1. Innate immunity and non-specific antimicrobial mechanisms

a. Antimicrobial factors on skin and mucous membranes and in the blood and tissues
   (1) Mechanical antimicrobial factors (mechanical barrier of skin and mucous membranes, ciliated epithelium, normal flora, mucous secretions)
   (2) Chemical antimicrobial factors (lysozyme, muramidase, spermine, mucin, peroxides, acids, complement, cytokines)
   (3) Microbial antagonism (adherence, metabolic endproducts)

b. Phagocytic cells and the process of phagocytosis
   (1) Polymorphonuclear leukocytes, monocytes and macrophages (blood and tissue types; role of macrophage as antigen presenting cell and mediator of inflammation)
   (2) Phagocyte cell surface receptors and markers: complement, Fc, Class II
   (3) Receptor-mediated chemotaxis (chemotactic agents: C5a, LTB₄, f-met peptides, chemokines [IL-8, MIP, MCP])
   (4) Adherence to endothelium (margination and emigration: ICAMs and selectins on endothelium, integrins and selectins on phagocytes)
   (5) Particle attachment, phagocytosis, formation of phagolysosomes and role of degranulation in tissue damage
   (6) Metabolic burst and mechanisms of bacterial killing and digestion
      (a) Oxygen-dependent antibacterial factors: Superoxide generated by NADPH oxidase; Hydrogen peroxide generated by superoxide dismutase; hypochlorite and hypoiodite generated by myeloperoxidase
      (b) Oxygen-independent antimicrobial proteins: acid hydrolases, muramidase, lysozyme, lactoferrin, defensins, cathelicidins, and BPI.

c. Inflammation
   (1) Definition and overall results: (acute versus chronic) cell activation, cell migration, increased vascular permeability, pain, tissue damage, tissue repair
   (2) Cells involved: endothelial, PMN, mast, basophils, platelets
   (3) Inflammatory mediators, their origin and actions
      Cytokines: IL-1, IL-6, IL-8, TNFα, IFNγ
      Vasoactive molecules: histamine (H1,2, & 3 receptors), PAF, PGE₂, LTD₄,
      LTB₄, serotonin, nitric oxide
      Plasma enzyme systems: clotting, fibrinolytic (fibrinopeptides), kinin (bradykinin), and complement (C3a, C5a)
   (4) Clinical evaluation: fever, leukocytosis (band forms)

d. Complement
   (1) Components, sources, and activators
   (2) Classic pathway, lectin pathway (MBP), and alternative pathway (C3 tick-over): activation, components, and biologically active end products
   (3) Membrane attack complex
   (4) Complement receptors (opsonization, cell activation)
   (5) Regulation of complement activation (DAF, Factor I, H, & P, MCP, C1 INH, CR1, CD59)
   (6) Complement fixation assay: technique and clinical uses (e.g. measure antibody titers in viral and fungal infections)
2. **Antigens**
   a. Types of antigens (T-dependent, T-independent, antigen processing and presentation via Class I or Class II MHC molecules)
   b. Antigenic determinants (epitopes) recognized by B and T cells: immunodominance; conformational versus sequence recognition
   c. Haptens and carriers (application to vaccinology)

3. **Antibodies**
   a. Immunoglobulin structure and basis for classification: heavy chains (γ,μ, ε, α, δ), light chains (κ, λ), variable, hypervariable, and constant regions, loop domains, hinge region, J-chains, disulfide bridges, enzyme fragmentation (Fab, Fc, F(ab')₂), effector regions (antigen binding site, Fc receptor site, complement binding site); definition of allotypes and idiotypes.
   b. Functions (neutralization, opsonization, complement activation, anti-tumor activity), harmful activity (allergies and autoimmune diseases) and the receptors for the various isotypes and the cells where they occur, distributions, approximate concentrations and half-lives of the different immunoglobulin isotypes: IgG (IgG₁,₂,₃,₄), IgM, IgA (IgA₁,₂), sIgA, IgE, IgD
   c. Hybridoma technology and the generation and clinical uses of monoclonal antibodies

4. **Antigen-antibody interactions**
   a. Definitions of specificity, cross-reactivity, affinity, and avidity
   b. Forces binding antigens and antibodies: specificity for three-dimensional conformation of the epitope and the formation of multiple non-covalent bonds
   c. Antibody interactions with soluble antigen (the precipitin reaction): lattice formation, antigen excess, zone of equivalence, antibody excess, and soluble immune complexes
   d. Classic immunologic methods to detect soluble antigen-antibody reactions (principles, methods and uses)
      (1) Precipitation in solution: tube precipitin reaction (titer)
      (2) Precipitation in solid medium (principles, methods and uses): Ouchterlony double diffusion, radial immunodiffusion, rocket immunoelectrophoresis, immunoelectrophoresis, 2-D immunoelectrophoresis (methods and uses)
   e. Classic immunologic methods to detect insoluble antigen-antibody reactions (principles, methods and uses):
      Tube (microtiter plate) agglutination (passive and active), hemagglutination, hemagglutination inhibition, Coombs test
   f. Modern immunologic techniques (principles, methods and uses):
      Immunoblotting (Western blotting), Radioimmunoassay, Enzyme-linked immunosorbent assay, Immunofluorescence (direct and indirect), fluorescence activated flow cytometry

