The Immune System and Immune Mediated Diseases
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Outline:

1. Review of Hypersensitivity Reactions
2. Systemic Autoimmune Diseases
   a. Tolerance and mechanisms of autoimmunity
   b. Autoantibodies
   c. Systemic Lupus Erythematosus
   d. Sjogren Syndrome
   e. Systemic Sclerosis
   f. Inflammatory myopathies
   g. Mixed connective tissue disease
3. Pathology of Transplantation
   a. Mechanisms of rejection
   b. Morphologic features of rejection
   c. Increasing graft survival
   d. Graft versus host disease
   e. Other complications.
4. Laboratory Assessment of Immune Status
5. Immunodeficiency: Congenital and Acquired
   a. Acquired versus congenital immunodeficiencies
   b. Clinical manifestations of congenital immunodeficiencies
   c. Selected Congenital Immunodeficiencies
      X-linked agammaglobulinemia (Bruton's)
      Common Variable Immunodeficiency
      IgA Deficiency
      Hyper IgM Syndrome
      Thymic hypoplasia (DiGeorge Syndrome)
      Severe Combined Immunodeficiency (SCID)
      Wiskott-Aldrich Syndrome
   d. Acquired Immunodeficiency
      Pathology and Pathogenesis of HIV Infection
6. Amyloidosis

Reading: Robbins Basic Pathology pp 110-120 (review-hypersensitivity), 120-159 (new)
Autoimmunity and Autoimmune Disease

Tolerance and Mechanisms of Autoimmunity

Mechanisms of Immunologic *Tolerance*

Central:

Peripheral:

Mechanisms of *Autoimmunity*

Barriers to intrathymic deletion

**PROTECTED SITES**
- AUTOIMMUNE REGULATOR (AIRE): stimulates expression of self Ag
- SEQUESTERED: lens, testis

Genetic factors and "susceptibility genes"

**HLA ASSOCIATIONS**: “predisposition”
- Mutations: FAS-FAS ligand, AIRE (not single gene)

Infections and Autoimmunity

**TISSUE DAMAGE**: altered Ag structure (epitope spreading)
- INDUCTION OF INFLAMMATORY CYTOKINES, HLA expression
- COSTIMULATORY MOLECULE EXPRESSION
- MOLECULAR MIMICRY

Tissue injury (UV light)

Other factors

**DRUGS** (procainamide), COMPLEMENT DEFICIENCY, EXTRINSIC ANTIGEN
Autoantibodies

Role in autoimmune disease:

1) DIRECT CELLULAR DAMAGE

2) RECEPTOR STIMULATION

3) IMMUNE COMPLEX DISEASE

4) UNCERTAIN SIGNIFICANCE

Antinuclear Antibodies

Definition:

Detection of ANA: Immunoassay (automated) versus indirect immunofluorescence.

ANA: patterns of immunofluorescence:

1) HOMOGENEOUS/DIFFUSE
   anti-chromatin, histone, dsDNA

2) RIM/PERIPHERAL
   anti- dsDNA

3) SPECKLED
   non-DNA nuclear antigens (ENA’s)

4) NUCLEOLAR
   assoc with PSS

Systemic Autoimmune Diseases

Tests for systemic inflammation:

C-reactive protein
FROM LIVER, ACUTE PHASE REACTANT, SHORT T1/2, EARLY MARKER

Erythrocyte sedimentation rate (ESR or Sed rate)
INCREASED PROTEIN (globulin, fibrinogen)
NORMAL 1-20 mm/hr
INCREASED: pregnancy, anemia, macrocytosis
DECREASED: polycytemia, abnormal RBCs, technical factors, abnormal proteins
Other: HYPERGAMMAGLOBULINEMIA, HYPOCOMPLEMENTEMIA

Systemic Lupus Erythematosus

Defining: multisystem, variable signs/symptoms and clinical course

Diagnostic criteria (Revised Criteria)

Demographics

Prevalence: 40/100,000 (Northern European) 200/100,000 (blacks)

