Diseases of Immunity

Dr. Gary Mumaugh – Campbellsville University

Immune refers to protection against infections

- The immune system is the collection of cells and molecules that are responsible for defending the body against the count- less pathogenic microbes in the environment.
- Deficiencies in immune defenses result in an increased susceptibility to infections.
    - Defense against microbes consists of two types of reactions.
- Innate Immunity
    - AKA natural immunity
    - AKA native immunity
- Adaptive Immunity
    - AKA acquired immunity
    - AKA specific immunity

Innate Immunity

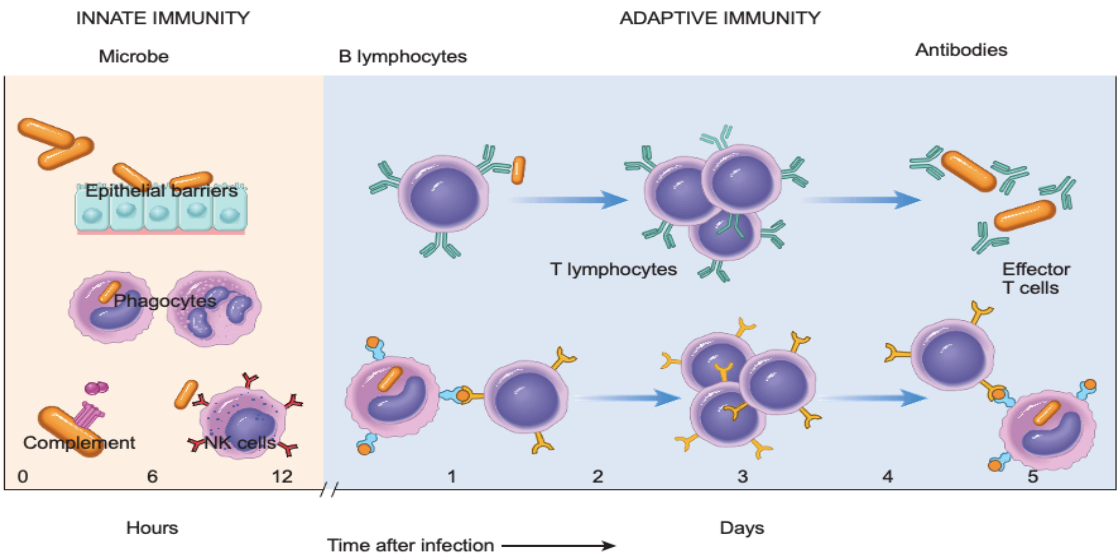
- Is mediated by cells and proteins that are always present and poised to fight against microbes, being called into action immediately in response to infection.
- The major components of innate immunity are epithelial barriers of the skin, gastrointestinal tract, and respiratory tract.
- The innate immune response is able to prevent and control many infections.

Adaptive Immunity

- Many pathogenic microbes have evolved to overcome the early defenses, and protection against these infections requires the more specific and powerful mechanisms of adaptive immunity.
- Also called acquired immunity, or specific immunity.
- Adaptive immunity is normally silent and responds (or “adapts”) to the presence of infectious microbes by becoming active.
- Generates potent mechanisms for neutralizing and eliminating the microbes.
- The components of the adaptive immune system are lymphocytes and their products

Inflammation

- When the immune system is inappropriately triggered or not properly controlled, the same mechanisms that are involved in host defense cause tissue injury and disease.
- The reaction of the cells of innate and adaptive immunity may be manifested as inflammation.



