (IF) tests are negative. These patients have no tendency to develop chronic renal failure, and they respond to steroid therapy. The glomeruli are known for their rather normal appearance on light microscopy—at worst, there is mild and focal sclerosis. Electron microscopy is necessary for demonstrating characteristic attenuation and flattening of the foot processes of the podocytes attached to the Bowman's space side of the glomerular basement membrane. The podocytes may revert to normal (with steroid immunosuppressive therapy), or the foot process attenuation may persist to some extent, in which case the proteinuria also persists.

335. The answer is c. *(Cotran, pp 956–958.)* Focal segmental glomerulosclerosis (FSGS) is a glomerular disorder that accounts for about 10% of the cases of nephrotic syndrome. FSGS, which affects children and adults, begins as a focal process, affecting only some glomeruli. In the earliest stage, only some of the juxtamedullary glomeruli show changes. Eventually, some glomeruli in other parts of the cortex are affected. In the late stages of the disease, the process may become diffuse, affecting most or all glomeruli. Initially, the process is also segmental, involving some but not all of the lobules within an individual glomerular tuft. The involved area shows sclerosis and may show hyalinosis lesions. Eventually some glomeruli show sclerosis of the entire tuft (global sclerosis). Electron microscopy shows increased mesangial matrix and dense granular mesangial deposits. Immunofluorescence typically shows granular mesangial fluorescence for IgM and C3. Because of the focal nature of FSGS, early cases can be difficult to distinguish from minimal change disease (MCD). Clinically, the nephrotic syndrome of FSGS is more severe than that of minimal change disease and is nonselective. The process is much less responsive to steroids and is much more prone to progress to chronic renal failure. It tends to recur in transplanted kidneys. FSGS can be seen in the setting of AIDS nephropathy and heroin nephropathy. [Note: FSGS, with no cellular proliferation, is different from focal segmental glomerulonephritis (FSGN), which involves cellular proliferation. The main cause of FSGN is IgA (Berger's) nephropathy, while FSGS is most notably seen in patients with AIDS.]

336. The answer is a. *(Cotran, pp 949–951. Rubin, pp 882–884.)* In a young patient who presents with signs of edema, three renal diseases are in the differential diagnosis. These diseases have similar names and findings, which makes them easily confused with each other. For example, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and post-streptococcal glomerulonephritis may all produce nephrotic syndrome, which is characterized by marked proteinuria. This finding can be documented by the presence of protein in a dipstick examination of the urine. Although signs of nephritic syndrome, such as hematuria, may be seen with FSGS, young children are more often found to have acute post-streptococcal glomerulonephritis. This illness typically occurs 1 to 3 weeks after a group A α-hemolytic streptococcal infection of the pharynx or skin, such as impetigo or scarlet fever. Patients develop hematuria, red cell casts,

mild periorbital edema, and increased blood pressure. Laboratory tests reveal increased ASO titers and decreased C3. Cultures taken at the time of presentation with renal symptoms are negative. Light microscopy reveals diffuse endothelial and mesangial cell proliferation with neutrophil infiltration, so that narrowing of capillary lumina and enlargement of the glomerular tuft to fill the Bowman's space occur. Electron microscopy reveals the mesangial deposits and large, hump-shaped subepithelial deposits in peripheral capillary loops that are characteristic. Immunofluorescence shows granular deposits containing IgG, C3, and often fibrin in glomerular capillary walls and mesangium. Children with post-streptococcal glomerulonephritis usually recover, and therapy is supportive only.

337. The answer is d. *(Cotran, pp 943–947, 958–961.)* Electron-dense deposits composed of immunoglobulin and complement are deposited in characteristic locations of the glomerulus in different renal diseases. Deposits within the basement membrane are seen in type II membranoproliferative glomerulonephritis (MPGN or "dense deposit disease"), while subendothelial deposits are seen in type I MPGN. Note that membranoproliferative glomerulonephritis occurs in two types. Type I, which is associated with nephrotic syndrome, is driven by immune complexes; type II is associated with hematuria and chronic renal failure, and, in addition to immune complexes, involves alternate complement activation. In both types there is mesangial proliferation accompanied by thickening of the glomerular basement membranes, and a special finding that often supports the diagnosis of membranoproliferative glomerulonephritis is the presence of actual splitting of the glomerular basement membranes. In type I there are subendothelial deposits of IgG, C3, C1, and C4. In type II there are dense deposits of C3 with or without IgG, and no C1.

Subepithelial deposits are seen in acute glomerulonephritis (GN), such as post-streptococcal glomerulonephritis. Epimembranous deposits (similar to subepithelial deposits) are found in patients with membranous GN or in the experimental disease Heymann's GN. Note that the deposits in MGN are relatively small and are deposited in a very uniform fashion, while the deposits in post-streptococcal GN are comparably large (subepithelial humps) and are not uniformly distributed. Subendothelial deposits are also seen with systemic lupus erythematosus. Deposits within the mesangial matrix are found in IgA nephropathy (Berger's disease) and Henoch-

Schönlein glomerulonephritis. Electron-dense deposits are not usually found within Bowman's space, nor are they usually found in patients with Goodpasture's disease or lipoid nephrosis.

338. The answer is a. *(Cotran, pp 961–962.)* Many diseases involve hematuria, and a few of these diseases occur in the setting of an upper respiratory infection or of upper respiratory signs and symptoms. When hematuria follows within 2 days of the onset of an upper respiratory infection without skin lesions in a young patient, IgA nephropathy (Berger's disease) should be considered. This disease involves the deposition of IgA in the mesangium of the glomeruli. Light microscopic examination may suggest the disease, but renal biopsy immunofluorescence (IF) must be performed to confirm it. This disorder may be the most common cause of nephritic syndrome worldwide. The hematuria may become recurrent, with proteinuria that may approach nephrotic syndrome proportions. Serum levels of IgA may be elevated. A small percentage of patients may progress to renal failure over a period of years. In contrast to Berger's disease, a linear IF pattern suggests a type II hypersensitivity reaction, such as Goodpasture's disease, while a granular pattern is seen with post-streptococcal glomerulonephritis (GN), membranous GN, focal segmental glomerulosclerosis, and membranoproliferative GN. Most positive immunofluorescence patterns involve IgG and C3, except that a granular IgM pattern is present in focal segmental glomerulosclerosis, while mesangial IgA is seen in IgA nephropathy (Berger's disease). Lipoid nephrosis would have a negative IF pattern; that is, there would be no staining present.

339. The answer is a. *(Cotran, pp 951–952.)* The finding of crescents within the Bowman's space of many glomeruli is diagnostic of rapidly progressive (crescentic) glomerulonephritis (RPGN). RPGN may be subdivided into three types based on the immunofluorescence (IF) staining pattern. Type I RPGN reveals linear staining of IgG and C3. The majority of these patients are found to have Goodpasture's disease (anti-GBM disease). Type II RPGN reveals immune complex deposition (granular staining). These patients may have other glomerular or systemic diseases, including post-streptococcal GN, membranoproliferative GN, IgA nephropathy (Berger's disease), and SLE. Type III RPGN reveals minimal immune changes and is referred to as pauci-immune crescentic GN. Antineutrophil

cytoplasmic antibodies (ANCAs), which are found in some patients with vasculitis, are found in many of these patients with pauci-immune GN. ANCAs are either perinuclear (P-ANCAs, against myeloperoxidase) or cytoplasmic (C-ANCAs, against proteinase 3). P-ANCAs are found in patients with microscopic polyarteritis and idiopathic crescentic GN, while C-ANCAs are found in patients with Wegener's granulomatosis, a disorder that is characterized by acute necrotizing granulomas of the respiratory tract, focal necrotizing vasculitis, and diffuse necrotizing GN.

340. The answer is c. *(Cotran, pp 739, 945, 951.)* In Goodpasture's syndrome, circulating antibodies reactive with the glomerular basement membrane bind in a linear pattern along the entire length of the glomerular basement membrane, which is their specific antigen. IgG is deposited in the basement membrane, along with complement. There are focal interruptions of the glomerular basement membrane as well, along with deposits of fibrin, as seen with electron microscopy.

341. The answer is e. *(Cotran, pp 220–222.)* The glomerular diseases of patients with systemic lupus erythematosus (SLE) are many and include mesangial lupus glomerulonephritis (GN), focal or diffuse proliferative GN, and membranous GN. The World Health Organization (WHO) classifies SLE renal disease into five classes as follows: class I = no changes; class II = mesangial GN; class III = focal proliferative GN; class IV = diffuse proliferative GN (the most common class); class V = diffuse membranous GN. All of these glomerular diseases are the result of the deposition of immune complexes (DNA–anti-DNA complexes) that may be in a mesangial, intramembranous, subepithelial, or subendothelial location. In membranous lupus GN, the deposits are in a subepithelial location, while in diffuse proliferative lupus GN (WHO class IV) the deposits are mainly in a subendothelial location and produce a characteristic "wire-loop" appearance due to thickening of the capillary wall. None of these changes are specific for lupus.

In contrast to the "wire-loop" appearance of the glomerular capillaries with lupus nephritis, "holly leaf" mesangial deposits are seen with focal segmental GN (IgA deposits suggests Berger disease), "spike and dome" appearance of the basement membrane is seen with membranous glomerulonephropathy, a "string of popcorn" immunofluorescence pattern is also seen with membranous glomerulonephropathy, and "tram-track"

splitting of the basement membrane is seen with both types of membranoproliferative GN.

342. The answer is b. *(Cotran, pp 922–924.)* The thickening of the basement membrane in systemic lupus erythematosus and membranous glomerulonephritis is thought to result from deposition of immune complexes. The pathogenesis of this same lesion in diabetes mellitus and renal vein thrombosis is unknown. Electron-dense deposits are classically seen in a subendothelial position on the glomerular basement membrane but may be subepithelial as well in some cases.

343. The answer is b. *(Cotran, pp 969–971.)* Acute tubular necrosis (ATN) may produce oliguria, decreased glomerular filtration rate (GFR), increased fractional excretion of sodium, and an abnormal urinary sediment. ATN may be caused by renal ischemia (ischemic ATN) or chemical toxins (toxic ATN). Renal ischemia is the most common cause of ATN, while toxic ATN may be caused by antibiotics (such as aminoglycosides and amphotericin B), heavy metals (such as cisplatin), radiographic agents, and endogenous toxins (such as myoglobin and hemoglobin). Both ischemic ATN and toxic ATN are characterized by the finding of eosinophilic hyalin or pigmented granular casts in the urine. Histologically, both ischemic and toxic ATN reveal interstitial edema, flattening of the tubular epithelial cells, and tubular epithelial cell necrosis. One difference between these two etiologies is that the tubular epithelial cell necrosis is extensive with toxic ATN, while the necrosis with ischemic ATN is patchy with interposed unaffected segments. This can be quite variable, however, and certain causes may be associated with damage to specific portions of the kidney. Both ischemia and heavy metals primarily damage the epithelial cells of the proximal straight tubules, while aminoglycosides primarily affect the proximal convoluted tubule.

344. The answer is c. *(Cotran, pp 975–977.)* The kidney shown is typical of chronic pyelonephritis with dilation of the renal pelvis, clubbing of the calyces, and irregular reduction in parenchymal mass. Chronic pyelonephritis is an asymmetric, irregularly scarring process that may be unilateral or bilateral. Microscopically, there is atrophy and dilation of tubules with colloid in some tubules. Chronic inflammation and fibrosis occur in the cortex and medulla. Chronic glomerulonephritis causes bilat-

eral symmetrically shrunken and scarred kidneys. Histologic changes depend on the stage of the disease. Cystic dysplasia is characterized by undifferentiated mesenchyme and immature cartilage and collecting ductules.

345. The answer is c. *(Cotran, pp 984–985.)* A rare cause of hypertension is renal artery stenosis, which may occur secondary to either an atheromatous plaque at the orifice of the renal artery or fibromuscular dysplasia of the renal artery. The former is more common in elderly men, while the latter is more common in young women. The decrease in blood flow to the kidney with the renal artery obstruction (Goldblatt's kidney) causes hyperplasia of the juxtaglomerular apparatus and increased renin production. This produces increased secretion of angiotensin and aldosterone, which leads to retention of sodium and water and produces hypertension. Increased levels of aldosterone also produce a hyperkalemic alkalosis. The kidney with stenosis of the renal artery becomes small and shrunken due to the effects of chronic ischemia, but the stenosis protects this kidney from the effects of the increased blood pressure. The other kidney, however, is not protected and may develop microscopic changes of benign nephrosclerosis (hyaline arteriolosclerosis).

346. The answer is c. *(Cotran, pp 981–984, 987–989.)* Renal arteriolar changes in malignant nephrosclerosis (malignant hypertension) include fibrinoid necrosis of arterioles (necrotizing arteriolitis), hyperplastic arteriolosclerosis (onion-skinning), necrotizing glomerulitis, and often a thrombotic microangiopathy. Grossly, multiple small petechial hemorrhages are found on the surface of the kidneys. The clinical course is often downhill, with only 50% of patients surviving 5 years; marked proteinuria, hematuria, cardiovascular problems, and finally renal failure contribute to death. The disease is often associated with accelerated preexisting benign essential hypertension, chronic renal disease (glomerulonephritis), or scleroderma.

In contrast, benign nephrosclerosis (renal disease occurring in benign hypertension) is characterized by hyaline arteriolosclerosis with thickened, hyalinized arteriolar walls and narrowed lumina. Fibroelastic hyperplasia occurs in the larger muscular arteries. Small kidneys with a finely granular surface often result because of ischemic atrophy of nephrons. Broad U-shaped cortical scars overlying dilated calyces in the renal poles are seen with chronic pyelonephritis (reflux causes scars involving poles only, while

obstruction produces scars all over the kidney), depressed cortical areas overlying necrotic papillae of varying stages are seen with analgesic nephropathy and diabetes mellitus, multiple small white areas on the surface are seen with acute pyelonephritis, and wedge-shaped (i.e., V-shaped) pale cortical scars are seen with renal infarcts.

347. The answer is e. *(Cotran, pp 989–990.)* The combination of severe flank pain (renal colic) and hematuria is highly suggestive of urolithiasis. The formation of urinary stones relates to decreased urine volume and increased urine concentrations of certain substances. Most stones contain calcium (either calcium oxalate or calcium phosphate) and are seen in patients with hypercalcinuria (with or without hypercalcemia), such as with hyperparathyroidism or diffuse bone disease. Magnesium ammonium phosphate stones are formed in alkaline urine as the result of urease-producing (urea-splitting) bacteria such as *Proteus*. The ammonia released from the breakdown of urea combines with magnesium and phosphate. These stones are large and may fill the renal pelvis (staghorn or struvite calculi). Examination of the urine with a dipstick reveals an alkaline urine that is positive for esterase (from the leukocytes in the urine) and nitrite (since *Proteus* reduces nitrate). Uric acid stones may form in patients with hyperuricemia, such as patients with gout or patients being treated for leukemias or lymphomas. Cystine stones are rare, but may be found in children with hereditary defects in the renal transport of some amino acids.

348. The answer is a. *(Cotran, pp 991–994.)* Renal cell carcinoma accounts for 85% of primary renal tumors and usually occurs in the sixth decade, although sometimes at a much younger age. Renal cell carcinoma is predominantly of clear cell type (clear cell carcinoma) with intracytoplasmic glycogen and lipid, but less often granular cells with numerous mitochondria or spindle cells occur. Grossly, the lesions are greater than 3 cm in diameter and are yellow in color (similar to tumors of the adrenal cortex; thus another name for renal cell carcinoma is hypernephroma). These tumors arise from the renal epithelial cells and thus may be classified as adenocarcinomas, but tubular formation, not glandular formation, may be present. Carcinomas originating in the renal pelvis (not the cortex) arise from transitional epithelial cells and microscopically are similar to tumors arising in the urinary bladder, i.e., transitional cell carcinomas. The combination of costovertebral pain, a palpable mass, and hematuria is the classic

triad of symptoms seen in about 10% of patients with renal cell carcinoma. These tumors may produce hormones or hormone-like substances: for example, renin (hypertension), glucocorticoids (Cushing's syndrome), and gonadotropins (feminization and masculinization). More frequently, though in only 5 to 10% of patients, polycythemia or erythrocytosis occurs owing to production of erythropoietin. Renal cell carcinoma is associated with von Hippel-Lindau syndrome, in which many patients develop bilateral renal cell carcinomas. Translocations between chromosomes 3 and 8 and between 3 and 11 have been found in some cases of familial renal cancer and in a few sporadic cases of renal cancer. Hematuria is often the first symptom, but it often occurs late, after invasion of the renal vein or widespread metastases, frequently to lung, bone, or brain.

349. The answer is b. *(Cotran, pp 487–489.)* Malignant tumors of the kidney in children are called nephroblastomas (Wilms tumor) and histologically reveal a combination of metanephric blastema, undifferentiated mesenchymal cells, and immature tubule or glomerular formation. Children present with an enlarging abdominal mass that, in contrast to adrenal neuroblastoma, is associated with normal urinary vanillylmandelic acid (VMA) levels. Deletions involving WT1, located on chromosome 11, are associated with the development of Wilms tumor (nephroblastoma). Several syndromes are associated with genetic deletions of WT1 that lead to an increased incidence of Wilms tumor. These include WAGR syndrome (characterized by aniridia, genital abnormalities, and mental retardation) and Denys-Drash syndrome (characterized by gonadal dysgenesis and renal failure). Deletions involving a second Wilms tumor gene (WT2) are associated with Beckwith-Wiedemann syndrome (characterized by hemihypertrophy, renal medullary cysts, and adrenal cytomegaly).

350. The answer is e. *(Cotran, pp 1000–1001. Damjanov, pp 1710–1711, 2190–2191. Larsen, pp 222–226.)* The cloaca is an embryonic structure that connects ventrally to the allantoic stalk and laterally to the mesonephric ducts. At about the eighth week of development a cloacal membrane forms within the cloaca and separates the cloaca into a dorsal rectum and a ventral urogenital sinus. The latter is the origin of the urachus, urinary bladder, and proximal urethra. Initially the urinary bladder is continuous with the allantois, which constricts and forms the thick, fibrous urachus. The urachus in turn becomes attenuated, but still remains attached to the bladder dome and forms the median umbilical ligament in the adult. Incom-

plete attenuation of the urachus (persistent urachus) can lead to formation of a urachal cyst, urachal sinus, or urachal fistula. The end attached to the bladder can remain and form a bladder diverticulum, while the central portion can remain and form a urachal cyst. Urachal sinuses and fistulas still connect the umbilicus to the urinary bladder, and therefore urine can leak at the site of the umbilicus.

Normally, mesodermal tissue grows onto the cloacal membrane to form the muscles of the lower abdominal wall. During this process the cloacal membrane is obliterated and disappears. In some embryos mesoderm does not grow onto the cloacal membrane. This leads to persistence of the cloacal membrane, which can become quite thin and rupture. This in turn causes the posterior bladder mucosa to evert through this defect in the anterior abdominal wall. This condition is called exstrophy and is associated with recurrent urinary infections and epispadias in males. There is also an increased incidence of neoplastic transformation, most commonly adenocarcinoma.

Meckel's diverticulum is a diverticulum found in the terminal ileum that is the result of persistence of the omphalomesenteric duct. It is usually about 2 in. long and is located less than 2 ft from the ileocecal valve. An omphalocele refers to protrusion of the intestines through an unclosed umbilical ring. This abnormality results from incomplete internalization of the intestines during fetal growth. A similar defect, gastroschisis, does not involve the umbilicus. Instead, viscera herniate through a defect in the anterior abdominal wall just lateral to the umbilicus.

351. The answer is e. *(Cotran, pp 1001–1002. Rubin, p 925.)* Nonspecific urethritis may actually be the most common cause of dysuria in sexually active males, although gonorrhea should always be excluded by laboratory examination. Causes of nonspecific urethritis include some bacteria, such as *E. coli* and streptococci, but recent evidence implicates chlamydiae of the TRIC group as being perhaps the most common cause of nongonococcal urethritis. The organism may take up residence in the prostate, producing chronic and active prostatitis. Prostatic hypertrophy, epididymitis, orchitis, and renal stones may cause urinary symptoms but also produce other signs and symptoms that distinguish them from nonspecific urethritis.

352. The answer is b. *(Cotran, pp 1001–1002. Rubin, p 925.)* Inflammation of the urinary bladder (cystitis) may be caused by many different etiologies, all of which produce symptoms of frequency, dysuria, and lower

abdominal pain. Acute cystitis histologically reveals stromal edema and an infiltrate of neutrophils. Grossly, the bladder mucosa is hyperemic. In most cases cystitis is secondary to infections of the bladder, usually by coliform bacteria, e.g., *E. coli.* Cystitis occurs more commonly in females and is associated with sexual intercourse, pregnancy, and instrumentation. Hemorrhage may also be present (hemorrhagic cystitis) and is usually the result of radiation injury, chemotherapy, or an adenovirus infection.

353. The answer is d. *(Cotran, pp 1003–1008.)* Neoplastic lesions of the urinary bladder may either be benign or malignant. There is some controversy involving some types of benign lesions of the bladder. In particular, there is disagreement as to whether papillary lesions may be benign (papillomas). Many pathologists would classify papillary transitional lesions that lack cellular atypia or numerous mitoses as grade I (low-grade) papillary transitional cell carcinomas (TCCs) and not papillomas. Pathologists do agree, however, on the existence of a rare type of benign lesion called an inverted papilloma, which is characterized by nodular mucosal lesions that histologically have an endophytic growth pattern. Malignant neoplasms of the bladder may be transitional cell carcinomas, which are by far the most common type of tumor of the urinary bladder; squamous cell carcinomas, which produce keratin; or adenocarcinomas, which form glandular structures. TCCs may be either papillary or flat lesions. Papillary TCCs, which are the most common type of bladder cancer, may be either invasive or noninvasive. Noninvasive papillary TCCs are not referred to as being in situ, as that term implies a noninvasive, nonpapillary lesion. Nonpapillary (flat) TCCs may also be invasive (into the lamina propria or muscularis) or noninvasive (in situ). In contrast, squamous cell carcinomas of the urinary bladder are quite rare except in Egypt and other areas of the Middle East, where they are associated with schistosomiasis. Similarly, adenocarcinomas of the urinary bladder are quite rare, except that they may be associated with urachal epithelial remnants located in the dome of the bladder, glandular metaplasia, or cystitis glandularis.

Reproductive Systems

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

354. The term *hypospadias* refers to an abnormal location of the

a. Testes due to failure of the normal descent of the intraabdominal testes
b. Urethral opening on the dorsal surface of the penis due to faulty positioning of the genital tubercle
c. Urethral opening on the inferior surface of the penis due to failure of fusion of the paramesonephric (Müllerian) ducts
d. Urethral opening on the superior surface of the penis due to failure of downgrowth of mesoderm over the anterior bladder
e. Urethral opening on the ventral surface of the penis due to failure of the urethral folds to close

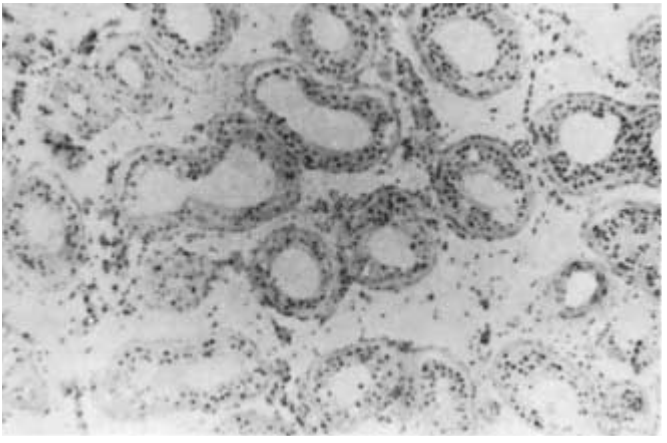
355. An uncircumcised 49-year-old male presents with the sudden onset of severe pain in the distal portion of his penis. The emergency room physician examines the patient and finds that the foreskin is retracted but cannot be rolled back over the glans penis. The ER physician calls the urologist, who performs an emergency resection of this patient's foreskin. What is the correct diagnosis for this individual's condition?

a. Balanoposthitis
b. Epispadias
c. Omphalocele
d. Paraphimosis
e. Phimosis

356. Histologic examination of an excision specimen from a lesion on the dorsal surface of the penis reveals a papillary lesion with clear vacuolization of epithelial cells on the surface and extension of the hyperplastic epithelium into the underlying tissue along a broad front. The correct diagnosis for this lesion is

a. Condyloma acuminatum
b. Bowen's disease
c. Erythroplasia of Queyrat
d. Verrucous carcinoma
e. Squamous cell carcinoma

357. The photomicrograph below is of a section from a testis removed from the inguinal region of a man aged 25. Which of the following statements is true regarding the condition illustrated?



a. It is bilateral in the majority of cases
b. Teratoma is the most common malignancy to arise
c. Risk of associated malignancy is reduced by orchiopexy
d. There is increased risk of malignancy in the contralateral testis
e. Both Leydig and Sertoli cells are reduced in number

358. A 32-year-old male presents with scrotal enlargement. Physical examination, including scrotal transillumination, reveals the presence of a testicular cyst containing clear fluid. This abnormality most likely results from fluid accumulating within the

a. Ampulla of the ductus deferens
b. Appendix testis
c. Epididymis
d. Seminal vesicles
e. Tunica vaginalis

359. Which of the following testicular tumors is most radiosensitive?

a. Seminoma
b. Embryonal carcinoma
c. Choriocarcinoma
d. Yolk sac tumor
e. Immature teratoma

360. A 27-year-old male presents with a testicular mass, which is resected and diagnosed as being a yolk sac tumor. Which one of the listed substances is most likely to be increased in this patient's serum as a result of being secreted from the cells of this tumor?

a. Acid phosphatase
b. α fetoprotein (AFP)
c. Alkaline phosphatase
d. β-human chorionic gonadotropin (β-hCG)
e. Prostate-specific antigen (PSA)

361. A 47-year-old male presents with the sudden onset of fever, chills, and dysuria. During the review of symptoms you discover that he has no history of recurrent urinary tract infections. Rectal examination finds that the prostate gland is very sensitive and examination is painful. What is the most likely diagnosis for this patient?

a. Acute prostatitis
b. Chronic bacterial prostatitis
c. Chronic abacterial prostatitis
d. Granulomatous prostatitis
e. Benign prostatic hyperplasia

362. A 69-year-old male presents with urinary frequency, nocturia, dribbling, and difficulty in starting and stopping urination. Rectal examination reveals the prostate to be enlarged, firm, and rubbery. A needle biopsy reveals increased numbers of glandular elements and stromal tissue. The glands are found to have a double layer of epithelial cells. Prominent nuclei or back-to-back glands are not seen. What is the correct diagnosis?

a. Acute prostatitis
b. Chronic bacterial prostatitis
c. Granulomatous prostatitis
d. Benign prostatic hyperplasia
e. Prostatic adenocarcinoma

363. A 67-year-old male is found on rectal examination to have a single, hard, irregular nodule within his prostate. A biopsy of this lesion reveals the presence of small glands lined by a single layer of cells with enlarged, prominent nucleoli. From what portion of the prostate did this lesion most likely originate?

a. Anterior zone
b. Central zone
c. Peripheral zone
d. Periurethral glands
e. Transition zone

364. A newborn female is being worked up clinically for several congenital abnormalities. During this workup, it is discovered that normal development of the vagina and uterus in this female infant has not occurred. Failure of the uterus to develop (agenesis) is directly related to the failure of what embryonic structure to develop?

a. Urogenital ridge
b. Mesonephric duct
c. Paramesonephric duct
d. Metanephric duct
e. Epoophoron

365. Multiple small mucinous cysts of the endocervix that result from blockage of endocervical glands by overlying squamous metaplastic epithelium are called

a. Bartholin's cysts
b. Chocolate cysts
c. Follicular cysts
d. Gartner's duct cysts
e. Nabothian cysts

366. A 75-year-old woman presents with a pruritic vulvar lesion. Physical examination reveals an irregular white, rough area involving her vulva. If this area of leukoplakia is due to lichen sclerosis, then biopsies from this area will most likely reveal

a. Atrophy of epidermis with dermal fibrosis
b. Epidermal atypia with dysplasia
c. Epithelial hyperplasia and hyperkeratosis
d. Individual malignant cells invading the epidermis
e. Loss of pigment in the epidermis

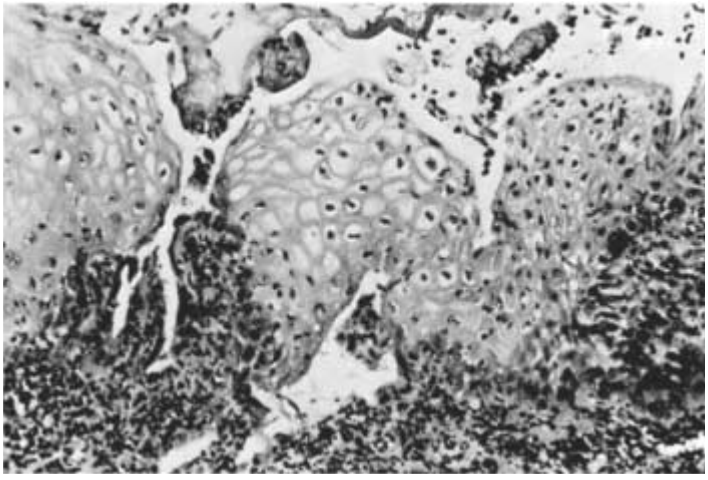
367. The most common primary sites for the origin of Paget's disease are the nipple and the

a. Anal canal
b. Liver
c. Nasopharynx
d. Penis
e. Vulva

368. Vaginal adenosis is most likely to precede the development of

a. Condyloma acuminatum
b. Cervical carcinoma
c. Clear cell carcinoma
d. Carcinoma of the endometrium
e. Squamous carcinoma of the vagina

369. The photomicrograph below depicts a biopsy of the uterine cervix that was done following an abnormal Pap smear report. This histologic section shows koilocytosis, which results from infection with



a. Adenovirus
b. Cytomegalovirus (CMV)
c. Epstein-Barr virus (EBV)
d. Herpes simplex virus (HSV)
e. Human papillomavirus (HPV)

370. A 29-year-old female presents with severe pain during menstruation (dysmenorrhea). During workup, an endometrial biopsy is obtained. The pathology report from this specimen makes the diagnosis of chronic endometritis. Based on this pathology report, which one of the following was present in the biopsy sample of the endometrium?

a. Neutrophils
b. Lymphocytes
c. Lymphoid follicles
d. Plasma cells
e. Decidualized stromal cells

371. A 25-year-old female presents to your office for workup of infertility. In giving a history she describes severe pain during menses, and she also tells you that in the past another doctor told her that she had "chocolate in her cysts." Based on this history, what abnormality would you most expect to be present in this patient?

a. Metastatic ovarian cancer
b. Endometriosis
c. Acute pelvic inflammatory disease
d. Adenomyosis
e. A posteriorly located subserosal uterine leiomyoma

372. Abnormal menstrual bleeding characterized by excessive bleeding at irregular intervals is best referred to as

a. Dysmenorrhea
b. Menometrorrhagia
c. Menorrhagia
d. Metrorrhagia
e. Oligomenorrhea

373. A 24-year-old female presents with a 2-year history of infertility. An endometrial biopsy is obtained approximately 5 to 6 days after the predicted time of ovulation. This biopsy specimen reveals secretory endometrium, but there is a significant difference (asynchrony) between the estimated chronologic menstrual date and the estimated histologic menstrual date. No proliferative endometrium is seen. Based on this information, what is the correct diagnosis for this biopsy specimen?

a. Anovulatory cycle (no corpus luteum formed)
b. Inadequate luteal phase (decreased functioning of the corpus luteum)
c. Irregular shedding (prolonged functioning of the corpus luteum)
d. Normal endometrium during the follicular phase of the cycle (no corpus luteum formed)
e. Normal endometrium during the luteal phase of the cycle (normal corpus luteum)

374. Which one of the listed endometrial abnormalities has the greatest risk of developing into endometrial cancer?

a. Simple hyperplasia
b. Complex hyperplasia
c. Atypical hyperplasia
d. Cystic hyperplasia
e. Polyp

375. Prolonged unopposed estrogen stimulation in an adult female increases the risk of development of endometrial hyperplasia and subsequent carcinoma. What is the most likely histologic appearance of this endometrial carcinoma?

a. Adenocarcinoma
b. Clear cell carcinoma
c. Small cell carcinoma
d. Squamous cell carcinoma
e. Transitional cell carcinoma

376. A 46-year-old woman undergoes an abdominal hysterectomy for a "fibroid" uterus. The surgeon requests a frozen section on the tumor, which is deferred because of the lesion's degree of cellularity. Which of the following criteria will be used by the pathologist in determining benignancy versus malignancy in permanent sections?

a. Mitotic rate
b. Cell pleomorphism
c. Cell necrosis
d. Nucleus-to-cytoplasm ratio
e. Tumor size

377. A 25-year-old female presents with lower abdominal pain, fever, and a vaginal discharge. Pelvic examination reveals bilateral adnexal (ovarian) tenderness and pain when the cervix is manipulated. Cultures taken from the vaginal discharge grow *Neisseria gonorrhoeae*. What is your diagnosis of the cause of this patient's adnexal pain?

a. Adenomatoid tumor
b. Ectopic pregnancy
c. Endometriosis
d. Luteoma of pregnancy
e. Pelvic inflammatory disease

378. A 19-year-old female presents with oligomenorrhea. Physical examination reveals an obese young female with acne and increased facial hair. A pelvic examination is essentially within normal limits, excluding the adnexal regions, which could not be palpated secondary to obesity. Ultrasound examination reveals bilateral enlargement of the ovaries with multiple subcortical cysts. Which one of the listed sets of serum laboratory values is most likely to be present in this individual?