Sex: 90% are FEMALE, 9:1 female: male
Age: young-middle age (females 15-50 years of age)
Race: 1/245 prevalence in black women, more severe disease

Pathogenesis

Genetic factors

1) TWINS: 25% CONCORDANCE IN MZ TWINS vs 2% DZ

2) WHOLE GENOME SCANNING: MULTIPLE SUSCEPTIBILITY GENES, INCL HLA IDENTIFIED

3) NULL ALLELES IN COMPLEMENT GENES AND EARLY COMPLEMENT COMPONENT DEFICIENCIES

Environmental factors

1) HORMONES: SEX HORMONES

2) DRUGS: PROCAINAMIDE, HYDRALAZINE, QUINIDINE

3) INFECTIONS: EVB

4) UV LIGHT

5) CIGARETTE SMOKING ? mechanism
Immune system abnormalities

1) **IFN alpha STIMULATION**

2) **TOLL-LIKE RECEPTOR MEDIATED SIGNALING ACTIVATES SELF-REACTIVE B CELLS**

3) **FAILURE OF B CELL TOLERANCE (CENTRAL AND PERIPHERAL TOLERANCE BREAKDOWN)**

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**Autoantibodies**

Antinuclear antibodies:

*anti-dsDNA (peripheral/rim distrib)*
*anti-Sm*
- **ANA R/O SLE**

Antiphospholipid antibodies:

Assoc w/thrombosis (arterial)
Present in 40-50% of pts w/SLE
Also **PRIMARY APS** occurs
Interacts with plasma proteins/phospholipid in PTT assay “lupus anticoagulant”
Related: **Anti-cardiolipin antibody**
False + RPR

Other autoantibodies:

*Mechanism of tissue injury:*
1) **DNA/ANTI DNA complexes in vessel walls (Type III)**

2) **Anti-RBC/Anti-WBC antibodies + complement (Type II)**

3) **LE cell (obsolete)**
Pathology of Systemic Lupus Erythematosus

Blood vessels:

NECROTIZING VASCULITIS

Kidneys:

Glomerulonephritis: (Class I-VI)
“Normal” – may still have deposits by EM/IF
Diffuse Proliferative: most serious, crescents, necrotizing lesions
Deposits: mesangial, subepi, subendothelial
Wire Loop lesions: worse prognosis
TITER of anti-dsDNA correlates with renal disease activity

May also see tubule-interstitial inflammation/damage

Skin:

MALAR RASH 50%
typical HISTOLOGY: basal layer liquifactive change, deposits of Ig/Comp at D-E jct
PHOTOSENSITIVITY

Joints:

SYNOVITIS- non-EROSIVE, ARTHRALGIAS, MYALGIAS
Fusiform swelling of fingers, wrists, knees

Central nervous system:

NON-VASCULITIC OCCLUSION (APA), PSYCHOSIS, SEIZURES, OTHER-
FATIGUE, DEPRESSION

Cardiovascular:

ACCELERATED CAD
LIBMAN SACKS ENDOCARDITIS

Other:

Lungs ALVEOLAR INJURY, FIBROSIS
Liver AUTOIMMUNE HEPATITIS
Spleen ONIONSKIN LESIONS
Serosal Surfaces: PLEURITIS, PERICARDITIS
Presentation and clinical course

VARIABLE PRESENTATION AND CLINICAL COURSE

3 “GROUPS”
1) Anti RNP, Anti-Sm
2) Anti Ro, LA, anti ds-DNA
3) Anti cardiolipin, LA, (APS) anti ds-DNA

Treatment

Mild- Moderate disease: HYDROXYCHLOROQUINE-mainstay of therapy
Severe disease: STEROIDS, CYTOTOXIC AGENTS: azathioprine, anti-TNF
B-cell targeted therapy: anti BLyS, anti CD20 (rituximab)

Survival

80% 5 year survival (compared with 50% in 1950’s)
Death from infection, accelerated atherosclerosis
Other: severe CNS disease, thromboembolism

Variants of Lupus:

Discoid lupus
SKIN INVOLVEMENT WITH ONLY RARE SYSTEMIC DISEASE (5%)
DIFFERENT SKIN LESIONS

Drug Induced
HYDRALAZINE, ISONIAZID, PENICILLAMINE
DISEASE USUALLY REMITS AFTER WITHDRAWAL OF DRUG
ASSOC W/ +ANA - dsDNA

SUBACUTE CUTANEOUS LUPUS: WIDESPREAD NON-SCARRING SKIN LESIONS, MILD SYSTEMIC DISEASE.
Sjogren Syndrome

**Definition:**
AUTOIMMUNE DISEASE CHARACTERIZED BY--

1) **DRY EYES : XEROPHTHALMIA**
2) **DRY MOUTH: XEROSTOMIA**
3) **LYMPHOCYTIC INFILTRATION OF SALIVARY GLANDS**

**PRIMARY : SICCA SYNDROME**
SECONDARY “ associated with another autoimmune disorder –RA”

**Clinical presentation**
90% are female 40-60 years old
Bilateral salivary gland (parotid) enlargement
SICCA syndrome as above
Other manifestations similar to other systemic CTD: arthralgia/arthritis, Raynaud, lymphadenopathy, respiratory symptoms, myositis

**Pathogenesis:**
Cellular and Humoral mechanisms
CD4 mediated inflammation directed at exocrine duct cell antigens
B cell activation—ANA, RF
? mech of tissue injury
? viral etiol- EBV, HIV HCV

**Laboratory findings:**
ANA: positive in 50-80%
90% are anti-RNP: SS-A (Ro) , SS-B (La)

Rheumatoid factor (RF) : 75%

**Pathologic features:**
1) lymphocytic infiltrate in salivary/lacrimal glands, atrophy
2) non Hodgkin lymphoma (40X increase)
3) renal involvement ( 
Multisystem disease

Extraglandular involvement occurs in 25-30 %
Associated with HIGH TITER OF Anti-SSA

Examples:

1) peripheral neuropathy
2) lung- fibrosis
3) kidney- T-I disease
4) myositis, arthritis

Diagnosis:

ANA testing
minor salivary gland biopsy
tear/salivary studies

Treatment:

Symptomatic, anti-inflammatory
Tear/Salivary replacement
Steroids- for severe extra glandular involvement
Systemic Sclerosis (Scleroderma)

**Definition:**
AUTOIMMUNE DISEASE CHARACTERIZED BY EXCESSIVE FIBROSIS THROUGHOUT THE BODY: SKIN, GI TRACT, LUNGS, KIDNEYS, HEART

**Prevalence:**
3X MORE COMMON IN WOMEN  
INCIDENCE: 2/100,000/yr  
PREVALENCE: 25-75 /100,000

Diffuse scleroderma:  
RAPID COURSE  
SYMmetric SKIN THICKENING  
HIGH RISK OF VISCERAL INVOLVEMENT

Localized scleroderma:  
SKIN CHANGES LIMITED TO FACE AND EXTREMITIES

CALCINOSIS  
RAYNAUDS  
ESOPHAGEAL DYSMOT  
SCLERODACTYL  
TELANGIETASIAS

**Etiology/Pathogenesis:**

Endothelial cell injury  
? MECHANISM  
Immune activation  
T CELLS AND SELF ANTIGEN

Fibrogenic cytokines  
TGF-BETA  
PDGF

B-CELL ACTIVATION AND  
Autoantibodies:

1) ANTI DNA TOPOISOMERASE I(SCL-70)  
70% W/DIFFUSE DISEASE  
2) ANTI-CENTROMERE  
90% W/LOCALIZED-CREST
Pathologic features:

Skin
DIFFUSE SCLEROTIC ATROPHY
FINGERS FIRST, THEN MORE PROXIMAL
VASCULAR THICKENING
CALCINOSIS
LOSS OF NAIL FOLD CAPILLARIES

