Immune System

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Anatomy of an Illness

by Norman Cousins

- It started the revolution in patients working with their doctors and using humor to boost their bodies' capacity for healing.
- When Norman Cousins was diagnosed with a crippling and irreversible disease, he forged an unusual collaboration with his physician, and together they were able to beat the odds.
- The doctor's genius was in helping his patient to use his own powers: laughter, courage, and tenacity. The patient's talent was in mobilizing his body's own natural resources, proving what an effective healing tool the mind can be.
- This remarkable story of the triumph of the human spirit is truly inspirational reading.

2

Immune System

1. GRATITUDE
2. HUMOR
3. SUNLIGHT
4. MOVEMENT
5. SLEEP
6. COMMUNITY
7. HEALTHY EATING & DRINKING

3

Immune System

- VERY COMPLEX SYSTEM
- This program is not a school on Functional Medicine, although we will cover overview and some crucial elements.
- It is Mentorship Program akin to a Master Class
- Clinical Pearls and PRACTICAL OUTCOME

- THE MAIN QUESTION AS A PURPOSE OF THIS LECTURE IS:

WHAT CAN WE DO TO CHANGE OR OPTIMIZE IMMUNE SYSTEM RESPONSE?

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"We've exhausted all conventional measures. One last desperate option is to put you on an alternative natural medicine that has a 96% success rate."

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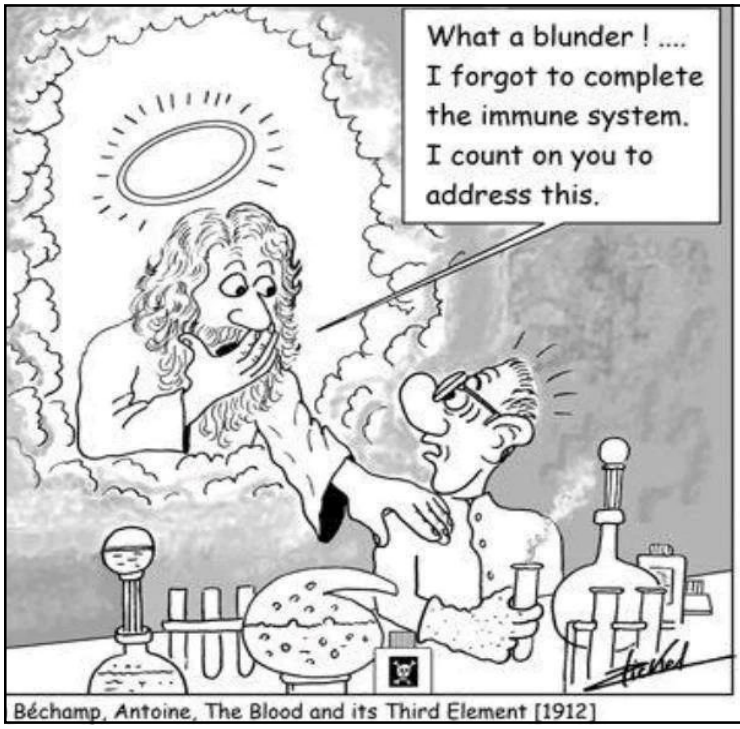

Béchamp, Antoine, The Blood and its Third Element [1912]

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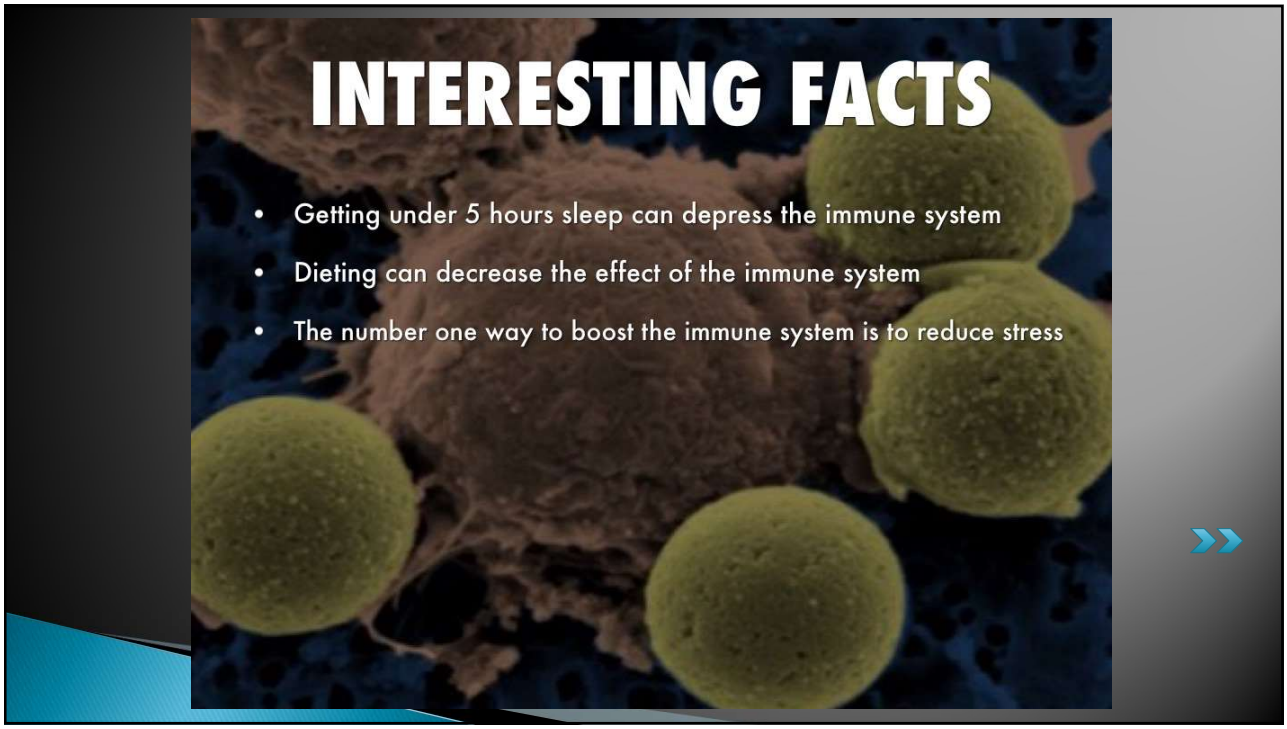
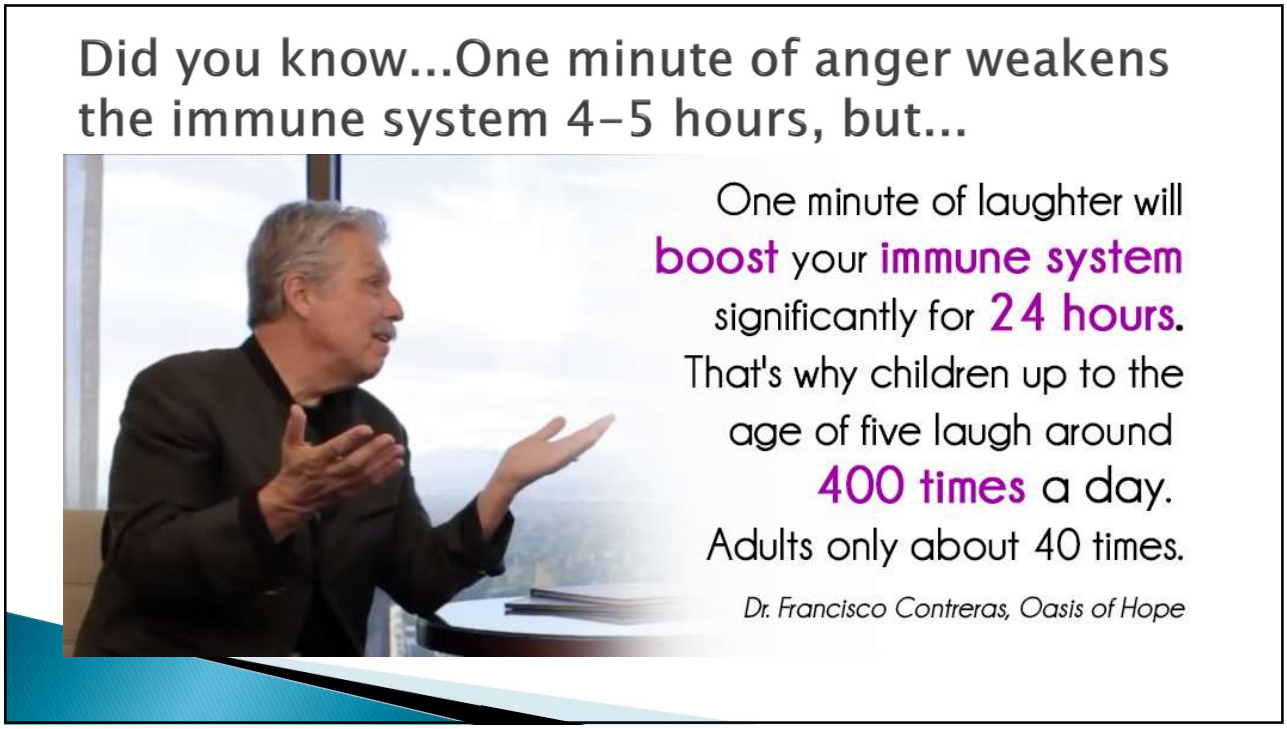

INTERESTING FACTS
Getting under 5 hours sleep can depress the immune system
Dieting can decrease the effect of the immune system
The number one way to boost the immune system is to reduce stress

7


Did you know...One minute of anger weakens the immune system 4-5 hours, but...
One minute of laughter will boost your immune system significantly for 24 hours. That's why children up to the age of five laugh around 400 times a day. Adults only about 40 times.
Dr. Francisco Contreras, Oasis of Hope

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TO

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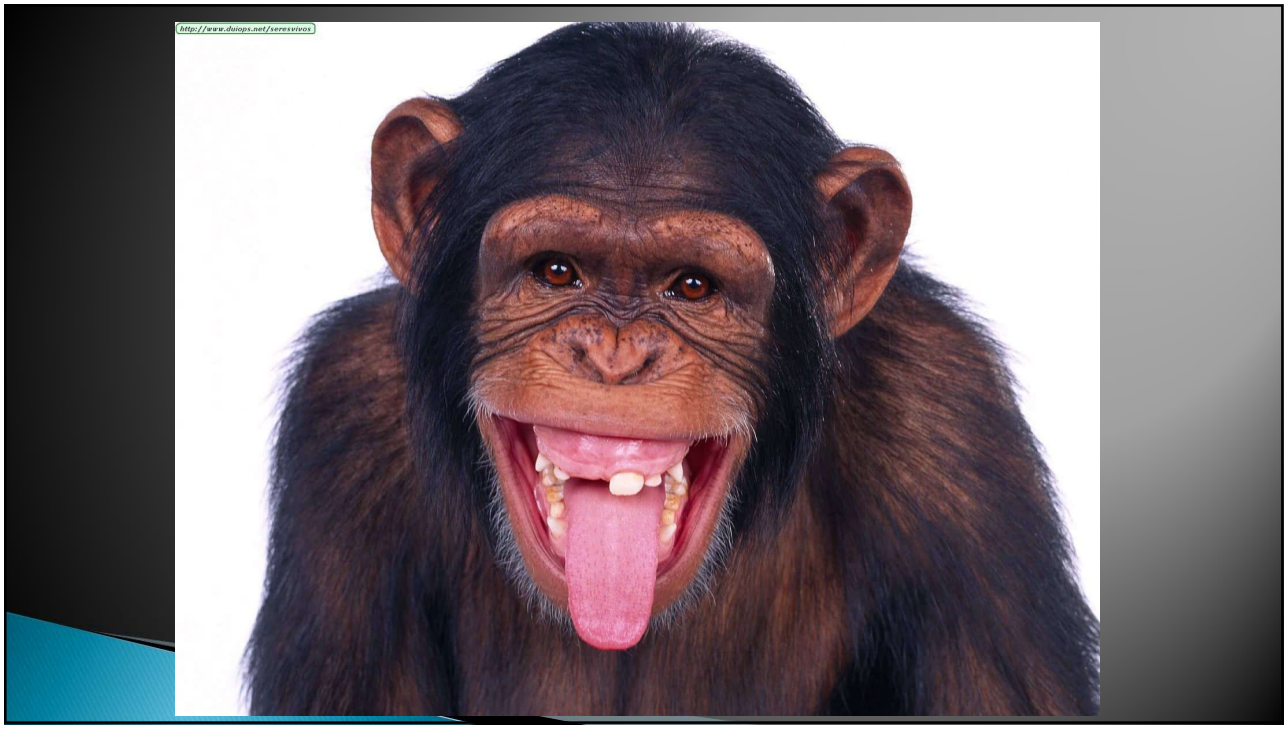

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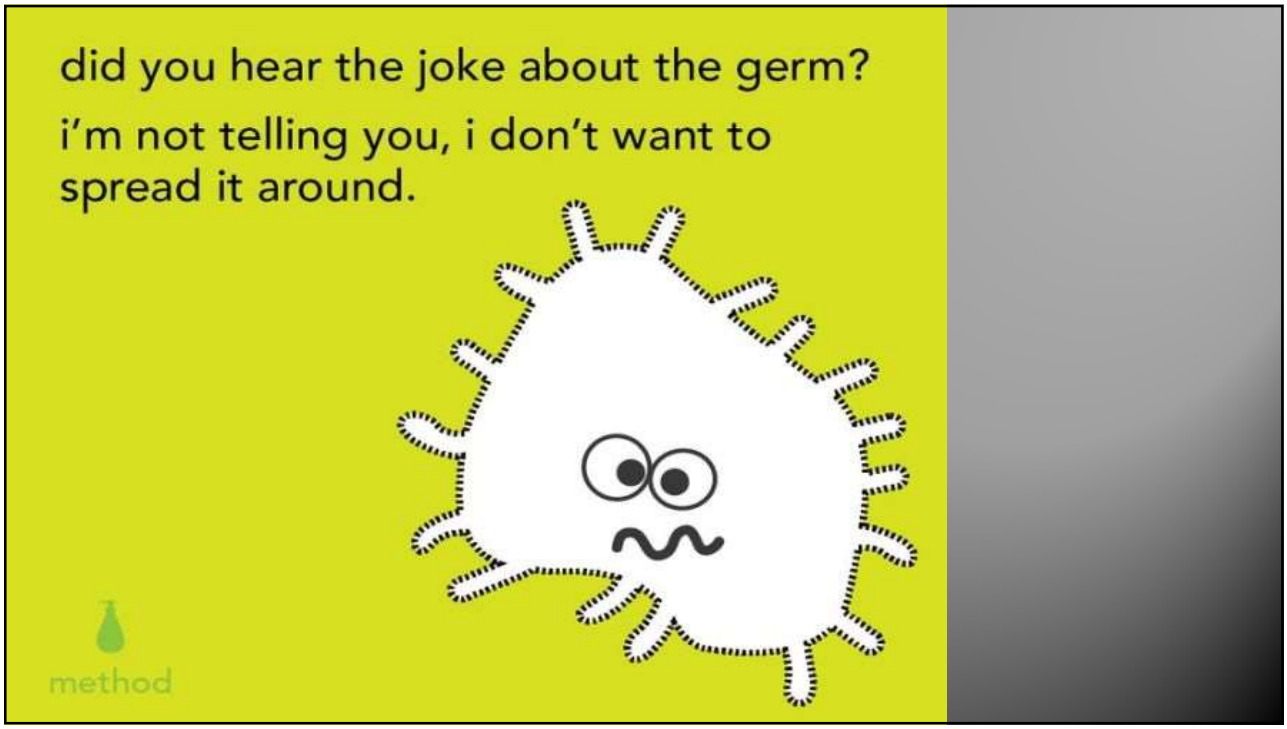
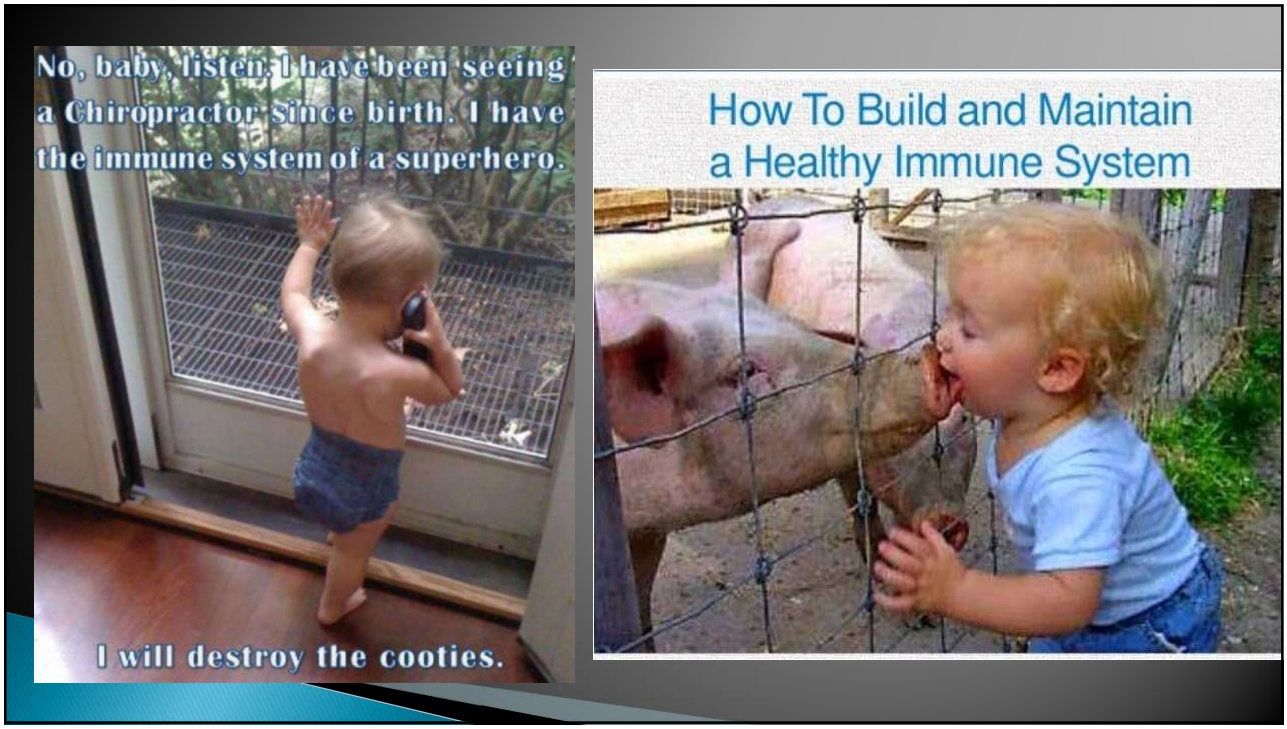

