Ch. 11: Immune Physiology

Objectives:
1. Review immune organs & cells.
2. Two categories of immunity: innate vs adaptive
3. Understand functions of adaptive immunity cells (T-cells and B-cells)
4. Natural vs artificial immunity
4. Understand autoimmunity disorders.

1. Review Immune Organs & Cells.

Immune system = The cells and organs involved in defense against pathogens and cancer.

1) Lymph Organs:
A. Primary lymph organs
   > Bone marrow - make B lymphocytes (B-cells) & T-lymphocytes (T-cells)
   > Thymus – where T-cells mature.
1. **Review Immune Organs & Cells.**

**Immune system** = The cells and organs involved in defense against pathogens and cancer.

1) **Lymph Organs:**
   A. **Primary lymph organs**
   > **Bone marrow** - make B lymphocytes (B-cells) & T-lymphocytes (T-cells)
   > **Thymus** – where T-cells mature

   B. **Secondary lymph organs**
   > **Lymph nodes** - activate lymphocytes, where B cells mature
   > **Lymphatic & blood vessels** - transport immune cells
   > **Tonsils** – first line of defense from inhaled substances
   > **Brain** – microglia
   > **Spleen** - activate lymphocytes
   > **Intestines** - Peyer’s patches
   > **Appendix** - on cecum
   > **Liver** - Kupffer cells

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3 Lines of Defense from Pathogens!

A) **External Innate Immunity (non-specific)**
   - External barriers to entry for orifices of the body. KEEP PATHOGENS OUT!

B) **Internal Innate Immunity (non-specific)**
   – If a pathogen makes it past external barriers and gets inside, a non-specific internal defense happens.

C) **Adaptive or Acquired Immunity (specific)**
   Involves:  > **Lymphocytes** (T-cells & B-cells)
   > **Antibodies** (a.k.a. immunoglobulins)
1) Innate Immunity (non-specific)

A. External Innate Defense (barriers to keep things OUT of your body)

- Epithelial membranes
  > skin blocks entrance of pathogens into body
  > sweat is acidic and has lysozymes that are antimicrobial.
- Stomach acid - kills ingested microorganisms
- Respiratory tract - mucus & alveolar macrophages
- Urinary / genital defense = pH barriers
  > acidic vagina & urethra
- Eyes - Lysozyme in tears is antimicrobial

B. Internal innate defense (if things get in, try & kill them without antibodies)

Step 1. Phagocytic WBC Cell response.
  > Neutrophils & Monocytes in blood attack, engulf, & kill pathogens
  > WBCs secrete endogenous pyrogens to cause fever response.
  > WBCs secrete chemical cries for help (cytokines & chemokines)

Step 2. Natural killer (NK) cells
  > secrete interferons to kill viruses.
  > toxic granules to kill tumor/cancer cells.

Step 3. Inflammatory response
  > Mast cells – secrete histamine for inflammation.
  > Complement proteins – proteins that cause inflammation and bacteria to lyse them.
Step 1: Phagocytic WBC response:

1. In bloodstream - **Neutrophils** & **Monocytes** are **phagocytes** that destroy pathogens & secrete endogenous pyrogens (cause fever).

2. Histamine secreted by mast cells makes blood vessels “leaky” so WBC can escape

3. **Monocytes** migrate from blood into tissues by **extravasation** to become **Macrophages** that destroy pathogens in tissue.

4. Macrophages places pathogen’s antigen it cell surface – now macrophage is called an **Antigen-Presenting Cell (APC)**. **APCs will activate Helper T-cells (see later in notes)**

- Phagocytes then send chemical “Cries for help” = cytokines, chemokines

![Macrophage becoming an APC](image1)

![An APC activating a helper T-cell](image2)

![Macrophages “eating” bacteria](image3)
**Step 2. Natural Killer (NK) Cell response**
- are activated by cries for help (cytokines, chemokines)
- release interferon to kill virus-infected cells.
- release toxic granules to kill tumor cells.

**Step 3. Inflammatory Response**
- **Mast cells** – secrete histamine for inflammation. Causes vasodilation of blood vessels. (Allows more WBCs to enter into tissue as macrophages!)

- **Complement proteins** - kill bacteria by making holes in them (bacteria burst!) & cause inflammation.
**Activation of Internal Innate Immunity**

1. Neutrophil and monocytes attack pathogen in blood, secrete pyrogens (fever)
2. Extravasation of macrophages in tissue
3. Macrophages eat pathogen, become APC (will activate T-cells, & cry for help (cytokines & chemokines)
4. Mast cells release histamine (start redness & swelling)
5. Cytokines & chemokines cells of adaptive immunity To the rescue!

