Resistance of the Body to Infection

2. *Leukocytes, Granulocytes, the Monocyte-Macrophage System, and Inflammation*

1. Innate immunity *(overview)*

- **Immunity**: the ability of the body to resist almost any **harmful organisms** or **toxins**.

1. Innate immunity
2. Acquired immunity

Innate immunity	Acquired (adaptive, active) immunity
Non specific	**Specific** against individual invaders
General process	Directed process
Many components	Limited components
Do not require previous exposure	Require previous exposure
Immediately evoked	Require **weeks** or months to develop
Participants 1. *Phagocytes – neutrophils and macrophages* 2. *Acid and digestive enzymes of the stomach* 3. *Skin barrier* 4. *Lysozymes, basic polypeptides, complement complex* 5. *Natural killer lymphocytes*	**Participants** 1. *Activated lymphocytes (cellular immunity – by T-lymphocytes)* 2. *Antibodies (humoral immunity by B-lymphocytes)*

(1) *Lysozyme,* a mucolytic polysaccharide that attacks bacteria and causes them to dissolute;
(2) *Basic polypeptides,* which react with and inactivate certain types of gram-positive bacteria;
(3) The *complement complex* that is described later, a system of about 20 proteins that can be activated in various ways to destroy bacteria;
(4) *Natural killer lymphocytes* that can recognize and destroy foreign cells, tumor cells, and even some infected cells.

- This innate immunity makes the human body resistant to such diseases as some paralytic viral infections of animals, hog cholera, cattle plague, and distemper—a viral disease that kills a large percentage of dogs that become afflicted with it.
- Conversely, many animals are resistant or even immune to many human diseases, such as poliomyelitis, mumps, human cholera, measles, and syphilis, which are very damaging or even lethal to human beings.

2. Acquired (Adaptive, Active) Immunity

- Acquired immunity can often bestow (give) an extreme degree of protection
- Immunization can protect against as the paralytic botulinum toxin or the tetanizing toxin of tetanus, in doses as high as 100,000 times the amount that would be lethal without immunity.
- Immunization is so important in protecting human beings against disease and against toxins.

Basic Types of Acquired Immunity–Humoral and Cell Mediated

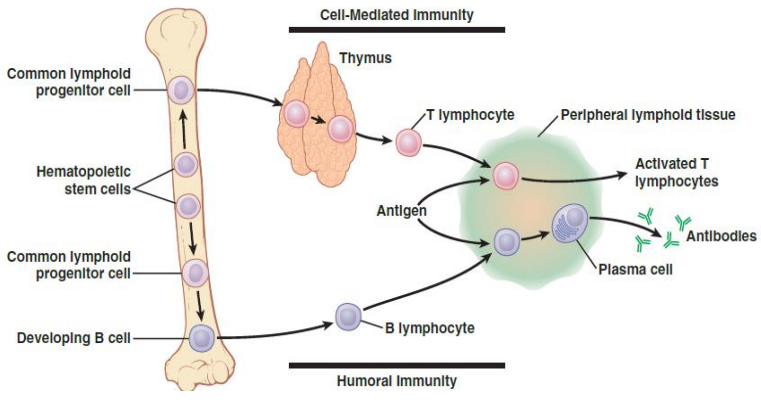
Character	T lymphocytes	B lymphocytes
Microscopic appearance	Small size, clear cytoplasm, large round nucleus	Small size, clear cytoplasm, large round nucleus
Responsibility (function)	Cell-mediated immunity	Humoral immunity
Lymphoid origin	Bone marrow stem cells	Bone marrow stem cells
Preprocessing, differentiation, maturation	Thymus	Bone marrow (liver in mid-fetal life)
Residence	Lymphoid tissue	Lymphoid tissue
Naming	Thymus in animals	Bursa of Fabricius in birds

- T & B lymphocytes developed from common lymphoid progenitor cells

Lymphocytes are Responsible for Acquired Immunity

- The lymphocytes are essential to the survival of the human being. How that?
- Genetic lack of lymphocytes or lymphocytes destruction by radiation or chemicals results in no acquired immunity and death within days (due fulminating bacterial infection unless treated by heroic measures)
- **Lymphocytes location**
  - Most extensively in the lymph nodes
  - Also in special lymphoid tissues (spleen, submucosal areas of GIT, thymus, and bone marrow)
- **Area of fighting**
- The invading agent first enters the tissue fluids and then is carried by lymph vessels to the lymph node or other lymphoid tissue.
- The lymphoid tissue is distributed in the body to intercept invading organisms or toxins before they can spread too widely.