did you hear the joke about the germ?
i'm not telling you, i don't want to spread it around.
method

13


No, baby, listen. I have been seeing a Chiropractor since birth. I have the immune system of a superhero.
I will destroy the cooties.
How To Build and Maintain a Healthy Immune System

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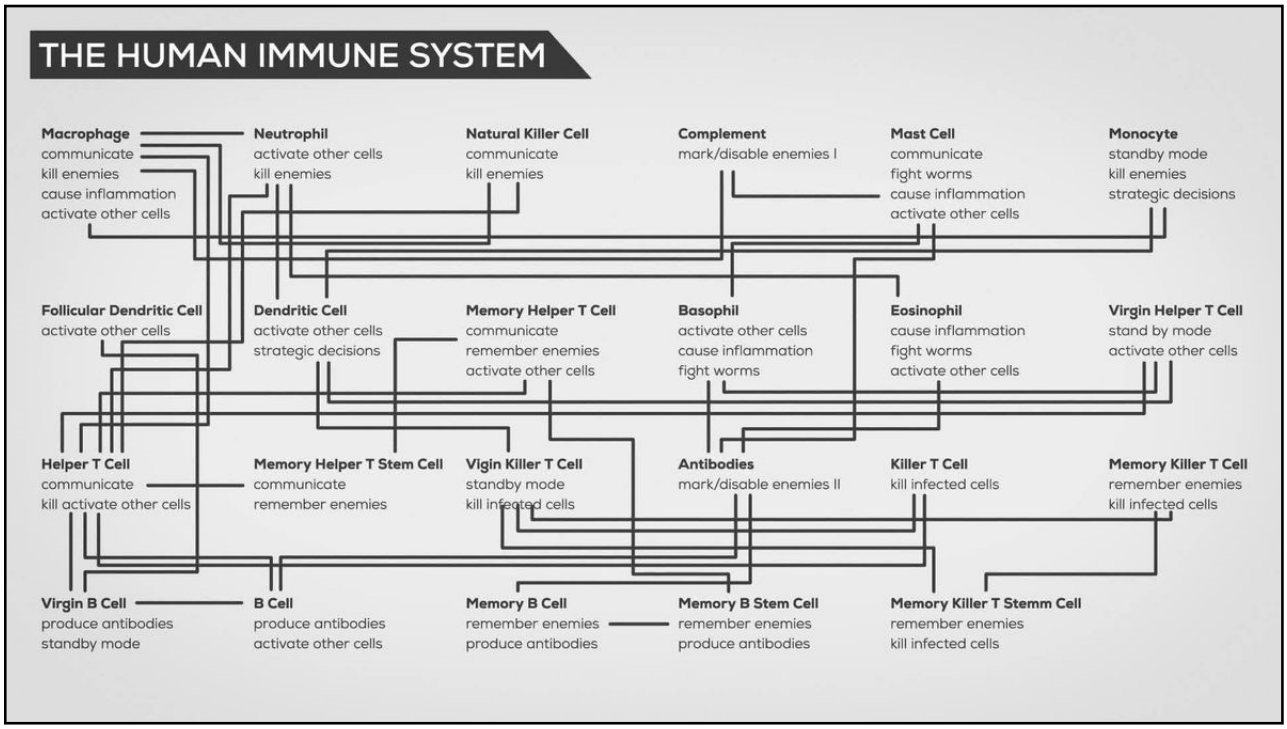

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3 LINE OF GEOPOLITICAL DEFENSE

1. BORDERS
2. POLICE, REGULAR SECURITY FORCES
3. SPECIAL UNITS

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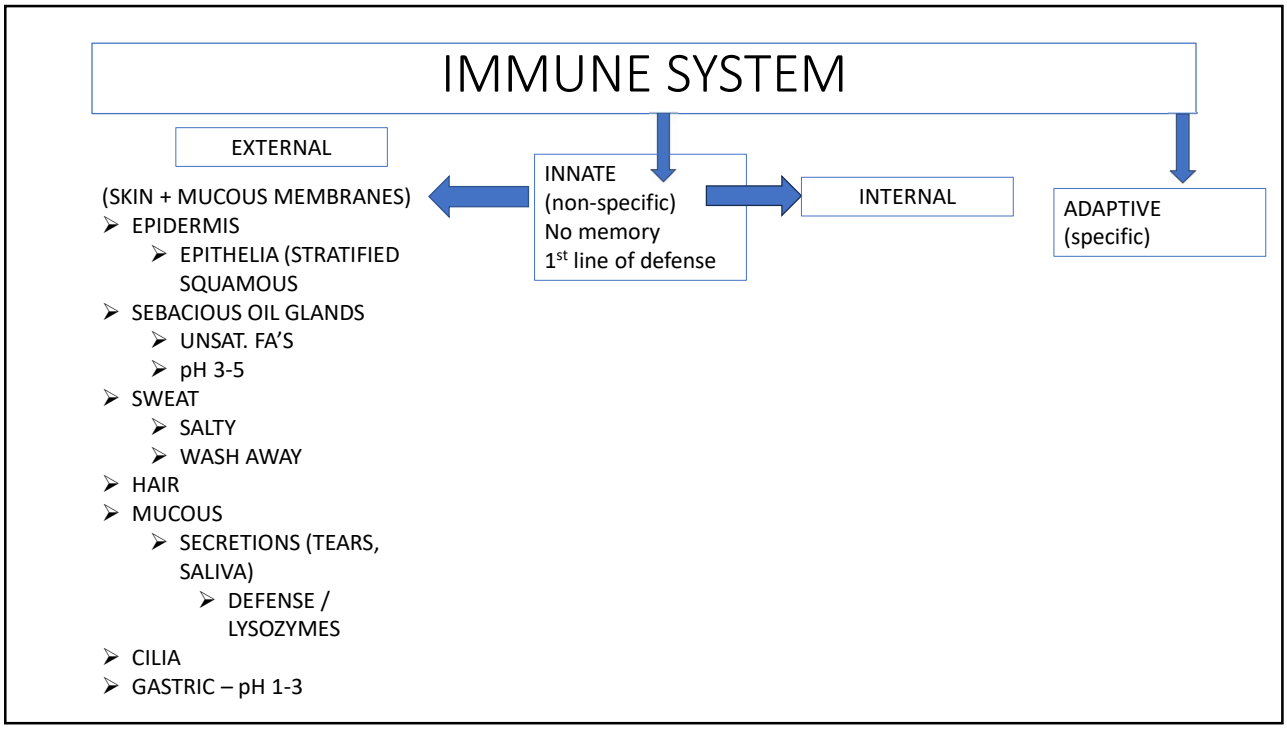
IMMUNE SYSTEM
EXTERNAL
(SKIN + MUCOUS MEMBRANES)
EPIDERMIS
EPITHELIA (STRATIFIED SQUAMOUS
SEBACIOUS OIL GLANDS
UNSAT. FA'S
pH 3-5
SWEAT
SALTY
WASH AWAY
HAIR
MUCOUS
SECRETIONS (TEARS, SALIVA)
DEFENSE / LYSOZYMES
CILIA
GASTRIC – pH 1-3
INNATE
(non-specific)
No memory
1st line of defense
INTERNAL
ADAPTIVE
(specific)

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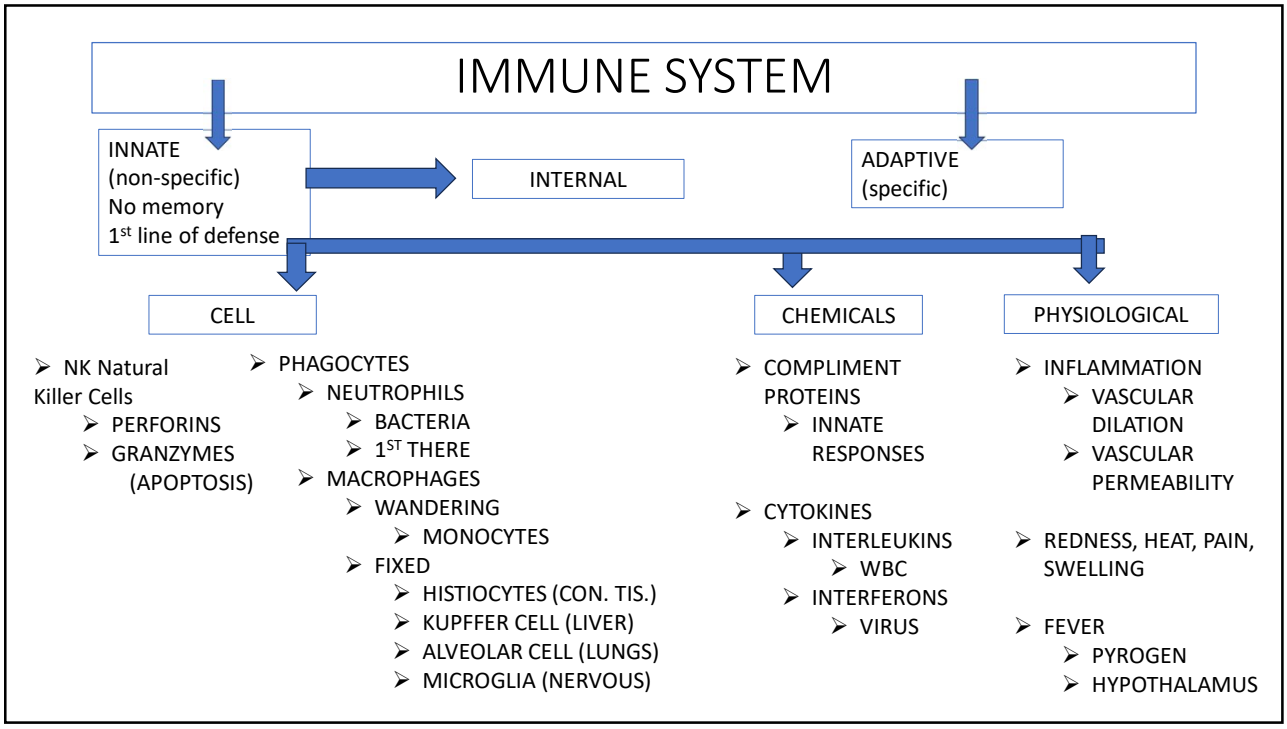
IMMUNE SYSTEM
INNATE
(non-specific)
No memory
1st line of defense
INTERNAL
ADAPTIVE
(specific)
CELL
CHEMICALS
PHYSIOLOGICAL
NK Natural Killer Cells
PERFORINS
GRANZYMES (APOPTOSIS)
PHAGOCYTES
NEUTROPHILS
BACTERIA
1ST THERE
MACROPHAGES
WANDERING
MONOCYTES
FIXED
HISTIOCYTES (CON. TIS.)
KUPFFER CELL (LIVER)
ALVEOLAR CELL (LUNGS)
MICROGLIA (NERVOUS)
COMPLIMENT PROTEINS
INNATE RESPONSES
CYTOKINES
INTERLEUKINS
WBC
INTERFERONS
VIRUS
INFLAMMATION
VASCULAR DILATION
VASCULAR PERMEABILITY
REDNESS, HEAT, PAIN, SWELLING
FEVER
PYROGEN
HYPOTHALAMUS

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OUTLINE

1. Location
2. Cells
3. Types of immunity

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1. LOCATION

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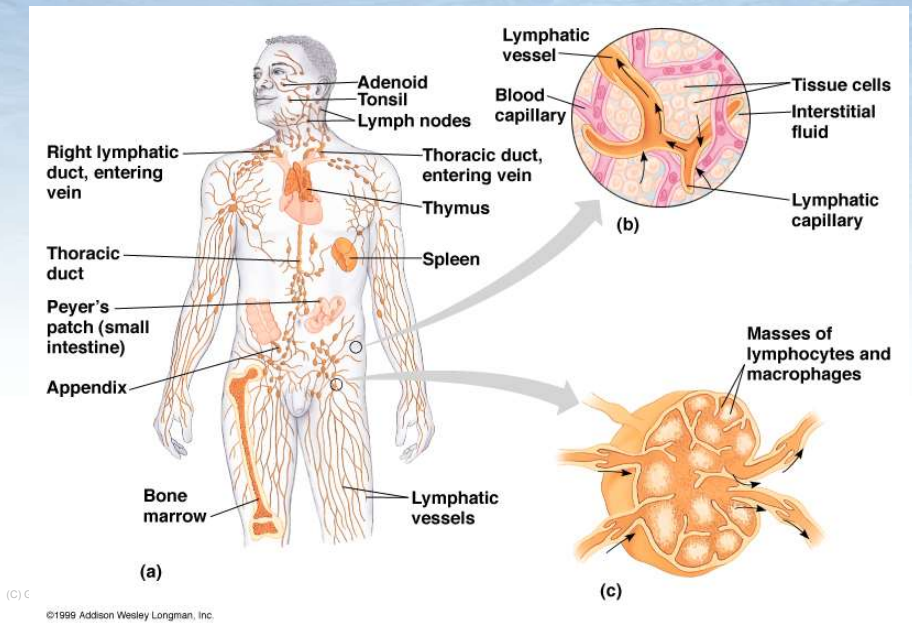
Components of the Immune System



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Overview

- Homeostasis by recognizing harmful or '**non-self**' from nonharmful or '**self**' organisms and produces an appropriate response.
- Distinguishes between normal, **healthy cells** vs **unhealthy cells** by recognizing a variety of "danger" cues called **DANGER-ASSOCIATED MOLECULAR PATTERNS - DAMPs**
- Cells may be unhealthy because of infection or cellular damage caused by non-infectious agents like sunburn or cancer. Infectious microbes such as **viruses and bacteria** release another set of signals recognized by the immune system called **PATHOGEN-ASSOCIATED MOLECULAR PATTERNS - PAMPs**

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Overview

- If an immune response cannot be activated when there is sufficient need, **INFECTION** arise
- If an immune response is **activated** without a real threat or is not **turned off** once the danger passes, different problems arise, such as allergic reactions and **AUTOIMMUNE** disease.
- The immune system is complex and pervasive.
- Cell Types:
  - **CIRCULATE** throughout the body or
  - **RESIDE** in a particular tissue.
  - Each cell type has a unique role, with different ways of recognizing problems, **COMMUNICATING** with other cells.

