Lecture 1 (This handout also contains the notes for Lecture 2 and most of Lecture 3; it covers the material in Chapters 1 and 3 in your text.) (Chapter 2 will be covered later in the course.)

Elements of the Immune System and their Roles in Defense

Introduction:

- Definition of immunology: “Immunology is the study of the physiological mechanisms that humans and other animals use to defend their bodies from invasion by other organisms.”

- It was observed historically that people who survived an epidemic disease were resistant to that disease if they subsequently encountered it; i.e., they were immune to subsequent infection. Microorganisms have the advantage of reproducing and evolving more rapidly than their human hosts. In response, the human body invests heavily in cells dedicated to defense, which collectively form the immune system.

- In spite of the presence of an immune system, all humans suffer from infections, especially when young. This is because it takes time for the adaptive immune system to build up a strong response to an invading microorganism. During this time, the invader can multiply and cause disease. (As we will be discussing, the innate immune system does the best it can to hold the line until the adaptive immune system can kick in.)

- To provide protective immunity for the future, the immune system must first do battle with the microorganism. This puts individuals at greatest risk during their first encounter with a microorganism, and explains the historically high incidence of child mortality. When an entire population encounters a completely new pathogen, a catastrophic epidemic can occur, as experienced by Native Americans when they encountered European pathogens (Measles, smallpox, etc).


- In medicine, the greatest triumph of immunology has been the discovery of vaccination, or immunization.
  In 1796, Edward Jenner\(^1\) showed that inoculation with cowpox virus protected his patients against infection by the related (and much more severe) smallpox virus. (vacca = cow, hence the name of the cow disease, “vaccinia”, and thus the word “vaccination” for the immunization with cow virus.) (Fig 1.1)

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\(^1\) Hundreds of years earlier, in Asia, it was discovered that scratching the skin with small amounts of smallpox virus itself can induce protective immunity. (This process is called variolation.) Lady Mary Worthy Montagu introduced this method into Western Europe 75 years before Jenner’s work. Jenner’s innovation was to use cowpox virus: much less risk.
Smallpox has been eradicated worldwide by vaccination!

Should the few remaining stocks of smallpox virus be destroyed?
- Diphtheria, poliomyelitis, and measles have been virtually eliminated in U.S.
- US residents must still be vaccinated because these viruses are still endemic in other parts of the world.

Fig 1.27 (p. 24) (3rd Ed), SSPE = "subacute sclerosing panencephalitis" (A late complication in some cases of measles infection.)
### Diseases for which vaccines are available:

(Not all vaccines are equally effective; some are expensive, and/or require refrigeration.)

<table>
<thead>
<tr>
<th>Bacterial diseases</th>
<th>Types of vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>Toxoid</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxoid</td>
</tr>
<tr>
<td>Pertussis (Bordetella pertussis)</td>
<td>Killed bacteria. Subbunit vaccine composed of pertussis toxoid and other bacterial antigens</td>
</tr>
<tr>
<td>Paratyphoid fever (Salmonella paraatyphi)</td>
<td>Killed bacteria</td>
</tr>
<tr>
<td>Typhus fever (Rickettsia prowazeki)</td>
<td>Killed bacteria</td>
</tr>
<tr>
<td>Cholera (Vibrio cholerae)</td>
<td>Killed bacteria or cell extract</td>
</tr>
<tr>
<td>Plague (Yersinia pestis)</td>
<td>Killed bacteria or cell extract</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Attenuated strain of bovine Mycobacterium tuberculosis (BCG)</td>
</tr>
<tr>
<td>Typhoid fever (Salmonella typhi)</td>
<td>Vi polysaccharide subunit vaccines. Live-attenuated oral vaccine</td>
</tr>
<tr>
<td>Meningitis (Neisseria meningitidis)</td>
<td>Purified capsular polysaccharide</td>
</tr>
<tr>
<td>Bacterial pneumonia (Streptococcus pneumoniae)</td>
<td>Purified capsular polysaccharide</td>
</tr>
<tr>
<td>Meningitis (Haemophilus influenzae)</td>
<td>H. influenzae polysaccharide conjugated to protein</td>
</tr>
</tbody>
</table>

