The Medical Importance of the Immune System

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* with strong tribute to Gailen Marshall, MD, Ph.D.
Course Objectives

- To appreciate the components of the human immune response that work together to protect the host from clinical disease.

- To understand the concept of immune-based diseases as either a deficiency of components or excess activity as hypersensitivity.
Normal physiologic functions of the immune system include the ability to recognize foreign pathogens.
A Functional Immune System Confers Health by Effective Elimination of Infectious Agents
(bacteria, viruses, fungi, and parasites)

- Immune responses are designed to interact with the environment to protect the host against pathogenic invaders.
IMMUNE DISEASES

Deficiency vs. Dysregulation
IMMUNE DEFICIENCY
(hyporeactivity)

- Occurs when a particular immune response or function is absent from the host, leading to a detrimental state.
IMMUNE DYSREGULATION
(including hypereactivity/hypersensitivity)

Occurs when the immune response functions in an inappropriate manner which results in:

- absence of protective response
- active response which damages host tissue, leading to a detrimental state.
IMMUNODYSTREGULATION = DISEASE
Hypersensitivity Diseases

- A definable immune response
- Produces harm not protection
- Mechanisms
  - inappropriate antigen
  - excessive magnitude of response
  - prolonged duration of response
  - innocent bystander effect
HOW THE IMMUNE SYSTEM WORKS

An Introduction to 7 Main Concepts of the Course
1. The chief function of the immune system is to distinguish between self and non-self.

IMMUNITY: (L. Immunitas) The condition of being immune; the protection against infectious disease conferred either by the immune response generated by immunization or previous infection or by other nonimmunologic factors.
Health – effective elimination or control of health-threatening agents

(Hyporeactivity)  (Hyperreactivity)
Immunodeficiency  Health  Immunopathology

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Control of infectious agents and tumors is required for life.
Hyporeactivity (immunodeficiency) – inability to recognize and control health-threatening agents

(Hyporeactivity) \ Immunodeficiency
\ Health

( Hyperreactivity ) \ Immunopathology

Many Disease States are Associated with Clinical Immunodeficiency
Hyporeactivity (immunodeficiency)

Causes of immunodeficiency include:
- Congenital or Acquired
- Immune senescence (old age)
- Iatrogenic
- Malnutrition or metabolic imbalances
- Malignancies or infectious diseases
- Trauma or stress

The broad categories of immunodeficiency include:
- Neutrophil disorders
- Antibody deficiency
- Complement deficiency
- T cell dysfunction
Immunodeficiency Example: Human Immunodeficiency Virus-I (HIV-1)

- Destruction of CD4+ T helper cells leads to vulnerability of host by opportunistic infections.
Thought to be caused by Herpesvirus, Human Herpesvirus-8 (HHV-8), also known as the Kaposi sarcoma-associated herpesvirus (KSHV), and lack of T cell responses to control infection.
Hyperreactivity – aberrant immune responses

(Hyporeactivity)
Immunodeficiency Health (Hyperreactivity)
Immunopathology
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Hyperreactivity (Immunopathology)

In many cases the condition occurs when an individual's immune system reacts against his or her own tissues (autoimmunity), or against common environmental factors (allergies).

Alternatively, an over-aggressive immune response to a pathogen leads to deleterious responses within the host (immunopathology).
2. The immune system consists of two overlapping compartments: the innate immune system and the adaptive immune system.
Innate immunity: consists of “non-specific” components.

Acquired immunity: requires recognition “specificity” to foreign (usually non-self) substances.
Innate immune system

- Most primitive type of immune system; found in virtually all multicellular animals
- Always present and active, constitutively expressed (some components can be up-regulated)
- Nonspecific; not specifically directed against any particular infectious agent or tumor
- Same every time; no ‘memory’ as found in the adaptive immune system
- First line of defense against infection
Innate Immunity

Innate immunity is conferred by all those elements with which an individual is born and which are always present and available at very short notice against foreign invaders.

