BASIC IMMUNOLOGY II

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LEARNING OBJECTIVES FOR IMMUNOLOGY OVERVIEW

UPON COMPLETION OF THIS LECTURE AND EXERCISES THE STUDENT WILL BE ABLE TO:

- DEFINE THE TERMS IMMUNITY, IMMUNOLOGY
- DESCRIBE MAJOR HISTORICAL EVENTS IN THE DEVELOPMENT OF IMMUNOLOGY
- DIFFERENTIATE INNATE AND ADAPTIVE IMMUNITY IN TERMS OF COMPONENTS AND TYPE OF IMMUNE RESPONSE.
- EXPLAIN THE MAJOR DEFENSES OF INNATE IMMUNITY
- DESCRIBE THE MECHANISMS USED BY THE BODY TO DEFEND ITSELF IN AN INNATE RESPONSE

DEFINITION OF TERMS

- **IMMUNOLOGY**
  - THE STUDY OF IMMUNE SYSTEM OR IMMUNITY
  - THE STUDY OF ALL ASPECTS OF HOST DEFENSE AGAINST INFECTION AND OF ADVERSE CONSEQUENCES OF IMMUNE RESPONSES.
  - THE STUDY OF THE PHYSIOLOGICAL MECHANISMS WHICH ENABLE THE BODY TO RECOGNIZE MATERIALS AS FOREIGN AND TO NEUTRALIZE, METABOLIZE OR ELIMINATE THEM WITHOUT INJURY TO THE HOST TISSUE.

- **IMMUNITY**
  - STATE OF PROTECTION FROM INFECTIOUS DISEASES

IMMUNE SYSTEM

- A REMARKABLY VERSATILE DEFENSE SYSTEM THAT HAS EVOLVED TO PROTECT ANIMALS FROM INVADING PATHOGENIC MICROORGANISMS AND CANCER.
- IT IS ABLE TO GENERATE AN ENORMOUS VARIETY OF CELLS AND MOLECULES CAPABLE OF SPECIFICALLY RECOGNIZING AND ELIMINATING AN APPARENTLY LIMITLESS VARIETY OF FOREIGN INVADERS.

History of immunology

- Its principles among the earliest written observations;
- Individuals recovering from certain disease rarely contracted that same disease again.
- observation promoted deliberate attempts to induce immunity
- Athens plague as of Thucydides in 430BC (recovered people only nurse sick one)

- CHINESE(1500A.D) CUSTOM OF INHALING CRUSTS FROM SMALLPOX LESIONS TO PREVENT DEVELOPMENT OF SMALL POX IN LATER LIFE.
- INJECTING MATERIALS FROM CRUSTS OR FLUID FROM SMALLPOX BLISTERS ("VARIOLATION"), USED THROUGH OUT THE EASTERN WORLD, IN 1718 WAS INTRODUCED INTO WESTERN MEDICINE BY BRITISH AMBASSADOR'S WIFE, TO TURKEY, HAD HER CHILDREN SO TREATED.
    - **NOTE-** THE VIRUS USED COULD BE TRANSMITTED => PROTECTION BY VARIOLATION WAS HAZARDOUS TO THE COMMUNITY AT LARGE!!

- **IN 1798, JENNER'S** WORK ON VACCINATION, DESCRIBING A RELATED, *YET SAFE PROCEDURE*.
  - NOTED PEOPLE, WHO HAD **COW POX**, WERE SPARED IN SMALL POX EPIDEMICS,
  - INOCULATED BOY WITH PUS FROM MILK MAID WITH COW POX, AND
  - RE-INOCULATED SAME BOY WITH INFECTIOUS PUS FROM A PATIENT IN THE ACTIVE SMALL POX.
  - NO DISEASE STATE FOLLOWED THESE INOCULATIONS, AND EXPERIMENT WAS REPEATED SEVERAL TIMES WITH GREAT SUCCESS!

Louis Pasteur- demonstrating that it was possible to **attenuate,** or weaken, a pathogen and administer the attenuated strain as a vaccine.

In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog

Wood engraving of Louis Pasteur watching Joseph Meister receive the rabies vaccine. [*From Harper's Weekly* ***29:836;*** *courtesy of the National Library of Medicine.]*

- JENNER`S PROVIDED FIRST CLEAR EVIDENCE THAT **ACTIVE IMMUNIZATION** COULD BE USED SAFELY TO PREVENT AN INFECTIOUS DISEASE.

- **ALMOST 70 YEARS LATER, PASTEUR** - INTRODUCED **PASTEURIZATION ALSO**
  - RECOGNIZED AND EXPLOITED THE **GENERAL PRINCIPLE UNDERLYING VACCINATION**

- **AT ABOUT 1900,**
  - ROLE OF PHAGOCYTES AND CELLULAR IMMUNITY WERE ELUCIDATED

- KILLED VACCINES WERE INTRODUCED
- COMPLEMENT WAS DESCRIBED

- **IN 20TH CENTURY,**
  - *ACQUIRED IMMUNITY* RESULTED FROM BOTH CELLULAR AND HUMORAL ELEMENTS WERE DEMONSTRATED.
  - *OPSONIZATION* WAS DESCRIBED
  - THE TERM *ANTIGEN* CAME IN TO REGULAR USE

