DISEASES OF IMMUNITY
Disorders of the Immune System

- Hypersensitivity reactions
- Autoimmune diseases
- Immunologic deficiency syndromes
- Amyloidosis
General features of hypersensitivity disorders

~ Both exogenous and endogenous antigens may cause hypersensitivity reactions

~ Often associated with the inheritance of particular susceptibility genes

~ Hypersensitivity reflects an imbalance between the effector mechanisms of immune responses and the control mechanisms that serve to normally limit such responses
Hypersensitivity Reactions and Tissue Injury

- Results in tissue injury or other pathophysiological changes
- Occurs when an already sensitized individual is re-exposed to the same foreign substance
- May be immediate or delayed
Hypersensitivity Reactions and Tissue Injury

Ensuing tissue injury may be caused by:

- Release of vasoactive substances
- Phagocytosis or lysis of cells
- Activation of inflammatory & cytolytic components of complement system
- Release of cytokines, proteolytic enzymes and other mediators of tissue injury or inflammation
<table>
<thead>
<tr>
<th>Type</th>
<th>Prototype Disorder</th>
<th>Immune Mechanisms</th>
<th>Pathologic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate (type I) hypersensitivity</td>
<td>Anaphylaxis; allergies; bronchial asthma (atopic forms)</td>
<td>Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)</td>
<td>Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation</td>
</tr>
<tr>
<td>Antibody-mediated (type II) hypersensitivity</td>
<td>Autoimmune hemolytic anemia; Goodpasture syndrome</td>
<td>Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes</td>
<td>Cell lysis; inflammation</td>
</tr>
<tr>
<td>Immune complex-mediated (type III) hypersensitivity</td>
<td>Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction</td>
<td>Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules</td>
<td>Necrotizing vasculitis (fibrinoid necrosis); inflammation</td>
</tr>
<tr>
<td>Cell-mediated (type IV) hypersensitivity</td>
<td>Contact dermatitis; multiple sclerosis; type I, diabetes; transplant rejection; tuberculosis</td>
<td>Activated T lymphocytes → i) release of cytokines and macrophage activation; ii) T cell-mediated cytotoxicity</td>
<td>Perivasculary cellular infiltrates; edema; cell destruction; granuloma formation</td>
</tr>
</tbody>
</table>
Immediate (Type I) Hypersensitivity

~ Anaphylactic type

- Occurs within minutes
- IgE mediated
- Provoked by re-exposure to the same antigen (by contact, inhalation, ingestion, or injection)
- Mediated by antigen binding with antibody previously bound to mast cells or basophils
- Local or systemic
Immediate (Type I) Hypersensitivity

Two Phase Reaction

♣ Initial response is rapid - 5-30 min after exposure to antigen (subsides in 60 minutes)
  - Vasodilatation, edema, smooth muscle spasm

♣ Late phase response - 2-8 hrs later
  - Occurs in 50% of patients
  - Infiltration by monocytes, eosinophils, basophils, PMN’s and CD4 T cells
  - With mucosal epithelial damage
Type I Hypersensitivity

♦ Mast cells in tissues; Basophils circulate
♦ Both contain granules with Inflammatory Mediators
♦ Activated by cross-linking to IgE Fc receptors
Figure 6–7. Sequence of events leading to type I hypersensitivity. TCR = T cell receptor; APC = antigen-presenting cell; T\(_{h2}\) = T-helper 2 CD4+ cells.
<table>
<thead>
<tr>
<th>Mediator</th>
<th>Histamine</th>
<th>PAF</th>
<th>Leukotrienes C4, D4, E4</th>
<th>Neutral proteases that activate complement and kinins</th>
<th>Prostaglandin D2</th>
<th>Leukotrienes C4, D4, E4</th>
<th>Histamine</th>
<th>Prostaglandins</th>
<th>PAF</th>
<th>Cytokines, e.g., TNF</th>
<th>Leukotriene B4</th>
<th>Eosinophil and neutrophil chemotactic factors (not defined biochemically)</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatation, increased vascular permeability</td>
<td></td>
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<td></td>
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<tr>
<td>Smooth muscle spasm</td>
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<tr>
<td>Cellular infiltration</td>
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</tr>
</tbody>
</table>
Immediate (Type I) Hypersensitivity

Primary Mediators

♣ Preformed and stored in granules
♣ Histamine
♣ Chemotactic factors for eosinophils and PMN’s
♣ Proteases
Immediate (Type I) Hypersensitivity

Secondary Mediators

♠ Lipid Mediators
- Platelet Activating Factor
- Arachidonic Acid
  ☻ Leukotrienes and Prostaglandin

♠ Cytokines
- TNF-alpha
- Interleukins 1, 4, 5, 6
Types Immediate (Type I) Hypersensitivity