Invader (antigen) entry	Lymphoid tissue
Gut (contaminated food)	GI wall
Upper respiratory tract	Throat and pharynx (tonsils and adenoids)
Peripheral tissues	Lymph nodes
Reaching the blood	Spleen, thymus, and bone marrow



Both Types of Acquired Immunity are initiated by Antigens

- Acquired immunity **does not develop** until after invasion by a foreign organism or toxin
- Antigens initiate the acquired immunity.
- Mechanism:
  - Each toxin or each type of organism contains one or more specific chemical compounds in its makeup called Antigens (antibody generations protein or large polysaccharides)
  - Antigens are differing from all other compounds (natural body cpds or other foreign cpds).

Antigenicity		
Molecular weight	≥ 8000 Dalton	Large polysaccharide; protein
Epitopes	Regularly recurring molecular groups of large surface molecules	Large polysaccharide; protein

Preprocessing of the T and B Lymphocytes

- Lymphocyte-committed stem cells → further differentiated in appropriate processing areas → cells that are capable of forming directly either activated T lymphocytes or antibodies.

The Thymus Gland Preprocesses the T Lymphocytes.

- Lymphoid progenitor cells first migrate from bone marrow to the thymus gland and there:
  - **Divide rapidly**
  - Develop extreme reactive diversity (**clonal selection**).
  - Avoid self-reactivity (**clonal deletion**)
  - **Released** in to the blood and circulate in the body and lodge in lymphoid tissues

- **Reactive diversity (clonal selection):**
  - Means: one thymic lymphocyte develops specific reactivity against one antigen. **Another** lymphocyte develops specificity against **another** antigen
  - Continues: processing continue until there are 1000s of different types of thymic lymphocytes with specific reactivities against 1000s of different antigens

- **Avoid self-reactivity (clonal deletion)**
  - The thymus ensures that any released T lymphocytes would not react against body's own tissues proteins or antigens that are present in.
  - Mechanism:
    - ✓ Thymus first **mixing** processed T-lymphocytes with virtually all the specific "**self-antigens**" from the body's own tissues.
    - ✓ **Non-reactive** T-lymphocytes would be released **(90%).**
    - ✓ **Self-reactive** T-lymphocytes would be **destroyed** "apoptosis) and **phagocytized** (10%) - otherwise → autoimmunity → lethal in only a few days.

- Active lymphocytes are nonreactive against the body's own antigens; **but**, **react** against **foreign** antigens (from a **bacterium**, a **toxin**, or even **transplanted** tissue from another person).
- Preprocessing in the thymus occurs shortly before birth of a baby and for a few months after birth.
- Beyond birth, removal of the thymus gland diminishes (but does not eliminate) the T-lymphocytic immune system (cellular immunity).
- Cellular immunity mainly responsible for rejection of transplanted organs
- Removal of the thymus several months before birth can prevent development of all cell-mediated immunity and transplant rejection.

Liver and Bone Marrow Preprocess the B Lymphocytes

Parameter	B lymphocyte	T lymphocyte
Differentiation	Bone marrow (liver during mid fetal life)	Thymus
Reactivity	Non-reactive	Reactive
Function	Secrete antibodies	Whole cell reactivity against antigen
Diversity	Millions of different antibodies	Thousands of different active cells

- *[Antibodies are large proteins that are capable of combining with and destroying the antigenic substance]*
- *[B lymphocytes form many millions of types of antibodies with different specific reactivities]*
- Processed B lymphocytes (like the T lymphocytes) migrate to lymphoid tissue throughout the body, where they lodge near but slightly removed from the T-lymphocyte areas.

T-Lymphocytes and B-Lymphocyte Antibodies React Highly Specifically Against Specific Antigens–Role of Lymphocyte Clones

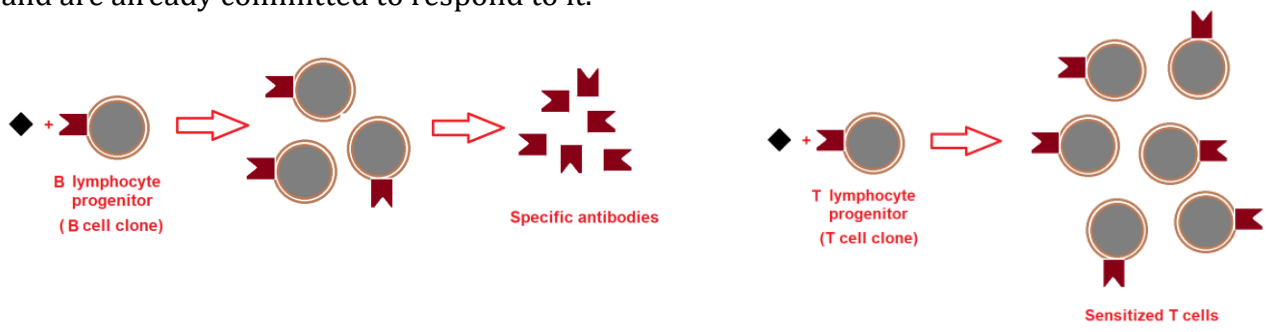
- In lymphoid tissue:
  - Millions processed (preformed) B and T lymphocytes are stored in the lymph tissue.
  - Each has **antigen specificity** (called **clone**)
  - Lymphocyte clone are alike and are derived originally from specific type.
  - When specific antigens come in contact with **preformed** T and B lymphocytes they are **activated**.
- The clones then released into the blood → circulated through all the tissue fluids → back into the lymph *[sometimes circulating in this circuit for months or years]*.