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Location

- All immune cells come from **PRECURSORS** in the bone marrow and develop into **MATURE CELLS** through a series of changes.
- ***SKIN***: The first line of defense: antimicrobial proteins.
- ***BONE MARROW***: Stems cells; develop into a variety of cell types.
- A) The **MYELOID** stem cell: the precursor to innate immune cells—neutrophils, eosinophils, basophils, mast cells, monocytes, dendritic cells, and macrophages (the first-line responders).
- B) **LYMPHOID** progenitor stem cell leads to adaptive immune cells—B cells and T cells: responses based on previous encounters (immunological memory). NK share features of both innate and adaptive immune cells i.e. immediate and memory cells.

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Location

- ***BLOODSTREAM***: Immune cells constantly circulate throughout the bloodstream, patrolling for problems.
- ***THYMUS***: T cells mature in the thymus.
- ***Lymphatic system***: The lymphatic system is a conduit for travel and **communication between tissues and the bloodstream**. Immune cells are carried through the lymphatic system and converge in lymph nodes: communication hub where immune cells sample information brought in from the body. If adaptive immune cells in the lymph node recognize pieces of a microbe brought in from a distant area, they will activate, replicate, and leave the lymph node to circulate and address the pathogen

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Location

- ***SPLEEN***: Not directly connected to the lymphatic system but it is important for processing information from the bloodstream. Immune cells are enriched in specific areas of the spleen, and upon recognizing blood-borne pathogens, they will activate and respond accordingly.
- ***MUCOSAL TISSUE***: Mucosal surfaces are prime entry points for pathogens, and specialized immune hubs are strategically located in mucosal tissues like the respiratory tract and gut. For instance, Peyer's patches are important areas in the small intestine where immune cells can access samples from the gastrointestinal tract.

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AND...

The GUT

It is becoming increasingly clear that disease (and health) really does begin in the gut! Studies have shown that the gut flora has a profound influence on the development and maturation of the immune system after birth (Bouskra et al., 2008; Macpherson & Harris, 2004). In addition, it has been estimated that as much as 80 -85% of the immune system is located in the gut.

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The GUT and the IMMUNE SYSTEM

Our immune system has co-evolved along with a diverse gut flora, not only to create defenses against pathogens, but also to develop TOLERANCE FOR BENEFICIAL MICROBES. As a consequence, the immune system and the gut microbiota developed a mutualistic relationship, regulating one another and cooperating to support each other.

The dialogue between the immune system and the microbiota starts the moment our body gets in contact with microbes—at birth. As we grow, the microbiota shapes the development of our immune system, and the immune system shapes the composition of the microbiota. This communication and mutual regulation is maintained throughout life and is the key for a healthy interaction between the microbiota and the immune system.

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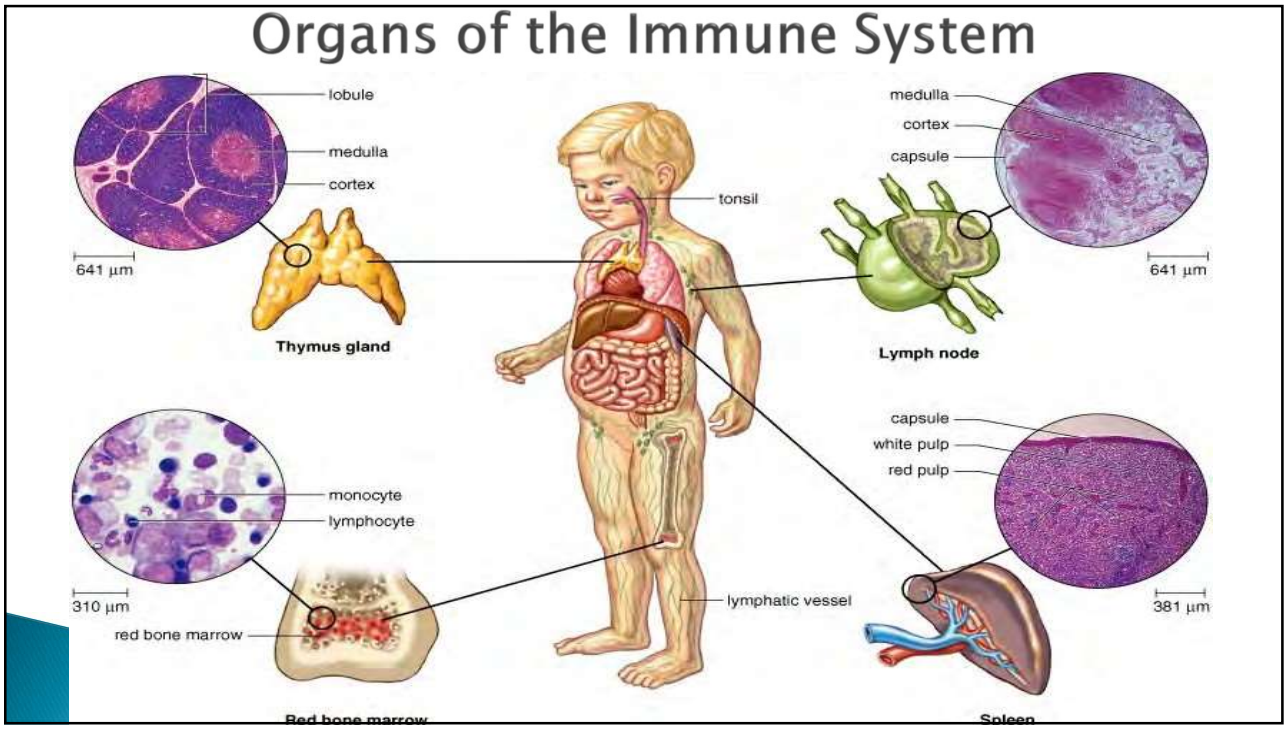
Organs of the Immune System
lobule
medulla
cortex
641 µm
Thymus gland
tonsil
medulla
cortex
capsule
641 µm
Lymph node
monocyte
lymphocyte
310 µm
red bone marrow
Red bone marrow
lymphatic vessel
capsule
white pulp
red pulp
381 µm
Spleen

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2. CELLS

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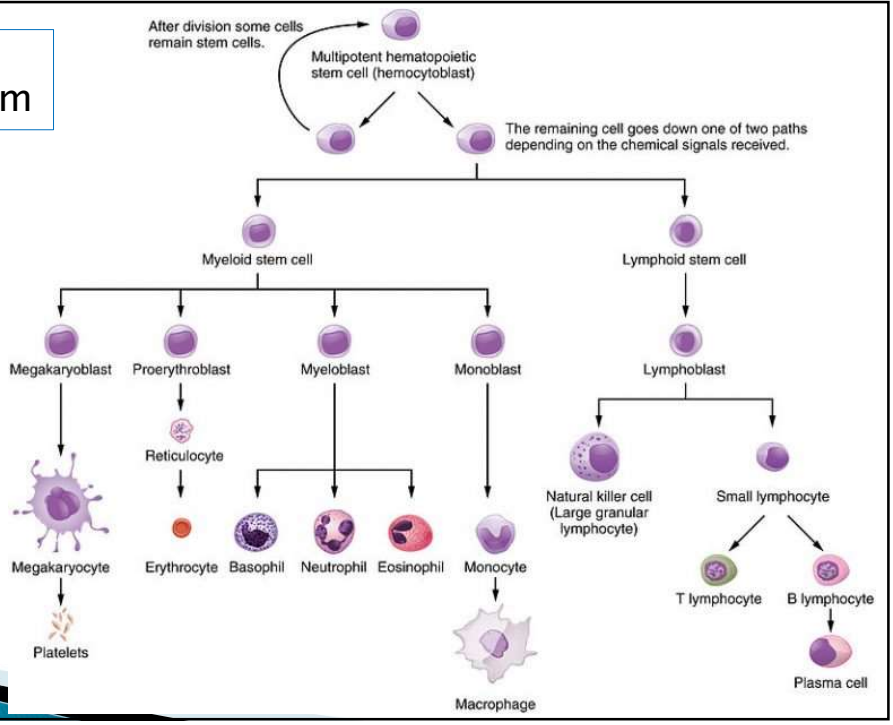
Cells of the Immune System

The **bone marrow** gives birth to **hemocytoblasts** from which all other blood cells are produced.

Some will remain stem cells and the others generate two lineages:

Myeloid and Lymphoid



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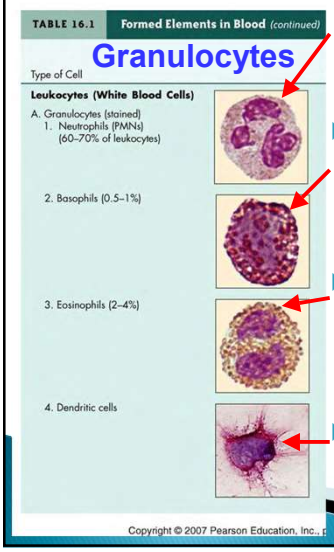
Cells of the Immune System…

These include all of the white blood cells (aka <u>leukocytes</u>), some of which appear "granular"…



- Neutrophils (60-70% of leukocytes)
  - poorly stained granular vesicles
- Basophils (0.5–1%)
  - release histamine, other mediators of inflammation, vesicles bind basic dyes
- Eosinophils (2–4%)
  - phagocytic, attack parasites w/toxic proteins, vesicle bind acidic eosin dye
- Dendritic Cells
  - phagocytes with very important roles in initiating adaptive immune response

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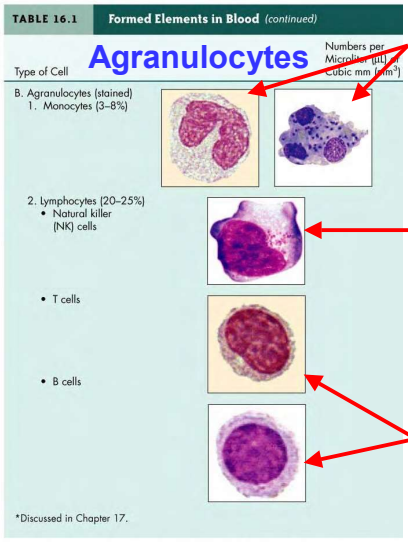
…more Cells of the Immune System

…& others which have an "agranular" appearance



Monocytes/Macrophages (3-8%)

- **monocytes become actively phagocytic macrophages when stimulated via infection, injury**

LYMPHOCYTES (20–25%)

Natural Killer (NK) cells

- **recognize and destroy cells with features of tumor cells, cells with intracellular pathogens**

T & B cells

- **have central roles in adaptive immunity**

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3. TYPES

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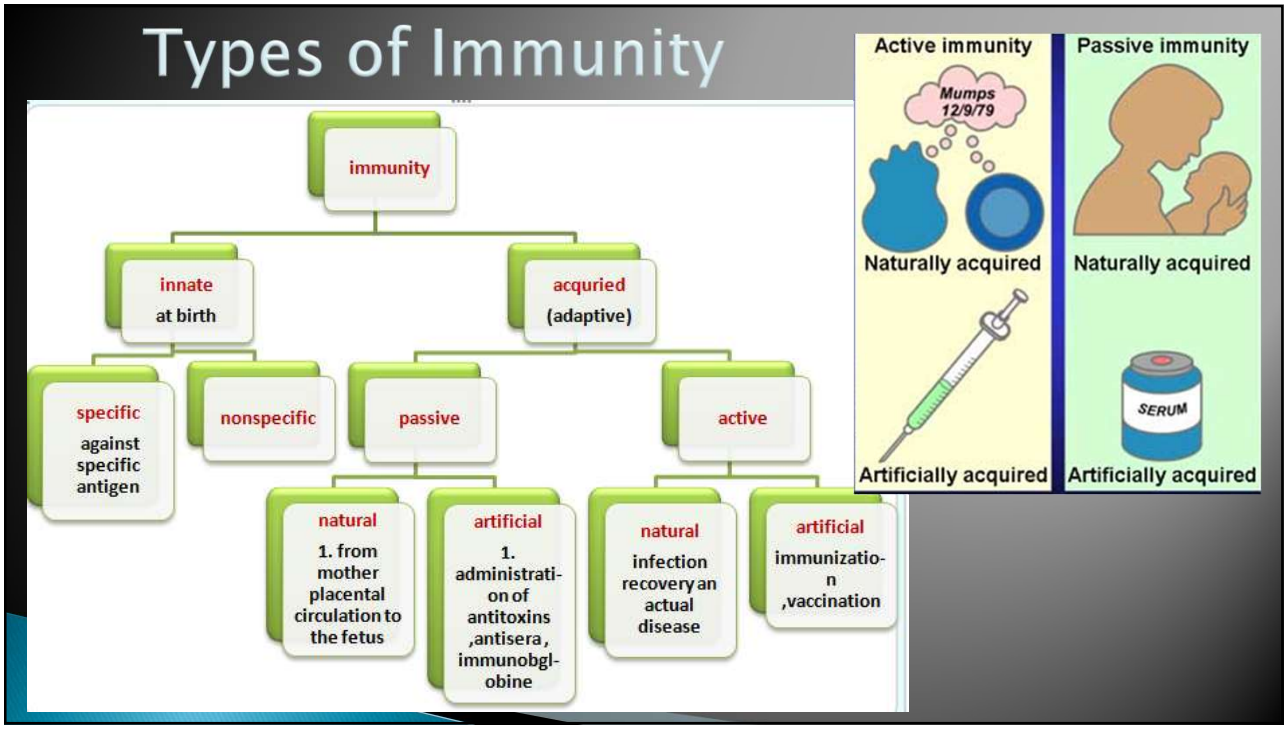

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A. Innate Immunity

a. Overview of Innate Immunity

b. Inflammation & Phagocytosis

c. Antimicrobial Substances

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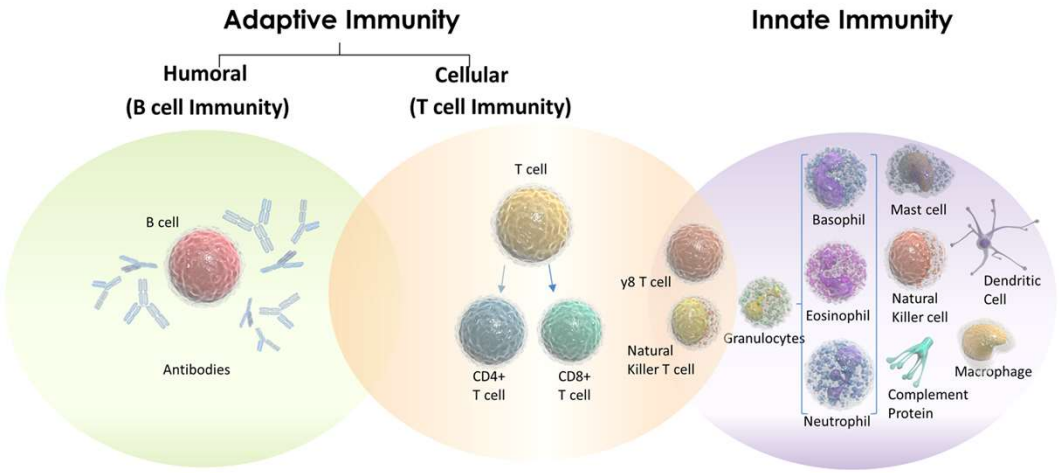
a. Overview of Innate Immunity



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NON-SPECIFIC DEFENCES (INNATE IMMUNITY)		SPECIFIC DEFENCES (ADAPTIVE IMMUNITY)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic leukocytes • Antimicrobial proteins • Inflammatory response • Fever	• Lymphocytes • Antibodies • Memory cells

