The Lymphatic System (Immune System)
Nonspecific Resistance, Specific Immunity

Taft College
Human Physiology
Lymph
• Another body fluid in addition to the blood (plasma) and interstitial fluid.

The Nature of Lymph
• As blood makes its way through the capillaries, the heart exerts enough pressure to force blood plasma out through the capillary walls.
• At this point, the fluid is called tissue fluid or interstitial fluid.

![Diagram of body fluids](image-url)
• Tissue fluid is similar in function to blood in that the fluid baths the cells in a medium full of nutrients and oxygen.
• Tissue fluid returns back through the venous side capillary walls and into general circulation.

• The excess interstitial fluid that does not return directly into the blood capillaries will enter the lymph system through the porous walls of the lymph capillaries.
• It is now called lymph.
• Lymph and plasma are very similar, the major difference being that plasma contains more protein.
In the lymphatic system, the lymph makes its way back toward the heart through progressively larger lymph vessels through lymph nodes that serve to filter the lymph.

The lymph nodes contain:

- mature lymphocytes which recognize foreign proteins (non-self antigens) that are carried by lymph fluid from tissues or blood.
- Foreign antigens in the lymph will trigger an immune response.

Located at intervals along lymph vessels
Act as a filter for lymph
Contain lymphocytes that can recognize a foreign invader
• From the lymph nodes the lymph passes through progressively larger lymphatic ducts that empty the filtered lymph into some large veins associated with the heart.

• Lymph movement is relatively slow as there is no dedicated organ pump such as the heart.
The Flow of Lymph

- The lymph vessels generally follow the surface veins or deep arteries on their path to the heart.

- The surface lymph vessels become visible as red streaks when there is inflammation with an aggressive pathogen.
Lymph Flow Back To General Circulation

Five things serve to return lymph back in the direction of the heart.

1. **Skeletal muscle pump** - Lymph is circulated by skeletal muscle action, that squeezes the vessels and move the lymph along.
2. **One-way valves** - The lymphatic vessels contain one-way valves. Once lymph is moved past a valve, it cannot move backwards, and thus is kept moving towards the heart.
3. **Thoracic pump** - Inhaling also aids in lymphatic circulation by creating negative pressure.
   As the thorax expands, so do the large veins within the thoracic region which act like a suction pump to draw venous blood and lymph toward the heart.
4. **Gravity** aids the return of lymph for vessels above the heart.
5. **Ventricular relaxation** creates suction (negative pressure) along with the thoracic pump.

Skeletal Muscle Pump
w/ One-way valves
Aids in the return of “tissue fluid” back into blood vessel circulation.

The lymphatic system carries out the immune response. It defends against foreign (non-self) antigens (organisms, toxins, etc.)

A. Lymphocytes recognize foreign cells and substances.
B. Serves as a major immunological activity center with two lymphocyte populations:

1. Some lymphocytes (B cells) produce antibodies specific to foreign organism and macromolecules).
2. Other lymphocytes (T cells = killers) destroy the foreign organisms by causing them to rupture and by releasing cytotoxic chemicals.
Functions of The Lymphatic System

2. The lymphatic system carries out the immune response.
   C. Lymph nodes filter foreign materials (e.g. bacteria) from the “blood”. The lymph nodes are the focus of this activity where the majority of lymphocytes reside.
   D. Produces clones (multiple identical copies) of activated lymphocytes when stimulated by a foreign antigen.

3. Absorbs fats from the small intestine.
The body’s defenses against disease has **2 major categories**:

1. **Nonspecific Defenses** – Represents the body’s 1st and 2\(^{nd}\) Line of Defense. Nonspecific means they are designed to work on **any invader**.

2. **Specific Immunity** – Represents the body’s 3\(^{rd}\) Line of Defense. Specific means they target a **specified or particular invader**.

### Nonspecific defense mechanisms

<table>
<thead>
<tr>
<th>1st line of defense</th>
<th>2nd line of defense</th>
<th>3rd line of defense</th>
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<tbody>
<tr>
<td>Skin</td>
<td>Phagocytic white blood cells</td>
<td>Lymphocytes</td>
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<tr>
<td>Mucous membranes</td>
<td>Antimicrobial proteins</td>
<td>Antibodies</td>
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<tr>
<td>Secretions of skin and mucous membranes</td>
<td>Inflammatory response</td>
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### Specific defense mechanisms (Immune system)

- Lymphocytes
- Antibodies
Nonspecific Defense Mechanisms Against Disease

• **Nonspecific Defenses** offer **immediate protection** against a variety of pathogens and foreign substances.