	Serum Luteinizing Hormone (LH)	Serum Follicle-Stimulating Hormone (FSH)	LH/FSH Ratio
a.	Decreased	Decreased	High
b.	Decreased	Decreased	Low
c.	Decreased	Increased	Low
d.	Increased	Decreased	High
e.	Increased	Increased	Low

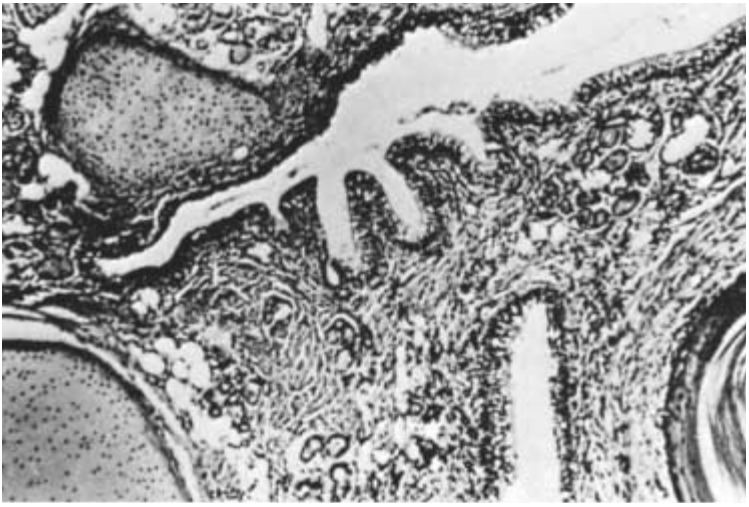
379. A 23-year-old female presents with pelvic pain and is found to have an ovarian mass of the left ovary that measures 3 cm in diameter. Grossly, the mass consists of multiple cystic spaces. Histologically, these cysts are lined by tall columnar epithelium, with some of the cells being ciliated. What is your diagnosis of this ovarian tumor, which histologically recapitulates the histology of the fallopian tubes?

a. Serous tumor
b. Mucinous tumor
c. Endometrioid tumor
d. Clear cell tumor
e. Brenner tumor

380. Pseudomyxoma peritonei is most likely to be associated with a

a. Clear cell tumor of the kidney
b. Cystic tumor of the gallbladder
c. Mucinous tumor of the ovary
d. Serous tumor of the ovary
e. Smooth-muscle tumor of the uterus

381. The ovarian lesion in the photomicrograph below is



a. Chronic salpingitis
b. An ectopic pregnancy
c. A granulosa cell tumor
d. A cystic teratoma
e. Metastatic squamous cell carcinoma

382. A 32-year-old female presents with the recent onset of oligomenorrhea followed by amenorrhea, and then the loss of female secondary characteristics. She has also developed acne, deepening of her voice, and temporal balding. Which one of the following ovarian tumors would most likely produce these symptoms?

a. Epithelial tumor
b. Stromal tumor
c. Germ cell tumor
d. Surface tumor
e. Metastasis

383. An 18-year-old female presents with amenorrhea and is found to have normal secondary sex characteristics and normal-appearing external genitalia. Her first menstrual period was at age 13, and her cycle has been unremarkable until now. She states that her last menstrual period was 8 weeks prior to this visit. A urine test for hCG is positive. What is the most likely diagnosis?

a. Ectopic pregnancy
b. Intrauterine pregnancy
c. Stein-Leventhal syndrome
d. Turner's syndrome
e. Weight loss syndrome

384. A 24-year-old female delivers a normal 8-lb baby boy at 40 weeks of gestation. She has no history of drug abuse, and her pregnancy was unremarkable. Examination had revealed the placenta to be located normally, but following delivery the woman fails to deliver the placenta and subsequently develops massive postpartum hemorrhage and shock. Emergency surgery is performed to stop the bleeding. The postpartum bleeding was most likely caused by

a. An abruptio placenta
b. A placenta previa
c. A placenta accreta
d. A hydatidiform mole
e. An invasive mole

385. A 26-year-old female acutely develops lower abdominal pain and vaginal bleeding. While in the bathroom she passes a cast of tissue composed of clot material and then collapses. She is brought to the hospital, where a physical examination reveals a soft, tender mass in right adnexa and pouch of Douglas. Histologic examination of the tissue passed in the bathroom reveals blood clots and decidualized tissue. No chorionic villi or trophoblastic tissue are present. Which one of the following conditions is most likely present in this individual?

a. Aborted intrauterine pregnancy
b. Complete hydatidiform mole
c. Ectopic pregnancy
d. Endometrial hyperplasia
e. Partial hydatidiform mole

386. A 26-year-old female in the third trimester of her first pregnancy develops persistent headaches and swelling of her legs and face. Early during her pregnancy a physical examination was unremarkable; however, now her blood pressure is 170/105 mmHg and urinalysis reveals slight proteinuria. What is the diagnosis?

a. Eclampsia
b. Gestational trophoblastic disease
c. Nephritic syndrome
d. Nephrotic syndrome
e. Preeclampsia

387. A 25-year-old woman in her fifteenth week of pregnancy presents with uterine bleeding and passage of a small amount of watery fluid and tissue. She is found to have a uterus that is much larger than estimated by her gestational dates. Her uterus is found to be filled with cystic, avascular, grapelike structures that do not penetrate the uterine wall. No fetal parts are found. The most likely diagnosis for this abnormality is

a. Partial hydatidiform mole
b. Complete hydatidiform mole
c. Invasive mole
d. Placental site trophoblastic tumor
e. Choriocarcinoma

388. A 50-year-old woman presents with fatigue, insomnia, hot flashes, night sweats, and absence of menses for the last 5 months (secondary amenorrhea). Her urine hCG test is negative. Laboratory tests reveal decreased serum estrogen and increased serum FSH and LH levels. What is the most likely diagnosis for this individual?

a. 17-hydroxylase deficiency of the adrenal cortex
b. Prolactin-secreting tumor of the anterior pituitary
c. Gonadotropin-releasing hormone–secreting tumor of the hypothalamus
d. Menopause
e. Menarche

389. A 27-year-old female who is actively training for a marathon presents with the new onset of a painful lump in the upper outer quadrant of her right breast. A mammogram shows an irregular mass with focal areas of calcification. An excisional biopsy reveals a localized area of granulation tissue and numerous lipid-laden macrophages surrounding necrotic adipocytes. What is the correct diagnosis?

a. Acute mastitis
b. Ectasia
c. Enzymatic fat necrosis
d. Foreign-body reaction
e. Traumatic fat necrosis

390. During a routine breast self-examination, a 35-year-old female is concerned because her breasts feel "lumpy." She consults you as her primary care physician. After performing an examination, you reassure her that no masses are present and that the "lumpiness" is due to fibrocystic changes. Considering this clinical opinion, a pathologic finding that is consistent with the nonproliferative form of fibrocystic change is

a. A blue-domed cyst
b. A radial scar
c. Atypical hyperplasia
d. Papillomatosis
e. Sclerosing adenosis

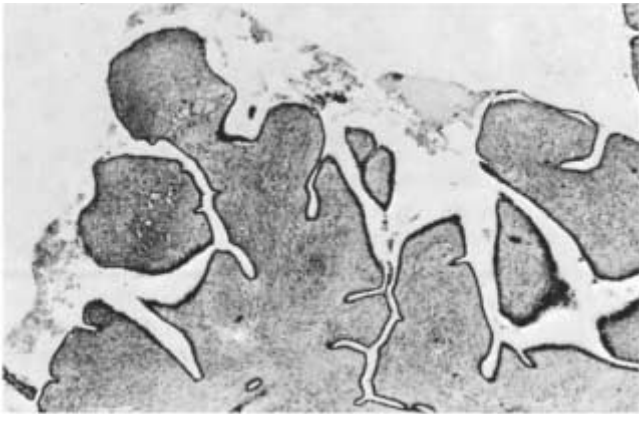
391. A 23-year-old woman presents with a rubbery, freely movable 2-cm mass in the upper outer quadrant of the left breast. A biopsy of this lesion would most likely histologically reveal

a. Large numbers of neutrophils
b. Large numbers of plasma cells
c. Duct ectasia with inspissation of breast secretions
d. Necrotic fat surrounded by lipid-laden macrophages
e. A mixture of fibrous tissue and ducts

392. A 39-year-old female presents with the new onset of a bloody discharge from her right nipple. Physical examination reveals a 1-cm freely movable mass that is located directly beneath the nipple. Sections from this mass reveal multiple fibrovascular cores lined by several layers of epithelial cells. Atypia is minimal. The lesion is completely contained within the duct and no invasion into underlying tissue is seen. What is the correct diagnosis?

a. Benign phyllodes tumor
b. Ductal papilloma
c. Intraductal carcinoma
d. Paget's disease
e. Papillary carcinoma

393. A 35-year-old female presents with a 2.2-cm mass in her left breast. The mass is excised, and histologic sections reveal a tumor composed of a mixture of ducts and cells, as seen in the photomicrograph below. The epithelial cells within the ducts are not atypical in appearance. There is a marked increase in the stromal cellularity, but the stromal cells are not atypical in appearance and mitoses are not found. What is the correct diagnosis for this breast lesion?



a. Atypical epithelial hyperplasia
b. Benign phyllodes tumor
c. Fibroadenoma
d. Malignant phyllodes tumor
e. Medullary carcinoma

394. The most important factor related to the prognosis of breast cancer is

a. The presence of activated oncogenes
b. The histologic type and grade
c. The size of the tumor
d. The status of axillary lymph nodes
e. The presence of estrogen receptors

395. A 48-year-old female presents with a 1.5-cm firm mass in the upper outer quadrant of her left breast. A biopsy from this mass reveals many of the ducts to be filled with atypical cells. In the center of these ducts there is extensive necrosis. No invasion into the surrounding fibrous tissue is seen. What is the correct diagnosis for this breast mass?

a. Colloid carcinoma
b. Comedocarcinoma
c. Infiltrating ductal carcinoma
d. Infiltrating lobular carcinoma
e. Lobular carcinoma in situ

396. Infiltrative lobular carcinoma of the breast is characterized histologically by

a. Large cells with clear cytoplasm within the epidermis
b. Single-file pattern of infiltration
c. Expansion of lobules by monotonous proliferation of epithelial cells
d. Large syncytium-like sheets of pleomorphic cells
e. Granulomatous inflammation

397. A 35-year-old woman who underwent a modified radical mastectomy of her right breast for infiltrating ductal carcinoma 2 years ago presents with enlargement of her right breast. The breast has a swollen, red-discolored appearance. It is diffusely indurated and tender on palpation. Multiple axillary lymph nodes are palpable in the lower axilla. The working clinical diagnosis is inflammatory carcinoma. Microscopic sections from this red, indurated area are most likely to reveal

a. Duct ectasia with numerous plasma cells
b. Extensive invasion of dermal lymphatics
c. Infiltrating malignant ducts surrounded by numerous neutrophils
d. Malignant vascular tumor forming slitlike spaces
e. Marked dermal desmoplasia

398. A 46-year-old woman presents with a 4-month history of a discharge from the nipple. An excisional biopsy of the nipple area reveals infiltration of the nipple by large cells with clear cytoplasm. These cells are found both singly and in small clusters in the epidermis and are PAS-positive and diastase-resistant. What is the correct diagnosis?

a. Ductal papilloma
b. Eczematous inflammation
c. Mammary duct ectasia
d. Paget's disease
e. Phyllodes tumor, malignant

399. A 13-year-old male presents with bilateral enlargement of his breasts. Physical exam is otherwise unremarkable, and the breast enlargement is thought to be a normal variation at puberty. Histologic sections of breast tissue would most likely reveal

a. Atrophic ductal structures with increased numbers of lipocytes
b. Dilated ducts filled with granular, necrotic, acidophilic debris
c. Expansion of lobules by monotonous proliferation of epithelial cells
d. Granulomatous inflammation surrounding ducts with numerous plasma cells
e. Proliferation of ducts in hyalinized fibrous tissue with periductal edema

Reproductive Systems

Answers

354. The answer is e. *(Cotran, pp 1011–1012. Rubin, pp 935, 938–939.)* Genital malformations may produce an abnormal location of the urethral opening, either on the ventral surface of the penis (hypospadias) or the dorsal surface (epispadias), and may cause problems with infertility. Hypospadias results from the failure of the urethral folds to close, while epispadias results from faulty positioning of the genital tubercle. Epispadias is also associated with exstrophy of the urinary bladder.

355. The answer is d. *(Cotran, p 1012. Rubin, p 936. Damjanov, pp 1710–1711, 2190–2191. Larsen, pp 222–226.)* Phimosis occurs when the orifice of the prepuce (foreskin) is too small to permit normal retraction. This may be due to inflammatory scarring or abnormal development of the prepuce. If a phimotic prepuce is forcibly retracted over the glans penis, a condition called paraphimosis may develop. This condition is extremely painful and may cause obstruction of the urinary tract or blood flow, which may lead to necrosis of the penis. Nonspecific infection of the glans and prepuce is called balanoposthitis. Genital malformations may cause an abnormal location of the urethral opening, either on the ventral surface of the penis (hypospadias) or the dorsal surface (epispadias). These abnormal developments may cause problems with infertility. Hypospadias is the result of failure of the urethral folds to close, while epispadias is the result of faulty positioning of the genital tubercle. The latter is also associated with exstrophy of the urinary bladder.

356. The answer is d. *(Cotran, pp 1012–1014.)* Clear vacuolization of the superficial layers of the epithelial cells (koilocytosis) is characteristic of infection by human papillomavirus (HPV). These changes are found in both condyloma acuminatum and verrucous carcinoma, but condyloma is a benign papillary lesion that does not grow into the underlying tissue, while verrucous carcinoma, also known as giant condyloma or Buschke-Löwenstein tumor, invades the underlying tissue along a broad front. This

type of invasion is in contrast to squamous cell carcinomas, which invade tissue as finger-like projections of atypical squamous epithelial cells. Three dysplastic, precancerous intraepithelial lesions of the penis that do not invade into the underlying tissue are Bowen's disease, erythroplasia of Queyrat, and Bowenoid papulosis.

357. The answer is d. *(Cotran, pp 1015–1016.)* The condition illustrated is cryptorchidism (failure of the testis to descend into the scrotum). It is present in up to 1% of males after puberty and is unilateral in the majority of cases. The testis is small, brown, and atrophic grossly. Microscopically, the tubules are atrophic with thickened basement membranes. The interstitial cells are usually prominent and occasional focal proliferations of Sertoli cells may be seen. The incidence of malignancy is increased 7- to 11-fold, and this risk is greater for abdominal than for inguinal locations. Seminoma is the most common malignancy. The risk of malignancy is not reduced by orchiopexy. There is a smaller but definite risk of malignancy in the contralateral, correctly placed testis.

358. The answer is e. *(Cotran, p 1025.)* Scrotal enlargement may be caused by cysts, tumors, inflammatory processes, or abnormalities of the blood vessels. Transillumination is helpful in differentiating between cysts (which transilluminate) and tumors (which do not). Examples of the latter include germ cell tumors and the adenomatoid tumor, a benign form of mesothelioma that histologically is composed of glandlike or slitlike spaces. Recall that the processus vaginalis is an outpouching of the peritoneum that enters into the scrotum. When the testis reaches the scrotum, the proximal portion of the processus vaginalis obliterates, but the distal portion persists and does not fuse. This forms the tunica vaginalis of the testis. Examples of cysts that involve this tunica vaginalis include hydroceles, hematoceles, chyloceles, and spermatoceles. Hydroceles contain clear fluid and result from developmental abnormalities or inflammatory processes. Hematoceles result from hemorrhage into a hydrocele, while chyloceles result from the accumulation of lymph fluid within the tunica as a result of elephantiasis. Spermatoceles refer to cystic enlargements of the efferent ducts or the rete testis with numerous spermatocytes present.

359. The answer is a. *(Cotran, pp 1018–1024.)* Germ cell tumors of the testis are clinically divided into two categories—seminomas and nonsemi-

nomatous germ cell tumors (NSGCTs)—because of their differences in presentation, metastasis, prognosis, and therapy. The NSGCTs include embryonal carcinomas, yolk sac tumors (infantile embryonal carcinomas or endodermal sinus tumors), choriocarcinomas, and immature teratomas. When compared with NSGCTs, seminomas are extremely radiosensitive, and they are more commonly present with stage I disease. NSGCTs are relatively radioresistant, are more aggressive, and have a worse prognosis. Seminomas typically spread via lymphatics after having remained localized for a long time. Embryonal carcinoma, choriocarcinoma, and mixed tumors with an element of choriocarcinoma tend to metastasize early via the blood. Choriocarcinomas are the most aggressive variant.

360. The answer is b. *(Cotran, pp 1018–1024.)* Germ cell tumors of the testis often secrete enzymes or polypeptide hormones, examples of which include α fetoprotein (AFP) and human chorionic gonadotropin (hCG). AFP is synthesized by the fetal gut, liver, and yolk sac. It may be secreted by either yolk sac tumors (endodermal sinus tumors) or embryonal carcinomas. AFP may also be secreted by liver cell carcinomas. β-hCG is a glycoprotein that is normally synthesized by placental syncytiotrophoblasts. Markedly elevated serum levels are most often associated with choriocarcinomas, which are characterized histologically by a mixture of malignant cytotrophoblasts and syncytiotrophoblasts. Mildly elevated serum levels of β-hCG may be found in patients with other types of germ cell tumors if they contain syncytiotrophoblast-like giant cells. This is found in about 10% of classic seminomas, which are characterized histologically by large cells with distinct cell membranes and clear cytoplasm. An important, distinct variant of seminoma is the spermatocytic seminoma. It is characterized by being found in older individuals and by the fact that it does not metastasize. Histologically, a spermatocytic seminoma is characterized by maturation of the tumor cells, some of which histologically resemble secondary spermatocytes. To summarize: markedly elevated levels of hCG are associated with choriocarcinomas, while elevated levels of AFP are most characteristic of yolk sac tumors and embryonal carcinomas. But there are many areas of overlap between tumors, and many tumors are composed of multiple types of germ cell cancers. The only definitive statement that can be made is that elevated serum levels of AFP cannot be seen in a tumor that is a pure seminoma.

361. The answer is a. *(Cotran, pp 1025–1027.)* Inflammation of the prostate (prostatitis) is characterized by finding at least 15 leukocytes per high-power field in prostatic secretions. Prostatitis is classified as being either acute or chronic. Patients with acute prostatitis present with the sudden onset of fever, chills, and dysuria. Acute prostatitis is usually caused by bacteria that cause urinary tract infections, such as *Escherichia coli*. Chronic prostatitis presents clinically as low back pain, dysuria, and suprapubic discomfort. It is divided into chronic bacterial prostatitis, which is associated with recurrent urinary tract infections (UTIs) with the same organism, and chronic abacterial prostatitis, which is not associated with recurrent UTIs. Instead, chronic abacterial prostatitis is associated with infections with either *Chlamydia trachomatis* or *Ureaplasma urealyticum*. Granulomatous prostatitis causes vague symptoms and has an unknown etiology. This diagnosis is made histologically.

362. The answer is d. *(Cotran, pp 1027–1029.)* Benign enlargement of the prostate is caused by benign prostatic hyperplasia (BPH) and produces clinical symptoms of urinary frequency, nocturia, difficulty in starting and stopping urination, dribbling, and dysuria. Histologically, the hyperplastic nodules are composed of a variable mixture of hyperplastic glands and hyperplastic stromal cells. Histologic signs of malignancy are not present. The development of BPH is associated with increased age and higher testosterone levels. BPH results from androgen-induced glandular proliferation, but estrogen also sensitizes the tissue to androgens. Urinary obstruction results because the inner, periurethral portions of the prostate (the middle and lateral lobes) are affected most commonly. BPH does not predispose the individual to cancer. In contrast to the benign histology of BPH, the histologic signs characteristic of prostatic adenocarcinoma include small glands that appear "back to back" without intervening stroma, or that appear to be infiltrating beyond the normal prostate lobules. Histologically, these malignant glands are composed of a single layer of cuboidal epithelial cells, as the outer basal layer of epithelial cells, seen in normal and hyperplastic glands, is not present. These malignant cells often contain one or more enlarged nucleoli.

363. The answer is c. *(Cotran, pp 1029–1033.)* Knowledge of the anatomic division of the prostate is important in understanding the locations of the major pathologic diseases of the prostate. Most adenocarcino-

mas of the prostate originate in the peripheral zone, while hyperplastic nodules originate in the transition zone. This anatomic differentiation is the result of the physiologic fact that the transition zone is particularly estrogen-sensitive, while the peripheral zone is particularly androgen-sensitive. Dihydrotestosterone (DHT), which is formed from testosterone by the action of 5-α-reductase, is responsible for the development of the prostate during fetal growth and also at the time of puberty. With aging, DHT levels are increased in the prostate, where DHT binds to nuclear DNA and causes prostatic hyperplasia. This hyperplastic effect by DHT is augmented by estrogen, which appears to function by induction of androgen receptors, and therefore this hyperplasia occurs in the portion of the prostate that is particularly estrogen-sensitive.

364. The answer is c. *(Cotran, p 1036. Larsen, pp 247–253.)* The paired genital ducts consist of the mesonephric (Wolffian) duct, which extends from the mesonephros to the cloaca, and the paramesonephric (Müllerian) duct, which runs parallel and lateral to the Wolffian duct. The mesonephric ducts in males, if stimulated by testosterone secreted by the Leydig cells, develop into the vas deferens, epididymis, and seminal vesicles. In contrast, because normal females do not secrete testosterone, the Wolffian ducts regress and form vestigial structures. They may, however, form mesonephric cysts in the cervix or vulva, or they may form Gartner duct cysts in the vagina. The cranial group of mesonephric tubules (the epoophoron) remains as vestigial structures in the broad ligament above the ovary, while the caudal group of mesonephric tubules (the paroophoron) forms vestigial structures in the broad ligament beside the ovary. The paramesonephric (Müllerian) ducts in the female form the fallopian tubes, the uterus, the uppermost vaginal wall, and the hydatid of Morgagni. The lower portion of the vagina and the vestibule develop from the urogenital sinus. Males secrete Müllerian-inhibiting factor (MIF) from the Sertoli cells of the testes, which causes regression of the Müllerian ducts. This results in the formation of the vestigial appendix testis. The metanephric duct in both sexes forms the ureter, renal pelvis, calyces, and renal collecting tubules. Several abnormalities result from abnormal embryonic development of the Müllerian ducts. Uterine agenesis may result from abnormal development or fusion of these paired paramesonephric ducts. Developmental failure of the inferior portions of the Müllerian ducts results in a double uterus, while failure of the superior portions to fuse (incomplete fusion) may form a bicornuate

uterus. Retarded growth of one of the paramesonephric ducts along with incomplete fusion to the other paramesonephric ducts results in the formation of a bicornuate uterus with a rudimentary horn.

365. The answer is e. *(Cotran, pp 1045–1047, 1057–1058, 1065–1066.)* Obstruction of the ducts of any of the glands found within the female genitalia may cause the formation of a genital cyst. The paired Bartholin's glands, which are analogous to the bulbourethral glands of the male, are located in the lateral wall of the vestibule. If these are obstructed, a cyst may form that is usually lined with transitional epithelium. Gartner's duct cysts, derived from Wolffian (mesonephric) duct remnants, are located in the lateral walls of the vagina. Cysts derived from the same Wolffian duct may also be found on the lateral aspect of the vulva and are called mesonephric cysts. Obstruction of the ducts of the mucous glands in the endocervix may result in small mucous (Nabothian) cysts. Cysts may also be found within the skin of the vulva. These cysts, which contain white, cheesy material, are called keratinous (epithelial inclusion) cysts. Clinically they are referred to as sebaceous cysts, which is a misnomer. Follicular cysts are benign cysts of the ovary, while "chocolate cysts" refers to cystic areas of endometriosis that include hemorrhages and blood clots.

366. The answer is a. *(Cotran, pp 1040–1042.)* Several pathologic conditions are associated with the formation of white plaques on the vulva, which are clinically referred to as leukoplakia. Lichen sclerosis is seen histologically as atrophy of the epidermis with underlying dermal fibrosis. This abnormality is seen in postmenopausal women, who develop pruritic white plaques of the vulva. It is not thought to be premalignant. Loss of pigment in the epidermis (vitiligo) can also produce leukoplakia. Inflammatory skin diseases, such as chronic dermal inflammation, squamous hyperplasia (characterized by epithelial hyperplasia and hyperkeratosis), and vulvar intraepithelial neoplasia (characterized by epithelial atypia or dysplasia), can also present with leukoplakia. A term related to leukoplakia is vulvar dystrophy, but this refers specifically to either lichen sclerosis or squamous hyperplasia. Because the latter is sometimes associated with epithelial dysplasia, it is also referred to as hyperplastic dystrophy. It is most commonly seen in postmenopausal women. The male counterpart of lichen sclerosis, called balanitis xerotica obliterans, is found on the penis. Paget's disease is a malignant tumor that can be found in the breast or the vulva. The latter is

seen clinically as pruritic, red, crusted, sharply demarcated maplike areas. Histologically, these malignant lesions reveal single anaplastic tumor cells surrounded by clear spaces ("halos") infiltrating the epidermis. These malignant cells stain positively with PAS and mucicarmine stains.

367. The answer is e. *(Cotran, pp 1044–1045.)* Two rare vulvar malignancies, characterized by malignant cells that individually infiltrate the epidermis, are Paget's disease and malignant melanoma. Paget's disease, which manifests grossly as pruritic, red, crusted, sharply demarcated maplike areas, histologically reveals single anaplastic tumor cells infiltrating the epidermis. These cells are characterized by having clear spaces ("halos") between them and the adjacent epithelial cells. These malignant cells stain positively with PAS or mucicarmine stains. Paget's disease of the vulva (extramammary Paget's disease) is similar to Paget's disease of the nipple except that 100% of cases of Paget's disease of the nipple are associated with an underlying ductal carcinoma of the breast, while vulvar lesions are most commonly confined to the skin. Malignant melanoma of the vulva may resemble Paget's disease both grossly and microscopically; however, these malignant cells stain positively with a melanin stain or an S100 immunoperoxidase stain.

368. The answer is c. *(Cotran, pp 1045–1046. Rubin, p 975.)* Adenocarcinomas of the vagina and cervix have always existed, but rates are increased in young women whose mothers received diethylstilbestrol (DES) while pregnant. DES, which has estrogenic activity, was used in the past to terminate an attack of threatened abortion and thereby stabilize the pregnancy. However, a side effect of this therapy proved to be a particular form of adenocarcinoma, clear cell carcinoma. This phenomenon was elucidated by Herpses and Scully in 1970. This unique adenocarcinoma was discovered in women between the ages of 15 and 20 whose mothers had received DES. The tumor, which carries a poor prognosis, has at least three histologic patterns. One is a tubulopapillary configuration, followed by sheets of clear cells and glands lined by clear cells, and solid areas of relatively undifferentiated cells. Many of the cells have cytoplasm that protrudes into the lumen and produces a "hobnail" (nodular) appearance. Prior to the development of adenocarcinoma, a form of adenosis consisting of glands with clear cytoplasm that resembles that of the endocervix can be seen. This has been termed vaginal adenosis and may be a precursor of clear cell carci-

noma. Clinically, adenosis of the vagina is manifested by red, moist granules superimposed on the pink-white vaginal mucosa.

369. The answer is e. *(Cotran, pp 1045–1046, 1048–1053.)* Cervical condylomata and cervical intraepithelial neoplasia (CIN), which comprises both dysplasia and carcinoma in situ (CIS), are associated with human papillomavirus (HPV) infection. More than 50 genotypes of HPV are known at present, and condylomata acuminata are associated with types 6 to 11, while types 16 to 18 are usually present in CIN. Histologically, HPV infection is characterized by prominent perinuclear cytoplasmic vacuolization with shrunken, dark, irregular nuclei (koilocytosis). Following an abnormal Pap smear report suggesting condyloma, CIN, or possible invasive carcinoma, workup of the patient should include colposcopy, multiple cervical punch biopsies, and endocervical curettage to distinguish among patients who have invasive cancer, CIN, or flat condylomata.

370. The answer is d. *(Cotran, pp 1054–1055, 1057.)* The endometrium and myometrium are relatively resistant to infections. Therefore, inflammation of the endometrium (endometritis) is rare. The diagnosis of endometritis depends on finding inflammatory cells within the endometrium that are not present during the normal menstrual cycle. Polymorphonuclear leukocytes (neutrophils) are normally present during menstruation, while a stromal lymphocytic infiltrate can be seen at other times during the menstrual cycle. Lymphoid aggregates and lymphoid follicles may also be seen in normal endometrium. Therefore the presence of any of these types of leukocytes is not diagnostic of endometritis. Acute endometritis is usually caused by bacterial infection following delivery or miscarriage and is characterized by the presence of neutrophils in endometrial tissue that is not menstrual endometrium. The histologic diagnosis of chronic endometritis depends on finding plasma cells within the endometrium. All it takes is one plasma cell to make the diagnosis. Chronic endometritis may be seen in patients with intrauterine devices (IUDs), pelvic inflammatory disease (PID), retained products of conception (postpartum), or tuberculosis. The latter is characterized histologically by the presence of caseating granulomas with Langhans giant cells. These are secondary causes of chronic endometritis. In a significant number of cases, no underlying cause is found. Decidualized stromal cells are the result of the effects of progesterone and are seen normally in the late secretory phase or in patients who are pregnant. Histologically, these stromal cells contain abundant eosinophilic cytoplasm.

371. The answer is b. *(Cotran, pp 1057–1058.)* Endometrial tissue located in abnormal locations is still under the cyclic influence of hormones and may produce menorrhagia, dysmenorrhea, and cyclic pelvic pain. The ectopic endometrial tissue may be located within the myometrium or it may be found outside of the uterus. The former type, consisting of nests of endometrial stroma within the myometrium, is called adenomyosis. It is thought to result from the abnormal downgrowth of the endometrium into the myometrium. Ectopic endometrial tissue outside of the uterus is called endometriosis and histologically reveals endometrial glands, stroma, and hemosiderin pigment (from the cyclic bleeding). Repeated cyclic bleeding in patients with endometriosis can lead to the formation of cysts that contain areas of new and old hemorrhages. Because they grossly contain blood clots, these cysts have been called "chocolate cysts." Endometriosis is thought to possibly arise from metaplasia of celomic epithelium into endometrial tissue, or implantation of normal fragments of menstrual endometrium either via the fallopian tubes or via the blood vessels. Other sites of endometriosis include the uterine ligaments (associated with dyspareunia), the rectovaginal pouch (associated with pain on defecation and low back pain), the fallopian tubes (associated with peritubular adhesions, infertility, and ectopic pregnancies), the urinary bladder (associated with hematuria), the GI tract (associated with pain, adhesions, bleeding, and obstruction), and the vagina (associated with bleeding).

372. The answer is b. *(Cotran, pp 1055–1056. Rubin, pp 991–992.)* With normal menstruation about 30 to 40 mL of blood is lost. Amounts greater than 80 mL lost on a continued basis are considered to be abnormal. Menorrhagia refers to excessive bleeding at the time of menstruation, either in the number of days or the amount of blood. A submucosal leiomyoma could produce menorrhagia. Metrorrhagia refers to bleeding that occurs at irregular intervals. Causes of metrorrhagia include cervical polyps, cervical carcinoma, endometrial carcinoma, or exogenous estrogens. Menometrorrhagia refers to excessive bleeding that occurs at irregular intervals. Postmenopausal bleeding occurs greater than 1 year after the normal cessation of menses at menopause. Oligomenorrhea refers to infrequent bleeding that occur at intervals greater than 35 days. Causes include polycystic ovarian syndrome and too low a total body weight. Polymenorrhea refers to frequent, regular menses that are less than 22 days apart. It is commonly associated with anovulatory cycles, which can occur at menarche. Dysmenorrhea refers to painful menses. It is associated with increased levels of prostaglandin F in the menstrual fluid.

373. The answer is b. *(Cotran, pp 1055–1056. Rubin, pp 991–992.)* Dysfunctional uterine bleeding (DUB) is defined as abnormal uterine bleeding that is due to a functional abnormality rather than an organic lesion of the uterus. In contrast, secondary dysmenorrhea refers to painful menses associated with an organic cause, such as endometriosis, which is the most common cause. Most cases of DUB are related to an endocrine abnormality affecting the hypothalamic-pituitary-ovarian axis. The three main categories of DUB are anovulatory cycles (the most common form), inadequate luteal phase, and irregular shedding. Anovulatory cycles consist of persistence of the Graafian follicle without ovulation. This results in continued and excess estrogen production without the normal postovulatory rise in progesterone levels. With no progesterone production, no secretory endometrium is formed. Instead, biopsies reveal nonsecretory (proliferative) endometrium with mild hyperplasia. The mucosa becomes too thick and is sloughed off, resulting in the abnormal bleeding. Anovulatory cycles characteristically occur at menarche and menopause. They are also associated with polycystic ovary (Stein-Leventhal) syndrome. It is important to note that other causes of unopposed estrogen effect can lead to this appearance of a proliferative endometrium with mild hyperplasia. These causes include exogenous estrogen administration or estrogen-secreting neoplasms, such as a granulosa cell tumor of the ovary or an adrenal cortical neoplasm. If there is ovulation but the functioning of the corpus luteum is inadequate, then the levels of progesterone are decreased, resulting in asynchrony between the chronologic dates and the histologic appearance of the secretory endometrium. This is referred to as an inadequate luteal phase (luteal phase defect) and is an important cause of infertility. Biopsies are usually performed several days after the predicted time of ovulation. If the histologic dating of the endometrium lags 4 or more days behind the chronologic date predicted by the menstrual history, the diagnosis of luteal phase defect can be made. Clinically, these patients exhibit low serum progesterone, FSH, and LH levels. In contrast, prolonged functioning of the corpus luteum (persistent luteal phase with continued progesterone production) results in prolonged heavy bleeding at the time of menses. Histologically, there is a combination of secretory glands mixed with proliferative glands (irregular shedding). Clinically, these patients have regular periods, but the menstrual bleeding is excessive and prolonged (lasting 10 to 14 days). Current oral contraceptives, being a combination of estrogen and progesterone, cause the endometrium to include inactive glands with

predecidualized stroma. The endometrium in postmenopausal women reveals an atrophic pattern with atrophic or inactive glands.

374. The answer is c. *(Cotran, pp 1059–1061.)* Endometrial hyperplasia, related to excess estrogens, is important clinically because of its relation to the development of endometrial adenocarcinoma. The types of endometrial hyperplasia include simple hyperplasia, complex hyperplasia, and atypical hyperplasia. Simple hyperplasia, which histologically resembles proliferative-type endometrium, was previously classified as mild hyperplasia or cystic hyperplasia. In cystic hyperplasia, some glands become dilated or form cysts. Complex hyperplasia consists of crowded endometrial glands having budding, but no cytologic atypia, while atypical hyperplasia is characterized by complex glandular crowding with cellular atypia. The most important prognostic feature is the presence of cytologic atypia. Therefore, both simple hyperplasia and complex hyperplasia are lower-grade hyperplasias, while atypical hyperplasia, which used to be called adenomatous hyperplasia with atypia, is a higher-grade hyperplasia. Adenocarcinoma is characterized by stromal invasion. Endometrial polyps are benign sessile masses that are found within the uterine cavity. Histologically, they are usually composed of cystic endometrial glands in a stroma having thick-walled blood vessels.

