Immunology Lecture to Resume

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Part 1: Generality
a Bacteria invade.  

b Substances accumulate.  

c The substances make plasma and proteins escape.  

d Plasma proteins attack bacteria, phagocytes, or repair damage.  

e Phagocytes engulf bacteria.
The Invaders . . .

- Bacteria
- Viruses
- Parasites such as fungi, protista, & worms

http://www.sdnhm.org/exhibits/epidemic/teachers/background.html
THREE "LIMBS" OF THE IMMUNE RESPONSE

Antigen

Ag/Ab complexes

Complement

Killing of bacteria

Inflammation

Inactivation of viruses

Allergy

ABO & Rh

Antigen processing (dendritic cells, MΦ et al.)

Antigen-specific triggering

Antigen "presentation"

APC

B

T

Proliferation

Differentiation

AFC

ANTIBODY

AUTOIMMUNITY

T-CELL FUNCTIONS

T<sub>0</sub>
T-cell killing: virus-infected cells, transplants

Mixed Lymphocyte Reaction (MLR)

 Delayed type hypersensitivity, (DTH); e.g. tuberculin reaction

T<sub>reg</sub>
Tolerance, suppression

TH<sub>2</sub>
T-cell "help"

TH<sub>1</sub>
Immunity: Two Intrinsic Defense Systems

- Innate (nonspecific) system responds quickly and consists of:
  - **First line of defense** - skin and mucosa prevent entry of microorganisms
    - **Second line of defense** - antimicrobial proteins, phagocytes, and other cells
      - Inhibit spread of invaders throughout the body
      - Inflammation is its most important mechanism

- Adaptive (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
Innate and Adaptive Defenses

(a) Innate defenses
- Surface barriers
  - Skin
  - Mucous membranes
- Internal defenses
  - Phagocytes
  - Fever
  - NK cells
  - Antimicrobial proteins
  - Inflammation

(b) Adaptive defenses
- Humoral immunity
  - B cells
- Cellular immunity
  - T cells
# Outline of the Immune System

## Innate Immunity

1st Line of Defense
- Skin
- Mucus
- Secretions
- Phagocytic Cells
- Antimicrobial Proteins

2nd Line of Defense
- Other tissues which participate in inflammatory responses

## Adaptive Immunity

3rd Line of Defense
- Lymphocytes
- Antibodies
- Attenuated Viruses

## Acquired Immunity

Vaccines / Immunotherapies
- Killed Viruses
- Toxoid Vaccines
- Component Vaccines
Mechanical, Physical and Chemical Barriers

What are the examples of Physiologic and Chemical Barriers at the skin and mucous membranes?

Acid pH -- this also relates to the stomach

Hydrolytic enzymes  Proteolytic enzymes

Interferon refers to a group of proteins that can help prevent the spread of viruses. There is one special one called gamma interferon -- this one is a cytokine produced by $T_H$ cells. Complement is a term that refers to a group of serum proteins that are normally found "inactive" in the serum.

Antibody-antigen reactions and the cell walls of certain microorganisms can "activate" complement. When this happens the active components can destroy cells in the area of complement activation.

Mucous producing membrane together with cilia help eliminate organisms = mucociliary escalator
**Surface Barriers**

- Skin, mucous membranes, and their secretions make up the first line of defense.

- Keratin in the skin:
  - Presents a physical barrier to most microorganisms.
  - Is resistant to weak acids and bases, bacterial enzymes, and toxins.

- Mucosae provide similar mechanical barriers.
Skin -

- **Tough**, no bacteria can penetrate unaided.
- **Dry** (most skin infections take place in the wetter areas).
- **Acid** (approximately pH 5), Low temperature, Skin cells are constantly shedding, high salt content.
- **Lysozyme** in the pores
- **Resident microflora**
- Skin Associated Lymphoid Tissue
Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
  - **Skin acidity** (pH of 3 to 5) inhibits bacterial growth
  - **Sebum** contains chemicals toxic to bacteria
  - **Stomach mucosae** secrete concentrated HCl and protein-digesting enzymes
  - **Saliva and lacrimal fluid** contain lysozyme
  - **Mucus** traps microorganisms that enter the digestive and respiratory systems
Mucous Epithelia

- GI
- Respiratory
- Urogenital
- Eyes

- These areas are warm and wet. They are sites of secretion and/or absorption and therefore cannot be thick like the skin.

mucus - contains polysaccharides and proteins which trap organisms. Ciliated cells and peristalsis and cough reflex moves trapped organisms out. (ie: Muco-ciliary escalator in the lungs)

Lots of lysozyme and lactoferrin (an enzyme that binds iron and keeps it away from microorganisms).
Respiratory Tract Mucosae

- **Mucus-coated hairs in the nose** trap inhaled particles.
- **Mucosa of the upper respiratory tract** is ciliated.
  - Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages.
Attributes of Selected areas

- **Mouth** - rich resident normal flora -- these help to keep the bad guys out.
- **Lungs** - sterile if not compromised. Otherwise this is a vulnerable area. If organisms get down into the alveolar area they have easy access to the blood. Mucociliary escalator is very important.
- **Stomach** - Low pH is an important barrier.
- **Small Intestine** - Paneth cells in the crypts produce lysozyme and defensins (these are small proteins which inhibit bacterial growth).
- **Urethra** - flow of urine important.
- **Female Genitalia** - microflora very important. Mucus plug in the cervix important in preventing movement of microbes into the uterus.
Complex Biological Responses of Innate Immunity

Complex biological responses include:

- Phagocytosis
- Complement Activation
- Inflammation and Fever
- Interferon
<table>
<thead>
<tr>
<th>CATEGORY/ASSOCIATED ELEMENTS</th>
<th>PROTECTIVE MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST LINE OF DEFENSE: SURFACE MEMBRANE BARRIERS</strong></td>
<td></td>
</tr>
<tr>
<td>Intact skin epidermis</td>
<td>Forms mechanical barrier that prevents entry of pathogens and other harmful substances into body</td>
</tr>
<tr>
<td>• Acid mantle</td>
<td>Skin secretions (perspiration and sebum) make epidermal surface acidic, which inhibits bacterial growth; sebum also contains bactericidal chemicals</td>
</tr>
<tr>
<td>• Keratin</td>
<td>Provides resistance against acids, alkalis, and bacterial enzymes</td>
</tr>
<tr>
<td>Intact mucous membranes</td>
<td>Form mechanical barrier that prevents entry of pathogens</td>
</tr>
<tr>
<td>• Mucus</td>
<td>Traps microorganisms in respiratory and digestive tracts</td>
</tr>
<tr>
<td>• Nasal hairs</td>
<td>Filter and trap microorganisms in nasal passages</td>
</tr>
<tr>
<td>• Cilia</td>
<td>Propel debris-laden mucus away from lower respiratory passages</td>
</tr>
<tr>
<td>• Gastric juice</td>
<td>Contains concentrated hydrochloric acid and protein-digesting enzymes that destroy pathogens in stomach</td>
</tr>
<tr>
<td>• Acid mantle of vagina</td>
<td>Inhibits growth of most bacteria and fungi in female reproductive tract</td>
</tr>
<tr>
<td>• Lacrimal secretion (tears); saliva</td>
<td>Continuously lubricate and cleanse eyes (tears) and oral cavity (saliva); contain lysozyme, an enzyme that destroys microorganisms</td>
</tr>
<tr>
<td>• Urine</td>
<td>Normally acid pH inhibits bacterial growth; cleanses the lower urinary tract as it flushes from the body</td>
</tr>
</tbody>
</table>
The diagram illustrates the activation and lysis of a target pathogen through the complement system. The process begins with the binding of antibodies or activated complement to the pathogen, leading to the formation of attack complexes. These complexes then lead to the lysis of the target pathogen.
MHC marker

T and B cells ignore this

processed antigen

T cells start an immune response

antigen

B cells start an immune response
Antibody-mediated immune response

1. MHC marker on a macrophage
2. Pathogen enters the macrophage
3. Antigen-MHC complex presented
4. Antigen-MHC receptor on helper T cell
5. Virgin or memory cytotoxic T cell
6. Mitosis and differentiation
7. Infected body cell
8. Effector cytotoxic T cell
9. Antibodies
10. Effect on pathogen
11. Memory B cell formation
12. Populations of effector and memory B cells

Antibody-mediated immune response
PART 2 : Cells and Chemicals
Immunological Synapse

Is the interface between an antigen-presenting cell and a lymphocyte
HIV-1-infected T cell displaying Lck (red) retained in recycling endosomes (marked by the transferrin receptor, green). Yellow color indicates the co-localization of both proteins.
Figure 21.8

Red bone marrow

Bone marrow

Thymus

Lymph nodes, spleen, and other lymphoid tissues

Circulation in blood

Immature lymphocytes

Immunocompetent, but still naive, lymphocyte migrates via blood

Activated Immunocompetent B and T cells recirculate in blood and lymph

Key:

= Site of lymphocyte origin

= Site of development of immunocompetence as B or T cells; primary lymphoid organs

= Site of antigen challenge, activation, and final differentiation of B and T cells

1. Lymphocytes destined to become T cells migrate to the thymus and develop immunocompetence there. B cells develop immunocompetence in red bone marrow.

