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

Individual Susceptibilities

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

eg. **Microbiome:** activate our immune system and affect our susceptability to diseases

The Immune System

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 kinds of **mechanisms** that protect the body:

1. Nonspecific Immunity

an **innate** reaction that acts as a general response against all kinds of pathogens

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

2. Specific Immunity

an **adaptive system** that fights **specific** individual pathogens in customized ways

Nonspecific Immunity

nonspecific mechanisms for protecting the body can be visualized as offering two distinct levels of protection

→ **physical & chemical barriers** that work to prevent entry of pathogens

→ **internal cells & chemicals** that attempt to remove pathogens if they get past the barriers

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

skin is rarely, if ever, penetrated while intact

only a few bacteria and parasitic worms (cercariae) can do this

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

a. consists of multiple layers of tightly packed dead cells filled with waxy **keratin**

b. shed regularly to prevent buildup of bacterial communities

c. **sebaceous glands** provides protective film over skin

d. acidity of skin secretions ('**acid mantle**') inhibit bacterial & fungal growth

e. skin also contains bacteriocidal chemicals

but if skin is moist, not cleaned frequently enough

→may permit yeasts and fungi already present to become a problem

f. Langerhans cells (& Granstein cells) → serve as **antigen presenting cells**

they expose skin antigens to T cells

2. Mucous Membranes

line all systems that open to outside of body

a. secretes **mucus**

thick, sticky, traps pathogens

b. in the nose **nasal hairs** help trap pathogens

c. many mucus membranes have **cilia**

in resp system move mucus out of system

('ciliary escalator' → 1-3 cm/hr)

coughing and sneezing speed up process

d. stomach lining secretes **gastric juices**

contains HCl and enzymes; highly acidic (pH~1.2-3.0)

kill and dissolve most bacteria and toxins except *S. aureus* and *C. botulinum*

but: *Helicobacter pylori* neutralizes acids to grow in stomach
may cause gastritis or ulcers

e. eye is protected by **lacrimal apparatus**

continual blinking flushes and wipes away pathogens

lysozyme in tears kills and dissolves some bacteria (most G+ and some G- bacteria)

(lysozyme also found in sweat, saliva, and nasal secretions)

f. **saliva** in mouth allows continual flushing of bacteria to stomach

lysozyme kills and dissolves some bacteria

g. **urine provides** continual flushing of bacteria entering urethra

low flow → bladder infection

acidity also inhibits bacterial growth

h. **vaginal secretions**

flushing and trapping pathogens in mucous

acidity also inhibits bacterial growth

but: some pathogens thrive in moisture and if they occur in large enough numbers they are able to penetrate eg. *Treponema*

Internal Cells & Chemicals

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

some macrophages are "fixed macrophages" that screen blood as it passes by

→ esp in liver, bronchial tubes of lungs, nervous system, , spleen, lymph nodes, bone marrow peritoneal cavity

[referred to as the reticuloendothelial system]

mechanism of phagocytosis:

a. Chemotaxis

chemical attraction to invaders, microbial products, components of WBC's or damaged cells

b. Adherence

attachment to surface of foreign material
may be hampered by capsules (eg. S. pneumonia, H. Influenza) or M proteins (eg. S. pyogenes)
→ must trap them against rough surface (eg. blood vessel wall, clot, etc)

also can be more readily phagocytized if 1st coated with certain plasma proteins that promote attachment (=opsonization)

c. Ingestion

plasma membrane of phagocyte extends around microorganism or cell

d. Digestion

forms food vacuole inside WBC
fuses with lysozomes

takes 10-30 minutes to kill most bacteria
enzymes:
lysozyme → hydrolyzes peptidoglycan of cell wall
lipases, proteases, ribonucleases → hydrolyzes other cellular components
some enzymes also produce toxic oxygen products: eg. O_2^-, H_2O_2, OH^-

residual body discharges wastes

not all microorganisms are killed once phagocytized

eg. *Staph* and *Actinobacillus* actually produce toxins that kill phagocytes

eg. *Chlamydia*, *Shigella*, *Mycobacterium*, *Leishmania* (protozoan), and *Plasmodium* can survive inside phagocyte
→ they can prevent fusion of lysozome