5. **Cells involved with the immune response, hematopoiesis, and lymphatic organs**
   a. Cells (description, function, important mediators they release, half-lives, relative concentrations in blood)
      Non-antigen specific: neutrophil, basophil, eosinophil, mast cell, macrophage, NK (LGL)
Antigen-specific: T lymphocytes (T<sub>C</sub>, T<sub>H1</sub>, T<sub>H2</sub>, T<sub>H3</sub>), B lymphocytes

Antigen presenting cells (function, location, and important cell surface markers): macrophages (Kupffer, intraglomerular, alveolar, serosal, brain [microglia], spleen sinus, lymph node sinus; central role of macrophages in immunity and inflammation [cytokines secreted, vasoactive molecules, tissue damage and healing], B-cells, follicular dendritic cells, interdigitating cells, Langerhans cells

b. Hematopoiesis
Stem cells and cytokines (Stem cell factor, IL-1,3,6,7, GM-CSF, G-CSF, M-CSF)
Use of stem cells and cytokines to reconstitute or augment the immune system (e.g. recombinant GM-CSF for neutropenia)

c. Primary (central) and secondary (peripheral) lymphatic tissue (functions and histologic organization as it pertains to immune function)
Primary: bone marrow and fetal liver (B cells)
       thymus (T cells)
Secondary: spleen, lymph nodes, mucosa-associated lymphoid tissue (MALT)
       MALT: tonsils, adenoids, bronchial, gastrointestinal (including the appendix), and genitourinary tract lymphoid tissues, Peyer’s patches (function of M cells)

d. Lymphocyte (lymph) traffic: high endothelial venules, efferent lymphatic vessels, thoracic duct, blood lymphocyte pool, and afferent lymphatic vessels

6. Cytokines and chemokines (major sources, principal targets, major activities)
(1) IL-1 (α and β): from phagocytes, lymphocytes, endothelial cells, and many other cells; major targets are lymphocytes, macrophages, endothelium, tissue cells; activates cells, increases adhesion molecule expression, induces fever, induces release of acute phase proteins, associated with sepsis syndrome (shock).
(2) IL-2: source and target are T cells; induces T cell proliferation, activates T<sub>C</sub> cells, stimulates B cells.
(3) IL-3: from T cells; targets hematopoietic stem cells; induces growth and differentiation.
(4) IL-4: from T<sub>H2</sub> cells, mast cells, macrophages; targets T and B cells, eosinophils, mast cells; induces T<sub>H2</sub> conversion from T<sub>H0</sub>, B cell growth, IgE and IgG1 isotype selection, eosinophil and mast cell activation.
(5) IL-5: from T<sub>H2</sub> cells, mast cells; targets B cells and eosinophils; induces B cell growth and differentiation, IgA isotype selection, eosinophil activation.
(6) IL-6: from T cells (T<sub>H2</sub>), B cells, macrophages, fibroblasts, endothelial cells; targets B cells, hepatocytes; induces B cell differentiation, production of acute phase proteins, fever.
(7) IL-7: from bone marrow stromal cells; targets B and T precursors; induces proliferation.
(8) IL-8: from macrophages, endothelial cells, fibroblasts; targets neutrophils, basophils, T cells; chemotactic and angiogenic.
(9) IL-10: from activated T cells, macrophages; targets T<sub>H1</sub> cells; inhibits cytokine synthesis, promotes B cell proliferation, suppresses cell mediated immunity (CMI).
(10) IL-12: from B cells, macrophages; targets T cells, NK cells; induces T<sub>H1</sub> cell conversion from T<sub>H0</sub>, suppresses T<sub>H2</sub> activities, activates T<sub>C</sub> and NK cells, promotes CMI.
(11) IL-13: from T<sub>H2</sub> cells; targets macrophages, B cells; induces B cell growth and differentiation, inhibits production of pro-inflammatory cytokines.
(12) IL-15: from macrophages, T cells; targets T cells, activated B cells; actions similar to IL-2.
(13) IL-18: (formerly known as IFNγ-inducing factor) from phagocytes; target T cells; induces production of IFNγ, IL2, and GM-CSF.
(14) TNFα: from phagocytes, mast cells, lymphocytes, endothelial cells; targets and effects similar to IL-1 plus induces MHC class I protein expression, tumor necrosis, and stimulates angiogenesis.
(15) TNFβ (lymphotoxin): from lymphocytes; targets and effects similar to TNFα except not associated with inducing shock.
(16) IFNα: from lymphocytes, macrophages, epithelial cells; targets tissue cells (e.g. epithelial cells; induces antiviral state, MHC class I expression, stimulates NK cells, production of IL-12, and T_{h1} cells.
(17) IFNβ: from fibroblasts, epithelial cells; targets tissue cells, leukocytes; induces anti-viral state, MHC class I expression.
(18) IFNγ: from T cells, NK cells; targets leukocytes, tissue cells, T_{h2} cells; induces expression of MHC class I and II, activates phagocytes, inhibits T_{h2} cells, enhances leukocyte-endothelial adherence.
(19) M-CSF: from macrophages, fibroblasts, endothelial cells; targets monocytes and monocyte precursors; induces proliferation of monocyte precursors.
(20) G-CSF: from macrophages, fibroblasts, endothelial cells; target granulocyte precursors; induces proliferation of precursors to mature granulocytes.
(21) GM-CSF: from T cells, macrophages, fibroblasts, endothelial cells; targets granulocyte precursors and a number of other cells; promotes the differentiation of precursors, stimulates neutrophils, eosinophils, and macrophages.
(22) MCP-1: from macrophages, fibroblasts, epithelial and endothelial cells; targets monocytes, basophils, mast cells; chemotactic agent for monocytes, induces histamine release by mast cells and basophils.
(23) TGFα: from macrophages and other cells; targets fibroblasts, epithelial and endothelial cells; stimulates fibroblast growth and angiogenesis.
(24) TGFβ: from activated T cells (T_{h1}), monocytes, and other cells; targets T cells; inhibits cytokine production, inhibits proliferation, stimulates IgA production