• The **1st line of defense** is the use of physical or mechanical barriers to attempt to **prevent initial invasion or access** into the body.

• **If invasion occurs**, the **2nd line of defense** includes chemicals, heat, and killer cells that make survival conditions difficult for the invader.
Nonspecific Defense Mechanisms Against Disease

1st Line of Defense Denies Access
1. **Mechanical Factors** (skin, mucous membranes, mucous, hairs, cilia, lacrimal apparatus, saliva, urine, defecation and vomiting)

2nd Line of Defense Attacks with Chemicals, Killer Cells, and Heat if Foreign Invader Gains Access

2. **Chemical Factors** (pH of skin, unsaturated fatty acids, lysosome, hyaluronic acid, gastric juice)
3. **Antimicrobial substances** (interferons, complement system)
4. **Natural killer cells** – nonspecific lymphocytes that can perforate foreign cells
5. **Phagocytosis** – neutrophils, eosinophils, and macrophages
6. **Inflammation** – confines and destroys microbes. Appear as redness, pain, heat, and swelling.
7. **Fever** – inhibits some microbes, fever increases their metabolic rate and they die.

Does your body take invasion seriously?
Specific Defense Mechanisms (Immunity) = 3rd Line of Defense

- Some Invaders get through the 1st line and 2nd line of non-specific defense mechanisms!!
- It is now up to the 3rd line of defense, specific immunity to try to protect you.

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<tr>
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<th>Specific defense mechanisms (Immune system)</th>
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Specific Defense Mechanisms (Immunity) = 3rd Line of Defense

- **Specific Immunity** is the immune response that is directed towards specific foreign invaders that include bacteria, toxins, viruses, or foreign tissues.

- This immune response is triggered by a substance that is part of the invader called a foreign antigen. The invading cell has cell identity markers “foreign antigens” that essentially state “this cell is not you!!”.

There are 2 types of Specific Immunity.

1. **Cellular Immunity** administered by the **T Lymphocytes**
2. **Antibody Immunity** administered by the **B Lymphocytes**
Lymphocytes Role in Immunity

• Immunity is administered by **T lymphocytes** (T cells) and **B lymphocytes** (B cells). These cells develop cell surface markers, some that act as antigen receptors that will recognize (specific) foreign antigens.

• During development, lymphocytes that “mistakenly” recognize self antigens are destroyed or inactivated to prevent unwanted attack of self tissue and proteins = an **auto-immune disease** in which the body is attacking its own normal tissues.
Foreign Antigen

- A foreign antigen is a specific chemical that can provoke the lymphocytes to respond by reacting with their surface antigen receptors. An invader may have many different foreign antigens embedded in its cell surface (epitopes).
  - Examples: Pollen, foreign proteins (chicken egg white), incompatible blood cells, bacteria, and transplanted tissues.
Cell mediated (cellular) immunity by T Lymphocytes = T cells

- Cell-mediated immunity starts with activation of a small number of T cells by a particular antigen.

- Once activated T cells will undergo cell division to form a clone (large population) of T cells that can recognize the foreign antigen.
Cell mediated (cellular) immunity by T Lymphocytes = T cells

There are 2 types of T cells: TH (helper) cells and TC (cytotoxic) cells

1. TH Helper cells- regulate (control) the immune response of both T cells and B cells. They secrete chemicals (interleukin 2) that recruit other immune cells and attract phagocytes.
   - **TH Helper cells signal the alarm or invasion** by foreign antigens.
     - Example: IL-2 (interleukin 2) activates B cells to produce antibodies and TC to cells attack the foreign cells. IL-2 can be given as a drug to enhance the immune response to cancer cells.
   - Without TH cells there is no effective immune response.
   - The HIV virus specifically destroys the TH cells which weakens our immune response to the point that death may ensue from overwhelming infection as person can no longer signal the alarm that foreign invaders are present.
Cell mediated (cellular) immunity by T Lymphocytes = T cells

There are 2 types of T cells: TH (helper) cells and TC (cytotoxic) cells

2. **TC (cytotoxic) cells** are killer T cells that can kill (cells, microbes, foreign antigens) in 2 ways by 2 chemicals they produce.
   1. **perforin** – perforin punches holes in the cell membrane of the invader
   2. **lymphotoxin** - fragments DNA of the invader.
Antibody mediated (humoral) immunity by B Lymphocytes = B cells

- B cells respond to a foreign antigen (extracellular = bacteria) by producing great amounts of antibody that will attach to the antigen and act in two ways:
  1. Inactivate it (such as a toxin)
  2. Mark it for destruction by phagocytosis or complement (as a bacteria or infected cell).
- Antibodies are proteins that can chemically bind to antigens and form a complex. It can only bind to the antigen that stimulated its production.
**Immunological Memory** – The immune system has a memory for what foreign antigens have been recognized and processed before so a second encounter will produce a quicker and stronger response.