eg. other microbes can remain dormant for months

phagocytosis also plays a role in specific immunity

3. **eosinophils**

can produce toxins and are most active against parasitc worms

4. **Natural Killer Cells**

the "pit bulls" of the defense system

another kind of WBC; not phagocytic

police the body in blood and lymph

promote cell lysis of virus infected cells or cancer cells

5. **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

occurs in three major stages:

a. vasodilation

b. phagocyte migration and phagocytosis

c. tissue repair

a. Vasodilation and Increased Permeability

damaged tissues release **histamines** and **kinins**

blood vessels dilate in area of damage

→increased blood flow to area

causes swelling (**edema**), **redness** and **heat**

this allows defensive chemicals and clotting factors and cells to move to the area

clot forms around area to prevent spread of infection

b. Phagocyte Migration and Phagocytosis

within an hour phagocytes begin to accumulate at the site

as the flow of blood decreases, phagocytes stick to lining of blood vessels then squeeze out into tissue spaces

chemical attractants, eg. kinins, draw WBC's to site

neutrophils arrive first, monocytes predominate during later stages

as WBC's die → **pus** accumulates

c. Tissue Repair

cant be completed until all harmful substances have been removed or neutralized

6. **Fever**

systemic rather than local response

involves coordinated autonomic, neuroendorine and behavioral response

used by all vertebrates as acute phase reaction to immune challenge

hypothalamic thermostat is reset usually to 1-4 degrees above normal

eg. 102.2 ºF

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

very high temperatures (>40º C) may be life threatening

7. **Complement Reactions**

foreign substance may trigger cascade which activates complement proteins =**complement fixation**

~5% of all blood proteins (20 different ones) are complement proteins

they can operate nonspecifically or specifically

complement proteins formed from liver cells, lymphocytes, monocytes

trigger a cascade reaction (inactive→ active)
→ initiation
→ amplification
→ effects

complement fixation can cause any of the following effects:

a. cell lysis (cytolysis)

membrane attack complex forms "transmembrane channels"

→digests a hole in bacterial cell, killing it

b. opsonization

makes pathogens stickier and easier for the leukocytes to phagocytize

c. enhances infllammatory response

helps trigger release of histamine and chemical attractants for WBC's

the effects of complement activation are short lived
→ they are quickly destroyed

malfunctions of system may result in some hypersensitivity disorders

8. **Interferon**

antiviral chemical secreted by infected cells

they are host cell specific, not virus specific

→ different tissues in same host produce different interferons

all interferons are small proteins

stable at low pH
heat resistant

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

interferon is now produced in quantity by recombinant DNA technology

has only very limited effects on cancer cells

high doses have side effects:
fatigue, fever, chills, joint pain, seizures

experimentally used to treat HIV, Hepatitis, genital herpes, influenza, common cold

might work better with other agents in combination

Specific Immunity

functionally, the third line of defense against infections

non innate, but **adaptive**:

1. carefully **targeted**

   → recognizes a specific foreign substance and acts to immobilize or neutralize it

2. **amplifies** the immune response, complement reactions, etc against specific pathogen

3. is a **systemic** response

   effective throughout the entire body

4. Has **memory**

   protects you if you're ever reinfected with same pathogen

   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

the ability of a molecule to act as an antigen depends

on its size and complexity

most are large complex organic molecules (MW >10,000), not normally found in the body

