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.

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
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)

**Step 1. Phagocytic WBC Cell response** – engulf and destroy pathogens.

You’re dead sucka!  
Blaargh!

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

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**Step 1. Phagocytic WBC response:**

- In bloodstream - *Neutrophils & Monocytes* are phagocytes 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 “Cries for help” = *cytokines, chemokines*

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**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 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
   2. Macrophages eat pathogen, become APC (will activate T-cells, & cry for help (cytokines & chemokines)
3. Mast cells release histamine (start redness & swelling)
4. Cytokines & chemokines cells of adaptive immunity to the rescue!

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.

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)

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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. **Neutrophils** = Phagocytic non-specific WBC in the blood stream.

3. **Monocytes** = Cell that extravasates from blood vessel into tissue. (is now called an APC)

4. **APC** = Phagocytic cell in tissue, which finds pathogen, kills it, and puts antigen on its surface.

5. **Helper Tcell** = Cell of cell-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:
   - **Cytotoxic Tcell** = Cell of cell-mediated adaptive immunity, which directly kills pathogen.
   - **Memory Tcell** = Cell of cell-mediated adapted immunity, which keeps a memory of pathogen.
   - **B cell** = Cell that is part of antibody-mediated adaptive immunity.

7. Cell from 6C above can make **antibodies** (otherwise known as immunoglobulins)

8. Cell from 6C above encounters its pathogen and the following happens:
   - **Agglutination**
   - **Clonal production of plasma B cells (Fight now)**}

   **Memory B cells (Fight later)**
**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.

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

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

- **Secondary response**: have lots of memory B-cells that were stored & waiting for future exposure = stronger, faster immune response!
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>18,730</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>11</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>91</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>152</td>
<td>11</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!**

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**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>
4. Autoimmunity Disorders

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.

> diabetes (certain forms) – destruction of beta cells in the pancreas.

> 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