- **Physical barriers:** skin, mucous membranes
- **Phagocytic cells:** macrophages, neutrophils
- **Protective chemicals:** acid pH, surface lipids
- **Enzymes:** saliva, digestive tract enzymes
- **Alternate complement pathway:** serum proteins activated by bacterial cell wall components
Adaptive - Acquired Immune System

• Found only in vertebrates (fish, amphibians, birds and mammals)
• Must be induced to be active against infections or tumors
Immunogens and Antigens

- **Immunogens** - substances capable of inducing an immune response
- **Antigens** - substances capable of reacting with preformed antibodies or activated cells
Properties of adaptive immunity

• **Antigen-specific** – adaptive immune responses recognize antigens, which can be proteins, carbohydrates, lipids and nucleic acids.

• **Memory** - results in increased reactivity upon repeated exposures to the antigen or infectious agent.

• **Regulation** – discriminates between self and non-self, prevents autoimmune reactions in most individuals.
The adaptive immune system involves:

- **B Lymphocytes** – differentiate into plasma cells that produce antibodies

- **T Lymphocytes**
  - **Helper activity** – help other lymphocytes respond to antigen; activate macrophages to phagocytose, kill pathogens
  - **T cell-mediated cytotoxicity** – cytotoxic T cells bind to and kill infected or tumor target cells
  - **Suppressor/Regulatory T cells** – down-regulate or tolerize the responses of other lymphocytes

- **Accessory Cells** – antigen-presenting cells
  - Macrophages, Dendritic Cells, Langerhans’ Cells, etc., present foreign material to adaptive cells
The innate and adaptive (acquired) immune systems interact and share many components.
3. The antigenic specificity of the adaptive immune system is due to antigen-specific receptors.
Immunoglobulins (also called antibodies) – produced by B cells; antigen-specific receptor

- 2 Heavy Chains and 2 Light Chains (polypeptides) linked by disulfide bonds.
- Gives rise to 5 subtypes: IgM, IgD, IgG, IgA, IgE
  - Surface immunoglobulin (Ig) – antigen-specific receptor of B lymphocytes
  - Secreted immunoglobulin (Ig) – Ig molecules secreted by plasma cells
T cell receptor (TCR) – antigen-specific receptor of T lymphocytes

- 2 Chains, non-covalently associated.

Binding of TCR to antigen is a complex interaction that occurs only on cell surfaces and involves several cell surface proteins.
Basic Reaction in Immunology

\[ \text{Ag} + \text{Ab} \leftrightarrow \text{AgAb} \]

\( \text{Ag} = \text{Antigen} \)
\( \text{Ab} = \text{Antibody} \)

\( \sim 10^6 - 10^8 \) different Ab specificities!
4. The generation of antigen-binding diversity occurs prior to antigen exposure through a DNA rearrangement process called VDJ joining.

Gene rearrangement gives rise to antibody and T cell diversity.
During B and T cell development, DNA recombination occurs to join gene segments in a random manner.

- Random selection of gene segments resulting in thousands of different variable region sequences.
- Contributes to antibody diversity and T cell receptor diversity.
- Ensures that different antibodies or TCRs interact with different antigens.
5. To generate an active immune response against a certain antigen, a small number of B and T cell clones that bind to the antigen with high affinity undergo activation, proliferation, and differentiation into plasma cells (for B cells) or activated T cells. This process is called ‘clonal selection’.
Stem cell

Early differentiation of lymphoid precursor cells

Uncommitted cells

Self

Self

Self

Removal of self-reactive immature lymphocytes

Pool of non-self-reactive mature lymphocytes

Antigen-stimulation of lymphocyte clones

Antiserum to Antigen

Antigen

3 4 7

3 4 7

3 4 7

Anti-3 Ig

Anti-4 Ig

Anti-7 Ig
6. The adaptive immune system has memory, meaning that the response against an antigen is much greater after the first exposure.
Secondary responses have:

- Higher antibody levels and magnitude of response
- Shorter lag period and Higher affinity for antigen
7. The immune system is tightly regulated.
Mechanisms of Regulation

• The adaptive immune system has developed several mechanisms to eliminate or inhibit self-reactive or over-reactive B and T cells.
  
