Body Defenses & Immunity

**immunity** = resistance to disease

the immune system provides defense against all the microorganisms and toxic cells to which we are exposed

\* without it we would not survive till adulthood

our body has many ways to prevent or to slow infections

Many factors not directly related to our “immune system” affect an individual’s overall ability to resist infections:

eg. **Genetics**: human diseases, zoonoses, etc

eg. **Age**: mainly an immune response

eg. **Health**: eg. protein deficiency \* less phagocytic activity

eg. stress \* lower resistance to disease

eg. **Hormones**: eg. cortisone (a glucocorticoid)

reduces inflammatory response

the immune system is a functional system rather than a system with discrete organs

\* parts of many organs contribute to body defense

almost all organs in body play some role in immunity

\* dispersed chemicals, cells and tissues

\* dispersal and transport via circulatory and lymphatic systems

two major mechanisms that protect the body:

1. **Innate, nonspecific system** of

   a. physical and chemical barriers
   b. internal cells and chemicals

2. **Adaptive system** that fights **specific** pathogens

or, can view the immune system as a three tiered system of defense

a. physical and chemical barriers
b. chemical and cellular barriers
c. specific defense mechanisms

**Innate, Nonspecific Resistance**

**Physical Barriers**
1st major level of protection from invasion and infection

nonspecific – treats all potential pathogens the same way

attempt to prevent entry of pathogens into body

1. Intact Skin

   tightly packed cells filled with waxy keratin

   thick, multiple layers of dead keratinized cells

   shed regularly

   rarely, if ever, penetrated while intact
       only a few parasitic worms (cercariae) can do this

   if skin is broken:
       staphs and streps are most likely to get in

sebaceous glands

   provides protective film over skin

   acidity of skin secretions ('acid mantle') inhibit bacterial & fungal growth; also contains bacteriocidal chemicals

melanocytes ‡ protect from UV radiation

2. Mucous Membranes

   line all systems that open to outside of body

   nasal hairs
       trap pathogens

   mucous
       thick, sticky, traps pathogens

   cilia
       in resp sys move mucous out of system
       ('ciliary escalator' ‡ 1-3 cm/hr)
       coughing and sneezing speed up process

   gastric juices
       secreted by lining of stomach
       contains HCl and enzymes; highly acidic (pH~1.2-3.0)
       kill and dissolve most bacteria and toxins

Lacrimal Apparatus

   continual blinking flushes and wipes away pathogens

   lysozyme kills and dissolves some bacteria
       (lysozyme also found in sweat, saliva, and nasal
secretions)

**Saliva**
continual flushing of bacteria to stomach
lysozyme kills and dissolves some bacteria

**Urine**
continual flushing of bacteria entering urethra
‡ low flow ‡ bladder infection
acidity also inhibits bacterial growth

**Vaginal Secretions**
flushing and trapping pathogens in mucous
acidity inhibits bacterial growth

**Internal Cellular and Chemical Defenses**

1. **blood** has nonspecific, antimicrobial chemicals that help to fight invaders:
   
   eg. transferrins – bind to Fe to inhibit bacterial growth

2. **Simple Phagocytosis**
   many WBC’s travel through blood and tissues and gobble up bacteria
   and foreign material
   mostly **neutrophils** and **macrophages** (formed from monocytes)
   migrate to area of infection
   monocytes enlarge on way to become macrophages
   engulf and destroy circulating pathogens especially bacteria
   **eosinophils** ‡ can produce toxins and are most active against parasitic
   worms

3. **Natural Killer Cells**
   the “pit bulls” of the defense system
   another kind of WBC
   police the body in blood and lymph
   promote cell lysis of virus infected cells or cancer cells
   not phagocytic

4. **Inflammatory Response**
   larger response that prevents spread of infection from localized area
   damage to body’s tissues causes:
   **redness, pain, heat** and **swelling**
   sometimes loss of function
   overall, has beneficial effect:
   a. destroys injuring agent
   b. removes it and its byproducts or limits its effects
   c. repairs or replaces damaged tissues

5. **Fever**
systemic rather than local response
hypothalamic thermostat is reset to eg. 102.2 °F
produced by **pyrogens** secreted by macrophages when exposed to
certain pathogens

fever symptoms:
- blood vessels constrict
- metabolism increases
- shivering helps maintain high temp
- skin remains cold – chills

slight increase in temperature:
- a. inhibits growth of some pathogens
- b. speed metabolism
  - for repair of body cells
  - and to enhance phagocytosis
- c. cause liver and spleen to store zinc and iron
  - both are nutrients needed by bacteria
- d. intensifies effects of other chemicals
  - eg interferon

