Immunology: An Overview
Definitions

**Law.** Exemption from a service, obligation, or duty; Freedom from liability to taxation, jurisdiction, etc.; Privilege granted to an individual or a corporation conferring exemption from certain taxes, burdens, or duties.

**Health.** Nonsusceptibility (resistance) to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances.
Immunity and Health

- Immunology is the study of our protection from foreign macromolecules or invading organisms and our responses to them.
- Host – e.g. you!!!!
- Foreign macromolecule, antigen – e.g. virus protein, worm, parasite (Everything that should not be in our bodies)
Immunity refers to all mechanisms used by the body as protection against environmental agents that are foreign to the body.

Basically, a constant state of war exists between would-be pathogens and the host, and the immune system is responsible for defending the body against the threat of pathogenic attack.
### The functional importance of the immune system

<table>
<thead>
<tr>
<th>Role of the immune system</th>
<th>Implications</th>
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<tr>
<td>Defense against infections</td>
<td>Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections</td>
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<td>Defense against tumors</td>
<td>Potential for immunotherapy of cancer</td>
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<tr>
<td>Clearance of dead cells and tissue repair</td>
<td>Deficient immunity can lead to secondary infections after injury, and excessive immune responses can lead to fibrosis and organ dysfunction</td>
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<tr>
<td>The immune system can injure cells and induce pathologic inflammation</td>
<td>Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases</td>
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<td>The immune system recognizes and responds to tissue grafts and newly introduced proteins</td>
<td>Immune responses are barriers to transplantation and gene therapy</td>
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Defense Mechanisms

1. External defense
2. Internal Defense
3. Immune Defense

<table>
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<th>Nonspecific defense mechanisms</th>
<th>Specific defense mechanisms (immune system)</th>
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<tr>
<td><strong>First line of defense</strong></td>
<td><strong>Third line of defense</strong></td>
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<tr>
<td>• Skin</td>
<td>• Lymphocytes</td>
</tr>
<tr>
<td>• Mucous membranes</td>
<td>• Antibodies</td>
</tr>
<tr>
<td>• Secretions of skin and mucous membranes</td>
<td>• Phagocytic white blood cells</td>
</tr>
<tr>
<td></td>
<td>• Antimicrobial proteins</td>
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<td></td>
<td>• The inflammatory response</td>
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</table>
The Immune Response

- **Immune Response:** Third line of defense. Involves production of antibodies and generation of specialized lymphocytes against specific antigens.

- **Antigen:** Molecules from a pathogen or foreign organism that provoke a specific immune response.
The field of immunology has been in the public limelight since the mid of the 20th century when successful transplantation of the human kidney was achieved.

More recently, the spectacular, but not always successful, transplantation of the human heart and other major organs has been the focus of much publicity.

The public interest in immunology was intensified with advances in tumor immunology and the emergence of AIDS.
The immune system may be viewed both as an armory—where tools and weapons are constructed for use in defense of the host—and as an army capable of wielding them.

Both cellular and molecular weapons are wielded with extreme ferocity, often resulting in the death and degradation of invasive organisms.
Each cellular or molecular weapon has at least one deadly use; many have multiple uses.

And, like any tool, it can harm its user if not properly operated.

The analogy of weaponry is a useful one to keep in mind as we explore the various ways that the immune system defends the host.
The Innate and Adaptive Immune Systems

- 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 to protect the individual from challenges by foreign invaders.

- Adaptive (acquired) immunity is more specialized and it supplements protection provided by innate immunity but it comes into play latter.
Innate Immunity

- Initial protection against infection is provided by mechanical and chemical barriers which try to prevent entry of microbes into the body.

- These barriers constitute an important part of the innate immune system. If breached, these barriers’ function is replaced by adaptive immunity.

- The innate system uses pattern recognition receptors (PRRs) that are genetically encoded and are expressed by a variety of leukocytes.
In the innate system, glycoproteins and glycolipids are more stimulatory than are proteins which is in contrast to the adaptive system where proteins are more stimulatory.

Effector mechanisms of innate immunity include; anatomic and physiologic barriers like skin and mucous membranes, phagocytosis, inflammation and fever.
Adaptive Immunity

- The adaptive immune system is based on lymphocytes that bear receptors that are not directly encoded within germ line DNA.

- Instead, the receptors of lymphocytes are generated by rearrangement of DNA-segments.

- Lymphocyte receptors can recognize and interact with extraordinary specificity with a very large number of substances called antigens.
Interactions and Effectors

- The innate immune system interacts with the adaptive immune response via antigen processing and presentation.