  – **Elimination** of self-reactive cells during their development through apoptosis
  
  – **Permanent inactivation** of self-reactive cells through a process called clonal anergy
  
  – **Inhibition** of self-reactive cells by regulatory or suppressor T cells, inhibitory cytokines
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4. The generation of antigen-binding diversity occurs prior to antigen exposure through a DNA rearrangement process called VDJ joining.
5. To generate an active immune response against a certain antigen, a small number of B and T cell clones that bind to the antigen with high affinity undergo activation, proliferation, and differentiation into plasma cells (for B cells) or activated T cells. This process is called ‘Clonal Selection’.

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http://www.xtranormal.com/watch/7614177/
I Was Born to Be an Immunologist!

Dr. Actor at age 1yr.

Dr. Actor’s 1st toy.
## Table: Elements of Innate and Acquired Immune Responses

<table>
<thead>
<tr>
<th>Innate</th>
<th>Adaptive</th>
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</thead>
<tbody>
<tr>
<td>Rapid response (minutes to hours)</td>
<td>Slow Response (days to weeks)</td>
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<tr>
<td>PMNs and Phagocytes</td>
<td>B cells and T cells</td>
</tr>
<tr>
<td>Preformed effectors with limited variability</td>
<td>B cell and T cell receptors with highly selective specificities</td>
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<tr>
<td>Pattern Recognition Molecules recognizing structural motifs</td>
<td></td>
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<tr>
<td>Soluble activators</td>
<td>Antibodies (humoral)</td>
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<tr>
<td>Proinflammatory mediators</td>
<td>Cytokines (cellular)</td>
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<tr>
<td>Non-specific</td>
<td>Specific</td>
</tr>
<tr>
<td>No memory, no increase in response upon secondary exposure</td>
<td>Memory, maturation of secondary response</td>
</tr>
</tbody>
</table>
What is the Number 1 Technological Development that Has Impacted Infant Mortality More than Any Other?
Immunizations

- Induction of protective immune response against a specific organism or its associated toxin prior to encounter with the pathogen.
Salk = inactive
Sabin = oral
Which Scientist Discovered the Process of Immunization?
Discovery of Acquired Immunity (1790’s)

• Edward Jenner experimentally induced immunity to smallpox by inoculating a boy with pus from a lesion of a dairy maid who had cowpox.
• He then deliberately exposed the youth to smallpox; no disease occurred.
Ethical Considerations…Today vs Yesterday

• Edward Jenner was trying to cure a life-threatening disease. He noticed that persons who survived smallpox infection were resistant to further infections.

• However, his experiments were totally unethical by today’s standards. He would have his license revoked, and probably a lawsuit on his hands!

• But…consider the alternative…
Vaccination: Small Pox

Vaccinia: \( L. \text{vacca} = \text{cow} \). Thus the process of inducing immunity was referred to as vaccination.
Hypersensitivity Diseases

Classification

A. **Type I** - Immediate (allergic) hypersensitivity
   - IgE mediated
     • allergies

B. **Type II** - Cytotoxic antibody
   - Ab mediated cell destruction
     • autoimmune hemolytic anemia

C. **Type III** - Immune complexes
   - Ab/Ag complex deposition
     • serum sickness

D. **Type IV** - Delayed hypersensitivity
   - T cell/macrophage mediated
     • Tuberculosis
Hypersensitivity

Type I depends on an interaction between antigen and IgE antibody attached to mast cells. Clinical examples include allergic rhinitis (hay fever), allergic asthma and food reactions (peanut hypersensitivity).

Type II is a cytotoxic reaction between tissue- or cell-bound antigen and IgM or IgG antibody (ADCC). Clinical situations include cytopenias (autoimmune hemolytic anemia, immune thrombocytopenia).

Type III is an immune-complex reaction between circulating antigen and IgG antibody with subsequent deposition in walls of blood vessels, joints, kidneys or skin (ie. serum sickness, allergic alveolitis).