NOBLE PRIZE WINNERS FOR IMMUNOLOGIC RESEARCH

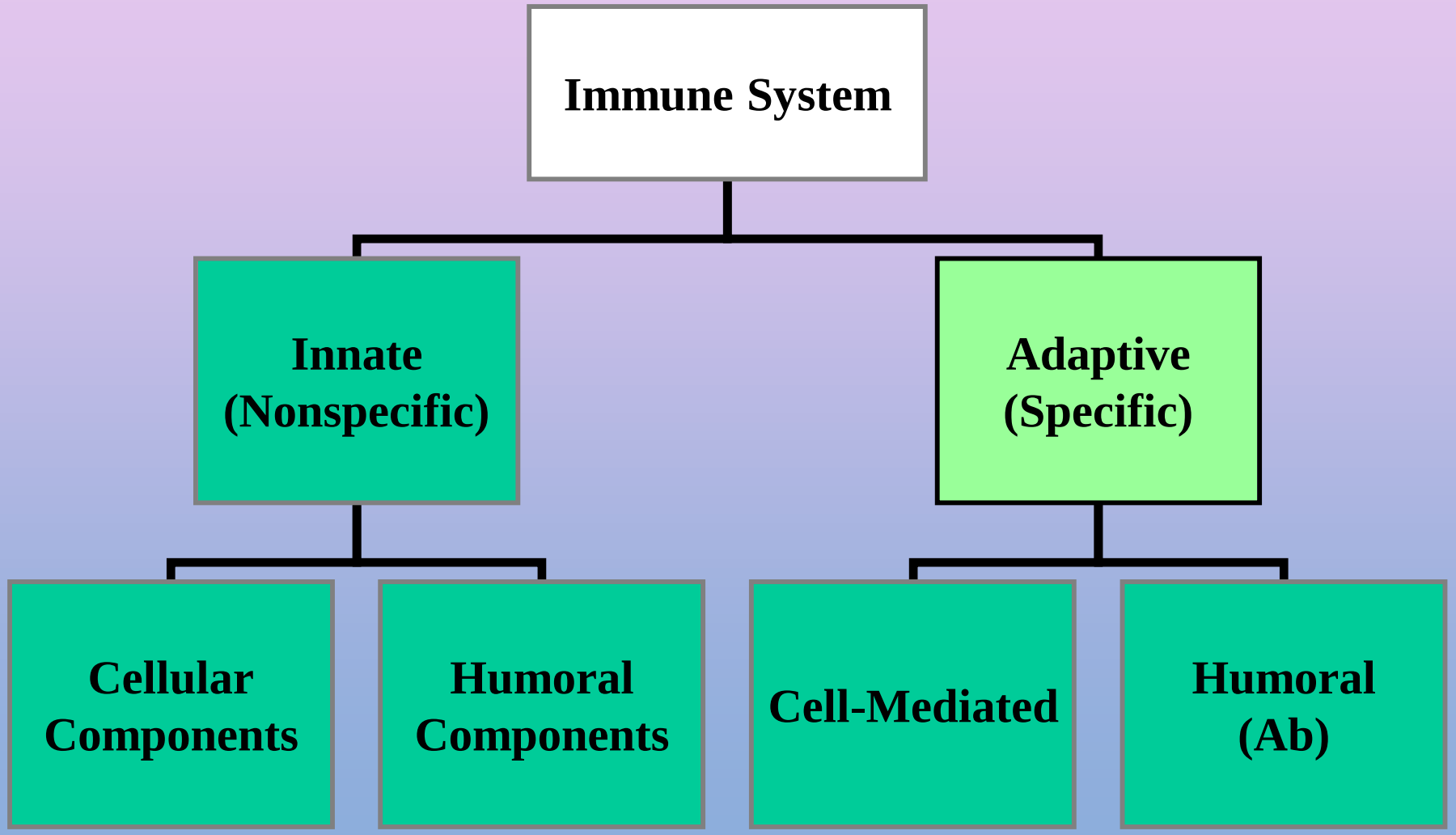
- 1901 EMIL VON BEHRING, SERUM ANTITOXINS
- 1905 ROBERT KOCH, CELLULAR IMMUNITY TO TUBERCULOSIS
- 1908 ELIE METCHNIKOFF, ROLE OF PHAGOCYTOSIS
- 1908 PAUL EHRLICH, ANTITOXINS IN IMMUNITY
- 1913 CHARLES RICHET, ANAPHYLAXIS
- 1919 JULES BORDER, COMPLEMENT-MEDIATED BACTERIOLYSIS
- 1930 KARL LANDSTEINER, DISCOVERY OF HUMAN BLOOD GROUPS

- 1951 MAX THEILER, DEVELOPMENT OF YELLOW FEVER VACCINE
- 1957 DANIEL BOVET ,ANTIHISTAMINES
- 1960 F. MACFARLANE BURNET AND PETER MEDAWAR, DISCOVERY OF ACQUIRED IMMUNOLOGICAL TOLERANCE
- 1972 RODNEY R. PORTER AND GERALD M. EDELMAN, CHEMICAL STRUCTURE OF ANTIBODIES
- 1977 ROSALYN R. YALOW, DEVELOPMENT OF RADIOIMMUNOASSAY
- 1980 GEORGE SNELL, JEAN DAUSSCT AND BARUJ BENACERRAF