Immunity: Two Intrinsic Defense Systems

- Nonspecific system responds quickly and consists of:
  - First line of defense – intact skin and mucosae prevent entry of microorganisms
  - Second line of defense – antimicrobial proteins, phagocytes, and other cells
    - Inhibit spread of invaders throughout the body
    - Inflammation is its hallmark and most important mechanism
- Specific defense system
  - Third line of defense – mounts attack against particular foreign substances
    - Takes longer to react than the innate system
    - Works in conjunction with the innate system

Nonspecific (Innate) Immunity

- Physical Barriers
  - Skin, mucous membranes, sebaceous secretions, genitourinary tracts, mucociliary blanket of respiratory passages, surface flushing: tears, urine, GI contents
- Antibacterial Agents
  - Acidity of stomach, skin, urinary tract; lysozyme in tears; rapidity of pH change in GI tract
- Commensal Microorganisms
  - Symbiotic bacteria
- Ongoing Phagocytosis
  - Routine destruction of threatening organisms
- Inflammatory Response
  - Cellular- neutrophils, macrophages, NK cells
  - Soluble factors- complement cascade, C-reactive protein, interferon
- Fever
  - Enhances phagocytosis

Specific Immunity

- Acquired after birth
- Acquired Immunity Characteristics
    - Recognition - Its capacity to recognize a microorganism
    - Learning - System is more effective response to second and subsequent exposure to the same pathogen
    - Memory - Long-term retention of improved response
- Acquired Immunity Characteristics
    - Self-discrimination- It direct attacks only against invaders by discriminating between foreign substances and those that make up our own body
- No clean boundary between specific and non-specific defenses – basic function of specific immunity is to focus and reinforce nonspecific defenses

Specific Immunity

- Immune response mediated by:
    - T Lymphocytes
    - B Lymphocytes
    - Antibodies
    - Natural Killer Cells

Specific Defenses

- The adaptive immune system is a functional system that:
    - Recognizes specific foreign substances
    - Acts to immobilize, neutralize, or destroy foreign substances
    - Amplifies inflammatory response and activates complement

Adaptive Immune Defenses

- This is the third line of defense called immune response
- It is based on the ability to distinguish molecules that are part of the body (“self” from “non-self”)
- Antigens are molecules that can elicit an immune response
- The adaptive immune system is:
    - Specific
    - Systemic
    - Has memory

Cells of the Adaptive Immune System

- Two types of lymphocytes
    - B lymphocytes – oversee humoral immunity
    - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
- Based on their functions Lymphocytes can be divided in two parts: B and T Cells
- T lymphocytes and B lymphocytes can be differentiated on the basis of their functions, they are guards and responders of body’s immune system.

Two types of lymphocytes

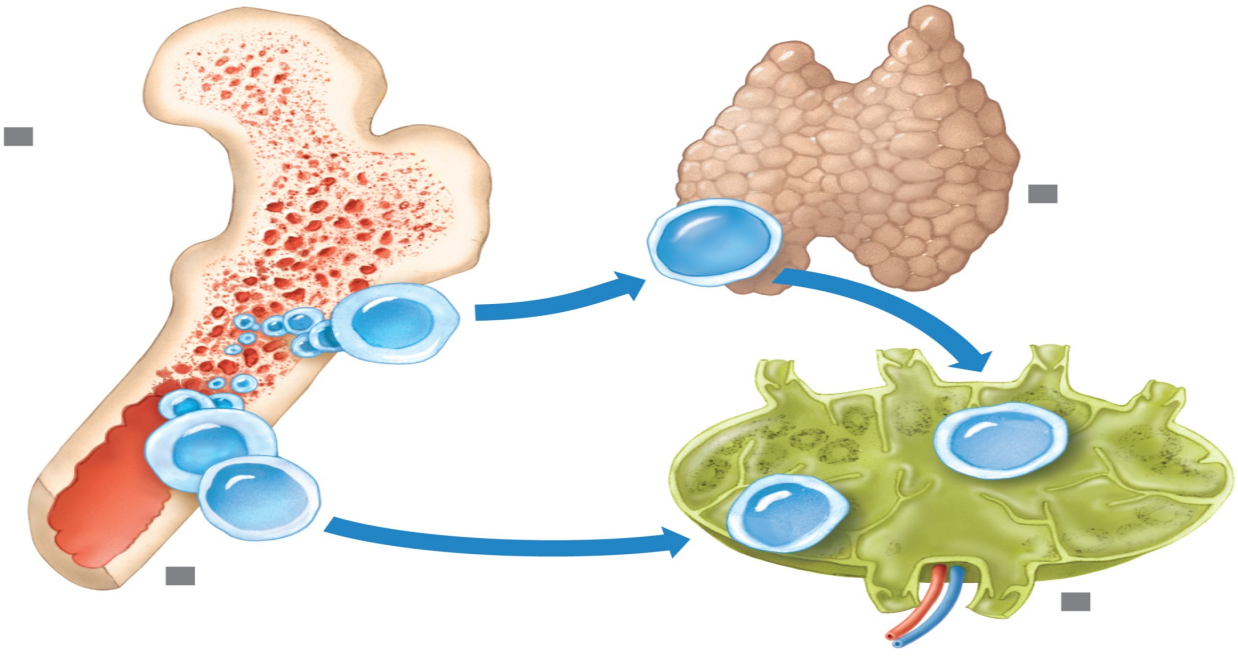
- **B lymphocytes** – oversee humoral immunity – specific antibodies
    - B lymphocytes grow and mature in lymph nodes
    - B lymphocytes secrete antibodies which neutralize the antigen
    - Produce antibodies
    - Produced in red bone marrow
- **T lymphocytes** – non-antibody-producing cells that constitute the cell-mediated arm of immunity
    - T lymphocytes grow and complete their maturity phase in Thymus
    - The function of T lymphocytes is to kill the infected cells.
    - Some of them can be classified as Helper cells as well.