The Body's Defenses

The body has 2 types of defense against infection

1. Innate Immunity
   - physical barriers (the skin & mucous membranes)
   - immediate, non-specific responses to pathogens, injuries
2. Adaptive Immunity
   - delayed, highly specific responses to foreign material

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Innate Immunity (non-specific)

The innate immune response is the body's 1st line of defense and includes:

1) physical barriers between inside & outside

- **the skin and the mucous membranes of the digestive, respiratory and genito-urinary tracts**
- **all substances secreted at these barriers and all of the normal microbiota that live on these surfaces**

2) non-specific cellular & physiological responses

- **i.e., inborn (innate) general responses to the presence of pathogens that breach the body's physical barriers**
- **independent of prior exposure, response is immediate**
- **eliminates the vast majority of pathogens that gain entry**

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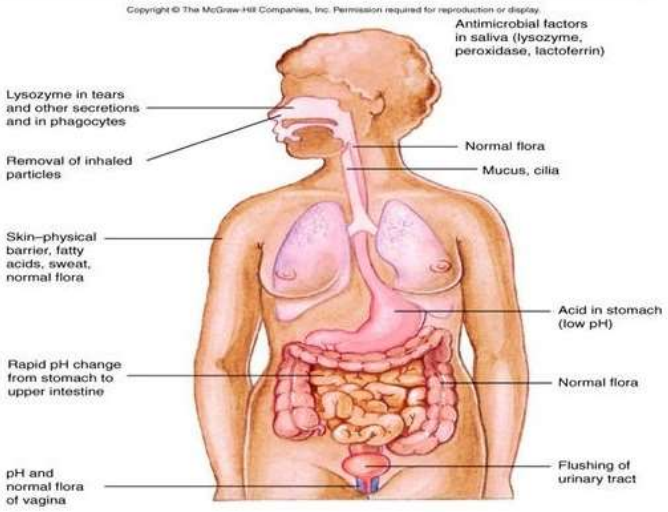
Physical and Chemical Barriers

- Physical Defenses
  - skin
  - membrane linings
  - Cilia
- Chemical Defenses
  - Sweat and oils
  - saliva
  - stomach acid
  - urine
  - tears
  - Mucus
  - Interferons *



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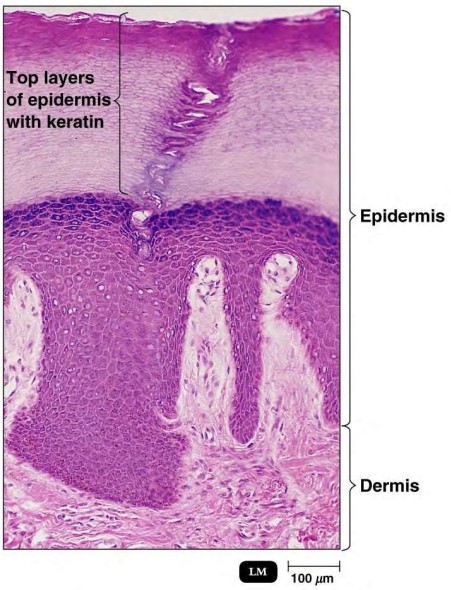
Physical Defenses

Key features of the Skin:

- dry, acidic surface resists microbial growth (pH 3 to 5)
- multiple layers of tough yet dead keratinized cells
- continual loss of outer dead skin layers removes potential pathogens
- sebum from hair follicles (lowers pH) & lysozyme from sweat resist microbial growth



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Roles of the Normal Microbiota

The "normal microbiota" are the microorganisms that live on the body surfaces of a healthy individual and inhibit the growth of pathogens in the following ways:

- acidifying body surfaces
  - e.g., in the female reproductive tract, inhibits yeast inf.
- the production of bacteriocins and other toxins
  - i.e., toxins that are specific for other microorganisms
  - e.g., in the large intestine (*E. coli*)
- out-competing pathogens for nutrients
  - on the skin and basically all mucous membranes

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Summary of Physical / Chemical Defenses

TABLE 16.3 Summary of Innate Immunity Defenses

Component	Functions
FIRST LINE OF DEFENSE: SKIN AND MUCOUS MEMBRANES	
Physical Factors	
Epidermis of skin	Forms a physical barrier to the entrance of microbes.
Mucous membranes	Inhibit the entrance of many microbes, but not as effective as intact skin.
Mucus	Traps microbes in respiratory and gastrointestinal tracts.
Lacrimal apparatus	Tears dilute and wash away irritating substances and microbes.
Saliva	Washes microbes from surfaces of teeth and mucous membranes of mouth.
Hairs	Filter out microbes and dust in nose.
Cilia	Together with mucus, trap and remove microbes and dust from upper respiratory tract.
Epiglottis	Prevents microbes from entering lower respiratory tract.
Urine	Washes microbes from urethra.
Vaginal secretions	Move microbes out of female reproductive tract.
Defecation and vomiting	Expel microbes from body.

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A. Innate Immunity

a. Overview of Innate Immunity

b. Inflammation & Phagocytosis

c. Antimicrobial Substances

b. Inflammation & Phagocytosis
2nd line of defense

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What is Inflammation?

Inflammation is a localized response initiated by damaged or infected tissues to aid tissue repair and the elimination of pathogens.

The basic stages of inflammation are as follows:

Vasodilation & increased capillary permeability

- increases blood flow to area, blood fluid in tissue

Migration of phagocytes, phagocytosis

- phagocytes exit the blood, enter affected tissue via chemotaxis & consume pathogens

Tissue repair

- removal of dead cells, regeneration of the tissue

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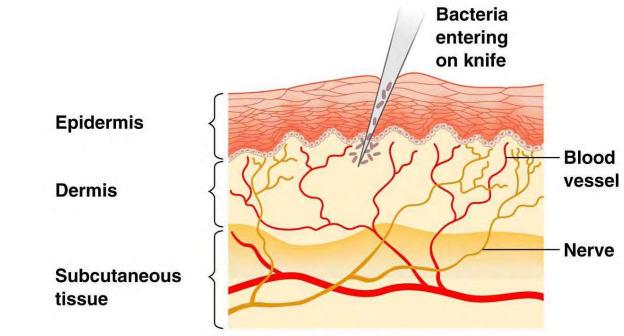
Inflammation Triggers

Any type of physical damage to and/or microbial penetration of a tissue will trigger a local inflammatory response:

- can be short-lived (acute) or extended (chronic)



(a) Tissue damage

- initiated by the release of inflammatory mediators from cells in the tissue that is damaged

e.g.

histamine
prostaglandins
leukotrienes

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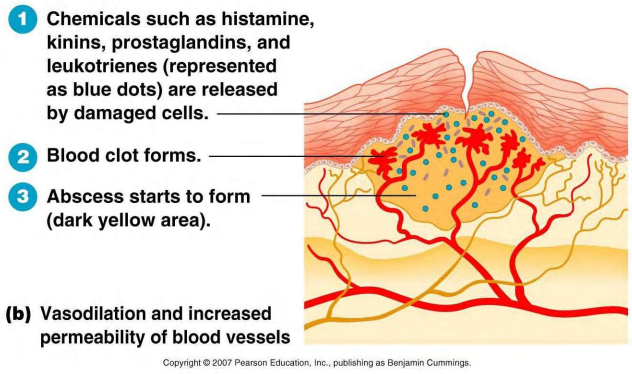
Vasodilation & Increased Permeability

Increased blood flow due to <u>vasodilation</u> and the increased permeability of capillaries results in fluid from blood seeping into affected tissue:

- **causes swelling of the region (edema)**
- **facilitates clotting**
- **facilitates entry of antimicrobial proteins, leukocytes**



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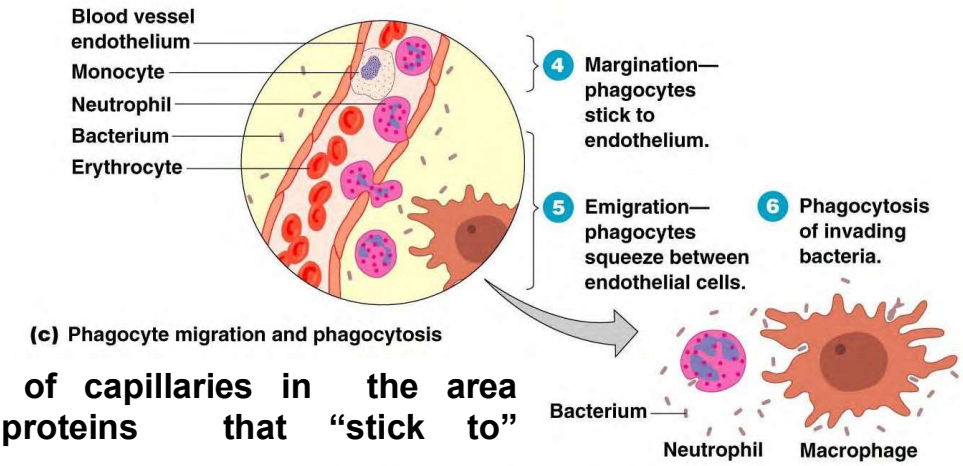
Phagocyte Migration (Chemotaxis)



- **endothelium of capillaries in the area expresses proteins that "stick to" phagocytes**
- **phagocytes then "squeeze" their way out into the tissue and follow a "trail" of chemical signals toward the source (chemotaxis) and gobble up microbes**

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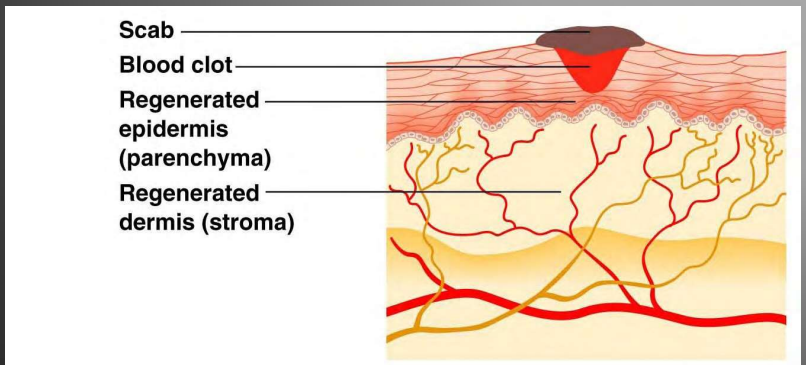
Tissue Repair

Once the area has been secured (all pathogens are destroyed, all breaches are sealed), dead & damaged cells can be broken down and the tissue can regenerate.



(d) Tissue repair

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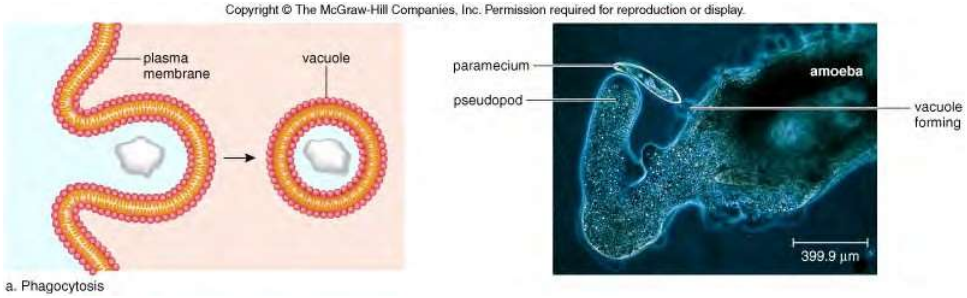
What is Phagocytosis?

It's the process by which a cell ingests a solid extracellular particle (such as a bacterium) by engulfing it within a membrane enclosed vesicle (sometimes called a vacuole).



a. Phagocytosis

- **cells that normally carry out this function are referred to as *phagocytic*, or simply as <u>phagocytes</u>**

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Types of Phagocytes

All of the phagocytes in the human body are types of white blood cells (leukocytes):

Neutrophils

- **highly phagocytic cells that rapidly exit the blood into damaged or infected tissue, "gobble up" bacteria, etc…**

Macrophages

- **monocytes migrate to damaged, infected tissue from blood & differentiate into highly phagocytic macrophages**
- **some are fixed (non-mobile) in various tissues & organs**

Dendritic Cells

- **found in skin, mucous membranes, thymus, lymph nodes**

Eosinophils (occasionally act as phagocytes) – other functions

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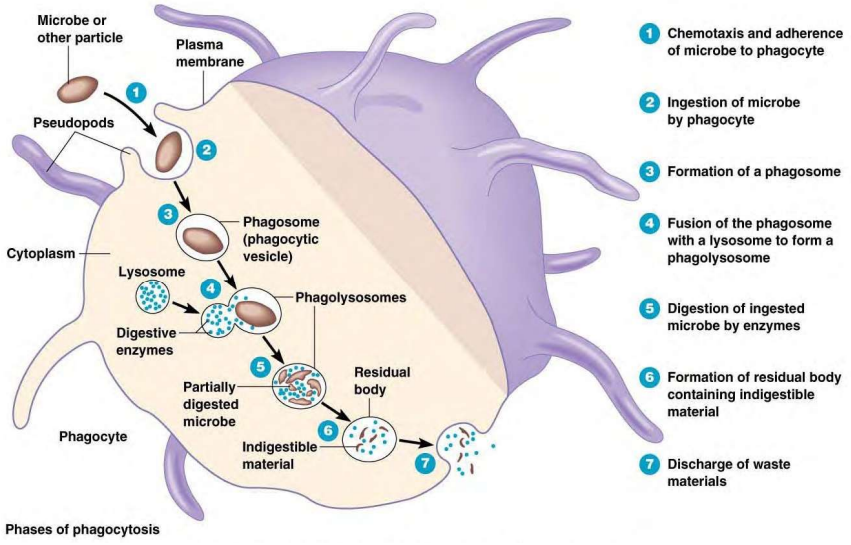
The Phagocytic Process

- **all phagocytic white blood cells ingest & destroy pathogens & other debris by this basic process**



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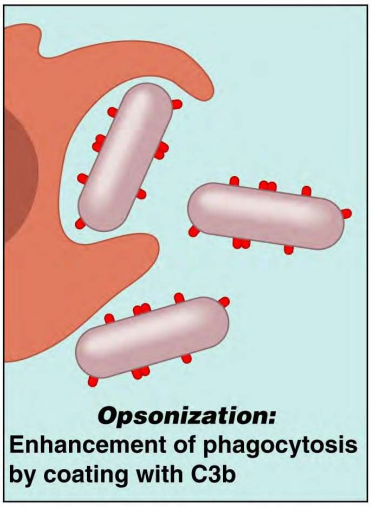
Opsonization

Bacteria have a variety of ways to resist phagocytosis.

2 kinds of molecules involved in the immune response bind to pathogens and greatly enhance phagocytosis:

- **antibodies**
- **complement protein C3b**

This process is called opsonization and such proteins are called opsonins.



Opsonization:
Enhancement of phagocytosis by coating with C3b

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A. Innate Immunity

a. Overview of Innate Immunity

b. Inflammation & Phagocytosis

c. Antimicrobial Substances

c. Antimicrobial Substances

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Antimicrobial Substances

- Enhance the innate defenses by:
  - Attacking microorganisms directly
  - Hindering microorganisms' ability to reproduce

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Antimicrobial Substances

There are many different kinds of antimicrobial substances, however we will focus our attention on the 2 most important*:

***Complement system**

- **a set of proteins present in the blood important for the destruction of pathogenic cells**

***Interferons**

- **a class of cytokines that are especially important in controlling viral infections**

Transferrins (bind & keep iron away from pathogens)

Antimicrobial peptides (cause lysis of microbes)

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The Complement System

The complement system (aka "complement") is a set of >30 proteins produced by the liver that circulate in the blood in an inactive state.