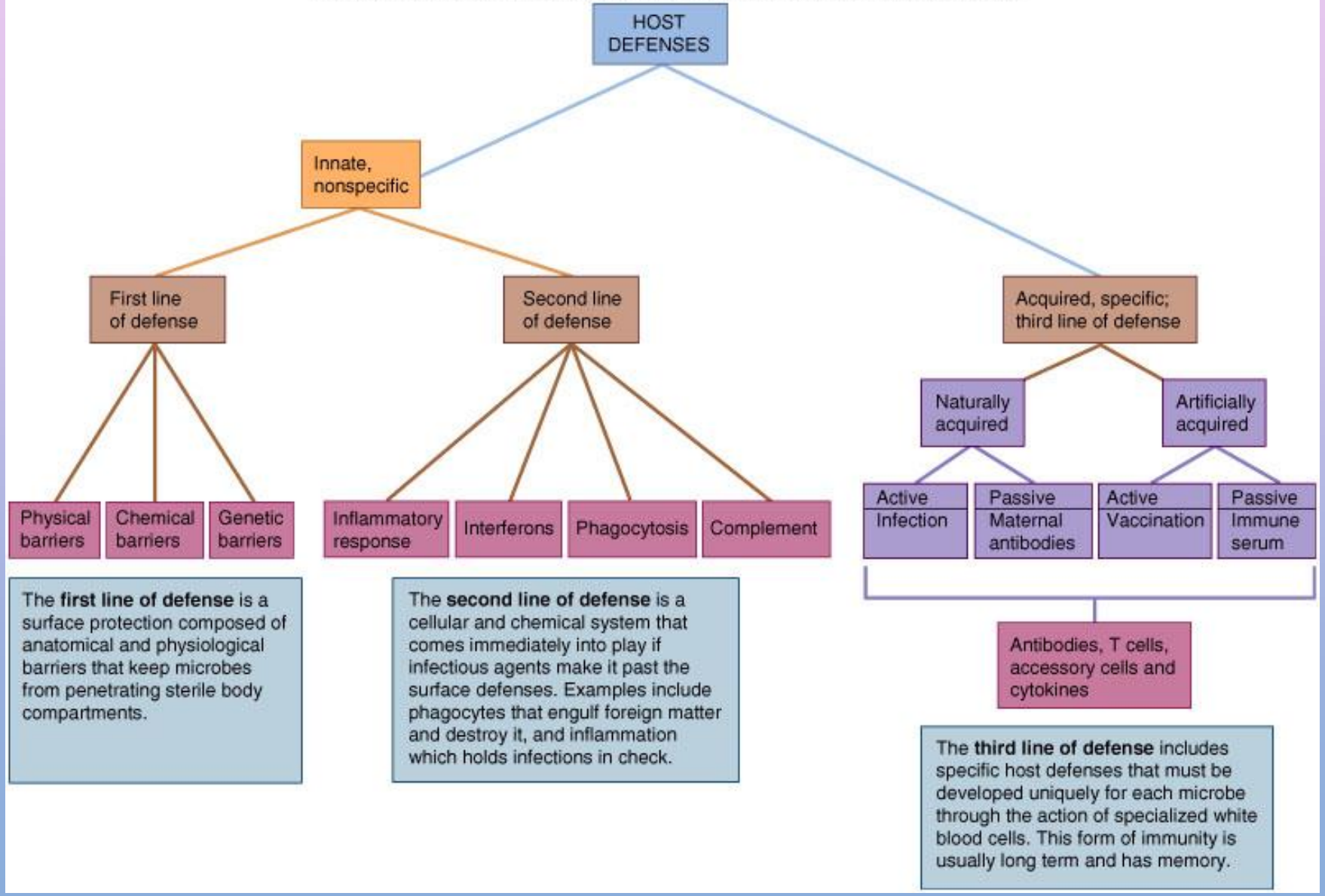
  MAJOR HISTOCOMPATIBILITY COMPLEX

- 1984 CESAR MILSTEIN AND GEORGES E. KÖHLER, MONOCLONAL ANTIBODY
- 1984 NIELS K. JERNE, IMMUNE REGULATORY THEORIES
- 1987 SUSUMU TONEGAWA, GENE REARRANGEMENT IN ANTIBODY PRODUCTION
- 1991 E. DONNALL THOMAS AND JOSEPH MURRAY TRANSPLANTATION IMMUNOLOGY
- 1996 PETER C. DOHERTY, ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX
- 1996 ROLF M. ZINKERNAGEL, IN ANTIGEN RECOGNITION BY BY T CELLS

THE IMMUNE SYSTEM



The immune system



THE INNATE IMMUNITY

NATURAL IMMUNE SYSTEM (INNATE IMMUNITY)