6. **Complement Reactions:**
   foreign substance may trigger cascade which activates complement
   proteins =**complement fixation**
   they can operate nonspecifically or specifically
   complement proteins formed from liver cells, lymphocytes, monocytes
   trigger a cascade reaction (inactive\(\rightarrow\) active)
   complement fixation can cause any of the following effects:
   - a. **cell lysis (cytolysis)**
     \(\rightarrow\) digests a hole in bacterial cell, killing it
   - b. **opsonization**
     makes pathogens stickier and easier for the leukocytes to
     phagocytize
   - c. **enhances inflammatory response**
     helps trigger release of histamine and chemical attractants for
     WBC’s

   the effects of complement activation are short lived
   \(\rightarrow\) they are quickly destroyed
   malfunctions of system may result in some hypersensitivity disorders

7. **Interferon**
   antiviral chemical secreted by infected cells
   different tissues in same host produce different interferons
   all interferons are small proteins produced by infected cells and spread to
   uninfected cells
stimulate synthesis of antiviral proteins that
disrupt various stages of viral multiplication
effective for only short periods
‡ good for acute, short term infections eg. colds, influenza
experimentally used to treat HIV, Hepatitis, genital herpes,
influenza, common cold

**Specific Resistance (The Immune Response)**
functionally, the third line of defense against infections

non innate, but adaptive:
carefully targeted
‡ recognizes a specific foreign substance and acts to immobilize or neutralize it
amplifies the immune response, complement reactions, etc

has the following characteristics:
1. **Response to a Specific Antigen**
   protein or organic molecule,
   free or attached to bacterial cell or other pathogen
2. **Systemic Response**
   effective throughout the entire body
3. **Has Memory**
   resistance lasts a long time

**Antigens**

any substance that can mobilize the immune system
‡ ie. provoke an immune response

can be free molecules or attached to cells of bacteria, fungi, etc

most are large complex organic molecules (MW >10,000), not normally found in the body
   ie. intruders = nonself

especially immunogenic:
   foreign proteins
   nucleic acids
   some lipids
   many large polysaccharides

must be foreign to the host
our body is programmed to recognize our own
proteins as “self” ie. not immunogenic

microorganisms and pollen grains are immunogenic
    because their surface membranes have many such foreign molecules on them

The immune response (specific immunity) involves the
    interaction of two major processes in the body, directed by two different
    kinds of lymphocytes (WBC’s):

A. Antibody Mediated Immunity
    (AMI; Humoral Immunity)

B. Cell Mediated Immunity
    (CMI)

Antibody Mediated Immunity

=AMI; =Humoral Immunity

involves the release of proteins called antibodies

Mediated by B lymphocytes (B-cells)

Activation of B cells:
    a. specific B cells activated by exposure to an antigen
    b. triggers clonal selection and multiplication
        ‡ produces numerous copies of identical
            cells with identical antibodies on cell membranes
    c. differentiation into plasma cells and memory cells
    d. plasma cells secrete antibodies
        2,000 Ab/sec over few (4-5) days, then dies
    e. memory cells do not secrete antibodies
        live for months or years
        if later exposed to same antibody they can
        develop into plasma cells and secrete antibodies
            ie. they “remember” an earlier encounter with the antigen

Antibodies

antibodies are proteins called immunoglobins
    =gamma globulin of plasma proteins

each of us has ~ a billion different kinds of antibodies
    and each of these has a unique shape
antibodies bind to antigens to cause a variety of possible effects:

1. **Agglutination**
   - bind to antigens on cells to cause them to clump together
   - makes it easier for WBC’s to remove

2. **Precipitation**
   - binds soluble antigens together causing them to precipitate out of solution
   - makes it easier for WBC’s to remove them

3. **Neutralization**
   - binds to bacterial toxins (esp. exotoxins) and causes them to be nontoxic

4. **Prevents viral attachment**
   - binds to viral receptor sites to prevent viral invasion of cells
   - (doesn’t work for latent viruses)

5. **Stimulates Natural Killer Cells**
   - antibodies coat and mark a cell for destruction by the NK cells
     - = antibody dependent cell mediated cytotoxicity

6. **Complement Fixation**
   - triggers complement reactions especially against cellular antigens
   - cascade reactions can cause:
     - cell lysis
     - opsonization
     - inflammatory enhancement

**primary vs secondary response**

**primary**
- ♡: persons initial exposure to an antigen
  - lag of several days before antibodies begin being produced
  - peak production in ~10 days

**secondary**
- ♡: reexposure to same pathogen triggers memory cell response
  - memory cells can persist for 20 years or more
  - much quicker response
  - much stronger response

**Cell Mediated Immunity**

= CMI

Mediated by T lymphocytes (T-cells)
involves a more diverse group of cells than for B cell activation

usually, slower to respond

most active in:
  - bacterial infections
  - destruction of malignant tumor cells
  - transplant rejections

Activation of T cells:
  a. specific T cells activated by exposure to a specific antigen (on a cell)
  b. initiate clonal selection and multiplication
  c. differentiation into several cell types
  d. various T-cells secrete immunoactive chemicals
     = lymphokines; = cytokines, NOT antibodies
     - which direct the activities of both B and T cells and phagocytes