**Primary response** – 1st or initial invasion or exposure

- It may take 3-6 days before the antibodies begin to appear in the body fluids. This lag phase is the time required for the few T and B cells with that antigen’s receptor to multiply into clones of cells that can respond.
- Antibody will peak at about 10 days and then decline.
- The primary response is often too slow and weak to protect you, so you show the symptoms of the disease.
- If you survive, the sets of cloned lymphocytes persist and are known as memory cells. These cells form what is called ‘immunological memory’.
- You now have some protection against that specific invader if exposed again.
Secondary response- 2nd invasion by the same invader

- Upon a second (or any subsequent) encounter with the same antigen, a quick and vigorous response occurs.
- Within hours an army of plasma cells is generated from the memory cell clones and within 2-3 days the antibody concentration is much higher than the original response.
- This is why measles and mumps immunize us against a second infection.
- You typically do not show the symptoms of disease.
- You have immunity.
Types of Immunity

There are 4 ways to acquire immunity:

Terminology
- Naturally exposed – in nature (normal) vs. Artificial exposure – by medical injection
- Active immunity – you produce antibodies/T cytotoxic cells vs. Passive immunity – you receive antibodies from mother or from injection from other source (often a horse), you do not produce them.

1. **Naturally acquired active immunity** - the body encounters the antigen from nature by infection, ingestion, breathing, etc. As a result of the exposure, you start producing antibodies/cytotoxic T cells.

2. **Naturally acquired passive immunity** - The transfer of antibodies across the placenta of a mother to its fetus or through the breast milk to baby.

3. **Artificially acquired active immunity** - Foreign antigens from dangerous microbes are made into a non invasive vaccine that will stimulate a primary, protective response and protect against subsequent encounters with that pathogen. Vaccines may contain: 1. killed organisms, 2. weakened organisms or 3. similar organisms.

4. **Artificially acquired passive immunity** - Injection of pre-formed antibodies (often obtained from a horse) into a person without active immunity to an antigen that is very dangerous.
   - Example: snake anti-venom contains (horse serum) antibodies produced by a horse that has been injected with the venom.
   - You don’t have time to wait for your body to produce its own antibodies!!!!
   - You may develop an immune reaction to the horse serum so only may be able to use this type of immunity one time safely.
Allergy (hypersensitivity)

- Sometimes the immune system overreacts to “weak” foreign antigen that most of us tolerate. These antigens are called allergens.
  - E.g. foods (milk, peanuts, shellfish, eggs), antibiotics (penicillin), venoms (bee, wasp, ants), chemicals in plants (pollens, poison oak, dust mites, molds).

- The range of reactions can be from the local reactions/irritations to death, as the reaction escalates and becomes systemic.

- Respiratory allergy results as pollens trigger an immune response where an inflammation occurs. Fluid secretion (mucous and tears), smooth muscle contraction of bronchioles, swelling of soft tissue due to fluid accumulation closes off the airway.
Blood Groups & Transfusions

• Red blood cells have over 100 antigens on their surface, but **only 2 of these make up your blood type.**
  – These antigens trigger such strong reactions in all people that we routinely test for their presence.

• The 2 major types of antigens important in blood type are: **Antigen A** and **Antigen B**.