- ✓ NON – SPECIFIC
- ✓ FIRST LINE OF DEFENSE
- ✓ REPEATED EXPOSURE - NO AUGMENTATION

- **COMPONENTS**
  - ✓ BIOCHEMICAL
  - ✓ PHYSICAL
  - ✓ CELLS

1. COMPONENTS

a. BIOCHEMICAL

- ENZYMES, C', ETC.
- SECRETIONS
- PH

b. PHYSICAL

- SKIN
- CILIA

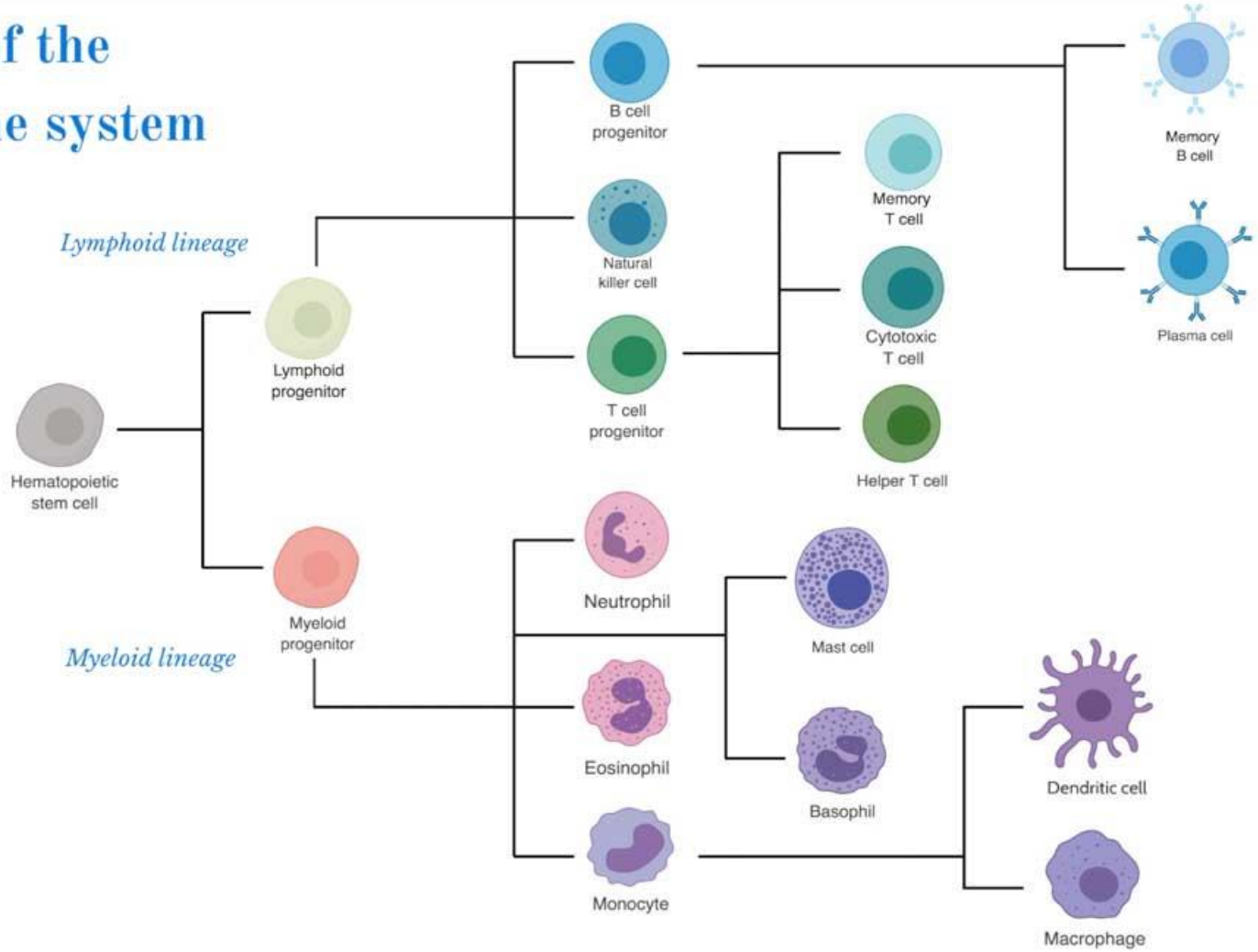
c. CELLS

- PHAGOCYTES, NK

2. EXAMPLE

a. BURN RESPONSE

Cells of the immune system



https://www.ibiology.org/

- OVERALL NON-SPECIFIC REACTION OF BODY TO INJURY OR INVASION – STARTS IMMEDIATELY WITH INFECTION OR TRAUMA
  - REACTANTS MAY INITIATE, EXPAND, OR SUSTAIN THE RESPONSE
  - CAN BE ACUTE (SHORT DURATION) OR BECOME CHRONIC (PROLONGED DURATION)
- HAS 4 CARDINAL SIGNS: **HEAT, PAIN, REDNESS, LOSS OF FUNCTION** RESULTING FROM:

- INCREASED BLOOD AND PLASMA FLOW TO THE AREA
- INCREASED CAPILLARY PERMEABILITY BY RETRACTION OF ENDOTHELIAL CELLS
- MEDIATED BY VASO ACTIVE AGENTS SUCH AS **HISTAMINE AND PROSTAGLANDINS.**
    - DERIVED FROM INJURED CELLS AND LATER FROM CELLS THAT INFILTRATE THE AREA.
- MIGRATION OF LEUCOCYTES, PARTICULARLY NEUTROPHILS AND MACROPHAGES, FROM THE CAPILLARIES TO THE SITE OF INJURY IS DUE TO A PROCESS CALLED C*HEMOTAXIS*.

- MIGRATION OF WHITE CELLS, ESPECIALLY EARLY MIGRATION OF NEUTRAPHILS THEN MACROPHAGES TO THE AREA
- INCREASED RELEASE OF MEDIATORS SUCH AS HISTAMINE FROM DAMAGED MAST CELLS – FURTHERING CAPILLARY DILATION
- INCREASED CONCENTRATION OF ACUTE PHASE REACTANTS THAT CAN AMPLIFY AND/OR CONTROL THE RESPONSE

- **COMPLEMENT** – A SERIES OF ENZYMES NORMALLY CIRCULATING IN AN INACTIVE FORM MAY BE ACTIVATED RESULTING IN LYSIS OR ENHANCED PHAGOCYTOSIS OF CELLS

EXTERNAL INNATE DEFENSE SYSTEMS

- PREVENT ENTRANCE:
  - **STRUCTURAL** BARRIERS – EFFECTIVE WITH MOST MICROORGANISMS
    - **SKIN** - EPIDERMIS = LAYERS OF TIGHTLY PACKED EPITHELIAL CELLS. OUTER LAYER IS DEAD CELLS AND KERATIN, WATERPROOFING PROTEIN
    - **INNER LAYER SKIN** - DERMIS = BLOOD VESSELS, HAIR FOLLICLES, SWEAT GLANDS, AND SEBACEOUS GLANDS THAT PRODUCE AN OILY SECRETION CALLED **SEBUM**
    - **CILIA** AND **COUGH REFLEX** – HELPS EXPEL MICROBE CONTAINING MUCOUS
    - SNEEZE

EXTERNAL INNATE DEFENSE SYSTEMS

- **MUCUS** - CONJUNCTIVAE, ALIMENTARY, RESPIRATORY, AND UROGENITAL TRACTS
    - SALIVA, TEARS, AND MUCOUS SECRETIONS WASH AWAY INVADERS AND CONTAIN ANTIBACTERIAL OR ANTIVIRAL SUBSTANCES.
    - ACIDITY (PH 5.6) OF SWEAT, SEBACEOUS GLANDS, VAGINA (PH 5) AND STOMACH (PH 1) – UNFRIENDLY TO MANY MICROORGANISMS
    - ENZYMES PRESENT IN THE SKIN AND STOMACH, TEARS
- **NORMAL FLORA** - OUT COMPETE PATHOGENS FOR ATTACHMENT SITES ON THE EPITHELIAL CELL SURFACE AND FOR NECESSARY NUTRIENTS.