### Viral diseases

<table>
<thead>
<tr>
<th>Virus</th>
<th>Form of vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Measles</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Mumps</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Rubella</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Polio</td>
<td>Attenuated virus (Sabin) or killed virus (Salk)</td>
</tr>
<tr>
<td>Varicella (chickenpox)</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Rotavirus diarrhea</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated virus</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated virus (human). Attenuated virus (dogs and other animals). Recombinant live vaccine-rabies (animals)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Subunit vaccine (recombinant hepatitis antigen)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Subunit vaccine (recombinant hepatitis antigen)</td>
</tr>
</tbody>
</table>

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4.
Currently, North American children are vaccinated against 9 pathogens:

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<table>
<thead>
<tr>
<th>Vaccine giver</th>
<th>1-2 months</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>15 months</th>
<th>16-18 months</th>
<th>4-6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria–tetanus–pertussis (DTP/DTaP)* (Whooping Cough)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivalent oral polio (TVOP) (Sabin) 335</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles/mumps/rubella (MMR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus E conjugate (HIBC)* (Meningitis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B† [used to contain Hg⁺⁺] Thimerosal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| † Attenuated viruses cause disease in some individuals (extremely rare)

* "p" = whole, heat-killed pertussis bacteria

"aP" = acellular pertussis = pertussis toxoid + some cellular components of pertussis bacteria

⇒ reduced incidence of inflammation, pain, fever (less neurological side effects)
There remain many diseases for which a vaccine is not available (or the current vaccine is not very effective):

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual mortality</th>
<th>Annual incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>856,000</td>
<td>213,743,000</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>8000</td>
<td>No numbers available</td>
</tr>
<tr>
<td>Worm infestation</td>
<td>22,000</td>
<td>No numbers available</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,960,000</td>
<td>6,346,000</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>2,946,000</td>
<td>4,073,920,000</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>4,299,000</td>
<td>362,424,000</td>
</tr>
<tr>
<td>AIDS (HIV)</td>
<td>138,000</td>
<td>411,000</td>
</tr>
<tr>
<td>Measles†</td>
<td>1,458,000</td>
<td>44,334,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>No numbers available</td>
<td>~170,000,000</td>
</tr>
</tbody>
</table>

[These diseases are due to chronic infections; the pathogens are adept at evading and subverting the immune system.]
Any organism is potential for causing disease = "pathogen."

There are 4 broad categories:

<table>
<thead>
<tr>
<th>Type of pathogen</th>
<th>Examples</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Salmonella enteritidis, Mycobacterium tuberculosis</td>
<td>Food poisoning, Tuberculosis</td>
</tr>
<tr>
<td>Viruses</td>
<td>Varicella, Influenza, HIV</td>
<td>Smallpox, Flu, AIDS</td>
</tr>
<tr>
<td>Fungi</td>
<td>Epidermophyton floccosum, Candida albicans</td>
<td>Ringworm, Thrush, candidiasis</td>
</tr>
<tr>
<td>Parasites</td>
<td>Trypanosoma brucei, Leishmania donovani, Plasmodium falciparum, Ascaris lumbricoides, Schistosoma mansoni</td>
<td>Sleeping sickness, Leishmaniasis, Malaria, Ascariasis, Schistosomiasis</td>
</tr>
</tbody>
</table>

These organisms have evolved ways to invade our bodies, replicate, and be transmitted.
Three

What are our defenses against pathogens?

1. Skin and mucosal surfaces form physical barriers against infection.

Skin: keratinized cells form tough, impermeable barrier.
(Cuts, burns breach this barrier)

Mucosa: Internal mucosal surfaces are protected by the thick, viscous mucous they secrete; or by enzymes like lysozyme in tears; or by acidic pH (vagina, stomach), etc.
If the physical barriers are breached, the body mounts an immune response.

here are 2 types of immune response: **Innate** and **Adaptive**:

a. **Innate immunity**
   1. Immediate response, evolutionarily selected to recognize general features common to most pathogens, not always able to eliminate infection and does not in itself lead to long-term immunity. The innate immune response is designed to contain the infection until the more powerful forces of the adaptive immune response are marshalled.

b. **Adaptive immunity**
   1. Slower onset, but very specific response to individual pathogen.
   2. Based on lymphocytes: B-cells and T-cells. B-cells produce antibodies and T cells have T-cell receptor molecules on their surfaces; the T-cell receptor is very specific, just like antibodies.
   3. Adaptive immunity has memory, and responds more rapidly and more strongly upon second encounter with a pathogen.