Mechanism for Activating a Clone of Lymphocytes

- Each clone of lymphocyte has surface protein (receptor, TCR or BCR)
  - On B-lymphocyte "BCR" it is the antibody molecule, about 100,000 on each cell

On T-lymphocyte "TCR" it is the surface receptor protein (T-cell marker, or T-cell receptor), one for each antigen (count: 100,000 receptor sites on a single T cell)

- Each receptor reacts specifically with a single type of antigen (or to several similar antigens that have almost exactly the same stereochemical characteristics) causing cell activation.
- An antigen therefore stimulates only those cells that have complementary receptors for the antigen and are already committed to respond to it.

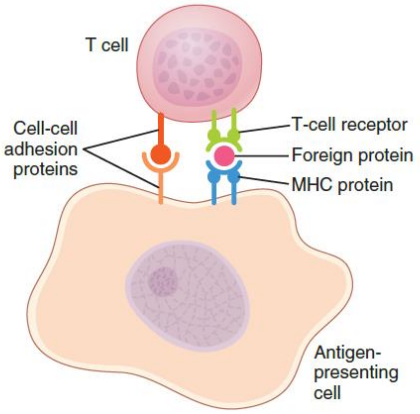


Origin of the Many Clones of Lymphocytes

- **Stem** cells "Common lymphoid progenitor" **do not have the whole gene**, but; have "gene segments" for forming T- lymphocytes or B-lymphocytes.
- Several 100s types of gene segments can be **mixed randomly during processing** in lymphoid tissue
- The whole gene then **reformed** by such random mixing "**millions of combinations**"
- The mature cells become highly specific that spread to and populate the lymphoid tissue.
- Thus, several 100s to a few 1000s genes code for the millions of different types of antibodies (B lymphocytes) and active T lymphocytes.

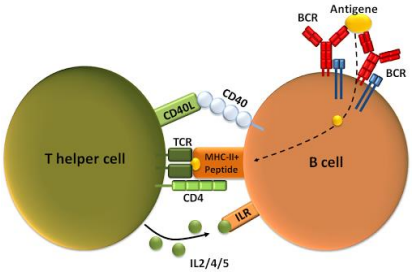
Role of Macrophages in the Activation Process

- Macrophage causes activation of specified lymphocytic clones. How it doing that?
- Lymphoid tissue sinusoids (lymph nodes, spleen and others) lined by millions of lymphocytes and macrophages (in the same site "in apposition")
- Invading organisms are first phagocytized and partially digested by the macrophages
- The antigenic products are liberated into the macrophage cytosol and presented to lymphocyte (hence macrophages called antigen presenting cells "APC")
- Clone of lymphocytes with the complementary receptor for the antigen on APC are activated (cell-to-cell contact)
- **Macrophages also secrete interleukin-1 "IL-1" that**:
  (1) Activation of lymphocytes
  (2) Growth and reproduction of new specific lymphocytes.



Role of the T Cells in Activation of the B Cells

- Most antigens activate **both** T lymphocytes and B lymphocytes at the same time.
- Types of T cells: (**1**) Cytotoxic cells "$CD8^+$" (**2**) T-helper cells "$CD4^+$" (**3**) T-suppressor cells
- T-helper cells secrete lymphokines that activate the specific B lymphocytes.
- **Without** the aid of these T-helper cells, the quantity of antibodies formed by the B lymphocytes is usually slight.