INTERNAL INNATE DEFENSE SYSTEM

- TO PREVENT EXPANSION OF PENETRATION
  - RECOGNIZE CARBOHYDRATES NOT NORMALLY PRESENT ON CELLS SUCH AS MANNOSE
  - MAY CAUSE NONSPECIFIC ACTIVATION OF WHITE CELLS
    - PHAGOCYTOSIS – BY NEUTRAPHILS, EOSINOPHILS, BASOPHILS, OR MACROPHAGES, MAST CELLS, AND DENDRITIC CELLS
  - CLOTTING MECHANISM WHICH ENTRAPS ORGANISMS IN FIBRIN CLOTS
  - COMPLEMENT SYSTEM CAN LYSE CELLS OR ENHANCE PHAGOCYTOSIS

PHYSIOLOGIC BARRIERS

- SOLUBLE FACTORS CONTRIBUTE TO INNATE IMMUNITY, THEY ARE COLLECTIVELY KNOWN AS ACUTE PHASE REACTANTS.
- NORMAL SERUM COMPONENTS, NON-SPECIFIC RESPONDERS TO INFLAMMATION
- INCREASE BECAUSE OF INFECTION, INJURY, TRAUMA
- PRODUCED MOSTLY BY LIVER IN RESPONSE TO INFLAMMATION AND CYTOKINE STIMULATION
  - CYTOKINES: IL-1, IL-6 AND TNF ALPHA WHICH ARE PRODUCED BY MACROPHAGES AND MONOCYTES AT INFLAMMATORY SITE ARE ACTIVATORS

- ACUTE PHASE REACTANTS ARE CHEMICALLY VARIED AND INCLUDE:
  - C-REACTIVE PROTEIN,
  - SERUM AMYLOID A,
  - MANNOSE BINDING PROTEIN,
  - ALPHA-1 ANTI-TRYPSIN,
  - HAPTOGLOBULIN,
  - FIBRINOGEN,
  - CERULOPLASMIN,
  - ALPHA-1 ACID GLYCOPROTEIN
  - COMPLEMENT

- **COMPLEMENT** – A SERIES OF ENZYMES NORMALLY CIRCULATING IN AN INACTIVE FORM
  - MAY BE ACTIVATED BY THE CLASSICAL OR ALTERNATE PATHWAYS
  - CAN RESULT IN LYSIS OR ENHANCED PHAGOCYTOSIS OF CELLS

- **LYSOZYME,** A HYDROLYTIC ENZYME IN MUCOUS SECRETIONS AND IN TEARS, CAN CLEAVE THE PEPTIDOGLYCAN LAYER OF BACTERIAL CELL WALL.

- **INTERFERON,** PROTEINS PRODUCED BY VIRUS-INFECTED CELLS. HAS MANY FUNCTIONS INCLUDING ABILITY TO BIND TO NEARBY CELLS AND INDUCE A GENERALIZED ANTIVIRAL STATE.

C-REACTIVE PROTEIN

- NORMALLY TRACE LEVELS IN SERUM

- **EARLY ACUTE INFLAMMATION INDICATOR:**
  - INCREASES WITHIN 4-6 HRS OF INFECTION OR TRAUMA
  - 100 TO 1000 FOLD INCREASE SERUM CONCENTRATION
  - CONCENTRATION DROPS RAPIDLY IN SERUM WHEN STIMULUS REMOVED
- ENHANCES OPSONIZATION, AGGLUTINATION, PRECIPITATION, AND CLASSICAL PATHWAY COMPLEMENT ACTIVATION – ENHANCES REMOVAL OF IRRITANT