375. The answer is a. *(Cotran, pp 1061–1063. Damjanov, pp 2269–2271.)* Cancers that originate from the endometrium grossly may present as a polypoid mass within the uterine cavity or a diffuse tumor involving the endometrium with possible spread into the myometrium. Histologically they are adenocarcinomas that are composed of malignant, infiltrating glandular structures. If there are areas of squamous differentiation within these tumors, they are called adenoacanthomas. If there are areas of malignant squamous differentiation, they are called adenosquamous carcinomas. Endometrial carcinoma affects menopausal and postmenopausal women, with the peak incidence at 55 to 65 years of age. Although it was much less common than squamous cervical cancer several decades ago, it has not been controlled as effectively as cervical cancer by the Papanicolaou smear technique and therapy, so that it is now more common than invasive cervical cancer. However, the major symptom of endometrial carcinoma—postmenopausal bleeding—results in diagnosis while the tumor is still confined to the uterus (stage I or II), which permits cure by surgery or

radiotherapy. The annual death rate in the U.S. from endometrial cancer is 3000, while more than 6000 deaths result from squamous cervical cancer. Risk factors for endometrial cancer include obesity and glucose intolerance or diabetes.

376. The answer is a. *(Damjanov, pp 2273–2275. Rubin, pp 998–1000.)* "Fibroids" of the uterus are among the most common abnormalities seen in uteri surgically removed in the United States in women of reproductive age. They arise in the myometrium, submucosally, subserosally, and midwall, both singly and several at a time. Sharply circumscribed, they are benign smooth-muscle tumors that are firm, gray-white, and whorled on cut section. Their malignant counterpart, leiomyosarcoma of the uterus, is quite rare in the de novo state and arises even more rarely from an antecedent leiomyoma. Whereas cell pleomorphism, tissue necrosis, and cytologic atypia per se are established criteria in assessing malignancy in tumors generally, they are important to the pathologist in uterine fibroids only if mitoses are also present. Regardless of cellularity or atypicality, if 10 or more mitoses are present in 10 separate high-power microscopic fields, the lesion is a leiomyosarcoma. If five or fewer mitoses are present in 10 fields with bland morphology, the leiomyoma will behave in a benign fashion. Problems arise when the mitotic counts range between three and seven per 10 fields with varying degrees of cell and tissue atypicality. These equivocal lesions should be regarded by both pathologist and clinician as "gray-area" smooth-muscle tumors of unpredictable biologic behavior. Fortunately, the gray-area leiomyoma of the uterus is rarely seen. Thus mitoses are the most important criteria in assessing malignancy in smooth-muscle tumors of the uterus.

377. The answer is e. *(Cotran, pp 1039–1040, 1065.)* Pelvic inflammatory disease (PID) is a common disorder caused by infection with either gonococci (the most common cause), chlamydiae, or enteric bacteria. Gonococcal infection, seen microscopically as gram-negative intracellular diplococci, begins in the Bartholin's glands and then spreads upward to involve the fallopian tubes and tuboovarian regions. This produces PID, which is characterized by pelvic pain, fever, adnexal tenderness, and pain when the cervix is manipulated. Complications of PID include peritonitis from rupture of a tuboovarian abscess, infertility, and intestinal obstruction.

378. The answer is d. *(Cotran, pp 1066–1067. Chandrasoma, pp 764–767.)* Infertility affects close to 20% of married couples in the United States, and in many of these cases the infertility is related to polycystic ovary (Stein-Leventhal) syndrome in the female. The symptoms of patients with this syndrome are related to increased androgen production, which causes hirsutism, and decreased ovarian follicle maturation, which can lead to amenorrhea. These patients typically have excess androgens (androstenedione), increased estrogen levels, increased LH levels, increased GnRH levels, and decreased FSH levels (with a high LH/FSH ratio). The cause of this syndrome is thought to be the abnormal secretion of gonadotropins by the pituitary. Increased secretion of LH stimulates the thecal cells to secrete excess amounts of androgens, which are converted to estrone by the peripheral aromatization of androgens by the adrenal gland. Excess estrogens in turn increase the levels of gonadotropin-releasing hormone (GnRH) but decrease the levels of FSH. The GnRH increases the levels of LH, which then stimulate the thecal cells of the ovary to secrete more androgens, and the hormonal cycle begins again. The ovaries in these patients are enlarged and show thick capsules, hyperplastic ovarian stroma, and numerous follicular cysts, which are lined by a hyperplastic theca interna. Since these patients do not ovulate, there is a markedly decreased number of corpora lutea, which in turn results in decreased progesterone levels. These patients also have an increased risk of developing endometrial hyperplasia and endometrial carcinoma because of the excess estrogen production. Treatment for these patients in the past involved surgical wedge resection of the ovary, but now clomiphene, which stimulates ovulation, is used.

379. The answer is a. *(Cotran, pp 1067–1073.)* The surface epithelial tumors of the ovary are derived from the surface celomic epithelium, which embryonically gives rise to the Müllerian epithelium. Therefore these ovarian epithelial tumors may recapitulate the histology of organs derived from the Müllerian epithelium. For example, serous ovarian tumors are composed of ciliated columnar serous epithelial cells, which are similar to the lining cells of the fallopian tubes. Endometrioid ovarian tumors are composed of nonciliated columnar cells, which are similar to the lining cells of the endometrium. Mucinous ovarian tumors are composed of mucinous nonciliated columnar cells, which are similar to the epithelial cells of the endocervical glands. Other epithelial ovarian tumors are similar histologically to other organs of the urogenital tract, such as the clear cell ovarian

carcinoma and the Brenner tumor. Clear cell carcinoma of the ovary is similar histologically to clear cell carcinoma of the kidney, or more accurately, the clear cell variant of endometrial adenocarcinoma or the glycogen-rich cells associated with pregnancy. The Brenner tumor is similar to the transitional lining of the renal pelvis or bladder. This ovarian tumor is associated with benign mucinous cystadenomas of the ovary.

380. The answer is c. *(Cotran, pp 1070–1071.)* Pseudomyxoma peritonei refers to the formation of multiple mucinous masses within the peritoneum. This condition results from the spread of mucinous tumors, either from metastasis or rupture of an ovarian mucinous cyst. It may also result from spread of a mucinous tumor located in the appendix. This condition is difficult to treat surgically and if widespread can lead to intestinal obstruction and possibly death.

381. The answer is d. *(Damjanov, pp 2293–2294. Cotran, pp 1073–1075.)* Benign cystic teratomas constitute about 10% of cystic ovarian tumors. The cysts contain greasy sebaceous material mixed with a variable amount of hair. The cysts' walls contain skin and skin appendages, including sebaceous glands and hair follicles. A variety of other tissues—such as cartilage, bone, tooth, thyroid, respiratory tract epithelium, and intestinal tissue—may be found. The presence of skin and skin appendages gives the tumor its other name, dermoid cyst. Dermoid cysts are benign, but in less than 2%, one element may become malignant, most frequently the squamous epithelium.

382. The answer is b. *(Cotran, pp 1076–1079. Chandrasoma, pp 775–776.)* Ovarian neoplasms are divided into four main categories: epithelial tumors, sex cord–stromal tumors, germ cell tumors, and metastases. Examples of ovarian stromal tumors include thecomas, fibromas, granulosa cell tumors, and Sertoli-Leydig cell tumors. Histologically, thecomas are composed of spindle-shaped cells with vacuolated cytoplasm. They are vacuolate because of steroid hormone (estrogen) production, which can be stained with an oil red O stain. Fibromas are also composed of spindle-shaped cells, but they do not produce steroid hormones and are oil red O–negative. Fibromas are associated with Meigs' syndrome, which consists of an ovarian fibroma, ascites, and hydrothorax. Granulosa cell tumors vary in their clinical behavior, but they are considered to be potentially malignant. The stromal cells of

the ovary are the precursors of endocrine active cells, so it is easy to understand that neoplasms derived from these stromal cells are often associated with hormone production. For example, granulosa cells normally secrete estrogens, thecal cells normally secrete androgens, and hilar cells (Leydig cells) may secrete androgens. Excess androgen production in females may lead to masculinization and produce symptoms such as amenorrhea, loss of secondary female sex characteristics, and the development of secondary male characteristics, such as hirsutism, temporal balding, and deepening of the voice. Ovarian tumors associated with excess androgen production include androblastomas (Sertoli-Leydig cell tumors). Other ovarian diseases associated with excess androgen production include polycystic ovarian disease and hyperthecosis. Excess estrogen production is associated with precocious puberty in the young and with endometrial hyperplasia and cancer in older women. Ovarian tumors that may secrete estrogens include granulosa cell tumors and thecomas.

383. The answer is b. *(McPhee, pp 531–536. Cotran, pp 1056, 1079.)* Secondary amenorrhea refers to absent menses for 3 months in a woman who had previously had menses. Causes of secondary amenorrhea include pregnancy (the most common cause), hypothalamic/pituitary abnormalities, ovarian disorders, and end organ (uterine) disease. Pregnancy can be diagnosed by obtaining a clinical history along with a pregnancy test that determines serum or urine β-human chorionic gonadotropin (β-hCG) levels. Placental human chorionic gonadotropin (hCG), secreted by syncytiotrophoblasts, functions early in pregnancy to stimulate the corpus luteum to continue secreting progesterone until the mature placenta, working together with the mother and the fetus, can produce progesterone. Levels of hCG reach a peak at approximately 8 to 10 weeks of development and then rapidly decline.

The remainder of the disorders causing secondary amenorrhea can be differentiated by examining gonadotropin (FSH and LH) levels along with the results of a progesterone challenge test. Withdrawal bleeding following progesterone administration indicates that the endometrial mucosa had been primed with estrogen, which in turn indicates that the hypothalamus/pituitary axis and ovaries are normal. Hypothalamic/pituitary disorders, which are characterized by decreased FSH and LH levels, include functional gonadotropin deficiencies, such as can be seen in patients with a weight loss syndrome. In these patients, markedly decreased body weight

(>15% below ideal weight) causes decreased secretion of GnRH from the hypothalamus. Decreased gonadotropin levels decrease estrogen levels, which results in amenorrhea and an increased risk for osteoporosis. Because of the decreased estrogen levels, a progesterone challenge does not result in withdrawal bleeding. Ovarian conditions, such as surgical removal of the ovaries, would most likely produce elevated gonadotropin levels due to the lack of negative feedback from estrogen and progesterone. Because of the decreased estrogen levels, a progesterone challenge would not result in withdrawal bleeding. Uterine (end organ) disorders are characterized by normal FSH and LH levels. An example is Asherman's syndrome, in which numerous and overly aggressive dilatation and curettage of the endometrium for menorrhagia removes the stratum basalis and no glandular epithelium remains. A patient with Asherman's syndrome would have no response to progesterone.

384. The answer is c. *(Cotran, pp 1080–1082. Chandrasoma, pp 809–811.)* Abruptio placenta refers to premature separation of a normally located placenta. This abnormality produces marked hemorrhage, premature labor, and fetal demise. Factors that predispose an individual to abruptio placenta include use of certain drugs (cocaine, alcohol, tobacco), maternal hypertension, preeclampsia, multiparity, and increasing maternal age. Placenta previa occurs when the placenta implants in the lower uterine segment. This may also result in severe bleeding problems at the time of delivery. Vaginal examination of a patient with this condition could also be dangerous. Placenta accreta refers to the absence of the decidua and the direct attachment of the placenta to the myometrium. There is no plane of separation between the placental villi and the myometrium. It is an important cause of postpartum hemorrhage because the placenta fails to separate from the myometrium at the time of labor. The hemorrhage can be life-threatening, and a total hysterectomy is the treatment of choice. In both placenta accreta and placenta previa the villi are histologically normal and there is no trophoblastic proliferation.

In contrast, gestational trophoblastic disease refers to abnormal proliferation of trophoblastic tissue and includes hydatidiform mole, invasive mole, and malignant choriocarcinoma. These neoplasms all secrete β-human chorionic gonadotropin (β-hCG) and should be suspected clinically whenever the uterus is too large for the estimated gestational age and no fetal movement or heart sounds are present.

385. The answer is c. *(Cotran, p 1079–1080.)* Ectopic pregnancy is a potentially life-threatening condition if it is not treated by removal before rupture and hemorrhage with fatal exsanguination. The most common location for extrauterine implantation is the fallopian tube (more than 85% of cases), with rare implantation in the ovary or abdomen. If the tubal implantation has existed for 1 to 4 weeks, the β-hCG test result is likely to be negative; thus a negative result does not exclude pregnancy. It is always worthwhile to repeat a laboratory test when the result is unexpected. Tubal pregnancy is not uncommon and should always be considered if endometrial samples suggest gestational change without chorionic villi.

386. The answer is e. *(Cotran, pp 1082–1084. Chandrasoma, pp 811–814.)* Toxemia of pregnancy refers to the combination of hypertension, proteinuria, and pitting edema. This combination of signs is also called preeclampsia. When convulsions develop in an individual with preeclampsia, the condition is then referred to as eclampsia. These signs and symptoms result from abnormal placental implantation with incomplete conversion of the blood vessels of the decidua. Both of these result in placental ischemia. Normally the blood vessels of the uterine wall at the site of implantation increase in diameter and lose their muscular components. These changes increase the blood flow to the placenta and are the result of increased production of prostacyclin (a strong vasodilator) and decreased production of thromboxane (a potent vasoconstrictor). These changes do not take place at the implantation site in patients who develop preeclampsia. This causes placental ischemia and damages the endothelial cells of the blood vessels of the placenta. This endothelial damage disrupts the normal balance between vasodilation and vasoconstriction. As a result, there are increased levels of vasoconstrictors, such as thromboxane, angiotensin, and endothelin, and decreased levels of vasodilators, such as PGI_2, PGE_2, and nitric oxide. This results in arterial vasoconstriction, which produces systemic hypertension and can lead to activation of intravascular coagulation (DIC). Risk factors for the development of preeclampsia include nulliparity, twin gestation, and hydatidiform mole. Other complications associated with preeclampsia include renal disease and liver disease, such as the HELLP syndrome, which refers to hemolytic anemia, elevated liver enzymes, and low platelets.

387. The answer is b. *(Cotran, pp 1084–1089.)* Gestational trophoblastic diseases include benign hydatidiform mole (partial and complete), invasive

mole (chorioadenoma destruens), placental site trophoblastic tumor, and choriocarcinoma. Hydatidiform moles are composed of avascular, grape-like structures that do not invade the myometrium. In complete (classic) moles, all the chorionic villi are abnormal and fetal parts are not found. They have a 46,XX diploid pattern and arise from the paternal chromosomes of a single sperm by a process called androgenesis. In partial moles, only some of the villi are abnormal and fetal parts may be seen. These moles have a triploid or a tetraploid karyotype and arise from the fertilization of a single egg by two sperm. About 2% of complete moles may develop into choriocarcinoma, but partial moles are rarely followed by malignancy. Invasive moles penetrate the myometrium and may even embolize to distant sites. A similar lesion is the placental site trophoblastic tumor, which is characterized by invasion of the myometrium by intermediate trophoblasts. Gestational choriocarcinomas, composed of malignant proliferations of both cytotrophoblasts and syncytiotrophoblasts without the formation of villi, can arise from either normal or abnormal pregnancies; 50% arise in hydatidiform moles, 25% in cases of previous abortion, 22% in normal pregnancies, and the rest in ectopic pregnancies or teratomas. Both hydatidiform moles and choriocarcinomas have high levels of human chorionic gonadotropin (hCG); the levels are extremely high in choriocarcinoma unless considerable tumor necrosis is present.

388. The answer is d. *(McPhee, pp 519, 527–528. Cotran, p 1056.)* Menopause refers to cessation of menstrual cycles in females, while menarche refers to the first menstrual cycle. Characteristics of menopause include elevated gonadotropins (FSH is the best indicator), secondary amenorrhea, hot flushes, decreased vaginal secretions, and night sweats. In addition, atrophy begins in estrogen-dependent tissues, such as the vagina. Gradual loss of bone density can lead to osteoporosis.

389. The answer is e. *(Cotran, pp 1096–1098.)* Fat necrosis of the breast is characterized by necrotic fat surrounded by lipid-laden macrophages and a neutrophilic infiltration. It is associated with trauma to the breasts, usually in women with pendulous breasts. Traumatic fat necrosis differs from enzymatic fat necrosis because it does not involve the pancreatic enzyme lipase. Fat necrosis may be confused clinically with cancer; however, in contrast to cancer, fat necrosis is painful. Numerous neutrophils are seen in acute bacterial infection of the breast (acute mastitis), which is usually seen in the

postpartum lactating or involuting breast. Dilation of the breast ducts (ectasia) with inspissation of breast secretions is characteristic of mammary duct ectasia, which is common in elderly women. If large numbers of plasma cells are also present, the lesion is called plasma cell mastitis. Reaction to silicone, as occurs with a ruptured or leaking silicone implant, is characterized histologically by a foreign-body-type granulomatous reaction with multinucleated giant cells and numerous foamy histiocytes.

390. The answer is a. *(Cotran, pp 1098–1101.)* Fibrocystic change of the breast is one of the most common features seen in the female breast. It is most likely associated with an endocrine imbalance that causes an abnormality of the normal monthly cyclic events within the breast. These fibrocystic changes are subdivided into nonproliferative and proliferative changes. Nonproliferative changes include fibrosis of the stroma and cystic dilation of the terminal ducts, which when large may form blue-domed cysts. A common feature of the ducts in nonproliferative changes is apocrine metaplasia, which refers to epithelial cells with abundant eosinophilic cytoplasm with apical snouts. Proliferative changes include epithelial hyperplasia of the ducts. This hyperplastic epithelium may form papillary structures (papillomatosis when pronounced), or may be quite abnormal (atypical hyperplasia). Two benign, but clinically important, forms of proliferative fibrocystic change include sclerosing adenosis and radial scar. Both of these may be mistaken histologically for infiltrating ductal carcinoma, but the presence of myoepithelial cells is a helpful sign that points to the benign nature of the proliferation. Sclerosing adenosis is a disease of the terminal lobules that is typically seen in patients 35 to 45 years old. It produces a firm mass, most often located in the upper outer quadrant. Microscopically there is florid proliferation of small ductal structures in a fibrous stroma, which on low power is stellate in appearance and somewhat maintains the normal lobular architecture. A radial scar refers to ductal proliferation around a central fibrotic area.

391. The answer is e. *(Cotran, pp 1102–1103. Rubin, pp 1035–1037.)* The most common benign neoplasm of the breast is fibroadenoma, which typically occurs in the upper outer quadrant of the breast in women between the ages of 20 and 35. These lesions originate from the terminal duct lobular unit and histologically reveal a mixture of fibrous connective tissue and ducts. Clinically, fibroadenomas are rubbery, freely movable, oval nodules

that usually measure 2 to 4 cm in diameter. Numerous neutrophils are seen in acute bacterial infection of the breast (acute mastitis), which is usually seen in the postpartum lactating or involuting breast. Dilation of the breast ducts (ectasia) with inspissation of breast secretions is characteristic of mammary duct ectasia, which is common in elderly women. If large numbers of plasma cells are also present, the lesion is called plasma cell mastitis. Fat necrosis of the breast, associated with traumatic injury, is characterized by necrotic fat surrounded by lipid-laden macrophages and a neutrophilic infiltration.

392. The answer is b. *(Damjanov, pp 2365, 2375–2376. Cotran, p 1104.)* Ductal papillomas are usually found near the nipple and present with a bloody nipple discharge. The histologic distinction between benign cystic intraductal papillomas of the breast and papillary adenocarcinomas is based on multiple criteria. The age of the patient is not of immense importance, since papillomas occur in both younger and older women. Benign papillomas are structured with a complex arrangement of papillary fronds of fibrovascular stalks, covered by one or (usually) two types of cells (epithelial and myoepithelial). Papillary carcinomas are usually of one monotonous cell type and have either no or only a few fibrovascular stalks. Papillary carcinomas show a uniform growth of cells with similar appearance with enclosed tubular spaces; the whole arrangement bridges across the entire lumen at times or simply lines the outer rim of the duct (cribriforming). Peripheral invasion of the stroma, if present at all, makes the diagnosis of carcinoma rather certain. There are lesions in which the differentiation is exceedingly difficult, even in the hands of renowned surgical pathologists. Many competent pathologists understandably prefer to defer the diagnosis on all papillary lesions of the breast on frozen section until well-fixed and optimally prepared permanent sections are available.

393. The answer is b. *(Damjanov, pp 2205–2206, 2363–2364. Cotran, pp 1103–1104.)* Neoplastic proliferations of the stroma of the breast may lead to the formation of either fibroadenomas or phyllodes tumors. Fibroadenomas are characterized histologically by a mixture of fibrous tissue and ducts, with no increase in cellularity or mitoses. Only the stromal cells, not the glandular cells, are clonal proliferations. Another neoplastic tumor that arises from the stromal cells is the phyllodes tumor. It is distinguished from fibroadenomas by a more cellular stroma and the presence of stromal

mitoses. The phyllodes tumor, which has been called a cystosarcoma phyllodes, may either be benign or malignant. A benign phyllodes tumor is characterized by increased stromal cells with few mitoses, while a malignant phyllodes tumor has increased numbers of stromal cells that are atypical along with numerous mitoses.

394. The answer is d. *(Cotran, pp 1104–1107.)* Carcinoma of the breast still causes about 20% of female cancer deaths and is the leading cause of death worldwide in women over 40 years of age. It is difficult to predict survival rate, but the status of the axillary nodes is of major importance since negative nodes suggest 70 to 80% 10-year survival. There is a significant decrease in 5-year survival if one to three nodes are positive (only 50%), and four or more positive nodes at the time of diagnosis usually mean about 20% disease-free survival. Obviously, a large number of involved nodes, invasion of the capsule, and fixation to adjacent tissue adversely affect survival. The histologic type and grade of tumor and its size are also important, but nodal involvement (number and size) is the outstanding factor in prognosis. Unfortunately, more than 20% of patients with negative lymph nodes do have recurrences and die within 10 years. Although they are of lesser prognostic importance in breast cancers, high levels of estrogen receptors mean a better prognosis than lower levels or none, although the best response to endocrine (antiestrogen) ablation therapy is noted with tumors containing both estrogen and progesterone receptors. Amplified or activated tumor oncogenes, particularly *c-erb B2,* may be associated with an aggressive tumor and poor prognosis.

395. The answer is b. *(Cotran, pp 1107–1110.)* Malignant carcinomas of the breast may be either noninvasive or invasive. Noninvasive carcinomas (carcinoma in situ) may be located within the ducts (intraductal carcinoma) or within the lobules (lobular carcinoma in situ). There are several variants of intraductal carcinoma, including comedocarcinoma, cribriform carcinoma, and intraductal papillary carcinoma. Comedocarcinoma grows as a solid intraductal sheet of cells with a central area of necrosis. It is frequently associated with the *erb B2/neu* oncogene and a poor prognosis. Cribriform carcinoma is characterized by round, ductlike structures within the solid intraductal sheet of epithelial cells, while intraductal papillary carcinoma has a predominant papillary pattern. In contrast, invasive malignancies are characterized by infiltration of the stroma, which may produce

a desmoplastic response within the stroma (schirrous carcinoma). Infiltrating ductal carcinomas also produce yellow-white chalky streaks that result from the deposition of elastic tissue around ducts (elastosis). Other patterns of invasion that produce specific results include infiltration of cells in a single file in infiltrating lobular carcinoma, and mucin production in colloid carcinoma.

396. The answer is b. *(Cotran, pp 1109–1111.)* Lobular carcinoma of the breast, both in situ and invasive, is an important lesion clinically because of its tendency to occur multicentrically within the same breast and also because of its association with a high frequency of disease (both ductal and lobular carcinoma) in the opposite breast. Lobular carcinoma in situ is characterized histologically by proliferation of cells of the terminal duct lobular unit, which fills and expands the lobules. Unlike the case with intraductal carcinoma, papillary and cribriform structures are not formed and neither is central necrosis present. Invasive lobular carcinoma is distinguished by its tendency to infiltrate the stroma in a single file. This pattern is not seen with invasive ductal carcinoma, which tends to cause a marked desmoplastic response, causing a schirrous carcinoma. Infiltrating lobular carcinomas also form concentric "targets" around ducts, and they have an increased frequency of being estrogen receptor–positive.

397. The answer is b. *(Cotran, p 1114.)* Inflammatory breast carcinoma is often misunderstood because of the qualifying adjective *inflammatory.* The term does not refer to the presence of inflammatory cells, abscess, or any special histologic type of breast carcinoma; rather, it refers to more of a clinical phenomenon, in that the breast is swollen, erythematous, and indurated and demonstrates a marked increase in warmth. These changes are caused by widespread lymphatic and vascular permeation within the breast itself and in the deep dermis of the overlying skin by breast carcinoma cells. The clinical induration and erythema are presumably related to lymphatic-vascular blockage by tumor cells; if present, these findings mean a worse prognosis.

398. The answer is d. *(Cotran, pp 1108–1109. Rubin, pp 1041–1042.)* Infiltration of the nipple by large cells with clear cytoplasm is diagnostic of Paget's disease. These cells are usually found both singly and in small clusters in the epidermis. Paget's disease is always associated with (in fact, it

begins with) an underlying intraductal carcinoma that extends to infiltrate the skin of nipple and areola. Paget cells may resemble the cells of superficial spreading melanoma, but they are PAS-positive and diastase-resistant (mucopolysaccharide- or mucin-positive), unlike melanoma cells. Eczematous dermatitis of the nipples is a major differential diagnosis, but is usually bilateral and responds rapidly to topical steroids. Paget's disease should be suspected if the "eczema" persists more than 3 weeks with topical therapy. Paget's disease occurs mainly in middle-aged women but is unusual. In Paget's disease of the vulvar-anal-perineal region, there is very rarely underlying carcinoma. Mammary fibromatosis is a rare, benign spindle cell lesion affecting women in the third decade. Clinically, it may mimic cancer with retraction or dimpling of skin. It should be treated by local excision with wide margins since there is risk of local recurrence.

399. The answer is e. *(Cotran, pp 1117–1118.)* Gynecomastia (enlargement of the male breast) histologically reveals epithelial hyperplasia within the ducts that is surrounded by hyalinized fibrous tissue. It is caused by an increase in the estrogen-to-androgen ratio. This abnormality may sometimes be found in males at the time of puberty. Other causes of gynecomastia include Klinefelter's syndrome (decreased secretion of testosterone), testicular feminization (androgen insensitivity), testicular tumors, cirrhosis of the liver, alcohol abuse, increased gonadotropin levels (such as choriocarcinoma of the testis), increased prolactin levels, drugs (such as digoxin), or hyperthyroidism. Testicular neoplasms that are associated with gynecomastia are tumors that secrete human chorionic gonadotropin (hCG), which increases the synthesis of estradiol. Testicular tumors associated with the production of hCG include germ cell tumors (choriocarcinoma and seminoma), Leydig cell tumors, and Sertoli cell tumors.

This page intentionally left blank.

Endocrine System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

400. A 42-year-old man presents because recently he has had to change his shoe size from 9 to 10½. He also says that his hands and jaw are now larger. The disorder is most likely mediated through the actions of excess

a. Prolactin
b. ACTH
c. Somatomedin
d. Antidiuretic hormone
e. Thyrotropin

401. A 25-year-old female presents with the acute onset of cessation of lactation. She delivered her first child several months ago and has been breast-feeding since then. She reports that she has not menstruated since the delivery. She also says that lately she has been tired and has been "feeling cold" all of the time. Laboratory workup reveals a deficiency of ACTH and other anterior pituitary hormones. What is the most likely cause of this patient's signs and symptoms?

a. Craniopharyngioma
b. Cushing's disease
c. Empty sella syndrome
d. Nonsecretory chromophobe adenoma
e. Sheehan's syndrome

402. What is the classic visual disturbance produced early by a large pituitary adenoma (>1 cm) that compresses the central portion of the optic chiasm?

a. Bitemporal hemianopsia
b. Homonymous hemianopsia
c. Homonymous inferior field defect
d. Homonymous superior field defect
e. Mononuclear anopsia

403. Which one of the listed individuals is most likely to have a prolactin-secreting tumor of the anterior pituitary?

a. A 25-year-old female with amenorrhea, galactorrhea, and a negative pregnancy test
b. A 27-year-old female with polyuria, polydipsia, and hypernatremia
c. A 45-year-old female with coarse facial features, large hands and feet, and headaches
d. A 49-year-old male with psychosis, ophthalmoplegia, and ataxia
e. A 54-year-old male with central obesity, purple abdominal stria, and mental changes

404. A 49-year-old man who smokes two packs of cigarettes a day presents with a lung mass on x-ray and recent weight gain. Laboratory examination shows hyponatremia with hyperosmolar urine. The patient probably has

a. Renal failure
b. Pituitary failure
c. Conn's syndrome
d. Cardiac failure
e. Inappropriate ADH

405. A 5-year-old girl is brought to the doctor's office by her mother, who states that the girl has been drinking a lot of water lately and has been urinating much more often than normal. Physical examination reveals a young girl whose eyes protrude slightly. An x-ray of her head reveals the presence of multiple lytic bone lesions involving her calvarium and the base of her skull, a biopsy of which reveals aggregates of Langerhans cells with intracytoplasmic Birbeck's granules. Which one of the following sets of laboratory values is most consistent with the expected findings for this girl's disorder?

	Serum Sodium	Urine
a.	Hypernatremia	Low osmolarity and low specific gravity
b.	Hypernatremia	High osmolarity and high specific gravity
c.	Hyponatremia	Low osmolarity and low specific gravity
d.	Hyponatremia	High osmolarity and high specific gravity
e.	Normal	Normal osmolarity and normal specific gravity

406. A lesion that originates within and selectively destroys the ventromedial nucleus of the hypothalamus would most likely result in

a. Decreased appetite
b. Increased appetite
c. Increased urination
d. Paralysis of the extraocular muscles
e. Tunnel vision

407. An individual with cirrhosis who has decreased production of thyroid-binding globulin (TBG) yet clinically is euthyroid would most likely have which one of the listed sets of laboratory values?