2. After leaving the thymus or bone marrow as naïve immunocompetent cells, lymphocytes “seed” the lymph nodes, spleen, and other lymphoid tissues where the antigen challenge occurs.

3. Antigen-activated immunocompetent lymphocytes circulate continuously in the bloodstream and lymph and throughout the lymphoid organs of the body.
<table>
<thead>
<tr>
<th>CHEMICAL</th>
<th>SOURCE</th>
<th>PHYSIOLOGICAL EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Granules of basophils and mast cells; released in response to mechanical injury, presence of certain microorganisms, and chemicals released by neutrophils</td>
<td>Promotes vasodilation of local arterioles; increases permeability of local capillaries, promoting exudate formation</td>
</tr>
<tr>
<td>Kinins (bradykinin and others)</td>
<td>A plasma protein, kininogen, is cleaved by the enzyme kallikrein found in plasma, urine, saliva, and in lysosomes of neutrophils and other types of cells: cleavage releases active kinin peptides</td>
<td>Same as for histamine; also induce chemotaxis of leukocytes and prompt neutrophils to release lysosomal enzymes, thereby enhancing generation of more kinins: induce pain</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Fatty acid molecules produced from arachidonic acid—found in all cell membranes; generated by enzymes of neutrophils, basophils, mast cells, and others</td>
<td>Sensitize blood vessels to effects of other inflammatory mediators; one of the intermediate steps of prostaglandin generation produces free radicals, which themselves can cause inflammation; induce pain</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Secreted by platelets and endothelial cells</td>
<td>Stimulates fibroblast activity and repair of damaged tissues</td>
</tr>
<tr>
<td>Complement</td>
<td>See Table 21.2 (p. 796)</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>See Table 21.4 (pp. 817–818)</td>
<td></td>
</tr>
</tbody>
</table>
Internal Defenses: Cells and Chemicals

- The body uses nonspecific cellular and chemical devices to protect itself

- **Phagocytes and natural killer (NK) cells**
- **Antimicrobial proteins in blood and tissue fluid**
- **Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals**

- Harmful substances are identified by surface carbohydrates unique to infectious organisms
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
- Antigen-presenting cells (APCs):
  - Do not respond to specific antigens
  - Play essential auxiliary roles in immunity
Lymphocytes [see the specific in blood slides]

- Immature lymphocytes released from bone marrow are essentially identical.
- 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.
The Cells of the Immune Response

**T cells**: Lymphocytes that regulate response

- **Cytotoxic T cells**: destroy specific targeted cells
- **Helper T cells**: stimulate immune responses
- **Suppressor T cells**: stop immune response
- **Memory T cells**: provide future immunity
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function</th>
<th>Type of Antigen Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-LYMPHOCYTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helper T-lymphocyte</td>
<td>Initiates and oversees the immune response</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>Cytotoxic T-lymphocyte</td>
<td>Directly kills foreign cells; must be activated by a helper T-lymphocyte first</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>Memory T-lymphocyte</td>
<td>A type of cytotoxic T-lymphocyte that has already killed; patrols the body looking for the same antigen again</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>Suppressor T-lymphocyte</td>
<td>Helps “turn off” the immune response once it has been activated</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>B-LYMPHOCYTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma cell</td>
<td>Produces and secretes antibodies</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>Memory B-lymphocyte</td>
<td>Remembers an initial antigen attack and mounts a faster, more efficient response should the same antigen type attack again</td>
<td>Responds to a single antigen</td>
</tr>
<tr>
<td>NK (NATURAL KILLER) CELL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK (natural killer) cell</td>
<td>Kills a wide variety of infected and cancerous cells</td>
<td>Responds to multiple antigens</td>
</tr>
</tbody>
</table>
### Table 21.2 Summary of Nonspecific Body Defenses (continued)

<table>
<thead>
<tr>
<th>Category/Associated Elements</th>
<th>Protective Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SECOND LINE OF DEFENSE: INNATE, CELLULAR AND CHEMICAL DEFENSES</strong></td>
<td></td>
</tr>
<tr>
<td>Phagocytes</td>
<td>Engulf and destroy pathogens that breach surface membrane barriers; macrophages also contribute to immune response</td>
</tr>
<tr>
<td>Natural killer (NK) cells</td>
<td>Promote apoptosis (cell suicide) by direct cell attack against virus-infected or cancerous body cells; do not require specific antigen recognition; do not exhibit a memory response</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Prevents spread of injurious agents to adjacent tissues, disposes of pathogens and dead tissue cells, and promotes tissue repair; chemical mediators released attract phagocytes (and immunocompetent cells) to the area</td>
</tr>
<tr>
<td>Antimicrobial proteins</td>
<td></td>
</tr>
<tr>
<td>- Interferons (α, β, γ)</td>
<td>Proteins released by virus-infected cells and certain lymphocytes that protect uninfected tissue cells from viral takeover; mobilize immune system</td>
</tr>
<tr>
<td>- Complement</td>
<td>Lyses microorganisms, enhances phagocytosis by opsonization, and intensifies inflammatory and immune responses</td>
</tr>
<tr>
<td>Fever</td>
<td>Systemic response initiated by pyrogens; high body temperature inhibits microbial multiplication and enhances body repair processes</td>
</tr>
</tbody>
</table>

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A mast cell (or mastocyte) is a resident cell of several types of tissues and contains many granules rich in histamine and heparin. Although best known for their role in allergy and anaphylaxis, mast cells play an important protective role as well, being intimately involved in wound healing and defense against pathogens. Prominent near the boundaries between the outside world and the internal milieu, such as the skin, mucosa of the lungs and digestive tract, as well as in the mouth, conjunctiva and nose.

Mast cells can be stimulated to degranulate by direct injury (e.g. physical or chemical), cross-linking of Immunoglobulin E (IgE) receptors, or by activated complement proteins.
Basophils / Mast Cells

These cells are filled with mediators of inflammation:

- **histamine** - causes vasodilation (blood vessels dilate) and bronchoconstriction (because it causes smooth muscles to constrict)

  - heparin - inhibits blood coagulation

  - leukotrienes - prolonged constriction of smooth muscles, pain

  - prostaglandins - smooth muscle constriction and vasodilation, pain
- Mast cells / basophils
  - release histamine that dilates blood vessels
  - causes redness [erythema], swelling [edema], and heat
Cells of Immune Response

Non hematopoietic cells:
- Dendritic cells
- Astrocytes and
- Endothelial cells

**Function**: antigen presentation
Self-Antigens: MHC Proteins

Our cells are dotted with protein molecules (self-antigens) that are not antigenic to us but are strongly antigenic to others.

One type, MHC proteins, mark a cell as self.

The two classes of MHC proteins are:

- **Class I MHC proteins** - found on virtually all body cells
- **Class II MHC proteins** - found on certain cells in the immune response

Are coded for by genes of the major histocompatibility complex (MHC) and are unique to an individual.
Part 3 : Mechanisms
Phagocytes

- **Macrophages are the chief phagocytic cells**
- Free macrophages wander throughout a region in search of cellular debris
- Kupffer cells (liver) and microglia (brain) are fixed macrophages
Phagocytes

- **Neutrophils** become phagocytic when encountering infectious material.
- **Eosinophils** are weakly phagocytic against parasitic worms.
- **Mast cells** bind and ingest a wide range of bacteria.
Mechanism of Phagocytosis

1/ Microbes adhere to the phagocyte
2/ Pseudopods engulf the particle (antigen) into a phagosome
3/ Phagosomes fuse with a lysosome to form a phagolysosome
4/ Invaders in the phagolysosome are digested by proteolytic enzymes
5/ Indigestible and residual material is removed by exocytosis
1. Microbe adheres to phagocyte.
2. Phagocyte forms pseudopods that eventually engulf the particle.
3. Phagocytic vesicle is fused with a lysosome.
4. Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body.
5. Indigestible and residual material is removed by exocytosis.