PHAGOCYTOSIS

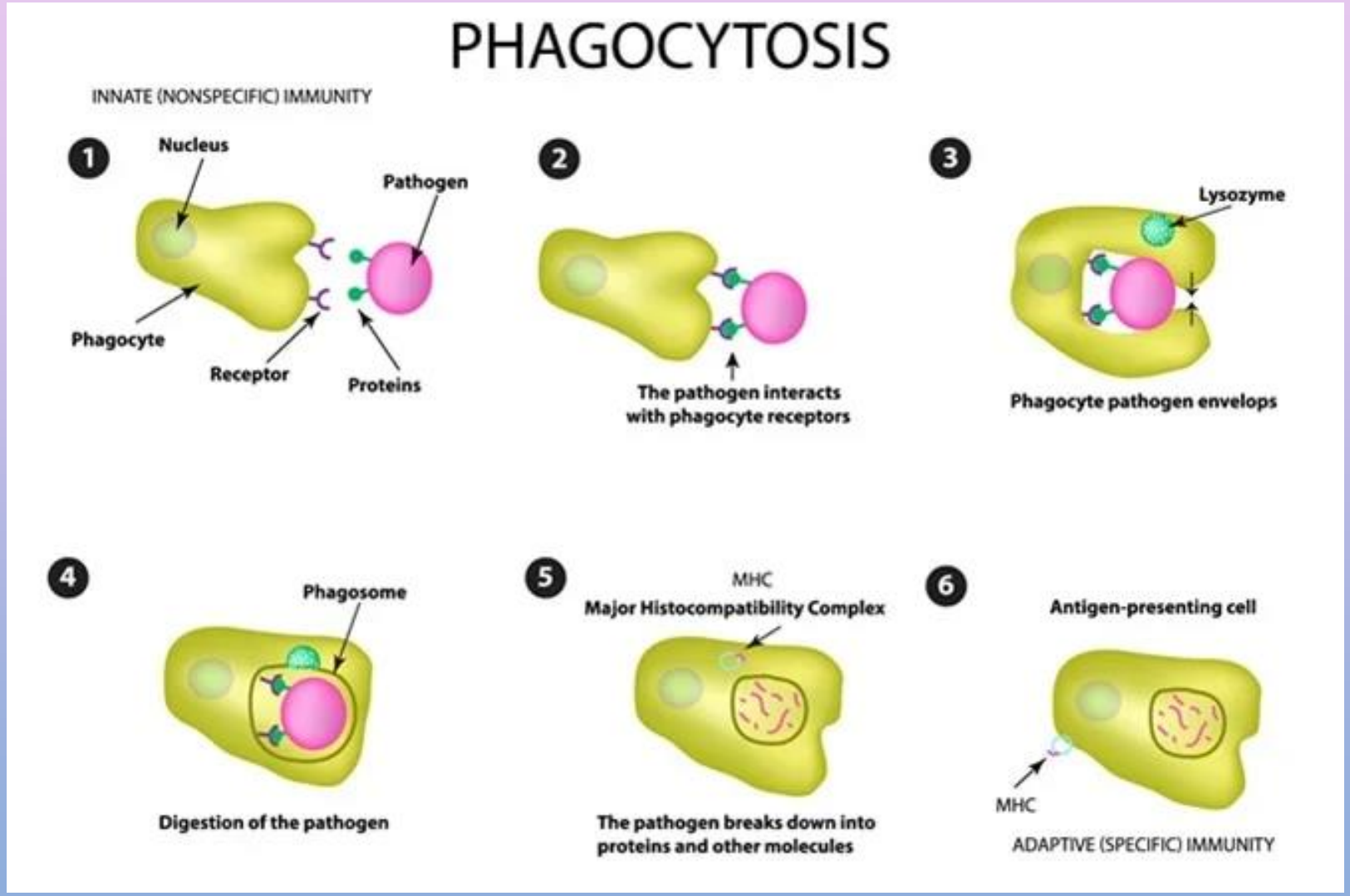
- PHAGOCYTIC CELLS CHEMOTAXINS SUCH AS
  - COMPLEMENT COMPONENTS
  - COAGULATION CASCADE PROTEINS
  - BACTERIAL AND VIRAL PRODUCTS
- ATTRACT PHAGOCYTIC CELLS INCLUDING:
  - MAST CELL, LYMPHOCYTE, MACROPHAGE, NEUTROPHIL PRODUCTS
- PHYSICAL CONTACT BETWEEN PHAGOCYTIC CELL AND FOREIGN OBJECT RESULTS IN
  - FORMATION OF PHAGOSOME
  - FORMATION OF PHAGOLYSOSOME
  - DIGESTION
  - RELEASE OF DEBRIS

- **PHAGOCYTOSIS**
  - IS A FORM OF ENDOCYTOSIS.
  - IMPORTANT BODY DEFENSE MECHANISM IS PROCESS IN WHICH SPECIALIZED CELLS ENGULF AND DESTROY FOREIGN PARTICLES SUCH AS MICROORGANISMS OR DAMAGED CELLS.
  - MACROPHAGES AND SEGMENTED NEUTROPHIILS ARE THE MOST IMPORTANT PHAGOCYTIC CELLS.

- CAN BE DIVIDED IN TO SEVERAL STAGES:
  - CHEMOTAXIS – ATTRACTION OF LEUKOCYTES OR OTHER CELLS BY CHEMICALS
  - MOVEMENT OF NEUTRAPHILS IS INFLUENCED BY CHEMOTAXINS – CHEMICAL MESSANGERS
    - COMPLEMENT, PROTEINS FROM COAGULATION,
    - PRODUCTS FROM BACTERIA AND VIRUSES,
    - SECRETIONS FROM MAST CELLS, LYMPHOCYTES, MACROPHAGES, AND OTHER NEUTRAPHILS

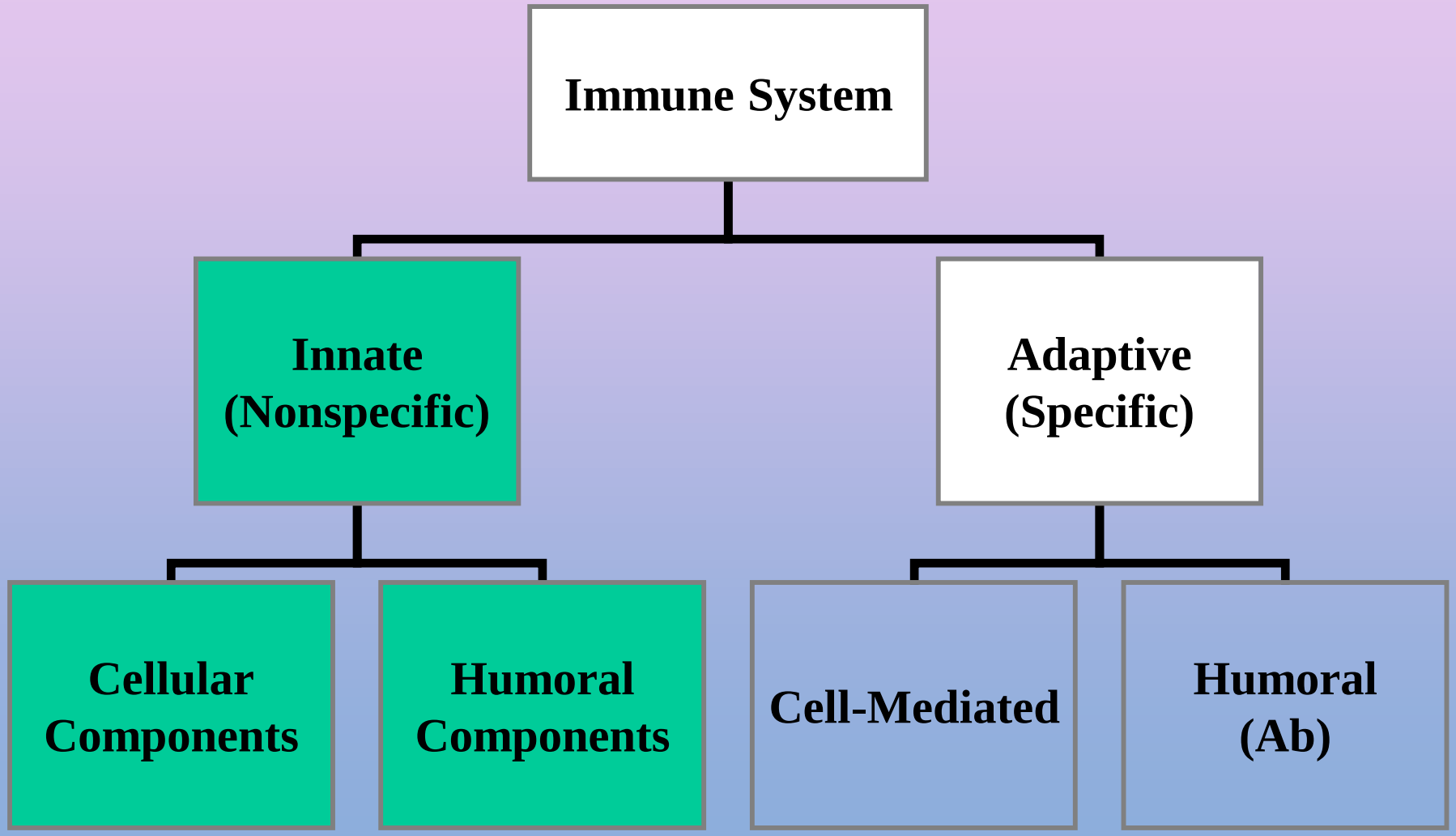
- **PHAGOCYTOSIS …**
  - **ADHERENCE** – BINDING OF ORGANISM TO THE SURFACE OF PHAGOCYTIC CELL.
  - **ENGULFMENT**:- IS THE INJESTION OF M/OS AND FORMATION OF PHAGOSOMES.
  - **DIGESTION** – AFTER THE FOREIGN PARTICLE OR M/OS IS INGESTED, CYTOPLASM LYSOSOME FUSE WITH PHAGOSOME THE ENZYMES OF LYSOSOME THEN CONTRIBUTE TO MICROBIAL KILLING AND LYSIS.