GI tract 90% OF PATIENTES
FIBROSIS OF MUSCULARIS
ESOPHAGEAL DYSMOTILITY
PEPTIC/REFLUX DISEASE
MALABSORPTION

Kidney
ARTERIAL CHANGES-ONIONSKIN
30% DEVELOP HYPERTENSION, HIGHER INCIDENCE OF MALIGNANT HYPERTENSION

Lungs
FIBROTIC LUNG DISEASE

Heart
MYOCARDIAL FIBROSIS

OTHER…

Presentation and Clinical Course

Raynaud phenomenon PRECEDING SYMPTOM IN 70%

Skin changes

Visceral involvement and associated symptoms

JOINT PAIN STIFFNESS
RESPIRATORY SX/SX
RENAL INSUFF, MALIGNANT HTN

Treatment:
ASA/NSAID
STEROIDS
STRONGER IMMUNOSUPPRESSIVES FOR SEVERE DISEASE
D-PENICILLAMINE: DECREASES SKIN CHANGES
Prognosis/Survival:
10 YEAR SURVIVAL 35-70% OVERALL. BETTER WITH LOCALIZED SS

Other Autoimmune Disorders:

Inflammatory Myopathies DISCUSSED ELSEWHERE

Dermatomyositis
ADULTS AND CHILDREN
HELIOTROPE SKIN RASH
MYOPATHY: MUSCLE WEAKNESS
PROXIMAL THEN DISTAL
MAY HAVE EXTRAMUSCULAR DZ: LUNG
CAPILLARIES ARE MAJOR TARGET OF INFLAMM

Polymyositis
ADULTS
DIRECT IMMUNE ATTACK OF MUSCLE
ASSOC W/ NEOPLASMS, OTHER CTD
6-45% HAVE UNDERLYING CANCER (LUNG, STOMACH, OVARY)

Associated autoantibody:
ANTI T-RNA SYNTHETASE (ANTI JO-1)

OTHER FDGS: ELEVATED CPK
DX: EMG, MUSCLE BIOPSY

Mixed Connective Tissue Disease

Definition
OVERLAP SYNDROME (? SPECIFIC ENTITY)
mixed features of lupus, pss, polymyositis

Associated autoantibody:
ANTI –U1-RNP
EVENTUALLY MAJORITY DEVELOP DIAGNOSTIC CLINICAL CRITERIA FOR
ONE OF CTDZ WITHIN 5 YEARS
Mechanisms of Transplant (allograft) Rejection

**Complex response of cell-mediated and humoral immunity**

*Antigens involved: ABO (all cells), HLA (I and II)*

**Antigen recognition: direct versus indirect**

**Direct:** T cells recognize foreign Ag via APC

**Indirect:** Ag shed from graft processed by APC and presented to host CD4 cells

**Cell mediated rejection:**

- **CD4 activation:** TH1—DTH
- **TH2—antibody**
- **CD8 mediated cytotoxicity**

**Antibody mediated rejection:**

- **Pre-formed antibody**
- **B cell activation and response to foreign antigen**
- **Type II and Type III response**

**Morphology:**

Depends on time frame

**Example:** Renal allograft

- **Hyperacute:** Immediate, pre-formed antibodies (ABO)? How formed
- **Kidney example:** cyanotic, mottled
- **Necrotizing vasculitis, thrombosis, ischemic necrosis of graft**
- **Crossmatch:** Donor cells w/ recipient serum

- **Acute:** Days, weeks, maybe years if immunosuppression decreased
- **Cellular:** Lymphocytic infiltration (CD4, CD8)
- **Tubulitis**
- **Endothelialitis**
- **Responds to immunosuppression**
CAN MIMIC CYCLOSPORINE TOXICITY
VASCULAR: ACUTE AND SUBACUTE VASCULAR INJURY
INTIMAL PROLIFERATION, LUMEN COMPROMISE, ISCHEMIA

Chronic
CORRELATES WITH PRIOR EPISODES OF ACUTE REJECTION, CUMULATIVE EFFECT
VESSELS: INTIMAL FIBROSIS
GRAFT: INTERSTITIAL FIBROSIS AND ATROPHY