Cells of the Adaptive Immune System

- In chronic ailments such as HIV, the virus attack T Lymphocytes and destroy them thus, eliminating the natural defense mechanism of a body.
- Both of them are produced in bone marrow but mature in spleen and lymph nodes respectively.

Lymphocytes

- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
    - B cells mature in the bone marrow
    - T cells mature in the thymus



T Cell Summary

- Each T cell has unique roles to play in the immune response
- Each T cell is heavily involved in interactions with other immune cells and elements
- Without helper T cells, there would be no adaptive immune response
- The helper T cells direct and help complete the activation of other cells
- Their role is evident when they are destroyed in AIDS

MHC (major histocompatibility complex)

- The major histocompatibility complex (MHC) (also called human leukocyte antigens, HLAs) is the mechanism by which the immune system is able to differentiate between self and non-self cells.
- The MHC is a collection of glycoproteins (proteins with a carbohydrate) that exist on the plasma membranes of nearly all body cells.
- The immune system is able to identify non-self cells by aberrations in the MHC displayed on the plasma membrane.

Natural Killer (NK) Cells

- Cells that can lyse and kill cancer cells and virus-infected cells
- Natural killer cells:
    - Are a small, distinct group of large granular lymphocytes
    - React nonspecifically and eliminate cancerous and virus-infected cells
    - Kill their target cells by releasing perforins and other cytolytic chemicals
    - They “police” the blood and lymph and are the “pits bulls” of the defense system
- They are called "natural" killers because they do not need to recognize a specific antigen before swinging into action.
- They target tumor cells and protect against a wide variety of infectious microbes.
- In several immunodeficiency diseases, including AIDS, natural killer cell function is abnormal.

Immunological Memory

- Primary immune response – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
    - Lag period: 3 to 6 days after antigen challenge
    - Peak levels of plasma antibody are achieved in 10 days
    - Antibody levels then decline
- Secondary immune response – re-exposure to the same antigen
    - Sensitized memory cells respond within hours
    - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
    - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months

Lymphoid Tissue

- Primary Tissue
    - Red bone marrow and thymus
    - House lymphoid stem cells- produce T and B cells
- Secondary Tissue
    - Lymph nodes, spleen, tonsils, and Peyer's patches in intestines- encounter antigens if they violate outer defenses
    - Allow immune cells to remain in close proximity in order to cooperate in the development of a full response
    - T and B cells circulate in blood or lymph, or reside in secondary tissue