SYSTEMIC ANAPHYLAXIS

- characterized by vascular shock, widespread edema, and difficulty in breathing
- Hospital setting = Antisera, hormones, enzymes, polysaccharides, and drugs (penicillin)
- Community setting = food allergies, insect toxins
- Itching, hives, skin erythema within minutes
  → respiratory difficulty or GIT symptoms
- Shock and Death can occur within minutes
Mast-cell activation and granule release

Gastrointestinal tract
- Increased fluid secretion, increased peristalsis
  - Expulsion of gastrointestinal tract contents (diarrhea, vomiting)

Airways
- Decreased diameter, increased mucus secretion
  - Congestion and blockage of airways (wheezing, coughing, phlegm)
  - Swelling and mucus secretion in nasal passages

Blood vessels
- Increased blood flow, increased permeability
  - Increased fluid in tissues causing increased flow of lymph to lymph nodes, increased cells and protein in tissues, increased effector response in tissues
Antibody-Mediated (Type II) Hypersensitivity

Mediated by antibodies directed toward antigens present on the cell surfaces or extracellular matrix

IgG and IgM

Antigenic determinants – intrinsic or exogenous
Antibody-Mediated (Type II) Hypersensitivity

MECHANISMS:

♥ **Opsonization and Complement-and Fc Receptor-Mediated Phagocytosis**

→ Cells targeted by antibodies are coated (opsonized) with molecules that make them attractive for phagocytes
→ Activates the complement system producing C3b and C4b
→ Deposited on the surface of the cells and recognized by phagocytes (Fc receptors)
→ Results to the phagocytosis of the opsonized cells and their destruction
→ Complement activation → formation of MAC  → disrupts membrane integrity  → osmotic lysis of cells
Type II Hypersensitivity Reaction – Opsonization and Complement-and Fc-Receptor Mediated Phagocytosis
Antibody-Mediated (Type II) Hypersensitivity

• **Clinical Conditions**
  1. **Transfusion reaction**
     - cells from an incompatible donor react with and are opsonized by preformed antibody in the host
  2. **Erythroblastosis fetalis**
     - there is an antigenic difference b/w the mother and the fetus, and antibodies (IgG) from the mother cross the placenta and cause destruction of RBCs
  3. **Autoimmune hemolytic anemia, agranulocytosis, thrombocytopenia**
     - individuals produce antibodies to their own blood cells which are then destroyed
  4. **Certain drug reactions**
     - antibodies are produced that reacts with the drug, which may be attached to the surface of RBCs or other cells
<table>
<thead>
<tr>
<th>Disease</th>
<th>Target Antigen</th>
<th>Mechanisms of Disease</th>
<th>Clinicopathologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Erythrocyte membrane proteins (Rh blood group antigens, I antigen)</td>
<td>Opsonization and phagocytosis of erythrocytes</td>
<td>Hemolysis, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet membrane proteins (gpllb:IIIa intergrin)</td>
<td>Opsonization and phagocytosis of platelets</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Proteins in intercellular junctions of epidermal cells (epidermal cadherin)</td>
<td>Antibody-mediated activation of proteases, disruption of intercellular adhesions</td>
<td>Skin vesicles (bullae)</td>
</tr>
<tr>
<td>Vasculitis caused by ANCA</td>
<td>Neutrophil granule proteins, presumably released from activated neutrophils</td>
<td>Neutrophil degranulation and inflammation</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli</td>
<td>Complement- and Fc receptor-mediated inflammation</td>
<td>Nephritis, lung hemorrhage</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen</td>
<td>Inflammation, macrophage activation</td>
<td>Myocarditis, arthritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Antibody inhibits acetylcholine binding, down-modulates receptors</td>
<td>Muscle weakness, paralysis</td>
</tr>
<tr>
<td>Graves disease (hyperthyroidism)</td>
<td>TSH receptor</td>
<td>Antibody-mediated stimulation of TSH receptors</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
<td>Antibody inhibits binding of insulin</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor of gastric parietal cells</td>
<td>Neutralization of intrinsic factor, decreased absorption of vitamin B₁₂</td>
<td>Abnormal erythropoiesis</td>
</tr>
</tbody>
</table>
Immune Complex-Mediated (Type III) Hypersensitivity

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition
Immune Complex-Mediated (Type III) Hypersensitivity

- Antigen - Antibody Complexes initiate acute inflammation
  - Complement activation and accumulation of PMN’s
- Endogenous Antigens – DNA
  - circulating Ag’s present in the blood, or, more commonly, antigenic components of one’s own cells and tissues
- Exogenous Antigens - Bacteria, Viruses, Foreign protein, etc.
- Immune Complexes form in circulation or
- Antigens are ‘planted’ and IC’s form in situ
- Can be generalized or localized
### Table 7-5. Some Antigens Associated with Immune Complex Disorders

