The immune system protects from two types of disease:

1. caused by infection with a **pathogen**
2. cancer

The immune system is not always protective

* tissue damage in severe inflammation
* allergy
* autoimmunity
* organ transplant rejection

**Pathogen**: A pathogen is any organism that has the potential to cause disease to the host.

-- usually a microorganism or parasite (Fig. 1.3, 1.4).

-- Review: bacteria vs. virus vs. fungi vs. protozoa.

-- Some are called “**opportunistic pathogens**” since they only cause disease in immunologically weakened or compromised hosts, e.g. HIV-infected or patients undergoing immunosuppressive therapy. Many microorganisms are not pathogens though they co-exist in the body. e.g. the normal “flora” of the gut. Term for normal gut flora is **commensal species**. Some of these have essential “symbiotic” functions.

-- “Microbiome” = hot topic

-- most pathogens don’t kill the host; best to allow host to survive and transmit disease. Even severe diseases like influenza usually don’t kill the patient, as the immune system eventually eliminates the virus.

**Antigen**: a substance that induces an immune response

-- usually a macromolecule derived from a pathogen

-- can be any molecule not normally found in the host

### The Body’s Defenses

# **Innate Immunity:** Mechanisms that recognize and control/eliminate pathogens without requiring prior exposure. A first line of defense that is “pre-existing” in the host but relatively non-specific.

**Adaptive Immunity:** Mechanisms that are not pre-existing but develop over time after exposure to a pathogen. The adaptive immune response is mediated by **lymphocytes** (T cells and B cells), is antigen-specific and provides lifelong immunity to re-infection.

First some definitions:

**Leukocyte**: white blood cell

**Lymphocyte** = a subtype of leukocyte that includes T cells and B cells. Also includes Natural Killer (NK) cells that are part of innate immunity.

**Antibody**: antigen-binding protein in plasma and other body fluids

**Plasma**: the liquid component of the blood. Plasma leaks out of the blood vessels into tissues and mixes with extracellular fluids. Together this material is called **lymph**. Blood plasma can be obtained from blood by removal of the cells (leukocytes, red blood cells and platelets) using centrifugation, without clotting (blood collection tube has to contain an anti-clotting agent).

**Serum**: the liquid component of the blood when clotting occurs before separation of the cells. The protein composition of serum is different than plasma!! This is because clotting causes cleavage of some plasma proteins, and secretion of additional proteins by activated platelets.

Innate immunity: relatively nonspecific but selective for non-self

anatomic barriers (skin, mucous, cilia, **epithelium**; Fig. 1.5, 1.6)

physiological barriers (low pH of stomach)

polypeptide mediators: **lysozyme** is an enzyme in saliva and tears, breaks bacterial cell walls; **defensins** are anti-bacterial peptides in GI tract and other epithelial surfaces

**phagocytosis**: cells internalize and break down foreign cells and macromolecules

**inflammation**: tissue damage and infection induce leakage of vascular fluid and cells that help fight infection

Normal flora protect against infection by pathogens by competing for resources/niches.

the innate immune response plays a critical role in the initiation and direction of the adaptive response through secretion of **cytokines** (general term for secreted small protein with biological activity on other cells) and **chemokines** (proteins that attract and activate other leukocytes), along with processing and presenting pieces of the pathogen (antigens) to lymphocytes.

## Inflammation (Fig. 1.8)

heat, pain, redness, swelling

cells of the innate immune system recognize pathogens (see below) and secrete cytokines that cause local dilation of capillaries

increased blood flow causes local warming and redness

gaps in vessel walls allow leakage of fluid from bloodstream into infected tissue site; causes swelling and pressure on local nerve endings 🡪 pain

cells are attracted by chemokines and cross openings in vessel walls to enter infected tissue; these release further inflammatory substances

Recognition of pathogens and response by innate immune system

Two phases: **recognition** and **destruction** (Fig. 1.7)

Plasma proteins (e.g. components of the **complement** system) bind to pathogen surfaces and mark them as dangerous.

Cells of the innate immune system have surface receptors that recognizes complement-coated pathogens and mediate uptake and destruction.

Cells of the innate immune system can also directly recognize pathogen surfaces that have common invariant structures (“pathogen-associated molecular patterns”, i.e. **PAMPs**) that are not present in the host.

Adaptive immunity

is antigen-specific (i.e. can distinguish one strain of bacteria or virus from another)

requires a delayed period of induction (4-10 days)

provides long-lasting immunological **memory**; second encounter with antigen induces a much stronger and faster response. This is the basis for vaccination. The memory is specific.

is mediated by lymphocytes and antibodies

enhances effector mechanisms of innate immunity by focusing the effective elements to the site of invasion and by enhancing responses such as phagocytosis

# Preview of adaptive immune response and clonal selection of lymphocytes

Definitions

## Proliferation: Cell division leading to expansion of a single parent cell into a population of “clonal” daughter cells.

**Differentiation**: Change in cell phenotype and function; often irreversible.

Adaptive immunity is mediated by lymphocytes, specifically **T cells** and **B cells**

Each lymphocyte has a single antigen receptor---but the sequence is unique for each cell. This sequence diversity is unprecedented in biology and is generated by random cutting, splicing and modification of small gene segments. Therefore, each lymphocyte has a different antigen **specificity**.

In contrast, cells of the innate immune system have a series of receptors that recognize different PAMPs that are routinely encountered, but every such receptor is the same on every cell.

Each antigen/pathogen is recognized by a very small fraction of lymphocytes that have an antigen receptor that binds specifically; these clones are “selected” to fight the invader

**Clonal selection** (Fig. 1.10) refers to the proliferation of antigen-specific clones that are useful in combating an infection. In other words, the immune system is prepared to respond to an almost infinite array of antigens, but each pathogen selects only a few cells that then make many copies of themselves. The reason that adaptive immunity requires time to develop is because it takes time for selected cells to proliferate and make enough copies of themselves to carry out their immune function.

During proliferation the cells also differentiate to acquire effector functions. These functions of expanded clones of lymphocytes will be discussed in later lectures.

Fig. 1.9 compares innate and adaptive immunity.

Loss of components of the innate immune system generally leads to more rapid death by infection than loss of adaptive immune system (e.g. burn victims, radiation ablation of bone marrow vs. HIV). See Fig. 1.11

A key outcome of the adaptive response is **immunological memory** of the antigen so that **secondary immune response** is faster and stronger (**protective immunity**). (Fig. 1.26, 1.27)