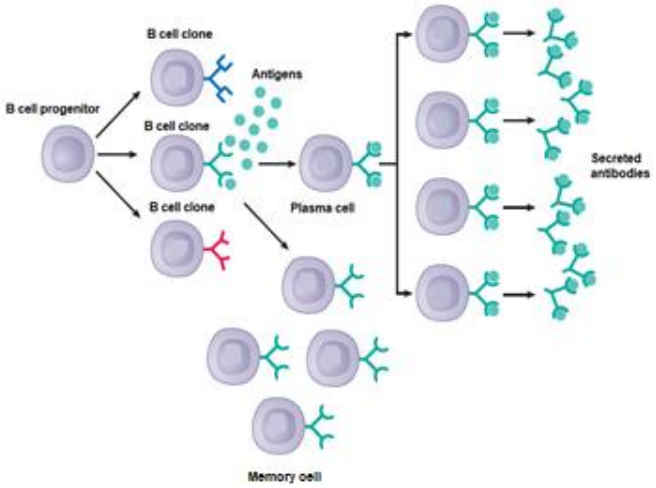


Specific Attributes of the B-Lymphocyte System (Humoral Immunity and the Antibodies)

Formation of Antibodies by Plasma Cells

- Before exposure to a specific antigen, B lymphocytes clones remain dormant in lymphoid tissue.
- When foreign antigen enter the body

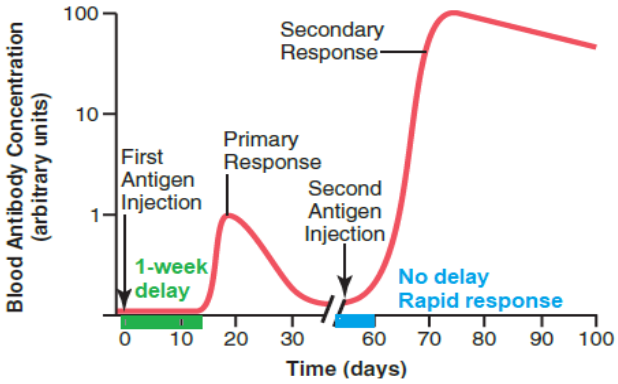
1) **APC**: **phagocytize**, **processes** and **present** to B and T cell
2) **Active T-helper**: activate B cells
3) **Specific active B cell clone**: enlarges to become **lymphoblasts**.
4) **<u>Some</u> B lymphoblasts**: differentiate to plasmablasts
5) **<u>Some</u> <u>other</u> B lymphoblasts:** differentiate to memory cells



- **Plasmablasts_(precursor of plasma cells)**
  - Cytoplasm expands
  - Rough endoplasmic reticulum vastly proliferates.
  - Begin to divide [at a rate of about once /10 hours for about 9 divisions for 4days → giving 500 cells for each original plasmablasts].
  - Maturate to **plasma cell** and **produces gamma globulin antibodies** [at an extremely rapid rate - about 2000 molecules/sec for each plasma cell] giving the **primary response**.
- The antibodies are secreted into the lymph and carried to the circulating blood.
- This process continues for several days or weeks until finally exhaustion and death of the plasma cells occur.

Formation of "Memory" Cells Enhances the Antibody Response to Subsequent Antigen Exposure

- Memory cells also circulate throughout the body and they remain immunologically dormant until activated by subsequent exposure to the same antigen.
- During subsequent exposure to the same antigen, a more rapid and much more potent antibody response "**secondary response**" occurs (why?)
  [Answer: because there are many more memory cells than the original B lymphocytes of the specific clone]
- **The primary response**:
  - 1-week delay; weak potency; short lived antibody _few weeks.
- **The secondary response**:
  - Rapid within house; more potency; long lived antibody _many months.
- The increased potency and duration of the secondary response explain why immunization is usually accomplished by injecting antigen in multiple doses with periods of several weeks or several months between injections.

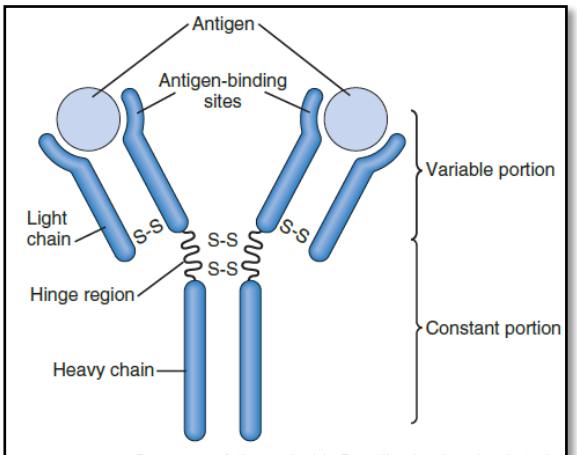


Time course of the antibody response in the circulating blood to a primary injection of antigen and to a secondary injection several weeks later.