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

but large simple molecules of many small repeating units (eg. plastics) have little or no immunogenicity

must be foreign to the host

our body is programmed to recognize our own proteins as "**self**" ie. not immunogenic

but these same proteins may be strongly immunogenic to others

eg. transfusions, transplants

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

examples of antigen containing structures:
bacterial capsules
cell wall lipopolysaccharides of G- bacteria
glycoproteins in cell membranes
attachment sites for viruses
bacterial toxins and extracellular enzymes

small molecules such as peptides, nucleotides, and

many hormones are NOT immunogenic

→but may become so by attaching to the body's own proteins (=Haptens)

eg. chemicals in poison ivy, animal dander, some detergents, cosmetics, etc

actually, only certain parts of an entire antigen are immunogenic

usually a small sequence of amino acids (~10) that triggers an immune reactions

→ = **antigenic determinants (=epitopes)**

most naturally occurring antigens have a variety of antigenic determinants

eg. large proteins have 100's

Antigen Processing

immune surveillance is a search for **antigens**

uses a large population of white blood cells = **lymphocytes**

to control bacteria and large parasites immune system deploys soluble antigen receptors called antibodies

antibodies bind directly to parasite and provide a

focus for the immunologic molecules and cells

for viruses and other organisms that establish themselves within body cells the immune system uses a different process

the infected cells display major histocompatability complex (**MHC**) molecules on their surface which bind to and display small peptides or fragments of proteins that come from the parasite

these MHC with foreign peptides form antigens that can be recognized by antigen receptors on certain lymphocytes which identify and kill infected cells, leaving healthy cells alone

The Immune Response

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

Mediated by B lymphocytes (B-cells)

involves the release of proteins called antibodies

B-Cell Development & Activation

1. by the time an infant is a few months old B lymphocytes (B cells) have completed the 1st stage of their development:

   manufactured in fetal liver

   they synthesize up to 100,000 antibody molecules that they hold in the cell membrane

2. The next stage of development occurs in lymph nodes and spleen and only occurs if B cell encounters an antigen it recognizes:

   a. specific B cells activated by exposure to an antigen

      →antigen binds to antibodies on cell membrane of B cell

   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**

      plasma cells secrete **antibodies**

      2,000 Ab/sec over few (4-5) days, then dies

      memory cells do not secrete antibodies live for months or years

      if later exposed to same antigen they can develop into same kind of 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

each immunoglobin molecule consists of 4 polypeptide chains joined together to form a "Y" shaped molecule

each antibody has 2 or more **combining sites**

→ small concave areas at tip of arms of "Y" that are uniquely shaped and complementary to the epitope

two long (=heavy, ~400 AA's) chains and two short (=light, ~200 AA's) chains linked by disulfide bonds

constant region → same AA sequence for all in same class

variable region → =antigen binding sites (tips of Y)

the body uses ~300 gene "pieces" to make >1 Billion different kinds of antibody molecules

the amino acid sequence determines the specific shape of these polypeptide chains

this unique shape allows a specific antibody to combine with specific antigen

Classes of Antibody Molecules:

IgG
- most abundant antibody in plasma
- 75-80% of gamma globulin
- also found in internal secretions (synovial fluid, spinal fluid, peritoneal fluid)
- effective against bacteria, viruses, and toxins
- plasma levels increase dramatically during secondary responses
- only Ig that can cross placenta

IgM
- largest of the antibodies
- only found in blood
- 5-10% of plasma immunoglobins

- 1st antibody released to blood by plasma cells during primary response
- attacks specific toxins eg. diptheria, tetanus, botulism toxin
- blood group antibodies belong to this group
  → cause agglutination

Ig A
- dimer
- 10-25% in serum
- also found in body secretions: mucus, saliva, urine, milk, tears
- active against bacterial and viral infections
- inhibits attachment of parasites in gut
- 1st to encounter bacteria in GI tract
- passed to nursing child in mothers milk

Ig E
- associated with allergies
- causes certain WBC's to release histamine
  → dilates capillaries
  → constricts bronchi

Ig D
- very low concentrations in serum
- levels increase during chronic infections

formation of the antigen/antibody complex by B-cell activity does not generally destroy the invader

→ it prepares it for destruction by
- non-specific phagocytosis (WBC's)
- triggering complement fixation
- CMI (T-cell activity)