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exogenous</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious agents</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteria:</td>
<td></td>
</tr>
<tr>
<td><em>Streptococci</em></td>
<td>Glomerulonephritis, infective endocarditis</td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td>Arthritis</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Viruses:</td>
<td></td>
</tr>
<tr>
<td><em>Hepatitis B</em></td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
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<tr>
<td>Parasites:</td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium sp.</em></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td><em>Schistosoma sp.</em></td>
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<tr>
<td>Fungi:</td>
<td></td>
</tr>
<tr>
<td><em>Actinomycetes</em></td>
<td>Farmer’s lung</td>
</tr>
<tr>
<td><strong>Drugs or chemicals</strong></td>
<td></td>
</tr>
<tr>
<td>Foreign serum (antithymocyte globulin)</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
</tr>
<tr>
<td><strong>Endogenous</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Nuclear antigens</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Immunoglobulins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tumor antigens</strong></td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis of immune-complex disease

[Ag-Ab complexes]

Complement activation

Chemotactic factors

NEUTROPHIL AGGREGATION

Phagocytosis of complexes

Release of lysosomal enzymes

VASODILATION AND EDEMA

Release of vasoactive amines

Anaphylatoxin generation

Platelet aggregation

Microthrombi formation

Activation of Hageman factor

Ischemia

Activation of kinins

Necrosis
Systemic Immune Complex Disease

- Prototype disorder – Acute serum sickness
- Frequent sequela to the administration of large amounts of foreign serum (e.g. horse immune serum for passive immunization)
- Pathogenesis (3 phases)
  1. formation of Ag-Ab complexes
  2. deposition of immune complexes
  3. inflammatory reaction at the site of deposition
PHASE I
Immune complex formation

Antigen
B cell

Plasma cell

Antigen-antibody complex

Free antibody

Endothelium

PHASE II
Immune complex deposition; complement and Fc receptor-mediated leukocyte recruitment and activation

Neutrophil

Complement (C3b) receptor

Fc receptor

Antigen-antibody complex

Complement deposition

PHASE III
Immune complex-mediated inflammation and tissue injury

Platelet aggregation

Vasculitis

Neutrophil lysosomal enzymes
Systemic Immune Complex Disease

Two mechanisms causing inflammation at the site of deposition

1. activation of the complement cascade
2. activation of neutrophils and macrophages through their Fc receptors → release of pro-inflammatory substances (prostaglandins, vasodilator peptides, chemotactic substances, lysosomal enzymes, oxygen free radicals)
Systemic Immune Complex Disease

***Chronic form of serum sickness results from repeated or prolonged exposure to an antigen

***Continuous antigenemia is necessary for the development of chronic immune complex disease because complexes in antigen excess are the ones deposited in vascular beds – e.g. SLE
Systemic Immune Complex Disease

Morphology

→ acute necrotizing vasculitis, with necrosis of vessel wall and intense neutrophilic infiltration
→ fibrinoid necrosis – smudgy, eosinophilic deposit that obscures the underlying cellular detail
→ affected glomeruli are hypercellular because of swelling and proliferation of endothelial and mesangial cells, accompanied by neutrophilic and monocytic infiltration
→ IF microscopy – granular lumpy deposits of Ig and Complement
→ Electron microscopy – electron-dense deposits along GBM
Systemic Immune Complex Disease

- Tissues affected
  - ☼ Kidneys, joints, skin, heart, serosal surfaces and small vessels
- The reason(s) for this specific organ/tissue predeliction is unknown
Local Immune Complex Disease

♦ LOCAL (ARTHUS REACTION)
  • Localized tissue necrosis from acute immune vasculitis
  • Can induce experimentally by injecting antigen into the skin of a pre-sensitized recipient
  • Local PMN recruitment and fibrinoid necrosis → thrombi formation → local ischemic injury
<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen Involved</th>
<th>Clinicopathologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, nucleoproteins, others</td>
<td>Nephritis, arthritis, vasculitis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B virus surface antigen (in some cases)</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Streptococcal cell wall antigen(s); may be “planted” in glomerular basement membrane</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>Bacterial antigens <em>(Treponema)</em>; parasite antigens (malaria, schistosomes); tumor antigens</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>Bacterial antigens <em>(Yersinia)</em></td>
<td>Acute arthritis</td>
</tr>
<tr>
<td>Arthus reaction</td>
<td>Various foreign proteins</td>
<td>Cutaneous vasculitis</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Various proteins, e.g., foreign serum (anti-thymocyte globulin)</td>
<td>Arthritis, vasculitis, nephritis</td>
</tr>
</tbody>
</table>
T Cell-Mediated (Type IV) Hypersensitivity