<table>
<thead>
<tr>
<th>Recognition mechanisms of Innate Immunity</th>
<th>Recognition mechanisms of adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid response (hours)</td>
<td>Slow response (days to weeks)</td>
</tr>
<tr>
<td>Invariant</td>
<td>Variable</td>
</tr>
<tr>
<td>Limited number of specificities</td>
<td>Numerous highly selective specificities</td>
</tr>
<tr>
<td>Constant during response</td>
<td>Improve during response</td>
</tr>
</tbody>
</table>

Common effector mechanisms for the destruction of pathogens

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Cells of the Immune System

The cells responsible for both innate and adaptive immune responses are principally the white blood cells, known collectively as leukocytes ("leuko" = white). There are 3 broad categories of leukocytes: (a) lymphocytes, (b) phagocytes, and (c) auxiliary cells (Roitt, Fig 1.4, above). A fourth type of cell that plays a very important role is the dendritic cell.

a. Lymphocytes

There are three kinds of lymphocytes:

1. **B-cells**: produce antibody (any of 5 kinds: IgA, IgD, IgG, IgE, IgM)

2. **T-cells**: produce cytokines, that activate themselves and other lymphocytes.
   - There are 2 broad categories of T-cells: CD4 T-cells and CD8 T-cells.
     a. CD4 T-cells can differentiate into **T**_{Helper} cells: 2 kinds: T_{H1} cells (activate macrophages) and T_{H2} cells (activate B cells).
     b. CD8 T-cells can differentiate into **T**_{Cytotoxic} cells (otherwise known as CTLs ["cytotoxic lymphocytes"], or T_{Killer} cells). CTLs kill virus-infected cells.

3. **Large granular lymphocytes** (aka natural killer cells [NK cells]). NK cells produce cytokines and also exocytose the contents of their granules to release molecules that kill their target cells (often the targets of NK cells are cancer cells)

Phagocytes

There are three kinds of phagocytes:

1. **Macrophages** (aka mononuclear phagocyte). (Macrophages arise from monocytes. Monocytes circulate in the blood; when they leave the blood and enter the tissues, they differentiate into macrophages.) Many macrophages are resident in various tissues: skin: Tissue Macrophages; liver: Kupffer cells; brain: Microglial cells; bone: Osteoclasts. Are important in innate immune response. Also present antigen to lymphocytes to initiate adaptive response.

   - **T**_{H1} dominated response \(\rightarrow\) Tuberculous leprosy (mild leprosy)
   - **T**_{H2} dominated \(\rightarrow\) Lepromatous leprosy (bad)
2. Neutrophils. (aka Polymorphonuclear Neutrophils [PMNs]) Neutrophils are smaller than macrophages, and are by far the most abundant white blood cell. They are not resident in tissue, but migrate to an infected or damaged tissue site. Are on the front line of defense and play an important role in innate response. Neutrophils belong to a class of cells called Granulocytes. Phagocytose bacteria, and release cytotoxic contents of granules to kill bacteria.

3. Eosinophils. Eosinophils can act as phagocytes, but they are also granulocytes, and their most well known role is to release the toxic contents of their granules to attack parasites.

c. "Auxiliary Cells" (not a term used in your text)
Three kinds of auxiliary cells:
1. Basophils
2. Mast Cells
3. Platelets
Basophils and mast cells are granulocytes; they bind IgE, and in response to antigen, release the inflammatory contents of their granules. Both cell types are associated with allergic responses, and play a role in immunity to parasites. Platelets play a role in blood clotting, and also release inflammatory mediators.

The three kinds of granulocytes (Neutrophils, eosinophils, & basophils) are also called polymorphonuclear leukocytes

d. Dendritic Cells Dendritic cells are another very important component of the immune system. They play a big role in initiating the adaptive response, by endocytosing large quantities of foreign material, digesting it, and presenting the peptide components to T cells. They are star-shaped.
In a blood smear, you will see mostly red blood cells. White blood cells are relatively rare, and when you do come across one in a field, it is most likely either a neutrophil or a small lymphocyte (T or B cell):

**Figure 1.12 (3rd Ed.)**

3rd Ed.: Figure 1.12 in your book lists the relative abundance of the various leukocytes in the blood:

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Proportion of leukocytes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>40–75</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>1–6</td>
</tr>
<tr>
<td>Basophil</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Monocyte</td>
<td>2–10</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>20–50</td>
</tr>
</tbody>
</table>
The cells of the immune system derive from precursors in the bone marrow.