	Serum T_4	Serum T_7	Serum TSH
a.	Normal	Normal	Normal
b.	Decreased	Normal	Normal
c.	Normal	Decreased	Normal
d.	Decreased	Normal	Decreased
e.	Decreased	Decreased	Normal

408. An 8-month-old infant is being evaluated for growth and mental retardation. Physical examination reveals a small infant with dry, rough skin; a protuberant abdomen; periorbital edema; a flattened, broad nose; and a large, protuberant tongue. Which one of the listed disorders is the most likely cause of this infant's signs and symptoms?

a. Graves' disease
b. Cretinism
c. Toxic multinodular goiter
d. Toxic adenoma
e. Struma ovarii

409. A perimenopausal woman presents with increasing swallowing difficulty and fatigue. Physical examination reveals that her thyroid is enlarged (palpable goiter). Laboratory examination of her serum reveals T_4 of 4.9 mg/dL, free T_4 of 2.5 ng/dL, and TSH of 5.5 mIU/mL. No thyroid-stimulating immunoglobulins are identified in the serum, but antimicrosomal antibodies are present. Which one of the listed histologic findings, if present in a thyroid biopsy from this individual, would be most consistent with a diagnosis of Hashimoto's thyroiditis?

a. Lymphocytic infiltrate without follicle formation
b. Intense lymphoplasmacytic infiltrate with lymphoid follicles and scattered oxyphilic cells
c. Hyperplasia of follicular cells with scalloping of colloid at the margin of follicles
d. Granulomatous inflammation with multinucleated giant cells surrounding fragments of colloid
e. Dense fibrosis within the thyroid gland extending into adjacent soft tissue

410. Graves' disease is characterized clinically by finding

a. Central obesity, "moon" face, and abdominal striae
b. Hyperthyroidism, exophthalmus, and pretibial myxedema
c. Polyuria, polydipsia, and hyponatremia
d. Polyuria, polydipsia, and polyphagia
e. Progressive lethargy, cold intolerance, and myxedema

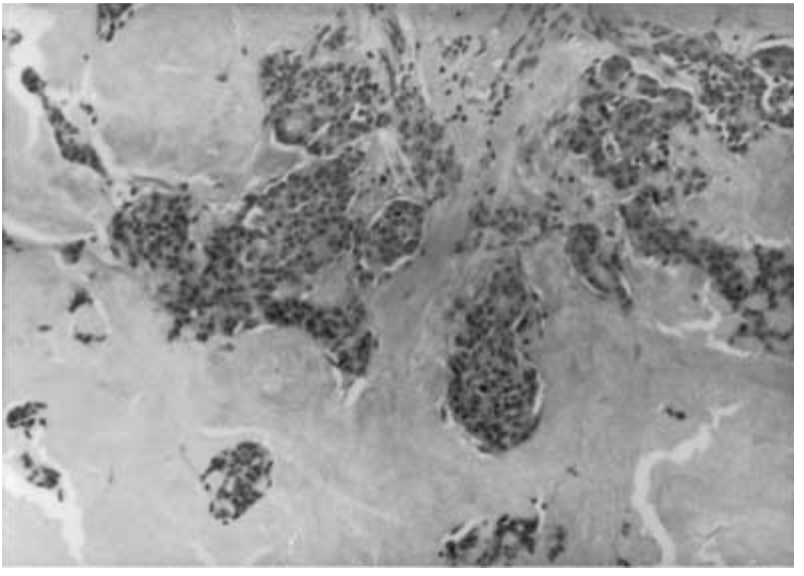
411. The term *goiter* refers to

a. Any enlargement of the thyroid regardless of the etiology
b. Any involution of the thyroid regardless of the etiology
c. Enlargement of the thyroid secondary to Graves' disease
d. Enlargement of the thyroid secondary to the ingestion of goitrogens
e. Involution of the thyroid secondary to Hashimoto's thyroiditis

412. Histologic sections of a follicular carcinoma of the thyroid would characteristically reveal

a. An amyloid stroma intermixed with neoplastic C cells
b. Blood vessel and capsular invasion by malignant thyroid follicles
c. Diagnostic nuclear changes including "Orphan Annie eyes," nuclear grooves, and intranuclear inclusions
d. Papillary fronds with fibrovascular cores and psammoma bodies
e. Undifferentiated anaplastic cells with occasional giant cells

413. A 37-year-old man presents with a single, firm mass within the thyroid gland. This patient's father developed a tumor of the thyroid gland when he was 32 years of age. Histologic examination of the mass in this 37-year-old male reveals organoid nests of tumor cells separated by broad bands of stroma, as seen in the photomicrograph below. The stroma stains positively with Congo red stain and demonstrates yellow-green birefringence. The most likely diagnosis of this lesion is



a. Follicular carcinoma
b. Papillary carcinoma
c. Squamous cell carcinoma
d. Medullary carcinoma
e. Anaplastic carcinoma

414. Which one of the listed signs or symptoms is more characteristic of hypocalcemia than of hypercalcemia?

a. Calcium stones in the urine
b. Metastatic calcification
c. Peptic ulcers
d. Psychiatric changes
e. Tetany

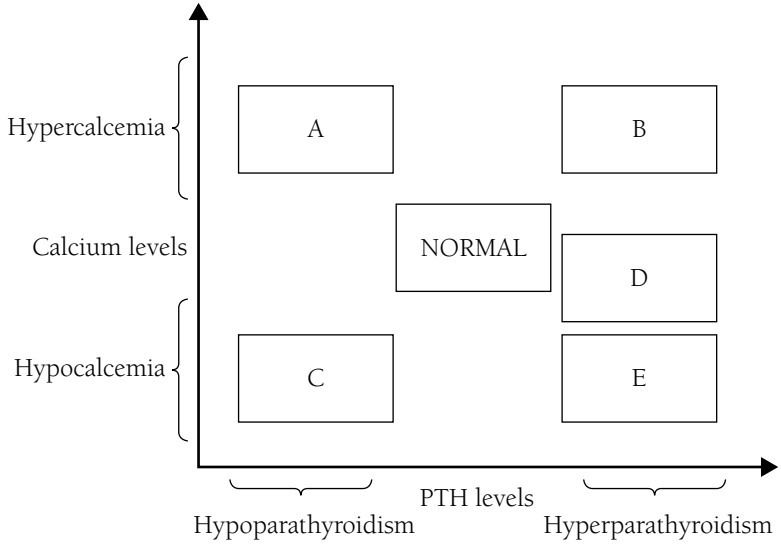
415. A 52-year-old female presents with nausea, fatigue, muscle weakness, and intermittent pain in her left flank. Laboratory examination reveals an increased serum calcium and a decreased serum phosphorus. The patient's plasma parathyroid hormone levels are increased, but parathyroid hormone–related peptide levels are within normal limits. Urinary calcium is increased, and microhematuria is present. The patient's abnormality is most likely caused by

a. Primary hyperparathyroidism
b. Primary hypoparathyroidism
c. Pseudohypoparathyroidism
d. Secondary hyperparathyroidism
e. Secondary hypoparathyroidism

416. A 65-year-old male presents with bone pain and is found to have hypocalcemia and increased parathyroid hormone. Surgical exploration of his neck finds all four of his parathyroid glands to be enlarged. Without any other information, which one of the following is most likely the cause of the enlargement of the parathyroid glands?

a. Primary hyperplasia
b. Parathyroid adenoma
c. Chronic renal failure
d. Parathyroid carcinoma
e. Lung carcinoma

417. A 65-year-old female presents with numbness and tingling of her hands, feet, and lips. Physical examination reveals hyperactivity of her muscles, which is illustrated by a positive Chvostek's sign. Which one of the labeled boxes in the graph below best depicts the expected serum levels of calcium and parathyroid hormone in this individual?



a. Box A
b. Box B
c. Box C
d. Box D
e. Box E

418. A 10-year-old female with mental retardation presents with cramping in her legs and numbness and tingling around her mouth. Physical examination reveals a short, obese young female who has several subcutaneous calcified masses. Laboratory examination reveals hypocalcemia despite her PTH being elevated. X-rays of her hands and feet reveal shortened fourth and fifth metacarpal and metatarsal bones. The basic defect in this disorder is

a. Decreased production of ACTH by the anterior pituitary
b. Defective binding of hormones to guanine nucleotide–binding proteins
c. Malformation of pharyngeal pouches 3 and 4
d. Secretion of parathyroid-related peptide by a benign parathyroid adenoma
e. The presence of autoantibodies to the parathyroid hormone receptor

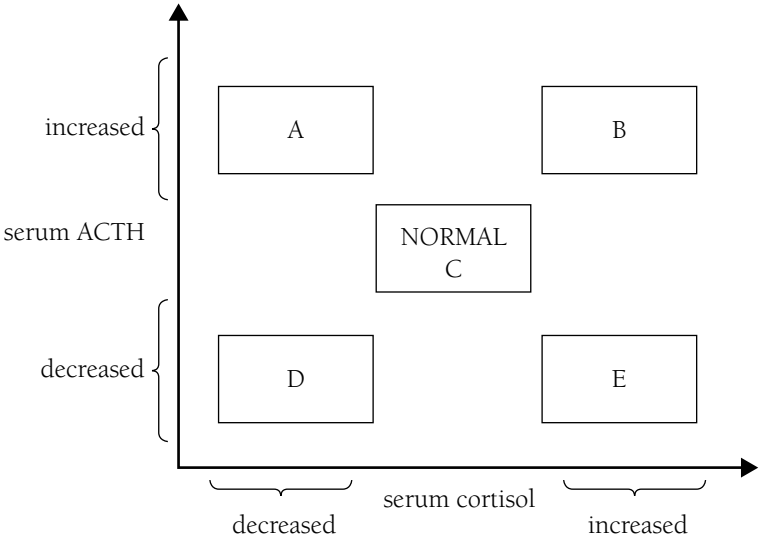
419. An XX infant is found to have external male genitalia and internal female genitalia. Physical examination reveals decreased blood pressure, while laboratory examination reveals a serum sodium level of 132 meq/L. Additionally, bilateral adrenal cortical hyperplasia is present. The findings in this infant are most likely the result of a deficiency of

a. 3-β-dehydrogenase
b. 11-hydroxylase
c. 17-hydroxylase
d. 21-hydroxylase
e. 1-α-hydroxylase

420. The clinical effects of excess serum cortisol are referred to as

a. Addison's disease
b. Bartter's syndrome
c. Conn's syndrome
d. Cushing's syndrome
e. Schmidt's syndrome

421. Which box in the schematic below represents the most likely serum findings for an individual on long-term exogenous glucocorticoid administration?



a. Box A
b. Box B
c. Box C
d. Box D
e. Box E

422. Which one of the following combinations of findings is most likely to be present in an individual with primary hyperaldosteronism?

	Serum Renin	Serum Aldosterone	Serum Sodium	Serum Potassium
a.	Decreased	Increased	Decreased	Increased
b.	Decreased	Increased	Increased	Decreased
c.	Increased	Decreased	Decreased	Increased
d.	Increased	Increased	Decreased	Increased
e.	Increased	Increased	Increased	Decreased

423. A 42-year-old male presents with weakness and dizziness associated with stress. Physical examination reveals a slightly decreased blood pressure along with a diffuse increase in skin pigmentation. Laboratory examination reveals hyponatremia and hyperkalemic acidosis with decreased aldosterone, decreased cortisol, decreased glucose, increased ACTH, decreased sex steroids, and increased LH and FSH. Thyroid function tests are found to be within normal limits. The most likely cause of the signs and symptoms in this individual is

a. A benign adenoma of the adrenal cortex
b. A malignant tumor of the adrenal medulla
c. Autoimmune destruction of the adrenal cortex
d. Bilateral hyperplasia of the adrenal cortex
e. Tuberculosis of the adrenal medulla

424. In type II polyglandular autoimmune syndrome (Schmidt's syndrome), autoimmune adrenocortical insufficiency may occur along with

a. Hypoparathyroidism
b. Mucocutaneous candidiasis
c. Hashimoto's thyroiditis
d. Islet cell adenoma of the pancreas
e. Medullary carcinoma of the thyroid

425. A 35-year-old male who presents with a neck mass is found to have a serum calcium level of 11.8 mg/dL and periodic elevation of his blood pressure. Extensive workup reveals the presence of a medullary carcinoma of the thyroid, a pheochromocytoma, and hyperplasia of the parathyroid glands. This patient most likely has

a. Multiple endocrine neoplasia syndrome (MEN) type 1
b. MEN syndrome type 2A
c. MEN syndrome type 2B
d. Polyglandular syndrome type I
e. Polyglandular syndrome type II

426. A 34-year-old female presents with recurrent episodes of severe headaches, palpitations, tachycardia, and sweating. A physical examination reveals her blood pressure to be within normal limits; however, during one of these episodes of headaches, palpitations, and tachycardia, her blood pressure is found to be markedly elevated. Workup finds a small tumor of the right adrenal gland. Which one of the following is most likely to be increased in the urine of this individual?

a. Acetone
b. Aminolevulinic acid (ALA)
c. Hydroxy-indoleacetic acid (HIAA)
d. *N*-formiminoglutamate (FIGlu)
e. Vanillylmandelic acid (VMA)

427. A 2-year-old boy presents with repeated viral and fungal infections and tetany. Workup reveals hypocalcemia and a marked impairment of cell-mediated immunity resulting from an absence of T cells. Because of these signs and symptoms, the diagnosis of DiGeorge's syndrome is made. Considering this diagnosis, the absence of T cells is a direct consequence of failure of which embryonic structure to develop?

a. Third pharyngeal pouch
b. Fourth pharyngeal pouch
c. Fifth pharyngeal pouch
d. Ultimobranchial body
e. Foramen cecum

428. Histologic sections of the thymus that reveal reactive follicles with germinal centers are diagnostic of

a. Acute inflammation
b. Chronic inflammation
c. Thymic hyperplasia
d. Thymic hypoplasia
e. Thymoma

429. What type of cell in the normal thymus gland is the cell of origin for a thymoma?

a. Epithelial cell
b. Lymphocyte
c. Myoid cell
d. Neuroendocrine cell
e. Thymocyte

Endocrine System

Answers

400. The answer is c. *(Henry, pp 323–324. Cotran, p 1126.)* The constellation of cartilaginous-periosteal soft tissue growth of the distal extremities (acromegaly) and growth of the skull and face bones is characteristic of hypersecretion of growth hormone (GH) from an anterior pituitary adenoma. GH modulates the production of hepatic somatomedin (sulfation factor). Somatomedins are small peptides that act on the target organs after being synthesized under the influence of growth hormone. They have insulin-like properties but are immunologically distinct from insulin. In addition to acral-skeletal expansion, patients with hyperpituitarism of the adult-onset variety (occurring after epiphyseal plate closure) have organomegaly, including increased size of the heart, kidneys, liver, and spleen. Cardiac failure is usually the mechanism of death.

401. The answer is e. *(Cotran, pp 1127–1129.)* Hypopituitarism results from destructive processes that involve the adenohypophysis (anterior pituitary). These processes may be acute (sudden) or chronic. Sheehan's syndrome, also known as postpartum pituitary necrosis, results from the sudden infarction of the anterior lobe of the pituitary. This can occur with obstetric complications, such as hemorrhage or shock. The pituitary gland normally doubles in size during pregnancy; hypovolemia during delivery decreases blood flow and may result in infarction of the anterior pituitary. Sheehan's syndrome produces symptoms of hypopituitarism. The initial sign is cessation of lactation, which may be followed by secondary amenorrhea due to the loss of gonadotropins. Other signs of hypopituitarism include hypothyroidism and decreased functioning of the adrenal gland. Acute destruction of the pituitary is also associated with DIC and thrombosis of the cavernous sinus. Chronic causes of hypopituitarism include nonsecretory chromophobe pituitary adenomas, empty sella syndrome, and suprasellar (hypothalamic) tumors. Nonsecretory chromophobe adenomas present as space-occupying lesions that cause decreased hormone production. The gonadotropins are lost first, which results in signs of

hypogonadism. Types of chromophobe adenomas include null cell adenomas (no cytoplasmic granules), chromophobes (sparse granules), and oncocytic adenomas (increased cytoplasmic mitochondria). The term *pituitary apoplexy* refers to spontaneous hemorrhage into a pituitary tumor, while the empty sella syndrome is caused by a defective diaphragma sellae, which permits CSF from the third ventricle to enter the sella. It may also be secondary to infarction or necrosis. A CT scan reveals the sella to be enlarged or to appear empty.

402. The answer is a. *(Cotran, pp 1122–1125.)* The visual pathway extends from the retina through the optic nerve, then the optic chiasm, through the optic tract, through the lateral geniculate body, and then through the optic radiations of the temporal and parietal lobes to end in the occipital lobes. Lesions in any of these areas produce characteristic visual field defects. For example, bitemporal hemianopsia is classically produced by lesions that involve the optic chiasm. The pituitary gland, which normally weighs about 0.5 g, lies in a bone depression (the sella turcica) and is covered by dura (diaphragma sellae). Anterior to the diaphragma sellae is the optic chiasm. Pituitary tumors may easily compress the optic chiasm and result in bilateral loss of peripheral vision. Involvement of the optic nerve produces blindness in one eye (mononuclear anopsia), while involvement of the optic tract on one side results in homonymous hemianopsia (loss of the same side of the visual field in both eyes). A lesion involving the temporal lobe optic radiations produces a homonymous superior field defect, while a lesion involving the parietal lobe optic radiations produces a homonymous inferior field defect.

403. The answer is a. *(Cotran, pp 1125–1127.)* Pituitary adenomas are the most common neoplasms of the pituitary gland. These benign neoplasms are classified according to the hormone or hormones that are produced by the neoplastic cells. The cell types, in order of decreasing frequency, are the following: lactotrope adenomas (which secrete prolactin), null cell adenomas (which do not secrete hormones), somatotrope adenomas (which secrete growth hormone), corticotrophic adenomas (which secrete ACTH), gonadotrope adenomas (which secrete FSH and LH), and thyrotrope cell adenomas (which secrete TSH). Prolactin-secreting tumors (lactotrope adenomas or prolactinomas) produce symptoms of hypogonadism and galactorrhea (milk secretion not associated

with pregnancy). In females this hypogonadism produces amenorrhea and infertility, while in males it produces impotence and decreased libido. The same symptoms that are seen with a prolactin-secreting pituitary adenoma can also be produced by certain drugs, such as methyldopa and reserpine. A somatotropic adenoma that secretes growth hormone may produce gigantism if it occurs in children prior to the closure of the epiphyseal plates or acromegaly if it occurs in adults after the closure of the epiphyseal plates. Additional findings in patients with excess growth hormone production include enlargement of the viscera, thickening of the skin, and diabetes mellitus. A functioning thyrotroph adenoma may produce hyperthyroidism, while a functioning gonadotroph cell adenoma usually presents with hypogonadism. Excess production of adrenocorticotropin (ACTH) by a corticotrophic adenoma causes Cushing's disease (central obesity, purple abdominal striae, and mental changes).

404. The answer is e. *(Cotran, p 1129.)* The syndrome of inappropriate antidiuretic hormone (SIADH) is an important cause of dilutional hyponatremia that has been identified in tumors of the thymus gland, malignant lymphoma, and pancreatic neoplasms. It occurs predominantly, however, as a result of ectopic secretion of ADH by small cell carcinomas of the lung. Since the tumor cells per se are autonomously producing ADH, there is no feedback inhibition from the hypothalamic osmoreceptors, and the persistent ADH effect on the renal tubules causes water retention even with concentrated urine; hence the term inappropriate ADH. Laboratory findings include low plasma sodium levels (dilutional hyponatremia), low plasma osmolality, and high urine osmolality caused by disproportionate solute excretion without water.

405. The answer is a. *(Cotran, pp 685, 1129.)* Diabetes insipidus (DI) results from a deficiency of antidiuretic hormone (ADH) and is characterized by polyuria and polydipsia, but not the polyphagia or hyperglycemia of diabetes mellitus. The hallmark of DI is a dilute urine (low urine osmolarity) with an increased serum sodium (hypernatremia). Many cases of diabetes insipidus are of unknown cause (idiopathic), but DI may be the result of hypothalamic tumors, inflammations, surgery, or radiation therapy. Multifocal Langerhans cell histiocytosis (Hand-Schüller-Christian disease) is one of the Langerhans cell histiocytoses (histiocytosis X). The disorder, which usually begins between the second and sixth years of life,

is associated with the characteristic triad of bone lesions (particularly in the calvarium and the base of the skull), diabetes insipidus, and exophthalmos.

406. The answer is b. *(Ganong, pp 215–217. Cotran, p 1129.)* Lesions that selectively destroy portions of the hypothalamus produce characteristic signs and symptoms that depend upon the normal functions controlled by the area. For example, destruction of the hypothalamic ventromedial nucleus leads to rage, obesity, and hyperphagia, which is due to increased appetite. These same symptoms can result from stimulation rather than destruction of the dorsomedial nucleus. In contrast to obesity, starvation due to decreased appetite results from lesions that destroy the lateral hypothalamus (lateral nuclei). Destruction of the supraoptic nucleus leads to decreased production of antidiuretic hormone (ADH) and to the development of diabetes insipidus, one symptom of which is polyuria. Destruction of the posterior hypothalamus (posterior nucleus) results in the inability to produce heat when cold. An affected person would become "cold-blooded" (poikilotherm), like a reptile. In contrast, destruction of the anterior hypothalamus (anterior nucleus) results in excess heat production (hyperthermia).

In contrast, vision loss, such as tunnel vision, can result from large pituitary tumors impinging upon the optic chiasm, while hyperglycemia can result from pituitary tumors that secrete growth hormone. A deficiency of thiamine can produce Wernicke-Korsakoff syndrome. Wernicke's encephalopathy consists mainly of foci of hemorrhage and necrosis in the mammillary bodies. Symptoms of Wernicke's syndrome include progressive dementia, ataxia, and paralysis of the extraocular muscles (ophthalmoplegia). Korsakoff's psychosis is a thought disorder that produces memory failure and confabulation.

407. The answer is b. *(Cotran, pp 1130–1131. Henry, pp 333–335.)* Tests used to determine thyroid function include serum thyroxine (T_4), resin T_3 uptake (RTU), thyroxine uptake (TU), free thyroxine index (FTI), thyrotropin-releasing hormone (TRH) levels, and thyroid-stimulating hormone (TSH) levels. Serum T_4 measures total T_4, which includes T_4 bound to thyroid-binding globulin (TBG) and free T_4. Therefore, increased serum T_4 levels can be due to increased free T_4 (Graves' disease) or increased TBG, which can be the result of liver stimulation by increased estrogen from birth control pills or pregnancy. Even though the total T_4 is increased,

patients can be euthyroid if the increase is due only to this increased TBG, since the free T_4 is within normal limits. Conversely, decreased serum T_4 may be due to decreased free T_4 (such as in Hashimoto's disease) or decreased TBG, such as in patients taking anabolic steroids, patients losing protein in the urine (nephrotic syndrome), or patients with cirrhosis. Decreased synthesis of TBG results in a shift in the equilibrium between free and bound T_4. Increased free T_4 causes decreased TSH secretion, which results in a decrease of free T_4 to normal levels. Therefore, serum T_4 (bound and free) is decreased, but since the free T_4 is within normal limits, the metabolic activity is normal and the patient is euthyroid. The resin T_3 uptake (RTU) essentially measures the TBG concentration by measuring the binding of radioactive T_3 to TBG; note that this is not the serum T_3 concentration. The same thing is essentially determined using the thyroxine uptake (TU). Sometimes the patient's TU value is divided by the TU value from the blood of a pooled group of patients. This ratio is called the thyroid hormone binding ratio (THBR). These values then can be used to artificially determine the free thyroxine index (FTI), which is an estimate of the free thyroxine. The FTI (T_7) can be determined using either T_4 times TU or T_4 times T_3U. The measurement of serum TSH levels is the best test to determine if thyroid function is normal or abnormal. A normal TSH level indicates that free T_3 and free T_4 levels in the serum are normal. Increased serum TSH indicates low free T_3 and T_4 levels (primary hypothyroidism), while decreased serum TSH levels indicate either decreased production by the pituitary (hypopituitarism) or increased thyroid production by the thyroid gland (hyperthyroidism).

408. The answer is b. *(Cotran, pp 1132–1133.)* The consequences of excess or inadequate thyroid hormone are directly attributed to abnormalities involving the normal functioning of thyroid hormones, such as regulation of body processes. For example, excess thyroid hormone (hyperthyroidism) results in weight loss (increased lipolysis) despite increased food intake, heat intolerance, increased heart rate, tremor, nervousness, and weakness (due to loss in muscle mass). Inadequate levels of thyroid hormone (hypothyroidism) produce different signs and symptoms in children compared to older children and adults. In young children hypothyroidism produces cretinism, a disease that is characterized by marked retardation of physical and mental growth (severe mental retardation). Patients develop dry, rough skin and a protuberant abdomen. Char-

acteristic facial features include periorbital edema; a flattened, broad nose; and a large, protuberant tongue. In contrast, hypothyroidism in older children and adults produces myxedema. This disease is characterized by a decrease in the metabolic rate, which can result in multiple signs and symptoms, such as cold intolerance and weight gain. Neurologic features of this abnormality include slowing of intellectual and motor function (fatigue, lethargy, and slow speech), apathy, sleepiness, depression, paranoia, and prolonged relaxation phase in deep tendon reflexes ("hung-up" reflexes). Other signs and symptoms of hypothyroidism include dry skin and brittle hair, which can produce hair loss; decreased erythropoiesis, which produces a normochromic normocytic anemia; increased cholesterol, which increases the risk of atherosclerosis; and myxedema, which is the increased interstitial deposition of mucopolysaccharides. The latter abnormality can result in diffuse nonpitting edema of the skin, hoarseness, and enlargement of the heart. Other systems affected by hypothyroidism include the heart, the GI tract, and the GU tract. Patients may develop a slowed heart rate and decreased stroke volume (resulting in cool, pale skin) and constipation, as well as impotence (in men) or menorrhagia and anovulatory cycles (in women).

409. The answer is b. *(Cotran, pp 1133–1136.)* Four types of thyroiditis may be associated with hypothyroidism. Hashimoto's thyroiditis, one of the autoimmune thyroid diseases, is associated with the HLA-B8 haplotype and high titers of circulating autoantibodies, including antimicrosomal, antithyroglobulin, and anti-TSH receptor antibodies. This abnormality is not uncommon in the United States. Histologically, there is infiltration of the thyroid stroma by an intense lymphoplasmacytic infiltrate, with the formation of lymphoid follicles and germinal centers. This produces destruction and atrophy of the follicles and transforms the thyroid follicular cells into acidophilic cells. There are many different names for these cells, including oxyphilic cells, oncocytes, Hürthle cells, and Askanazy cells. Not uncommonly, patients develop hypothyroidism as a result of follicle disruption, and the manifestations consist of fatigue, myxedema, cold intolerance, hair coarsening, and constipation. Rarely, cases of Hashimoto's thyroiditis may develop hyperthyroidism (Hashitoxicosis), while the combination of Hashimoto's disease, pernicious anemia, and type I diabetes mellitus is called Schmidt's syndrome. This is one type of multiglandular syndrome.

Although subacute thyroiditis and Riedel's thyroiditis may have similar symptoms to Hashimoto's thyroiditis, biopsy findings in these disorders are distinctly different. Subacute (de Quervain's, granulomatous, or giant cell) thyroiditis is a self-limited viral infection of the thyroid. It typically follows an upper respiratory tract infection. Patients develop the acute onset of fever and painful thyroid enlargement, and may develop a transient hypothyroidism. Histologically there is destruction of the follicles with a granulomatous reaction and multinucleated giant cells that surround fragments of colloid. One-half of patients with Riedel's thyroiditis are hypothyroid, but, in contrast to the other types of thyroiditis, microscopic examination reveals dense fibrosis of the thyroid gland, often extending into extrathyroidal soft tissue. This fibrosis produces a rock-hard enlarged thyroid gland that may produce the feeling of suffocation. This combination of signs and symptoms may be mistaken clinically for a malignant process. Additionally, these patients may develop similar fibrosis in the mediastinum or retroperitoneum. Subacute lymphocytic thyroiditis is also a self-limited, painless enlargement of the thyroid that is associated with hypothyroidism, but that lacks antithyroid antibodies or lymphoid germinal centers within the thyroid.

410. The answer is b. *(Cotran, pp 1136–1138.)* Graves' disease, or diffuse toxic goiter, is one of the three most common disorders associated with thyrotoxicosis or hyperthyroidism (the other two are toxic multinodular goiter and toxic adenoma). This hyperfunctioning and hyperplastic diffuse goiter is accompanied by a characteristic triad of clinical findings: signs of hyperthyroidism, exophthalmus, and pretibial myxedema. Graves' disease is an autoimmune form of goiter caused by thyroid-stimulating immunoglobulins or thyroid-stimulating hormone receptor antibodies. Autoantibodies to TSH receptor antigens are produced because of a defect in antigen-specific suppressor T cells. The antibodies bind to TSH receptors on thyroid follicular cells and function as TSH, with resultant thyroid growth and hyperfunction. Such antibodies can be identified in almost all cases of Graves' disease. Cardiac manifestations include tachycardia, cardiomegaly, and occasional arrhythmias (atrial fibrillation), and these are often early features. Diffuse toxic goiter is associated with HLA-DR3 genotype.

In contrast to the triad of signs and symptoms seen with Grave's disease, central obesity, "moon" face, and abdominal striae are seen with

Cushing's syndrome; polyuria, polydipsia, and hyponatremia are seen with diabetes insipidus; polyuria, polydipsia, and polyphagia are seen with diabetes mellitus; and progressive lethargy, cold intolerance, and myxedema are seen with hypothyroidism.

411. The answer is a. *(Cotran, pp 1138–1140.)* Goiter is a general clinical term that is used to describe any enlargement of the thyroid. Goiters may be endemic or sporadic. Endemic goiters are due either to an iodine deficiency or goitrogens in the diet. Iodine deficiency results in decreased synthesis of thyroid hormone and secondary increased TSH, which causes hypertrophy and hyperplasia of the thyroid follicles. Inland highland areas, such as the Alps, Andes, and Himalayas, are deficient in iodine. Goitrogens may be found in certain plants, such as cabbage and cassava. Goiters may be either functional or nonfunctional. Most patients with goiter are euthyroid (nonfunctional goiter), as hyperthyroidism (toxic goiter) is relatively rare. In the early stages of goiter formation, there is diffuse hyperplasia of the small thyroid follicles, which histologically resembles the changes of Graves' disease. This early stage is called a diffuse nontoxic goiter or simple goiter. The thyroid gland then undergoes repeated episodes of involution and hyperplasia. Over time this produces an enlarged multinodular goiter that histologically consists of multiple nodules, some of which consist of colloid-filled enlarged follicles and others of which show hyperplasia of small follicles lined by active epithelium. There are also areas of fibrosis, hemorrhage, calcification, and cystic degeneration. The last stage of goiter formation consists of nodules composed primarily of enlarged colloid-filled follicles. This stage is called a colloid goiter.

412. The answer is b. *(Cotran, pp 1142–1147.)* The four major histologic subtypes of thyroid carcinoma are papillary, follicular, medullary, and undifferentiated (anaplastic). Papillary carcinomas of the thyroid are composed of papillary structures with fibrovascular cores, while follicular carcinomas typically show a microfollicular pattern. It is important prognostically to differentiate papillary carcinomas from follicular carcinomas, as papillary carcinomas tend to be indolent (up to 80% survival at 10 years), while follicular carcinomas are much more aggressive (5-year mortality of up to 70%). Follicular areas may be present within a papillary carcinoma and in fact may be quite extensive. If present, these changes can make diagnosis difficult. It is important to recognize this follicular variant

of papillary carcinoma because its behavior remains similar to that of indolent papillary carcinoma. Features consistent with papillary carcinoma, even in predominantly follicular areas, include optically clear nuclei ("ground glass," "Orphan Annie eyes"), nuclear grooves, calcospherites (psammoma bodies), and intranuclear cytoplasmic pseudoinclusions. Medullary carcinoma is characterized by its amyloid stroma, its genetic (familial) associations, and its elaboration of calcitonin and other substances. Undifferentiated (anaplastic) carcinoma, seen in individuals over the age of 50, is characterized by anaplastic spindle or giant cells with frequent mitoses. This tumor is characterized by rapid growth and a poor prognosis.

413. The answer is d. *(Cotran, pp 1145–1147.)* The development of a thyroid mass in a young person who gives a familial history for a similar lesion should raise high clinical suspicion of the possibility that the mass is a medullary carcinoma of the thyroid (MCT). MCT is a tumor of the parafollicular (C) cells of the thyroid, and as such is associated with secretion of calcitonin. The procalcitonin is deposited in the stroma of the tumor and appears as amyloid, which stains positively with Congo red stain. The tumor cells have peripheral nuclei that give them a plasmacytoid appearance when viewed cytologically with fine-needle aspiration (FNA). Electron microscopy reveals membrane-bound dense-core neurosecretory granules in the neoplastic cells. MCT may secrete other substances in addition to calcitonin, such as ACTH, CEA, and serotonin. It is also associated with paraneoplastic syndromes, such as carcinoid syndrome (due to serotonin) and Cushing's syndrome (due to ACTH).

414. The answer is e. *(Henry, pp 178–184.)* Hypocalcemia may produce numbness and tingling of the hands, feet, and lips or tetany (spontaneous tonic muscular contractions). Two clinical tests to demonstrate tetany are Chvostek's sign (tapping on the facial nerve produces twitching of the ipsilateral facial muscles) and Trousseau's sign (inflating a blood pressure cuff for several minutes produces painful carpal muscle contractions). Hypocalcemia results from either parathyroid causes (primary hypoparathyroidism) or nonparathyroid causes, which include hypoalbuminemia, hypomagnesemia, decreased vitamin D, chronic renal failure, and hyperventilation (respiratory acidosis increases bound calcium and decreases free calcium).

In contrast to hypocalcemia, hypercalcemia may produce soft-tissue (metastatic) calcification, nephrocalcinosis, calcium stones in the urine, peptic ulcer disease, and psychiatric changes. Disorders associated with hypercalcemia include paraneoplastic secretion of parathyroid-related peptide (PTHrP), adult T cell leukemia/lymphoma (ATLL), primary hyperparathyroidism, immobilization, multiple myeloma, excess vitamin D, milk-alkali syndrome, and sarcoidosis.

415. The answer is a. *(Cotran, pp 1148–1151. Chandrasoma, pp 857–863.)* Hyperparathyroidism is caused by excess production of parathyroid hormone (PTH). In patients with hyperparathyroidism, it is important to distinguish primary hyperparathyroidism from secondary hyperparathyroidism. Both forms may be associated with the development of bone lesions, but excess PTH production in primary hyperparathyroidism leads to different laboratory values than those seen with secondary hyperparathyroidism. Increased levels of PTH in primary hyperparathyroidism result in increased serum calcium (hypercalcemia) and decreased serum phosphorus. The serum calcium levels are elevated because of increased bone resorption and increased intestinal calcium absorption, the result of increased activity of vitamin D. PTH also increases calcium reabsorption in the distal renal tubule, but, because the filtered load of calcium exceeds the ability for reabsorption, calcium is increased in the urine (hypercalciuria). PTH also increases urinary excretion of phosphate. The excess calcium in the urine predisposes to renal stone formation, especially calcium oxalate or calcium phosphate stones. Urinary stones can produce flank pain and hematuria. This is the most common presentation for patients with hyperparathyroidism. The hypercalcemia of hyperparathyroidism may also cause peptic ulcer disease due to the stimulation of gastrin release and increased acid secretion from the parietal cells. The hypercalcemia also results in muscle weakness, fatigue, and hypomotility of the GI tract, which can lead to constipation and nausea. Alterations of mental status are also common.

In contrast to primary hyperparathyroidism, secondary hyperparathyroidism results from hypocalcemia. This causes secondary hypersecretion of PTH and produces the combination of hypocalcemia and increased PTH production. It is primarily found in patients with chronic renal failure. Patients with hypoparathyroidism develop hypocalcemia and hyperphosphatemia but have normal serum creatinine levels. Primary hypoparathy-

roidism and pseudohypoparathyroidism also result in decreased 24-h excretion of calcium and phosphate.

416. The answer is c. *(Cotran, p 1151. Rubin, pp 1180–1183.)* Parathyroid hyperplasia may be associated with either primary or secondary hyperparathyroidism. In contrast to primary hyperparathyroidism, secondary hyperparathyroidism results from hypocalcemia and causes secondary hypersecretion of parathyroid hormone (PTH). This results in the combination of hypocalcemia and increased PTH. This abnormality is principally found in patients with chronic renal failure, where phosphate retention is thought to cause hypocalcemia. Since the failing kidney is not able to synthesize 1,25-dihydroxycholecalciferol, the most active form of vitamin D, this deficiency leads to poor absorption of calcium from the gut and relative hypocalcemia, which stimulates excess PTH secretion. Chronic renal failure is the most important cause, but secondary hyperparathyroidism also occurs in vitamin D deficiency, malabsorption syndromes, and pseudohypoparathyroidism. In any of the causes of parathyroid hyperplasia, all four parathyroid glands are typically enlarged. Parathyroid hyperplasia can be differentiated from parathyroid adenomas by the fact that parathyroid hyperplasia, either primary or secondary, results in enlargement of all four glands, while a parathyroid adenoma or parathyroid carcinoma produces enlargement of only one gland. In most cases the other three glands are smaller than normal.

417. The answer is c. *(Cotran, pp 1148–1151. Chandrasoma, pp 857–863.)* To summarize the diseases of the parathyroid glands, since serum calcium levels are affected by serum PTH levels, plotting serum calcium levels and serum PTH on a graph will separate the different abnormalities of PTH functioning into different areas of the graph. Increased levels of PTH (hyperparathyroidism) may be either primary or secondary. Primary hyperparathyroidism is associated with increased PTH and increased calcium (area B), while secondary hyperparathyroidism is associated with increased PTH and decreased or normal calcium levels (boxes E and D, respectively). This can be seen in patients with a deficiency of 1-α-hydroxylase, because decreased active vitamin D levels produce decreased absorption of calcium, hypocalcemia, and resultant hyperparathyroidism.