Immunization

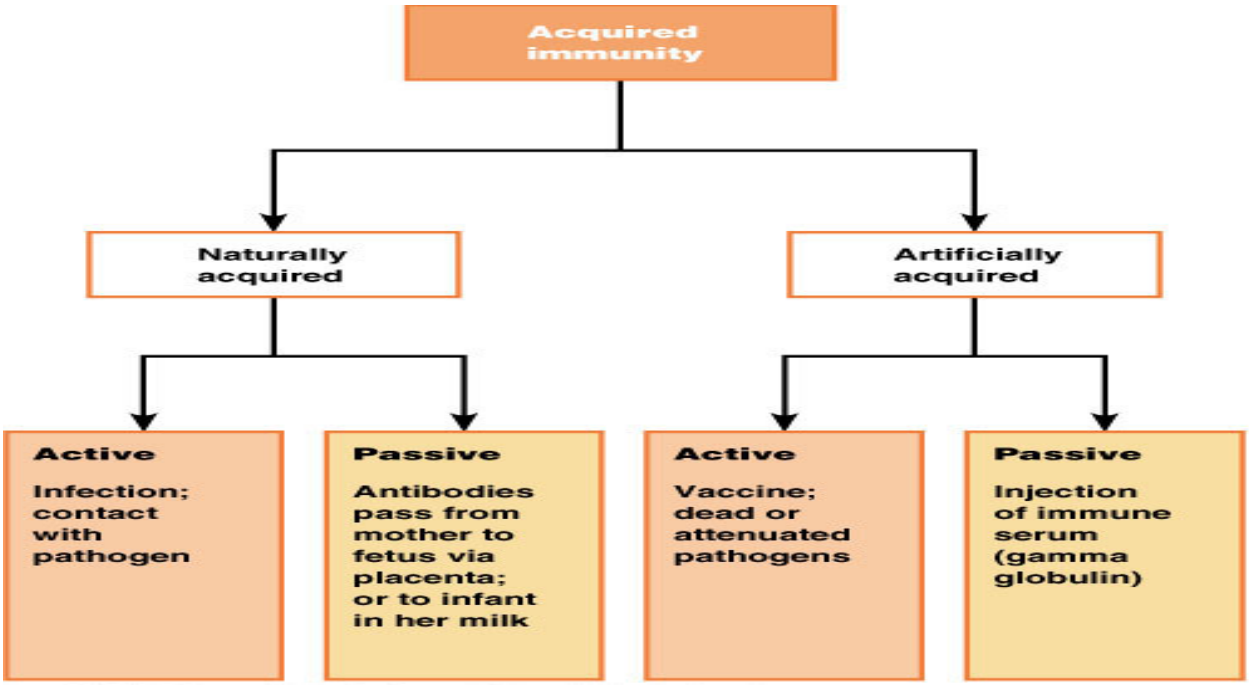
- Immunization- Prophylactic technique of artificially inducing an immune response without exposing the body to infection
    - Developed before essentials of immune function understood
- Vaccine- preparation of harmless antigenic components of microorganisms or of its toxins

Active Humoral Immunity

- B cells encounter antigens and produce antibodies against them
    - Naturally acquired – response to a bacterial or viral infection
    - Artificially acquired – response to a vaccine of dead or attenuated pathogens
- Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive

Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
- Naturally acquired – from the mother to her fetus via the placenta
- Artificially acquired – from the injection of serum, such as gamma globulin



Passive Immunity

- **Passive Immunity-** protection imported in the form of ready-made antibodies from outside the system
    - Short duration- lasts weeks or months
    - Naturally occurring- maternal antibodies transfer to a fetus across placental barrier and through breast milk
    - Artificial- antibodies from sensitized host (e.g. animal) to a non-immune recipient (**antiserum**)