Like all blood cells, lymphocytes are derived from pluripotent stem cells located in the bone marrow. The pluripotent precursor of all blood cells is called the **hematopoietic stem cell**. Daughter cells of this cell type can become other, less pluripotent stem cell types: the **erythroid progenitor**, for example, is the source of both erythrocytes and megakaryocytes (produce platelets). Lymphocytes stem from the **common lymphoid progenitor**. Macrophages, dendritic cells, mast cells, & granulocytes (the “**myeloid lineage**”) stem from myeloid progenitor cells (“**myeloid**” = bone marrow). (Fig. 1.7)
The sites of the principal lymphoid tissues within the human body

B-cells stay in the bone marrow while they rearrange their non-functional germ-line genes to produce a functional immunoglobulin gene. T-cells leave the bone marrow, and go to the thymus; in the thymus, the genes encoding the T-cell receptor are rearranged to yield functional T-cell receptor (TCR) genes. **Bone marrow and the thymus are called “primary lymphoid tissues.”** *(Shown in red.)* After B- and T-cells have rearranged their immunoglobulin and TCR genes, these cells migrate to **secondary or peripheral lymphoid tissues**: lymph nodes, spleen, tonsils, etc. *(Shown in yellow.)*
Circulating lymphocytes meet lymph-borne pathogens in draining lymph nodes

Lymphocytes constantly leave the blood and enter lymph nodes. If they encounter pathogens in a particular lymph node, B- and T-cells remain in the lymph node and interact with each other to mount an adaptive immune response, becoming activated effector cells. Otherwise, they leave the node and return via efferent lymph to the thoracic duct, where they re-enter the blood.

Figure 1.0

Venous blood enters lymph node via venous blood

Arterial blood

Left subclavian vein

Lymphocytes re-enter the blood via the Thoracic Duct (drains into the left subclavian vein).

Pathogens from infected lymph drain into thoracic duct
defense

Lymph node

Lymphocytes and lymph return to the blood via the lymphatics

Pathogens from site of infection reach lymph nodes via lymphatics

Infected peripheral tissue

Patient confined to bed:
No muscle movement
No circ. of lymph
Fluid accum. in tissues
Edema
What lymph nodes look like:

B cells and T cells enter node through wells in a High Endothelial Venule. If B cells encounter antigen and are activated, T cell migrates out to form germinal center.

**The lymph node**

- **germinal center** (proliferating, activated B and T cells)
- **afferent lymphatic vessel**
- **-cell area**
- **lymph-born antigen**
- **germinal center**
- **lymphoid follicle** (mostly B cells)
- **medullary sinus**
- **artery**
- **vein**
- **afferent lymphatic vessel**
- **marginal sinus**

White = cortex (B cells)
Blue = paracortex (T cells)
Red = medulla
Pink = hilus

But when B and T cells pass through these subsequent lymph nodes, the do not enter the cortical or paracortical areas. They access the latter areas only via HEVs from the blood circulation.

Band T cells enter the lymph node via High Endothelial Venules, and leave via the efferent lymphatic vessel; they then travel from node to node, entering each subsequent node via efferent lymphatic vessels, leaving via efferent vessels. Lymphatic Fluid with B and T cells then ends up in the Thoracic duct (or right lymphatic duct), which drains into the left and right subclavian veins (which feed into the heart).
What happens in a lymph node:

Pathogens, and dendritic cells carrying pathogens (and their antigens), arrive at a lymph node in the afferent lymphatic vessel draining from the site of an infection. Macrophages resident in the lymph node engulf the pathogens. The incoming dendritic cells move to the T-cell areas of the lymph node, there they present antigen to "naïve" CD4 and CD8 T cells. Naïve T cells specific for the pathogen proliferate and differentiate into effector T cells (T_{Helper} and T_{Killer}). T_{Helper} cells then assist the proliferation and differentiation of B cells specific for the pathogen into antibody-secreting plasma cells.

Fig 1.18 (2nd Ed.) (Corresponds to Fig 1.22, 3rd Ed.)
Sometimes pathogens get directly into the blood (insect bite); in this case, the spleen captures the pathogen, and "white pulp" structures act like lymph nodes.