Nature of the Antibodies

- Antibodies are gamma globulins called immunoglobulins (Ig)
- Molecular weights between 160,000 and 970,000
- Constitute about 20% of all the plasma proteins.
- All the Igs are composed of combinations of **light** and **heavy** polypeptide chains.
- Most are a combination of 2 light and 2 heavy chains (**bivalent** antibodies)
- Some are a combination of 10 light and 10 heavy chains (**Decavalent** antibodies)
  [Each (1) heavy chain is paralleled by (1) light chain at one of its ends [forming a heavy-light pair]

- **Variable portion**:
  - **Different** for each specific antibody
  - Attaches specifically to a particular type of **antigen**
- **Constant portion**:
  - Determines **biological properties** of the antibody like:
    - ✓ Membrane diffusivity
    - ✓ Adherence to tissue
    - ✓ Attachment to the complement complex
    - ✓ Ease of pass through membranes
- A combination of noncovalent and covalent bonds (**disulfide**) holds the light and heavy chains together.



Structure of the typical IgG antibody, showing it to be composed of two heavy polypeptide chains and two light polypeptide chains. The antigen binds at two different sites on the variable portions of the chains.

Specificity of Antibodies

- Each antibody is **specific** for a particular **antigen**
- Specificity is due to the **unique structural** organization of amino acids in the **variable** portions of both the **light** and **heavy** chains.
- The amino acid organization has a different steric shape for each antigen specificity
- So when an antigen comes in **contact** with antibody, **multiple prosthetic groups** of the antigen fit with those of the antibody
- This allows rapid and tight **bonding** between the antibody and the antigen.
- When the antibody is highly specific, many **bonding** sites make antibody-antigen coupling is exceedingly strong, held together by (1) hydrophobic bonding, (2) hydrogen bonding, (3) ionic attractions, and (4) van der Waals forces. Binding is reversible. It also follows the thermodynamic mass action law.
- Bivalent antibody has 2 binding sites (on each light chain)
- Decavalent antibody, have as many as 10 binding sites.

Five General Classes of Antibodies (IgM, IgG, IgA, IgD, and IgE.)

Antibody class	Valence	% from normal total antibodies	Response
IgG	Bivalent	75%	Secondary immune reaction
IgE	Bivalent	a small percentage	Allergy
IgM	Decavalent	Very small	Primary immune reaction *[exceedingly effective in protecting]*

Mechanisms of Action of Antibodies

- Antibodies act mainly in two ways
  (1) by direct attack on the invader (insufficient protection)
  (2) by activation of the "complement system" (Most potent protection)

Direct Action of Antibodies on Invading Agents

- Antibody is a specific receptor for specific antigen
- Invader surface has multiple antigenic sites
- The antibodies can inactivate the invading agent in one of several ways:

Inactivating way	Mechanism	Example of antigen	Result
Agglutination	Antigen crosslink	On RBCs or bacteria surface	Clumping
Precipitation	antigen-antibody complex	Soluble tetanus toxin	Precipitate
Neutralization	Covering toxic sites of an antigen	diphtheria toxin	Inactivation
Lysis	Direct cell membrane attack	Malaria	Cell rupture

- These direct actions of antibodies often are **not strong enough** to play a major role in protecting the body against the invader.
- **Most of the protection** comes through the amplifying effects of the **complement system**

COMPLEMENT SYSTEM FOR ANTIBODY ACTION *(overview)*

Background

- 20 blood proteins collectively term "complement system"
- Many of them are enzyme precursors (i.e.; normally inactive)
- The principal actors in this system are 11 proteins designated C1 → C9, B, and D
- Found in plasma and may leak into the tissue during inflammation

Classical activation pathway

- Antigen-antibody reaction → uncover the specific reactive site on the "constant" portion of the antibody → antibody binds directly with the proenzyme C1a → enzyme C1b → initiate cascade of sequential reactions → "amplified" reaction.

[Note: the letter "a" denote inactive form or proenzyme; while the letter "b" denote the active form or enzyme]

Role of complements in immunity

- Active complements prevent pathogen or toxin damage to the body's tissues
- Among the more important effects are the following:

Effect	Mechanism	Result
Opsonization	C3a → C3b; C3b attach Ag-Ab	**Phagocytosis**
Lysis	C5b6789	Cell rupture; bursting
Agglutination	change the surfaces of large antigen	Large antigens adhere to one another (clump)
Neutralization	attack the structures of some virulent viruses (influenza)	Nonvirulent viruses
Chemotaxis	C5a migrate neutrophils and macrophages	Enhance phagocytosis
Inflammation	C3a, C4a, C5a activate mast cells and basophils activation	Congestion; exudation; walling-off; inactivate or immobilize antigens

SPECIAL ATTRIBUTES OF THE T-LYMPHOCYTE SYSTEM—ACTIVATED T CELLS AND CELL-MEDIATED IMMUNITY *(overview)*

Release of Activated T Cells from Lymphoid Tissue and Formation of Memory Cells

- Before exposure to a specific antigen, T lymphocytes clones remain dormant in lymphoid tissue.
- When foreign antigen enter the body