Phagocytic vesicle containing antigen (phagosome).

Acid hydrolase enzymes

Phagolysosome

Lysosome

Phagocyte / Monocyte approaches antigen

Phagocyte or Monocyte

Antigen
• injury & infection
• macrophages slip between cells [extravasation] to arrive
• cytokine chemicals attract other “troops” [chemotaxis]
• histamine chemicals dilate blood vessels for easier access to injury [vasodilation]
<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Present On</th>
<th>Interacts With</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Lymphocytes</td>
<td>MHC II</td>
</tr>
<tr>
<td>CD8</td>
<td>Lymphocytes</td>
<td>MHC I</td>
</tr>
<tr>
<td>MHC I</td>
<td>General Body Cells</td>
<td>CD8</td>
</tr>
<tr>
<td>MHC II</td>
<td>Phagocytes</td>
<td>CD4</td>
</tr>
</tbody>
</table>

The **major histocompatibility complex** (MHC) is a complex of class I and class II molecules. HIV infects primarily vital cells in the human immune system such as helper T cells (to be specific, CD4+ T cells), macrophages, and dendritic cells.
Acquired (Adaptive) Immunity

Defensive mechanisms include:

1) Innate immunity (Natural or Non-specific)

2) Acquired immunity (Adaptive or Specific)

- Cell-mediated immunity
- Humoral immunity
Aquired (specific) immunity

Two mechanisms

1) **Humoral immune response:**
   - Antibodies are produced by B-lymphocytes
   - These have the ability to recognize and bind specifically to antigen that induced their formation

2) **The cell mediated immune response (CMI):**
   - It is mediated by certain types of T-lymphocytes
   - T-lymphocytes recognize foreign material by means of surface receptors
   - T-lymphocytes attack and destroy foreign material directly or through release of soluble mediators i.e. cytokines
Types of Acquired Immunity

- Naturally acquired
  - Active: Infection; contact with pathogen
  - Passive: Antibodies pass from mother to fetus via placenta; or to infant in her milk
- Artificially acquired
  - Active: Vaccine; dead or attenuated pathogens
  - Passive: Injection of immune serum (gamma globulin)
Acquired Or Adaptive Immunity

I- Passive acquired immunity
   a- Naturally passive acquired immunity
      Antibodies are passed through placenta to the fetus
   b- Artificially passive acquired immunity
      The injection of already prepared antibodies, such as gamma globulin (short-term immunization)
II- Active acquired immunity

a- Natural active acquired immunity:

- Following clinical or subclinical infections

- measles or mumps, in which immunity is long lasting

b- Artificial active acquired immunity:

- Following vaccination with live or killed infectious agents or their products
Mechanism of Humoral immunity

* Antibodies induce resistance through:

1) Antitoxin neutralize bacterial toxins (diphtheria, tetanus)

   Antitoxin are developed actively as a result of:

   a- Previous infection

   b- Artificial immunization

   c- Transferred passively as antiserum

* Neutralization of toxin with antitoxin prevents a combination with tissue cells
Mechanism of Humoral immunity

2) Antibodies attach to the surface of bacteria and

a- act as opsonins and enhance phagocytosis

b- prevent the adherence of microorganisms to their target cells, e.g. IgA in the gut

c- Activate the complement and lead to bacterial lysis

d- Clump bacteria (agglutination) leading to phagocytosis
**Cell Mediated Immunity**

* Host defenses against extracellular infection are mediated by:
  - Antibody
  - Complement
  - Macrophages

* Intercellular infections are mediated by CMI

* CMI are responsible for:
  - Resistance to intracellular pathogens
  - Resistance to fungal and protozoal infections
  - Resistance to tumors
Cell Mediated Immunity

* CMI may play a role in some harmful conditions:
  - Hypersensitivity reactions type IV (contact dermatitis)
  - Graft rejection
  - Autoimmune diseases

* Cell mediated cytotoxicity mediated by:
  - T-cytotoxic cells
  - Natural killer cells
  - Activated macrophages
T-lymphocytes:
- Antigen specific cells carrying CD3 complex, CD4, CD8
- Dominant blood lymphocytes (70%)
- Produce cytokines
- **Activation of other cells** (Th CD4)
- **Suppressors for others** (Ts CD8)

B-lymphocytes:
- Antigen specific cells with surface receptor
- Less common lymphocytes (20%)
- Responsible for antibody production

* NK, K cells:
  - Not antigen specific
  - Carry Fc receptors, NK-target cell receptor
a) NK cells promote autoreactive T cells

- T_{H1} cell
- Cytokine production
- IFNγ
- APC activation
- OX40
- 2B4
- Co-stimulatory molecule expression
- MHC class II expression
- T cell

b) NK cells inhibit autoreactive T cells

- T cell
- APC lysis
- NK cell
- T-cell lysis
- IL-10
- TGFβ
- Cytokine production
- Increased WAF1 (cell-cycle inhibitor) expression
- Regulatory T-cell population induction
- NKT cells
- T_{Reg} cells

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Natural Killer (NK) Cells

- Can **lyse and kill cancer cells and virus-infected 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
- Secrete potent chemicals that enhance the inflammatory response
<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>FUNCTION IN IMMUNE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELLS</strong></td>
<td></td>
</tr>
<tr>
<td>B cell</td>
<td>Lymphocyte that matures in bone marrow. Induced to replicate by antigen binding, usually followed by helper T cell interactions in lymphoid tissues. Its progeny (clone members) form memory cells and plasma cells</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>Antibody-producing “machine”; produces huge numbers of antibodies (immunoglobulins) with the same antigen specificity. Specialized B cell clone descendant</td>
</tr>
<tr>
<td>Helper T cell (T&lt;sub&gt;H&lt;/sub&gt;)</td>
<td>A CD4 T cell that is central to both humoral and cellular immunity. After binding with a specific antigen presented by an APC, it stimulates production of cytotoxic T cells and B cells to help fight invader; activates macrophages, and acts both directly and indirectly by releasing cytokines</td>
</tr>
<tr>
<td>Cytotoxic T cell (T&lt;sub&gt;C&lt;/sub&gt;)</td>
<td>A CD8 cell; also called a cytolytic (CTL) T cell. Activated by antigen presented by an antigen-presenting cell, often with helper T cell involvement. Its specialty is killing virus-invaded body cells and cancer cells; also involved in rejection of foreign tissue grafts</td>
</tr>
<tr>
<td>Regulatory T cell (T&lt;sub&gt;Reg&lt;/sub&gt;)</td>
<td>Formerly called suppressor T cell; slows or stops activity of immune system. Thought to be important in controlling autoimmune diseases; likely several different populations exist</td>
</tr>
<tr>
<td>Memory cell</td>
<td>Descendant of activated B cell or any class of T cell; generated during initial immune response (primary response); may exist in body for years after, enabling it to respond quickly and efficiently to subsequent infections or meetings with same antigen</td>
</tr>
<tr>
<td>Antigen-presenting cell (APC)</td>
<td>Any of several cell types (dendritic cell, macrophage, B cell) that engulfs and digests antigens that it encounters, presenting parts of them on its plasma membrane (bound to an MHC protein) for recognition by T cells bearing receptors for same antigen. This function, antigen presentation, is essential for normal cell-mediated responses. Macrophages also release chemicals (cytokines) that activate T cells</td>
</tr>
</tbody>
</table>
Part IV: Inflammation
Inflammation

Steps of the Inflammatory Response

The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?

1. Damaged tissues release histamines, increasing blood flow to the area.
2. Histamines cause capillaries to leak, releasing phagocytes and clotting factors into the wound.
3. Phagocytes engulf bacteria, dead cells, and cellular debris.
4. Platelets move out of the capillary to seal the wounded area.
Inflammation

- Pulmonary diseases
- Neurological diseases
- Autoimmune diseases
- Arthritis
- Cancer
- Cardiovascular diseases
- Alzheimer
- Diabetes II
Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are injured
  - Prevents the spread of damaging agents to nearby tissues
  - Disposes of cell debris and pathogens
  - Sets the stage for repair processes
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain
Plasma cascade systems

- **The complement system**, when activated, results in the increased removal of pathogens via opsonisation and phagocytosis.

- **The kinin system** generates proteins capable of sustaining vasodilation and other physical inflammatory effects.