Primary hypoparathyroidism refers to decreased levels of PTH and decreased levels of calcium (box C). Causes of primary hypoparathyroidism include iatrogenic factors, such as surgical accident during thy-

roidectomy, congenital abnormalities (DiGeorge's syndrome), and type I polyglandular autoimmune syndrome. Patients with the latter abnormality have at least two of the triad of Addison's disease, hypoparathyroidism, and mucocutaneous candidiasis. Pseudohypoparathyroidism refers to decreased levels of calcium and increased levels of PTH (box E, which is the same as hyperparathyroidism). Pseudohyperparathyroidism would theoretically refer to decreased levels of PTH and increased levels of calcium (box A). This combination does not occur with diseases of the parathyroid glands, but instead can be seen in patients with hypercalcemia as the result of production of a substance with parathyroid hormone–like function (paraneoplastic syndrome). This substance is called parathyroid-hormone-related protein. In these patients, serum levels of PTH are decreased because of the high levels of calcium.

418. The answer is b. *(Cotran, p 1151. Rubin, pp 1179–1180.)* Hypoparathyroidism may be caused by either decreased secretion of parathyroid hormone (PTH) or end organ insensitivity to PTH (pseudohypoparathyroidism), both of which are associated with hypocalcemia and hyperphosphatemia. Many patients with pseudohypoparathyroidism have a defect in binding of many hormones to guanine nucleotide–binding protein (G protein). These hormones include PTH, thyroid-stimulating hormone, glucagon, and the gonadotropins follicle-stimulating hormone and luteinizing hormone. These patients have characteristic signs and symptoms including short stature, round face, short neck, reduced intelligence, and abnormally short metacarpal and metatarsal bones. In contrast to patients with hypothyroidism caused by decreased levels of PTH, patients with pseudohypoparathyroidism (Albright's hereditary osteodystrophy) have normal or increased levels of circulating PTH and in fact have hyperparathyroidism.

419. The answer is d. *(Cotran, pp 1157–1159. Rubin, pp 1184–1186.)* In the adrenal cortex, cholesterol is converted into either mineralocorticoids (aldosterone) in the zona glomerulosa, glucocorticoids (cortisol) in the zona fasciculata, or sex steroid precursors in the zona reticularis. Congenital adrenal hyperplasia (CAH) is a syndrome that results from a defect in the synthesis of cortisol. This leads to excess ACTH secretion by the anterior pituitary and resultant adrenal hyperplasia. The defect in the synthesis of cortisol is the result of a deficiency in one of the enzymes in the normal pathway of cortisol synthesis, such as 21-hydroxylase or 11-hydroxylase.

Most cases of CAH result from a deficiency of 21-hydroxylase. Two forms of this deficiency include salt-wasting adrenogenitalism and simple virilizing adrenogenitalism. The salt-wasting syndrome results from a complete lack of the hydroxylase. There is no synthesis of mineralocorticoids or glucocorticoids in the adrenal cortex. Decreased mineralocorticoids cause marked sodium loss in the urine, hyponatremia, hyperkalemia, acidosis, and hypotension. Because of the enzyme block there is increased formation of 17-hydroxyprogesterone, which is then shunted into the production of testosterone. This may cause virilism (pseudohermaphroditism) in female infants. That is, XX females with CAH develop ovaries, female ductal structures, and external male genitalia. Much more often there is only a partial deficiency of 21-hydroxylase, which leads to decreased production of both aldosterone and cortisol. The decreased cortisol levels cause increased production of ACTH by the pituitary, which results in adrenal hyperplasia, enough to maintain adequate serum levels of aldosterone and cortisol. In contrast to a complete deficiency of 21-hydroxylase, there is no sodium loss with a partial deficiency of 21-hydroxylase. The excess stimulation by ACTH, however, leads to increased production of androgens, which may cause virilism in female infants.

A deficiency of 11-hydroxylase, which is rare, also leads to decreased cortisol production and increased ACTH secretion. This in turn leads to the accumulation of deoxycorticosterone (DOC) and 11-deoxycortisol, both of which are strong mineralocorticoids. This results in increased sodium retention by the kidneys and hypertension. Patients also develop hypokalemia and virilization due to androgen excess. Patients with a deficiency of 17-hydroxylase also exhibit impaired cortisol production, increased ACTH, and secondary increased DOC. These patients, however, cannot synthesize normal amounts of androgens and estrogens. This is because the gene that codes for 17-hydroxylase is the same for the enzyme in the adrenal cortex and the gonads, and the deficiency is the same in both organs. Because of decreased sex hormones, genotypic females develop primary amenorrhea and fail to develop secondary sex characteristics, while genotypic males present as pseudohermaphrodites. Additionally, the plasma LH levels are increased due to decreased feedback inhibition.

420. The answer is d. *(Cotran, pp 1152–1155.)* The clinical effects of excess cortisol are called Cushing's syndrome. Many of the symptoms of Cushing's syndrome that result from excess cortisol production can be

directly related to the normal function of cortisol. Since cortisol is a glucocorticoid, its major function involves the maintenance of normal blood glucose levels. In this regard cortisol increases gluconeogenesis and glycogen storage in the liver. To provide the protein for liver gluconeogenesis, muscle is broken down. Because muscle is primarily located in the extremities, patients lose muscle in the extremities. This produces muscle wasting and proximal muscle weakness. Cortisol, in contrast to insulin, inhibits glucose uptake by many tissues. Therefore, excess cortisol causes symptoms of glucose intolerance, hyperglycemia, and diabetes mellitus. Cortisol also stimulates the appetite and lipogenesis in certain adipose tissues (the face and trunk), while promoting lipolysis in the extremities. Therefore, excess cortisol is associated with truncal obesity, "moon" face, and "buffalo hump." Excess cortisol inhibits fibroblasts, which in turn leads to loss of collagen and connective tissue. This produces thinning of the skin and weakness of blood vessels, which in turn results in easy bruising (ecchymoses), purple abdominal striae, and impaired wound healing. Cortisol also decreases the intestinal absorption of calcium, decreases the renal reabsorption of calcium and phosphorus, and increases the urinary excretion of calcium (hypercalcinuria). The combination of decreased bone formation and increased bone resorption with excess cortisol produces osteoporosis (decreased bone mass). Hypertension also occurs in a majority of patients with Cushing's syndrome; the exact mechanism is unknown. Cortisol enhances erythropoietin function, resulting in secondary polycythemia, which is seen clinically as plethora. Cortisol also normally functions to inhibit many inflammatory and immune reactions. Hypercortisolism produces decreased neutrophil adhesion in blood vessels and increased destruction of lymphocytes and eosinophils. This results in an absolute neutrophilia, absolute lymphopenia, eosinopenia, and increased vulnerability to microbial infections. Patients with Cushing's syndrome also develop psychiatric symptoms that include euphoria, mania, and psychosis. Gonadal dysfunction also is frequent, which in premenopausal women leads to hirsutism, acne, amenorrhea, and infertility.

421. The answer is e. *(Cotran, pp 1152–1155. Rubin, pp 1189–1194.)* Increased serum cortisol, which produces clinical symptoms of Cushing's syndrome, may be secondary to excess ACTH production or independent of ACTH production. Causes of increased cortisol levels that are independent of ACTH (box E in the diagram) may involve abnormalities of the

adrenal gland itself, such as a cortical adenoma or cortical carcinoma, or they may involve exogenous (iatrogenic) corticosteroids. Increased cortisol levels that are dependent on ACTH are associated with excess ACTH production (box B in the diagram) and may result from an abnormality of the pituitary itself, such as a tumor of the anterior pituitary (Cushing's disease), or from the ectopic production of ACTH outside of the pituitary, such as paraneoplastic syndromes, one example being small cell carcinoma of the lung.

The high-dose dexamethasone suppression test is used to distinguish ACTH-induced Cushing's disease from the ACTH-independent type. Dexamethasone suppresses pituitary ACTH production, but has no effect on the adrenal gland. Therefore decreased cortisol levels with dexamethasone administration indicate the anterior pituitary as the cause of the ACTH-induced cortisol overproduction.

422. The answer is b. *(Cotran, pp 1155–1157.)* Excess aldosterone secretion may be due to an abnormality of the adrenal gland (primary aldosteronism) or an abnormality of excess renin secretion (secondary aldosteronism). Causes of primary hyperaldosteronism (Conn's syndrome), which is independent of the renin-angiotensin-aldosterone (RAA) system, include adrenal cortical adenomas (most commonly), hyperplastic adrenal glands, and adrenal cortical carcinomas. These diseases are associated with decreased levels of renin. The signs of primary hyperaldosteronism include weakness, hypertension, polydipsia, and polyuria. The underlying physiologic abnormalities include increased serum sodium and decreased serum potassium, the latter due to excessive potassium loss by the kidneys, which together with the loss of hydrogen ions produces a hypokalemic alkalosis. The elevated level of serum sodium causes expansion of the intravascular volume.

In contrast to Conn's syndrome, secondary hyperaldosteronism results from conditions causing increased levels of renin, such as renal ischemia, edematous states, and Bartter's syndrome. Causes of renal ischemia include renal artery stenosis and malignant nephrosclerosis, while Bartter's syndrome results from renal juxtaglomerular cell hyperplasia.

423. The answer is c. *(Cotran, pp 1159–1162.)* Hypofunctioning of the cortex of the adrenal gland (adrenocortical insufficiency) may be the result of abnormalities involving either the adrenal gland itself (primary adreno-

cortical insufficiency) or the pituitary gland, which controls the adrenal (secondary adrenocortical insufficiency). Primary insufficiency may arise from either an acute process or a chronic process. Causes of primary acute adrenocortical insufficiency include acute hemorrhagic necrosis of the adrenals, seen in children as Waterhouse-Friderichsen syndrome. This syndrome is most commonly due to *Neisseria meningitidis* septicemia, which is characterized by meningitis, septicemia, DIC, and hypovolemic shock. Acute adrenocortical insufficiency may also occur with too rapid a withdrawal of steroid therapy if a patient has additional stress. Causes of primary chronic adrenocortical insufficiency (Addison's disease) include autoimmune adrenalitis, infections, amyloidosis, and metastatic cancer. Previously the most common cause of Addison's disease was tuberculosis of the adrenal gland, but now the majority of patients have adrenal autoantibodies and are thought to have autoimmune adrenalitis. Half of these cases involve other autoimmune endocrine diseases, the resulting syndromes being called polyglandular autoimmune (PGA) syndromes.

Secondary adrenocortical insufficiency, such as in decreased functioning of the pituitary or in prolonged suppression of the pituitary by exogenous glucocorticoid therapy, results in decreased ACTH and hypofunctioning of the adrenal. This produces symptoms similar to those of Addison's disease, such as weakness and weight loss. In contrast to the case with Addison's disease, secretion of aldosterone in patients with secondary adrenocortical insufficiency is normal, because aldosterone production is not controlled by the pituitary gland. Therefore these patients do not develop symptoms of aldosterone deficiency such as volume depletion, hypotension, hyperkalemia, or hyponatremia. Additionally, since ACTH levels are not elevated, there is no hyperpigmentation.

424. The answer is c. *(Cotran, pp 1160–1161. Rubin, pp 1187–1188.)* In 1855, when Thomas Addison first described primary adrenal insufficiency, the most common cause was tuberculosis of the adrenal gland. Now the majority of patients have adrenal autoantibodies and are thought to have autoimmune Addison's disease. Half of these patients have other autoimmune endocrine diseases. Patients with type I polyglandular autoimmune syndrome have at least two of the following three diseases or abnormalities: Addison's disease, hypoparathyroidism, and mucocutaneous candidiasis. Type II polyglandular autoimmune syndrome, also called Schmidt's syndrome, lacks hypoparathyroidism and mucocutaneous candidiasis, and

instead is associated with autoimmune thyroid disease (Hashimoto's thyroiditis) and insulin-dependent diabetes. Islet cell adenomas of the pancreas may be found in multiple endocrine neoplasia type 1 (MEN 1) syndrome along with pituitary adenomas and parathyroid hyperplasia or adenomas. Medullary carcinoma of the thyroid along with pheochromocytomas of the adrenal gland and parathyroid hyperplasia is seen in MEN 2A (Sipple's syndrome).

425. The answer is b. *(Cotran, pp 1160–1161, 1166–1167. Rubin, pp 853–858, 1195–1196.)* Combinations of neoplasms affecting different endocrine organs in the same patient are referred to as multiple endocrine neoplasia (MEN) syndromes. There are several types of MEN syndromes. Patients with type 1 MEN syndrome (Wermer's syndrome) have pituitary adenomas, parathyroid hyperplasia (or adenomas), and neoplasms of the pancreatic islets. The latter most commonly are gastrinomas, which secrete gastrin and produce Zollinger-Ellison syndrome. Type 2A MEN syndrome (Sipple's syndrome) is characterized by the combination of medullary carcinoma of the thyroid, pheochromocytoma of the adrenal medulla, and hyperparathyroidism. MEN type 2B syndrome (also known as type 3) is associated with medullary carcinoma of the thyroid, pheochromocytoma of the adrenal medulla, and multiple mucocutaneous neuromas.

In contrast to the MEN syndromes, combinations of autoimmune diseases affecting different endocrine organs are called polyglandular syndromes. There are several types of polyglandular syndromes. Patients with type I polyglandular autoimmune syndrome have at least two of the triad of Addison's disease, hypoparathyroidism, and mucocutaneous candidiasis. Type II polyglandular syndrome (Schmidt's syndrome) is not associated with either hypoparathyroidism or mucocutaneous candidiasis, but instead is associated with autoimmune thyroid disease (Hashimoto's thyroiditis) and insulin-dependent diabetes mellitus.

426. The answer is e. *(Cotran, pp 1164–1166.)* Tumors of the adrenal medulla include pheochromocytomas, ganglioneuromas, and neuroblastomas. Pheochromocytomas are composed of cells that contain membrane-bound, dense-core neurosecretory granules and have high cytoplasmic levels of catecholamines. Secretion of these catecholamines produces the characteristic symptoms associated with pheochromocytomas, such as hypertension, palpitations, tachycardia, sweating, and glucose intolerance

(diabetes mellitus). Pheochromocytomas are associated with the urinary excretion of catecholamines or their metabolic breakdown products. The catecholamines include dopamine, norepinephrine, and epinephrine. These catecholamines are broken down by two enzymes, catecholamine orthomethyltransferase (COMT) and monoamine oxidase (MAO), into homovanillic acid, normetanephrine, metanephrine, or vanillylmandelic acid (VMA). Any of these metabolic products may be found in the urine of patients with pheochromocytomas; however, VMA is most common. The best screening tests are 24-h urinary metanephrine and VMA levels. Pheochromocytomas have been called the "10% tumor" as 10% are malignant, 10% are multiple (bilateral), 10% are extraadrenal, 10% calcify, and 10% are familial. These familial tumors are associated with neurofibromatosis, MEN 2A, or MEN 2B.

427. The answer is b. *(Cotran, pp 173, 235, 691.)* The branchial apparatus consists of the branchial clefts (ectoderm), the branchial arches (mesoderm and neural crest), and the branchial (pharyngeal) pouches (endoderm). The dorsal wings of the third pouch develop into the inferior parathyroid glands; the ventral wings of the third pouch develop into the thymus; the fourth pouch develops into the superior parathyroids; and the fifth pouch develops into the ultimobranchial bodies, which in turn give rise to the C cells of the thyroid. DiGeorge's syndrome results from failure of the third and fourth pharyngeal pouches to develop. This abnormality is associated with tetany and an absence of T cells. The tetany results from the hypocalcemia caused by the lack of the parathyroid glands, while the absence of T cells is caused by the lack of the thymus gland.

428. The answer is c. *(Cotran, pp 690–693.)* The thymus, derived from the third pair of pharyngeal pouches and inconsistently from the fourth pair, is divided into an outer cortex and an inner medulla and is composed of lymphocytes and epithelial cells. The lymphocytes are mainly T cells, which are immature (thymocytes) in the cortex and are mature in the medulla, where they have phenotypic characteristics of peripheral blood T lymphocytes. The epithelial cells are mainly located in the medulla, forming Hassall's corpuscles. The thymus normally has a few neuroendocrine cells, which may give rise to carcinoid tumors or small cell carcinoma, and a few myoid cells, which are similar to striated muscle cells and may play a role in the autoimmune pathogenesis of myasthenia gravis. The appearance

of lymphoid follicles with germinal centers is diagnostic of thymic hyperplasia.

429. The answer is a. *(Cotran, pp 691–693.)* Thymomas are tumors arising from thymic epithelial cells and are among the most common mediastinal neoplasms, especially in the anterosuperior mediastinum. There is a scanty or rich lymphocytic infiltrate of T cells, which are not neoplastic, although their size and prominent nucleoli may cause histologic confusion with lymphoma. About 90% of thymomas are benign and occur at a mean age of 50 years. They are very rare in children. They may be asymptomatic or may cause pressure effects of dysphagia, dyspnea, or vena cava compression. Associated systemic disorders include myasthenia gravis, hematologic cytopenias, collagen vascular disease (lupus), and hypogammaglobulinemia. Malignant thymomas show infiltration and capsular invasion plus pleural implants or distant metastasis.

Skin

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

430. A 35-year-old male presents with a 0.3-cm flat light brown lesion on his left forearm. The lesion is excised, and microscopy reveals nests of round nevus cells within the lower epidermis at the dermal-epidermal junction. There is no "fusion" present of adjacent nests of nevus cells. Cytologic atypia is not present, nor are nevus cells seen in the superficial or deep dermis. What is the correct diagnosis for this lesion?

a. Compound nevus
b. Dysplastic nevus
c. Halo nevus
d. Junctional nevus
e. Spitz nevus

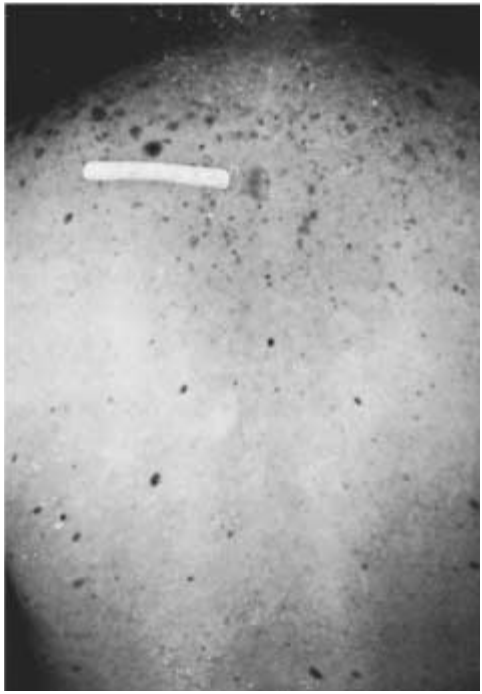
431. A 68-year-old female presents with a uniformly brown, round lesion which appears to be "stuck on" the right side of her face. Histologically, this lesion will most likely reveal

a. Hyperkeratosis with horn and pseudohorn cysts
b. Hyperkeratosis with papillomatosis but no koilocytosis
c. Hyperkeratosis with papillomatosis and koilocytosis
d. A cup-shaped lesion with a central keratin-filled crater
e. Atypia of epidermal keratinocytes

432. A 23-year-old female presents with a 0.4-cm nodule within the skin of the left side of her neck. The clinician removes the lesion and sends it to the pathology lab, calling it a "sebaceous cyst." Histologic sections reveal a cystic structure in the dermis that is filled with keratin and lined by a stratified squamous epithelium, which has a granular cell layer. This cyst is not ruptured, no adnexal structures are seen within the wall of the cyst, and no atypia is present. What is the correct diagnosis?

a. Acrochordon
b. Cystic hygroma
c. Epithelial inclusion cyst
d. Intradermal nevus
e. Pilar cyst

433. Which one of the listed syndromes, seen in the clinical photograph below, poses the greatest risk for development of a malignant melanoma?

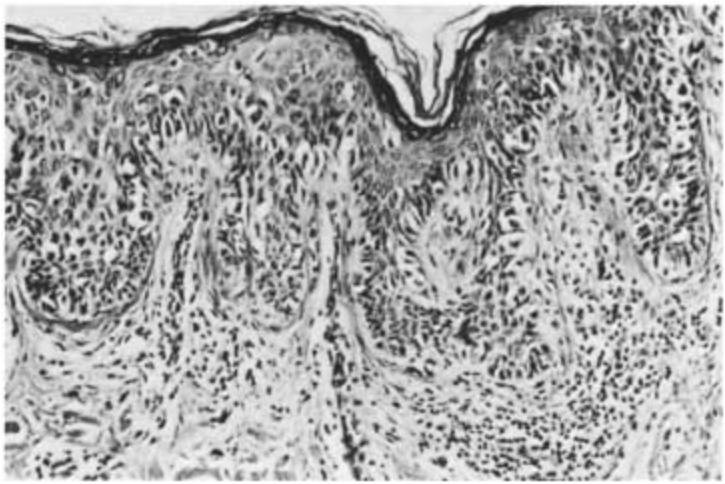


a. Basal cell nevus syndrome
b. Dysplastic nevus syndrome
c. Leser-Trelat syndrome
d. Scalded skin syndrome
e. Stevens-Johnson syndrome

434. A 65-year-old male farmer presents with a small, scaly erythematous lesion on the helix of his left ear. A biopsy from this lesion reveals marked degeneration of the dermal collagen (solar elastosis) along with atypia of the squamous epidermal cells. The atypia, however, does not involve the full thickness of the epidermis, and no invasion into the underlying tissue is seen. What is the correct diagnosis for this skin lesion?

a. Actinic keratosis
b. Bowen's disease
c. Keratoacanthoma
d. Seborrheic keratosis
e. Squamous cell carcinoma

435. Which of the following pairs of disorders would most appropriately be considered in the differential diagnosis for the lesion seen in the photomicrograph below?



a. Superficial spreading malignant melanoma in situ and Paget's disease
b. Mycosis fungoides and metastatic carcinoma
c. Psoriasis and lichen planus
d. Lupus erythematosus and lupus vulgaris
e. Leukemia and lymphoma

436. Where are acral lentiginous malignant melanomas most commonly located?

a. Groin and upper thighs
b. Head and neck
c. Mucosal membranes, especially the oral cavity
d. Palms, soles, and subungual areas
e. Trunk and proximal extremities

437. A 72-year-old male presents with a slowly growing, ulcerated lesion located on the pinna of his right ear. The lesion is excised, and histologic sections reveal infiltrating groups of cells in the dermis. These cells have eosinophilic cytoplasm, intercellular bridges, and intracellular keratin formation. What is the correct diagnosis for this lesion?

a. Basal cell carcinoma
b. Dermatofibrosarcoma protuberans
c. Merkel cell carcinoma
d. Poorly differentiated adenocarcinoma
e. Squamous cell carcinoma

438. A 67-year-old male presents with a slowly growing lesion that involves the lower portion of his left lower eyelid. You examine the lesion and find it to be a pearly papule with raised margins and a central ulcer (rodent ulcer). Histologic sections from this lesion would most likely reveal

a. Reactive epidermal cells surrounding a central superficial ulcer
b. Infiltrating groups of basaloid cells with peritumoral clefting
c. Infiltrating groups of eosinophilic cells with keratin formation
d. Dermal aggregates of small cells histologically similar to oat cell carcinoma
e. An in situ lesion with full-thickness epidermal atypia

439. A 65-year-old man presents with multiple plaquelike pruritic lesions scattered over his body. These lesions do not respond to topical steroid therapy. A biopsy of one of the lesions reveals a dermal infiltrate of atypical-appearing mononuclear cells, some of which occupy spaces within the epidermis. A periodic acid–Schiff (PAS) stain demonstrates areas of PAS-positive material in the cytoplasm of these cells. The peripheral smear exhibits similar atypical mononuclear cells, many of which have a prominent nuclear cleft. These malignant cells originated from

a. CD4-positive T cells
b. CD5-positive B cells
c. CD8-positive T cells
d. CD16-positive natural killer cells
e. CD21-positive B cells

440. A 23-year-old female presents with a 0.4-cm firm brown lesion on her upper right thigh. Histologic sections from this lesion reveal an irregular area in the upper dermis that is composed of a mixture of fibroblasts, histiocytes, stromal cells, and capillaries. The majority of cells in this mixture are fibroblasts. The overlying epidermis reveals hyperplasia of the basal layers. What is the correct diagnosis?

a. Dermatofibroma
b. Dermatofibrosarcoma protuberans
c. Fibroxanthoma
d. Pyogenic granuloma
e. Sclerosing hemangioma

441. A 26-year-old female presents with multiple red-brown macules and papules, pruritus (itching), and flushing. Physical examination reveals that skin lesions can be produced by firm rubbing. A biopsy of one of these skin lesions reveals perivascular collections of mononuclear cells that stain positively with toluidine blue. What is the correct diagnosis?

a. Mycosis fungoides
b. Merkel cell carcinoma
c. Weber-Christian disease
d. Letterer-Siwe disease
e. Urticaria pigmentosa

442. Histologic examination of a skin biopsy from an adult male reveals hyperkeratosis without parakeratosis, an increase in the granular cell layer, acanthosis, and a bandlike lymphocytic infiltrate in the upper dermis involving the dermal-epidermal junction. Which one of the following describes the most likely clinical appearance of this patient's lesions?

a. Generalized skin eruptions with oval salmon-colored papules along flexure lines
b. Macules, papules, and vesicles on the trunk along with several target lesions
c. Pruritic purple papules and plaques on the flexor surfaces of the extremities
d. Red plaques covered by silver scales on the extensor surfaces of the elbows and knees
e. Soft yellow-orange plaques along the neck, axilla, and groin

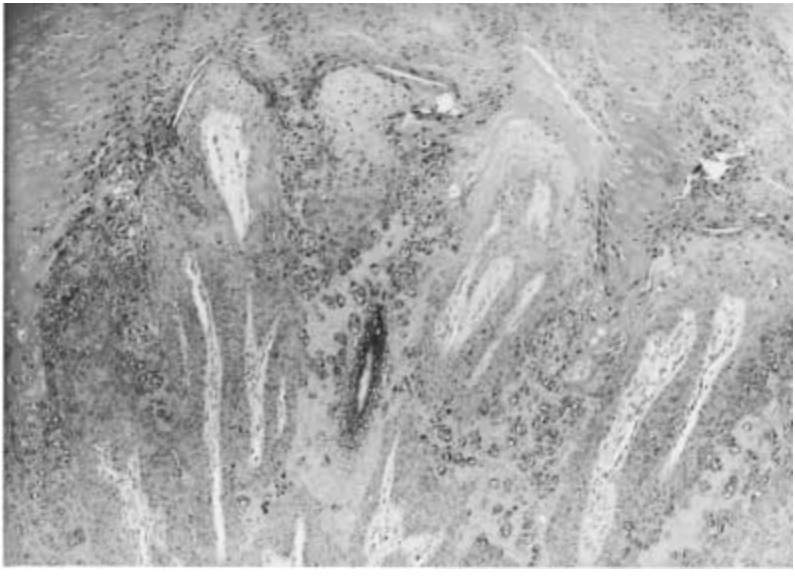
443. A 34-year-old male presents with multiple large, sharply defined, silver-white scaly plaques on the extensor surfaces of his elbows and knees and on his scalp. Physical examination reveals discoloration and pitting of his fingernails. Lifting of one of the scales on his elbows produces multiple minute areas of bleeding (positive Auspitz sign). Histologic sections from one of the scaly plaques would most likely reveal

a. Subepithelial bullae
b. Regular elongation of the rete ridges
c. Liquefactive degeneration of the basal layer of the epidermis
d. Increased granular cell layer
e. Chronic inflammation below a zone of degenerated collagen

444. A 52-year-old male presents with multiple tense bullae that involve his skin but not his oral mucosa. Physical examination finds that none of the bullae have ruptured, and the Nikolsky sign is negative. A biopsy from one of the skin lesions reveals acantholytic intraepidermal bullae. No deposition of IgA is seen with special staining techniques. What is the correct diagnosis for this individual's skin disorder?

a. Pemphigus vulgaris
b. Bullous pemphigoid
c. Dermatitis herpetiformis
d. Psoriasis
e. Lichen planus

445. The photomicrograph below is from a small papillary lesion found on the dorsal surface of the left hand of a 18-year-old. Describe the microscopic appearance of this lesion.



a. Acute necrotizing hemorrhagic vasculitis
b. Aggregates of epidermal cells with molluscum bodies
c. Dermal edema and mild superficial perivascular mixed inflammation
d. Hyperkeratosis, papillomatosis, and prominent keratohyalin granules
e. Intraepidermal vesicle, multinucleated giant cells, and Cowdry A inclusions

446. A 19-year-old male presents with a rash that involves a large, irregular portion of his trunk. Examination reveals several annular lesions that have a raised papulovesicular border with central hypopigmentation. Examination of this area under a Wood's lamp reveals a yellow fluorescence. A scraping of this area viewed under the microscope after KOH is added reveals characteristic "spaghetti and meatball" forms. What is the cause of this skin lesion?

a. *Malassezia furfur*
b. Molluscum contagiosum
c. *Sarcoptes scabiei*
d. *Staphylococcus aureus*
e. *Trichophyton rubrum*

Skin

Answers

430. The answer is d. *(Cotran, pp 1173–1177. Rubin, pp 1277–1280.)* Melanocytic hyperplasia, which causes hyperpigmentation of the skin, can be classified into several types of lesions. A lentigo consists of melanocytic hyperplasia in the basal layers of the epidermis along with elongation and thinning of the rete ridges. Two types of lentigines are lentigo simplex and lentigo senilis ("liver spots"). Increased numbers of melanocytes may form clusters located at the tips of the rete ridges in the epidermis (junctional nevus), within the dermis (intradermal nevus), or both at the tips of the rete ridges and within the dermis (compound nevus). A blue nevus is composed of highly dendritic melanocytes that penetrate more deeply into the dermis. This deep location gives the lesion its characteristic blue color. The Spitz tumor (epithelioid cell nevus) is a benign lesion composed of groups of epithelioid and spindle melanocytes and is found in children and young adults. It may be mistaken histologically for a malignant melanoma. A freckle (ephelis) is a pigmented lesion caused by increased melanin pigmentation within keratinocytes of the basal layer of the epidermis. There is no increase in the number of melanocytes. These lesions fade with lack of sun exposure.

431. The answer is a. *(Cotran, pp 1179–1181.)* Keratosis refers to the proliferation of keratinocytes with excess keratin production. Seborrheic keratoses are benign, elevated ("stuck-on") lesions that usually occur in older individuals. Histologically, these lesions reveal hyperkeratosis with horn and pseudohorn cyst formation. The sudden development of large numbers of seborrheic keratoses (Leser-Trelat sign) may occur in association with malignancy. This association with malignancies may also be seen with the malignant type of acanthosis nigricans, which consists of hyperpigmented areas of skin in the groin and axilla.

In contrast, keratoacanthomas (KAs) are rapidly growing lesions that microscopically reveal a cup-shaped lesion with a central keratin-filled crater surrounded by keratinocytes having eosinophilic ("glassy") cytoplasm. Atypia may be present, but these lesions are not considered to be malignant. The histologic appearance can make differentiating keratoacan-

thomas from squamous cell carcinomas on a histologic basis quite difficult. The clinical history of rapid development within several weeks is very helpful in making the correct diagnosis. Most cases of KA spontaneously resolve over several months. Human papillomavirus (HPV) causes several types of verrucae (warts), which are hyperkeratotic lesions. Verrucae vulgaris histologically reveal hyperkeratosis, papillomatosis, and koilocytosis. The latter term refers to large vacuolated cells with shrunken nuclei. Characteristically present are numerous enlarged keratohyalin granules. Actinic (solar) keratoses, found on sun-damaged skin, microscopically show hyperkeratosis, parakeratosis, atypia of the epidermal keratinocytes, and degeneration of the elastic fibers in the dermis. The latter finding is referred to as solar elastosis. Clinically, actinic keratoses appear as irregular erythematous brown papules. When the atypia of the intraepidermal keratinocytes is extreme (full thickness), the lesion is referred to as Bowen's disease. These lesions are in fact carcinomas in situ since there is no invasion into the underlying dermis. If invasion were present, the lesion would be diagnostic of a squamous cell carcinoma.

432. The answer is c. *(Cotran, p 1181.)* Skin lesions may be polypoid or cystic. The most common polyp of the skin is called an acrochordon (skin tag), which histologically reveals a large polyp lined by squamous epithelium. Skin tags are polypoid or pedunculated. Epithelial cysts are also very common lesions, but are not pedunculated. Epidermal inclusion cysts are keratin-filled cysts that are lined by squamous epithelium having a granular cell layer. No adnexal structures are attached to this type of cyst. Clinically these very common cysts are called sebaceous cysts. This in fact is a misnomer, as these cysts have no sebaceous component. Other types of cysts include pilar cysts, which are keratin-filled cysts (lined by squamous epithelium not having a granular cell layer) found typically on the scalp, and dermoid cysts, which are similar to epidermal inclusion cysts with the addition of multiple adnexal structures, such as sebaceous glands or hair follicles.

433. The answer is b. *(Cotran, pp 1176–1177, 1186–1187. Rubin, p 1280.)* The clinical photograph depicts the presence of the dysplastic nevus syndrome, first described by Dr. Wallace Clark and his co-workers Drs. Mark Greene, David Elder, and Elliott Bondi in Philadelphia during the mid-1970s. This valuable finding elucidated the presence of abnormal nevi that

are at least a marker for the development of malignant melanoma. These nevi, while not malignant, have atypical features compared with normal nevi, such as irregular borders, a pink base, and irregular pigmentation. The Leser-Trelat sign refers to the development of multiple seborrheic keratoses over a short period of time in older patients who have visceral malignancy, while the basal cell nevus syndrome is dominantly inherited with the association of numerous basal cell carcinomas forming throughout life, bifid ribs, keratocysts of the mandible, unusual facies, and abnormalities of the central nervous system and reproductive system. A familial occurrence of dysplastic nevus syndrome with basal cell nevus syndrome was elucidated at the 1985 meeting of the International Academy of Pathologists by Elliot Foucar. The leopard syndrome refers to multiple flat lentigines that are not premalignant for melanoma, in addition to cardiac abnormalities and ocular hypertelorism. Recent studies have shown that the dysplastic nevus syndrome is not only familial, but may be sporadic in about 6% of the general population. The risk of developing melanoma in the dysplastic nevus familial situation is greatly increased over that in the general population. It has been stated that patients with dysplastic nevi whose family members have dysplastic nevi and familial malignant melanoma have a 100-fold greater risk of developing malignant melanoma over their entire lifetimes.