The presence of microbial pathogens activates the "complement cascade" in 1 of 3 ways (classical, alternative, leptin) to eliminate the pathogens by:

- **cytolysis (cell lysis)**
  - **eukaryotic pathogens, Gram$^-$ bacteria (not Gram$^+$)**
- **triggering inflammation**
- **enhancing phagocytosis (opsonization)**

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Antimicrobial Substances

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- **a class of cytokines that are especially important in controlling viral infections**

Transferrins (bind & keep iron away from pathogens)

Antimicrobial peptides (cause lysis of microbes)

58

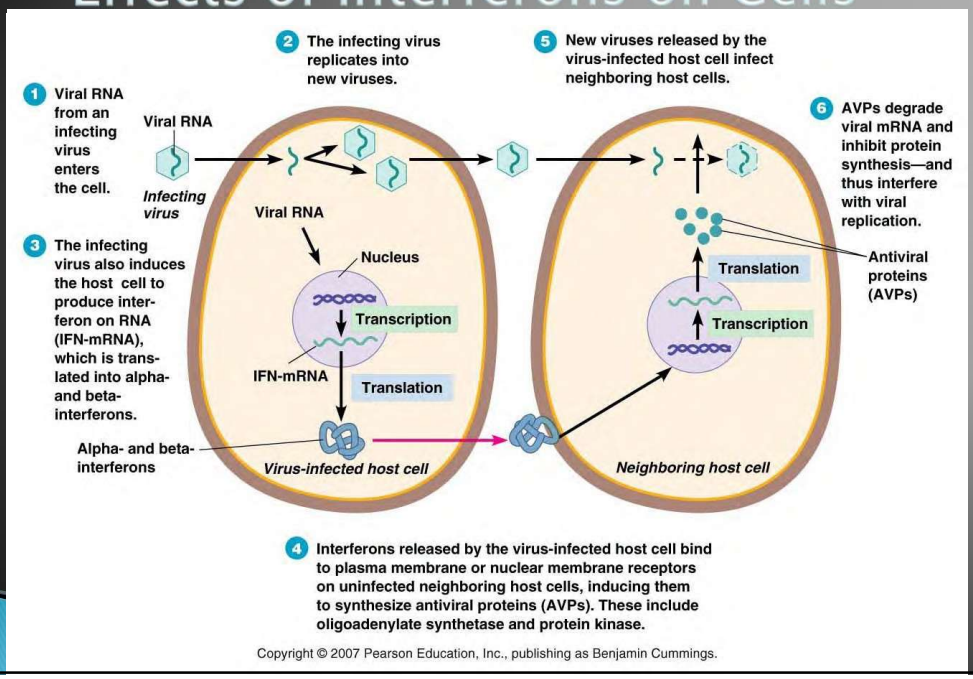
Interferons

The interferons (IFN-α, IFN-β & IFN-γ) are a class of cytokines (soluble protein signals) released by virally infected cells and certain white blood cells to stimulate other cells to protect themselves from viral infection:

- **the presence of viral proteins, RNA in a cell triggers IFN production & release**
- **neighboring cells bind IFNs via specific receptors**
- **this triggers the expression of various anti-viral genes in the cell receiving the IFN signal**
- **the resulting anti-viral proteins (AVPs) degrade viral RNA, thus protecting cell from infection**

59

Effects of Interferons on Cells



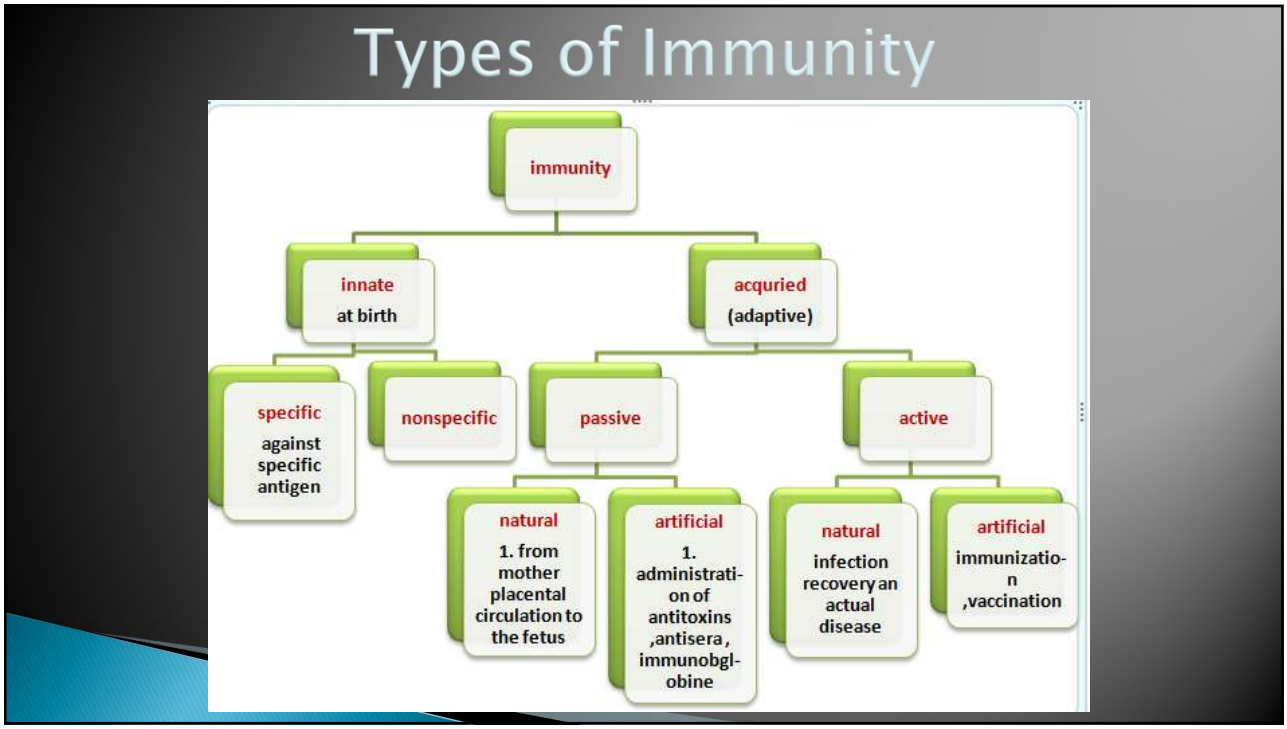
60

61

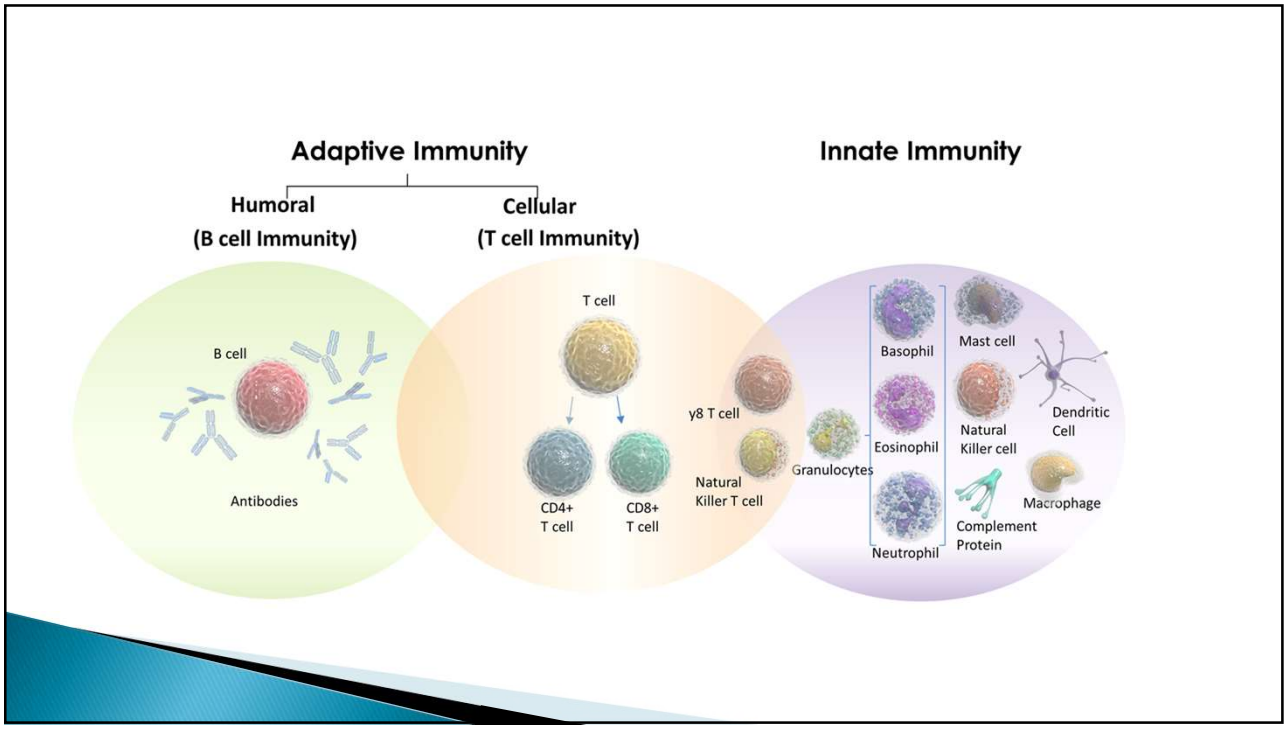
Adaptive Immunity – Part I

1. **Overview of Adaptive Immunity**
2. **T and B Cell Production**
3. **Antigens & Antigen Presentation**
4. **Helper T cells**

62


Types of Immunity
immunity
innate
at birth
acquried
(adaptive)
specific
against specific antigen
nonspecific
passive
active
natural
1. from mother placental circulation to the fetus
artificial
1. administrati-on of antitoxins ,antisera , immunobgl-obine
natural
infection recovery an actual disease
artificial
immunizatio-n ,vaccination

63


Adaptive Immunity
Innate Immunity
Humoral
(B cell Immunity)
Cellular
(T cell Immunity)
B cell
Antibodies
T cell
CD4+
T cell
CD8+
T cell
y8 T cell
Natural
Killer T cell
Granulocytes
Basophil
Eosinophil
Neutrophil
Mast cell
Natural
Killer cell
Dendritic
Cell
Macrophage
Complement
Protein

64

"Innate and adaptive immunity are not mutually exclusive mechanisms of host defense, but rather are *complementary,* with defects in either system resulting in host vulnerability."

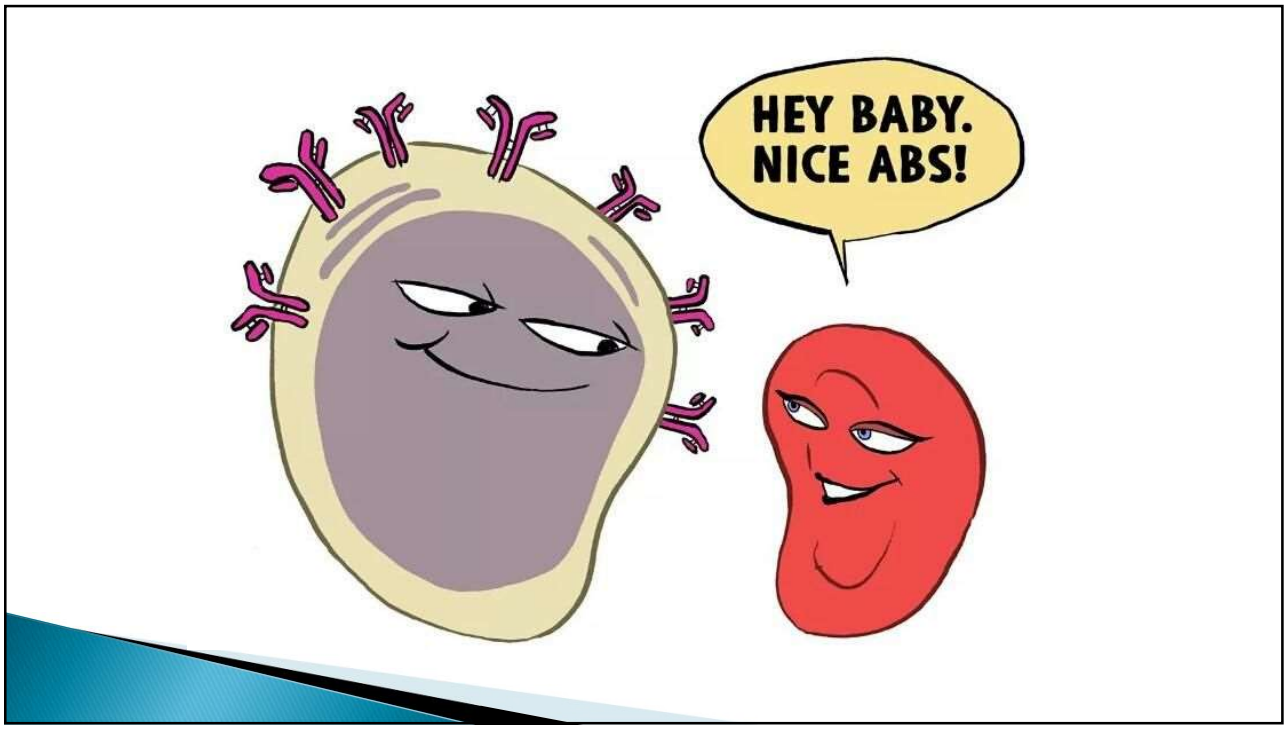
Warrington R, et al. An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology. 2011 7(Suppl 1):S1.

65

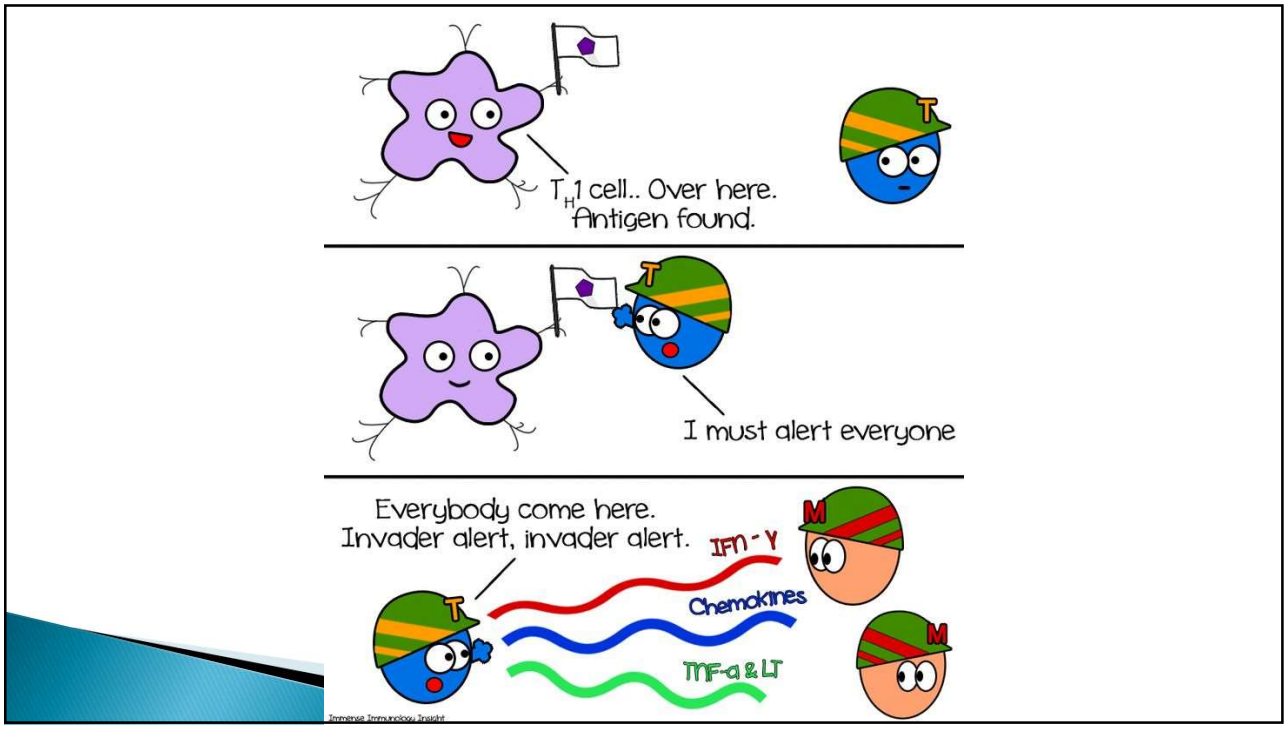
1. Overview of Adaptive Immunity

NON-SPECIFIC DEFENCES (INNATE IMMUNITY)		SPECIFIC DEFENCES (ADAPTIVE IMMUNITY)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic leukocytes • Antimicrobial proteins • Inflammatory response • Fever	• Lymphocytes • Antibodies • Memory cells

66


HEY BABY.
NICE ABS!