- **The coagulation system or clotting cascade** which forms a protective protein mesh over sites of injury.

- **The fibrinolysis system**, which acts in opposition to the coagulation system, to counterbalance clotting and generate several other inflammatory mediators.
Comparison between acute and chronic inflammation:

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative agent</strong></td>
<td>Pathogens, injured tissues</td>
<td>Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions</td>
</tr>
<tr>
<td><strong>Major cells involved</strong></td>
<td>Neutrophils, mononuclear cells (monocytes, macrophages)</td>
<td>Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts</td>
</tr>
<tr>
<td><strong>Primary mediators</strong></td>
<td>Vasoactive amines, eicosanoids</td>
<td>IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Few days</td>
<td>Up to many months, or years</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Resolution, abscess formation, chronic inflammation</td>
<td>Tissue destruction, fibrosis</td>
</tr>
</tbody>
</table>
The classic signs and symptoms of acute inflammation:

<table>
<thead>
<tr>
<th>Redness</th>
<th>Rubor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>Tumor/ Turgor</td>
</tr>
<tr>
<td>Heat</td>
<td>Calor</td>
</tr>
<tr>
<td>Pain</td>
<td>Dolor</td>
</tr>
<tr>
<td>Loss of function</td>
<td>Functio læsa</td>
</tr>
</tbody>
</table>
Figure. Pharmacology of Traditional NSAIDs and Selective COX-2 Inhibitors on Prostaglandin Synthesis

Membrane Phospholipids

→ Phospholipase A₂

→ Arachidonic Acid

COX-1 (Constitutive)

COX-2 (Inducible)

Traditional NSAID

COX-2 inhibitor

Prostaglandins associated with:
- GI mucosal integrity
- Platelet function
- Renal function

Prostaglandins associated with:
- Pain
- Fever
- Inflammation
• **acute inflammation**: inflammation, usually of sudden onset, characterized by the classical signs in which the vascular and exudative processes predominate.

• **subacute inflammation**: a condition intermediate between chronic and acute inflammation, exhibiting some of the characteristics of each.

• **chronic inflammation**: inflammation of slow progress and marked chiefly by the formation of new connective tissue; it may be a continuation of an acute form or a prolonged low-grade form, and usually causes permanent tissue damage.

**granulomatous inflammation**: an inflammation, usually chronic, characterized by the formation of granulomas.
Inflammation Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid
- Inflammatory mediators:
  - Kinins, prostaglandins (PGs), complement, and cytokines
  - Released by injured tissue, phagocytes, lymphocytes, and mast cells
  - Cause local small blood vessels to dilate, resulting in hyperemia
Toll-like Receptors (TLRs)

- Macrophages and cells lining the gastrointestinal and respiratory tracts bear TLRs
- TLRs recognize specific classes of infecting microbes
- Activated TLRs trigger the release of cytokines that promote inflammation
Inflammatory Response: **Vascular Permeability**

- Chemicals liberated by the inflammatory response increase the permeability of local capillaries.
- **Exudate**—fluid containing proteins, clotting factors, and antibodies:
  - Exudate seeps into tissue spaces causing local edema (swelling), which contributes to the sensation of pain.
Inflammatory Response: Edema

- The surge of protein-rich fluids into tissue spaces (edema):
  - Helps dilute harmful substances
  - Brings in large quantities of oxygen and nutrients needed for repair
  - Allows entry of clotting proteins, which prevents the spread of bacteria
Inflammatory Response: **Phagocytic Mobilization**

- **Four main phases**:
  - **Leukocytosis** - neutrophils are released from the bone marrow in response to leukocytosis-inducing factors released by injured cells.
  - **Margination** - neutrophils cling to the walls of capillaries in the injured area.
  - **Diapedesis** - neutrophils squeeze through capillary walls and begin phagocytosis.
  - **Chemotaxis** - inflammatory chemicals attract neutrophils to the injury site.
Figure 21.4 Neutrophils enter blood from bone marrow

1. Neutrophils enter blood from bone marrow
2. Margination
3. Diapedesis
4. Positive chemotaxis

Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents

Innate defenses → Internal defenses
Transudate is extravascular fluid with

- low protein content
- a low specific gravity (< 1.012).
- low nucleated cell counts (less than 500 to 1000 / microlit) and the primary cell types are mononuclear cells: macrophages, lymphocytes and mesothelia cells.

For instance, an ultrafiltrate of blood plasma is transudate. It results from increased fluid pressures or diminished colloid oncotic forces in the plasma.

In females, transudation is a method of lubrication during sexual arousal.
Exudate [pus like]

- extravascular fluid due to vessel alteration during inflammation (increased permeability, vascular constriction then dilation).

- high protein content,
- cell debris present
- high specific gravity (>1.020).

This is in contrast to transudate where the extracellular fluid is an ultrafiltrate of blood plasma and thus larger molecules such as proteins and cell debris are absent.
Exudate Types

**Purulent** or **suppurative** exudate consists of plasma with both active and dead neutrophils, fibrinogen, and necrotic parenchymal cells. This kind of exudate is consistent with more severe infections, and is commonly referred to as pus.

**Fibrinous** exudate is composed mainly of fibrinogen and fibrin. It is characteristic of **rheumatic carditis**, but is seen in all severe injuries such as strep throat and bacterial pneumonia. Fibrinous inflammation is often difficult to resolve due to the fact that blood vessels grow into the exudate and fill the space that was occupied by fibrin. Often, large amounts of antibiotics are necessary for resolution.

**Catarrhal** exudate is seen in the nose and throat and is characterized by a high content of mucus.

**Serous** exudate (sometimes classified as serous transudate) is usually seen in mild inflammation, with little protein content. Its consistency resembles that of serum, and can usually be seen in certain disease states like tuberculosis. (See below for difference between transudate and exudate)

**Malignant** (or cancerous) pleural effusion is effusion where cancer cells are present. It is usually classified as exudate.
## Transudate vs. Exudate

<table>
<thead>
<tr>
<th>Main causes</th>
<th>Transudate</th>
<th>Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased hydrostatic pressure</td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Decreased colloid osmotic pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Appearance       | Clear                             | Cloudy†                  |
| Specific gravity | < 1.012                           | > 1.020                  |
| Protein content  | < 2 g/ dL                          | > 2.9 g/ dL              |
| fluid protein    | < 0.5                              | > 0.5                    |
| serum protein    |                                    |                          |
| Difference of albumin content with blood albumin | > 1.2 g/ dL              | < 1.2 g/ dL              |
| fluid LDH        | < 0.6 or < ⅔                      | > 0.6 or > ⅔             |
| upper limit for serum |                                 |                          |
| fluid glucose    | < 0.8                             | > 0.8                    |
| serum glucose    |                                    |                          |
| Cholesterol content | < 45 mg/ dL                      | > 45 mg/ d               |
4.56 Blood-stained pleural aspirate. This patient had pleural secondaries from carcinoma of the breast.

4.57 Chyloous pleural effusion. This patient had bronchial carcinoma, which had invaded and obstructed the thoracic duct.

4.58 Pleural transudate. This pale effusion is typically found in patients with heart failure or other causes of generalized oedema.
- Fibrosis within alveolar walls
- Hemosiderin-laden macrophages
- Transudate
- Dilated capillaries within alveolar walls
- Red blood cells (microhemorrhages)
Dilated capillaries within alveolar walls

Transudate

Hemosiderin-laden macrophages

Red blood cells (microhemorrhages)
**Rivalta test** is used in order to differentiate a transudate from an exudate\(^1\). A test tube is filled with distilled water and acetic acid is added. To this mixture one drop of the effusion to be tested is added. If the drop dissipates, the test is negative, indicating a transudate. If the drop precipitate, the test is positive, indicating an exudate\(^2\).

Using a pH 4.0 acetic acid solution, 8 types of proteins were identified in Rivalta reaction-positive turbid precipitates: C-reactive protein (CRP), Alpha 1-antitrypsin (alpha1-AT), Orosomucoid ((Alpha 1-acid glycoprotein or AGP)), haptoglobin (Hp), transferrin (Tf), ceruloplasmin (Cp), fibrinogen (Fg), and hemopexin (Hpx). Since those are Acute-phase proteins, a positive Rivalta’s test may be suggestive of inflammation.