434. The answer is a. *(Cotran, pp 1181, 1184–1185.)* Actinic (solar) keratoses, found on sun-damaged skin, microscopically show hyperkeratosis, parakeratosis, atypia of the epidermal keratinocytes, and degeneration of the elastic fibers in the dermis (referred to as solar elastosis). Clinically, actinic keratoses appear as irregular erythematous brown papules. When the atypia of the intraepidermal keratinocytes is extreme (full thickness), the lesion is referred to as Bowen's disease (carcinoma in situ). Obviously in this lesion there is no invasion into the underlying dermis, which, if present, would be diagnostic of a squamous cell carcinoma. Keratoacanthoma, a benign tumor, may resemble squamous cell carcinoma both clinically and histologically, but penetration of the dermis never extends deeper than adjacent hair follicles. The lesion is cup-shaped with central keratin; biopsy or excision excludes squamous carcinoma.

435. The answer is a. *(Cotran, pp 1177–1179, 1191, 1198–1200.)* The photomicrograph was taken from a patient with superficial spreading malignant melanoma in situ; it shows individual cells resembling Paget's disease invading the upper regions of the epidermis. The basement membrane zone

is intact and there are lymphocytes in the underlying dermis. Cells with clear cytoplasm and malignant-appearing nuclei such as shown here resemble those of Paget's disease, from which they must be distinguished. Some cells of mycosis fungoides resemble these, but they occur in nest formations called Pautrier's abscesses. Metastatic carcinoma can produce lesions that resemble malignant melanoma, but these are problems relating to the dermis. Leukemia-lymphoma infiltrates mainly involve the dermis, although the epidermis may become ulcerated and atrophic. Lupus erythematosus and lichen planus produce subepidermal lymphocytic infiltrates with no involvement of the epidermis itself. Psoriasis produces parakeratosis and elongated rete ridges but no abnormal cells in the epidermis.

436. The answer is d. *(Cotran, pp 1177–1179. Rubin, pp 1281–1288.)* Although malignant melanoma of the skin is not as common as squamous or basal cell carcinoma, it is an exceedingly important and somewhat mysterious tumor owing to its often devastating clinical course and occasionally unpredictable behavior. There are basically four types of invasive malignant melanoma. The most common type is the superficial spreading melanoma, which is characterized by its lateral (radial) growth and upward infiltration of malignant cells within the epidermis, having a "buckshot" appearance (Pagetoid cells). Nodular melanomas are characterized by their dermal (vertical) growth and their minimal lateral (radial) growth. Acral lentiginous melanoma is an uncommon type of melanoma that is characterized by its unique location on the palm, sole, of subungual area. Lentigo maligna melanoma, which is found in older individuals (mean age of 70 years), arises from a preexisting in situ lesion called a lentigo maligna (Hutchinson's freckle). Lentigo maligna are found on sun-exposed skin and clinically are seen as large, flat, irregularly pigmented lesions. Histologically, lentigo maligna reveal atypical melanocytes scattered throughout the basal layer of an atrophic epidermis with sun damage to the dermis. Since the lesion is in situ, no dermal invasion (vertical phase) is seen. When dermal invasion is present, the lesion is then invasive and is called a lentigo maligna melanoma. The most important predictors of outcome are the level of penetration into the subepidermis and reticular dermis (Clark levels I through V: I, in situ, V, invasion of subcutaneous fat) and the actual depth of invasion, measured in millimeters with an ocular micrometer (Breslow depth). The survival at 5 years is 90% if the tumor is Clark I or II and 0.76 mm or less in depth, but survival falls to 40 to 48% if the tumor is level III or IV and greater than 1.9 mm in depth.

437. The answer is e. *(Cotran, pp 1184–1187.)* Squamous cell carcinomas (SCCs) are one of the most common malignancies of the skin. They are usually found on sun-exposed skin of fair persons as a result of sun damage. This exposure to ultraviolet radiation with DNA damage is the most common etiology of SCCs, as indicated by the precursor lesion to SCC, actinic keratosis; however, SCCs are also associated with other conditions such as immunosuppression or inherited defects in DNA repair (xeroderma pigmentosa). SCCs may also develop in an area of chronic scarring, such as an osteomyelitis sinus tract or an old burn scar. An SCC arising in the latter is more likely to metastasize than an SCC occurring in sun-damaged skin. Basal cell carcinomas are also typically found in sun-damaged skin and are also associated with immunosuppression and xeroderma pigmentosa. Neither adnexal tumors nor Merkel cell carcinomas (a malignancy of small neural-crest-derived cells having neurosecretory cytoplasmic granules) are associated with old burn scars.

438. The answer is b. *(Cotran, pp 1186–1187. Rubin, pp 1291–1292.)* Basal cell carcinoma, arising from the pluripotential cells in the basal layer of the epidermis, is the most common tumor in patients with pale skin. This carcinoma is locally invasive and may be quite destructive. Metastasis, however, is quite rare. The classic clinical appearance is a pearly papule with raised margins and a central ulcer. Variants, which are not infrequent, include the superficial type (which may be multifocal), the morphea-like type (which has marked fibrosis and is difficult to eradicate locally), and the pigmented type (which may be mistaken clinically for malignant melanoma). Histologically the cells are deeply basophilic with palisading at the periphery of groups of tumor cells and peritumoral clefting. Abundant eosinophilic cytoplasm may be seen in squamous cell carcinomas, not basal cell carcinomas.

439. The answer is a. *(Cotran, pp 670, 1191.)* Mycosis fungoides is part of the spectrum of malignant T cell lymphomas, mostly of the CD4+ T cell subset, with a predilection for the skin. It is more common in males and the incidence increases with age. It arises primarily in the skin, but more than 70% of patients have extracutaneous spread, with the lymph nodes, spleen, liver, and lungs most often involved. Clinically mycosis fungoides presents as cutaneous patches, plaques, or nodules and is often misdiagnosed as psoriasis or other dermatitides. Histologically there is a bandlike infiltrate in the upper dermis of atypical lymphocytes with markedly con-

voluted nuclei—Sézary-Lutzner cells. These show epidermotropism and form characteristic intraepidermal clusters known as Pautrier's microabscesses. In some cases there is generalized erythroderma and Sézary-Lutzner cells in the peripheral blood. This is known as the Sézary syndrome.

440. The answer is a. *(Cotran, pp 1187–1188.)* Two tumors that arise from fibroblasts in the dermis of the skin are the benign fibrous histiocytoma and the malignant dermatofibrosarcoma protuberans (DFSP). Benign fibrous histiocytomas are composed of a mixture of fibroblasts, histiocytes (some of which are lipid-laden), mesenchymal cells, and capillaries. Depending on which element predominates, these lesions have also been called dermatofibromas (mainly fibroblasts), fibroxanthomas (mainly histiocytes), and sclerosing hemangiomas (mainly blood vessels). Hyperplasia of the epidermis overlying a dermatofibroma is quite characteristic. In contrast, the lesions of dermatofibrosarcoma protuberans are cellular lesions composed of fibroblasts that form a characteristic pinwheel (storiform) pattern. They have irregular, infiltrative margins and are locally aggressive. They frequently extend into the underlying fat and complete excision is difficult. The overlying epidermis is characteristically thinned.

441. The answer is e. *(Cotran, pp 1189–1193. Rubin, pp 1093, 1245.)* Skin tumors may arise directly from epidermal or dermal cells, or may arise from cells that migrate to the skin, such as Langerhans cells (Langerhans cell histiocytosis, histiocytosis X), T lymphocytes (mycosis fungoides, cutaneous T cell lymphoma), or mast cells (mastocytosis, urticaria pigmentosa). Mast cells contain numerous basophilic cytoplasmic granules that contain many different vasoactive substances, such as histamine and serotonin. In tissue sections, these granules are best seen with metachromatic stains, such as Giemsa stain or toluidine blue. Urticaria pigmentosa is caused by a local proliferation of mast cells within the dermis resulting in effects produced by histamine and heparin release, such as urticaria and flushing. These effects can be induced by firm rubbing (Darier's sign or dermatographism). Clinically, patients develop multiple red-brown macules and papules.

442. The answer is c. *(Cotran, pp 1194–1200.)* Lichen planus is characterized by the formation of pruritic, purple, polygonal papules, usually on flexor surfaces of the extremities, such as the wrists and elbows. These

lesions may also have white dots or lines within them, which are called Wickham's striae. The basic defect in lichen planus is a decreased rate of keratinocyte proliferation, which is the exact opposite of the increased rate of keratinocyte proliferation in psoriasis. Histologically, the skin reveals a characteristic bandlike lymphocytic infiltrate in the superficial dermis, which destroys the basal cell layer of the epidermis and causes a "sawtooth" appearance of the rete ridges. Anucleate, necrotic basal epidermal cells may be found in the inflamed papillary dermis. These cells are called colloid bodies or Civatte bodies. Because of the decreased rate of keratinocyte proliferation, there is an increase in the size of the granular cell layer, which is again the opposite of psoriasis.

Pityriasis rosea is a common idiopathic self-limited disease of the skin that is characterized by multiple oval salmon-pink papules that are covered by thin scales. The lesions typically follow flexure lines. Also present is a characteristic larger, sharply defined scaling plaque, which is called the "herald patch." Erythema multiforme (EM) is a hypersensitivity reaction to certain drugs and infections. Clinically, patients develop lesions that are quite varied (multiform) and include macules, papules, vesicles, and bullae. The characteristic lesion, however, is a target lesion that consists of a red macule or papule that has a pale center. Microscopic examination reveals epidermal spongiosis and necrosis with dermal vasculitis and edema. Psoriasis is a chronic skin disease characterized by large, sharply defined silver-white scaly plaques. These skin lesions are usually found on the extensor surfaces of the elbows and knees, the scalp, and the lumbosacral areas. Pseudoxanthoma elasticum is a hereditary disorder characterized by fragmented and thickened elastic fibers in the dermis and thickened, yellow-orange skin in the axillary folds and inguinal regions.

443. The answer is b. *(Cotran, pp 1198–1199.)* Psoriasis is a chronic skin disease characterized by large, sharply defined silver-white scaly plaques. These skin lesions are usually found on the extensor surfaces of the elbows and knees, the scalp, and the lumbosacral areas, but additionally about one-third of patients have nail changes including discoloration, pitting, and crumbling. The pathogenesis is not well understood, but about one-third of patients have a familial history. The pathogenesis involves a faster turnover time of the epidermal keratinocytes. The normal turnover time is about 28 days, but in patients with psoriasis this is decreased to about 3 days. Psoriasis is sometimes associated with other diseases, such as

seronegative rheumatoid arthritis and AIDS. Clinically, if the scale of psoriasis is lifted, it forms multiple, minute areas of bleeding. This is referred to as an Auspitz sign and is due to increased, dilated vessels within the papillary dermis. The formation of new lesions at sites of trauma, referred to as the Koebner phenomenon, is also present. In patients with psoriasis, trauma may cause thickening of the epidermis (acanthosis), downward regular elongation of the rete ridges, hyperkeratosis, and parakeratosis. These changes may be related to faulty α-adrenergic receptors and decreased activity of adenyl cyclase in the lower epidermis. Because the keratinocyte turnover time is faster, there is no granular cell layer. Characteristically, neutrophils infiltrate the epidermis and form Munro's microabscesses in the stratum corneum or Kogoj spongiform pustules in the subcorneal region. These areas within the epidermis are slightly spongiotic, but no bullae are formed. Lymphocytes below a zone of degenerated collagen in the superficial dermis are found in lichen sclerosis, not psoriasis.

444. The answer is b. *(Cotran, pp 1201–1205. Rubin, pp 1254–1264.)* Numerous skin diseases result in the formation of vesicles and bullae (blisters). These vesiculobullous diseases include pemphigus vulgaris, bullous pemphigoid, and dermatitis herpetiformis. These bullae may have characteristic locations and microscopic appearances. Pemphigus vulgaris is a chronic, severe, possibly fatal skin disease that is characterized by the formation of large bullae in the skin and oral mucosa. It is an autoimmune disease (type II hypersensitivity) caused by IgG antibodies to keratinocyte antigens involved in intercellular attachment. Immunofluorescence reveals a uniform "chicken-wire" appearance. Pemphigus vulgaris is characterized by acantholysis (separation of the keratinocytes) that produces intraepidermal (suprabasal) bullae. Clinically the bullae are large, flaccid, and easily ruptured because of their thin roof. Rupture produces denuded areas. Physical examination is positive for Nikolsky's sign (pressure extends the bullae). Systemic symptoms such as fever and weight loss are also present.

445. The answer is d. *(Silverberg, p 195. Cotran, pp 1208–1209. Rubin, pp 1288–1289.)* Verrucae (warts) are cutaneous lesions caused by human papillomaviruses (HPVs) that belong to the DNA-containing papovavirus group. Verrucae are classified according to their location and morphology. Verruca vulgaris, the most common type of wart, may occur anywhere on the body, but most commonly is located on the dorsal surfaces of the hands. The pho-

tomicrograph reveals characteristic features of verrucae vulgaris, including hyperkeratosis, papillary hyperplasia of the epidermis, and numerous large keratohyalin granules within the epidermal cells. Verrucae vulgaris have been associated with several types of HPV, including types 2 and 4. Plantar warts (hyperkeratotic lesions on the soles similar to a callus) are associated with HPV type 1, while verruca plana, typically found on the face, is associated with HPV type 3. Venereal warts, also called condyloma acuminata, are associated with HPV types 6 and 11. Carcinoma may develop in condyloma acuminata, in which case HPV types 16 and 18 are more frequently identified. Bowenoid papulosis (multiple hyperpigmented papules on the genitalia) is associated with HPV types 16 and 18. Epidermodysplasia verruciformis is an autosomal recessive disease associated with impaired cell-mediated immunity and the widespread development of multiple flat warts. These lesions have been associated with HPV types 5 or 8. Some of these lesions may develop into squamous cell carcinomas.

446. The answer is a. *(Cotran, p 1210.)* Fungal infections of the skin can be classified into superficial mycoses, cutaneous mycoses, and subcutaneous mycoses. The superficial mycoses are characterized by infection of the superficial layers of the skin. The most common type is pityriasis versicolor (tinea versicolor), an infection of the upper trunk that is caused by *M. furfur* (*Pityrosporum orbiculare*). Clinically, there are multiple groups of macules (discolorations) with a fine peripheral scale. These macules are hyperpigmented (dark) in white-skinned races but hypopigmented (light) in dark-skinned races. These areas fluoresce yellow under a Wood's lamp. Potassium hydroxide (KOH) is used to identify fungal infections from scrapings of the skin. The KOH dissolves the keratin, and then the mycelial fungi can be seen. With tinea versicolor, KOH examination reveals a characteristic "spaghetti and meatball" appearance. The fragments of hyphae are the "spaghetti," while the round yeast cells are the "meatballs." Different types of tinea include tinea capitis, tinea corporis, tinea pedis (athlete's foot), and tinea versicolor.

Musculoskeletal System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

447. A young boy is being evaluated for a history of numerous fractures in the past. These fractures have resulted from minimal trauma. Examination of his peripheral blood reveals leukoerythroblastosis with numerous target cells. Which one of the following abnormalities is most characteristic of this boy's disease process?

a. Abnormal "tunneling" of osteoclasts into bone trabeculae
b. Abnormal osteoclasts that lack the normal ruffled border
c. Decreased calcification of osteoid matrix
d. Decreased cartilage cell proliferation at epiphyseal plates of long bones
e. Defective synthesis of type I procollagen

448. A 4-year-old boy presents with a history of numerous fractures that are not related to excessive trauma. Physical examination reveals evidence of previous fractures along with abnormally loose joints, decreased hearing, and blue scleras. X-rays of the boy's arms reveal the bones to be markedly thinned. What is the correct diagnosis?

a. Osteopetrosis
b. Osteoporosis
c. Osteomalacia
d. Osteogenesis imperfecta
e. Osteitis deformans

449. A 71-year-old female presents with the sudden onset of severe lower back pain. Physical examination reveals severe kyphosis, while an x-ray of her back reveals a compression fracture of a vertebral body in the lumbar area along with marked thinning of the bones. Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels are all within normal limits. This woman's bone changes are most likely due to

a. Osteopetrosis
b. Osteoporosis
c. Osteomalacia
d. Osteitis fibrosa cystica
e. Osteitis deformans

450. Sections of bone showing normal-sized trabeculae that are only partially calcified with enlarged seams of uncalcified osteoid are most likely the result of

a. Failure of bone remodeling
b. Failure of bone mineralization
c. Failure of osteoid formation
d. Reactive bone formation
e. Reduction in the amount of normally mineralized bone

451. A section of bone shows prominent osteoid seams, very large osteoclasts with more than 12 hyperchromatic nuclei, and viral-type inclusion particles. This is most characteristic of

a. Paget's disease
b. Gaucher's disease
c. Fibrous dysplasia
d. Giant cell tumors of bone
e. Brown tumor of bone

452. The part of a long bone initially involved in hematogenous osteomyelitis is the

a. Metaphyseal region
b. Diaphysis
c. Epiphysis
d. Area around the entrance of the nutrient artery
e. Medullary cavity

453. Which one of the listed abnormalities is most likely to produce a spinal cord lesion that destroys both bone and the disk space (cartilage)?

a. Metastatic carcinoma
b. Multiple myeloma
c. Non-Hodgkin's lymphoma
d. Syringomyelia
e. Tuberculosis

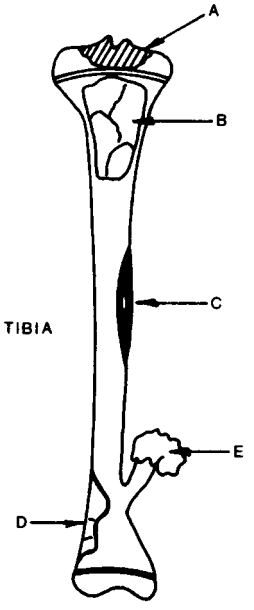
454. Bilateral segmental osteonecrosis or avascular necrosis (AVN) of the femoral head is most often associated with

a. Systemic steroid therapy
b. Irradiation therapy
c. Sickle cell disease
d. Alcoholism
e. Fracture of the femoral neck

455. Histologic sections from a mass diagnosed as being an osteosarcoma would reveal

a. Endothelial-lined spaces surrounded by multinucleated giant cells
b. Haphazard arrangement of immature bony trabeculae forming "Chinese letters"
c. Lobules of hyaline cartilage with few cells
d. Malignant anaplastic cells secreting osteoid
e. Thick bone trabeculae with osteoclasts that lack a normal ruffled border

456. Select the lettered location and general configuration in the diagram below that is most characteristic for osteochondromas.



457. A 17-year-old male presents with nocturnal pain in the bone of his left leg. He relates that the pain is quickly relieved by taking aspirin. X-rays reveal a round, radiolucent area with central mineralization that is surrounded by thickened bone. The lesion measures approximately 1.2 cm in diameter. What is the correct diagnosis?

a. Chondroma
b. Chondrosarcoma
c. Osteoblastoma
d. Osteoma
e. Osteoid osteoma

458. Which one of the listed statements best describes the most characteristic location and x-ray appearance for a chondroma?

	Location	X-ray Appearance
a.	Cortex of metaphysis	Radiolucent area surrounded by thickened bone
b.	Medulla of diaphysis	Destructive lesion with concentric "onion-skin" layering
c.	Medulla of diaphysis	Radiolucent central cartilage surrounded by a thin layer of bone ("O-ring sign")
d.	Medulla of metaphysis	Bone destruction with subperiosteal elevation (Codman's triangle)
e.	Metaphysis or epiphysis	"Soap bubble" appearance

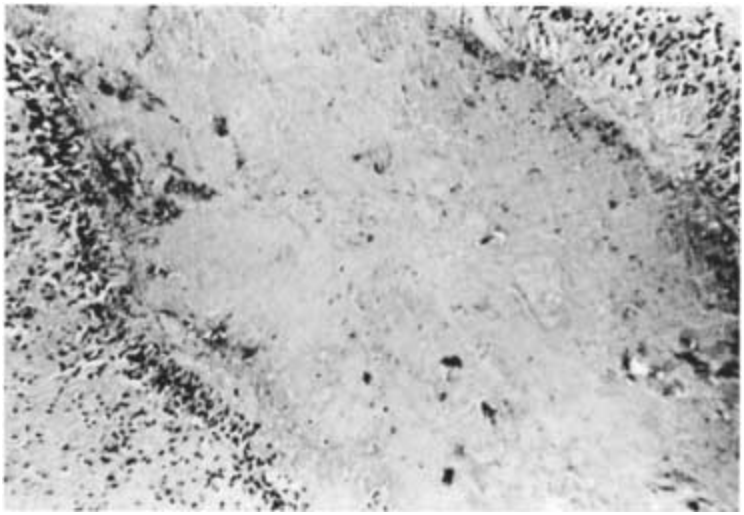
459. An 11-year-old boy presents with an enlarging, painful lesion that involves the medullary cavity of his left femur. X-rays reveal an irregular, destructive lesion that produces an "onion-skin" periosteal reaction. The lesion is resected surgically, and histologic sections reveal sheets of uniform small, round, "blue" cells. What is the correct diagnosis?

a. Chondroblastoma
b. Ewing's sarcoma
c. Fibrosarcoma
d. Osteoblastoma
e. Osteogenic sarcoma

460. A 65-year-old female presents with pain, stiffness, and swelling of her knees. Physical examination of her knees reveals marked crepitus. Reconstructive surgery is performed on her knees. The resected bone reveals destruction of the articular cartilage and eburnation of the underlying exposed bone. Which one of the following best describes the etiology of this woman's disease?

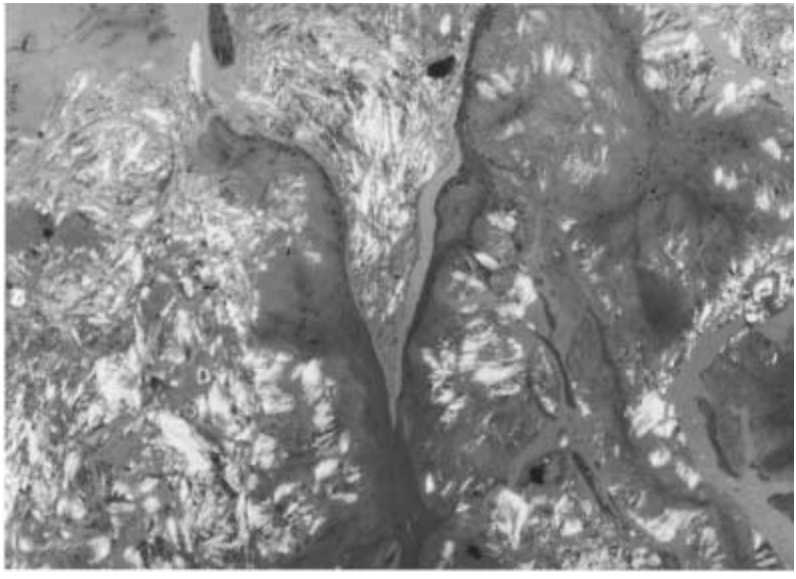
a. "Wear and tear" destruction of articular cartilage
b. Anti-IgG autoantibodies
c. Deficient enzyme in the metabolic pathway involving tyrosine
d. Deposition of needle-shaped negatively birefringent crystals
e. Deposition of short, stubby, rhomboid-shaped positively birefringent crystals

461. The photomicrograph below is taken from an inflamed joint of a 46-year-old female who presents with increasing pain in her hands and knees. Physical examination finds ulnar deviation of her metacarpophalangeal joints, hyperextension of her proximal interphalangeal joint, and flexion of her distal interphalangeal joint. This photomicrograph illustrates



a. Pus extending into intervertebral discs
b. Proliferative synovitis with pannus formation
c. Extensive gumma formation
d. Tophus formation
e. Caseous necrosis of bone

462. A 54-year-old man presents with chronic knee pain. Resection of the patella reveals chalky white deposits on the surface of intraarticular structures. Histologic sections reveal long, needle-shaped, negatively birefringent crystals. The photomicrograph below was taken under polarized light These findings are most consistent with a diagnosis of



a. Osteoarthritis
b. Rheumatoid arthritis
c. Ochronosis
d. Gout
e. Pseudogout

463. A pathognomonic feature of denervation followed by reinnervation is the histologic finding of

a. Atrophic fibers
b. Angular fibers
c. Type-specific grouping of fibers
d. Eosinophilic infiltrates
e. Lymphohistiocytic infiltrates

464. A 28-year-old male presents with vague muscle pain involving his right arm that developed several weeks after eating undercooked pork. Examination of his peripheral blood reveals an increased number of eosinophils, and laboratory examination reveals increased serum activity of CPK. A biopsy from the affected muscle reveals rare encysted organisms. What organism is most likely to cause these signs and symptoms?

a. *Echinococcus granulosa*
b. *Taenia saginata*
c. *Taenia solium*
d. *Toxocara canis*
e. *Trichinella spiralis*

465. A 34-year-old female runner presents with pain in the plantar portion of her foot between the third and fourth metatarsal bones. Based on her symptoms, the most likely cause of her pain is which one of the listed abnormalities?

a. Ganglion
b. Ganglioneuroma
c. Traumatic neuroma
d. Morton's neuroma
e. Schwannoma

466. A 5-year-old boy presents with clumsiness, a waddling gait, and difficulty climbing steps. Physical examination reveals that this boy uses his arms and shoulder muscles to rise from the floor or a chair. Additionally, his calves appear to be somewhat larger than normal. This boy's physical findings are most consistent with a diagnosis of

a. Inclusion body myositis
b. Werdnig-Hoffmann disease
c. Dermatomyositis
d. Duchenne's muscular dystrophy
e. Myotonic dystrophy

467. A 59-year-old woman presents with difficulty swallowing, ptosis, and diplopia. Which of the following is most consistent with these symptoms?

a. Antibodies to the acetylcholine receptor
b. Antibodies to the microvasculature of skeletal muscle
c. Lack of lactate production during ischemic exercise
d. Rhabdomyolysis
e. Corticosteroid therapy

468. An 8-year-old boy presents with weakness and pain over several of his proximal muscle groups. Physical examination reveals periorbital edema along with a lilac discoloration around his eyes and erythema over his knuckles. Which of the following statements is most consistent with the cause of this young boy's symptoms?

a. Antibodies to the acetylcholine receptor
b. Antibodies to the microvasculature of skeletal muscle
c. Antibodies to calcium channels on the motor nerve terminals
d. Lack of lactate production during ischemic exercise
e. Rhabdomyolysis

Musculoskeletal System

Answers

447. The answer is b. *(Cotran, pp 1216–1218, 1224–1225. Rubin, pp 1351–1352.)* Osteopetrosis (marble bone disease) is a rare inherited disease characterized by abnormal osteoclasts that histologically lack the usual ruffled borders and show decreased functioning. This abnormality results in reduced bone resorption and abnormally thickened bone. Long bones are widened in the metaphysis and diaphysis and have a characteristic "Erlenmeyer flask" appearance. In these patients multiple fractures are frequent as the bones are structurally weak and abnormally brittle; hence the name marble bone disease. The thickened bone can entrap cranial nerves and obliterate the marrow cavity, causing anemia and extramedullary hematopoiesis. The severe autosomal recessive form causes death in infancy, but the more common autosomal dominant adult form is relatively benign.

Osteopetrosis does not primarily affect the epiphyseal plate (growth plate), which is a layer of modified cartilage lying between the diaphysis and the epiphysis. This plate consists of the following zones: reserve (resting) zone, proliferating zone, zone of hypertrophy, zone of calcification, and zone of ossification. Disorders that do affect the growth plate include cretinism, achondroplasia, scurvy (vitamin C deficiency), and Hurler's syndrome. Cretinism (congenital hypothyroidism) results in mental retardation and dwarfism. The skeletal abnormalities result in defects in cartilage maturation of the epiphyseal plate. In achondroplasia, the most common inherited form of dwarfism, the zone of proliferating cartilage is either absent or greatly thinned. This in turn causes the epiphyseal plate to be thin. Vitamin C is essential for the normal synthesis and structure of collagen. In scurvy (vitamin C deficiency) there is a lack of osteoblastic synthesis of collagen (causing excess growth of chondrocytes at the epiphyseal plate) and fragility of the basement membrane of capillaries (causing periosteal hemorrhage). Many of the mucopolysaccharidoses (MPSs) involve skeletal deformities. Hurler's syndrome (MPS IH) is associated with increased tissue stores and excretion of dermatan sulfate and heparan sulfate. These mucopolysaccharides also accumulate in the chondrocytes of the growth plate, resulting in dwarfism.

448. The answer is d. *(Cotran, pp 1221–1222.)* Osteogenesis imperfecta (OI), or brittle bone disease, constitutes a group of disorders often inherited as autosomal dominant traits and caused by genetic mutations involving the synthesis of type I collagen, which comprises about 90% of the osteoid, or bone matrix. Very early perinatal death and multiple fractures occur in OI type II, which is often autosomal recessive. The major variant of OI, type I, is compatible with survival; after the perinatal period fractures occur in addition to other signs of defective collagen synthesis such as thin, translucent, blue scleras; laxity of joint ligaments; deafness from otosclerosis; and abnormal teeth. A hereditary defect in osteoclastic function with decreased bone resorption and bone overgrowth, which sometimes narrows or obliterates the marrow cavity, is characteristic of osteopetrosis, or marble bone disease. Osteomalacia is seen in adults due to vitamin D deficiency, while osteitis deformans is Paget's disease of bone.

449. The answer is b. *(Cotran, pp 1222–1224. Chandrasoma, pp 963–966.)* Osteopenia (reduction in the amount of bone) is seen in osteoporosis, osteomalacia, and osteitis fibrosa. Osteoporosis is characterized by qualitatively normal bone that is decreased in amount. Histologic bone sections reveal thin trabeculae that have normal calcification and normal osteoblasts and osteoclasts. Osteoporosis predisposes patients to fractures of weight-bearing bones, such as the femurs and vertebral bodies. Patients typically have normal serum levels of calcium, phosphorus, alkaline phosphatase, and parathyroid hormone. Osteoporosis is classified as being primary or secondary. Primary osteoporosis, the most common type of osteoporosis, occurs most often in postmenopausal women and has been related to decreased estrogen levels. Cigarette smoking is also associated with an increased incidence of osteoporosis. Clinically significant osteoporosis is related to the maximum amount of bone a person has (peak bone mass), which is largely genetically determined. Secondary osteoporosis develops secondary to many conditions such as corticosteroid administration, hyperthyroidism, and hypogonadism.

In contrast, osteopetrosis is a rare inherited disease characterized by abnormal osteoclasts showing decreased functioning. This abnormality results in reduced bone resorption and abnormally thickened bone. In these patients, multiple fractures are frequent as the bones are structurally weak and abnormally brittle. Increased fragility of bones is also present in osteomalacia (caused by abnormal vitamin D metabolism in adults) and

osteitis deformans (Paget's disease). Osteitis fibrosa cystica (von Recklinghausen's disease of bone) is seen with severe hyperparathyroidism and is characterized by increased bone cell activity, peritrabecular fibrosis, and cystic bone lesions.

450. The answer is c. *(Cotran, pp 1227–1228. Rubin, pp 1369–1372.)* Osteomalacia (soft bones) is a disorder of adults characterized by inadequate mineralization of newly formed bone matrix and is most often associated with abnormalities of vitamin D metabolism (such as dietary deficiency or intestinal malabsorption of vitamin D), hypoparathyroidism, or chronic renal diseases. Rickets is a similar condition that occurs in children. Defective mineralization results in an increase in the thickness of the osteoid seams, such as is seen in vitamin C deficiency (scurvy), and not in failure of osteoid formation. Osteopetrosis (marble bone) is a bone modeling abnormality related to hypofunction of the osteoclasts. Osteoporosis results from a reduction in the mass of bone, which still has the normal ratio of mineral to matrix. Reactive bone formation occurs in bone or soft tissue in response to such conditions as tumors, infections, or trauma.

451. The answer is a. *(Cotran, pp 1225–1227, 1229.)* Paget's disease (osteitis deformans) is characterized by an uncoupling of osteoblastic and osteoclastic activity and is divided into three phases: an initial osteoclastic (osteolytic) resorptive stage, a mixed osteoblastic and osteoclastic activity stage, and a late sclerotic, burnt-out stage. Histologically, prominent osteoid seams separate irregular islands of bone into a mosaic ("jigsaw") pattern. The osteoclasts of Paget's disease are characteristically large with an increased number of hyperchromatic nuclei and viral inclusions. Because of the high bone turnover, the serum alkaline phosphatase level is markedly increased, and amounts of collagen breakdown products, such as hydroxyproline and hydroxylysine, are increased in the serum and the urine. Gaucher's disease is characterized by the accumulation of glucocerebroside in macrophages, which then have an appearance described as "wrinkled tissue paper." These cells accumulate in many organs, including the bone. Fibrous dysplasia histologically reveals a "Chinese letters" effect in the bony trabeculae, which are surrounded by a cellular, fibrous stroma, with osteoblasts and osteoclasts decreased at the periphery of entrapped woven bone. Giant cell tumors of bone, which usually occur at the junction of the metaphysis and the epiphysis of a long bone, produce a multiloculated

("soap bubble") appearance on x-ray. They are composed of numerous osteoblastic giant cells found in a background of fibroblast-like neoplastic spindle cells. Brown tumors of bone are areas of fibrosis with hemosiderin-laden macrophages and many osteoclastic and foreign-body-type giant cells. They occur in patients with primary hyperparathyroidism.

452. The answer is a. *(Rubin, pp 1359–1360. Cotran, pp 1332–1333.)* Nutrient arteries to long bones divide to supply the metaphyses and diaphyses. In the metaphyses, the arteries become arterioles and finally form capillary loops adjacent to epiphyseal plates. This anatomic feature allows bacteria to settle in the region of the metaphysis and makes it the site initially involved in hematogenous osteomyelitis. As a consequence of vascular and osteoclastic resorption, the infected bone is replaced by fibrous connective tissue. Persistent chronic osteomyelitis is often associated with sequelae that include amyloidosis and the appearance of malignant tumors in old sinus tracts within the damaged bone.

453. The answer is e. *(Cotran, pp 1232–1233. Rubin, pp 1360–1363.)* Pott's disease of the spine is caused by tuberculous infection of the lower thoracic and the lumbar vertebrae. Destruction of the intervertebral disks and adjacent vertebral bodies is characteristic of tuberculosis. This destruction causes the bone to collapse, and these compression fractures may result in angular kyphosis or scoliosis. Caseous material may extend from the vertebrae into paravertebral muscles and along the psoas muscle sheath to form a psoas abscess in the inguinal regions. Tuberculous osteomyelitis occurs most often in the long bones and spine and via hematogenous spread from a primary site elsewhere.

