Ch. 11: Immune Physiology

Objectives:
1. Review immune organs & cells.
2. Two types of immunity.
3. Understand functions of immune cells (T-cells and B-cells)
4. Understand autoimmunity disorders.

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
3 Lines of Defense from Pathogens!

1st Line = **External Innate Immunity (non-specific)**
- External barriers to entry for orifices of the body. KEEP PATHOGENS OUT!

2nd Line = **Internal Innate Immunity (non-specific)**
- If a pathogen makes it past external barriers and gets inside, a non-specific defense happens through
  - Phagocytic (patrolling) cells & Fever
  - NK cells
  - Inflammation

3rd Line = **Adaptive or Acquired Immunity (specific)**
- Slower defense based on prior exposure to a pathogen
- Specific defense (memory of a pathogen)
- 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, and sweat is acidic and has lysozymes that are antimicrobial.
- Stomach acid - kills various microorganisms ingested
- Respiratory tract - mucus & alveolar macrophages
- Urinary / genital defense = pH barriers (acidic vagina, urethra)
- Eyes - Lysozyme in tears is antimicrobial
1) Innate Immunity (non-specific)

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


You're dead sucka!

WBC also secrete endogenous pyrogens to cause fever response.

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 - antimicrobial proteins (kill bacteria) & cause inflammation

Step 1. Phagocytic WBC response:
- In bloodstream - Neutrophils & Monocytes are phagocyes that destroy pathogens & secrete endogenous pyrogens (cause fever).

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

- 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 “Click for help” = cytokines, chemokines

Macrophages “eating” bacteria

Blaargh! You're dead sucka!
**Step 2. Natural Killer (NK) Cell response**
- are activated by cries for help (cytokines, chemokines), & interferon
- 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

**Review**

Review of Immune Organs and Cells

**Innate Immunity**
- External innate immunity
- Internal innate immunity

**Activation of Innate immunity**
- Phagocytic cells
- Fever (from endogenous pyrogen)
- Natural killer (NK) cells > interferon & toxic granules for viruses and tumor cells
- Inflammation response (mast cells & histamine, edema, redness, pain, vasodilation, complement proteins)
**Activation of Adaptive Immunity** – or long term *specific* defenses

**Adaptive immunity:**

Provided by lymphocytes
- T-lymphocytes (T-cells) & B-lymphocytes (B-cells)
- Produced in bone marrow
- B-cells mature in lymph nodes & spleen, T-cells mature in thymus. These cells clone themselves to make more.

**Two basic types adaptive immunity:**

1. **Cell-mediated immunity** = activated T-cells
   - *Adaptive immunity MUST start with activation of T-cells.*
   - *Without this you won’t get B-cells to make antibodies!*

2. **Antibody-mediated immunity** = activating B-cells to make antibodies.

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**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 activate Cytotoxic T cells, which can phagocytize pathogens.
   - Helper T-cells also activate formation of memory T cells specific to an antigen
   - Helper T-cells activate B-cells to make antibodies.

2. Antibody-Mediated Immunity (B-cells)
   - B-cells (which were 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 with antibodies (the white blob), 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.
**3 types of T-cells**

- produced in bone marrow
- mature in the thymus (childhood); then 2nd lymphoid organs
- produce cytokines to activate other immune cells & directly kill infected cells

**$T_H$ – helper T cells**
- become activated in response to antigen from **APCs** (antigen-presenting cells).
- stimulate B-cells to make plasma B-cells (with antibodies).
- activate cytotoxic (killer) T-cells.

**$T_C$ – cytotoxic T cells (a.k.a. natural killer t-cells or NKT cells)**
- recognize and destroy cancerous or virus-infected cells.
  *(do not confuse these with NK cells of innate immunity!!!)*

**$T_{reg}$ – regulatory T cells**
- inhibit $T_C$ and B cells.
- may guard against allergies and autoimmune disease.

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**B-Cells**

- Activated by stimulation by activated Helper T-cells.
- produce **antibodies (immunoglobulins)** to specific antigens.

- 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.

- Provides **humoral (or antibody-mediated, or specific immunity)**.

**Effects of antibodies:**
- Activate complement proteins
- Agglutination reaction (antibodies sticks antigen-bearing cells together)
- Agglutination “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).

**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.
Vaccinations and Halt of Communicable Disease: THE SCIENCE

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><em>H. influenzae</em> (invasive, &lt;5 years of age)</td>
<td>20,000</td>
<td>31†</td>
<td>&gt;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>200,752</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>&gt;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>4,085,120‡</td>
<td>167,400‡</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.

There has been an increase in cases of Measles, Mumps is the US – especially in counties where vaccination rate below 90%.

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).

### Table 15.9 | Comparison of Active and Passive Immunity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active Immunity</th>
<th>Passive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection of person with</td>
<td>Antigens</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Source of antibodies</td>
<td>The person inoculated</td>
<td>Natural—the mother; artificial— injection with antibodies</td>
</tr>
<tr>
<td>Method</td>
<td>Injection with killed or attenuated pathogens or their toxins</td>
<td>Natural—transfer of antibodies across the placenta; artificial— injection with antibodies</td>
</tr>
<tr>
<td>Time to develop resistance</td>
<td>5 to 14 days</td>
<td>Immediately after injection</td>
</tr>
<tr>
<td>Duration of resistance</td>
<td>Long (perhaps years)</td>
<td>Short (days to weeks)</td>
</tr>
<tr>
<td>When used</td>
<td>Before exposure to pathogen</td>
<td>Before or after exposure to pathogen</td>
</tr>
</tbody>
</table>
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.

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### Allergies

**Allergies** – over-reaction of the immune system (mast cells) to antigens
Review

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

Classification of Immunity

Autoimmune Disorders