♠ T-Cells are the active agents not Antibodies
☼ Otherwise Type II is very similar to Type IV
♠ Delayed-Type
   → mediated by CD4+ T cells
♠ Direct Cell Cytotoxicity
   → mediated by CD8+ T cells
Mechanisms of Delayed Type Hypersensitivity Reactions
Mechanism of Direct T Cell Cytotoxicity
Type IV Hypersensitivity
Delayed Type

♣ “The Type of inflammation characteristic of this Reaction is called Granulomatous Inflammation”

♣ The key cell is the epithelioid macrophage NOT the Giant Cell!!
Type IV - Cell Mediated Delayed Hypersensitivity

♣ TB antigen processing by macrophages ➖
  • presentation to CD4 T cells - sensitized CD4 cells that remain in the circulation
  • Re-exposure - activation, amplification and recruitment of *Macrophages* which cause the majority of tissue damage
  • IL-2 and IFN-gamma are the most important cytokines
Type IV - Cell Mediated Delayed Type

♣ Major defense against Tuberculosis & Fungi
♣ Patients with AIDS have little defense against these organisms due to the extreme decline in CD4 cells
Type IV - T-cell Mediated Cytotoxicity

- Sensitized T cell directly kill cells
- Major role in Transplant Rejection
- Protects against Viral Infections
Type IV - T-cell Mediated Cytotoxicity

♣ CD8 or Cytotoxic T Lymphocytes are the effector cells

◼ Lyse target cells
  – Perforin release leads to osmotic lysis
  – Fas binding leads to apoptosis

◼ Release cytokines e.g. interferon gamma
Key Facts on Hypersensitivity Reactions

- Type I: IgE/mast cell-mediated liberation of histamine. Local and systemic anaphylaxis.
- Type II: antibodies bind to cell surface. Damage by complement activation or cellular cytotoxicity, or may stimulate/block a receptor.
- Type III: antigen-antibody complexes, either local or circulating. Cause damage by activating complement in tissues at site of trapping of complexes.
- Type IV: T-cell mediated: CD4 cells recruit macrophages; CD8 cells cause cytotoxicity.
TRANSPLANT REJECTION
Transplant Rejection

Factors enhancing graft survival

- ABO blood group compatibility between recipients and donors
- Absence of pre-formed anti-HLA cytotoxic antibodies in recipients
  - People must have previous exposure to blood products to develop HLA cytotoxic antibodies
- Close matches of HLA-A, -B, and -D loci between recipients and donors
Transplant Rejection

~ Type of grafts

• Autograft (i.e., self to self)
  – Associated with the best survival rate

• Syngeneic graft (isograft)
  – Between identical twins

• Allograft
  – Between genetically different individuals of the same species

• Xenograft
  – Between two species
  – Example = transplant of heart valve from pig to human
Transplant Rejection

- Involves recognition of major histocompatibility antigens (HLA)
  - The most important HLA presenting cells are the donor lymphocytes, especially dendritic cells, contained within the graft
  - Mediated by: CD8+ & CD4+ T cells
## SOME TYPES OF TRANSPLANTS

<table>
<thead>
<tr>
<th>TYPE OF TRANSPLANT</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| Cornea             | Best allograft survival rate  
                      Danger of transmission of C-J disease |
| Kidney             | Better survival with kidney from living donor than from cadaver |
| Bone marrow        | Graft contains pluripotential cells that repopulate host stem cells  
                      Host assumes donor ABO group  
                      Danger of graft-versus-host reaction and CMV infection |
Introduction

- Autoimmunity- immune reaction against “self-antigens” → Tissue damage
- Single organ or multi-system diseases
- More than 1 auto-antibody in a given disease may occur
- Common in females
Autoimmunity

~ Three Requirements

1. The presence of an immune reaction specific for some self-antigen or self-tissue
2. Evidence that such a reaction is not secondary to tissue damage but is of primary pathogenic significance
3. The absence of another well-defined cause of the disease
Mechanism of Autoimmunity

- Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes.

- These genetic and environmental influences conspire to create an imbalance between control mechanisms that normally function to prevent self-reactivity and pathways that lead to activation of pathogenic effector lymphocytes.
Pathogenesis of Autoimmunity

Genetic susceptibility

- Susceptibility genes

Failure of self-tolerance

Self-reactive lymphocytes

Infection, tissue damage

- Necrosis, inflammation

- Influx of self-reactive lymphocytes into tissues

Activation of self-reactive lymphocytes

Tissue injury: autoimmune disease

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General Features of Autoimmune Diseases

~ Once induced it tends to be progressive, sometimes with sporadic relapses and remissions, and the damage becomes inexorable