Phagocytosis …

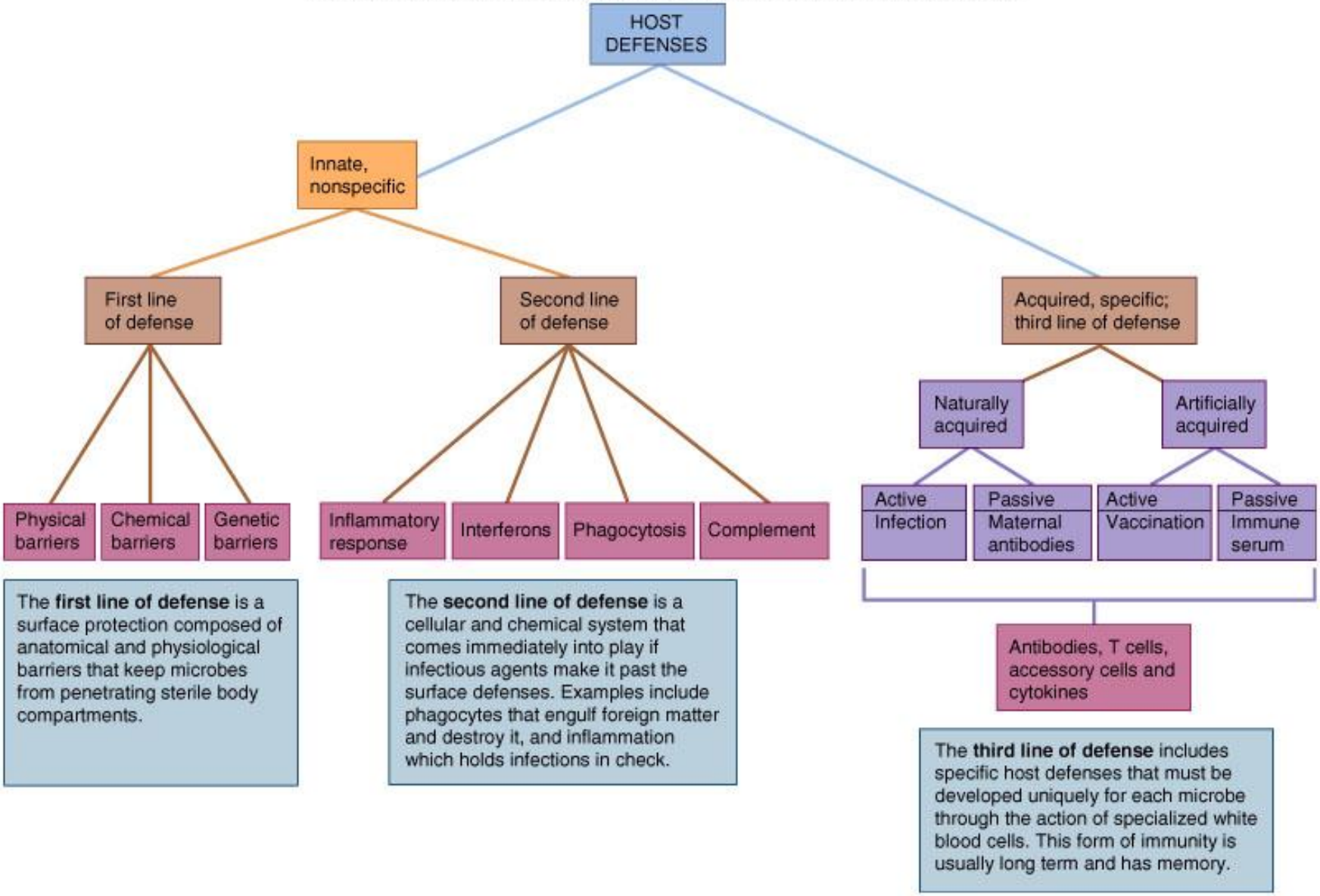


https://www.news-medical.net/life-sciences/What-is-the-difference-Between-a-Phagocyte-Macrophage-Neutrophil-and-Eosinophil.aspx