1) **APC**: **phagocytize**, **processes** and **present** to T and B cell
2) **Active T-helper**: activate T cells
3) **Specific active T cell clone**: enlarges to become **lymphoblasts**.
4) **Some T lymphoblasts**: differentiate to active T cells
5) **Some other T lymphoblasts:** differentiate to memory cells

[These T cells then circulate between body tissues and blood, sometimes lasting for months or even years]

- On subsequent exposure to the same antigen anywhere in the body, release of activated T cells occurs more rapidly and much more powerfully than during first exposure *[in the same way that antibodies are released by B-cells]*

Antigen-Presenting Cells (APC), MHC Proteins, and Antigen Receptors on the T Lymphocytes

- T-cell responses are extremely antigen specific *[like the antibody responses of B cells]*
- Acquired immune responses **require assistance from T cells to begin the process**
  [T cells play a major role in helping to eliminate invading pathogens]
- In lymphoid tissue:
  - B lymphocytes recognize intact antigens
  - T lymphocytes respond "Activated" to antigens only when they are bound to MHC proteins on the surface of APC in lymphoid tissue.
- 3 type of APC *(1) Macrophages, (2) B lymphocytes, and (3) Dendritic cells*
- Steps of antigen presentation
  - APC engulf the invader, digest it and the digested fragments bounded to MHC and the complex presented on the surface of APC
- T cell recognition
  - Specific T-cell receptor bound to antigen on APC (similar to binding of antibody to antigen)
  - Cell adhesion proteins (another surface protein on both T cell and APC) **long lasting the binding** for full activation of T cells
- Two types of MHC proteins
  (1) MHC I proteins, which present antigens to cytotoxic T cells
  (2) MHC II proteins, which present antigens to T-helper cells
- T cell receptor composed of a **variable** portion and **constant** portion *(like antibody from B cell)*
- Constant portion (also called *the stem section*) is firmly **bound to the cell membrane of the T** lymphocyte (count: 100,000 receptor on a single T cell)

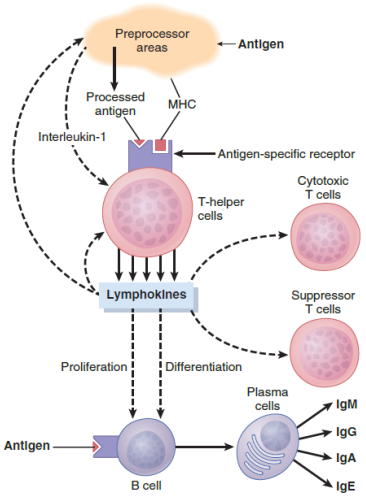
- Dendritic cells:
  - The most potent of the APCs
  - Located throughout the body
  - Function to present antigens to T cells

SEVERAL TYPES OF T CELLS AND THEIR DIFFERENT FUNCTIONS

- 3 major groups: *(1) T-helper cells*, *(2) cytotoxic T cells* and *(3) suppressor T cells*
- The functions of each of these T cells are distinct

T-Helper Cells are the most numerous of the T Cells

- **Count**: The most numerous of the T cells (constituting > ¾ of T cells)
- **Function**: Regulatory cells *[help in many ways the functions of the immune system]*
- **Mechanism**: Secrete lymphokines (protein mediators) that majorly regulate all immune functions
- **Targets**: Lymphokines act on **other cells of the immune system** and on **bone marrow cells**.
- The most important lymphokines secreted by the T-helper cells are:
  (1) Interleukins (IL-2 →IL-6),
  (2) Granulocyte-monocyte colony-stimulating factor
  (3) Interferon-γ



Specific Regulatory Functions of the Lymphokines

- Without T-helper lymphokines the immune system is almost paralyzed
  HIV *(human immunodeficiency virus)* inactivates or destroys T-helper cells → debilitating and lethal effects of AIDS *[AIDS = acquired immunodeficiency syndrome]*

Regulated cell	Lymphokines	Proliferation	Growth (differentiation)	Activation	Function
Cytotoxic T-Cells	IL-2	+	+	+	Direct attack
Suppressor T-Cells	IL-2	+	+	+	Suppress T-helper and cytotoxic T cells
B-Cell	IL-4, -5, -6	+	+	+	Antibody formation
Macrophage				Prevent escape from infected area	More efficient phagocytosis

- *Absence of T-helper cells causes slight growth, proliferation and activation of cytotoxic T cells, suppressor T cells and B-cell clones]*
- *T-helper cells slow or stop the migration of the macrophages after they have been chemotactically attracted into the inflamed tissue area*