**Review**

> Review of Immune Organs and Cells

> Innate Immunity (2 types)

- **External innate immunity** (keep pathogens OUT)
- **Internal innate immunity** (activate when pathogens get in)

> Activation of Internal Innate immunity

- Neutrophils & monocytes (phagocytic cells in blood that attack pathogens)
  > secrete endogenous pyrogens (fever)
  > secrete chemical cries for help (cytokines & chemokines)

- Phagocytic cells in tissue (macrophages, which become APC)

- Natural killer (NK) cells
  > interferon to kill viruses & toxic granules to kill tumor cells

- Mast cells
  > secrete histamine for inflammation response (edema, redness, pain, vasodilation)

- Complement proteins
  > poke holes in bacteria to lyse them
Adaptive immunity: Provided by lymphocytes

- Are produced in bone marrow
- T-lymphocytes (T-cells) & B-lymphocytes (B-cells)
- T-cells mature in thymus.
  - Are involved in Cell-Mediated Immunity
  - T-cells must activate first in order to activate B-cells
- B-cells mature in lymph nodes & spleen
  - Are involved in Antibody-Mediated Immunity

How do T-cells get “activated”?

By Antigen-Presenting Cells (APCs) of the internal innate immunity
- APC presents antigen to Helper T-cells
- Helper T-cell then is ACTIVATED!
Tissue macrophages engulf pathogen. Part of pathogen moves to outside of macrophage – now an antigen-presenting cell (APC), and APC then activates Helper T-cells.

Two types of Adaptive Immunity:

1. Cell-Mediated Immunity (T-cells!)
   - Helper T-cells (activated by APCs)
     - Now activates other T-cells:
       > Cytotoxic T cells (T\(_c\))
         - can phagocytize pathogens.
       > Memory T cells (T\(_m\))
         - retain memory of a specific antigen
   - Regulatory T-cells (T\(_{reg}\))
     - inhibit T\(_c\) and B cells.
     - may guard against allergies & autoimmune disease.
   - Helper T-cells activate B-cells to make antibodies.

2. Antibody-Mediated Immunity (B-cells)
   - B-cells are activated by Helper T-cells) & make antibodies (or immunoglobulins) specific to the pathogen.
   - Results in formation of both Plasma B-cells & Memory B cells that have antibodies specific to the antigen.
Activated T-cells stimulate B-cells (plasma cells) to make antibodies to an antigen.

Plasma B-cell (the white blobs) with antibodies (the yellow Y’s), attacks the pathogen by binding to it.
Antibodies of B-cells stick to antigen on pathogen cells and “stick them together” – process called **agglutination**.

The agglutinated blob will attract macrophages, which will engulf the blob & destroy it.

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**More about B-Cells**

- Activated by stimulation by activated Helper T-cells.
- produce antibodies (immunoglobulins) to specific antigens.
- Provides *humoral (or antibody-mediated, or specific immunity).*

- Exposure of B-cell to its specific antigen causes
- release of antibodies to bind to antigens
- causes clonal production of more B-cells with antibodies:
  - A) **plasma B cells** for immediate defense, and
  - B) **memory B cells** for future encounters.

**Effects of antibodies:**
- Activate complement proteins
- Agglutination reaction (antibodies sticks antigen-bearing cells together)
  - “tags” pathogenic cells so they’re recognized & destroyed by phagocytes.
**Action of B Lymphocytes**

1. Antigen binds to antibody receptors on B-cells.

2. On contact with the antigen B-cells replicate by **cloning** to make lots and lots more B-cells.

3. **Plasma B-cells** formed (for immediate action), and

**Memory B-cells** formed (kept in storage for later activation).

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**Sequence of events, from entry of pathogen into the body to the formation of antibodies:**

1. Bacteria enters tissue from a break in skin.
2. _______ = Phagocyte non-specific WBC in the blood stream.
3. _______ = Cell that entravasates from blood vessel into tissue. (is now called an _______)
4. _______ = Phagocyte in tissue, which finds pathogen, kills it, and puts antigen on its surface.
5. _______ = Cell of mediated adaptive immunity, which becomes activated by interaction with the cell in #4 above.
6. Activated cell from #5 above can now activate these cells:
   - A. _______ = Cell of mediated adaptive immunity, which directly kills pathogen.
   - B. _______ = Cell of mediated adaptive immunity, which keeps a memory of pathogen.
   - C. _______ = Cell that is part of antibody-mediated adaptive immunity.
7. Cell from #6 above can make _______ (otherwise known as immunoglobulin).
8. Cell from #6 above encounters its pathogen and the following happens:
   - A. _______
   - B. _______
Review

Adaptive Immunity

Cell-mediated adaptive immunity
Antibody-mediated adaptive immunity

Types of T and B Cells

T-cell formation and activity
$T_H$, $T_C$, and $T_{reg}$
B-cell formation and activity
**Vaccinations**

- Late 1700s → Edward Jenner noticed milkmaids rarely had smallpox.

- Jenner reasoned that milkmaids were immune to smallpox because they had been exposed to cowpox.

- To test his hypothesis, he inoculated a boy with cowpox pathogens and then with smallpox pathogens. As predicted, the boy did not contract smallpox.