• Epitope Spreading
  • Infections and initial autoimmune response → damage tissues, release self antigens and exposed epitopes of the antigens that are normally concealed from the immune system → continuing activation of lymphocytes

~ The clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response

~ Different autoimmune diseases show substantial clinical, pathologic, and serologic overlaps
Systemic Lupus Erythematosus (SLE)

~ Etiology: Unknown
~ Pathogenesis: Failure to maintain self-tolerance due to polyclonal autoantibodies
~ Multisystem: Skin, kidneys, serosal surfaces, joints, CNS & heart
~ Incidence: 1:2500 more common in black Americans; 10X F > M; 2nd-3rd decades
SLE: Predisposing Factors

- Genetic factors
  - 30% concordance in monozygotic twins
  - Associated w/ HLA-DR 2 & 3 loci

- Non-genetic factors
  - Drugs (procainamide, isoniazid, d- penicillamine & hydralazine) \( \rightarrow \) LE like s/s
  - Androgens protect, estrogens enhance
  - UV light may trigger B-cell hyper-reactivity caused by excess T-helper activity
Multisystem manifestations of Systemic Lupus Erythematosus. SLE affects a wide range of tissues and organ systems.
3-1: Malar rash in systemic lupus erythematosus showing the butterfly-wing distribution. (From Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed. St. Louis, Mosby, 2003, Fig. 3-77.)
SLE

~ Antinuclear antibodies
  - Antibodies to DNA (Classic SLE)
  - Antibodies to histones (Drug induced SLE)
  - Antibodies to non-histone proteins bound to RNA
  - Antibodies to nucleolar antigens

~ ANA test is sensitive, but non specific
SLE

~ Joint: No striking anatomic changes nor deformities, non-specific lymphocytic infiltrates

~ Spleen: Splenomegaly, capsular thickening, and follicular hyperplasia

~ Lungs: Pleuritis and pleural effusions

~ CNS: Multifocal cerebral infarcts from microvascular injury

~ Other Organs and Tissues: LE or hematoxylin bodies in the bone marrow or other organs. Lymph nodes may be enlarged with hyperplastic follicles or even demonstrate necrotizing lymphadenitis
Rheumatic Fever

~ Etiology: Group A, streptococcal pharyngitis
~ Pathogenesis: antibody cross-react with connective tissue in susceptible individuals → Autoimmune reaction (2-3 wks) → Inflammation (T cells, macrophages) → Heart, skin, brain & joints
Morphology:

~ **Acute RF**
  - Acute Inflammatory Phase
  - Heart– Pancarditis
  - Skin– Erythema Marginatum
  - CNS– Sydenham Chorea
  - Migratory polyarthritis

~ **Chronic RF**
  - Deforming fibrotic valvular disease
Rheumatoid Arthritis: Etiology

~ HLA-DR4/DR1 associated (increased incidence)
~ Incidence: 1% of population; 4th & 5th decades; 3 - 5X F > M
~ 80% of patients with Rheumatoid Factors (Abs against Fc portion of IgG)
Rheumatoid Arthritis: Pathogenesis

~ Precise trigger is unknown

~ Activation of T-helper cells $\rightarrow$ cytokines $\rightarrow$ activate B cells $\rightarrow$ Abs $\rightarrow$ Non-suppurative proliferative synovitis (destruction of articular cartilage & progressive disabling arthritis)

~ Extra-articular manifestations resemble SLE or scleroderma
Multisystem manifestations of Rheumatoid arthritis. Although the initial manifestation is usually arthritis, Rheumatoid disease is a systemic illness.
IMMUNODEFICIENCY SYNDROMES
IMMUNODEFICIENCY SYNDROMES

~ Primary immunodeficiency disorders
  • Almost always genetically determined
  • Affect the humoral and/or cellular arms of adaptive immunity or the defense mechanisms of innate immunity

~ Secondary immunodeficiency states
  • May arise as complications of cancers, infections, malnutrition, or side-effects of immunosuppression, irradiation, or chemotherapy for cancer and other diseases
IMMUNODEFICIENCY SYNDROMES

~ Risk factors for immune disorders

- Prematurity
- Autoimmune diseases (e.g., SLE)
- Lymphoproliferative disorders
- Infections (e.g., HIV)
- Immunosuppressive drugs (e.g., corticosteroids)
<table>
<thead>
<tr>
<th>Pathogen Type</th>
<th>T-Cell Defect</th>
<th>B-Cell Defect</th>
<th>Granulocyte Defect</th>
<th>Complement Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Bacterial sepsis</td>
<td>Streptococci, staphylococci, <em>Haemophilus</em></td>
<td>Staphylococci, <em>Pseudomonas</em></td>
<td>Neisseria infections, other pyogenic bacterial infections</td>
</tr>
<tr>
<td>Viruses</td>
<td>Cytomegalovirus, Epstein-Barr virus, severe varicella, chronic infections with respiratory and intestinal viruses</td>
<td>Enteroviral encephalitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi and parasites</td>
<td><em>Candida, Pneumocystis carinii</em></td>
<td>Severe intestinal giardiasis</td>
<td><em>Candida, Nocardia, Aspergillus</em></td>
<td></td>
</tr>
<tr>
<td>Special features</td>
<td>Aggressive disease with opportunistic pathogens, failure to clear infections</td>
<td>Recurrent sinopulmonary infections, sepsis, chronic meningitis</td>
<td></td>
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</tbody>
</table>
PRIMARY IMMUNODEFICIENCIES