7. **B lymphocytes**
   a. Origin (bone marrow and fetal liver) and events associated with maturation (cytokines: IL-3, 4, 7)
      Maturation:
      (1) pre-B cell (expresses cytoplasmic μ chains; surface class II MHC)
      (2) V,D, and J gene rearrangement: generation of diverse antigen receptors (recombination of H and L chains hypervariable regions; junctional diversity; isotype switching (e.g. μ to δ))
      (3) immature B cell (expresses surface IgM, class II MHC)
      (4) positive/negative selection, apoptosis of self-reactive cells
      (5) mature B cell (expresses surface polymorphic IgM and IgD, class II MHC, CD19-23, CR1 and 2, Fc receptor)
      (6) collection of B cells in secondary lymphatic tissues
   b. B cell antigen receptor (structure, accessory proteins and signal transduction)
   c. Antigen-induced B cell activation and differentiation
      Clonal selection, isotype switching (somatic mutation and maturation of immune
response), V-region hypermutation, differentiation into plasma cells (Ig secretion) and memory cells (surface IgG, IgA, or IgE); cytokine influence on isotype.

8. T lymphocytes
   a. Origin (bone marrow) and events associated with maturation in the thymus (cytokines: IL-1, 2, 3, 6, 7, GM-CSF; thymic hormones)
      (1) Stem cells (multipotent) collect in thymus and move from cortex to medulla while interacting with MHC Class II-bearing nurse, epithelial and interdigitating cells.
      (2) Maturation progression: Early thymocyte (CD4+8, T cell receptor (TCR) gene rearrangements)
      Common thymocyte (CD4+4+8, T cell receptor gene rearrangements; low TCR and CD3 surface expression)
      Mature thymocyte (CD4 or CD8 subsets; high TCR and CD3 surface expression; somatic recombination of TCR genes)
      Positive and negative selection occurs and most self-reactive T cells eliminated.
      All T cells positive for TCR and CD3
   b. T cell antigen receptor (genetics, structure, accessory proteins and signal transduction)
      (1) Antigen-specific TCR dimers: αβ (90-95% of all T cells) or γδ
      V, D, J, C (constant) genes for β and δ chains; V, J, and C genes for α and γ chains.
      (2) CD3 complex (εζγδ) associated with TCR has signal transduction role.
      (3) Activation of T cells by mitogens and superantigens
   c. Functional subsets of CD4 cells based on cytokine profile (note all Ag-activated T cells produce IL-2).
      \( T_{Ho} = \) Low levels of IL-2, 4, 5, 6, 10, 13, TNFβ, IFNγ
      \( T_{H1} = \) TNFβ, IFNγ (Type 1 cytokines promote cell mediated immunity)
      \( T_{H2} = \) IL-4, 5, 6, 10, 13 (Type 2 cytokines promote humoral immunity)
      \( T_{H3} = \) IL-5, TGFβ (down-regulation)
      \( T_{HC} = \) CD4 cells that demonstrate Fas-induced cytotoxicity
      Subset control: \( T_{Ho} > T_{H1} \) promoted by IL-12 and IFNγ (example: IFNα produced during viral infection stimulates macrophages to produce IL-12); IL-4 & 10 inhibit.
      \( T_{Ho} > T_{H2} \) promoted by IL-4; IFNγ inhibits
   d. Functional subsets of CD8 cells (Cytotoxic T cells [T_C])
      (1) Pre-T_C > cytolytic T_C promoted by IL-2 & IFNγ (IL-6 & 12 also have role)
      Active T_C lyse targets with TNFβ, degranulation (perforin, granzymes), and/or Fas-induced apoptosis.
      (2) “Regulatory” T_C: T_{C1} and T_{C2} subsets have cytokine profiles like T_{H1} (Type 1 cytokines) and T_{H2} (Type 2 cytokines), respectively.
   e. “Suppressor” T cells: both CD4+ and CD8+ cells can have suppressor activity based on their cytokine profile.