- Although the immune response originates in cells, it is convenient to consider the effector mechanisms as consisting of two major arms: humoral and cellular.
The two features that best distinguish adaptive from innate immunity are specificity and memory.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Functional significance</th>
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<tr>
<td>Specificity</td>
<td>Ensures that distinct antigens elicit specific responses</td>
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<tr>
<td>Diversity</td>
<td>Enables immune system to respond to a large variety of antigens</td>
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<td>Memory</td>
<td>Leads to enhanced responses to repeated exposures to the same antigens</td>
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<tr>
<td>Clonal expansion</td>
<td>Increases number of antigen-specific lymphocytes to keep pace with microbes</td>
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<tr>
<td>Specialization</td>
<td>Generates responses that are optimal for defense against different types of microbes</td>
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<tr>
<td>Contraction and homeostasis</td>
<td>Allows immune system to respond to newly encountered antigens</td>
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<tr>
<td>Nonreactivity to self</td>
<td>Prevents injury to the host during responses to foreign antigens</td>
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The Immunologic Concept of Self

- Immunology and religion

- The essence of religion, “which is hateful to you, do not do it to others; the rest is complementary.”

- The essence of immunology can be similarly stated; “Immunology deals with the understanding of how the body distinguishes what is self from what is non self, all the rest is technical detail.”
Mechanisms

- The immune system must distinguish self molecules and cells from non self ones utilizing soluble and cell-bound molecules.

- It uses barriers to exclude external agents. Memory is an important characteristic in this regard.

- Multiple mechanisms with overlapping functions are used so that if one mechanism is ineffective, another may be. Biological defense mechanisms are diverse.
The human immune system is complex, composed of multiple organs, cell types, and molecules that must work together.

At times, the immune system appears to be a collection of paradoxes.

It is diffusely distributed throughout the body, yet many of its cells are concentrated within specific lymphoid organs.
Education and Regulation

- It can be very general and yet highly specific in detecting and responding to potential threats.

- It is highly regulated but it can sometimes become confused that it harms itself.

- The immune system learns what is non self by first learning what is self, a process referred to as education.
The ability to respond to non self is the basis for protection against environmental threats and is generally, but not always, beneficial.

The ability to recognize self, while critical to immunologic education, is potentially dangerous.
Autoreactivity

- When self-reactive lymphocytes become inappropriately activated, they can attack the body's own cells and tissues and lead to autoimmune responses.

- Several mechanisms exist also to eliminate or control potentially autoreactive lymphocytes providing protection against autoimmunity that is successful for most individuals.
Diversity

- Lymphocytes have overcome the problem of a limited number of germ line encoded receptors. Lymphocytes can somatically create $10^9$ to $10^{16}$ different antigen receptors.

- However, $10^9$-$10^{16}$ different antibodies cannot be simultaneously maintained at functional levels.

- This problem is solved by **clonal selection** (perhaps the most important concept in immunology)
Clonal Selection of Lymphocytes

- Lymphocytes are made randomly
  - Not directed by antigens
- Each lymphocyte bears a specific receptor
- Varied receptor specificity due to rearrangement of genes
- Antigen "selects" appropriate lymphocytes
- "Selected" cell undergoes clonal expansion
- Expansion produces clones of effector and memory cells
Clonal Selection

The somatic evolution of B and T cells

A single progenitor cell gives rise to a large number of lymphocytes, each with a different specificity

Removal of potentially self-reactive immature lymphocytes by clonal deletion

Pool of mature naive lymphocytes

Foreign antigen

Proliferation and differentiation of activated specific lymphocytes to form a clone of effector cells

Effector cells eliminate antigen

Bone marrow for B cells

Thymus for T cells

Antigen binding in the bone marrow leads to deletion whereas antigen binding in the periphery can lead to activation

periphery
### Postulates of the clonal selection hypothesis

| 1* | Each lymphocyte bears a single type of receptor with a unique specificity |
| 2 | Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation |
| 3 | The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived |
| 4 | Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes |

The self/nonself discrimination (or tolerance) is “learned” in the soma.

*Figure 1-12. Immunobiology, 7ed. (© Garland Science 2008)*
Clonal selection solves the problem of a repertoire that is too large to be fully functional all the times.

Clonal selection is the basis of immunological memory (to be dealt with later).

Clonal selection (i.e., Clonal deletion) deals with the problem of a “complete” repertoire (enough specificities in the individual to recognize everything) having the capacity to recognize and destroy self. Clonal deletion removes (kills) self-reactive (anti-self) B and T cells.
Origin of and Interactions Between Immune Cells

- Erythrocyte
  - EPO
  - Erythroid progenitor
    - GM-CSF
    - IL-3
    - EPO

- Myeloid Stem Cell
  - GM-CSF
  - IL-3
  - IL-11
  - EPO

- Megakaryocyte
  - GM-CSF
  - EPO
  - IL-6

- Basophil progenitor
  - GM-CSF
  - EPO
  - IL-6

- Eosinophil progenitor
  - GM-CSF
  - EPO
  - IL-5

- Granulocyte-monocyte progenitor
  - GM-CSF
  - G-CSF
  - M-CSF

- Neutrophil
  - GM-CSF
  - IL-8

- Mast Cell
  - IL-9

- B Cell
  - IL-6
  - IL-4
  - IL-2

- T cell
  - TCR
  - CD8

- Th cell
  - TCR
  - CD4

- Dendritic Cell
  - IL-7
  - IL-3

- NK cell
  - IL-7

- B progenitor
  - IL-6
  - IL-5
  - IL-4
  - IL-2
  - IL-7

- Thymocyte
  - IL-2
  - IL-7

- Macrophage
  - GM-CSF
Immune Responses
A Short History of Immunology

- ~ 430 B.C: Peloponnesian War, Thucydides describes plague – the ones who had recovered from the disease could nurse the sick without getting the disease a second time.
- 15th century: Chinese and Turks use dried crusts of smallpox as "vaccine".
- The term "immunity" was first used in 1775 by Van Sweiten, a Dutch physician, as "immunitas" to describe the effects induced by an early attempt at variolation.
Jenner - Smallpox vaccine