1. X-linked Agammaglobulinemia of Bruton

- Failure of B-cell precursors (pro-B cells and pre-B cells) to differentiate into B cells
- Maturation stops after the rearrangement of heavy-chain genes; light chains are not produced
- The block in differentiation is due to mutations in a cytoplasmic tyrosine kinase – Bruton tyrosinase kinase (btk)
X-linked Agammaglobulinemia of Bruton

- seen almost entirely in males but sporadic cases seen in females
- does not become apparent until about 6 months of life
- recurrent bacterial infections of the respiratory tract call attention to the underlying immune defect – H. influenzae, S. pneumoniae, or S. aureus
- 35% of children develop arthritis that respond to Ig therapy
- SLE and Dermatomyositis occur with increased frequency
- Treatment is replacement therapy with Ig
5. DiGeorge Syndrome (Thymic Hypoplasia)

- T cell deficiency that derives from failure of development of the 3rd and 4th pharyngeal pouches – thymus, parathyroids, some clear cells of the thyroid, and ultimobranchial body
- Variable loss of T cell-mediated immunity, tetany, congenital defects of the heart and great vessels
- Appearance of the mouth, ears, and facies maybe abnormal
DiGeorge Syndrome (Thymic Hypoplasia)

- Low levels of circulating T lymphocytes and a poor defense against certain fungal and viral infections
- Plasma cells are present in normal numbers in lymphoid tissues; depleted in paracortical areas of the LN and periateriolar sheaths of spleen
- Ig levels maybe normal or reduced, depending on the severity of the T cell deficiency
<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect(s)</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-Cell Disorders</strong></td>
<td></td>
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<tr>
<td>Bruton’s agammaglobulinemia</td>
<td>Failure of pre-B cells to become mature B cells</td>
<td>Sinopulmonary infections, Maternal antibodies protective from birth to age 6 months</td>
</tr>
<tr>
<td></td>
<td>Mutated tyrosine kinase</td>
<td>↓ Immunoglobulins</td>
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<tr>
<td></td>
<td>X-linked recessive disorder</td>
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<tr>
<td>IgA deficiency</td>
<td>Failure of IgA B cells to mature into plasma cells</td>
<td>Sinopulmonary infections, giardiasis, Anaphylaxis if exposed to blood products that contain IgA</td>
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<tr>
<td></td>
<td></td>
<td>↓ IgA and secretory IgA</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Defect in B-cell maturation to plasma cells</td>
<td>Sinopulmonary infections, GI infections (e.g., Giardia), pneumonia, autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>Adult immunodeficiency disorder</td>
<td>↓ Immunoglobulins</td>
</tr>
<tr>
<td><strong>T-Cell Disorder</strong></td>
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<tr>
<td>DiGeorge syndrome</td>
<td>Failure of third and fourth pharyngeal pouches to develop</td>
<td>Hypoparathyroidism (tetany); absent thymic shadow on radiograph; PCP Danger of GVH reaction</td>
</tr>
<tr>
<td></td>
<td>Thymus and parathyroid fail to develop</td>
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<tr>
<td>Combined B- and T-Cell Disorders</td>
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<tr>
<td><strong>Severe combined immunodeficiency (SCID)</strong></td>
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<tr>
<td>Adenosine deaminase deficiency; adenine toxic to B and T cells, ↓ deoxynucleoside triphosphate precursors for DNA synthesis</td>
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<tr>
<td>Autosomal recessive disorder</td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Progressive deletion of B and T cells</td>
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<td></td>
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<tr>
<td>X-linked recessive disorder</td>
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<td></td>
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<tr>
<td><strong>Ataxia-telangiectasia</strong></td>
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<td></td>
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<tr>
<td>Mutation in DNA repair enzymes</td>
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<td></td>
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<tr>
<td>Thymic hypoplasia</td>
<td></td>
<td></td>
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<tr>
<td>Autosomal recessive disorder</td>
<td></td>
<td></td>
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<tr>
<td><strong>Defective CMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Immunoglobulins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment: gene therapy, bone marrow transplant (patients with SCID do not reject allografts)</td>
<td></td>
<td></td>
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<tr>
<td>Symptom triad: eczema, thrombocytopenia, sinopulmonary infections</td>
<td></td>
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<tr>
<td>Associated risk of malignant lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Defective CMI</td>
<td></td>
<td></td>
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<tr>
<td>↓ IgM, normal IgG, ↑ IgA and IgE</td>
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<tr>
<td>Cerebellar ataxia, telangiectasias of eyes and skin</td>
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<tr>
<td>Risk of lymphoma and/or leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Serum α-fetoprotein</td>
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</tbody>
</table>