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

Natural vs Artificial Immunity

natural
→ immune response is triggered due to natural exposure to a pathogen

artificial (=acquired)
→ 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

Cell Mediated Immunity

= CMI

Mediated by T lymphocytes (T-cells)

involves a more diverse group of cells than for AMI

usually, slower to respond

antigens are usually larger than in AMI

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

T-cells also contain antigen receptors on their cell membranes

T-Cell Development & Activation

1. probably also first develop in fetal liver from stem cells
2. then move to thymus where they develop and proliferate
3. move into lymph nodes and spleen as T- cells

4. The next stage of development occurs only if T cell encounters an antigen it recognizes:

   a. specific T cells activated by exposure to a specific antigen (on a cell)

      T-cells cannot recognize *free* antigens in the blood
      generally need cell to cell contact to work

      eg. viral infected cell, cancer cell, bacterial cell

   b. initiate clonal selection and multiplication of specific kind of T-cell

   c. differentiation into several cell types

      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**

5. each T-cells secrete specific kinds of immunoactive chemicals = **cytokines (=lymphokines)**

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

      NOT antibodies

   cytokines direct the activities of both B and T cells and phagocytes

   Kinds of Cytokines

   eg. chemotactic factor

      → attracts macrophages to invaders

   eg. macrophage activating factor

      → tells macrophages to destroy antigen
      gives them enhanced antibacterial activity:
      increased metabolic activity
      more lysosomes
      increased phagocytosis

eg. lymphotoxin

→ poison which kills any cell it contacts
requires direct cell contact

eg. migration inhibition factor

→ halts macrophage migration

eg. Interleukin 1

→ stimulates helper T-cells in presence of antigen

→ attracts macrophages in inflammatory resonse

eg. Interleukin 2

→ proliferation of TH cells

→ proliferation and differentiation of B-cells

→ activation of Tc and NK cells

eg. alpha interferon

→ inhibits intracellular viral replication

→ increases activity of macrophages against microbes and tumor cells

eg. Tumor Necrosis Factor

→ toxic to tumor cells

→ enhances activity of phagocytic cells

eg. GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor)

→ stimulates the formation of RBC's and WBC's from stem cells

Interactions of AMI and CMI Systems:

both systems work together to increase the immune response against specific foreign antigens

eg. production of antibodies by B-cells often requires helper T-cells

esp. "T-dependent antigens" – proteins such as viruses, bacteria, foreign RBC's, hapten–carrier combinations

eg. stimulate B-cells to differentiate into plasma cells and produce antibodies

Neuroendocrine-Immune Interactions

all three systems are interconnected

neural links:

neurons innervate immune system organs such as spleen and lymph nodes

chemical links:

all three produce active chemicals neurotransmitters, hormones, lymphokines

sometimes one chemical can have effect in all three systems

all three coordinate and control the responses to the outside world

the immune system acts as a "diffuse sense organ"

relays data about inflammation or infections to brain

Examples of interactions:

eg. Brain might respond to an infection by causing fever and achy feeling (part of nonspecific defense)

eg. stress can activate parts of same pathway

eg. mental state can influence the body's resistance to disease: anxiety or psychological stress increased severity of a cold

hypothalamus→ pituitary→ adrenal→ stress

>bld sugar → reduced inflammatory response

eg. immune system can be taught to react to visual cue with an allergic reaction = conditioned response

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

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offers immediate protection, short term

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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 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
best known of all human autoimmune diseases
destruction of neuromuscular junctions
→ Ach receptors
results in muscle weakness and fatiguability
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
a group of diseases
arthritis and dermatitis are most common manifestations
attacks kidneys, heart, lungs, skin

eg. Narcolepsy
seems to have an autoimmune origin

2. Hypersensitivities

eg. allergies

up to 50 million in US suffer from allergies

35.9 million (>70%) →hay fever
10 million →allergic asthma
30,000 → food allergies

Ig E mistakes a harmless foreign substance for a dangerous invader and triggers runny nose, tears, itching, swelling

incidences of allergies are on the rise

some consider them a "disease of civilization"

a. immediate (acute) hypersensitivity
mediated by B cells
IGE → mast cells → histamine
may cause anaphylactic shock

b. delayed hypersensitivities
eg. poison ivy

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

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