Type IV is a cellular immune response mediated by sensitized lymphocytes (DTH), as seen in contact hypersensitivity.
In a patient with thrombocytopenia purpura, cytotoxic antibodies against platelets mediate hemolytic anemia. This is an example of which type of hypersensitivity?

A. Hypersensitivity Type I
B. Hypersensitivity Type II
C. Hypersensitivity Type III
D. Hypersensitivity Type IV

Option B (Hypersensitivity Type II) is correct. Type II reactions are defined as cytotoxic reactions between tissue- or cell-bound antigen and antibody. This includes cell destruction through antibody dependent cell cytotoxicity (ADCC) event. Clinical situations include cytopenias (such as autoimmune hemolytic anemia and immune thrombocytopenia).

Option A (Hypersensitivity Type I) is incorrect. The Type I reactions are mediated by IgE antibody and mast cells interactions, seen in allergic reactions.

Option C (Hypersensitivity Type III) is incorrect. The Type III reactions are immune-complex reaction between circulating antigen and IgG antibody with subsequent deposition in tissues or blood vessels.

Option D (Hypersensitivity Type IV) is incorrect. The Type IV reactions represent cellular responses mediated by sensitized lymphocytes (delayed type hypersensitivity; DTH), as seen in contact hypersensitivity.
This patient also experiences seasonal allergies to pollens. What is the molecular mechanism for mediation of this response?

A. Contact hypersensitivity  
B. Immune complex deposition  
C. Antibody Dependent Cell Cytotoxicity  
D. IgM and complement fixation  
E. IgE and mast cell degranulation

Option E (IgE and mast cell degranulation) is correct. Type I hypersensitivity reactions depend on an interactions between antigen and IgE antibody attached to mast cells, resulting in release of stored granules containing factors such as histamine, prostaglandins and leukotrienes. Clinical examples include allergic rhinitis (hay fever), allergic asthma and food reactions (peanut hypersensitivity).
This same unfortunate patient in the above question developed symptoms of runny nose, fever and cough. He visited his physician who misdiagnosed the viral infection as (incorrectly) being of bacterial in origin. He prescribed a bolus dose of ampicillin given intravenous, without knowing that the patient was allergic to penicillin. Within 24 hours, the patient developed fever, skin rashes, petechial haemorrhaging of the lower extremities, edema of the skin, glandular enlargement and severe pains in the joints. Which type of hypersensitive reaction is occurring?

A. Hypersensitivity Type I
B. Hypersensitivity Type II
C. Hypersensitivity Type III
D. Hypersensitivity Type IV

Option C (Hypersensitivity Type III) is correct. This is a case of drug induced serum sickness, which is a classic example of a type III hypersensitivity, "immune complex" disease, where the immune-complex reaction between circulating antigen and pre-existing IgG antibody occurs with subsequent deposition in walls of blood vessels, joints, kidneys or skin. Unknown to the physician, the individual had previous exposure to penicillin, and therefore had antibodies that were cross-reactive with the ampicillin.
A 46 year old American was visiting Guadalajara for the first time, and enjoyed sampling the salsa in small restaurants located outside the tourist district. The next morning, he developed severe intestinal pain, and diarrhea, due to infection with gram-negative invasive enteropathic *Eschericia coli*. Antibiotic treatment was sufficient to clear the infection. One year later, he visited the same restaurant, and ate salsa with no ill-effects. What was the most probable immune mechanism for protection if the salsa was again contaminated?

A. IgA Immunoglobulin (Antibodies)
B. Complement
C. Helper T lymphocytes
D. Cytotoxic T lymphocyte
E. Neutrophil

Option A (IgA Immunoglobulin (Antibodies)) is correct. In this case, prior encounter with the pathogen led to production of specific antibodies (IgA) available to combat the enteric pathogen on mucosal surfaces. The IgA is extremely effective at neutralizing bacteria, and is bactericidal for Gram negative organisms in the presence of lysozyme.