CMI, cell-mediated immunity; GVH, graft-versus-host; PCP, Pneumocystis jiroveci pneumonia.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary angioedema</td>
<td>Autosomal dominant disorder with deficiency of C1 esterase inhibitor</td>
</tr>
<tr>
<td></td>
<td>Continued C1 activation decreases C2 and C4 and increases their cleavage products, which have anaphylatoxic activity</td>
</tr>
<tr>
<td></td>
<td>Normal C3</td>
</tr>
<tr>
<td></td>
<td>Swelling of face and oropharynx</td>
</tr>
<tr>
<td>C2 deficiency</td>
<td>Most common complement deficiency</td>
</tr>
<tr>
<td></td>
<td>Association with septicemia (usually Streptococcus pneumoniae) and lupus-like syndrome in children</td>
</tr>
<tr>
<td>C6–C9 deficiency</td>
<td>Increased susceptibility to disseminated Neisseria gonorrhoeae or N. meningitidis infections</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Acquired stem cell disease</td>
</tr>
<tr>
<td></td>
<td>Defect in molecule anchoring decay accelerating factor (DAF), which normally degrades C3 and C5 convertase on hematopoietic cell membranes</td>
</tr>
<tr>
<td></td>
<td>Complement-mediated intravascular lysis of red blood cells (hemoglobinuria), platelets, and neutrophils</td>
</tr>
</tbody>
</table>
ACQUIRED IMMUNODEFICIENCY SYNDROME

- A retroviral disease characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations
- Second leading cause of death in men 25-44 years old
- 3rd leading cause of death in women
HUMAN IMMUNODEFICIENCY VIRUS (HIV)

~ Etiologic agent of AIDS
~ Discovered independently by Luc Montagnier of France and Robert Gallo of the US in 1983-1984
~ Former names of the virus include:
  • Human T cell Lymphotrophic virus (HTLV-III)
  • Lymphadenopathy associated virus (LAV)
  • AIDS associated retrovirus (ARV)

***HIV-2 discovered in 1986, antigenically distinct virus endemic in West Africa
Groups at risk of developing AIDS
1. Homosexual or bisexual men – over 50%
2. Intravenous drug abusers – 20%
3. Hemophiliacs – 0.5%
4. Recipients of blood and blood components – 1.0%
5. Heterosexual contacts of members of other high-risk groups – 10%
ACQUIRED IMMUNODEFICIENCY SYNDROME

- 2% of all cases occurs under 13 years old, 90% of these resulted from transmission of the virus from mother to child, remaining 10% are hemophiliacs or received blood/blood products.
- 3 major routes of transmission
  1. sexual transmission – 75%
  2. parenteral transmission
     → IV drug users, hemophiliacs, BT
  3. mother-to-infant transmission
ACQUIRED IMMUNODEFICIENCY SYNDROME

- mother-to-infant transmission – pediatric AIDS
  1. in utero by transplacental spread
  2. during delivery through an infected birth canal
  3. after birth by ingestion of breast milk

Extensive studies indicate that HIV infection cannot be transmitted by casual personal contact in the household, workplace, or school

Seroconversion after needle-stick injury – 0.3%
Pathogenesis of HIV infection

- Primary infection of cells in mucosal lymphoid tissues
  - CD4+ T cell
  - Dendritic cell
  - Drainage to lymph nodes, spleen
- Infection established in lymphoid tissues, e.g., lymph node
- Acute retroviral syndrome, spread of infection throughout the body
- Viremia
- Immune response
- Anti-HIV antibodies
- Partial control of viral replication
- Provirus
  - Latent infection
  - Low-level infection
  - Other microbial infections; cytokines (e.g., TNF)
- Extensive viral replication and CD4+ cell lysis
- AIDS
  - Destruction of lymphoid tissues: depletion of CD4+ T cells

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Mechanisms of CD4+ T-cell loss in HIV infection

1. Viral replication in infected CD4+ T cells
2. Activation of uninfected CD4+ T cells
3. Expression of HIV peptides on infected CD4+ T cells

- Death of infected cells (cytopathic effect of virus)
- Activation-induced cell death (apoptosis)
- Killing of infected cells by virus-specific CTLs