Antimicrobial Proteins

- Enhance the innate defenses by:
  - Attacking microorganisms directly
  - Hindering microorganisms’ ability to reproduce
- The most important antimicrobial proteins are:
  - Interferon
  - Complement proteins
Interferon (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a virus
- Interferon molecules leave the infected cell and enter neighboring cells
- Interferon stimulates genes for PKR (an antiviral protein)
- PKR nonspecifically blocks viral reproduction in the neighboring cell
Interferon Family

- Family of related proteins each with slightly different physiological effects

- Lymphocytes secrete gamma (γ) interferon, but most other WBCs secrete alpha (α) interferon

- Fibroblasts secrete beta (β) interferon

- Interferons also activate macrophages and mobilize NKs

- FDA-approved alpha IFN is used:
  - As an antiviral drug against hepatitis C virus
  - To treat genital warts caused by the herpes virus
C-reactive Protein (CRP)

- CRP is produced by the liver in response to inflammatory molecules.
- CRP is a clinical marker used to assess:
  - The presence of an acute infection.
Functions of C-reactive Protein

- Binds to PC receptor of pathogens and exposed self-antigens
- Plays a surveillance role in targeting damaged cells for disposal
- **Activates complement**
### Table 21.4  Cells and Molecules of the Adaptive Immune Response (continued)

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>FUNCTION IN IMMUNE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOLECULES</strong></td>
<td></td>
</tr>
<tr>
<td>Antibody (immunoglobulin)</td>
<td>Protein produced by B cell or by plasma cell. Antibodies produced by plasma cells are released into body fluids (blood, lymph, saliva, mucus, etc.), where they attach to antigens, causing complement fixation, neutralization, precipitation, or agglutination, which “mark” the antigens for destruction by complement or phagocytes</td>
</tr>
<tr>
<td>Perforin, granzymes</td>
<td>Released by T&lt;sub&gt;C&lt;/sub&gt; cells. Perforin creates large pores in the target cell’s membrane, allowing entry of apoptosis-inducing granzymes</td>
</tr>
<tr>
<td>Complement</td>
<td>Group of bloodborne proteins activated after binding to antibody-covered antigens or certain molecules on the surface of microorganisms; enhances inflammatory response and causes lysis of some microorganisms</td>
</tr>
<tr>
<td>Antigen</td>
<td>Substance capable of provoking an immune response. Typically a large complex molecule (e.g., protein or modified protein) not normally present in the body</td>
</tr>
<tr>
<td><strong>CYTOKINES</strong></td>
<td></td>
</tr>
<tr>
<td>Interferons (IFNs)</td>
<td>Secreted by leukocytes, fibroblasts, and other cells; antiviral effects; activate macrophages and NK cells</td>
</tr>
<tr>
<td>- Alpha (α) and beta (β)</td>
<td></td>
</tr>
<tr>
<td>- Gamma (γ)</td>
<td>Secreted by lymphocytes; activates macrophages; stimulates synthesis and expression of more class I and II MHC proteins; promotes differentiation of T&lt;sub&gt;H&lt;/sub&gt; cells into T&lt;sub&gt;H&lt;/sub&gt;1</td>
</tr>
<tr>
<td>Interleukins (ILs)</td>
<td>Secreted by activated macrophages; promotes inflammation and T cell activation; causes fever (a pyrogen that resets the thermostat of the hypothalamus)</td>
</tr>
<tr>
<td>- IL-1</td>
<td>Secreted by T cells; stimulates proliferation of T cells; activates NK cells</td>
</tr>
<tr>
<td>- IL-2</td>
<td>Stimulates production of leukocytes and mast cells</td>
</tr>
<tr>
<td>CYTOKINES</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td><strong>INTERLEUKINS (ILs)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IL-4</strong></td>
<td>Secreted by T&lt;sub&gt;H&lt;/sub&gt; cells; promotes differentiation to T&lt;sub&gt;H&lt;/sub&gt;2; promotes B cell activation; switches antibody production to IgE</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td>Secreted by some T&lt;sub&gt;H&lt;/sub&gt; cells and mast cells; attracts and activates eosinophils; causes plasma cells to secrete IgA antibodies</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>Induces lymphocyte activation and increases antibody production; stimulates liver to secret C-reactive protein, which binds certain bacteria, resulting in complement activation and opsonization</td>
</tr>
<tr>
<td><strong>IL-7</strong></td>
<td>Induces lymphocyte proliferation and maturation</td>
</tr>
<tr>
<td><strong>IL-8 (also called CXCL8)</strong></td>
<td>Stimulates chemotaxis of neutrophils, basophils, and T cells; promotes angiogenesis</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td>Inhibits macrophages and dendritic cells; turns down cellular and innate immune response</td>
</tr>
<tr>
<td><strong>IL-12</strong></td>
<td>Secreted by dendritic cells and macrophages; stimulates T&lt;sub&gt;C&lt;/sub&gt; and NK cell activity; promotes T&lt;sub&gt;H&lt;/sub&gt;1 differentiation</td>
</tr>
<tr>
<td><strong>IL-13</strong></td>
<td>Secreted by T&lt;sub&gt;H&lt;/sub&gt; cells; switches antibody production to IgE</td>
</tr>
<tr>
<td><strong>MIGRATION INHIBITORY FACTOR (MIF)</strong></td>
<td>Inhibits macrophage migration and keeps them in the area of antigen deposition; a generic term for a number of cytokines</td>
</tr>
<tr>
<td><strong>SUPPRESSOR FACTORS</strong></td>
<td>A generic term for a number of cytokines that suppress the immune system, for example TGF-β and IL-10</td>
</tr>
<tr>
<td><strong>TRANSFORMING GROWTH FACTOR BETA (TGF-β)</strong></td>
<td>A suppressor factor similar to IL-10</td>
</tr>
<tr>
<td><strong>TUMOR NECROSIS FACTORS (TNFS)</strong></td>
<td>Produced by lymphocytes and in large amounts by macrophages. Enhance nonspecific killing; slow tumor growth by selectively damaging tumor blood vessels; enhance granulocyte chemotaxis; help activate T cells, phagocytes, and eosinophils; promote cell death by apoptosis</td>
</tr>
</tbody>
</table>
Complement

**Definition**: series of heat-labile serum proteins

**Site**: serum and all tissue fluids except urine and CSF

**Synthesis**: in liver - appear in fetal circulation during 1st 13W

**Function**: Responsible for certain aspects of immune response and inflammatory response

**Activation**: antigen-antibody complex or endotoxin, capsule series of proteins activated sequentially

**Inactivation**: inhibitors in plasma (short lived)

**Biological effects**: either beneficial or harmful to host
Complement

- 20 or so proteins that circulate in the blood in an inactive form
- Proteins include C1 through C9, factors B, D, and P, and regulatory proteins
- Provides a major mechanism for destroying foreign substances in the body
Complement

- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses
Complement Pathways

Classical pathway:
- Antigen-antibody complex + C1 + C4 + C2 Complex
- Opsonization: coats bacterial surfaces, which enhances phagocytosis
- Promotion of inflammatory response: release of histamine, attraction of phagocytes
- Lytic pathway: C5, C6, C7, C8, C9
- Cell lysis

Alternative pathway:
- Microorganisms’ cell wall polysaccharides + Factor B, Factor D, and Factor P (properdin)
- Causes inflammation: stimulates histamine release, increased blood vessel permeability, chemotactic attraction of phagocytes, etc.

Opsonization: integration of MAC and cell lysis (holes in target cell’s membrane)
The diagram illustrates the pathways of the complement system:

**Classical Pathway**
- Antigen-antibody complexes (pathogen surfaces)
- C1q, C1r, C1s, C4, C2

**MB-Lectin Pathway**
- Mannose-binding lectin binds mannose on pathogen surfaces
- MBL, MASP-1, MASP-2
  - C4, C2

**Alternative Pathway**
- Pathogen surfaces
  - C3, B, D

**C3 Convertase**
- C3

**Terminal Complement Components**
- C5b, C6, C7, C8, C9

**C3b**
- Binds to complement receptors on phagocytes
- Opsonization of pathogens
- Removal of immune complexes

**C3a, C5a**
- Peptide mediators of inflammation, phagocyte recruitment

Membrane-attack complex, lysis of certain pathogens and cells

*Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)*
Part v : Fever
Fever = pyrexia

- A systematic, non-specific defensive response caused by:
  - infection from bacteria and virus,
  - indicated by abnormal high body temperature.