• 4 possible blood types occur as result of the A and B antigens, each are determined by inheritance from your parents. These antigens make up the ABO Blood Grouping system.
**Antigen(s) Present Determine Blood Type**

- **Antigens** are found on the **surface of the RBC**.
- **Antibodies** are located in the **plasma**.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Blood Type</th>
<th>Antibody</th>
<th>Frequency in U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Only</td>
<td>A</td>
<td>Anti B</td>
<td>42%</td>
</tr>
<tr>
<td>B Only</td>
<td>B</td>
<td>Anti A</td>
<td>10%</td>
</tr>
<tr>
<td>A &amp; B</td>
<td>AB</td>
<td>None</td>
<td>4%</td>
</tr>
<tr>
<td>None</td>
<td>O</td>
<td>Anti A / Anti B</td>
<td>44%</td>
</tr>
</tbody>
</table>
Antigen(s) Present Determine Blood Type

- Notice that the type O person has neither A or B antigen.
- A and B antigens are prevalent in nature and people are exposed to them frequently. So, when a person does not have A or B antigen, they will be immunized and make an antibody to the antigen(s) they do not have on their cells. A type O person will have both anti-A and anti-B antibodies.
- A or B type person will only have 1 antibody, the antibody opposite their antigen.
- AB type persons will have no Anti A or Anti B.
Blood types are of utmost importance in transfusions

- The mixing of red blood cells with a particular antigen with plasma with the antibody to that same antigen, results in an antibody-antigen reaction.
- **When the cells are from the donor and the antibody from the recipient are incompatible, a life threatening immune reaction occurs.**
- The antigen-antibody complexes first cause immediate, severe hemolysis of the red cells followed by tubular necrosis of the kidney, and wide spread clotting. **The result is often death.**
• Remember that a type A, B, or O person will have antibodies in their plasma to antigens they do not possess.

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>- = major side reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>AB</td>
</tr>
<tr>
<td>A</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
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<tr>
<td>AB</td>
<td>-</td>
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<tr>
<td>O</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

• **AB** = Universal Recipient as it has no antibodies to react against antigens
• **O** = Universal Donor as it has no antigens
• A **major side reaction is not acceptable** – the antibodies of the recipient react against the antigens of the donor – death may result
• A **minor side reaction is acceptable only in emergency situations** – the antibodies of the donor react against the antigens of the recipient
• A perfect match is ideal – no reaction.
Rh Factor

- Another antigen, from the Rh antigen system, can frequently cause problems and must be monitored.
- The antigen known as the **Rh Factor** or D antigen appears on red cell surfaces of about **85% of people in the U.S.** They are considered **Rh+**.
- If the Rh factor or D antigen is absent the person is **Rh−** (**15% of people in U.S.**).
- Anti-D antibody is not normally present in the plasma of people without the D antigen.
- They must be exposed to the D antigen by transfusion or pregnancy to trigger the production of anti-D antibodies.
- When anti-D antibodies are present, they can react against transfusions with Rh pos blood or with Rh pos fetus during a subsequent pregnancy.
HDN (hemolytic disease of the newborn)

- When an Rh− mother is exposed to the Rh+ antigen, usually by her 1st Rh+ baby, she will develop anti-D antibody. She does not come in contact with the Rh+ antigen on the surface of the babies RBC’s until the placenta tears and the baby bleeds into the mother’s circulation causing immunization. This presents no problem for the first Rh+ child as the child is already born at this time. Remember, it takes 3-6 days to start to produce antibodies to the first exposure.

- Her 2nd Rh+ baby’s RBCs may be attacked and destroyed by antibodies in the mother’s plasma that move across the placenta into the child’s circulation. This leads to hypoxia, anemia, and brain damage and death may result.

- **Prevention**: give the mother anti-D antibodies that she would make when exposed. The injected anti-D will coat the baby’s Rh+ cells in her circulation and prevent them from being exposed to her T and B cells.

- So, no immunization (exposure) occurs, and her next Rh positive baby is unharmed. The antibody given to these mothers is called Rh immune globulin or a RhoGAM injection. Rhogam serves as an immunosuppressive “drug” that prevents the production of anti-D antibodies.
Transfusion Reactions

• Since there are many antigens on rbc's other than A and B, a person who gets many transfusions could make antibodies to some of them and suffer from a transfusion reaction when getting more blood with that antigen.

• These reactions are not usually as severe as ABO transfusion reactions and may cause:
  1. Hemolysis with anemia
  2. Increase bilirubin with mild jaundice.
  3. Fever

2 Tests to Prevent Transfusion Reactions

1. **Antibody screening = blood typing test**
   - To prevent these consequences, a recipient’s plasma can be screened for antibodies to the more common blood group antigens. This is done before each transfusion and is called an antibody screen test.

2. **Crossmatch = more extensive testing for antigens other than A, B, and Rh**
   - Further testing can be done where the donor cells are mixed with recipient plasma, and donor plasma is mixed with recipient cells. This test called a crossmatch, will be positive if an antibody is present, indicating an incompatibility between donor and recipient.