- Noticed that milkmaids that had contracted cowpox did NOT get smallpox
- Test on an 8 year old boy, injected cowpox into him (NOT very nice......)
- Followed by exposure to smallpox
- Vaccine was invented (Latin *vacca* means "cow")
Historical Background

- There have been various theories to explain acquired immunity, the formal explanation was provided by Edward Jenner’s reinfection studies (1790’s)

- The history of immunology is really slightly more than 100 years if Louis Pasteur is considered as the “Father of immunology” as some immunologists do.

- Cellular immunology, the “real” history begins after the World War II, along with the development of transplantation and the “clonal selection theory” formulated by the Australian immunologist, Sir Frank Macfarlane Burnet. Before that, most studies focused on the chemistry of the specificity.
An Inquiry into the causes and effects of the Variolae Vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow-pox.
Robert Koch showed that microorganisms cause infectious diseases and that different organisms cause different diseases.

Louis Pasteur first showed how vaccines could be made to a variety of bacterial pathogens.

Emil Von Behring and Shibasaburo Kitasato found, in the serum of immune individuals, a substance bound to the bacteria to which they were immune. Called the substance ANTIBODY.
Louis Pasteur (1822-1895)

- Stereochemist: molecular asymmetry. Fermentation and silk worker disease, Pasteurisation, Germ Theory of disease. Thus started microbiology

- Attenuated vaccines for cholera, anthrax, and rabies

- On July 4, 1886, 9-year-old Joseph Meister was bitten repeatedly by a rabid dog. Pasteur treated him with his attenuated rabies vaccine two days later. Meister survived.

- Joseph Meister later became a gatekeeper for the Pasteur Institute. In 1940, when he was ordered by the German occupiers to open Pasteur's crypt, Joseph Meister refused and committed suicide!
Robert Koch (1843-1910)

- German physician; also started to work on Anthrax in 1870's. Identified the spore stage. First time the causative agent of an infectious disease was identified.

- Koch's postulates: conditions that must be satisfied before accepting that particular bacteria cause particular diseases.

- Discovered the tubercle bacillus and tuberculin.

- Detailed tuberculin skin test (DTH).

- Awarded in 1905 the Nobel Prize.
Emil Adolf von Behring (1854 – 1917)

- A Student of Koch
- With Kitasato and Wernike, discovered anti-toxin for Diphtheria and Tetanus and applied as therapy.
- Awarded first Nobel Prize in physiology, 1901
Paul Ehrlich (1845-1915)

- Developed a series of tissue-staining dyes including that for tubercle bacillus.

- Worked with Koch. Developed anti-toxin (Diphtheria)

- Side-chain theory of antibody formation: "surface receptors bound by lock & key; Ag stimulated receptors"

- Shared 1908 Nobel Prize with Metchnikoff.
Elie Metchnikoff (1845-1916)

- Embryologist studying starfish development.
- Found phagocytosis. Formed the basis of leukocyte phagocytosis.
- Birth of cellular immunology
- Shared Nobel Prize with Ehrlich in 1908
Sir Frank Macfarlane Burnet (1899-1985)

- Trained as MD

- Important work on influenza. Discovery of an influenza viral enzyme with the specificity for particular forms of neuramic acid. Used today for detection.

- Clonal selection theory to explain tolerance

- 1960 Nobel Prize for the discovery of acquired immunological tolerance. Rejection of donor grafts was due to an immunological reaction and that tolerance can be built up by injections into embryos.
1972 Nobel Prize for their discoveries concerning the chemical structure of antibodies.

Gerald M. Edelman
1929-

Rodney R. Porter
1917-1985
Discovered genes that regulate immune responses (Ir gene),
Now known ad the major histocompatibility antigens

1980 Noble prize
Niels K. Jerne (1912-1994)

- Antibody avidity maturation
- Plaque forming assay
- Pre-existing repertoire (in host DNA) theory helped the formation of clonal selection theory.
- Host MHC is the driving force for the maturation and selection of T cells in the thymus.
- **Idiotype network**
- Nobel Prize, 1984, for theories concerning "the specificity in development and control of the immune system" and the discovery of "the principle for production of monoclonal antibodies."
Milstein (b. 1927) and Köhler (1946-1995)

- Monoclonal antibody production
Susumu Tonegawa (b. 1939)

- Cloning of the Immunoglobulin gene
- 1987 Nobel prize for his discovery of "the genetic principle for generation of antibody diversity".
Peter C. Doherty and Rolf M. Zinkernagel

- Two signals
- 1996 Nobel Prize for their discoveries concerning "the specificity of the cell-mediated immune defence".