Beneficial effects of fever:
- Helps set up specific defense (production of T cells)
- Speed up metabolism for tissue repair
- Increases the antiviral effect of interferons

IFNs are a class of anti-viral proteins that disrupt viral multiplication
- Not very effective (short-lived and no effect for infected cells)
- Nonspecific to viral types
Fever pyrexia

- The body’s thermostat is reset upwards in response to pyrogens, chemicals secreted by leukocytes and macrophages exposed to bacteria and other foreign substances.

- Fever can be classified as low (oral reading of 99° to 100.4° F [37.2° to 38° C]), moderate (100.5° to 104° F [38.1° to 40° C]), or high (above 104° F). Fever over 106° F (41.1° C) causes unconsciousness and, if sustained, leads to permanent brain damage.
Fever: causes

- Infectious disease is the most common cause of fever in primary patient care.
- Other possible causes of fever are:
  - inflammatory intestinal,
  - joint and connective tissue diseases,
  - allergic reactions,
  - malignant tumours,
  - hematological diseases.
Fever

- High fevers are dangerous because they can **denature enzymes**
- Moderate fever can be beneficial, as it causes:
  - The liver and spleen to sequester iron and zinc (needed by microorganisms)
  - An increase in the metabolic rate, which speeds up tissue repair
Disruption of hypothalamic thermostat by:
- central nervous system disease
- inherited malignant hyperthermia

Increased production of heat from:
- strenuous exercise or other stress
- chills (skeletal muscle response)
- thyrotoxicosis

Decreased loss of heat from:
- anhidrotic asthenia (heatstroke)
- heart failure
- skin conditions, such as ichthyosis and congenital absence of sweat glands
- drugs that impair sweating

Failure of the body’s temperature-regulating mechanisms

FEVER

Elevation of hypothalamic set point

Production of endogenous pyrogens

Entrance of exogenous pyrogens, such as bacteria, viruses, or immune complexes, into the body
Part VI: Immunoglobulins
Antibodies

- Also called immunoglobulins
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with that antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE
Antibodies with different specificities differ in the amino acid sequence of the variable regions of the heavy and light chains.

The two heavy chains are identical and the two light chains are identical so the two antigen binding sites are identical.
Two Forms of Immunoglobulin

- Membrane-bound receptor
  - B-cell receptor
  - Igβ Igα Igα Igβ

- Soluble antibody
  - Light chain
  - Heavy chain
  - Disulfide bonds

Figure 3.2 Immunobiology, 6/e, (© Garland Science 2005)
Immunoglobulin Classes

I. IgG
- **Structure:** Monomer
- **Percentage serum antibodies:** 80%
- **Location:** Blood, lymph, intestine
- **Half-life in serum:** 23 days
- **Complement Fixation:** Yes
- **Placental Transfer:** Yes
- **Known Functions:** Enhances phagocytosis, neutralizes toxins and viruses, protects fetus and newborn.
Immunoglobulin Classes

II. IgM

- **Structure**: Pentamer
- **Percentage serum antibodies**: 5-10%
- **Location**: Blood, lymph, B cell surface (monomer)
- **Half-life in serum**: 5 days
- **Complement Fixation**: Yes
- **Placental Transfer**: No

- **Known Functions**: First antibodies produced during an infection. Effective against microbes and agglutinating antigens.
III. IgA

- **Structure**: Dimer
- **Percentage serum antibodies**: 10-15%
- **Location**: Secretions (tears, saliva, intestine, milk), blood and lymph.
- **Half-life in serum**: 6 days
- **Complement Fixation**: No
- **Placental Transfer**: No
- **Known Functions**: Localized protection of mucosal surfaces. Provides immunity to infant digestive tract.
Immunoglobulin Classes

IV. IgD

- Structure: Monomer
- Percentage serum antibodies: 0.2%
- Location: B-cell surface, blood, and lymph
- Half-life in serum: 3 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: In serum function is unknown. On B cell surface, initiate immune response.
Immunoglobulin Classes

V. IgE

- Structure: Monomer
- Percentage serum antibodies: 0.002%
- Location: Bound to mast cells and basophils throughout body. Blood.
- Half-life in serum: 2 days
- Complement Fixation: No
- Placental Transfer: No

**Table 21.3 Immunoglobulin Classes**

<table>
<thead>
<tr>
<th>IgD</th>
<th>IgD is virtually always attached to the external surface of a B cell, where it functions as the antigen receptor of the B cell; important in B cell activation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>IgM exists in monomer and pentamer (five united monomers) forms. The monomer, which is attached to the B cell surface, serves as an antigen receptor. The pentamer (illustrated) circulates in blood plasma and is the first Ig class released by plasma cells during the primary response. (This fact is diagnostically useful because presence of IgM in plasma usually indicates current infection by the pathogen eliciting IgM's formation.) Because of its numerous antigen-binding sites, IgM is a potent agglutinating agent and readily fixes and activates complement.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Immunoglobin Classes (continued)</th>
</tr>
</thead>
</table>

**IgG** (monomer)

IgG is the most abundant and diverse antibody in plasma, accounting for 75–85% of circulating antibodies. It protects against bacteria, viruses, and toxins circulating in blood and lymph, readily fixes complement, and is the main antibody of both secondary and late primary responses. It crosses the placenta and confers passive immunity from the mother to the fetus.

**IgA** (dimer)

IgA monomer exists in limited amounts in plasma. The dimer (illustrated), referred to as secretory IgA, is found in body secretions such as saliva, sweat, intestinal juice, and milk, and helps prevent attachment of pathogens to epithelial cell surfaces (including mucous membranes and the epidermis).

**IgE** (monomer)

IgE is slightly larger than the IgG antibody. It is secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. Its stem region becomes bound to mast cells and basophils, and when its receptor ends are triggered by an antigen, it causes the cells to release histamine and other chemicals that mediate inflammation and an allergic reaction. Typically only traces of IgE are found in plasma, but levels rise during severe allergic attacks or chronic parasitic infections of the gastrointestinal tract.
Immunoglobulin, Ig

- **Definition:** Glycoprotein molecules that are produced by plasma cells in response to an immunogen and which function as antibodies.
- The immunoglobulins are a group of glycoproteins present in the serum and tissue fluids of all mammals.
Immune serum

Ag adsorbed serum

+ 

- 

albumin

globulins

\[ \alpha_1 \quad \alpha_2 \quad \beta \quad \gamma \]

Amount of protein

Mobility

Immune serum

Ag adsorbed serum
Amount of protein

Mobility

albumin
globulins

\[
\begin{align*}
\gamma & \quad \text{IgG} \\
\beta & \quad \text{IgM} \\
\alpha_2 & \quad \text{IgA} \\
\alpha_1 & \quad \text{IgM}
\end{align*}
\]
ADAPTIVE IMMUNE SYSTEM

T-lymphocytes

T-cytotoxic ➔ Cytoxic

B-lymphocytes

Plasma cells ➔ Antibodies

Response takes 7 to 10 days
Adaptive Immune System

- T and B Lymphocytes
- Highly specific for pathogen
- Response improves with repeated exposure
- Memory
- Life-long immunity
T versus B cell Response

B cells recognise native antigen
T cells recognise processed antigen
Part VII: Antibodies - Antigens
Consequences of Antibody Binding

- **Agglutination**: Enhances phagocytosis and reduces number of infectious units to be dealt with.
- **Opsonization**: Coating antigen with antibody enhances phagocytosis.
- **Neutralization**: Blocks adhesion of bacteria and viruses to mucosa.
- **Activation of complement**: Complement cell lysis.
- **Inflammation**: Blood vessel disruption of cell by complement/reactive protein attracts phagocytic and other defensive immune system cells.
- **Antibody-dependent cell-mediated cytotoxicity**: Antibodies attached to target cell cause destruction by non-specific immune system cells.
Consequences of Antigen-Antibody Binding

Antigen-Antibody Complex: Formed when an antibody binds to an antigen it recognizes.

Affinity: A measure of binding strength.

1. Agglutination: Antibodies cause antigens (microbes) to clump together.
   - IgM (decavalent) is more effective than IgG (bivalent).
   - Hemagglutination: Agglutination of red blood cells. Used to determine ABO blood types and to detect influenza and measles viruses.

2. Opsonization: Antigen (microbe) is covered with antibodies that enhance its ingestion and lysis by phagocytic cells.
Humoral Immunity (Continued)

3. **Neutralization**: IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.

4. **Antibody-dependent cell-mediated cytotoxicity**: Used to destroy large organisms (e.g., worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific immune cells.