454. The answer is a. *(Damjanov, p 2624. Cotran, p 1231.)* Avascular necrosis (AVN) of bone is a moderately frequent complication of high-dose systemic corticosteroid therapy—the usual cause of bilateral segmental infarction or AVN of the femoral head. Clinical features include the sudden onset of severe pain and difficulty in walking. Within the femoral head a triangular yellow area of necrotic bone is found beneath the viable articular cartilage, and x-ray may show a crescent sign or space between cartilage and underlying infarct. Fracture of the subcapital femoral neck is frequently associated with unilateral AVN; the other conditions listed are much less frequently associated.

455. The answer is d. *(Cotran, pp 1236–1237. Rubin, pp 1384–1385.)* Osteosarcoma is the most common primary malignant bone tumor except for multiple myeloma and lymphoma and is the most common bone cancer of children. Osteosarcomas usually arise in the metaphyses of long bones of the extremities, although they may involve any bone. They are composed of malignant anaplastic cells, which are malignant osteoblasts that secrete osteoid. There may be marked variation histologically depending on the amount of type I collagen, osteoid, and spicules of woven bone produced. Osteosarcomas produce a characteristic sunburst x-ray pattern due to calcified perpendicular striae of reactive periosteum adjacent to the tumor. They may also show periosteal elevation at an acute angle (Codman's triangle) or penetrate cortical bone with extension into the adjacent soft tissue. Two-thirds of cases are associated with mutations of the retinoblastoma (Rb) gene. Patients with retinoblastoma are at an increased risk for developing osteogenic sarcoma. In older patients, there is an association with multifocal Paget's disease of bone, radiation exposure (as in painters of radium watch dials), fibrous dysplasia, osteochondromatosis, and chondromatosis. Osteosarcomas metastasize hematogenously and usually spread to the lungs early in the course of the disease. With surgery, radiation, and chemotherapy the 5-year survival rate is now about 60%.

456. The answer is e. *(Damjanov, p 2532. Cotran, pp 1237–1238.)* Cartilage-forming tumors include osteochondromas, chondromas, and chondroblastomas. Osteochondromas (exostoses) usually occur at the cortex of the metaphysis near the growth plates of long tubular bones. They are thought to occur as a result of the displacement of the lateral portion of the growth plate. Histologically benign hyaline cartilage caps a stalk of mature bone.

457. The answer is e. *(Cotran, pp 1234–1236. Rubin, p 1383.)* Many benign tumors of bone are capable of producing either bone or cartilage. Bone-producing tumors include osteomas, osteoid osteomas (OOs), and osteoblastomas. Osteoid osteomas are bone tumors that are typically found in the cortex of the metaphysis. Osteoid osteoma occurs predominantly in children or young adults in the second and third decades of life as a benign osteoblastic (bone-forming) lesion of small size, which by definition is less than 3 cm. In osteoid osteoma malignant change does not occur, unlike the case for the closely related but larger osteoblastoma, in which there is occasional malignant change. OOs are often located in the diaphyseal cortex of the tibia or femur, unlike osteoblastomas, which occur in the spine (vertebral arch) or

medulla of long bones. OOs are characteristically painful because of the excess production of prostaglandin E_2. The pain occurs at night and is promptly relieved by aspirin. X-rays typically reveal a radiolucent area (the tumor itself) surrounded by thickened (reactive) bone. Histologic sections reveal an oval mass, the central nidus of which consists of interconnected trabeculae of woven bone containing numerous osteoblasts and uncalcified osteoid. This central nidus is surrounded by a rim of sclerotic bone. Treatment is complete excision of the nidus to prevent recurrence.

A histologic picture that is identical to the central nidus of an osteoid osteoma is seen with the osteoblastoma. Osteoblastomas are sometimes called giant osteoid osteomas. They differ from osteoid osteomas by their larger size (greater than 2 cm) and lack of a decreased pain response to aspirin. Osteoblastomas also lack the surrounding sclerotic bone formation of osteoid osteomas and are found in the medulla of bone rather than the cortex. Osteomas are usually solitary and clinically silent. They may be multiple in patients with Gardner's syndrome (familial colonic adenomatous polyposis with mesenchymal lesions). Osteomas are composed of a circumscribed mass of dense sclerotic bone and are typically found in flat bones, such as the skull and facial bones.

458. The answer is c. *(Cotran, pp 1238–1242.)* Chondromas usually occur at the diaphysis and may be found either within the medullary cavity (enchondromas) or on the surface of the bone. They are usually solitary lesions, but may be multiple (Ollier's disease). If they are associated with soft-tissue hemangiomas, the syndrome is called Maffucci's syndrome. X-rays reveal a characteristic "O-ring sign" (radiolucent central cartilage surrounded by a thin layer of bone). Solitary enchondromas are not associated with malignant transformation. There is, however, an increased risk of chondrosarcoma in patients with Ollier's disease. In contrast to benign chondromas, chondrosarcomas show a peak incidence in the sixth and seventh decades. Most chondrosarcomas (85%) arise de novo, but the peripheral type, unlike the central type, may arise in benign tumors of cartilage, especially if they are multiple. Frequent sites of origin include the pelvic bones (50%), humerus, femur, ribs, and spine. Although a fairly common form of bone cancer, chondrosarcoma is preceded in frequency by metastatic carcinoma, multiple myeloma, and osteosarcoma. Histologic grading is most important in prognosis, since grade I and grade II lesions present very good 5-year survival rates following surgery, unlike grade III poorly differentiated tumors, which invade quickly and metastasize to the lungs.

A radiolucent area surrounded by thickened bone describes the x-ray appearance of osteoid osteoma (found in the cortex of metaphysis); a destructive lesion with concentric "onion-skin" layering describes Ewing's sarcoma (found in the medulla of diaphysis); bone destruction with subperiosteal elevation (Codman's triangle) describes osteogenic sarcoma (found in the medulla of the metaphysis); and a "soap bubble" appearance describes giant cell tumor (found in the metaphysis or epiphysis).

459. The answer is b. *(Rubin, pp 1387–1389. Cotran, p 1244.)* Ewing's sarcoma is an uncommon tumor primarily affecting patients younger than 20 years of age and usually located in the diaphysis or metaphysis of the long bones. In Ewing's sarcoma, reactive new bone formation may cause concentric "onion-skin" layering in half of cases. Histologically, the tumor is composed of small, uniform, round cells that are similar in appearance to lymphocytes. Occasionally the tumor cells form rosettes around central blood vessels (Homer-Wright pseudorosettes), indicating neural differentiation. To differentiate this lesion from lymphoma and neuroblastoma, PAS staining of glycogen-positive, diastase-sensitive cytoplasmic granules within the tumor cells of Ewing's sarcoma is characteristic. Also useful in differentiation from neuroblastoma is the fact that Ewing's sarcoma is associated with the translocation t(11;22). With a combination of chemotherapy, radiation, and surgery, the 5-year survival rate is now 75%.

460. The answer is a. *(Cotran, pp 1246–1257.)* Osteoarthritis (degenerative joint disease), the single most common form of joint disease, is a "wear and tear" disorder that destroys the articular cartilage, resulting in smooth subchondral bone (eburnated, "ivory-like"). This loss of cartilage results in formations of new bone, called osteophytes, at the edges of the bone. Osteophytes located over the distal interphalangeal (DIP) joints are called Heberden's nodes, while osteophytes located at the proximal interphalangeal (PIP) joints are called Bouchard's nodes. Fragments of cartilage may also break free into affected joint spaces, producing loose bodies called "joint mice." Patients develop pain, stiffness, and swelling of the affected joints without acute inflammation. A characteristic clinical appearance is the presence of crepitus, a grating sound produced by friction between adjacent areas of exposed subchondral bone.

In contrast, anti-IgG autoantibodies (rheumatoid factor) are seen with rheumatoid arthritis, deficient enzyme in the metabolic pathway involving tyrosine (homogentisic acid oxidase) is seen with alkaptonuria, deposition

of needle-shaped negatively birefringent crystals (uric acid) is seen with gout, and deposition of short, stubby, rhomboid-shaped positively birefringent crystals (calcium pyrophosphate) is seen with pseudogout.

461. The answer is b. *(Damjanov, pp 2630–2634. Cotran, pp 1248–1251.)* Rheumatoid arthritis frequently affects the small joints of the hands and feet. The larger joints are involved later. Subcutaneous nodules with a necrotic focus surrounded by palisades of proliferating cells are seen in some cases. In the joints, the synovial membrane is thickened by a granulation tissue pannus that is infiltrated by many inflammatory cells. Nodular collections of lymphocytes resembling follicles are characteristically seen. The thickened synovial membrane may develop villous projections, and the joint cartilage is attacked and destroyed. In contrast, extensive gumma formation is seen with syphilis, tophus formation is seen with gout, and caseous necrosis of bone is seen with tuberculosis.

462. The answer is d. *(Cotran, pp 1253–1257.)* Gout is associated with increased serum levels of uric acid, even though less than 15% of all persons with elevated serum levels of uric acid develop symptoms of gout. Gout may be classified as primary or secondary. Secondary gout may result from increased production of uric acid or from decreased excretion of uric acid. Primary (idiopathic) gout usually results from impaired excretion of uric acid by the kidneys. Most patients present with pain and redness of the first metatarsophalangeal joint (the great toe). Needle-shaped, negatively birefringent crystals of sodium urate precipitate to form chalky white deposits. Urate crystals may precipitate in extracellular soft tissue, such as the helix of the ear, forming masses called tophi. Pseudogout is caused by deposition of calcium pyrophosphate dihydrate (CPPD) in synovial membranes, which also forms chalky white areas on cartilaginous surfaces. CPPD crystals are not needle-shaped like urate crystals, but are short, stubby, and rhomboid; they are also birefringent. The degenerative joint disease osteoarthritis is the single most common form of joint disease. It is a "wear and tear" disorder that destroys the articular cartilage, resulting in smooth (eburnated, "ivory-like") subchondral bone. Rheumatoid arthritis, a systemic disease frequently affecting the small joints of the hands and feet, is associated with rheumatoid factor. Rheumatoid factors are antibodies—usually IgM—that are directed against the Fc fragment of IgG. In the joints, the synovial membrane is thickened by a granulation tissue (a pannus) that consists of many inflammatory cells, mainly lymphocytes and plasma cells. Ochronosis,

caused by a defect in homogentisic acid oxidase, is associated with deposition of dark pigment in the cartilage of joints and degeneration of the joints.

463. The answer is c. *(Cotran, pp 1273–1275. Rubin, pp 1437–1438.)* Histologic features of muscle biopsy specimens may suggest certain muscle disorders. Denervation causes atrophy of the fibers, which become angulated. Another change seen in denervated muscle is the presence of distinctive three-zoned fibers called target fibers. Reinnervation is characterized by type-specific grouping of fibers, which is in contrast to the mixed "checkerboard" pattern of type 1 and type 2 fibers seen in normal skeletal muscle. Variation in size and shape along with degenerative changes and intrafascicular fibrosis are features of muscular dystrophy. Eosinophils within muscle are found in association with parasitic infections, the most common of which is trichinosis. Lymphocytes and macrophages within muscle are seen in polymyositis.

464. The answer is e. *(Cotran, pp 394–395.)* Eosinophils within muscle are found in association with parasitic infections, the most common of which is trichinosis, caused by infection with *T. spiralis*. In contrast, lymphocytes and macrophages within muscle are seen in polymyositis.

465. The answer is d. *(Cotran, pp 1280, 1352–1354.)* Peripheral nerve trauma may result in specific symptoms and pathologic changes at specific sites. Transection of a peripheral nerve may result in the formation of a traumatic neuroma if the axonal sprouts grow into scar tissue at the end of the proximal stump. Sometimes peripheral nerves may be compressed (entrapment neuropathy) due to repeated trauma. Carpal tunnel syndrome is the most common entrapment neuropathy and results from compression of the medial nerve within the wrist by the transverse carpal ligament. Symptoms include numbness and paresthesias of the tips of the thumb and second and third digits. Another type of compression neuropathy is associated with a painful swelling of the plantar digital nerve between the second and third or the third and fourth metatarsal bones. This lesion, called a Morton's neuroma, is most often found in females.

466. The answer is d. *(Cotran, pp 1281–1283.)* Duchenne's muscular dystrophy (DMD) is a noninflammatory inherited myopathy that causes progressive, severe weakness and degeneration of muscles, particularly the

proximal muscles, such as the pelvic and shoulder girdles. The defective gene is located on the X chromosome and codes for dystrophin, a protein found on the inner surface of the sarcolemma. Histologically, muscle fibers in patients with DMD show variations in size and shape, degenerative and regenerative changes in adjacent myocytes, necrotic fibers invaded by histiocytes, and progressive fibrosis. There are rounded, atrophic muscle fibers mixed with hypertrophied fibers. These muscle changes cause creatine kinase levels in the serum to be elevated. The weak muscles are replaced by fibrofatty tissue, which results in pseudohypertrophy. In Duchenne's muscular dystrophy, symptoms begin before the age of 4, are progressive and lead to difficulty in walking, and are eventually followed by involvement of respiratory muscles, which causes death from respiratory failure before the age of 20. The classification of the muscular dystrophies is based on the mode of inheritance and clinical features. X-linked inheritance characterizes Duchenne's muscular dystrophy, autosomal dominant inheritance characterizes both myotonic dystrophy and the fascioscapulohumeral type, and limb-girdle dystrophy is autosomal recessive. Sustained muscle contractions and rigidity (myotonia) are seen in myotonic dystrophy, the most common form of adult muscular dystrophy.

In contrast, dermatomyositis is an autoimmune disease that is one of a group of idiopathic inflammatory myopathies. The inflammatory myopathies are characterized by immune-mediated inflammation and injury of skeletal muscle and include polymyositis, dermatomyositis, and inclusion-body myositis. These diseases are associated with numerous types of autoantibodies, one of which is the anti-Jo-1 antibody. The capillaries are the principle target in patients with dermatomyositis. Damage is by complement-mediated cytotoxic antibodies against the microvasculature of skeletal muscle. In addition to proximal muscle weakness, patients typically develop a lilac discoloration around the eyelids with edema. Patients may also develop erythema over their knuckles (Gorton's sign). Histologically, examination of muscles from patients with dermatomyositis reveals perivascular inflammation within the tissue around muscle fascicles. This is in contrast to the other types of inflammatory myopathies, where the inflammation is within the muscle fascicles (endomysial inflammation). In particular, inclusion-body myositis is characterized by basophilic granular inclusions around vacuoles ("rimmed" vacuoles). Werdnig-Hoffmann disease is a severe lower motor neuron disease that presents in the neonatal period with marked proximal muscle weakness ("floppy infant").

467. The answer is a. *(Cotran, pp 1286–1287, 1289. Rubin, pp 141–142, 1430–1431.)* Myasthenia gravis is an acquired autoimmune disease with circulating antibodies to the acetylcholine receptors at the myoneural junction. These antibodies cause abnormal muscle fatigability, which typically involves the extraocular muscles and leads to ptosis and diplopia. Other muscles may also be involved, and this may cause many different symptoms, such as problems with swallowing. Two-thirds of patients with myasthenia gravis have thymic abnormalities; the most common is thymic hyperplasia. A minority of patients have a thymoma. Lack of lactate production during ischemic exercise is seen in metabolic diseases of muscle caused by a deficiency of myophosphorylase. Dermatomyositis is an autoimmune disease produced by complement-mediated cytotoxic antibodies against the microvasculature of skeletal muscle. Rhabdomyolysis is destruction of skeletal muscle that releases myoglobin into the blood. This may cause myoglobinuria and acute renal failure. Rhabdomyolysis may follow an influenza infection, heat stroke, or malignant hyperthermia. Corticosteroid therapy may cause muscle weakness and selective type 2 atrophy.

468. The answer is b. *(Cotran, pp 229–231.)* Dermatomyositis is an autoimmune disease that is one of a group of idiopathic inflammatory myopathies. The inflammatory myopathies are characterized by immune-mediated inflammation and injury of skeletal muscle and include polymyositis, dermatomyositis, and inclusion-body myositis (the most common type of myositis in the elderly). These disorders are associated with numerous types of autoantibodies, one of which is the anti-Jo-1 antibody. The capillaries are the principle target in patients with dermatomyositis. Damage is by complement-mediated cytotoxic antibodies against the microvasculature of skeletal muscle. In addition to proximal muscle weakness, patients typically develop a lilac discoloration around the eyelids with edema. Patients may also develop erythema over their knuckles (Gorton's sign). Histologically, examination of muscles from patients with dermatomyositis reveals perivascular inflammation within the tissue that surrounds muscle fascicles. This is in contrast to the other types of inflammatory myopathies, where the inflammation is within the muscle fascicles (endomysial inflammation). In particular, inclusion-body myositis is characterized by basophilic granular inclusions around vacuoles ("rimmed" vacuoles).

Nervous System

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

469. A 50-year-old male presents with headaches, vomiting, and weakness of his left side. Physical examination reveals his right eye to be pointing "down and out" along with ptosis of his right eyelid. His right pupil is fixed and dilated and does not respond to accommodation. Marked weakness is found in his left arm and leg. Swelling of the optic disk (papilledema) is found during examination of his retina. Which one of the following is most likely present in this individual?

a. Aneurysm of the vertebrobasilar artery
b. Arteriovenous malformation involving the anterior cerebral artery
c. Subfalcine herniation
d. Tonsillar herniation
e. Uncal herniation

470. A newborn infant is being evaluated for a cystic mass found in his lower back at the time of delivery. Physical examination reveals a large mass in the lumbosacral area that transilluminates. Workup finds flattening of the base of the skull along with a decrease in the size of the posterior fossa. Clinically it is thought that this infant might have an Arnold-Chiari malformation and would therefore be at the greatest risk for developing which one of the following within the first few days after delivery?

a. Holoprosencephaly
b. Hydrocephalus
c. Aplasia of the cerebellar vermis
d. Facial angiofibromata
e. Hemangioblastoma of the cerebellum

471. A young child with recurrent bacterial meningitis should be clinically evaluated for the presence of

a. Holoprosencephaly
b. Hypoplastic left heart syndrome
c. Spina bifida occulta with a dermal sinus tract
d. Syringomyelia of the lower cervical cord
e. Dandy-Walker malformation

472. An 18-year-old male high school baseball player gets hit in the head with a fastball in the temporal area. He does not lose consciousness, but afterward develops a slight headache. He is not taken to the emergency room. By evening he develops severe headache with vomiting and confusion. At that time he is taken to the emergency room, where, after being examined by a neurosurgeon, he is taken to the operating room for immediate surgery for an epidural hematoma. Which one of the following is most likely present in this individual?

a. Transection of a branch of the middle meningeal artery
b. Bleeding from torn bridging veins
c. Rupture of a preexisting berry aneurysm
d. Rupture of an arteriovenous malformation
e. Cortical bleeding occurring opposite the point of a traumatic injury

473. Rupture of a berry aneurysm of the Circle of Willis would likely produce hemorrhage into the

a. Epidural space
b. Cerebellum
c. Subarachnoid space
d. Subdural space
e. Thalamus

474. Laminar necrosis and watershed infarcts are most suggestive of

a. Shock
b. Hypertension
c. Fat emboli
d. Vascular thrombosis
e. Venous sinus thrombosis

475. The combination of left-right confusion, finger agnosia, dysgraphia, dyscalculia, and right hemianopsia is most consistent with a diagnosis of

a. Déjérine-Roussy syndrome
b. Gerstmann's syndrome
c. Parinaud's syndrome
d. Wallenberg's syndrome
e. Weber's syndrome

476. Hypertension is most closely related to the formation of which one of the following types of aneurysms?

a. Berry aneurysm
b. Atherosclerotic aneurysm
c. Mycotic aneurysm
d. Charcot-Bouchard aneurysm
e. Saccular aneurysm

477. A 69-year-old male in an underdeveloped country develops changes in his mental status along with ataxia, deformed knees and ankles, and an abnormal gait during which he slaps his feet as he walks. Physical examination reveals decreased vibration and proprioception in lower extremities along with absent pupillary light reflexes with normal accommodation. These signs are most likely due to

a. Cysticercosis
b. Neurosyphilis
c. Poliomyelitis
d. Rabies
e. Progressive multifocal leukoencephalopathy

478. A lumbar puncture is performed on a patient with headaches, photophobia, clouding of consciousness, and neck stiffness. If these symptoms are the result of bacterial infection of the meninges, then what would examination of the cerebrospinal fluid (CSF) most likely reveal?

	Pressure	Gross Appearance	Protein	Glucose	Inflammation
a.	Increased	Cloudy	Increased	Decreased	Neutrophils
b.	Increased	Clear	Increased	Normal	Lymphocytes
c.	Increased	Clear	Increased	Normal	Mononuclear cells
d.	Decreased	Clear	Decreased	Normal	Lymphocytes
e.	Increased	Clear	Increased	Normal	Mixed

479. Neuronophagia of anterior horn neurons is characteristic of

a. JC virus infection
b. *Treponema pallidum* infection
c. Poliovirus infection
d. St. Louis encephalitis
e. Subacute sclerosing panencephalitis

480. A 51-year-old male presents with rapidly progressive dementia and dies. At autopsy, marked spongiform degeneration of the brain is found. These changes are suggestive of

a. A deficiency of galactocerebrosidase
b. Abnormal folding of a prion protein
c. Decreased activity of superoxide dismutase
d. Ingestion of ova of taenia solium
e. Neuronal damage due to amyloid deposition

481. Physical examination of a 34-year-old female with the new onset of an intention tremor finds medial rectus palsy on attempted lateral gaze in the adducting eye and monocular nystagmus in the abducting eye with convergence. These findings are highly suggestive of

a. An apical lung cancer
b. A pituitary adenoma
c. Diabetes mellitus
d. Multiple sclerosis
e. Tertiary syphilis

482. A 45-year-old man presents with weakness and cramping that involves both of his hands. Physical examination reveals atrophy of the muscles of both hands, hyperactive reflexes and muscle fasciculations involving the arms and legs, and a positive Babinski reflex. Sensation appears normal in the arms and legs. The most likely diagnosis for this individual is

a. Metachromatic leukodystrophy
b. Amyotrophic lateral sclerosis
c. Guillain-Barré syndrome
d. Huntington's disease
e. Wilson's disease

483. Which one of the listed statements describes a major risk factor for both sporadic Alzheimer's disease and late-onset familial Alzheimer's disease?

a. α-secretase cleavage of β-amyloid precursor protein
b. Expansion of CAG trinucleotide repeats on chromosome 4
c. Ingestion of 1-methyl-4-phenyl-tetrahydrobiopteridine
d. Mutations of the superoxide dismutase 1 gene
e. Presence of apolipoprotein E4

484. A 65-year-old male presents with bradykinesia, tremors at rest, and muscular rigidity. Physical examination reveals the patient to have a "mask-like" facies. In this patient, where would intracytoplasmic eosinophilic inclusions most likely be found?

a. Basal ganglia
b. Caudate nucleus
c. Hippocampus
d. Midbrain
e. Substantia nigra

485. Shy-Drager syndrome, with symptoms that include orthostatic hypotension, impotence, abnormal sweating, increased salivation, and pupil abnormalities, is classified as a Lewy body disease because in this disorder Lewy bodies can be found within

a. α motorneurons in the spinal cord
b. Neurons in the cerebral cortex
c. Neurons in the dorsal vagal nuclei
d. Neurons in the nigrostriatal system
e. Sympathetic neurons in the spinal cord

486. A 41-year-old male presents with involuntary rapid jerky movements and progressive dementia. He soon dies, and gross examination of his brain reveals marked degeneration of the caudate nucleus. This individual's symptoms were caused by

a. Decreased functioning of GABA neurons
b. Increased functioning of dopamine neurons
c. Relative increased functioning of acetylcholine neurons
d. Relative decreased functioning of acetylcholine neurons
e. Decreased functioning of serotonin neurons

487. A 5-year-old boy presents with projectile vomiting and progressive ataxia. Workup finds obstructive hydrocephalus due to an infiltrative tumor originating in the cerebellum. What is the most likely diagnosis for this cerebellar tumor?

a. Ependymoma
b. Glioblastoma multiforme
c. Medulloblastoma
d. Oligodendroglioma
e. Schwannoma

488. A 55-year-old woman is suspected to have a brain tumor because of the onset of seizure activity. Computed tomography (CT) scans and skull x-rays demonstrate a mass in the right cerebral hemisphere that is markedly calcific. This tumor most likely originated from

a. Astrocytes
b. Microglial cells
c. Ependymal cells
d. Oligodendrogliocytes
e. Schwann cells

489. Which of the following tumors is characterized histologically by pseudopalisading, necrosis, endoneural proliferation, hypercellularity, and atypical nuclei?

a. Schwannoma
b. Medulloblastoma
c. Oligodendroglioma
d. Glioblastoma multiforme
e. Ependymoma

490. Histologic sections from a mass originating from the meninges would most likely reveal

a. Antoni A areas and rare Verocay bodies
b. A whorled pattern and rare psammoma bodies
c. Endothelial proliferation and serpentine areas of necrosis
d. "Fried-egg" appearance of tumor cells
e. True rosettes and pseudorosettes

491. A 63-year-old female is hospitalized secondary to markedly decreased vision. She has no history of polydipsia or nocturia. Physical examination finds bilateral sluggish light reflexes and a bitemporal hemianopsia. No papilledema is present, and her urine specific gravity is within normal limits. A CT scan of the head finds a suprasellar mass with calcification. What is the correct diagnosis for this tumor?

a. Craniopharyngioma
b. Germinoma
c. Juvenile pilocytic astrocytoma
d. Medulloblastoma
e. Meningioma

492. Juvenile pilocytic astrocytoma is the most likely diagnosis for which one of the listed clinical situations?

a. A poorly defined cystic calcified tumor in the hypothalamus of an adult
b. A well-circumscribed cystic tumor in the cerebellum of a child
c. A well-circumscribed noncystic tumor attached to the dura of an adult
d. An infiltrative noncystic tumor in the cerebellum of a child
e. An infiltrative necrotic tumor that crosses the midline in an adult

493. A 45-year-old female presents with unilateral tinnitus and unilateral hearing loss. Physical examination reveals facial weakness and loss of corneal reflex on the same side as the tinnitus and hearing loss. This patient's symptoms might be produced by a tumor located where?

a. Anterior horn of the spinal cord
b. Anterior pituitary
c. Cerebellopontine angle
d. Frontal cortex
e. Lateral ventricle

494. The combination of hemangioblastomas in the cerebellum and retina, multiple and bilateral renal cell carcinomas, and cysts of the pancreas and kidneys is characteristic of which one of the following neurocutaneous syndromes (phakomatoses)?

a. Neurofibromatosis type 1
b. Neurofibromatosis type 2
c. Sturge-Weber syndrome
d. Tuberous sclerosis
e. von Hippel-Lindau disease

495. A 9-year-old boy presents with progressive severe headaches along with signs of precocious puberty. Physical examination finds paralysis of upward gaze and increased intracranial pressure due to a mass of the pineal gland producing an obstructive hydrocephalus. What is the correct diagnosis?

a. Benedikt's syndrome (paramedian midbrain syndrome)
b. Jugular foramen syndrome (abnormality affecting CN IX, X, and XI)
c. Parinaud's syndrome (dorsal midbrain syndrome)
d. Subclavian steal syndrome
e. Weber syndrome (medial midbrain syndrome)

496. Wallenberg's syndrome, characterized by a large constellation of clinical findings that include nystagmus, vertigo, ataxia, ipsilateral laryngeal paralysis, loss of gag reflex, contralateral loss of pain and temperature from the trunk and extremities, ipsilateral loss of pain and temperature from the face, and ipsilateral Horner's syndrome, results from occlusion of the

a. Anterior cerebral artery supplying the medial portion of the cerebral hemisphere
b. Lenticulostriate artery supplying the posterior limb of the internal capsule
c. Middle cerebral artery supplying the lateral portion of the cerebral hemisphere
d. Posterior cerebral artery supplying the occipital lobe
e. Posterior inferior cerebellar artery supplying the cerebellum

497. Bilateral loss of pain and temperature sensations in both arms that spares the sense of touch and position is most suggestive of

a. A syrinx involving the ventral white commissure of the cervicothoracic region
b. A transection of the cord in the upper cervical region
c. Compression of the dorsal roots of the cervicothoracic portion of the cord
d. Hemisection of the anterior half of the spinal cord in the upper cervical region
e. Hemisection of the dorsal half of the spinal cord in the upper cervical region

498. An upper motor neuron (UMN) lesion involving cranial nerve VII would most likely produce

a. Contralateral weakness of the lower half of the face with sparing of the upper half of the face
b. Decreased gag (pharyngeal) reflex with decreased taste sensation from the posterior one-third of the tongue
c. Hemianesthesia of the face with flaccid paralysis of the muscles of mastication
d. Ipsilateral anosmia with primary amenorrhea in females
e. Ipsilateral paralysis of the soft palate with hoarseness and dysphagia

499. After recovering from a viral respiratory tract infection, a 23-year-old female presents with weakness in her distal extremities that rapidly ascends to involve proximal muscles. Physical examination reveals absent deep tendon reflexes, and a lumbar puncture reveals the CSF protein to be increased, but very few cells are present. A biopsy of a peripheral nerve reveals inflammation and demyelination (radiculoneuropathy). What is the best diagnosis?

a. Brown-Séquard's syndrome
b. Charcot-Marie-Tooth disease
c. Diabetes mellitus
d. Guillain-Barré syndrome
e. Syringomyelia

500. Carpal tunnel syndrome, produced by damage to or pressure on the median nerve deep to the flexor retinaculum, is characterized best by which one of the following abnormalities?

a. Hyperextension of fingers at metacarpophalangeal joints and flexion at interphalangeal joints (claw hand)
b. Numbness in fifth finger and medial portion of ring finger
c. Pain in thumb, index finger, middle finger, and lateral half of ring finger
d. Adduction, extension, and internal rotation of upper limb ("porter's tip" sign)
e. Weakness of extensors of wrist and fingers (wristdrop)

Nervous System

Answers

469. The answer is e. *(Cotran, pp 1297–1298.)* Increased intracranial pressure can result from mass lesions in the brain, cerebral edema, or hydrocephalus. Increased intracranial pressure can cause swelling of the optic nerve (papilledema), headaches, vomiting, or herniation of part of the brain into the foramen magnum or under a free part of the dura.

Brain herniations are classified according to the area of the brain that is herniated. Subfalcine herniations are caused by herniation of the medial aspect of the cerebral hemisphere (cingulate gyrus) under the falx, which may compress the anterior cerebral artery. Transtentorial herniation, which occurs when the medial part of the temporal lobe (uncus) herniates over the free edge of the tentorium, may result in compression of the oculomotor nerve, which results in pupillary dilation and ophthalmoplegia (the affected eye points "down and out"). Tentorial herniation may also compress the cerebral peduncles, within which are the pyramidal tracts. Ipsilateral compression produces contralateral motor paralysis (hemiparesis), while compression of the contralateral cerebral peduncle against Kernohan's notch causes ipsilateral hemiparesis. Further caudal displacement of the entire brainstem may cause tearing of the penetrating arteries of the midbrain (Duret hemorrhages). This caudal displacement may also stretch the trochlear nerve (cranial nerve VI), causing paralysis of the lateral rectus muscle (the abnormal eye turns inward). Masses in the cerebellum may cause tonsillar herniation, in which the cerebellar tonsils are herniated into the foramen magnum. This may compress the medulla and respiratory centers, causing death. Tonsillar herniation may also occur if a lumbar puncture (LP) is performed in a patient with increased intracranial pressure. Therefore, before performing an LP, check the patient for the presence of papilledema.

470. The answer is b. *(Cotran, pp 1298–1302. Rubin, pp 1452–1453.)* Developmental abnormalities of the brain include the Arnold-Chiari malformation, the Dandy-Walker malformation, and the phakomatoses, which include tuberous sclerosis, neurofibromatosis, von Hippel-Lindau disease, and Sturge-Weber syndrome. The Arnold-Chiari malformation

consists of herniation of the cerebellum and fourth ventricle into the foramen magnum, flattening of the base of the skull, and spina bifida with meningomyelocele. Newborns with this disorder are at risk of developing hydrocephalus within the first few days of delivery secondary to stenosis of the cerebral aqueduct.

In contrast, severe hypoplasia or absence of the cerebellar vermis occurs in the Dandy-Walker malformation. There is cystic distention of the roof of the fourth ventricle, hydrocephalus, and possibly agenesis of the corpus callosum. Tuberous sclerosis may show characteristic firm, white nodules (tubers) in the cortex and subependymal nodules of gliosis protruding into the ventricles ("candle drippings"). Other signs of tuberous sclerosis include the triad of seizures, mental retardation, and congenital white spots or macules (leukoderma). Facial angiofibromata (adenoma sebaceum) may also occur. In von Hippel-Lindau disease, multiple benign and malignant neoplasms occur, including hemangioblastomas of the retina, cerebellum, and medulla oblongata; angiomas of the kidney and liver; and renal cell carcinomas. Patients with Sturge-Weber syndrome, a nonfamilial congenital disorder, display angiomas of the brain, leptomeninges, and ipsilateral face, which are called port-wine stains (nevus flammeus).

471. The answer is c. *(Cotran, p 1300. Rubin, 1449–1450.)* Spina bifida is a general term that refers to abnormal fusion of the vertebral arches of the lowest vertebrae, usually in the sacrolumbar region. There are several disorders in this group of developmental abnormalities that have varying degrees of severity. Spina bifida occulta is the mildest form and is characterized by failure of vertebral fusion only. The spinal cord and meninges are normal. In spina bifida occulta the defect in the closure of the neural tube is covered by skin and dermis, with only a pinpoint sinus or hair-covered depression marking the site. Bacterial meningitis, or meningomyelitis, is the major potential risk in these patients. The remaining types of spina bifida are classified as spina bifida cystica. Spina bifida with a meningocele is characterized by protrusion through the vertebral defect of a meningeal sac filled with cerebrospinal fluid (CSF). Because the cord is in its normal location, there are minimal neurologic deficits. Next in severity is spina bifida with a myelomeningocele, which is characterized by herniation of the cord and a meningeal sac through the vertebral defect. This abnormality is often associated with severe neurologic defects in the lower extremities, bladder, and rectum. The most severe form of spina bifida, spina

bifida aperta or myeloschisis, results from complete failure of fusion of the caudal end of the neural plate, which lies open on the skin surface. This abnormality also results in severe neurologic defects in the legs, bladder, and rectum.