9. NK cells
   a. Distribution: 10-15% of circulating lymphocytes; lack typical T cell markers (i.e. TCR, CD3).
b. Markers: CD16 (IgG Fc receptor), CD56 (both used to identify NK cells), and CD28

c. Activation and cytokines secreted: secrete IFNγ, IL-1, GM-CSF, TNFα; activated by IFNγ, IL-2, IL-12 and IL-18

d. Cytotoxic mechanisms: Attack cells with reduced MHC class I expression.
   Release perforin.
   CD-28/B7-1 co-stimulating signal important
   Can also kill by antibody dependent cell mediated cytotoxicity (ADCC)

e. Lymphokine (cytokine) activate killer (LAK) cells and large granular lymphocytes:
   Activated NK cells

10. Major Histocompatibility Complex (MHC; Human Leukocyte antigens [HLA])

   a. Class I, II and III MHC genetic loci (short arm of chromosome 6)

      Major Class I genes: 
      Minor Class I-like genes: 
      Major Class II genes: 
      Class III genes: complement components

   b. Inheritance
      Definition of haplotype, example of inheritance pattern, pseudogenes, and cell surface expression (what cells express Class I, Class II). Define polymorphic nature of the MHC proteins and allotypes and gene polymorphism.

   c. Structure of Class I MHC proteins
      (1) α1, α2, and α3 domains of heavy chain (α1 & α2 form peptide binding site [groove]; amino acid differences account for polymorphism and antigen specificity)
      (2) β2 - Microglobulin (invariant but essential)

   d. Structure of Class II MHC proteins
      (1) Composed of α and β proteins (α1, α2, β1, β2)
      (2) α1 and β1 domains comprise the peptide binding site (groove). Again, amino acid differences account for polymorphism and antigen specificity. α2 and β2 domains constant.

   e. Role of MHC proteins in antigen processing and presentation; general aspects of HLA-restriction.
      (1) Processing and presentation of exogenous antigen via the MHC class II pathway (exogenous pathway): Professional antigen processing cell internalizes antigen. Antigen internalized into endosome & degraded into peptide fragments.
          MHC class II proteins synthesized in ER and peptide binding site protected by Ii (invariant chaperone; CLIP region of Ii mediates protection of site).
          Exocytic vesicle (from golgi) containing MHC II proteins fuses with endosome containing peptides.
          Ii degraded, CLIP removed by HLA-DM protein.
          MHC II bind peptides, vesicle fuses with plasma membrane, MHC II/peptides expressed on cell surface, and presented to CD4 cells.
          Interactions between CD4 and MHC II-expressing antigen presenting cells:
                  (T cell left, APC right)
                  LFA-1 —> ICAM-1 (adhesion)
CD2 → LFA-3 (adhesion)
CD4 (Lck) → MHC II (co-activation with TCR)
TCR/CD3 → MHC II / peptide (activation of T cell through PIP$_2$/DAG, IP$_3$ pathway)
CD28 → B7-1/B7-2 (co-activation with TCR)
T cell CD45 (tyr phosphatase)
End result: activation of transcription factors.

(2) Processing and presentation of endogenous antigen via the MHC class I pathway (endogenous pathway): Cytoplasmic protein (e.g. viral) ubiquitinated, hydrolyzed to peptide fragments in the proteasome, and peptides transported into the ER via TAP. MHC I proteins synthesized and assembled in ER and association with TAP mediated by calnexin chaperone.

MHC I bind peptides, vesicle fuses with plasma membrane, MHC I/peptides expressed on cell surface, and presented to CD8 cells.
Interactions between CD8 and MHC I-expressing antigen presenting cells:
(T cell left, APC right)
LFA-1 → ICAM-1 (adhesion)
CD2 → LFA-3 (adhesion)
CD8 (Lck) → MHC I (co-activation with TCR)
TCR/CD3 → MHC I / peptide (activation of T cell through PIP$_2$/DAG, IP$_3$ pathway)
CD28 → B7-1/B7-2 (co-activation with TCR)
T cell CD45 (tyr phosphatase; RO and RA isoforms)

f. Clinical importance of HLA antigens
(1) Transplantation and organ rejection
HLA typing: Microcytotoxicity (lymphocytotoxicity) test (describe method and use).
Mixed leukocyte reaction (describe method and use)
Use of flow cytometry for HLA typing.
RFLP analysis of class II genes.
PCR/sequence-specific oligonucleotide probes for HLA typing.

(2) Diseases associated with specific HLA antigens (see specific disease also):
DR3/DR2> Systemic Lupus Erythematosus
DR4> Rheumatoid Arthritis
B7 and DR2> Multiple Sclerosis
B8, DR3,4> Type I diabetes
B27> Ankylosing Spondylitis

11. Antibody-mediated immune (humoral) response
a. B cell differentiation into IgM-secreting plasma cells induced by T-independent antigen.
Types of T-independent antigens.
Signal transduction mediated by B cell antigen receptor and accessory molecules.
b. Primary and secondary responses to T-dependent antigen (kinetics of antibody production).
c. Effects of T$_{H2}$ cytokines on B cell differentiation, isotype switching, and memory cells:
Signals that generate a T$_{H2}$ response: IL-10 from macrophages (and other sources) and IL-4 from ag-activated T cells and other sources
IL-2,4,5 → promote differentiation and development of IgM-producing plasma cells
IL-2,4,6 → promote IgG-producing cells (plasma and memory)
IL-5 → promotes IgA-producing cells (plasma and memory; role in mucosal immunity)
IL-4 —> promotes IgE-producing cells (plasma and memory; role in hypersensitivereactions)

d. Cell surface molecules involved in T/B cell interactions
   (B cell left/T cell right)
   MHC II/Ag —> TCR/CD3 (signals generated for both cells)
   CD40 —> CD40L(CD154) (potent B & T cell signal; important for memory)
   CD80/86(B7-1/2) —> CD28 (potent T cell signal)
   associated adhesion molecules

e. Hypermutation and Ig affinity maturation
   Effects of route and antigen dose on response.
   Selective expansion of high-affinity clones.
   Role of anatomical site on response.