5. **Complement Activation**: Both IgG and IgM trigger the complement system which results in cell lysis and inflammation.
Consequences of Antibody Binding

Binding of antibodies to antigens inactivates antigens by:

1. **Neutralization** (blocks viral binding sites; coats bacteria and/or opsonization)
   - Virus
   - Bacterium

2. **Agglutination of antigen-bearing particles, such as microbes**
   - Bacteria

3. **Precipitation of soluble antigens**
   - Soluble antigens
   - Foreign cell

4. **Complement fixation (activation of complement)**
   - Complement
   - Lesion

Enhances:
- **Phagocytosis**
  - Macrophage

Leads to:
- **Cell lysis**
Vaccination

Vaccination prevents and control such diseases as cholera, rabies, poliomyelitis, diphtheria, tetanus, measles, and typhoid fever.

Vaccines can be:

a. prophylactic (e.g. to prevent the effects of a future infection by any natural or "wild" pathogen)

b. Therapeupic (e.g. vaccines against cancer are also being investigated)

Dr. Schreiber of San Augustine giving a typhoid inoculation at a rural school, San Augustine County, Texas. Transfer from U.S. Office of War Information, 1944.
Vaccination

Vaccination:

*Producing immunity against pathogens (viruses and bacteria) by the introduction of live, killed, or altered antigens that stimulate the body to produce antibodies against more dangerous forms

*Vaccines work with the immune system’s ability to recognize and destroy foreign proteins (antigens)
Vaccination

Immunization of young children and adolescents:

- Hepatitis B (HepB) and Hepatitis A (HepA)
- Diphtheria, tetanus and pertussis (whooping cough) given together as DTaP (formerly DTP)
- Haemophilus influenzae b (Hib)
- Poliomyelitis (IPV)
- Measles, Mumps, and Rubella, given together as MMR
- Chicken pox (Var)
- Neisseria meningitidis (meningococcal meningitis)
# TABLE 1. Catch-up schedule for children aged 4 months–6 years

<table>
<thead>
<tr>
<th>Dose one (minimum age)</th>
<th>Minimum interval between doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose one to dose two</td>
</tr>
<tr>
<td>DTaP (6 wks)</td>
<td>4 wks</td>
</tr>
<tr>
<td>IPV (6 wks)</td>
<td>4 wks</td>
</tr>
<tr>
<td>HepB (^3) (birth)</td>
<td>4 wks</td>
</tr>
<tr>
<td>MMR (12 mos)</td>
<td>4 wks (^4)</td>
</tr>
<tr>
<td>Varicella (12 mos)</td>
<td></td>
</tr>
<tr>
<td>Hib (^5) (6 wks)</td>
<td>4 wks: if 1(^{st}) dose given at age &lt;12 mos</td>
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<tr>
<td></td>
<td>8 wks (as final dose): if 1(^{st}) dose given at age 12–24 mos</td>
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<tr>
<td></td>
<td>No further doses needed: if 1(^{st}) dose given at age ≥15 mos</td>
</tr>
<tr>
<td>PCV (^7) (6 wks)</td>
<td>4 wks: if 1(^{st}) dose given at age &lt;12 mos and current age &lt;24 mos</td>
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<tr>
<td></td>
<td>8 wks (as final dose): if 1(^{st}) dose given at age ≥12 mos or current age 24–59 mos</td>
</tr>
<tr>
<td></td>
<td>No further doses needed: for healthy children if previous dose given at age ≥24 mos</td>
</tr>
</tbody>
</table>

1. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP): The fifth dose is not necessary if the fourth dose was given after the fourth birthday.
2. Inactivated Polio (IPV): For children who received an all-IPV or all-OPV series, a fourth dose is not necessary if third dose was given at age ≥4 years. If both OPV and IPV were given as part of a series, a total of 4 doses should be given, regardless of the child’s current age.
3. Hepatitis B vaccine (HepB): All children and adolescents who have not been vaccinated against hepatitis B should begin the hepatitis B vaccination series during any visit. Providers should make special efforts to immunize children who were born in, or whose parents were born in, areas of the world where hepatitis B virus infection is moderately or highly endemic.
4. Measles, mumps, and rubella vaccine (MMR): The second dose of MMR is recommended routinely at age 4–6 years, but may be given earlier if desired.
5. Haemophilus influenzae type b (Hib): Vaccine is not recommended generally for children aged ≥5 years.
6. Hib: If current age is <12 months and the first 2 doses were PRP-OMP (PedvaxHIB\(^8\) or ComVax [Merck]\(^9\)), the third (and final) dose should be given at age 12–15 months and at least 8 weeks after the second dose.
7. Pneumococcal conjugate vaccine (PCV): Vaccine is not recommended generally for children aged ≥5 years.
TABLE 2. Catch-up schedule for children aged 7–18 years

<table>
<thead>
<tr>
<th></th>
<th>Minimum interval between doses</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dose one to dose two</td>
<td>Dose two to dose three</td>
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<tr>
<td><strong>Td:</strong></td>
<td>4 wks</td>
<td>Td: 6 mos</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>IPV</strong></td>
<td>4 wks</td>
<td>IPV: 4 wks</td>
</tr>
<tr>
<td><strong>HepB:</strong></td>
<td>4 wks</td>
<td>HepB: 8 wks (and 16 wks after 1st dose)</td>
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<tr>
<td><strong>MMR:</strong></td>
<td>4 wks</td>
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</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>4 wks</td>
<td></td>
</tr>
</tbody>
</table>

1. **Tetanus toxoid**: For children aged 7–10 years, the interval between the third and booster dose is determined by the age when the first dose was given. For adolescents aged 11–18 years, the interval is determined by the age when the third dose was given.

2. **Inactivated Polio (IPV)**: Vaccine is not recommended generally for persons aged ≥18 years.

3. **Varicella**: Give 2-dose series to all susceptible adolescents aged ≥13 years.
## FIGURE. Recommended childhood and adolescent immunization schedule

**United States, 2003**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Range of recommended ages</th>
<th>Catch-up vaccination</th>
<th>Preadolescent assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>1 mo</td>
<td>2 mo</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
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<tr>
<td></td>
<td>HepB #1</td>
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<tr>
<td></td>
<td>(only if mother HepB neg)</td>
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<td></td>
<td>HepB #2</td>
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<tr>
<td><strong>Diphtheria, Tetanus, Pertussis</strong></td>
<td>DTaP</td>
<td></td>
<td>DTaP</td>
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<td></td>
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<tr>
<td><strong>Haemophilus influenzae Type b</strong></td>
<td>Hib</td>
<td></td>
<td>Hib</td>
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<tr>
<td><strong>Inactivated Polio</strong></td>
<td>IPV</td>
<td>IPV</td>
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<tr>
<td><strong>Measles, Mumps, Rubella</strong></td>
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<tr>
<td><strong>Varicella</strong></td>
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<tr>
<td><strong>Pneumococcal</strong></td>
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<tr>
<td><strong>Hepatitis A</strong></td>
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<tr>
<td><strong>Influenza</strong></td>
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</tbody>
</table>

1. Indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2002, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. Indicated age groups that warrant special effort to administer these vaccines not given previously. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine’s other components are not contraindicated. Providers should consult the manufacturers’ package inserts for detailed recommendations.

2. Hepatitis B vaccine (HepB). All infants should receive the first dose of HepB vaccine soon after birth and before hospital discharge; the first dose also may be given by age 2 months to HepB-negative mothers. Only maternal HepB vaccine can be used for the birth dose. Monovalent or combination vaccine containing HepB may be used to complete the series; 4 doses of vaccine may be administered when a birth dose is given. The second dose should be given at least 4 weeks after the first dose except for combination vaccines, which cannot be administered before age 6 weeks. The third dose should be given at least 16 weeks after the first dose and at least 4 weeks after the second dose. The last dose in the vaccination series (third or fourth dose) should not be administered before age 6 months. Infants born to HBsAg-positive mothers should receive HepB vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1–2 months. The last dose in the vaccination series should not be administered before age 6 months. These infants should be tested for HBsAg and anti-HBs at 9–15 months of age. Infants born to mothers whose HBsAg status is unknown should receive the first dose of the HepB vaccine series within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother’s HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The second dose is recommended at age 1–2 months. The last dose in the vaccination series should not be administered before age 6 months.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). The fourth dose of DTaP may be administered at age 12 months provided that 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. Tetanus and diphtheria toxoids (Td) is recommended at age 11–12 years if at least 6 years have elapsed since the last dose of Td-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

4. Haemophilus influenzae type b (Hib) conjugate vaccine. Three Hib conjugate vaccines are recommended for infants. If PEPOM (Pediatric Hib) or Conveax (Merck) is administered at age 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary vaccination in infants at age 2, 4, 6 months but can be used as boosters following any Hib vaccine.

