Resisting infection

- Innate defenses (ch. 16)
  - Physical & chemical barriers; cellular defenses; inflammation, fever; molecular defenses

- Adaptive defenses (ch. 17)
  - Sometimes called “specific” defenses
  - Mediated by lymphocytes
  - Exposure to specific antigens creates an improved ability to battle the same infection a second time (immunity)

Physical & Chemical Barriers

- **Sweat:**
  - High salt content, acid pH

- **Stomach:**
  - Extremely acid pH
  - (major defense against intestinal pathogens)

- **Lysozyme in tears**

- **Transferrin:**
  - Blood protein that binds free iron
  - Many bacteria require iron as an enzymatic cofactor
  - Some get iron from erythrocytes (RBC) using hemolysins
  - Transferrin minimizes the amount of iron accessible to bacteria

Physical & Chemical Barriers

- **Skin**
- **Mucous membranes**
  - Cover surfaces exposed to the outside world
  - Difficult to penetrate
    - Microbes can be **flushed out** by coughing & sneezing, vomiting & diarrhea, tears & saliva, urination

- **Cilia** (hairlike structures on the respiratory epithelium) “wave” together to drag microbes & other particles in a sea of mucus up & out of the lungs

Cellular Defenses: Leukocytes

- **All cells of the blood are derived from pluripotent stem cells** in the bone marrow
  - “pluripotent”: has the potential to differentiate into many cell types

- **Leukocytes** (white blood cells)
  - Critical for both innate & adaptive host defenses
  - Two major lineages (categories):
    - **Myeloid** (granulocytes)
    - **Lymphoid** (agranulocytes)

  - Number of leukocytes (white blood count) is **elevated** during infection

Leukocytes: **Myeloid cells**

- Most are “granulocytes”, a reference to their microscopic appearance
  - Cytoplasm has spots, or granules
  - Granules are storage compartments
    - Basophils
    - Mast Cells
    - Eosinophils
    - Neutrophils
    - Monocytes / Macrophages
Leukocytes: **Myeloid cells**

- **Basophils & Mast cells**
  - Release histamine
  - Mast cells reside in tissue, not blood
  - Associated with allergies

- **Eosinophils**
  - Prominent during allergic reactions
  - Major fighters against worm infestations

Leukocytes: **Lymphoid cells**

- **B lymphocytes**
- **T lymphocytes**
- **NK (natural killer) cells**

Crucial to adaptive host immunity

(Almost more on this later)

Phagocytosis

- Neutrophils & monocytes/macrophages are phagocytes
- Their job is to engulf and destroy:
  1. Dead cells, cellular debris
  2. Microbes

  A complex range of chemical signals attract phagocytes to invading microbes (chemotaxis).
  - Signals on the microbes (e.g., peptidoglycan, lipopolysaccharide)
  - Signals released by damaged host cells
  - Signals released by other leukocytes in the area

Phagocytosis

- First, microbe must adhere to the phagocyte’s cell membrane
  - Antigens, or substances the body recognizes as foreign, tend to adhere well to phagocytes
- Capsules on bacteria make adherence difficult, protecting the bacteria from phagocytosis

**Opsonization:**
- Bacteria can be coated with antibodies, or molecules of the complement system, that mark them for easy phagocytosis
- “Opsonization” is the process of marking antigens/bacterial cells to make them more appetizing to phagocytes
Phagocytosis

Phagocyte membrane forms extensions **pseudopodia** that surround the microbe, fuse, and create a membrane-bound cytoplasmic vacuole **phagosome** with the microbe trapped inside.

Ingested bacteria are destroyed.

★ **Phagosome** fuses with **Lysosomes**, organelles full of destructive enzymes
  - Within this “phagolysosome”, the microbe’s cell membrane is breached, all cell components broken down
  - In **macrophages**, toxic **reactive oxygen compounds** are also used to kill ingested microbes
    - hydrogen peroxide $\text{H}_2\text{O}_2$, nitric oxide $\text{NO}$,
    - superoxide $\text{O}_2^-$, hypochlorite $\text{OCI}^-$ (bleach)

Phagocytosis

- Doesn’t always work: some microbes survive phagocytosis
  - Acid-fast **mycobacteria** such as *M. tuberculosis* (TB) actually live inside macrophages
    - This gives them a stable, well-protected “home” hidden from other host defenses

Other killing

- Large parasites (like worms) are **too large** for neutrophils & macrophages to engulf
  - Intracellular killing by phagocytosis is not possible

★ **Eosinophils** attack worms (helminth infections) by excreting enzymes toxic to worms
  - “Major basic protein”

Other killing

- To kill viruses, host defenses must destroy infected cells
  - ★ **Natural killer (NK)** cells recognize virus-infected cells
  - ★ NK cells trigger death of the infected cell, often by **apoptosis** (suicide, or programmed cell death)
Lymphatic System

- A kind of parallel cardiovascular system
- Body fluid lymph circulates through lymphatic vessels, pumped by contraction of surrounding muscles
- Lymphatic system drains extracellular fluids from all over the body, delivers to venous system
- Lymphatic vessels are interrupted by lymph nodes

Lymphatic System

- Bacteria entering a lymph node:
  - May be phagocytosed
  - Can activate the adaptive (specific) immune response
  - Stimulate proliferation of leukocytes and migration to the site
  - May actually infect the node

★ Lymphadenopathy, or swelling of the lymph nodes, is a common symptom of various kinds of infections

Inflammation

- Inflammation is a set of nonspecific responses to injury or infection that minimize damage or infection, and promote healing

★ Cardinal signs of inflammation:
  - Calor: heat
  - Rubor: redness
  - Tumor: swelling
  - Dolor: pain