f. T cell memory

12. Cell mediated immune (CMI) responses
a. Function: Control intracellular pathogens, tumors
   Transplant rejection
   Role in tissue regeneration
   Type IV hypersensitivity
   Granulomas
   Chronic inflammation

b. Predominant cells and mediators (see above sections for details on activation and cell-surface interactions)
   (1) T<sub>H1</sub> lymphocytes (activated by Ag, IL-12, TGFβ, and IFNγ)
       release IL-2 and IFNγ: induce T cell proliferation, T<sub>C</sub>, NK, and macrophage
       activation
   (2) CD8<sup>+</sup> T<sub>C1</sub> and T<sub>C2</sub> (activated by Ag/MHC I [endogenous pathway] and T<sub>H1</sub>
       cytokines); have cytokine profile similar to T<sub>H1</sub> and T<sub>H2</sub>, respectively; both are cytotoxic
       via TNFβ, perforin, granzymes, and Fas-induced apoptosis
   (3) CD4<sup>+</sup> T<sub>HC</sub> (probably only use Fas-induced apoptosis to lyse targets)
   (4) NK cells (see above for activation, etc.)
       release IFNγ which activates macrophages and stimulates T<sub>H1</sub> activity
       also release GM-CSF that stimulates PMNs
       lyse targets predominantly via granule components (e.g. perforin)
   (5) Monocytes/Macrophages [mononuclear phagocytes] (activated by IFNγ and
       usually a second signal from an Ag [e.g. LPS] or another cytokine [e.g. GM-CS,
       TNFα])

   Tissue types: Kupffer, alveolar, etc.
   Surface markers: C3b receptor(CD35 or CR-1), LFA-1, Fc receptor
   (CD64), MHC II

   Macrophages play a central role in CMI and inflammation:
   important antigen presenting cell
   important in killing bacteria and lysing tumor cells
   effector/mediator of delayed type hypersensitivity (DTH, see Type
   IV hypersensitivity)
   release IL-12>induces T<sub>H1</sub> response (IFNα induces)
   release IL-10>induces T<sub>H2</sub> response by down-regulating cytokine
   production
   release IL-1, 6, TNFα and β, and IFNα and β
   release enzymes, coagulation factors, complement components,
   superoxide (etc.), leukotrienes, and prostaglandins
c. Role of endothelium
   Differential expression of adhesion molecules and their role in CMI.
   (ICAM-1/VCAM, P- and E-selectin)
d. Detection of cell-mediated immunity
   Cytolytic assays (Cr release assay)

13. **Regulation and termination of immune responses**
   a. Regulation by the nature of the antigen (e.g., polysaccharides > IgM)
   b. Regulation by individual history (and genetic background), antigen dose and route of 
drug administration
   c. Regulation by antigen-presenting cell (presence of co-stimulatory signals)
   d. Modulation by antibody (immune complexes, receptor cross-linking)
      (1) anti-idiotype antibodies
   e. Regulation by T cells (regulatory T cells and other cells)
      (1) \( T_h \) and \( T_c \) subsets and cytokine control
      (2) soluble forms of TCRs and cytokine receptors
   f. Neuroendocrine controls
      (1) hormonal controls
   g. Tolerance (effects of age and antigen dose)
      (1) Central tolerance (positive and negative selection)
      (2) Peripheral tolerance (clonal deletion, apoptosis and anergy)

14. **Cutaneous and Mucosal Immune systems**
   a. Cutaneous (cells, DTH)
   b. Mucosal (cells, tissue, IgA)

15. **Immunomodulation**
   a. Vaccines
      (1) active immunization (principles, complications, and examples; childhood
          immunizations; antigens [live, dead, toxoids]; adjuvants)
      (2) passive immunization (principles, complications, and examples)
      (3) DNA vaccines and recombinant vaccines
   b. Immunosuppressive drugs (mechanisms of action and examples of their uses)
      (1) Cycle nonspecific (radiation, corticosteroids, nonsteroidal anti-inflammatory
          agents, cyclosporin)
      (2) Cycle specific (cyclophosphamide, chlorambucil, azathioprine, methotrexate)
   c. Pathologically induced immunosuppression (immune deficiency diseases, disease-
      induced anergy)