Hypersensitivity vs. Immunological Tolerance

- Immunological Tolerance
    - The body does not generate immune or inflammatory reactions to any of the body's own tissues or to outside substances
- Hypersensitivity
    - There is an exaggerated or inappropriate response to body tissues or outside agents which act as antigens
    - Altered immunologic response to an antigen that results in disease or damage to the host
    - In hypersensitivity, the body is abnormally identifying substances as antigens which it should normally immunologically tolerate.
    - This abnormal, immunologically generated inflammatory reaction, can lead to damage of body tissues.
    - Clinically hypersensitivity gives rise to two categories.
        - Allergies
        - Autoimmune disease

Allergy

- Deleterious effects of hypersensitivity to environmental (exogenous) antigens
- There is an exaggerated inflammatory response to an environmental agent
- An antigen that generates an allergic reaction is called an allergen

Antibodies

- Antibodies are immune proteins which are specifically synthesized to combat a specific antigen
- Antibodies are made of protein molecules called immunoglobulins
    - IgA, IgD, IgE, IgE, IgM
- In an allergy, there is an abnormal antigen-antibody reaction which means the antibodies must be already present in body for the reaction to occur.
    - IE – the patient must have had a previous exposure

Alloimmunity

- Immune reaction to tissues of another individual
- Alloimmunity is the development of reactions to antigens produced by members of the same species.
- The body recognizes them as foreign and attacks them, just like it would if it was exposed to antigens from other organisms. (Friendly fire)
- Alloimmmunity can occur
    - In the recipient after transfusions of fluids such as blood or plasma.
    - In the recipient after allografts (grafts).
    - In the fetus after maternal antibodies have passed through the placenta into the fetus.
        - Hemolytic disease of the newborn
        - Fetomaternal alloimmune thrombocytopenia

Hypersensitivity

- Characterized by the immune mechanism
    - Type I
        - IgE mediated
    - Type II
        - Tissue-specific reactions
    - Type III
        - Immune complex mediated
    - Type IV
        - Cell mediated

Type I Hypersensitivity - Immediate hypersensitivity

- First exposure to antigen produces no noticeable reaction
- Next exposure to antigen- hypersensitive response of mast cells degranulation of histamine
    - **Hives-** degranulation in the skin
    - **Conjuctivitis-** degranulation in eye
    - **Rhinitis-** degranulation in mucous membrane of nasal cavity
- IgE mediated
- Type I reactions usually occur in less than 10 minutes after exposure to the causative allergen.
- Common allergens include molds, animals, foods, dust mites, pollens and some drugs.

Clinical and Pathologic Manifestations

- An immediate hypersensitivity reaction may occur as a systemic disorder or as a local reaction. The nature of the reaction is often determined by the route of antigen
- Without immediate intervention, there may be systemic vasodilation with a fall in blood pressure (anaphylactic shock), and the patient may progress to circulatory collapse and death within minutes.
- Manifestations – localized or systemic
    - Itching
    - Urticaria
    - Conjunctivitis
    - Rhinitis
    - Hypotension
    - Bronchospasm
    - Dysrhythmias
    - GI cramps and malabsorption
    - May also trigger asthma
- Clinical history of symptoms minutes after exposure to antigen
- Genetic predisposition
    - Tests
    - Food challenges
    - Skin tests
    - Laboratory tests

Type 1 – Management Principles

- Avoid exposure to sensitive allergens
    - Every exposure causes potential IgE synthesis , which can make future reactions more serious.
    - Problems encountered with processed foods and cross contamination
- Reactions treated with anti-inflammatory agents
    - Antihistamines and corticosteroids
- Bronchodilators
- Epinephrine

Healthy Dirt

- Early exposure to bacteria seems to increase the ability of the immune system to discriminate between antigens and causes immunological tolerance.
- Childhood exposure to soil bacteria is effective in promoting immunological tolerance
- Children in very clean environments suffer more allergic problems than those who grow up in “normal” levels of bacteria.