Figure 1.11: The spleen
- red pulp
- white pulp

Figure 1.12: Transverse section of white pulp of spleen
- marginal zone
- B-cell corona
- germinal center
- PALS (mostly T cells)
- central arteriole
- marginal sinus

The gut wall also has lymph node-like structures.

Figure 1.20: Peyer's patch
Gut-associated lymphoid tissues
- Gut lumen
- epithelium
- dome
- germinal center
- follicle (B-cell area)
- Gut wall

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More on the **Innate Immune Response:**

Macrophages and neutrophils (also known as polymorphonuclear neutrophils ["PMNs"]) have many different kinds of receptors that bind to certain bacterial cell surface components (eg, certain mannose-containing carbohydrates, peptidoglycans, bacterial lipopolysaccharides, etc). Binding leads to phagocytosis of the pathogen, and (via a class of receptors call "Toll-like receptors") to the release of inflammatory cytokines.

![Diagram of the innate immune response](image)
"calor, rubor, tumor, dolor"

In response to infection, macrophages trigger inflammation.

The inflammatory cytokines released by macrophages induce local dilation of blood capillaries, which by increasing the blood flow causes the skin to warm ("calor") and redden ("rubor"). Vascular dilation (vasodilation) introduces gaps between the capillary endothelial cells, increasing the leakage of blood plasma into the connective tissue. Such expansion of the local fluid volume causes edema or swelling ("tumor"); this in turn puts pressure on nerve endings, causing pain ("dolor").

These cytokines also alter the set of adhesion proteins expressed on the surface of the capillary endothelial cells, making these blood vessel cells "sticky" for other cells like neutrophils and monocytes. These cells then leave the circulation and enter the infected tissue area. The monocytes differentiate into macrophages ["MΦs"] at the site of infection.

![Diagram of immune response](image-url)
More on Neutrophils:

Neutrophils are stored in the bone marrow and move in large numbers to sites of infection, where they act to ingest and kill pathogens. After one round of ingestion and killing, a neutrophil dies. The dead neutrophils are eventually mopped up by long-lived tissue macrophages. Pus is largely composed of dead neutrophils.

Figure 1.13: Large reserves of neutrophils are stored in the bone marrow and are released when needed to fight infection.

Neutrophils travel to and enter the infected tissue, where they engulf and kill bacteria. The neutrophils die in the tissue and are engulfed and degraded by macrophages.

(Neutrophils are like worker bees— they sting one time, and then die.)
Innate immunity is also mediated by the serum proteins comprising the complement system:

Pathogen surface proteins activate the cleavage of certain serum proteins called "complement"; one cleavage product forms a covalent bond with the surface of the pathogen; the other (smaller) cleavage product serves as a chemo-attractant for macrophages and granulocytes. These cells have receptors for the complement fragment on the surface of the pathogen, and binding of these receptors to the complement leads to the phagocytosis of the pathogen.

![Diagram of complement system](image)
More on Adaptive Immunity:

- Adaptive immunity is based on the specific recognition of molecular structures ("antigens") by one or more of a large number of pre-existing immunoglobulins and T-cell receptors.

- Immunoglobulins are expressed on the surface of B cells, where they can bind pathogens. Effector B cells, called plasma cells, secrete soluble forms of these immunoglobulins.

- In contrast, T-cell receptors are only ever expressed as cell-surface recognition molecules.

- Immunoglobulins and T-cell receptors are structurally related molecules whose diversity of antigen-recognition sites is generated by similar genetic mechanisms.

- Immunoglobulins consist of domains called variable regions that contain antigen-binding sites, and a constant region that is identical among all immunoglobulin. The constant regions of immunoglobulins contain binding sites for cell-surface receptors on phagocytes and also for complement proteins.

- Like immunoglobulins, T-cell receptors contain constant and variable regions.
Clonal selection of lymphocytes by a pathogen:

- Millions of lymphocytes are generated, each expressing a particular surface immunoglobulin (or T-cell receptor).

- On infection, only the very small proportion of lymphocytes which happen to have receptors that bind to the pathogen will be activated to divide and differentiate into effector cells. This process is called Clonal selection.
The diversity of immunoglobulins and T-cell receptors is generated by gene rearrangement.

Rearrangement occurs during B-cell and T-cell development.