5. Measles, mumps, and rubella vaccine (MMR). The second dose of MMR is recommended routinely at age 4–6 years but may be administered during any visit at which 4 weeks have elapsed since the first dose and that both doses are administered beginning at or after age 12 months. Those who have not received the second dose previously should complete the schedule by the visit at age 11–12 years.

6. Varicella vaccine. Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons aged ≤13 years should receive 2 doses given at least 4 weeks apart.

7. Pneumococcal vaccine. The nonavalent pneumococcal conjugate vaccine (PCV) is recommended for all children aged 2–11 months and for certain children aged 24–59 months. Pneumococcal polysaccharide vaccine (PPV) is recommended in addition to PCV for certain high-risk groups. See MMWR 2002;51(No. RR-9):1–37.

8. Hepatitis A vaccine. Hepatitis A vaccine is recommended for children and adolescents in selected states and regions, and for certain high-risk groups. Consult local public health authority and MMWR 1999;48(No. RR-12):1–27. Children and adolescents in these states, regions, and high-risk groups who have not been immunized against hepatitis A can begin the hepatitis A vaccination series during any visit. The two doses in the series should be administered at least 6 months apart.

9. Influenza vaccine. Influenza vaccine is recommended annually for children aged ≥6 months with certain high-risk factors (including but not limited to asthma, cardiopulmonary disease, sickle cell disease, HIV, and diabetes, and household members of persons in groups at high risk (see MMWR 2002;51[No. RR-9]:1–37), and can be administered to all others wishing to obtain immunity. In addition, healthy children aged 6–23 months are encouraged to receive influenza vaccine if feasible because children in this age group are at substantially increased risk for influenza-related hospitalizations. Children aged ≤12 years should receive vaccine in a dosage appropriate for their age (0.25 mL if ≤35 months or 0.5 mL if ≥4 years). Children aged ≥6 years who are receiving influenza vaccine for the first time should receive 2 doses separated by at least 4 weeks.

Additional information about vaccines, including precautions and contraindications for vaccination and vaccine shortages, is available at http://www.cdc.gov/nip or at the National Immunization Information Hotline, telephone 800-232-2522 (English) or 800-232-0233 (Spanish). Copies of the schedule can be obtained at http://www.cdc.gov/nip/recs/child-schedule.htm. Approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/nip/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).
Hypersensitivity Reaction

Henoch-Schonlein purpura
Hypersensitivity Reaction

**Hypersensitivity or allergy**

* An immune response results in exaggerated reactions harmful to the host

* There **are four types** of hypersensitivity reactions:
  
  Type I, Type II, Type III, Type IV

* Types I, II and III are **antibody mediated**

* Type IV is **cell mediated**
Type I: Immediate hypersensitivity

* An antigen reacts with cell **fixed antibody (IgE)** leading to release of soluble molecules (mediators)

* Soluble molecules cause the manifestation of disease

* **Systemic life threatening; anaphylactic shock**

* Local atopic allergies; bronchial asthma; hay fever and food allergies
Pathogenic mechanisms

* Three classes of mediators **derived from mast cells**
  1) Preformed mediators stored in granules (histamine)
  2) Newly sensitized mediators: leukotrienes, prostaglandins, platelets activating factor
  3) Cytokines produced by activated mast cells, basophils e.g. TNF, IL3, IL-4, IL-5, IL-13, chemokines

* These mediators cause: smooth muscle contraction, mucous secretion and bronchial spasm, vasodilatation, vascular permeability and edema
Anaphylaxis

* Systemic form of Type I hypersensitivity

* Exposure to allergen to which a person is previously sensitized

* Allergens:
  - Drugs: penicillin
  - Serum injection: anti-diphtheritic or ant-tetanic serum anesthesia or insect venom

* Clinical picture:
  - Shock due to sudden decrease of blood pressure, respiratory distress due to bronhospasm, cyanosis, edema, urticaria

* Treatment: corticosteroids injection, epinephrine, antihistamines
Atopy
* Local form of type I hypersensitivity

* Exposure to certain allergens that induce production of specific IgE

* Allergens:
  - Inhalants: dust, mite, feces, tree or pollens, mould spores
  - Ingestants: milk, egg, fish, chocolate
  - Contactants: wool, nylon, animal fur
  - Drugs: penicillin, salicylates, anesthesia, insect venom

* There is a strong familial predisposition to atopic allergy

* The predisposition is genetically determined
Type II: Cytotoxic or Cytolytic Reactions

* An antibody (Ig G or Ig M) reacts with antigen on the cell surface

* This antigen may be part of cell membrane or circulating antigen (or hapten) that attaches to cell membrane
Clinical Conditions

1) Transfusion reaction due to ABO incompatibility

2) Rh-incompatability (Haemolytic disease of the newborn)

3) Autoimmune diseases
   The mechanism of tissue damage is cytotoxic reactions
   e.g. SLE, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrototoxic nephritis, Hashimoto’s thyroiditis

4) A non-cytotoxic Type II hypersensitivity is Graves’s disease
   It is a form of thyroditits in which antibodies are produced against TSH surface receptor
   This lead to mimic the effect of TSH and stimulate cells to over-produce thyroid hormones
Clinical Conditions

5- Graft rejection cytotoxic reactions:

In hyperacute rejection the recipient already has performed antibody against the graft.

6- Drug reaction:

Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis.

Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura.
Penicillin Allergy

Emory U./Dr. Sellers
Type III Hypersensitivity

Immune Complex Mediated Reaction
Type III: Immune Complex Mediated Reaction

*When antibodies (Ig G or Ig M) and antigen coexist: immune complexes are formed*

*Immune complexes are removed by reticuloendoth. syst.*

*Some immune complexes escape phagocytosis*

*Immune complexes deposited in tissues on the basement membrane of blood vessels and cause tissue injury*
Mechanism Of Tissue Injury

Immune complexes trigger inflammatory processes:

1) Immune complexes → activate the complement → release anaphylatoxins C3a, C5a

   → stimulate degranulation of basophiles and mast cells → release histamine

   Histamine increases vascular permeability and helps deposition of immune complexes

2) Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammation. Pro.

3) Platelets are aggregated with two consequences
   a) release of histamine
   b) form of microthrombi which lead to ischemia
Clinical conditions of Type III Hypersensitivity

Diseases produced by immune complexes are those in which antigens persists without being eliminated as:

a. Repeated exposure to extrinsic antigen
b. Injection of large amounts of antigens
c. Persistent infections
d. Autoimmunity to self components
1- Arthus Reaction

* This is a local immune complex deposition phenomenon, e.g., diabetic patients receiving insulin subcutaneously.

* Local reactions in the form of:
  - edema
  - erythema
  - necrosis

* Deposited immune complexes in small blood vessels leading to:
  - vasculitis
  - microthrombi formation
  - vascular occlusion
  - necrosis
2- Serum Sickness

* A systemic immune complex phenomenon
* Injection of large doses of foreign serum
* Antigen is slowly cleared from circulation
* Immune complexes are deposited in various sites

* 10 days after injection

- fever
- urticaria
- arthralgia
- lymphadenopathy
- splenomegaly
- glomerulonephritis
- antidiphtheritic serum

* e.g. treatment with
  - penicillin
  - sulphonamides
Type IV
Cell Mediated
Delayed Type Hypersensitivity
Type IV: Cell Mediated Delayed Type Hypersensitivity

- Triggering DTH reactions by TH1
  - T-cells cause tissue injury by
    or
  - Directly killing target cells by CD8

- TH1 and CD8 T cells secrete cytokines (IFN-γ and TNF)

- Cytokines attract lymphocytes, activate macrophages, and induce inflammation

- Tissue damage results from products of activated macrophages
Tuberculin – Type Hypersensitivity

* When PPD is injected intradermally in sensitized person

* Local indurated area appears injection site (48-72 hs)

* Indurations due to accumulation Of:
  - macrophages and lymphocytes

* Similar reactions observed in diseases
  - e.g. brucellosis, lepromin test in leprosy, Frei’s test in lymphogranuloma venereum

THERE IS MORE TO IT
The end

- Stop complaining, it has been resumed

It can be worst