472. The answer is a. *(Cotran, pp 1304–1305. Damjanov, pp 2733–2736.)* Epidural hemorrhages result from hemorrhages into the potential space between the dura and the bone of the skull. These hemorrhages result from severe trauma that typically causes a skull fracture. The hemorrhage results from rupture of one of the meningeal arteries, as these arteries supply the dura and run between the dura and the skull. The artery involved is usually the middle meningeal artery, which is a branch of the maxillary artery, as the skull fracture is usually in the temporal area. Since the bleeding is of arterial origin (high pressure), it is rapid and the symptoms are rapid in onset, although the patient may be normal for several hours (lucid interval). Bleeding causes increased intracranial pressure and can lead to tentorial herniation and death.

473. The answer is c. *(Cotran, pp 1310–1313.)* Subarachnoid hemorrhage is much less common than hypertensive intracerebral hemorrhage, and most often it results from rupture of a berry aneurysm. Berry aneurysms are saccular aneurysms that result from congenital defects in the media of arteries. They are typically located at the bifurcations of arteries. They are not the result of atherosclerosis. Instead, berry aneurysms are called congenital, although the aneurysm itself is not present at birth. Berry aneurysms are most commonly found in the circle of Willis, typically either at the junction of the anterior communicating artery with the anterior cerebral artery or at the junction of the middle cerebral artery and the posterior communicating artery. The chance of rupture of berry aneurysms increases with age (rupture is rare in childhood). Rupture causes marked bleeding into the subarachnoid space and produces severe headaches, typically described as the "worst headache ever." Additional symptoms include vomiting, pain and stiffness of the neck (due to meningeal irritation caused by the blood), and papilledema. Death may follow rapidly.

474. The answer is a. *(Cotran, pp 1306–1310. Rubin, pp 1470–1475.)* Decreased brain perfusion may be generalized (global) or localized. Global ischemia results from generalized decreased blood flow, such as with shock, cardiac arrest, or hypoxic episodes (e.g., near drowning or carbon

monoxide poisoning). Global hypoxia results in watershed (border zone) infarcts, which typically occur at the border of areas supplied by the anterior and middle cerebral arteries, and laminar necrosis, which is related to the short, penetrating vessels originating from pial arteries. The Purkinje cells of the cerebellum and the pyramidal neurons of Sommer's sector in the hippocampus are particularly sensitive to hypoxic episodes. Atherosclerosis, which predisposes to vascular thrombi and emboli, is related to regional ischemia. Hypertension damages parenchymal arteries and arterioles, producing small ischemic lesions (lacunar infarcts). Fat emboli, related to trauma of long bones, lodge in small capillaries to form petechiae. Venous sinus thrombosis is related to systemic dehydration, phlebitis, and sickle cell disease.

475. The answer is b. *(DeMyer, p 176–177, 312.)* Dyscalculia is characterized by problems with simple calculations. It is associated with damage to the dominant parietal lobe. It can also be seen with lesions of the visual association cortex (angular gyrus area 39), destruction of which results in Gerstmann's syndrome, which is characterized by right-left confusion, finger agnosia, agraphia, and dyscalculia. In contrast, Déjérine-Roussy syndrome refers to contralateral loss of sensory with contralateral dysthesia (pain); Parinaud's syndrome refers to large impaired conjugate vertical gaze, pupillary abnormality, and absence of accommodation reflex due to compression of upper midbrain and pretectal areas; Wallenberg's syndrome is the lateral medullary syndrome and results from occlusion of the vertebral artery or occlusion of the posterior inferior cerebellar artery (hence its other name, PICA syndrome); and Weber's syndrome refers to the medial midbrain syndrome.

476. The answer is d. *(Cotran, pp 1313–1314. Rubin, pp 1466–1470.)* Hypertension results in the deposition of lipid and hyaline material in the walls of cerebral arterioles, which is called lipohyalinosis. This weakens the wall and forms small Charcot-Bouchard aneurysms, which may eventually rupture. Berry aneurysms (small saccular aneurysms) are the result of congenital defects in the media of blood vessels and are located at the bifurcations of arteries. Atherosclerotic aneurysms are fusiform (spindle-shaped) aneurysms usually located in the major cerebral vessels. They rarely rupture, but may become thrombosed. Mycotic (septic) aneurysms result from septic emboli, most commonly from subacute bacterial endocarditis.

477. The answer is b. *(Cotran, pp 1317, 1319–1321.)* Neurosyphilis, a tertiary stage of syphilis, includes syphilitic meningitis, paretic neurosyphilis, and tabes dorsalis. Syphilitic meningitis is characterized by perivascular infiltrates of lymphocytes and plasma cells that cause obliterative endarteritis and meningeal fibrosis. Tabes dorsalis is the result of degeneration of the posterior columns of the spinal cord. This is caused by compression atrophy of the posterior spinal sensory nerves, which produces impaired joint position sensation, ataxia, loss of pain sensation (leading to joint damage, i.e., Charcot joints), and Argyll Robertson pupils (pupils that react to accommodation but not to light).

In contrast, rabies, caused by a single-stranded RNA rhabdovirus, is transmitted by the bite of a rabid animal, usually a dog. The virus is transmitted through peripheral nerves to the brain, where it forms characteristic inclusions within neurons (Negri bodies). Symptoms related to destruction of neurons in the brainstem include irritability, difficulty in swallowing and spasms of the throat (these two resulting in "hydrophobia"), seizures, and delirium. The illness is almost uniformly fatal. Poliomyelitis is caused by an enterovirus that produces a nonspecific gastroenteritis and then secondarily invades the anterior horn motor neurons of the spinal cord, where it causes muscular paralysis. Progressive multifocal leukoencephalopathy (PML) is a viral infection of oligodendrocytes that causes demyelination and symptoms of dementia and ataxia. The causative agents of PML are two closely related papovaviruses, JC virus and SV40. The pathognomonic feature of PML is oligodendrocytes in areas of demyelination with a "ground-glass" appearance of their nuclei. PML typically occurs as a terminal complication in immunosuppressed patients.

478. The answer is a. *(Cotran, pp 1314–1317.)* Meningitis [inflammation of the arachnoid and the cerebrospinal fluid (CSF)], may be classified as acute pyogenic, aseptic, or chronic. The etiology and CSF findings vary in these three groups. The CSF in acute pyogenic meningitis, which is usually caused by bacteria, is grossly cloudy (not bloody, which is suggestive of a subarachnoid hemorrhage) and displays increased pressure, increased neutrophils, increased protein, and decreased glucose. With chronic meningitis, such as that caused by *Mycobacterium tuberculosis,* the CSF is clear grossly, with only a slight increase in leukocytes (either mononuclear cells or a mixed infiltrate), a markedly increased protein level, increased pressure, and moderately decreased or normal amounts of sugar. Both brain

abscesses and subdural empyemas, which are parameningeal infections rather than direct meningeal infections, cause increased CSF pressure (more marked with abscess because of mass effect) along with increased inflammatory cells (lymphocytes and polys) and increased protein but a normal glucose level. The CSF is clear. Encephalitis, also not a direct infection of the meninges, results in clear CSF, increased pressure, increased protein, normal glucose, and possibly increased lymphocytes.

479. The answer is c. *(Cotran, p 1317–1322. Rubin, pp 1484–1491.)* Poliomyelitis is caused by an enterovirus that causes a nonspecific gastroenteritis and then secondarily invades the anterior horn motor neurons of the spinal cord. Microscopy reveals characteristic neuronophagia of anterior horn neurons; the dorsal roots are not affected. Infection causes acute muscular paralysis (atrophy, fasciculations, fibrillation, and hyporeflexia). Postpolio syndrome occurs more than 25 years later, with progressive weakness, decreased muscle mass, and pain.

In contrast, progressive multifocal leukoencephalopathy (PML) is a viral infection of oligodendrocytes that causes demyelination and symptoms of dementia and ataxia. The causative agents of PML are two closely related papovaviruses, JC virus and SV40. The pathognomonic feature of PML is oligodendrocytes in areas of demyelination having a "ground-glass" appearance of their nuclei. PML occurs as a terminal complication in immunosuppressed individuals. The arthropod-borne viruses (arboviruses) are transmitted by blood-sucking vectors such as ticks and mosquitoes. These viruses represent a heterogenous group of diseases responsible for most outbreaks of epidemic encephalitis, examples being eastern and western equine encephalitis and St. Louis encephalitis. Subacute sclerosing panencephalitis (SSPE), an encephalitis predominately of childhood, is usually related to previous measles infection, often at an unusually early age.

480. The answer is b. *(Cotran, pp 1323–1326.)* The spongiform encephalopathies, kuru and Creutzfeldt-Jakob disease (CJD), are thought to be caused not by a virus, but by abnormal prion protein (PrPsc or PrPCJD). The term *prion* stands for infectious particle and was coined by Prusiner in 1982. Disease results from alternate folding (normal α helix to abnormal β-pleated sheet) of the normally present PrPc. These abnormal forms are stable and can "crystallize" and form plaques. They are characterized by long incubation periods followed by slowly progressive ataxia and dementia. Patients with CJD initially have subtle changes in memory and behavior,

which are followed by a rapidly progressive dementia and death within several months. Microscopically, there is characteristic spongiform change in the gray matter ("cluster of grapes" vacuolation) without inflammation. Scrapie is a similar disease found in sheep and goats. Kuru is a disease confined to New Guinea and is related to cannibalism.

481. The answer is d. *(Ayala, pp 15–16, 24. Cotran, pp 1326–1329. Henry, pp 463–464.)* In primary CNS demyelination there is loss of myelin sheaths with relative preservation of axons. Primary demyelination is seen predominately in multiple sclerosis, in the perivenous encephalomyelopathies, and in progressive multifocal leukoencephalopathy (PML). Multiple sclerosis (MS), a disease of unknown etiology, causes disseminated but focal plaques of primary demyelination anywhere in the CNS, but often in the white matter near the angles of the lateral ventricles. It primarily affects young adults between 20 and 40 years of age, with the onset of symptoms such as abnormalities of vision, tremors, paresthesias, and incoordination. The course is typically remitting and relapsing. Early findings include weakness of the lower extremities and visual abnormalities with retrobulbar pain. The classic (Charcot) triad in patients with MS consists of scanning speech, intention tremor, and nystagmus (mnemonic is SIN). Also pathognomonic for MS is internuclear ophthalmoplegia (INO), also known as the MLF syndrome, which results from demyelination of the medial longitudinal fasciculus. It results in medial rectus palsy on attempted lateral gaze and monocular nystagmus in abducting eye with convergence. Examination of the CSF in patients with MS reveals increased T lymphocytes, increased protein, and normal glucose. Protein electrophoresis of the CSF reveals oligoclonal bands (individual monoclonal spikes), although this latter finding is not specific for MS.

482. The answer is b. *(Cotran, pp 1338–1341.)* Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a degenerative disorder of motor neurons, principally the anterior horn cells of the spinal cord, the motor nuclei of the brainstem, and the upper motor neurons of the cerebral cortex. Clinically, this disease is a combination of lower motor neuron (LMN) disease with weakness and fasciculations and upper motor neuron (UMN) disease with spasticity and hyperreflexia. Early symptoms include weakness and cramping, then muscle atrophy and fasciculations. Reflexes are hyperactive in upper and lower extremities, and a positive extensor plantar (Babinski) reflex develops because of the loss of upper motor neu-

rons. The triad of atrophic weakness of hands and forearms, slight spasticity of the legs, and generalized hyperreflexia—in the absence of sensory changes—suggests the diagnosis. The clinical course is rapid, and death may result from respiratory complications. There is no effective treatment for ALS. Theories about the etiology of ALS include viral infections, immunologic causes, or oxidative stress. The latter is related to a defect in zinc-copper binding superoxide dismutase (SOD) on chromosome 21. Decreased SOD activity leads to apoptosis of spinal motor neurons.

In contrast, metachromatic leukodystrophy is an autosomal recessive disorder of sphingomyelin metabolism that results from deficiency of cerebroside sulfatase (aryl-sulfatase A). Sulfatides accumulate in lysosomes and stain metachromatically with cresyl violet. Diagnostic measures include amniocentesis, enzyme analysis, and measuring decreased urinary arylsulfatase A. Demyelination is widespread in the cerebrum and peripheral nervous system. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) is a life-threatening disease of the peripheral nervous system. The disease usually follows recovery from an influenza-like upper respiratory tract infection and is characterized by a motor neuropathy that leads to an ascending paralysis that begins with weakness in the distal extremities and rapidly involves proximal muscles. Sensory changes are usually minimal. The disease is thought to result from immune-mediated segmental demyelination. Huntington's disease is characterized by choreiform movements and progressive dementia that appear after the age of 30. Wilson's disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper metabolism in which the total circulating copper is decreased, but the free copper is increased. This leads to athetoid movements, cirrhosis of the liver, and copper deposits in the limbus of the cornea that produce the Kayser-Fleischer ring.

483. The answer is e. *(Cotran, pp 1329–1333.)* Alzheimer's disease (AD) is the most common cause of dementia in elderly (followed by vascular multi-infarct dementia and diffuse Lewy body disease). AD often begins insidiously with impairment of memory and progresses to dementia. The etiology is not well understood (age is the main risk factor), but it is clear that there are multiple etiologic pathways to this disease state. Late-onset familial and sporadic AD are associated with the presence of the E4 isotype of ApoE, this being the most important factor in the general population. β-amyloid (A-β) deposition is necessary but not suffi-

cient for the development of Alzheimer's disease. The gene for β-amyloid is located on chromosome 21 (note the high incidence of Alzheimer's disease in individuals with trisomy 21). Cleavage of the β-amyloid precursor protein (β-APP) by α-secretase precludes β-A formation; cleavage by β- or γ-secretases produces pathogenic fragments. Early-onset familial Alzheimer's is related to mutations in presenilins or β-APP. Histologically, AD is characterized by numerous neurofibrillary tangles and senile plaques with a central core of amyloid α-protein. Both tangles and plaques are found to a lesser extent in other conditions, e.g., neurofibrillary tangles in Down's syndrome. Silver stains demonstrate tangles and plaques and Congo red shows amyloid deposition in plaques and vascular walls (amyloid angiopathy). In AD there are also numerous Hirano bodies, and granulovacuolar degeneration is found in more than 10% of the neurons of the hippocampus. Grossly, brain atrophy (narrowed gyri and widened sulci) is predominant in the frontal and superior temporal lobes. In contrast to AD, expansion of CAG trinucleotide repeats on chromosome 4 is associated with Huntington's disease, ingestion of 1-methyl-4-phenyl-tetrahydrobiopteridine is associated with production of Parkinsonian symptoms, and mutations of the superoxide dismutase 1 gene are associated with amyotrophic lateral sclerosis.

484. The answer is e. *(Cotran, pp 1333–1334.)* The degenerative diseases of the CNS are diseases that affect the gray matter and are characterized by the progressive loss of neurons in specific areas of the brain. In Parkinson's disease, characterized by a masklike facial expression, coarse tremors, slowness of voluntary movements, and muscular rigidity, there is degeneration and loss of pigmented cells in the substantia nigra, resulting in a decrease in dopamine synthesis. Lewy bodies (eosinophilic intracytoplasmic inclusions) are found in the remaining neurons of the substantia nigra. The decreased synthesis of dopamine by neurons originating in the substantia nigra leads to decreased amounts and functioning of dopamine in the striatum. This results in decreased dopamine inhibition and a relative increase in acetylcholine function, which is excitatory in the striatum. The effect of this excitation, however, is to increase the functioning of GABA neurons, which are inhibitory. The result, therefore, is increased inhibition or decreased movement. The severity of the motor syndrome correlates with the degree of dopamine deficiency. Therapy may be with dopamine agonists or anticholinergics.

485. The answer is e. *(Cotran, pp 1333–1334.)* The histologic presence of Lewy bodies can be seen in several disorders (Lewy body disorders) that differ in the location where the Lewy bodies are found. In classic Parkinson's disease, Lewy bodies are found in the nigrostriatal system (producing extrapyramidal movement disorder). In Lewy body dementia, Lewy bodies are found in the cerebral cortex (producing dementia; this is the third most common cause of dementia). In Shy-Drager syndrome, Lewy bodies are found in sympathetic neurons in the spinal cord (causing autonomic dysfunction, including orthostatic hypotension, impotence, abnormal sweat and salivary gland secretion, and pupillary abnormalities). In Lewy body dysphagia, Lewy bodies are found in the dorsal vagal nuclei (producing dysphagia).

486. The answer is a. *(Cotran, pp 1335–1336.)* Huntington's disease, an autosomal dominant disorder that results from an abnormal gene on chromosome 4, involves the extrapyramidal system and atrophy of the caudate nuclei and putamen. Choreiform movements and progressive dementia appear after the age of 30. There is degeneration of GABA neurons in the striatum, which leads to decreased function (decreased inhibition) and increased movement. Huntington's disease is one of four diseases that are characterized by long repeating sequences of three nucleotides (the other diseases being fragile X syndrome, myotonic dystrophy, and spinal and bulbar muscular atrophy). Therapy for excessive movement (hyperkinetic) disorders can be attempted with dopamine antagonists. Decreased dopamine in the striatum theoretically causes a relative increase in acetylcholine and an increase in excitation in the striatum. This causes increased GABA function, which leads to increased inhibition of movement. The same result could theoretically be achieved with inhibition of acetylcholine breakdown (cholinesterase inhibitors). Compare this to the same treatment of hypokinetic (Parkinsonian) disorders. Dopamine agonists increase the inhibition in the striatum, leading to decreased GABA in the striatum and decreased inhibition of movement (increased movement). The same result could theoretically be achieved with anticholinergics.

487. The answer is c. *(Cotran, pp 1348–1349. Rubin, p 1519.)* Astrocytomas are not at all uncommon in the younger age group, but when a child presents with clinical symptoms pointing to the intracranial posterior fossa, a cerebellar medulloblastoma should be suspected, especially if the child has no prior history of leukemia or neuroblastoma. Medulloblastomas occur predominantly in childhood and usually arise in the midline

of the cerebellum (the vermis). They do occur (less commonly) in adults, in whom they are more apt to arise in the cerebellar hemispheres in a lateral position. They grow by local invasive growth and may block cerebrospinal fluid circulation (CSF block) via compression of the fourth ventricle. Recently, aggressive treatment with the combined modalities of excision, radiotherapy, and chemotherapy has improved survival rates.

488. The answer is d. *(Cotran, p 1346. Rubin, p 1518.)* Oligodendrogliomas, which most commonly involve the cerebrum (hemispheres) in adults, are slow-growing tumors that have a high recurrence rate. Some oligodendrogliomas do proliferate in a rapid and aggressive fashion and may be associated with a malignant astrocytoma component. Histologically, these tumors consist of sheets of cells with clear halos ("fried-egg" appearance) and various amounts of calcification (which can be seen on x-ray). Cytogenetic abnormalities have therapeutic significance for this type of tumor, as only tumors with deletion involving 19q or 1p respond to PCV chemotherapy.

489. The answer is d. *(Cotran, pp 1343–1346.)* The features listed in the question are characteristic of a glioblastoma multiforme. Astrocytomas, the most common primary brain tumors in adults, range from low-grade to very high-grade (glioblastoma multiforme). These grades of astrocytomas include grade I (the least aggressive and histologically difficult to differentiate from reactive astrocytosis), grade II (some pleomorphism microscopically), grade III (anaplastic astrocytoma, characterized histologically by increased pleomorphism and prominent mitoses), and grade IV (glioblastoma multiforme). Glioblastoma multiforme is a highly malignant tumor characterized histologically by endothelial proliferation and serpentine areas of necrosis surrounded by peripheral palisading of tumor cells. It frequently crosses the midline ("butterfly tumor").

In contrast, schwannomas generally appear as extremely cellular spindle cell neoplasms, sometimes with metaplastic elements of bone, cartilage, and skeletal muscle. Medulloblastomas occur exclusively in the cerebellum and microscopically are highly cellular with uniform nuclei, scant cytoplasm, and, in about one-third of cases, rosette formation centered by neurofibrillary material. Oligodendrogliomas, which are marked by foci of calcification in 70% of cases, commonly show a pattern of uniform cellularity and are composed of round cells with small dark nuclei, clear cytoplasm, and a clearly defined cell membrane. Ependymomas are distinguished by

ependymal rosettes, which are ductlike structures with a central lumen around which columnar tumor cells are arranged in a concentric fashion.

490. The answer is b. *(Cotran, p 1350–1351. Rubin, pp 1519–1520.)* Meningiomas arise from arachnoid villi of brain or spinal cord and have a female/male ratio of 3:2. Although they are usually tumors of middle or later life, a small number occur in persons 20 to 40 years of age. They commonly arise along the venous sinuses (parasagittal, sphenoid wings, and olfactory groove). Although meningiomas are benign and usually slow-growing, some have progesterone receptors and rapid growth in pregnancy occurs occasionally. The rare malignant meningioma may invade or even metastasize. The typical case, however, does not invade the brain, but displaces it, causing headaches and seizures. Histologically, many different patterns can be seen, but psammoma bodies and a whorled pattern of tumor cells are somewhat characteristic. In contrast, Antoni A areas with Verocay bodies are seen in schwannomas, endothelial proliferation and serpentine areas of necrosis are seen in glioblastoma multiformes, a "fried-egg" appearance of tumor cells is characteristic of oligodendrogliomas, and true rosettes and pseudorosettes can be seen in medulloblastomas.

491. The answer is a. *(Cotran, p 1129.)* Both oligodendroglioma and craniopharyngioma show calcification fairly frequently; oligodendroglioma is often located in the frontal lobe, whereas craniopharyngioma occurs around the third ventricle and demonstrates suprasellar calcification. CT scan and particularly MRI are essential in diagnosis. Patchy intracerebral calcification may develop in tuberous sclerosis, an autosomal dominant disease characterized by the triad of epilepsy, mental retardation, and facial skin lesions (multiple angiofibromas). In addition, subependymal gliosis, cardiac rhabdomyoma, renal angiomyolipoma, and periungual fibroma occur. Calcification of the basal ganglia occurs in about 20% of patients with chronic hypoparathyroidism, which sometimes leads to a Parkinsonian syndrome.

492. The answer is b. *(Cotran, p 1346. Silverberg, pp 2093–2102.)* The location of a tumor and the age of the patient are both very important in the differential diagnosis of tumors of the central nervous system. Astrocytomas occur predominately in the cerebral hemispheres in adult life and old age, in the cerebellum and pons in childhood, and in the spinal cord in young adults. The pilocytic astrocytoma is a subtype that is the most com-

mon brain tumor in children, and therefore it is also called a juvenile pilocytic astrocytoma. It is characterized by its location in the cerebellum and better prognosis. Meningiomas, found within the meninges, have their peak incidence in the fourth and fifth decades. The highly malignant glioblastoma multiforme is also found primarily in adults. Oligodendrogliomas also involve the cerebrum in adults. Ependymomas are found most frequently in the fourth ventricle, while the choroid plexus papilloma, a variant of the ependymoma, is found most commonly in the lateral ventricles of young boys. The medulloblastoma is a tumor that arises exclusively in the cerebellum and has its highest incidence toward the end of the first decade. In children medulloblastomas are located in the midline, while in adults they are found in more lateral locations.

493. The answer is c. *(Cotran, pp 1352–1353.)* Schwannomas (neurilemomas) are single, encapsulated tumors of nerve sheaths, usually benign, occurring on peripheral, spinal, or cranial nerves. The acoustic neuroma is an example of a schwannoma that arises from the vestibulocochlear nerve (CN VIII). These tumors are typically located at the cerebellopontine angle or in the internal acoustic meatus. Initially, when they are small, these tumors produce symptoms by compressing CN VIII and CN VII (facial). CN VIII symptoms include unilateral tinnitus (ringing in the ear), unilateral hearing loss, and vertigo (dizziness). Involvement of the facial nerve produces facial weakness and loss of corneal reflex. Histologically, an acoustic neuroma consists of cellular areas (Antoni A) and loose edematous areas (Antoni B). Verocay bodies (foci of palisaded nuclei) may be found in the more cellular areas.

494. The answer is e. *(Cotran, pp 1354–1355. Rubin, pp 1524–1525.)* In von Hippel-Lindau disease, a rare autosomal dominant disorder, multiple benign and malignant neoplasms occur. These include hemangioblastomas of retina and brain (cerebellum and medulla oblongata), angiomas of kidney and liver, and renal cell carcinomas (multiple and bilateral) in 25 to 50% of cases. Classic neurofibromatosis (NF-1) is characterized by café-au-lait skin macules, axillary freckling, multiple neurofibromas, plexiform neurofibromas, and Lisch nodules (pigmented iris hamartomas). Lisch nodules are found in 95% of patients after age 6. Hamartomas of the iris are not present in central or acoustic neurofibromatosis (NF-2), though both types of neurofibromatosis produce café-au-lait macules and neurofibromas. Only the central, or acoustic, form produces bilateral acoustic neuro-

mas; the classic form may produce unilateral acoustic neuroma. There is increased risk of developing meningiomas or even pheochromocytoma. A major complication of NF-1 is the malignant transformation of a neurofibroma to a neurofibrosarcoma. The gene for the classic form (NF-1) is located on chromosome 17. It encodes for neurofibromin, a protein that regulates the function of p21 *ras* oncoprotein.

495. The answer is c. *(Fixx, pp 223–224. Cotran, p 1168.)* Lesions of the midbrain in general produce partial ophthalmoplegia and contralateral hemiplegia. In particular, the dorsal midbrain syndrome (Parinaud's syndrome) affects the superior colliculus and pretectal areas (producing paralysis of upward and downward gaze) and obstructs the cerebral aqueduct (producing a noncommunicating hydrocephalus). Parinaud's syndrome is frequently the result of a tumor of the pineal. Primary tumors of the pineal gland are very uncommon but are of interest, especially in view of the mysterious and relatively unknown functions of the pineal gland itself. The gland secretes neurotransmitter substances such as serotonin and dopamine, with the major product being melatonin. Tumors of the pineal gland include germ cell tumors of all types, including embryonal carcinoma, choriocarcinoma, teratoma, and various combinations of germinomas. Germ cell tumors may arise extragonadally within the retroperitoneal space and the pineal gland, with the only commonality being that these structures are in the midline. Primary tumors of the pineal gland occur in two forms: the pineoblastoma and the pineocytoma. Pineoblastomas occur in young patients and consist of small tumors having areas of hemorrhage and necrosis with pleomorphic nuclei and frequent mitoses. Pineocytomas occur in older adults and are slow-growing; they are better differentiated and have large rosettes. In contrast, the medial midbrain syndrome (Weber's syndrome) affects the oculomotor nerve roots, the corticobulbar tracts (producing contralateral weakness of the lower face (CN VII), the tongue (CN XII), the palate (CN X), and the corticospinal tracts (producing contralateral spastic paralysis of the trunk and extremities).

496. The answer is e. *(Fixx, pp 219–225.)* The lateral medullary syndrome (Wallenberg's syndrome) results from occlusion of the posterior inferior cerebellar artery (hence its other name, PICA syndrome). The signs and symptoms produced are related to the structures of the caudal medulla normally supplied by this vessel. These structures include the vestibular nuclei (nystagmus, nausea, vomiting, vertigo), the inferior cerebellar peduncle

(ipsilateral cerebellar signs), the nucleus ambiguus (ipsilateral laryngeal, pharyngeal, and palatine paralysis), the glossopharyngeal nerve roots (loss of gag reflex), the vagal nerve roots (same signs as the nucleus ambiguus), the spinothalamic tracts (contralateral loss of pain and temperature sensation from trunk and extremities), the spinal trigeminal nucleus (ipsilateral loss of pain and temperature sensation from the face), and the descending sympathetic tract (ipsilateral Horner's syndrome), which passes through the lateral aspects of the medulla in the dorsal longitudinal fasciculus.

497. The answer is a. *(Cotran, pp 1301–1302.)* Syringomyelia is a chronic myelopathy that results from formation of a cavity (syrinx) involving the central gray matter of the spinal cord, where pain fibers cross to join the contralateral spinothalamic tract. Interruption of the lateral spinothalamic tracts results in segmental sensory dissociation with loss of pain and temperature sense, but preservation of the sense of touch and pressure or vibration, usually over the neck, shoulders, and arms. Since the most common location of a syrinx is the cervicothoracic region, the loss of pain and temperature sensation affects both arms. Characteristic features also include wasting of the small intrinsic hand muscles (claw hand) and thoracic scoliosis. The cause of syringomyelia is unknown, although one type is associated with a Chiari malformation with obstruction at the foramen magnum.

498. The answer is a. *(DeMyer, pp 146–149. Ayala, pp 32–33.)* The physical finding of facial asymmetry is suggestive of an abnormality involving the facial nerve (CN VII). The facial nucleus, which is located within the pons, is divided in half; the upper neurons innervate the upper muscles of the face, while the lower neurons innervate the lower portion of the face. It is important to realize that each half receives input from the contralateral motor cortex, while only the upper half receives input from the ipsilateral motor cortex. Therefore an upper motor neuron (UMN) lesion will produce a defect involving only the contralateral lower half of the face. Causes of UMN lesions involving the facial nerve includes strokes that involve the cortex or the internal capsule. In contrast, lesions that affect the facial nerve from the facial nucleus to the remaining length of the nerve result in LMN lesions. Patients present with facial asymmetry involving the ipsilateral upper and lower quadrants. Lesions to the facial nerve within the facial canal (frequently due to cold weather) cause Bell's palsy. Patients present with paralysis of all muscles of facial expression. Bell's phenomenon refers to the finding of the affected eye looking up and out when patients try to

close their eyes. Because the lacrimal punctum in the lower eyelid moves away from the surface of the eye, lacrimal fluid does not drain into the nasolacrimal duct. This produces "crocodile tears."

499. The answer is d. *(Cotran, pp 1275–1276.)* Inflammatory polyneuropathies may be acute or chronic. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) is a life-threatening disease of the peripheral nervous system. The disease usually follows recovery from an influenza-like upper respiratory tract infection and is characterized by a motor neuropathy that leads to an ascending paralysis that begins with weakness in the distal extremities and rapidly involves proximal muscles. Sensory changes are usually minimal. The disease is thought to result from immune-mediated segmental demyelination. In rare patients, instead of an acute course, Guillain-Barré syndrome takes a chronic course with remissions and relapses. This process is called chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

500. The answer is c. *(Cotran, p 1280. Rubin, p 1530.)* Peripheral neuropathy is a clinical term that generally refers to nontraumatic diseases of the peripheral nerves. Peripheral neuropathies may either be focal or diffuse. Focal peripheral neuropathies may involve one nerve (mononeuropathy) or multiple nerves (multiple mononeuropathy or monoradiculopathy). An example of a mononeuropathy is compression of the median nerve, which produces carpal tunnel syndrome. The median nerve provides sensory information from the palmar surface of the lateral three and one-half digits and the lateral portion of the palm. Also innervated by the median nerve are the major pronators (pronator teres and pronator quadratus), the thumb flexors (flexor pollicus longus and flexor pollicus brevus), and the opponens pollicis. The median nerve does not innervate any muscles in the forearm. Damage to the median nerve at the wrist as it lies deep to the flexor retinaculum results in burning sensations in the thumb, index and middle fingers, and lateral half of the ring finger (carpal tunnel syndrome). This syndrome is found in people who use their hands a lot, such as jackhammer operators, typists, and tailors. Treatment may involve cutting the transverse carpal ligament to decompress the nerve.

Bibliography

Abenhaim L, Moride Y, Brenot F, et al: Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 335(9):609–616, 1996.

Alberts B, et al: *Molecular Biology of the Cell,* 3/e. New York, Garland, 1994.

Ayala C, Spellberg B: *Pathophysiology for the Boards and Wards,* 3/e. Malden, MA, Blackwell, 2000.

Champe PA, Harvey RA: *Biochemistry,* 2/e. Philadelphia, Lippincott, 1994.

Chandrasoma P, Taylor CR: *Concise Pathology,* 3/e. Stamford, CT, Appleton & Lange, 1998.

Connolly HM, Crary JL, et al: Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 337(9):581–588, 1997.

Cotran RS, Kumar V, Robbins SL: *Pathologic Basis of Disease,* 6/e. Philadelphia, Saunders, 1999.

Damjanov I, Linder J (eds): *Anderson's Pathology,* 10/e. St. Louis, Mosby, 1996.

DeMyer W: *Neuroanatomy,* 1/e. Philadelphia, Harwal, 1988.

Duchin JS, et al: Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. *N Engl J Med* 330:949–955, 1994.

Fawcett DW: *A Textbook of Histology,* 12/e. New York, Chapman & Hall, 1994.

Fixx JD: *Neuroanatomy,* 2/e. Baltimore, Williams & Wilkins, 1995.

Flake AW, Roncarolo MG, et al: Brief report: Treatment of x-linked severe combined immunodeficiency by in utero transplantation of paternal bone marrow. *N Engl J Med* 335(24):1806–1810, 1996.

Ganong WF: *Review of Medical Physiology,* 17/e. Norwalk, CT, Appleton & Lange, 1995.

Henry JB, et al (eds): *Clinical Diagnosis and Management by Laboratory Methods,* 19/e. Philadelphia, Saunders, 1996.

Isselbacher KJ, et al (eds): *Harrison's Principles of Internal Medicine,* 13/e. New York, McGraw-Hill, 1994.

Joklik WK, et al (eds): *Zinsser Microbiology,* 20/e. Norwalk, CT, Appleton & Lange, 1992.

Jorde LB, et al: *Medical Genetics,* 2/e. St. Louis, Mosby, 2000.

Larsen WJ: *Human Embryology,* 1/e. New York, Churchill Livingstone, 1993.

Lee GR, et al (eds): *Wintrobe's Clinical Hematology,* 9/e. Philadelphia, Lea & Febiger, 1993.

Lever WF, Schaumberg-Lever G: *Histopathology of the Skin,* 7/e. Philadelphia, Lippincott, 1990.

McPhee SJ, et al: *Pathophysiology of Disease,* 2/e. Stamford, CT, Appleton & Lange, 1997.

Rubin E, Farber JL: *Pathology,* 3/e. Philadelphia, Lippincott, 1999.

Silverberg SG (ed): *Principles and Practice of Surgical Pathology,* 2/e. New York, Churchill Livingstone, 1990.

Index