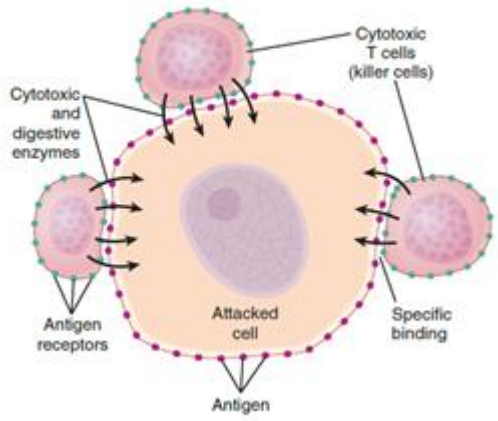
Feedback Stimulatory Effect on the T-Helper Cells

- IL-2 has direct (+ve) feedback effect in stimulating activation of the T-helper cells.
- IL-2 acts as an amplifier by further enhancing the **helper cell response**, as well as the entire immune response to an invading antigen

Cytotoxic T Cells Are "Killer" Cells

- The cytotoxic T cell "killer cells" directly attack foreign antigens
- Foreign antigen could be:
  (1) Whole bacteria
  (2) Body cell infected with virus
  [Virus particles become entrapped in the membranes of the tissue cells]
  (3) Cancer cell
  (4) Transplants
  (5) Natural body cell (in autoimmune disease)

- Killing Mechanism
  - **TCR binds** tightly to the **antigen** (whole organism or cell holding the antigen)
  - T cell secretes **perforin** (a hole-forming proteins) → **punch round holes** in the membrane of the attacked cell → **rapid influx** of **interstitial fluid** into the cell → **cell swell**, **burst** and **dissolves**
  - After making a whole, T cells **pull away** from the victim cells and then move on **to kill more cells**
- Life span: months



Suppressor T Cells

- They are **regulatory T cells**
- **Suppress** the functions of both **cytotoxic** and **T-helper** cells
- **Prevent cytotoxic cells** from causing **excessive immune reactions** that might be damaging to the body's own tissues.
- Plays an important role in *immune tolerance* ***[limiting the ability of the immune system to attack a person's own body tissues]***
- Failure of the tolerance mechanism causes **autoimmune** diseases like:

- *Rheumatic fever*
- *Glomerulonephritis*
- *Myasthenia gravis*
- *Systemic lupus erythematosus (SLE)*

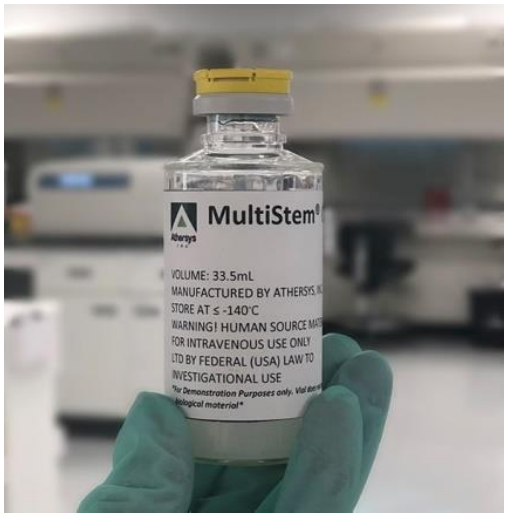
IMMUNIZATION BY INJECTION OF ANTIGENS

- Immunization: exposure to antigen (infection or injection) produce specific acquired immunity
- A person can be immunized by:
- Injecting dead organisms *[no longer capable of causing disease; still have antigenicity]*
- Injection of chemically inactivated toxins *[no longer toxic; still have antigenicity]*
- Injection with live organisms *[attenuated, mutated, lose infectious nature; still have antigenicity*
  Attenuation means:
  - *These organisms either cultured in vitro "in culture media" or in vivo "in animals"*
  - *They are subjected to mutations losing their infectious nature but still have antigenicity*

Injection of	Immunization against "example"
Dead organism	Typhoid fever, whooping cough, diphtheria
Chemically inactivated toxin	tetanus, botulism
Attenuated live organism	smallpox, yellow fever, poliomyelitis, measles

PASSIVE IMMUNITY

- Acquired immunity = active immunity *[can be achieved with injecting an antigen]*
- Temporary immunity = passive immunity *[can be achieved without injecting any antigen]*
- Passive immunity is achieved by **infusing antibodies**, **activated T cells**, or **both**.
- Source "**Donor**": Human or animal blood *[those actively immunized against the antigen]*
- Life span in **recipient** body:
  - Antibodies give protection for **2-3 weeks** against the invading disease.
  - Activated T cells give protection for a few weeks "**human source**" and for **few hours** "animal source"



3. ALLERGY AND HYPERSENSITIVITY

- Means: **undesirable** side effect of immunity
- Occurrence: only in people who have a specific allergic **tendency**.