Kinds of T-Cells Produced:
  i. **Helper T-cells** (esp CD4 cells)
     - most prevalent of all kinds of T cells, 65%
     - directly helps T and B cells to function
     - releases lymphokines:
     - † recruit lymphocytes
     - ‡ stimulate differentiation of lymphocytes
     - ‡ help B cells recognize antigens
     - there can be no immune response without them

  ii. **Cytotoxic T-cells** (CD8 cells)
     - directly kill specific target cells by lysis
     - especially effective against foreign cells, cancer cells, fungi, some protozoa and helminths
     - recognizes virally infected cells by viral antigens on cells surface

  iii. **Suppressor T-cells** (CD8 cells)
     - restricts rampant uncontrolled immune response
     - dampens activity of T and B cells
     - brings immune response to an end

  iv. **Delayed Hypersensitivity Cells**
     - chronic infections
     - cell mediated allergies

  v. **Memory Cells**
**Lymphokines:**
various T-cells secrete immunoactive chemicals = lymphokines = cytokines

soluble chemical messengers by which cells of the immune system communicate with each other

1. **chemotactic factor**
   ✦ attracts macrophages to invaders

2. **macrophage activating factor**
   ✦ tells macrophages to destroy antigen
   gives them enhanced antibacterial activity:
   - increased metabolic activity
   - more lysosomes
   - increased phagocytosis

3. **lymphotoxin**
   ✦ poison which kills any cell it contacts
   requires direct cell contact

4. **migration inhibition factor**
   ✦ halts macrophage migration

**Effects of Aging on Immune System**

reduced immune responsiveness:
- less red bone marrow and lymphatic tissue
- loss of thymus ✦ lymphocytes fail to mature
- fewer helper T cells and less responsive
- fewer NK cells ✦ weaker surveillance

✦ infections become more common and more serious
  epidemics have more severe impact on older population

but number of autoantibodies increases with age
✦ more autoimmune diseases
Clinical Applications of Immunity

1. Vaccinations

based on primary vs secondary response

**primary**
- persons initial exposure to an antigen
  - lag of several days before antibodies begin being produced
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**secondary**
- reexposure to same pathogen triggers memory cell response
  - memory cells can persist for 20 years or more
  - much quicker response
  - much stronger response

**natural vs acquired immunity**

**natural**
- immune response is triggered due to natural exposure to a pathogen

**acquired (=artificial)**
- immune response is triggered by a medical procedure, eg vaccination

**active vs passive immunity**

**active**
- exposure triggers body’s own immune response including memory cells

**passive**
- subject receives antibodies from another person or animal, rather than making them himself
  - offers immediate protection, short term
  - no active antibody production is stimulated
  - no memory develops

  eg. fetus gets antibodies from mom
  eg. gamma globulin to treat hepatitis, botulism, snake bites, etc

2. Monoclonal Antibodies

specific B cell (with desired antibodies) is fused to cancer cell
- rapid production of large numbers of the same antibody

3. Organ Transplants and Rejections

same principle as blood transfusions
usually need immunosuppressive drug therapy
Disorders of Immune System

most immune disorders can be categorized as:

1. autoimmune diseases
2. hypersensitivities
3. immunodeficiencies

1. Autoimmune Diseases

5% of adults in North America
‡ 2/3rd of victims are women

normal state of self tolerance breaks down due to:
‡ self reactive lymphocytes are normally silenced during development
   in this case some escape and attack body
‡ new self antigens (?antibodies) appear
due to gene mutation or hapten binding
‡ foreign antigens resembling self antigens
   trigger antibodies that not only attack foreign antigens but self antigens as well

autoantibodies & sensitized T-cells

some of most common autoimmune diseases:

eg. Multiple Sclerosis
destruction of myelin sheath of brain and spinal cord
especially in young adults
nerve fibers are severed
neurons short circuit
cycles of remission and relapse

eg. Myasthenia Gravis
destruction of neuromuscular junctions ♦ Ach receptors
results in muscle weakness
typical symptom = droopy eyelids

eg. Graves Disease
increased thyroid activity
♦ thyroid produces excessive amounts of thyroxine

eg. Juvenile Onset Diabetes Mellitis
destruction of beta cells in Islets of Pancreas
results in insulin deficiency
eg. **Rheumatoid Arthritis**
    joint inflammation and destruction

eg. **Lupus**
    attacks kidneys, heart, lungs, skin

2. **Hypersensitivities**
   immediate (acute) hypersensitivity
   mediated by B cells
   IGE ± mast cells ± histamine
   anaphylactic shock

   delayed hypersensitivities
   mediated by T cells
   antihistamines don’t work
   use corticosteroids

3. **Immunodeficiencies**
   failure of immune system to respond adequately to a pathogen

   eg. **SCID** (Severe Combined Immunodeficiency Disease)
       congenital
       born without functional immune system

   acquired
   eg. **AIDS** (Acquired Immunodeficiency Syndrome)
       results from infection with HIV virus
       usually acquired by sexual contact or drug injections
       HIV targets helper-T (CD4) cells