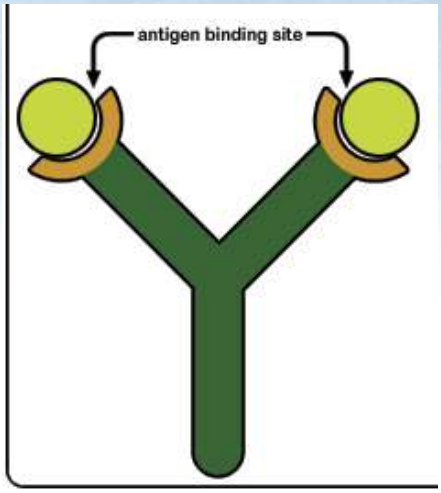
67


T
T_H1 cell.. Over here.
Antigen found.
T
I must alert everyone
Everybody come here.
Invader alert, invader alert.
IFN - γ
Chemokines
TNF-α & LT
M
M
T

68

The Third Line of Defense (Adaptive Immunity)
~Antibodies~

- Most infections never make it past the first and second levels of defense
- Those that do trigger the production and release of **antibodies**
  - Proteins that latch onto, damage, clump, and slow foreign particles
  - Each antibody binds only to one specific binding site, known as an **antigen**



69

Types of Acquired Immunity

I. Naturally Acquired Immunity: Obtained in the course of daily life

A. Naturally Acquired Active Immunity:

- *Antigens* or *pathogens* enter body naturally.
- Body generates an immune response to antigens.
- Immunity may be lifelong (chickenpox or mumps) or temporary (influenza or intestinal infections).

B. Naturally Acquired Passive Immunity:

- *Antibodies* pass from mother to fetus via placenta or breast feeding (colostrum).
- No immune response to antigens.
- Immunity is usually short-lived (weeks to months).
- Protection until child's immune system develops.

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The Nature of Adaptive Immunity

Unlike innate immunity, adaptive (acquired) immunity is highly specific and depends on exposure to foreign (non-self) material.

- **depends on the actions of T and B lymphocytes activated by exposure to specific antigens (Ag):**

Antigen = any substance that is recognized by an antibody or the antigen receptor of a T or B cell

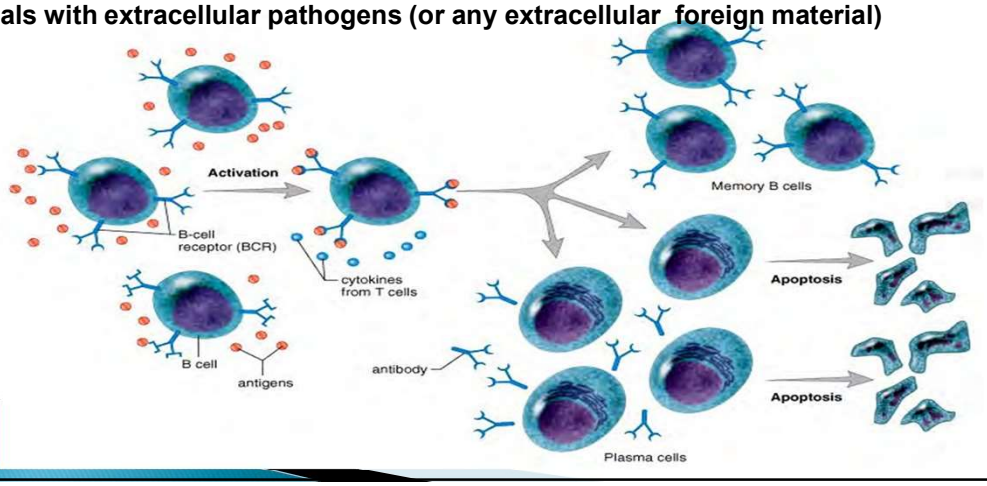
****Only antigenic material that is "foreign" should trigger an immune response, although "self antigens" can trigger autoimmune responses.****

71

2 basic types of adaptive immune response (IR):

1) HUMORAL IR

- **involves antibodies made by B cells & released into the extracellular fluids (blood, lymph, saliva, etc…)**
- **deals with extracellular pathogens (or any extracellular foreign material)**



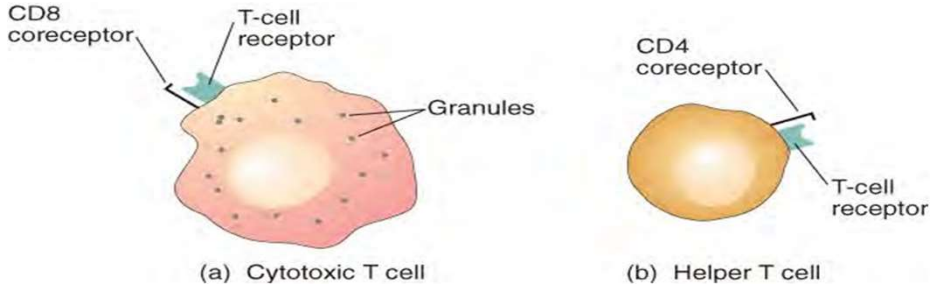
72

2 basic types of adaptive immune response (IR):

2) CELL-MEDIATED IR

- involves special cytotoxic T cells (CTLs) that kill cells containing intracellular pathogens (e.g., viruses)

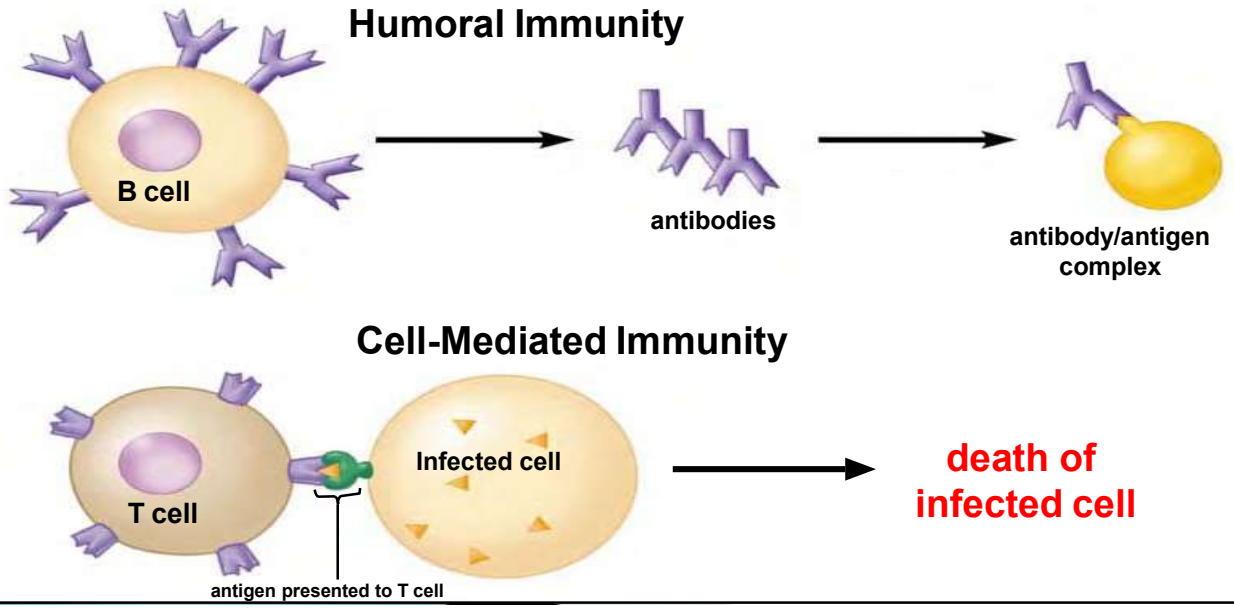
both Humoral and Cell-mediated IR depend on helper T cells



CD4 T helper cells activate an immune response while CD8 T cytotoxic cells produce antibodies and kill infected or cancerous cells

73

Humoral vs Cell-Mediated Immunity



74

Connection to Innate Immunity

The adaptive immune response is dependent on innate immunity in the following way:

- **helper T cells (T_H), which coordinate almost all adaptive immune responses, require processed antigen presented by certain phagocytes:**

  dendritic cells, macrophages & occasionally B cells

In this way, phagocytes involved in innate immune responses provide the adaptive part of the immune system with samples of what the body has been exposed to!

75

2. T and B Cell Production

76

Blood Cell Production

Hematopoietic stem cells in the bone marrow give rise to all types of blood cells

- **stem cells are undifferentiated cells capable of giving rise to multiple cell types (and themselves!)**
  - **in reality, hematopoietic stem cells give rise to more specific stem cells:**

Lymphoid stem cells – produce T & B cells (lymphocytes)

Myeloid stem cells – produce all other blood cells

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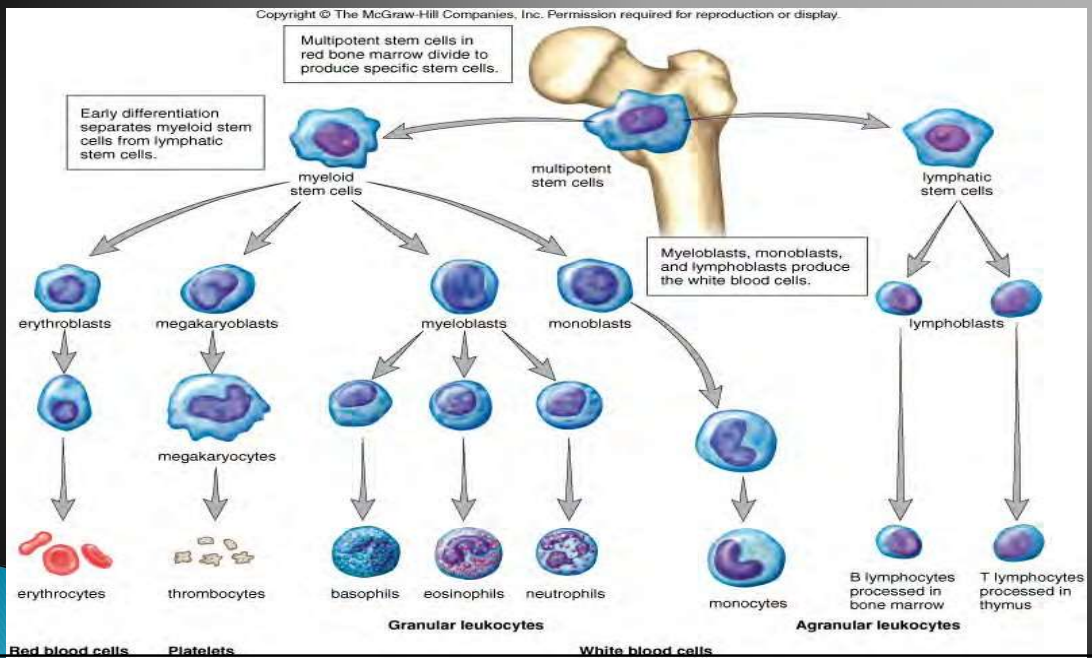
Stem Cells & Blood Cell Production



78

From the Bone Marrow…

Immature T cells 1st go to the thymus (via blood)

- **in the thymus T cells undergo a maturation process referred to as "education"**
- **basically, this is where T cells that would react to "self antigens" are eliminated**
  - **essential for preventing autoimmunity**
  - **eventually end up in lymph nodes, skin, gut or spleen**

B cells end up in lymph nodes, skin, gut or spleen

- **here they await foreign antigen they bind to**
- **"self-reactive" B cells eliminated in bone marrow**

79

3. Antigens & Antigen Presentation

80

Native vs Processed Antigen (Ag)

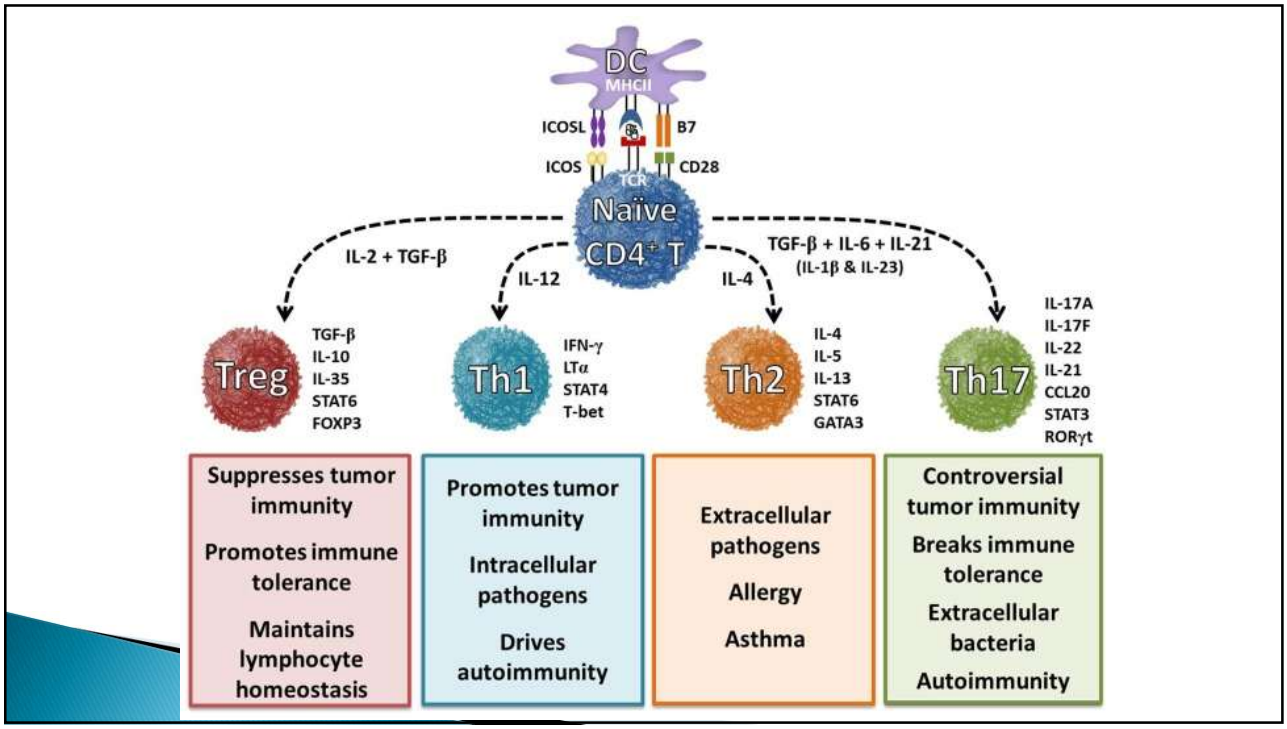
Native Antigen:

- **antigen that is in its natural, functional state**
  - **e.g., proteins that are folded "properly" (i.e., not denatured or broken down)**
- **antibodies (soluble or as a B cell receptor) bind to native antigens**

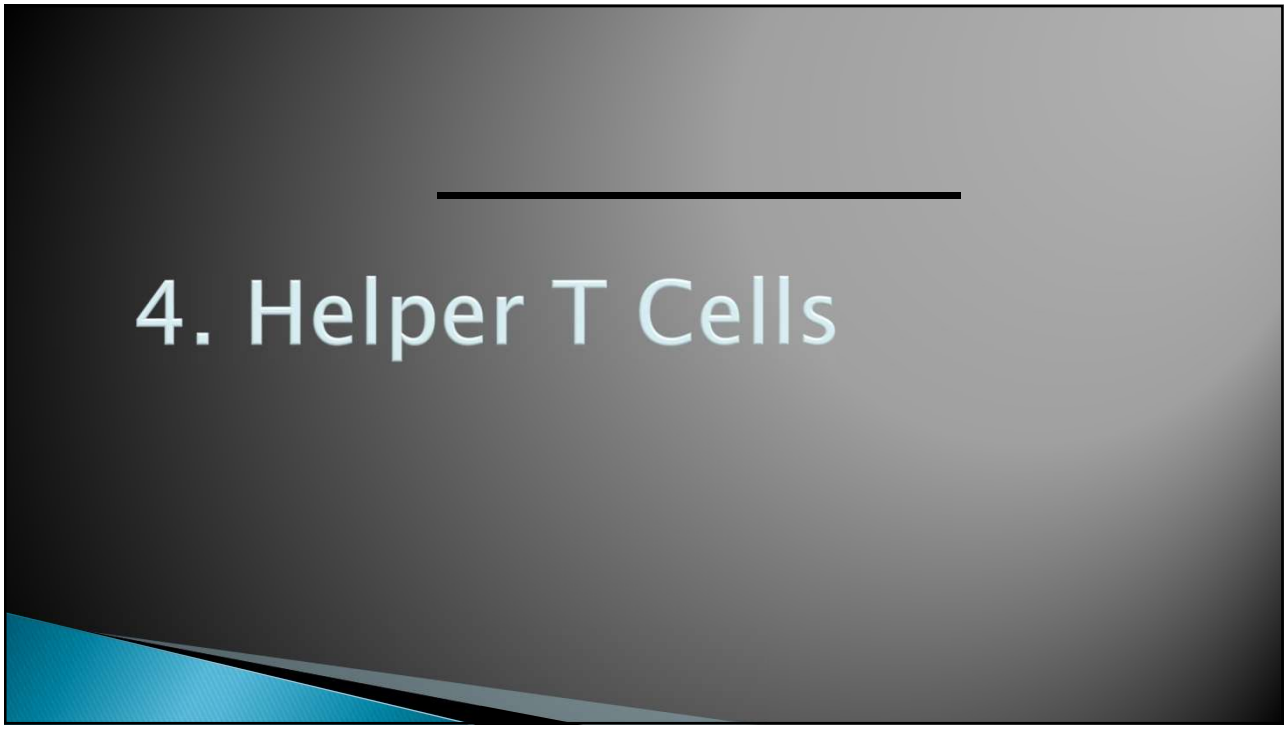
Processed Antigen:

- **antigen (usually protein) digested within a phagocyte & presented in "pieces" on its surface**
- **the T cell receptor binds to processed antigen**

81



82



83

What do Helper T Cells do?