Antibody molecule (Immunoglobulin)

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Two signals are required for lymphocyte activation:

**B cells**
1. Ag - Ab
2. Interleukin from Th

**T cells**
1. Ag - TCR
2. B7 - CD28 signal from "Antigen-Presenting cell" or dendritic cell

---

**Antigen receptor binding and activation of B cell by T cell**

1. T-cell receptor
2. Antigen
   - Peptide
   - MHC-I
   - B lymphocyte

**Antigen receptor binding and co-stimulation of T cell by dendritic cell**

1. Peptide
2. Antigen
3. B7
   - Co-stimulator
4. Ag - CD28
   - T lymphocyte
   - (CD4 or CD8)

---

B-cell Proliferation and differentiation to effector function B lymphocyte becomes Ab-secreting plasma cell

T-cell Proliferation and differentiation to effector function T lymphocyte becomes "armed effector T cell"

[TH1, TH2]

*peptides derived from the antigen are bound on the surface of a protein called the "MHC" molecule; T-cell receptors bind the peptide presented on an MHC molecule.

Janeway Fig 1.20
B cells recognize native proteins, whereas T cells recognize peptides presented by MHC molecules:

(MHC = "Major Histocompatibility Complex")
**B-cell activation: Role of TH cells**

**For example:** KLH

- **KLH** → Phosphotyrosine hapten → Keyhole Limpet, a carrier protein → Hemocyanin

**This is the one-in-a-million B cell**

- **TH cell** releases IL-4

- **B cell** proliferates to form clone because of T-cell lymphokine stimulation

- **TH cell** recognizes peptide-MHC complex on B cell

**Macrophage** binds hapten-carrier complex nonspecifically; internalizes and degrades

**Macrophage** internalizes hapten-carrier complex; peptide fragments are displayed on surface with class II MHC

**TH cell** binds to peptide-MHC complex, activating IL-2 secretion and production of IL-2 receptor

**CD4 T-cell**

**TH cell** proliferates to form clone because of IL-2 stimulation

**Not in your text**

**Figure 27-38** B-lymphocyte activation. A hapten-carrier complex activates B cells by first stimulating TH cells. The hapten-carrier complex is an intact protein to which several hapten molecules have been covalently coupled. The hapten portion binds to a B cell but cannot by itself initiate B-cell proliferation. The B cell internalizes the hapten-carrier complex and digests it, and peptide portions of the carrier are displayed on the B-cell surface as a complex with class II MHC protein. A macrophage cell also internalizes carrier protein and displays peptide fragments on its surface in association with class II MHC. The TH cells with peptide-specific receptors bind to the peptide-MHC complex displayed on the macrophage surface. This binding stimulates the TH cells, which then proliferate, recognize the identical peptide-MHC complex on the B cell, and secrete factors that stimulate the B cell to grow.
The two types of MHC molecule:

Expressed on all cells

Expressed on "Professional Antigen-presenting cells"

- MHC class I
- Peptide
- Beta 2 Microglobulin
- Cell membrane

- MHC class II

- Viral peptides
- MHC class I

- Human MHC genes are called HLA ("human leukocyte antigen").
- Mouse MHC genes are called H-2 (H = "Histocompatibility").
Processing of antigens presented by MHC I and MHC II molecules occurs in different cellular compartments:

- MHC II molecules present peptides derived from endocytosed antigens. This pathway only occurs in professional antigen presenting cells, such as macrophages, dendritic cells and B cells.

- Peptides from all intracellular proteins (including viral proteins if the cell is infected) are continuously being presented in all cell types by MHC I molecules. This is how the immune system learns if a cell is infected with a virus (or other intracellular pathogen).
Chromosomal organization of the major histocompatibility complex of genes in humans and in the mouse

- Human HLA genes are located on chromosome 6; mouse H-2 genes are on chromosome 17.
- MHC I and MHC II genes are highly polymorphic; the particular set of MHC alleles found on an individual chromosome is called the MHC haplotype.
- (MHC III genes code for peptide transporters, proteosome subunits and other non-polymorphic molecules.)

Each copy of chrom. 6 codes for:

- 3 MHC II molecules (DP, DQ, + DR genes)
- 3 MHC I molecules (A, B, + C genes)

The 6 on maternal chrom. Gene structure of the human MHC are usually different from the 6 on the paternal chromosome; so we usually HLA make 6 diff. MHC I and 6 diff. MHC II molecules

- Many/all of ours probably different from yours

Gene structure of the mouse MHC

H-2 "polymorph" alleles

(There are 7200 alleles of some HLA genes, eg HLA-DRβ, HLA-B.)