16. **Type I (Immediate) Hypersensitivity**
   a. Genetics (atopy, allergen-specific, IgE levels)
   b. Cells and allergens (\( F_{Ce} \) receptors, mast cells, basophils, eosinophils, APC, \( T_{H2} \), pollen, etc.)
   c. Cytokine control by \( T_{H2} \) cells (IL-4, 13)
   d. Measurement of IgE (RIST and RAST)
   e. Mechanism of IgE-mediated mast cell activation and degranulation
      (1) receptor cross-linking
      (2) kinase cascade
      (3) calcium mobilization, activation of arachidonic acid pathway, and myosin
          phosphorylation
   f. IgE-independent effects on degranulation (C3a, C5a; role of autonomic nervous
      system; effects of epinephrine, acetylcholine, theophylline)
g. Primary mediators: histamine (effects on H1 and H2 receptors), eosinophil and neutrophil chemotactic factors, TNFα, IL-6, heparin

h. Secondary mediators: leukotrienes (LTB₄, LTD₄, LTE₄, LTC₄), prostaglandins (PGD₂), PAF, IL-1, 3, 4, 5, 6, TNFα, GM-CSF

i. Clinical manifestations (incidence, symptoms, pathologic findings, examples of therapy and role of hypo- or desensitization; diagnostic techniques used [e.g. skin test])
   (1) Generalized anaphylaxis (bee sting, drug allergy)
   (2) Cutaneous reactions: urticaria, angioedema
   (3) Atopic (immediate and late responses): allergic rhinitis, asthma (extrinsic, intrinsic), atopic dermatitis, food allergy

17. Type II Hypersensitivity (IgG or IgM-mediated cytotoxicity)
   a. Mechanisms and results of Ig-mediated cytotoxicity
      (1) activation of complement
      (2) ADCC
      (3) major effector cells (macrophages, NK cells, neutrophils)
   b. Examples and clinical manifestations (incidence, symptoms, mechanisms of tissue destruction, pathologic findings, and examples of therapy [e.g. supportive, steroids, plasmapheresis])
      (1) Hemolytic anemias
         (a) lab findings indicative of hemolysis (elevated LDH, elevated hemoglobin, elevated bilirubin, hypocomplementemia)
         (b) warm and cold (autoimmune, drug-induced, secondary), including erythroblastosis fetalis (Coomb’s test)
      (2) Thrombocytopenias (autoimmune, drug-induced, secondary)
      (3) Nephrotic serum nephritis and Goodpasture’s syndrome
      (4) Pemphigus vulgaris
      (5) Myasthenia gravis
      (6) Pernicious anemia
      (7) Acute rheumatic fever

18. Type III (Immune complex) Hypersensitivity
   a. Mechanisms and results of immune complex-mediated reactions (Arthus reaction as the experimental model)
      (1) formation of antigen-antibody complexes; complexes form in or deposit in tissue
      (2) activation of complement (effects of C3a, C5a)
      (3) release of PAF; neutrophil and platelet aggregation and degranulation; increased vascular permeability and necrosis; end result = vasculitis
      (4) role of macrophages (release TNF and IL-1; release of enzymes)
   b. Examples of acute and chronic clinical manifestations (incidence, symptoms, mechanisms of tissue destruction, pathologic findings, and examples of therapy [e.g. steroids, supportive])
      (1) Serum sickness
      (2) Immune complex induced glomerulonephritis (proliferative [post-infectious], membranous, membranoproliferative)

19. Type IV (Delayed-type or Cell-mediated) Hypersensitivity
   a. Classification of Type IV reactions: Contact hypersensitivity, tuberculin, NK and T-cytotoxicity, granulomatous
   b. Contact hypersensitivity (allergic contact dermatitis)
(1) Immunologic mechanisms
Types of allergens; Sensitization and elicitation phases; Role of Langerhans cells and keratinocytes; Role of antigen-specific \( T_{H1} \) cells and their cytokines; mechanisms of down regulation.

(2) Signs, symptoms, incidence and treatment

c. Tuberculin-type hypersensitivity (recall response to antigen encountered during infection)
(1) Immunologic mechanisms
Infections associated with this response; Role of antigen-specific \( T_{H1} \) cells and their cytokines; Role of macrophages; role of endothelium [adhesion molecule expression and regulation of the influx of cells: PMN first, followed by monocytes and T cells]; macrophages the main cell type; mechanisms of down regulation (e.g. IL10 from macrophages, limited presence of antigen).

(2) Signs and symptoms
d. \( T_c \) and NK cell reactions: see previous section on T cell activation and cell mediated immunity

e. Granulomatous hypersensitivity
(associated with many pathologic effects seen in T cell-mediated immune reactions)
(1) Immunologic mechanisms
cells: (antigen-specific \( T_{H1} \) cells, macrophages [epithelioid cells, giant cells])
cytokines: IFN\( \gamma \), TNF\( \alpha \), IL-3, IL-12, GM-CSF