As we've learned, adaptive immunity involves the following:

1) the production of antibody by B cells

2) the killing of infected cells by cytotoxic T cells

However, neither B cells nor cytotoxic T cells take action unless they receive cytokine signals from helper T cells :

- **most are interleukins (e.g., IL-1, IL-2, etc…)**

84

Two Types of Helper T Cells

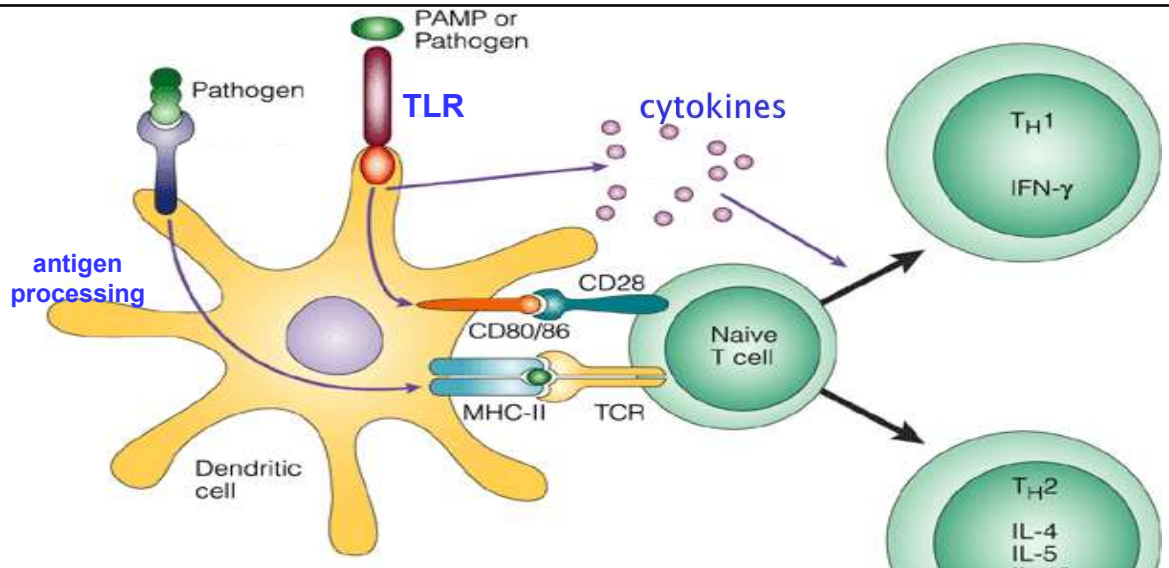
Type 1 helper T cells (T_{H1}):

- **secrete cytokines to activate CTLs, NK cells and macrophages**
- **trigger cellular immune response to deal with intracellular pathogens (e.g., viruses)**

Type 2 helper T cells (T_{H2}):

- **secrete cytokines to activate B cells, eosinophils**
- **trigger humoral immune response to deal with extracellular pathogens (e.g., most bacteria)**

85



The APC determines whether a naïve T_H cell will become a T_{H1} or T_{H2} based on pathogen.

- **via cytokines, cell-cell interactions**

86

In general, the role of Th1 immunity is to fight infections in the skin, mucous membranes, and cells.

When the essential flora is damaged, the production and function of Th1 cells becomes impaired, allowing more invaders into the body.

The body responds by overcompensating with a Th2 response.

The overactive Th2 response then predisposes the individual to allergic-type reactions, chronic inflammation, and autoimmunity.

Healthy essential gut flora is the key to keeping these arms of the adaptive immune system in balance, thus preventing disease.

87

Antibody Class Switching

Following the first exposure to its specific antigen, an activated B cell will generate IgM producing plasma cells.

Various cytokines produced by T_H and other cells in the vicinity can induce plasma cells to switch the antibody class to IgG, IgA or IgE:

- **usually switch to IgG and later to IgA or IgE**
- **involves DNA recombination in the gene encoding the antibody**

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B Cell Memory

Memory B cells remaining after the initial activation of a B cell have the following characteristics:

- **they are extremely long-lived (years!)**
- **BCRs (B Cell receptors) are of the IgG, IgA or IgE class**
- **activated directly upon subsequent exposure**
  - **no need for T cell help**
  - **generate more plasma cells & memory cells**
- **such secondary responses are much more rapid and much more intense than primary responses**
  - **generate more plasma cells & memory cells**

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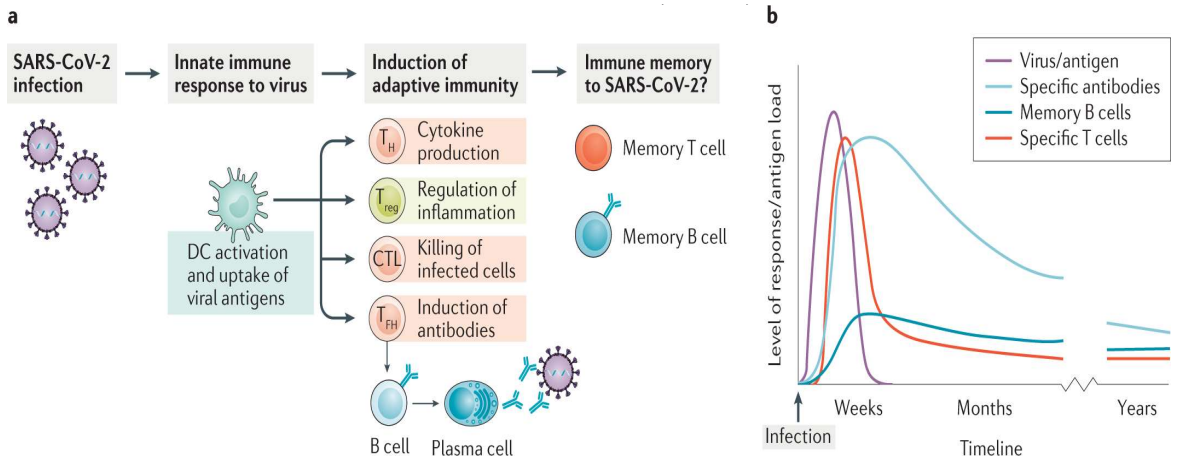
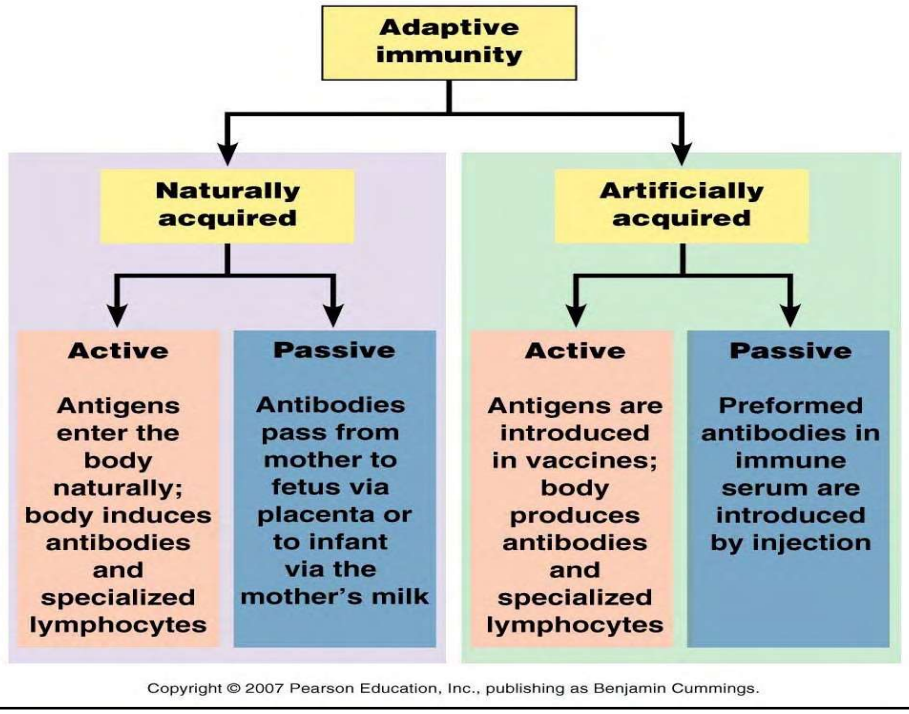
SARS-CoV-2

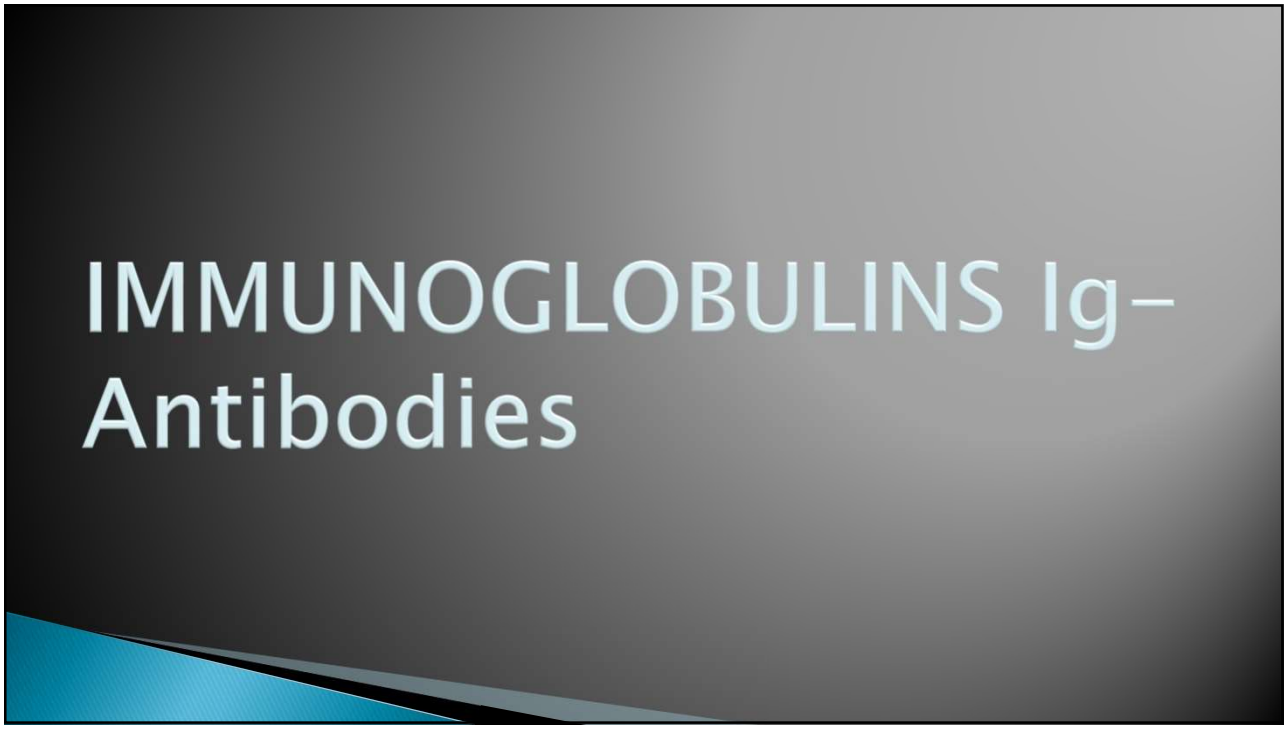


90

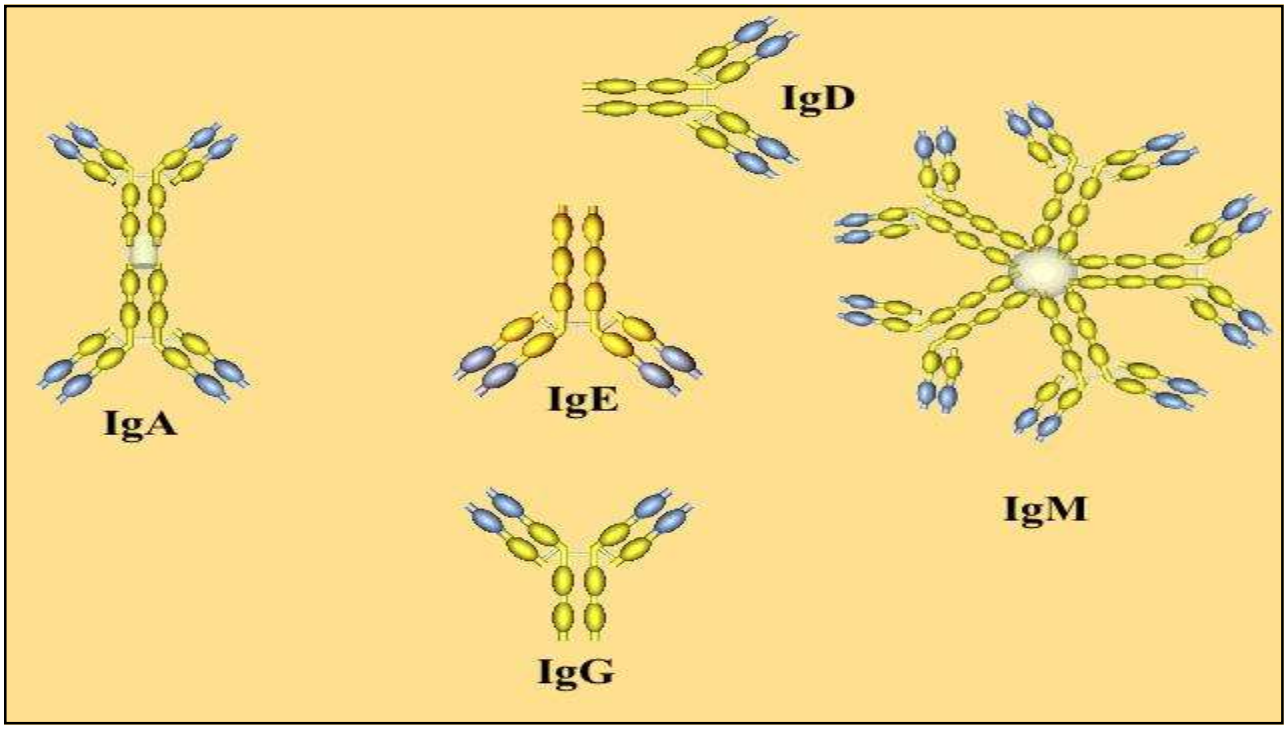


- artificial immunity results from the injection of antigen (active) or antibodies (passive)
- natural immunity results from natural expos. to antigen or transfer of antibodies fr. mother to child

91



92



93

IMMUNOGLOBULINS Ig- Antibodies

- Produced by the B lymphocytes that bind antigens
- Globular glycoproteins
- The heavy and light chains are polypeptides
- The chains are held together by disulphide bridges
- Each Ab has 2 identical Ag binding sites – variable regions.
- The order of amino acids in the variable region determines the shape of the binding site

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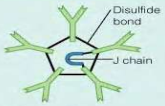
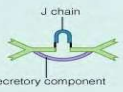
TABLE 17.1 A Summary of Immunoglobulin Classes

Characteristics	IgG	IgM	IgA	IgD	IgE
					
Structure	Monomer	Pentamer	Dimer (with secretory component)	Monomer	Monomer
Percentage of total serum antibody	80%	5–10%	10–15%*	0.2%	0.002%
Location	Blood, lymph, intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears, saliva, mucus, intestine, milk), blood, lymph	B cell surface, blood, lymph	Bound to mast and basophil cells throughout body, blood
Molecular weight	150,000	970,000	405,000	175,000	190,000
Half-life in serum	23 days	5 days	6 days	3 days	2 days
Complement fixation	Yes	Yes	No†	No	No
Placental transfer	Yes	No	No	No	No
Known functions	Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn	Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection	Localized protection on mucosal surfaces	Serum function not known; presence on B cells functions in initiation of immune response	Allergic reactions; possibly lysis of parasitic worms

*Percentage in serum only; if mucous membranes and body secretions are included, percentage is much higher.
† May be yes via alternate pathway.