28.
Cytotoxic T cells recognize viral peptides presented by MHC I molecules and kill virally-infected cells:

(Tc cells are also called "CD8 T cells")
Helper T cells are activated by foreign peptides presented by MHC II molecules

- Th1 cells mediate cellular immunity by, for example, activating macrophages.
- Th2 cells mediate humoral immunity by activating B cells to produce antibodies.

Figure 1.22

Macrophage engulfs and degrades bacterium, producing peptides

Bound peptides transported by MHC class II to the cell surface

Th1 cell recognizes complex of peptide antigen with MHC class II and activates macrophage

Th2 cell recognizes complex of peptide antigen with MHC class II and activates B cell

(TH cells are also called "CD4 cells") 30. (CD4 is the receptor for HIV, so HIV will kill Th cells)
How antibodies combat infection:

- There are 5 immunoglobulin isotypes (5 kinds of antibodies): IgA, IgD, IgE, IgG, IgM; surface IgM and IgD are the antigen receptors on circulating B cells; IgM is always the first antibody to be secreted in the immune response. IgM and IgG are the predominant antibodies found in blood. IgA is secreted across mucosal membranes to neutralize pathogens for example in the gut; it is also secreted in mother’s milk; IgE binds to mast cells and plays a role in allergic responses and in combating worms, protozoa and other parasites.

- The most important function of IgG antibodies is to facilitate the phagocytosis of extracellular microorganisms and microbial toxins. A bacteria coated with antibody is more efficiently phagocytosed, a phenomenon called opsonization; opsonization can also be achieved by a coating of complement. (IgM can bind complement.)

- Binding of antibodies to a toxin or organism can also inhibit its biological function; this mechanism is called neutralization.
Adaptive immune responses give rise to long-lived immunological memory and protective immunity:

- The severity of a first encounter with a pathogen arises because the primary immune response is developed from very few lymphocytes; the time taken to expand their numbers provides an opportunity for the pathogen to cause disease symptoms.
- The clones of lymphocytes produced in the primary response include long-lived memory cells, which can respond much more quickly and forcefully to subsequent encounters with the same pathogen.
- The potency of the secondary immune response is generally sufficient to repel the pathogen before it can produce and disease symptoms. This is the basis for the success of vaccination. If sufficient numbers of individuals in a population are vaccinated, epidemics are prevented.
Aberrations of the immune system have many consequences:

- The immune system can be compromised by inherited **immunodeficiencies** or by the actions of certain pathogens or toxins.

  **Examples of inherited immunodeficiencies:**
  
  (a) "**Bubble boy**": child in Houston who survived many years enclosed in a plastic bubble to protect him from infection. He suffered from X-linked severe combined immunodeficiency (SCID). This deficiency is due to a mutation in a gene encoding the common $\gamma$ chain of certain interleukin receptors; it results in the failure of both B and T cells to develop.
  
  (b) "**Nude mice**": Mice homozygous for mutations in the gene for the transcription factor *Whn* fail to develop fully functional thymus tissue (also fail to make functional hair follicles). This drastically reduces T cell production. Nude mice readily accept transplants of foreign tissue, which has made them useful in measuring, for example, the properties of various genetically modified experimental cancer cells.

  **Example of an immunodeficiency caused by a pathogen:**
  
  AIDS, caused by the HIV virus. HIV infects and kills $T_H$ cells, leading to the eventual collapse of the immune system.

- When misdirected against innocuous materials or normal components of the human body, the immune system can cause **allergies**, or **autoimmune diseases**.

  **Examples of autoimmune diseases:**
  
  - **Systemic lupus erythematosus** (immune reaction against self chromatin)
  - **Type I (juvenile) diabetes** (immune reaction against pancreatic $\beta$-cell antigen)
  - **Rheumatoid arthritis** (immune reaction against unknown synovial joint antigen)
  - **Multiple sclerosis** (immune reaction against myelin oligodendrocyte protein)

- For an increasing number of diseases, the replacement of tissues or organs by **transplantation** is being used. A major factor limiting transplantation has been tissue incompatibilities caused by the extensive polymorphism of MHC class I and class II genes. Transplant rejection that might be caused by relatively minor (and not so minor) MHC incompatibilities can be suppressed by a new generation of **immunosuppressive drugs**, such as **cyclosporin A**, **tacrolimus** (FK506), and **rapamycin** (sirolimus).