(2) Diseases associated with granulomatous hypersensitivity (brief descriptions)
(a) Leprosy
(b) Tuberculosis
(c) Schistosomiasis
(d) Sarcoidosis
(e) Crohn’s disease
(f) Hypersensitivity pneumonitis (early form involves Type III)

f. Evaluation of DTH
(1) Patch test
(2) Skin test to evaluate CMI

20. Autoimmunity and autoimmune diseases
a. Origins of autoimmune diseases
(1) Genetic factors: familial incidence; association with specific HLA haplotypes
(2) Failure to maintain self-tolerance (either central or peripheral)
(3) Loss of regulatory T cells (dysregulation of the cytokine network)
(4) Expression of cryptic self epitopes
(5) Inappropriate expression of MHC II molecules on specific tissue
(6) Cross-reacting antigens and antigenic mimicry
(7) Polyclonal B cell activation
(8) Association of certain infectious diseases with the onset of autoimmunity
(9) Hormonal influences

b. Pathogenic mechanisms of autoimmune diseases (see individual diseases)
c. Examples of autoimmune diseases (prevalence, signs, symptoms, pathologic consequences of autoimmune mechanisms, examples of treatments [some key features of the diseases are given below])
(1) Autoimmune Rheumatic Diseases
(a) Rheumatoid Arthritis (Type III and IV hypersensitive reactions; rheumatoid factors; vasculitis, synovitis; HLA-DR\(4 \); cellular and chemical effectors [PMN, \( T_{H1}, T_c \), IL-1, TNF\( \beta \), IL-8, PGE\(2 \), LTB\(4 \)])
(b) Systemic Lupus Erythematosus (Type II and III; multiple auto-antibodies; HLA-DR2, HLA-DR3; multiple organ involvement)
(c) Polymyositis/Dermatomyositis (HLA-DR3, HLA-DR; Type IV; serum muscle enzymes elevated)

(2) Autoimmune Endocrine Diseases
(a) Insulin-Dependent Diabetes Mellitus (Type II and IV; auto-antibodies to beta cell surface antigen, cytoplasmic antigen, and glutamic acid decarboxylase [associated with GABA synthesis]; HLA-DR proteins expressed on beta cells; HLA-DR3, HLA-DR4)
(b) Chronic Thyroiditis (Hashimoto’s Disease; Type II and IV; goiter; antithyroglobulin and antithyroid peroxidase are prevalent)
(c) Graves’ disease (hyperthyroidism; anti-TSH receptor autoantibodies; MHC II [HLA-DR] expression on thyroid cells; HLA-DR3)

(3) Autoimmune Liver and Gastrointestinal Diseases
(a) Inflammatory Bowel Disease: Crohn’s Disease (abnormality of mucosal T cell regulation; granulomatous reaction characteristic); Ulcerative colitis (Possibly Type II; continuous mucosal ulceration common)
(b) Pernicious Anemia (antiparietal cell antibodies and anti-intrinsic factor antibodies)
(c) Autoimmune Chronic Active Hepatitis (HLA-B8/DR3; liver cells express MHC II proteins; anti-liver cell antibodies are present)

(4) Autoimmune Neurologic Diseases
(a) Multiple Sclerosis (abnormal T cell regulation; Type II and IV; inflammatory demyelination in CNS white matter resulting in “plaques”; auto-antibodies & T_H1 directed at myelin antigens)
(b) Acute Disseminated Encephalomyelitis (follows infection or vaccination; Type IV directed at MBP and other myelin antigens)
(c) Acute Inflammatory Polyneuropathy (Guillain-Barre Syndrome; follows viral or Campylobacter infection; Type II and IV reaction to peripheral nerve antigens)

21. Human Blood Group Antigens
a. ABO blood groups (structure, inheritance, and naturally occurring antibodies)
b. Rh blood groups

22. Transplantation immunology
a. Definitions of autografts, syngrafts, allografts, and xenografts
b. The role of MHC antigens (alloantigens) and ABO blood type in graft acceptance and rejection
c. Mechanisms of graft rejection
   (1) Hyperacute rejection: recipient has pre-existing antibodies to ABO antigens or HLA antigens; occurs within minutes to hours
   (2) Accelerated Acute: occurs within a few days; mediated by sensitized T cells (CMI)
   (3) Acute: occurs within the second week; T cells (CMI) become sensitized to alloantigens (HLA antigens)
   (4) Chronic: occurs months to years after the transplant; multiple immunologic mechanisms; chronic inflammation, pro-inflammatory cytokines, and increased adhesion molecules on endothelium important
d. Graft-versus-host reaction (acute and chronic)
   Immunologic mechanisms and types of transplants involved
e. Tissue typing, preventing rejection, and inducing recipient unresponsiveness
   (1) ABO compatibility
   (2) Crossmatching
   (3) HLA typing
      (a) MLR
      (b) Lymphocytotoxicity tests (microcytotoxicity tests)
      (c) New methods (RFLP)
   (4) Inducing unresponsiveness
      (a) Azathioprine
      (b) Cyclosporin
      (c) Corticosteroids
      (d) Anti-lymphocyte antibodies (polyclonal anti-T, monoclonal anti-CD3,4,8)

f. Clinical transplantation
   (1) Kidney
   (2) Liver
   (3) Pancreas
   (4) Heart
   (5) Lung
   (6) Bone marrow