Atopy

- Atopy is a tendency to produce IgEs after exposure to everyday allergens.
- A state that makes persons more likely to develop allergic reactions of any type.
- A hereditary disorder marked by the tendency to develop immediate allergic reactions to substances such as pollen, food, dander, and insect venoms and manifested by hay fever, asthma, or similar allergic conditions.
- This is why people with one allergy are more likely to develop another allergy.
- Incidence is 15% of population

Remember Type I = Allergic Antibodies Atopy

Type II Hypersensitivity

- Autoimmune diseases - antibodies attack self-antigens
- Involves IgG and IgM antibodies.
- Antibodies can attack ‘self’ cells and tissues.
    - The presence of the antibodies targets the cell for phagocytosis, which kills body cells.
    - In some cases, antibodies mimic the function if natural chemical transmitters.
- For example in Grave’s disease antibodies are formed and attach to TSH receptors on the thyroid gland
- In Myastenia Gravis, antibodies occupy acetylcholine receptors on the motor end plates which prevents normal muscle stimulation, leading to muscle weakness and paralysis.

Remember Type II = antiBody

Examples of Type II Hypersensitivity

- Autoimmune hemolytic anemia
  - Hemolysis and anemia
- Autoimmune thrombocytopenic anemia
  - Bleeding
- Acute rheumatic fever
  - Myocarditis
- Myasthenia gravis
  - Muscle weakness and paralysis
- Grave's disease
  - Hypothyroidism
- Insulin resistant diabetes
  - Hyperglycemia, ketoacidosis

Type III Hypersensitivity Immune Complex Reactions

- These reactions are caused by the formation of immune complexes which lead to inflammatory changes.
  - An immune complex is a combination of antigens and antibodies which form clumps.
  - Several antigens, viral or bacterial, can be clumped together in the process called agglutination.
  - Once formed these immune complexes become fixed into tissues or can go into the circulation.

Type III Hypersensitivity Immune Complex Reactions

- The reaction can take hours, days, or even weeks to develop, depending on whether or not there is immunlogic memory of the precipitating antigen.
- Typically, clinical features emerge a week following initial antigen challenge, when the deposited immune complexes can precipitate an inflammatory response.
- Antigen-antibody complexes are formed in the circulation and are later deposited in vessel walls or extra-vascular tissues.
- Immune complexes are normally removed from the plasma by phagocytes in the liver and spleen.
- Some of the complexes are not easily removed and are deposited in body tissues or lead to inflammation in the blood vessel walls.
  - Common areas affected are the kidneys, blood vessels, joints, lungs and skin.
- Inflammatory mediators attract neutrophils and monocytes to the area to phagocytize the immune complexes.
- These cells can also damage local cells and tissues. Leading to further tissue injury and inflammation. (Collateral Damage)

Remember Type III = immune Complex

Type IV Hypersensitivity

- Does not involve antibody
- Develops 24-72 hours after exposure
- Examples
  - Acute graft rejection, skin test for TB, contact allergic reactions, and some autoimmune diseases
- Management includes allergen avoidance, corticosteroids and immunosuppressives.
  - Principle mechanism of damage in:
    - Tuberculosis
    - Contact dermatitis
    - Acute or chronic transplant rejections
    - Fungal, viral, and parasitic infections

Remember Type IV = Delayed

T Cell Mediated Hypersensitivity

- Several autoimmune disorders, as well as pathologic reactions to environmental chemicals and persistent microbes, are now known to be caused by T cells.
- Rheumatoid arthritis
  - Chronic arthritis with inflammation, destruction of articular cartilage and bone
- Multiple sclerosis
  - CNS demyelination
- Type 1 Diabetes mellitus
  - Destruction of beta cells of pancreas
- Hashimoto thyroiditis
  - Hypothyroidism
- Inflammatory bowel disease
  - Chronic intestinal inflammation, ulceration, obstruction
- Autoimmune myocarditis
  - Cardiomegaly
- Contact dermatitis

Tissue Transplantation

- Transplant Rejection Tissues vary in their tendency to generate an immune-mediated rejection
  - Expression of major histocompatibility complex (MHCs)
  - *Rapid rejection* if previous contact with specific foreign tissue antigens (transfusion, previous transplantation)
  - *Acute rejection* if MHC incompatibility generates antibodies