Inflammation

- There are a huge number of chemical mediators of inflammation
  - most have multiple effects, causing the cardinal signs of inflammation;
  - or act as chemotactic factors to attract leukocytes to the site

Inflammation

- Vasodilation, increased vascular permeability (leakiness)
  - Causes redness & heat from increased blood flow
  - Leaking fluids can cause swelling

- Increased blood flow brings clotting factors & phagocytes to the site
  - They exit the blood vessel by passing between endothelial cells: diapedesis★
Inflammation: Pus

- Phagocytes reach infected area and engulf microbes
- **Pus** may form
  - An accumulation of live & dead phagocytes, other cells & cell debris, remains of ingested microbes, etc.
  - *Streptococcus pyogenes*: produces leukocidins which kill phagocytes, enhance pus formation

**Pyogen = pus-inducing**

Fever

- Unlike the localized heat mentioned, fever is a **systemic response** that often accompanies inflammation
- Many things, including infections, can cause fever
- Exogenous pyrogens from microbes promote release of the endogenous pyrogen *Interleukin-1* (IL-1)★
  - IL-1 acts on the hypothalamus (brain) to reset body temperature

**Pyrogen = fever-inducing**

Fever

- Elevated temperature can be GOOD.
  1. Slows growth of pathogens who prefer 37°C
  2. Some microbial enzymes & toxins may be inactivated
  3. By making you feel lousy, it encourages rest (!)

Molecular Defenses: Interferons

- So named because these proteins “interfere” with multiplication of viruses
- 3 categories:
  - α (alpha)
  - β (beta)
  - γ (gamma)

Alpha & beta interferons (INF-α & INF-β)

- Released by a virus-infected cell
  - Other signals of infection, such as endotoxin, can also trigger INF release
- INF binds to receptors on neighboring, *uninfected* cells
  - This activates expression of various **antiviral proteins**

INF-α and INF-β

- Antiviral proteins target viral RNAs
  - All RNA-genome viruses go through at least one phase with **dsRNA**
    - dsRNA viruses: the genome itself
    - + sense RNA viruses: Replication of RNA genome depends on RNA-dependent RNA synthesis. Small bits of dsRNA exist during this process.
INF-α and INF-β

dsRNA structures are NOT normal in healthy cells; they are good targets for selectively toxic antiviral activity

★ Ultimately:
Interferon-induced antiviral proteins help block viral replication in the uninfected cell

INF-γ

• Gamma interferon is produced by lymphoid cells: lymphocytes & NK cells
  ★ – They do NOT need to be infected by a virus

• INF-γ has MANY effects that enhance both the specific and innate immune responses
  – “Activates” lymphocytes, NK cells, macrophages
  – Has some anti-tumor activity too

Interferons

• Various INFs can be manufactured using recombinant DNA techniques and are used therapeutically (as drugs)

  ★ – Limited applications at this time
  – Certain unusual cancers
  – Hepatitis C
  – LOTS of bad side effects

The Complement System

★ What is it?
A set of >20 proteins found in plasma (blood). The proteins function in a cascade

A → B → C → D → E

where A acts on B, B acts on C, etc.; NOT a metabolic pathway where A is converted into B, etc.

Amplification with each step (analagous to the clotting cascade)

The Complement System

★ What does it do?
1. Enhance phagocytosis (by opsonization)
2. Directly lyse microbes with membranes
3. Regulate inflammation & immune responses

Nonspecific & Fast
(doesn’t matter which microbe has entered the body; mobilizes long before adaptive immune defenses)
The Complement System

How does it work?

Step One:
Activate the system

Two ways:
1. Classical Pathway
2. Alternative Pathway

Activation of the Classical Pathway:

Antibodies bound to antigens
(for example, on the surface of bacteria)
activate complement proteins
C1-C4-C2

Activation of the Alternative Pathway:

Polysaccharide markers on the surface of pathogens
(for example, on the surface of bacteria)
activate complement proteins
Factor B/Factor D/Factor P

Both classical & alternative pathways of complement activation activate the central molecule of the cascade,

C3
which splits into C3a and C3b

1. Opsonization:
   - C3b binds to the surface of antibody-marked microbes
   - C3b is acts as an opsonin
     • phagocytes have C3b receptors
     • recognition of C3b stimulates phagocytosis

2. Inflammation:
   - C3a (and other complement proteins) can initiate & enhance inflammation
     • Chemotaxis promotes diapedesis of neutrophils out of blood vessels
The Complement System

3. Direct lysis of microbes (complement-mediated lysis):
   ★ The Membrane Attack Complex
   Complement molecules downstream of C3 catalyze formation of pores in membranes.
   ★ Pores are made of C9 molecules
   These pores, or holes, in cell membranes or viral envelopes, kill the organism.

**Innate host defenses summary**

**Phagocytes**
- Remove debris and pathogens
- Fixed macrophage
- Free macrophage
- Neutrophil
- Lysed abnormal cell

**Extracellular killing**
- Destroys abnormal cells
- Natural killer cell

**Physical barriers**
- Prevent approach and deny access to pathogens
- Hair
- Secretions
- Epithelium

**Inflammatory response**
- Multiple effects
- 1. Blood flow increased
- 2. Phagocytes activated
- 3. Capillary permeability increased
- 4. Complement activated
- 5. Clothing reaction walls off region
- 6. Regional temperature increased
- 7. Specific defenses activated

**Fevers**
- Mobilizes defenses, accelerates repairs, inhibits pathogens
- Body temperature rises above 37°C in response to pyrogens
- Lysed pathogen

**Interferons**
- Increase resistance of cells to infection, slow the spread of disease
- Released by activated lymphocytes and macrophages and by virus-infected cells

**Complement system**
- Attacks and breaks down cell walls, attracts phagocytes, stimulates inflammation