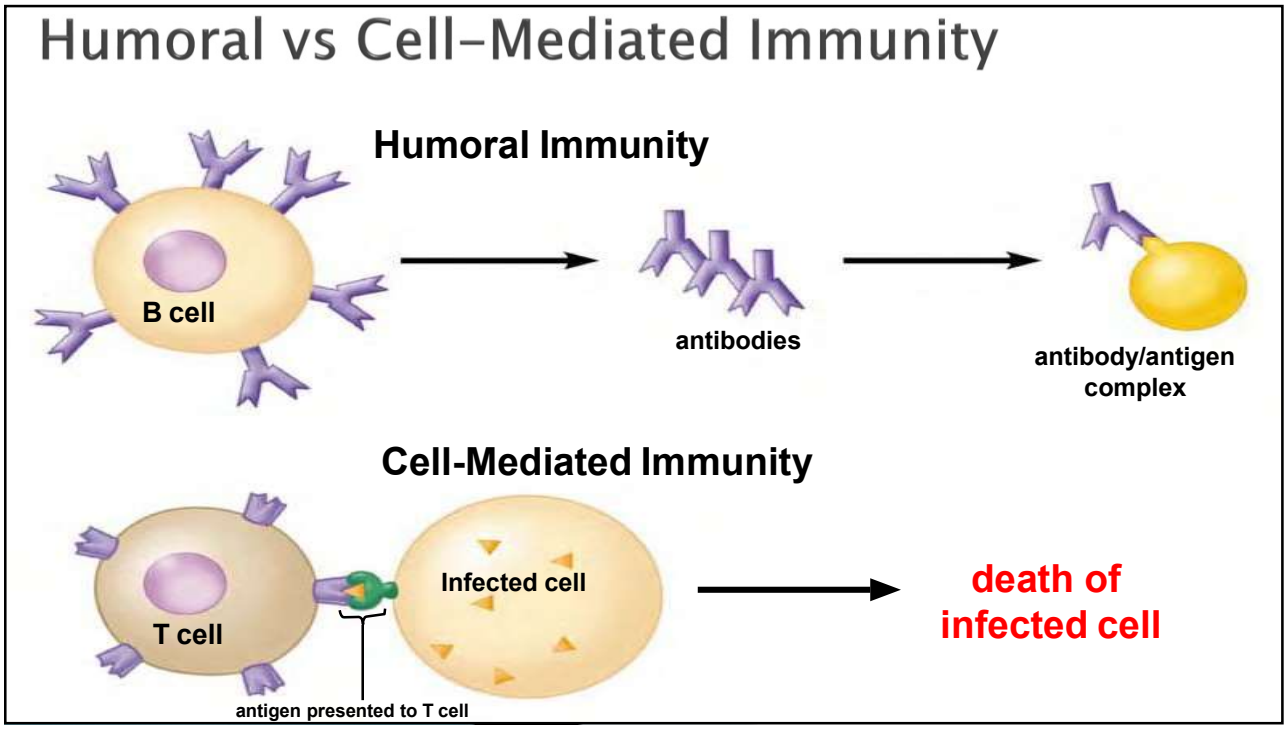
95

The Roles of Antibodies

Antibodies bind to antigens. There are 5 general consequences of the binding of antibody to antigen:

1) **neutralization**
   - **prevents antigen (e.g., virus, toxin) from functioning**
2) **agglutination**
   - **the "cross-linking" of antigens into a large complex**
3) **opsonization**
   - **enhancing the process of phagocytosis**
4) **antibody-dependent cell-mediated cytotoxicity**
   - **facilitating destruction of eukaryotic pathogens**
5) **activation of complement**

96



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SOLUTIONS

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VITAMIN C

- Concentrations in the plasma and leukocytes rapidly decline during infections and stress.
- Improves antimicrobial and natural killer cell activities,
- Lymphocyte proliferation,
- Chemotaxis,
- Delayed-type hypersensitivity.
- Maintains the redox integrity of cells, protects them against ROS

- https://pubmed.ncbi.nlm.nih.gov/16373990/

99

VITAMIN C

- **Vitamin C. Biosynthesis, recycling and degradation in mammals**
- Federation of European Biochemical Societies journal, 2007 Jan

High-Dose Vitamin C for Cancer Therapy

Finally, high-dose Vit-C has the definite potential to provide beneficial and cost-effective anti-cancer treatment options that should be investigated further. Ascorbic acid may become a significant treatment option in the fight against cancer, due to its widespread availability in nature, minimal toxicity, and low cost.
There is no benefit to intravenous delivery of Vit-C over oral treatment. However, more clinical trials evaluating the optimal method of high-dose Vit-C delivery are urgently required.
Pharmaceuticals (Basel). 2022 Jun
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9231292/

100

VITAMIN C

- Biology and Diseases of Guinea Pigs
- https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/l-gulonolactone-oxidase
- Humans lack the enzyme **L-gulono-lactone oxidase** (GLO), which is necessary for vitamin C synthesis from 6-carbon sugars.
- scavenging both intracellularly and extracellulary superoxide radicals and singlet oxygen, whose activity results in tissue damage (Chakrabarty *et al.*, 1992). It maintains vitamin E *in vitro* by reducing α-tocopherol radicals.
- https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/l-gulonolactone-oxidase

101

VITAMIN C

- **Ascorbic Acid Metabolism**
- *LINUS PAULING, in Search and Discovery, 1977*
- https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/ascorbic-acid-metabolism
- The Canadian physician W. J. McCormick (1954, 1959, 1963), on the basis of the literature and his own observations, developed the hypothesis that **cancer** is a preventable collagen disease that results from a deficiency of ascorbic acid.
- Stocks and Karn (1933) study of the diet of 462 patients with cancer and 435 control patients in England found a consistent negative correlation between the occurrence of cancer. Increased intake of vitamin C… decreases the incidence of cancer.

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VITAMIN C

- Bjelke (1974). In extensive epidemiological studies in Norway and Minnesota of cancer of the stomach, colon, and rectum in relation to diet, involving about 40,000 persons, has reported finding a negative correlation between these types of cancer and the intake of fruits, vegetables, and vitamin C.
- The most extensive clinical trial of ascorbic acid in human cancer is that of Cameron and Campbell (1974), who reported on 50 patients with advanced human cancer who received no treatment other than ascorbic acid, usually 10 g/day. They concluded that "this simple and safe form of medication is of definite value in the palliation of terminal cancer." The findings suggest that it should be employed as a standard supportive measure

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ARABINOGALACTANS POLYSACHARIDES

3 TYPES OF CARBOHYDRATES

1. Sugars
2. Starches (also known as complex carbohydrates)
3. Fiber – **COMPLEX POLYSACHARIDES**

- Arabinogalactan-proteins (AGPs) are highly glycosylated proteins (glycoproteins) found in the cell walls of plants.

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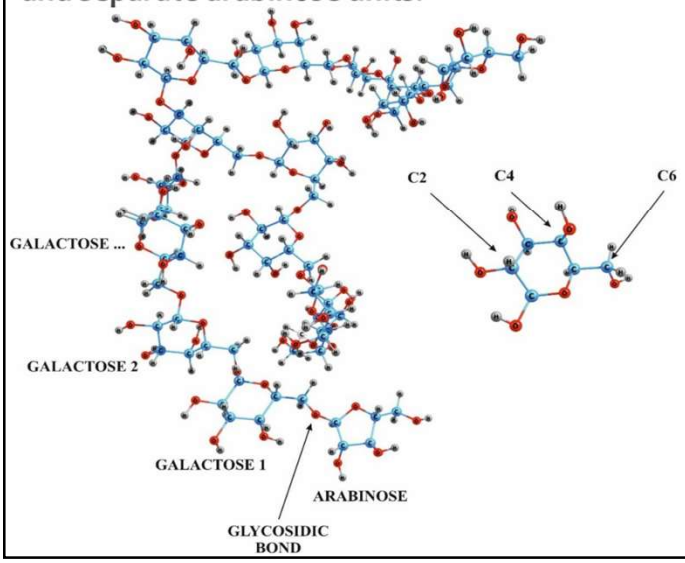
105

FRAGMENT of the arabinogalactan molecule with marked hydroxyl groups responsible for the occurrence of predominant sulphation. The main chain consists of galactose units linked by glycosidic bonds, and the side chains consist of galactose and arabinose units and separate arabinose units.



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ARABINOGALACTANS

- Arabinogalactan exhibits a wide range of biological properties: the immunobiological, hepatoprotective, antimutagenic, mitogenic, gastroprotective, and membranotropic activity; the probiotic, mycogenic, hypolipidemic, and immunomodulatory characteristics; the dispersing effect; etc. [27,29,30,31]. The macromolecule of arabinogalactan isolated from Siberian larch wood has a branched structure and a molecular weight of 15–20 kDa

Nutrition & Metabolism April 2016
https://www.mdpi.com/1420-3049/26/17/5364

107

Larch arabinogalactan effects on reducing incidence of upper respiratory infections Curr Med Res Opin 2013 Mar;

- Increase resistance to infections. Larch arabinogalactan seems to positively influence **NK cells, macrophage** activities and pro-inflammatory cytokine production. A clinical study demonstrated that larch arabinogalactan supplementation reduced the incidence of common cold infections.

https://pubmed.ncbi.nlm.nih.gov/23339578/

108

ARABINOGALACTANS

- **Synthesis of branched arabinogalactans up to a 140-mer from *Panax notoginseng* and their anti-pancreatic-cancer activity**
- **Nature Synthesis volume 3, pages 245–255 (2024)**

- **Combination of arabinogalactan and curcumin induces apoptosis in breast cancer cells in vitro and inhibits tumor growth via overexpression of p53 level in vivo**
- **Conclusion: Our findings suggest that the combination of AG and Cur is of great potential to induce apoptosis in breast cancer cells in vitro and in vivo.**
- **Biomedicine & Pharmacotherapy 2017 AprIL**

https://pubmed.ncbi.nlm.nih.gov/28152473/

109

EXERCISE

- ❑ Acute exercise is an immune system adjuvant that improves defense activity and metabolic health.
- ❑ Data support a clear inverse relationship between moderate exercise training and illness risk.
- ❑ Exercise training has an anti-inflammatory influence mediated through multiple pathways.
- ❑ Illness risk is increased in athletes during periods of intensified training and competition.
- ❑ Increased carbohydrate and polyphenol intake is an effective nutritional strategy for immune support.
- ❑ Habitual exercise improves immune regulation, delaying the onset of age-related dysfunction.
- ❑ Advances in mass spectrometry technology will provide new insights on exercise–immune responses.

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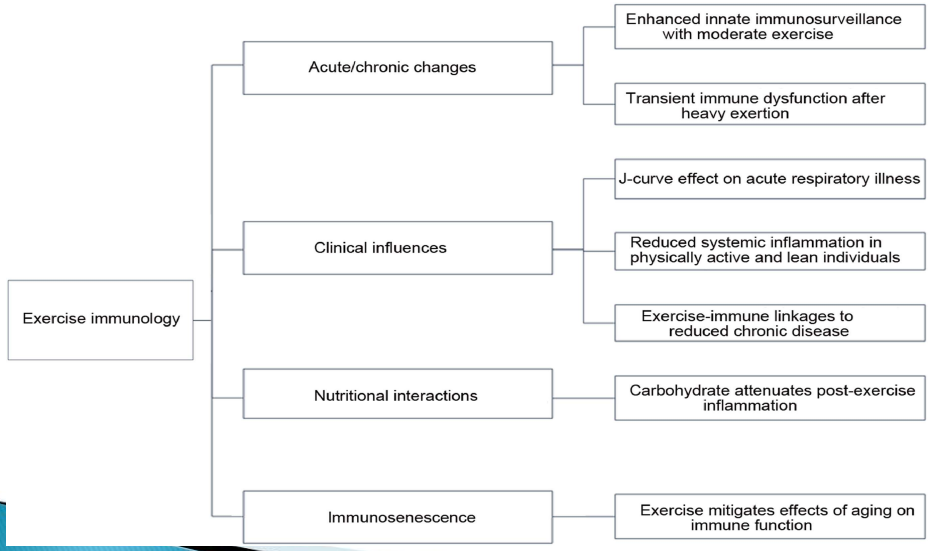
EXERCISE



111

Enhanced immunosurveillance with acute exercise bouts of less than 60 min

- Moderate- and vigorous-intensity aerobic exercise bouts of less than 60 min duration, the antipathogen activity of tissue macrophages occurs in parallel with an enhanced recirculation of immunoglobulins, anti-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells, and immature B cells, all of which play critical roles in immune defense activity and metabolic health
- Acute exercise bouts preferentially mobilize NK cells and $CD8^+$ T lymphocytes that exhibit high cytotoxicity and tissue migrating potential.

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Enhanced immunosurveillance with acute exercise

- Acute exercise is now viewed as an important immune system adjuvant to stimulate the ongoing exchange of leukocytes between the circulation and tissues. An ancillary benefit is that acute exercise may serve as a simple strategy to enrich the blood compartment of highly cytotoxic T-cell and NK cell subsets that can be harvested for clinical use. Metabolically, moderate exercise induces small, acute elevations in IL-6 that exert direct anti-inflammatory effects, improving glucose and lipid metabolism over time.

113

SLEEP

- During sleep, your immune system releases proteins called cytokines, some of which help promote sleep. Certain cytokines need to increase when you have an infection or inflammation, or when you're under stress. Sleep deprivation may decrease production of these protective cytokines. In addition, infection-fighting antibodies and cells are reduced during periods when you don't get enough sleep.
- Sleep needed to fight infectious diseases. Long-term lack of sleep also increases your risk of obesity, diabetes, and cardiovascular disease.

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Immune System

1. GRATITUDE
2. HUMOR
3. SUNLIGHT
4. MOVEMENT
5. SLEEP
6. COMMUNITY
7. HEALTHY EATING & DRINKING

115

PRODUCTS

- Bio C Plus 3 X 2 F
- IAG 1-2 tbsp E
- Bio Doph 7 1 x 2 E
- Zn Zyme Forte 1 F
- Biomega 1000 or EFA SIRT Supreme 2 F
- Chidren ENT/Adult ENT 1-2 sublingual
- Intenzyme Forte 10 x 3 E
- Bio FCTS 4 x 2 E

116