ALLERGY CAUSED BY ACTIVATED T CELLS: DELAYED-REACTION ALLERGY

- Delayed-reaction allergy is caused by activated T cells and **not by antibodies**.
  Example: (1) skin allergy from ivy poison or (2) lung allergy from airborne antigens
- Ivy poison itself does not harm the tissues
- Upon **repeated** exposure → activate **helper** and c**ytotoxic** T cells.
- After subsequent exposure (within a day) → activated T cells diffuse from blood to the skin (elicit local cell-mediated immune reaction *"where the instigating "promoting" antigen is present"*) → release toxic substances with invasion of macrophages → serious tissue damage

"ATOPIC" ALLERGIES ASSOCIATED WITH EXCESS IgE ANTIBODIES

- Means: Non-ordinary response of the immune system
- Occurrence: in some people have an "allergic" **tendency**
- Heredity: Allergic tendency is genetically passed from **parent to child**
- Antibody: large quantities of **IgE** in blood *[IgE also called reagins or sensitizing antibodies to distinguish from IgG]*
- Allergen: an antigen that **reacts specifically** with a specific type of IgE reagin antibody
- Mechanism:
  - When allergen "Ag" enters the body it reacts with reagin "Ab" → an allergen-reagin (Ag-Ab) complex → membrane damage of mast cells and basophils → cell rupture → release of chemical mediators → local allergic reaction manifestation
    [IgE has strong propensity "affinity" to attach to mast cells and basophils. Single mast cell or basophil can bind a **half million molecules** *of IgE, IgE is divalent antibody]*
  - Chemical mediators:
    (1) Histamine
    (2) Protease
    (3) Slow-reacting substance of anaphylaxis (a mixture of toxic leukotrienes)
    (4) Eosinophil chemotactic substance
    (5) Neutrophil chemotactic substance
    (6) Heparin
    (7) Platelet activating factors
  - Local allergic reaction manifestation: Vasodilation, fluid exudation (increase capillary permeability), eosinophil and neutrophil attraction and local smooth muscle contraction.

Several different tissue responses can occur, depending on the type of tissue involved

Anaphylaxis:

- Means: a widespread allergic vascular response to allergen
- Mechanism:

(1) Role of histamine:

- ✓ Direct blood injection of allergen → the *"Ag"* react with IgE *"Ab"* from previously sensitized basophils (in blood) and mast cells (in the tissues) →histamine release → body-wide vasodilation *(dilate small and large blood vessels)*, fluid exudation *(increase capillary permeability)*, hypotension *(low plasma volume)* → circulatory shock → death within a few minutes unless treated with epinephrine *"vasoconstrictor"* to oppose *"antagonize"* the effects of the histamine

(2) Role of slow-reacting substance of anaphylaxis

- ✓ Activated basophils and mast cells also release slow-reacting substance of anaphylaxis → smooth muscle spasm in the bronchioles → bronchospasm → asthma-like attack → suffocation and possible death

Urticaria

- Means: localized anaphylactoid reactions due to an antigen entering specific skin areas.
- Mechanism:
  - ✓ Local histamine release → (1) vasodilation "immediate skin redness" and (2) fluid exudation "local increase in capillary permeability" with subsequent local skin swelling "hives" within another few minutes
- Prophylaxis: administration of antihistamine drugs to a person before exposure will prevent the hives.

Hay Fever

- Means: local allergen-reagin in the nose.
- Mechanism:
  - ✓ Local histamine release → (1) local intranasal vasodilation and (2) fluid exudation "local increase in capillary pressure and permeability "rhinorrhea" with subsequent local skin swelling "hives" within another few minutes
    [Rhinorrhea: rapid fluid leakage into the nasal cavities and into associated deeper tissues of the nose, and the nasal linings become swollen and secretory]
- Prognosis: Removal of the reactive products of the allergic reaction attenuate the reaction
- Management: antihistamine drugs can prevent swelling reaction; but, other products of the allergen-reagin reaction can still cause irritation of the nose "sneezing syndrome"

Asthma

- Means: Sever allergic narrowing of bronchioles
- Mechanism:
  - ✓ Air-born allergens enter the lung → bronchial allergen-reagin reaction → release of the slow-reacting substance of anaphylaxis *(a mixture of three leukotrienes)* from mast cell →bronchospasm → difficult breathing
- Prognosis: Removal of the reactive products of the allergic reaction attenuate the reaction
- Management: Administration of antihistamine medication has less effect on the course of asthma because histamine does not appear to be the major factor eliciting the asthmatic reaction.