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Multiple effects of loss of CD4 + T cells as a result of HIV infection

- Decreased response to soluble antigens
- Decreased lymphokine secretion
- Decreased specific cytotoxicity
- Decreased killing of tumor cells
- Diminished cytotoxic ability, decreased chemotaxis, reduced IL-1 secretion, poor antigen presentation
- Depressed Ig production in response to new antigens

Diagram showing interactions between CD4, CD8, NK, B cells, HIV, and macrophages.
<table>
<thead>
<tr>
<th>Test</th>
<th>Use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>Screening test</td>
<td>Detects anti-gp120 antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity ~100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive within 6–10 weeks</td>
</tr>
<tr>
<td>Western blot</td>
<td>Confirmatory test</td>
<td>Used if ELISA is positive or indeterminate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive test: presence of p24 antigen and gp41 antibodies and either gp120 or gp160 antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~100% specificity</td>
</tr>
<tr>
<td>p24 Antigen</td>
<td>Indicator of active viral replication</td>
<td>Positive prior to seroconversion and when AIDS is diagnosed (two distinct peaks)</td>
</tr>
<tr>
<td></td>
<td>Present before anti-gp120 antibodies</td>
<td></td>
</tr>
<tr>
<td>CD4 T-cell count</td>
<td>Monitoring immune status</td>
<td>Useful in determining when to initiate HIV treatment and when to administer prophylaxis against opportunistic infections</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>Detection of actively dividing virus</td>
<td>Most sensitive test for diagnosis of acute HIV before seroconversion</td>
</tr>
<tr>
<td></td>
<td>Marker of disease progression</td>
<td></td>
</tr>
</tbody>
</table>

AIDS, acquired immunodeficiency syndrome; ELISA, enzyme-linked immunoabsorbent assay; HIV, human immunodeficiency virus.
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>AIDS-dementia complex</td>
<td>Caused by HIV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multinucleated microglial cells reservoir of virus</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Primary CNS lymphoma</td>
<td>Caused by EBV</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis</td>
<td>Most common extranodal site for lymphoma</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
<td>Cause of CNS fungal infection</td>
</tr>
<tr>
<td></td>
<td>CMV retinitis</td>
<td>Cause of space-occupying lesions</td>
</tr>
<tr>
<td>Hepatobiliary Renal</td>
<td>Esophagitis</td>
<td>Cause of blindness</td>
</tr>
<tr>
<td></td>
<td>Colitis</td>
<td>Caused by <em>Candida</em>, herpesvirus, CMV</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Biliary tract infection</td>
<td>Caused by <em>Cryptosporidium</em>, CMV</td>
</tr>
<tr>
<td></td>
<td>Focal segmental glomerulosclerosis</td>
<td>Causes hypertension and nephrotic syndrome</td>
</tr>
<tr>
<td>Skin</td>
<td>Pneumonia</td>
<td>Caused by <em>Pneumocystis jiroveci</em> and <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Kaposi sarcoma</td>
<td>Caused by HHV-8</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis</td>
<td>Caused by <em>Bartonella henselae</em></td>
</tr>
</tbody>
</table>

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-8, human herpes virus type B; HIV, human immunodeficiency virus.
AMYLOIDOSIS
AMYLOIDOSIS

- Amyloid is a pathologic proteinaceous substance, deposited in between cells in various tissues and organs of the body in a wide variety of clinical settings.
- With progressive accumulation, encroaches on and produces pressure atrophy of adjacent cells fibrils in extracellular tissues and disrupt normal function.
AMYLOIDOSIS

- Chemical nature
  - 95% consist of fibril proteins, 5% P component and other glycoproteins
  - 3 most common amyloid proteins
    1. AL (amyloid light chain) – derived from plasma cells and contains Ig light chains
    2. AA (amyloid-associated) – non-Ig protein synthesized by the liver
    3. Aβ amyloid – found in Alzheimer disease
- Other biochemical distinct proteins found in amyloid deposits
  - Transthyretin (TTR), β2-microglobulin, prion proteins
Types of Amyloidosis

1. Systemic
   - Similar tissue involvement in both primary and secondary types
   - Primary amyloidosis
     - AL amyloid deposition
     - Associated with multiple myeloma (30% of cases)
   - Secondary (reactive)
     - AA amyloid
     - Associated with chronic inflammation (e.g., RA, Tb)
Types of Amyloidosis

2. Localized
   - Confined to a single organ (e.g. brain)
   - Alzheimer’s disease
     - $\alpha$-A\text{3}
     - Most common cause of dementia

3. Hereditary
   - Autosomal recessive disorder involving AA amyloid
     (e.g., Familial Mediterranean fever)
THANK YOU!