Methods of Improving Graft Survival

Compatibilitiy:

ABO: CROSSMATCH, ESSENTIAL

HLA antigens
HLA ANTIGEN TESTING OF DONOR WHEN POSSIBLE USING SEROLOGIC AND DNA/MOLECULAR BASED ASSAYS
IDENTIFYING ANTIBODIES IN RECIPIENT: FLOW CYTOMETRY “CROSSMATCH”
FOR BONE MARROW: EXACT MATCH IS IMPORTANT TO AVOID GVHD

Immunosuppressive Therapy:

1) CORTICOSTEROIDS

2) CYCLOSPORIN (FUNGAL PRODUCT)
BLOCKS IL2 PROD. BY INHIB CALCINEURIN PATHWAY
3) AZATHIAPRINE, MYCOPHENOLATE MOFENETEIL
INTERFERE WITH DNA SYNTHESIS

4) TACROLIMUS (FK506)
SIMILAR TO CYCLOSPORINE

5) ANTI-CD3 (OKT3), ANTI IL2 RECEPTOR (DACLIZUMAB)

6) OTHER AS ILLUSTRATED

DATA:
1955- FIRST RENAL TXP 0% SUCCESS
1962- AZATHIAPRINE, PREDNISONE: 45-50% 1 YEAR SUCCESS
70S: LRD, NEW DRUGS
IMPROVED SUCCESS, LYMPHOCYTE-SPECIFIC, WEAK POTENCY AGAINST
MEMORY CELLS, MINIMAL SIDE EFFECTS

Other factors to consider:
ORGAN AVAILABILITY
SIZE CONSTRAINTS
RECURRENT DISEASE
Bone Marrow Transplantation (Hematopoietic Stem Cells)
SOURCE: PERIPHERAL BLOOD, UMBILICAL CORD BLOOD

PROBLEM:
Graft versus Host Disease

Pathogenesis
CD8, CD4 CELLS FROM GRAFT REACT AGAINST DONOR ANTIGENS
GREATER THE MISMATCH, GREATER THE CHANCE OF GVHD

Acute GVHD
DAYS-WEEKS
SKIN, LIVER, GI SYSTEM

Chronic GVHD
VARIABLE, YEARS
SCLERODERMA-TYPE SKIN CHANGE, CHRONIC MUCOSAL CHANGES GI TRACT
LYMPHOID ATROPHY

Treatment
IMMUNOSUPPRESSION
? ELIMINATE CELLS FROM GRAFT (INCREASED RELAPSE RATE OF LEUKEMIA)

NOTE: GVHD CAN ALSO OCCUR IN SOLID ORGANS WITH LOTS OF LYMPHS (LIVER) AND WITH NON-IRRADIATED BLOOD TRANSFUSION

Other Complications of Transplantation

Opportunistic infections
CMV, FUNGI, BACTERIA

Post Transplant Lymphoproliferative Disorders (PTLD)
EBV-DRIVEN
RELATED TO IMMUNOSUPPRESSION
RX: DECREASED IMMUNOSUPPRESSION RX, +/- CHEMO
Laboratory Assessment of Immune Status

Testing of Humoral Immunity:
1)

2)

Testing of Lymphocyte Number and Function:
1)

2)

3)

In Vivo Testing of Immune Function

Testing of Innate Immunity

Neutrophils:
Number and Function

NBT test:

Complement:
Total

Components
Immunodeficiency: Congenital and Acquired

Acquired versus Congenital Immunodeficiencies
1)

2)
**Congenital Immunodeficiencies**

Clinical Manifestations of Congenital Immunodeficiencies

Infections
T cell defects:

B cell defects:

Granulocytes:

Complement:

Time frame:

Other manifestations:
1)
2)
Selected Congenital Immunodeficiencies:

*Disease with abnormal Immunoglobulin Production*

**X-linked (Bruton's) Agammaglobulinemia**

Incidence:

Clinical features:
1) 
2) 
3) 

Molecular defect:

Other manifestations:

Treatment:

**Common Variable Immunodeficiency (CVID)**

Incidence:

Clinical features:
1) 
2) 

Molecular defect:

Other manifestations:

**Isolated IgA Deficiency**

Incidence:

Clinical features:
1) 
2)
Molecular defect

Other manifestations

**Hyper-IgM Syndrome**

Incidence:

Clinical features:
1) 
2) 

Molecular defect:

Other manifestations:

**Diseases with predominantly T cell abnormalities**

**Severe Combined Immunodeficiency (SCID)**

Incidence:

Clinical features:
1) 
2) 
3) 

Inheritance

Molecular defects:
1) 
2) 
3) 

Treatment (retroviral gene transfer, BM transplantation)
**Other Congenital Syndromes:**

**DiGeorge Syndrome (22q11 deletion syndrome)**
- C
- A
- T
- C
- H
- 22

**Wiskott-Aldrich Syndrome:**
Triad:
1) 
2) 
3) 

Inheritance
Molecular defect

Other manifestations:

**Deficiencies of Innate Immunity**

**Complement deficiencies**
1) 
2) 
3) 

**Neutrophil Deficiency**

Chronic Granulomatous Disease (CGD)
Acquired Immunodeficiency: Pathology and Pathogenesis of HIV Infection

Epidemiology

*Worldwide distribution of HIV Infection*

*Risk Groups:*

Men who have Sex with Men (MSM)

Intravenous Drug Users

Heterosexual contacts of high risk groups

Blood and Blood-product recipients

Hemophiliacs

Children born to HIV infected women (vertical transmission)

*Mode of Transmission*

Sexual

Parenteral

Mother-to-Infant

*Virology*

HIV 1 and HIV 2

Viral structure
Pathogenesis of Infection

T Cell Destruction
Immunologic Consequences of T Cell Loss

Macrophages and Dendritic Cells and HIV

CNS Involvement by HIV

Clinical and Immunologic features of Natural History of HIV Infection
Clinicopathologic Features of AIDS

"Acute HIV" Illness

HIV associated Lymphadenopathy

HIV and Lymphomas

Kaposi’s Sarcoma

Cervical and Anal HPV-mediated Neoplasia

Central Nervous system

1)
2)
3)
4)

Infections

Bacterial/Mycobacterial

Community acquired bacterial infection

Mycobacterium tuberculosis and Atypical mycobacteria
**Fungal and Protozoal**

- Candida albicans
- Pneumocystis jeroveci
- Histoplasma capsulatum
- Cryptococcus neoformans
- Cryptosporidium
- Toxoplasma gondii

**Viral**

- Cytomegalovirus
- Herpes simplex
- Epstein Barr Virus
- JC Virus

**Laboratory Testing in HIV Infection**

**Diagnosis:**

- Enzyme Linked Immunosorbant Assay (ELISA)
- Western Blot (confirmatory)
- P24 antigen testing
- PCR for HIV RNA/DNA

**Monitoring Disease Progression and Prognosis:**

- HIV mRNA by PCR
- CD4 lymphocyte Quantitation

**Tailoring Drug Therapy/Detecting Resistance:**

- HIV genotyping
Amyloidosis

**Definition:**

Characteristics of Amyloid

**Pathogenesis:**

A disorder of abnormal protein Folding.

*AL amyloid*

*AA amyloid*

*Aβ amyloid*

*Transthyretin*

*β2 microglobulin*

*Endocrine sources*
Pathology of Amyloidosis:

Clinical Presentation and Diagnosis

Treatment and Prognosis
Immunopathology Study Questions

Transplantation:
1. What is the difference between direct and indirect allograft recognition?
2. In acute rejection of the kidney, what pathologic change typifies cellular rejection? Antibody-mediated rejection?
3. What antigen system(s) are most important in graft rejection?
4. How does HLA mismatch affect the probability of Graft vs Host disease (GVHD)?
5. What major organ systems are affected by GVHD?
6. Post transplant lymphoproliferative disorder is associated with what viral pathogen?