THE ADAPTIVE IMMUNE SYSTEM



THE ADAPTIVE IMMUNE SYSTEM



The adaptive immune system

Adaptive Immunity

- Specific
- Second line of defense
- Repeated exposure - augmented – memory
- Faster response
- More vigorous response
- Longer lasting response
- Anamnestic

Components

Classic Immune System

- Cells (Cell mediated) =CMI
- Soluble Factors (Humoral immunity) = HI

THE ADAPTIVE IMMUNE SYSTEM

- CAPABLE OF RECOGNIZING AND SELECTIVELY ELIMINATING SPECIFIC FOREIGN MICROORGANISMS AND MOLECULES(I.E., FOREIGN ANTIGENS).
- UNLIKE INNATE IMMUNE RESPONSES, ADAPTIVE IMMUNE RESPONSES ARE REACTIONS TO SPECIFIC ANTIGENIC CHALLENGES
- DIFFERENT POPULATIONS OF LYMPHOCYTES AND THEIR PRODUCTS ARE THE MAJOR ACTORS TOGETHER WITH ACCESSORY CELLS – ANTIGEN PRESENTING CELLS (APCS)
- CARDINAL FEATURES ARE :
  - SPECIFICITY
  - DIVERSITY , MEMORY,

THE ADAPTIVE IMMUNE SYSTEM

CARDINAL FEATURES OF ADAPTIVE IMMUNE RESPONSES

- **SPECIFICITY –**
  - SPECIFIC FOR DISTINCT ANTIGEN, AND
  - FOR DIFFERENT STRUCTURAL COMPONENTS OF A SINGLE COMPLEX PROTEIN, POLYSACCHARIDE, OR OTHER MACROMOLECULES.
  - PORTIONS OF SUCH ANTIGENS RECOGNIZED BY INDIVIDUAL LYMPHOCYTES ARE CALLED *DETERMINANTS OR EPITOPES*.
  - THIS FINE SPECIFICITY EXISTS BECAUSE INDIVIDUAL LYMPHOCYTE EXPRESS MEMBRANE RECEPTORS ABLE TO DISTINGUISH SUBTLE (SLIGHT) DIFFERENCES IN STRUCTURE BETWEEN DISTINCT ANTIGENS.

THE ADAPTIVE IMMUNE SYSTEM

- **DIVERSITY**- TOTAL NUMBER OF ANTIGENIC SPECIFICITIES OF THE LYMPHOCYTES IN AN INDIVIDUAL, CALLED *THE LYMPHOCYTE REPERTOIRE*, IS EXTREMELY LARGE.
  - ESTIMATED MAMMALIAN IMMUNE SYSTEM CAN DISCRIMINATE 10^9 TO 10^{11} DISTINCT ANTIGENIC DATE RUMINANTS.
  - THIS PROPERTY OF THE LYMPHOCYTE REPERTOIRE IS CALLED DIVERSITY. IT IS THE *RESULT OF VARIABILITY IN THE STRUCTURES OF ANTIGEN- BINDING SITES OF LYMPHOCYTE RECEPTORS FOR ANTIGENS.*

THE ADAPTIVE IMMUNE SYSTEM

- **MEMORY-** EXPOSURE OF THE IMMUNE SYSTEM TO FOREIGN ANTIGEN:
  - ENHANCES ITS ABILITY TO RESPOND AGAIN TO THAT ANTIGEN.
  - RESPONSES TO SECOND AND SUBSEQUENT EXPOSURE TO THE SAME ANTIGEN, CALLED *SECONDARY IMMUNE RESPONSES*, ARE USUALLY MORE RAPID AND LARGER THAN THE FIRST OR PRIMARY IMMUNE RESPONSE.

THE ADAPTIVE IMMUNE SYSTEM

- AN EFFECTIVE IMMUNE RESPONSE INVOLVES THREE MAJOR GROUPS OF CELLS: CELLULAR IMMUNITY (*T LYMPHOCYTES*), *HUMORAL IMMUNITY (B CELLS)*, AND ACCESSORY CELLS (*ANTIGEN-PRESENTING CELLS*).
- THE TWO MAJOR POPULATIONS OF LYMPHOCYTES—**B LYMPHOCYTES (B CELLS) OF HUMORAL IMMUNITY** AND **T LYMPHOCYTES (T CELLS) OF CELLULAR IMMUNITY PROVIDE US WITH OUR SPECIFIC ADAPTIVE IMMUNITY**

THE ADAPTIVE IMMUNE SYSTEM

- **SPECIALIZATION** –THE IMMUNE SYSTEM RESPONDS IN DISTINCT AND SPECIAL WAYS TO DIFFERENT MICROBES, *MAXIMIZING THE EFFICIENCY* OF ANTIMICROBIAL DEFENSE MECHANISMS. THUS, HUMORAL IMMUNITY AND CELL MEDIATED IMMUNITY ARE ELICITED BY DIFFERENT CLASSES OF MICROBES OR BY THE SAME MICROBE AT DIFFERENT STAGES OF INFECTION (EXTRA CELLULAR & INTRA CELLULAR)
- **SELF –LIMITATION-** ALL NORMAL IMMUNE RESPONSES RETURNING THE IMMUNE SYSTEM TO ITS RESTING OR BASAL STATE WITH TIME AFTER ANTIGEN STIMULATIONS, PROCESS CALLED **HOMEOSTASIS**.

Summary of innate and adaptive immunity

COMPARISON OF INNATE AND ADAPTIVE IMMUNITY

Innate Immunity	Adaptive Immunity
• No time lag	• A lag period
• Not antigen specific	• Antigen specific
• NO MEMORY	• Development of memory