**vaccination** → 1° immune response → memory cells

*Secondary response*: have lots of memory B-cells that were stored & waiting for future exposure = stronger, faster immune response!

*Primary response*: takes ~2 weeks for good production of plasma B-cells with antibodies (high antibody titer) and memory B-cells after 1st exposure.
Example of Vaccine Effectiveness:

In the United States, before measles vaccine became available in the mid-1960s was estimated over 530,000 cases with 500 deaths per year. After vaccine – has been 99.9% decrease in incidence of the disease.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PRE-VACCINE ERA ESTIMATED ANNUAL MORBIDITY*</th>
<th>MOST RECENT REPORTS OR ESTIMATES OF U.S. CASES</th>
<th>PERCENT DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0*</td>
<td>100%</td>
</tr>
<tr>
<td>*H. influenzae (invasive, &lt;5 years of age)</td>
<td>20,000</td>
<td>31*</td>
<td>≥99%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>117,333</td>
<td>2,890†</td>
<td>98%</td>
</tr>
<tr>
<td>Hepatitis B (acute)</td>
<td>66,232</td>
<td>18,800†</td>
<td>72%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>187†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>584†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>206,752</td>
<td>28,639†</td>
<td>86%</td>
</tr>
<tr>
<td>Pneumococcal disease (invasive, &lt;5 years of age)</td>
<td>16,069</td>
<td>1,900†</td>
<td>88%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>1†</td>
<td>≥99%</td>
</tr>
<tr>
<td>Rotavirus (hospitalizations, &lt;3 years of age)</td>
<td>62,500†</td>
<td>12,500†</td>
<td>80%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>9†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>152</td>
<td>1†</td>
<td>99%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0†</td>
<td>100%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>26†</td>
<td>96%</td>
</tr>
<tr>
<td>Varicella</td>
<td>4,083,120</td>
<td>167,490†</td>
<td>96%</td>
</tr>
</tbody>
</table>

Vaccinations and Halt of Communicable Disease: THE CONTROVERSY

Do vaccinations cause Autism????

NO!

Where did the controversy start?
A study originally published in journal *Lancet* by Andrew Wakefield in 1995 claimed that his study of 12 children showed that the 3 MMR (measles, mumps, rubella) vaccines taken together (1st at 1 year, then at 5-6 yrs) could alter immune systems, causing intestinal woes that then reach, and damage, the brain (autism?)

Scientific community responded:
> Dozens of epidemiological studies found no merit to his work
> His claims were based on a tiny sample size.
> The British Medical Journal called his research “fraudulent.”
> The British journal *Lancet* retracted his publication.
> The British medical authorities stripped him of his license.

Problem:
People still believe Wakefield. Groups of people began to NOT vaccinate their children.
**Vaccinations and Halt of Communicable Disease:**

> Nationwide, vaccination rate against diseases has stayed at 90% or higher, but % in some of the country now well below that, making those communities more vulnerable to disease outbreak.

**Map of US**

> Medical doctors & epidemiology experts say that vaccination rate of ~95% needed to protect a community by “herd immunity”.

> **Herd immunity** = indirect protection from infectious disease when a large % of population has become immune (natural or vaccination-acquired) it reduces potential exposure of non-immune people (aren’t or can’t be vaccinated) to that disease.

**Herd Immunity**

The top box shows an outbreak in a community in which a few people are infected (shown in red) and the rest are healthy but unimmunized (shown in blue); the illness spreads freely through the population.

The middle box shows a population where a small number have been immunized (shown in yellow); those not immunized become infected while those immunized do not.

In the bottom box, a large proportion of the population have been immunized (yellow); this prevents the illness from spreading significantly, including to unimmunized people.
### Classification of Immunity

1) **Active immunity** = get immunity (antibodies) that you produce from actual exposure (natural) to disease organism or from vaccination (artificial exposure).

2) **Passive Immunity** = get immunity (antibodies) from source outside your body: Natural (breast milk) or artificial (injection of antibodies).

### Problems with the Immune Response

**autoimmunity** – when immune cells attack self; can be B or T cells.

*** Abnormal T-cells from Thymus associated with most autoimmune disorders!

**Ex. Of autoimmune disorders:**

- *rheumatoid arthritis* – attack on connective tissue of synovial joints.
- *rheumatic heart disease* – antibodies produced from strep throat attack heart valves.
- *lupus* – nuclear proteins.
- *multiple sclerosis* – attacks myelin sheaths on neurons.
- *Grave’s disease* – attack on thyroid gland TSH receptor.
- *Crohn’s disease* – attack on cecum of large intestine.
- *Myasthenia gravis* – destruction of nicotinic cholinergic receptors on skeletal muscles.
Review

Vaccination
   History of vaccination
   Action of vaccinations on immunity
   Controversy on vaccinations
   [There shouldn’t be!!!]

Classification of Immunity

Autoimmune Disorders