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 affect an individual’s overall ability to resist infections:
- **Genetics:** human diseases, zoonoses, etc
- **Age:** mainly an immune response
- **Health:** eg. protein deficiency → less phagocytic activity  
  eg. stress → lower resistance to disease
- **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
   
   **but**
   
   if skin is moist, not cleaned frequently enough
   
   → may permit yeasts and fungi already present to become a problem

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
except S. aureus and C. botulinum

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

Lacrimal Apparatus
continual blinking flushes and wipes away pathogens
lysozyme kills and dissolves some bacteria
(most G+ and some G- 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

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

   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]

   **eosinophils** → can produce toxins and are most active against parasitic worms

**mechanism of phagocytosis:**

1. **Chemotaxis**
   
   chemical attraction to invaders, microbial products, components of WBC’s or damaged cells

2. **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)

3. **Ingestion**
   
   plasma membrane of phagocyte extends around microorganism or cell

4. **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$_2$O$_2$, OH$	ext{-}$
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. **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
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  

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**

~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$\rightarrow$ active)

- initiation
- amplification
- effects

complement fixation can cause any of the following effects:

a. **cell lysis (cytolysis)**

membrane attack complex forms

“transmembrane channels”

$\rightarrow$ 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 they are host cell specific, not virus specific

$\rightarrow$ 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

$\rightarrow$ stimulate synthesis of antiviral proteins that disrupt various stages of viral multiplication effective for only short periods

$\rightarrow$ 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 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. **Responds 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

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
   ie. intruders = nonself

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

elements 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

specific immunity involves two different kinds of lymphocytes:
- T cells and B cells:
  both originate in bone marrow
  T cells move to thymus for further maturation
  B cells develop further in bone marrow
  after development both are dispersed to lymph nodes and spleen until needed

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)

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
   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
   d. plasma cells secrete antibodies
      2,000 Ab/sec over few (4-5) days, then dies
   e. memory cells do not secrete antibodies
      but 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
   eg. gamma globulin of plasma proteins

each of us has ~ a billion different kinds of antibodies
   and each of these has a unique shape

each immunoglobulin 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. diphtheria, 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 B cell activation

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

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

a. specific T cells activated by exposure to a specific antigen (on a cell)
  eg. viral infected cell, cancer cell, bacterial cell
b. initiate clonal selection and multiplication
c. differentiation into several cell types
d. various T-cells secrete immunoactive chemicals
  \( \text{lymphokines} = \text{cytokines} \), NOT antibodies
  \( \rightarrow \) 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:
  \( \rightarrow \) recruit lymphocytes
  \( \rightarrow \) 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
5. Miscellaneous other immunoactive chemicals

a. Interleukin 1
   → stimulates helper T-cells in presence of antigen
   → attracts macrophages in inflammatory response

b. Interleukin 2
   → proliferation of TH cells
   → proliferation and differentiation of B-cells
   → activation of Tc and NK cells

c. alpha interferon
   → inhibits intracellular viral replication
   → increases activity of macrophages against microbes and tumor cells

d. Tumor Necrosis Factor
   → toxic to tumor cells
   → enhances activity of phagocytic cells

e. 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 $\rightarrow$ pituitary $\rightarrow$ adrenal $\rightarrow$ stress

  $\rightarrow$ blood sugar $\rightarrow$ reduced inflammatory response

eg. Immune system can be taught to react to visual cue with an allergic reaction = conditioned response
Clinical Applications of Immunity

1. Vaccinations

based on primary vs secondary response

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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

4. Allergies
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

5. Immunodeficiencies
congenital
est. SCID

acquired
est. AIDS

6. 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