Autoimmunity
1. What are the major clinical signs and symptoms of systemic lupus (SLE)?
2. What is a wire loop lesion?
3. What is the significance of a positive ANA in an asymptomatic individual?
4. What specific autoantibodies are helpful in the diagnosis of SLE?
5. How do discoid and drug-associated lupus differ from SLE?
6. Based on current knowledge, what main mechanisms are involved in immunologic tolerance?
7. Lupus is latin for __________? 
8. What is the antiphospholipid antibody syndrome? What is the relationship of APS to lupus?
9. Give an example of each of 3 different types of hypersensitivity reactions occurring in SLE.
10. Fibrous tissue deposition occurs most commonly in which organs in progressive systemic sclerosis (scleroderma, PSS)?
11. What is the pathogenesis of PSS?
12. What specific autoantibody(ies) is/are helpful in diagnosis of PSS? CREST?
13. What does CREST stand for?
14. True or False. Some patients can have spontaneous softening of their dermal sclerosis after years of disease.
15. What severe complication can be seen in PSS associated renal disease?
16. What is Raynaud’s phenomenon?
17. What is sicca syndrome?
18. Sjogren’s syndrome is most commonly associated with what other autoimmune disease?
19. What specific autoantibody(ies) is/are helpful in the diagnosis of Sjogren syndrome?
20. Anti-Jo and Anti-La are associated with what autoimmune disease (es)
21. How do dermatomyositis and polymyositis differ in terms of the target of the inflammatory process?
22. Patients with mixed connective tissue disease commonly have what autoantibody?
23. What is the genetic basis for Bruton’s agammaglobulinemia?
24. What infections are commonly associated with B cell deficiencies? T cell deficiencies?
25. Adenosine deaminase deficiency and Jak 3 mutations are associated with what congenital immunodeficiency?
26. What immunodeficiency is associated with anaphylactic reaction to transfusion of plasma-containing products?
27. The triad of eczema, thrombocytopenia, and recurrent infections is seen in what congenital immunodeficiency?
28. Which inherited immunodeficiency syndrome is associated with hypocalcemia?
29. What risk group has shown the greatest increase in proportion of new HIV infection over the last decade in the US?
30. What are major determinants of sexual transmission of HIV?
31. What are major determinants of perinatal transmission of HIV?
32. What is the significance of the LTR (long terminal repeat) region of the HIV genome?
33. How do CD 4 cells and macrophages bind HIV? How do they differ in terms of their interaction with the virus?
34. How is B cell function affected by HIV disease?
35. HIV is an a. RNA b. DNA virus?
36. How do CD4 count and Viral RNA quantitation (viral load) differ in terms of their clinical significance?
37. What are the “co-receptors” involved in HIV binding and entry?
38. Where does HIV virus reside during the clinical “latent” period?
39. How does HIV gain access to the central nervous system?
40. List several important mechanisms for T cell destruction in the course of HIV infection
41. How do the ELISA and Western Blot assays differ in terms of their role in diagnosis of HIV infection? What are causes of false positive ELISAs?
42. What is the pathogenesis of kaposi’s sarcoma?
43. What happens to the lymphoid tissues during the course of HIV/AIDS?
44. What malignancies are seen in higher frequencies in patients with HIV infection?
45. What is PML?
46. What are the most common clinical manifestations of the following opportunistic pathogens in the setting of HIV infection?
   a. Cryptococcus neoformans
   b. Pneumocystis carinii
   c. M. tuberculosis and M. avium complex
   d. Histoplasma capsulatum
   e. Toxoplasmosis
   f. JC virus
47. What type of amyloid protein is associated with each of the following?
   a. Plasma cell dyscrasia
   b. Systemic infection/inflammatory disorder
   c. Alzheimer’s disease
   d. Medullary thyroid carcinoma
48. What special stain is used to identify amyloid on tissue biopsies?
49. What tissues are most commonly affected in systemic amyloidosis?