23. Tumor Immunology
a. Properties of tumor (transformed) cells
   (1) Abnormalities in growth and responses to regulation and apoptosis
   (2) Induction by carcinogens, viruses; spontaneous
   (3) Role of oncogenes (e.g. growth-promoting oncogenes and oncoproteins)
   (4) Role of tumor-suppressor genes and genes that control DNA repair
b. Tumor-specific and tumor-associated antigens
   (1) Tumor-specific shared antigens: melanoma antigen-1 (MAGE-1; found on melanomas and other transformed cells)
   (2) Tissue-specific antigens (on normal and transformed cells; such as Tyrosinase found on normal and transformed melanocytes)
   (3) Antigens resulting from mutation (such as the mutation of an oncogene)
   (4) Over expressed antigens
   (5) Viral antigens
   (6) Non-immunogenic: Oncofetal antigens: carcinoembryonic antigen (CEA)
       α-fetoprotein
       Differentiation antigens: common acute lymphoblastic leukemia antigen (CALLA, CD10) found on cells of acute lymphoblastic leukemia and PSA on prostate
c. Anti-tumor immunity
   (1) CMI (T_C, T_H1 cytokines, NK, macrophage)
   (2) Humoral (ADCC and activation of complement)
   (3) “Immunosurveillance”: There is an increased frequency of cancers in immunocompromised individuals, however, most cancers occur in individuals with no overt immunodeficiency. More likely that tumors develop ways of evading the immune system.
Examples of tumor evasion: (a) out-growth of antigen-negative variants
(b) loss or reduced expression of MHC proteins
(c) secretion of immunosuppressive cytokines
(d) inducing T<sub>c</sub> apoptosis
(e) lack of co-stimulatory signals
(f) soluble tumor antigens

d. Immunotherapy
   (1) Non-specific stimulation (adjuvant therapy)
   (2) Active immunization with tumor antigens
   (3) Cytokine therapy
   (4) Adoptive cellular immunotherapy (LAK cells, TIL)
   (5) Anti-tumor antibodies (coupled to cytotoxins or radioisotopes)

24. Immunodeficiency Diseases
   a. General signs and symptoms of immunodeficiency diseases
   b. Laboratory tests to assess immune function
      (1) T cell: Enumeration (flow cytometry), functional assays (mitogen response, MLR, DTH skin tests)
      (2) B cell: Enumeration, circulating antibody levels
      (3) Macrophage: Enumeration, functional assays (nitroblue tetrazolium)
      (4) Complement: Direct measurement of complement components, complement hemolysis assay
   c. Primary B cell immunodeficiencies (symptoms, description of defect, current therapy)
      (1) X-linked Agammaglobulinemia (Bruton’s syndrome)
      (2) Common Variable Immunodeficiency (acquired hypogammaglobulinemia)
      (3) Selective IgA Deficiency (most common immunodeficiency disorder)
      (4) Other (minor): Transient hypogammaglobulinemia of infancy
   d. Primary T cell immunodeficiencies (symptoms, description of defect, current therapy)
      (1) Congenital Thymic Aplasia (DiGeorge’s Syndrome)
      (2) Chronic Mucocutaneous Candidiasis
   e. Combined B and T cell immunodeficiencies (symptoms, description of defect, current therapy)
      (1) Severe Combined Immunodeficiency (SCID; a group of genetically determined diseases)
         (a) X-Linked Combined Immunodeficiency (accounts for 50-60% of all SCID; defect in cytokine receptors)
         (b) Adenosine Deaminase Deficiency (an autosomal recessive SCID; accounts for ~20% of all SCID)
         (c) Other mechanisms of SCIDs: Purine nucleoside phosphorylase deficiency, TCR Immunodeficiency, MHC class I or II deficiency (Bare Lymphocyte Syndrome), Defective IL-2 production
   f. Primary Phagocyte Deficiencies (symptoms, description of defect, current therapy)
      (1) Neutropenia
      (2) Chronic Granulomatous Disease
      (3) Leukocyte Adhesion Deficiency
   g. Primary Complement Deficiencies (symptoms, description of defect, current therapy)
      (1) Deficiency of Complement Components
         (a) Classic pathway: C1, C4, C2, C3
         (b) Alternative pathway: Factor D, Properdin
         (c) MAC: C5, 6, 7, 8, 9
(e) Regulator proteins: Factors H, I, C1 inhibitor
Hereditary Angioedema (C1Inh. deficiency)

h. Secondary Immunodeficiencies
(1) Drug or radiation-induced (steroids, other cytotoxic drugs)
(2) AIDS (HIV target cells and immune dysfunction [see Virology for other aspects of the viral infection])
(3) Nutritional deficiency (reduced protein, calorie, vitamins or minerals [e.g. biotin, B12, iron, Vit. A, zinc]; thymic atrophy is usual pathologic result)
(4) Autoimmune Disease
(5) Other (postviral, chronic infection, neoplastic diseases)

25. Immunology of Pregnancy
   a. Mucosal immunity of the female genital tract
   b. Implantation (cytokine and hormonal influences on attachment and implantation)
   c. Trophoblast invasion (theories on why the fetus isn’t rejected as an allograft: reduced immunogenicity of fetal cells; local altered immunity)

26. Immunity in the Elderly
   a. Effects of aging on the immune system

References

Useful Web Sites

cytokine information: http://www.copewithcytokines.de/cope

“Understanding the immune system”: http://rex.nci.nih.gov/PATIENTS/INFO_TEACHER/immune_sys/title.html

Allergy, Asthma, and Immunology online: http://allergy.mcg.edu

National Institute of Allergy and Infectious Diseases: http://niaid.nih.gov