Tissue and organ transplants

- The four major types of grafts are:
    - Autografts – graft transplanted from one site on the body to another in the same person
    - Isografts – grafts between identical twins
    - Allografts – transplants between individuals that are not identical twins, but belong to same species
    - Xenografts – grafts taken from another animal species

Transplant rejection times

- Hyperacute – minutes to hours
- Acute – first six months
- Chronic – months to years

Primary Immune Deficiency Syndromes

- Genetically determined
- Passive immunity passed on by mother not replaced by infant's active immune responses
    - **B-cell deficiencies-** recurrent or overwhelming infections by viruses that are normally neutralized by antibody or by bacteria that can resist phagocytosis unless they are opsonized by antibody
    - **T-cell deficiencies-** chronic or recurrent infections from viruses, yeast/fungi, or intracellular bacteria
    - **B and T cell deficiencies-** succumb to opportunistic infections and graft-versus-host disease

Secondary Immune Deficiency Syndromes

- Developed *in utero* or later in life
- Age - thymus function decreases with age→capacity to mount a T-cell response decreases
    - Increased levels of circulating autoantibodies w/ age
- Poor diet- severe caloric or protein malnutrition contributes to impaired T-cell, complement, and neutrophil function
- Extensive burns- general and focal suppression of immune function
- Secondary to other disorders:
    - Diabetes mellitus
    - Malignancies of bone marrow
    - While taking immunosuppressant drugs

Acquired Immune Deficiency Syndromes (AIDS)
Human Immunodeficiency Virus (HIV)

- Reverse transcriptase- integrates into host's DNA and be produced
- Target: Helper-T cells, macrophages, Langerhans cells, and dendrites
- Transmission: sexual contact, direct contamination of blood, mother to fetus during gestation, at birth, or through breast milk
- 10 year lag time between contraction of disease, **seroconversion** (antigenic HIV proteins in the blood), and 'full-blown' AIDS

- **AIDS**- positive HIV test and progression of the disease to the point at which the person has developed opportunistic infections
- **Opportunistic infections-** infection flourishes because of defects or impaired function in an individual's immune system
    - Pneumonia most common cause of death

Autoimmunity

- In health, the immune system protects against infections by reacting against foreign proteins.
- The immune system recognizes "self" and therefore not attack them.
- In autoimmune disease there is a breakdown in the self/non-self recognition system which results in the immune system attacking the bodies own proteins and tissues.
- The body attacks it's own tissues as if they were invading agents which need to be eliminated

Autoimmune Diseases

- Range from organ-specific to systemic
- Best-defined diseases influenced by genetics
- Extremes of autoantibody specificity
    - **Hashimoto's thyroiditis-** organ-specific→ destroy cells of thyroid gland causing goiters
    - **Insulin-dependent diabetes mellitus-** organ-specific→ attack on pancreatic islet cells
    - **Systemic Lupus Erythematosus (SLE)-** systemic→


GLYCOPROTEIN
RHEUMATOID
ACETYLCHOLINE
NEUROPATHY
ISLET
POLYNEUROPATHY
INFLAMMATORY
IMMUNOSUPPRESSION
PURPURA
CIRRHOSIS
PEPTIDE
ACID
HEPATITIS
CUTANEOUS
PLANUS
AUTOIMMUNE
ATTACKS
ANTIBODY
IDIOPATHIC
DISEASE
SYSTEMIC
ARTHRITIS
DEMYELINATING
MYOSITIS
ENCEPHALITIS
DERMATITIS
NEPHROPATHY
DERANGEMENTS
URTICARIA
UVEITIS
GLUTAMIC
LUPUS
STREPTOCOCCAL
ENDOTHELIUM
AUTOIMMUNE
EDS
CELL
DISORDER
BILIARY
FACTOR
COMPONENT
ENCEPHALOPATHY