

BCHEM 471

Immunology

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INTRODUCTION

- ▶ Immunology as a science; origin, definitions,
- ▶ Cells and tissues of the immune system.
 - ▶ B/T-lymphocyte development
- ▶ Innate and specific immune responses
- ▶ Basic aspects of the specific immune response; memory, specificity, recognition of non-self, adaptivity.
 - ▶ Cellular basis of the immune response.
 - ▶ B/T-lymphocyte activation

ANTIBODY STRUCTURE

- Purification, architecture, domains, classes of antibody

ANTIBODY FORMATION

- Response in the whole animal; interface with antibody formation;
 - immunological tolerance,
 - vaccination, development of vaccines, types of vaccines.

MONOCLONAL ANTIBODIES AND APPLICATIONS - **SELF STUDY**

COMPLEMENT

- Composition, biological properties, functions
- activation of complement; classical and alternative pathways
- regulation of activity, applications.

HYPERSensitivity (ALLERGY)

- Types; immediate and delayed, types of immediate hypersensitivity and methods of treatment.
- Autoimmune diseases, mechanisms underlying its occurrence.

ALLOANTIGENS ON CELL SURFACE

- ▶ ABO and Rh Blood group substances, blood typing and its applications, blood transfusion and associated reactions.
- ▶ Histocompatibility antigens in tissue transplantation, types of tissue grafts, immune response in tissue graft rejection, methods to achieve graft survival.

ASSESSMENT:

- ▶ Mid-semester/quiz/assignments.....30%
- ▶ End of Semester Examination.....70%

REFERENCES

- ▶ Several immunology textbooks are available in the library
 - ▶ Essentials of immunology
 - ▶ Immunology at a glance
 - ▶ Lecture notes on immunology
 - ▶ Immunology, A short course.
- ▶ All current biochemistry textbooks have a chapter on immunology, e.g Biochemistry by Voet and Voet, Mathews and Van Holde, Lubert Stryer, Rawn etc.

AIM

- ▶ To appreciate how components of the immune system work to protect against development of clinical disease.
- ▶ The basic systems and cells involved in immune responses.
- ▶ Components and systems will be defined to allow an understanding of concepts of innate and adaptive responses, and how these responses interact with one another to form the basis for protection against disease

Importance of Immunology

- ▶ A) Vaccines
- ▶ B) Recombinant DNA technology
- ▶ C) Monoclonal and Polyclonal Antibody technology
- ▶ D) Improving transplant outcomes
- ▶ E) Treatment outcomes
- ▶ F) Global eradication of diseases

Industrial Application

- ▶ Biomedical Research Institutions
- ▶ WHO, CDC
- ▶ Research Universities
- ▶ Pharmaceutical companies
- ▶ Ministry of Health
- ▶ Hospitals
- ▶ Veterinary centers
- ▶ Biomed and Biotech companies
- ▶ Forensic institutions

Salary Range

- ✓ 48,000-60,000 GHC p/a
- ✓ 80,000-120,000 USD p/a

What is Immunology?

- ▶ Immunology is defined at the study of the immune system.
- ▶ The immune system is a system of cells, tissues and their soluble products that recognizes, attacks and destroys agents that could be harmful to the health of an individual or organism.
- ▶ In principle the normal functioning of immune system lead to **immunity**.

What is Immunity?

- ▶ The Latin term ***immunitas***, meaning “exempt,” gave rise to the English word ***immunity***, which refers to all the mechanisms used by the body as protection against environmental agents that are foreign to the body.
- ▶ These agents may be microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair and dander.
- ▶ The concept of immunity dates back to 1500s, before the cause of disease was understood. Survivors after exposure to deadly disease were referred to as ***except from*** or ***immune***.
- ▶ **Immune system** consist of cells and molecules involved in such protection and the response to introduction of a foreign agent is known as the ***immune response***.

Not all responses protect from diseases

- some foreign agents, such as the allergens found in house dust mite, cat dander or rye grass pollen, cause disease as a consequence of inducing an immune response.
- Likewise some individuals mount immune responses to their own tissues as if they were foreign agents. Thus, the immune response can cause the autoimmune diseases common to man such as multiple sclerosis, diabetes.
- Most individuals do not suffer from **autoimmune disease** because they have developed tolerance towards their own (self) tissues.

Pioneers of Immunology

- ▶ **Edward Jenner** (1796), one of the pioneers who solidified the birth of immunology
- ▶ Jenner observed that dairymaids and farmers lacked the pock-marked complexions of their fellow citizens, and wondered whether those who worked with cattle might be resistant to smallpox because of their close contact with livestock.

- ▶ Cows of that era often suffered from cowpox disease, a disorder similar to smallpox but much less severe.
- ▶ In an experiment that would be prohibited on ethical grounds today, Jenner deliberately exposed an 8-year-old boy to fluid from a cowpox lesion.
- ▶ Two months later, he inoculated the same boy with infectious material from a smallpox patient.
- ▶ In this first example of successful vaccination, the boy did not develop smallpox. Jenner's approach to smallpox prevention was quickly adopted in countries throughout Europe.

ROBERT KOCH

- ▶ In 1884, Robert Koch proposed the “germ theory of disease,”
- ▶ Which stated “that microbes invisible to the naked eye were responsible for specific illnesses”
- ▶ The first human disease-causing organisms or **pathogens** were identified in the late 1800s

Today, **immunology** can be defined :

As the study of the cells and tissues that mediate immunity and the investigation of the genes and proteins underlying their function.

Smallpox Immunization

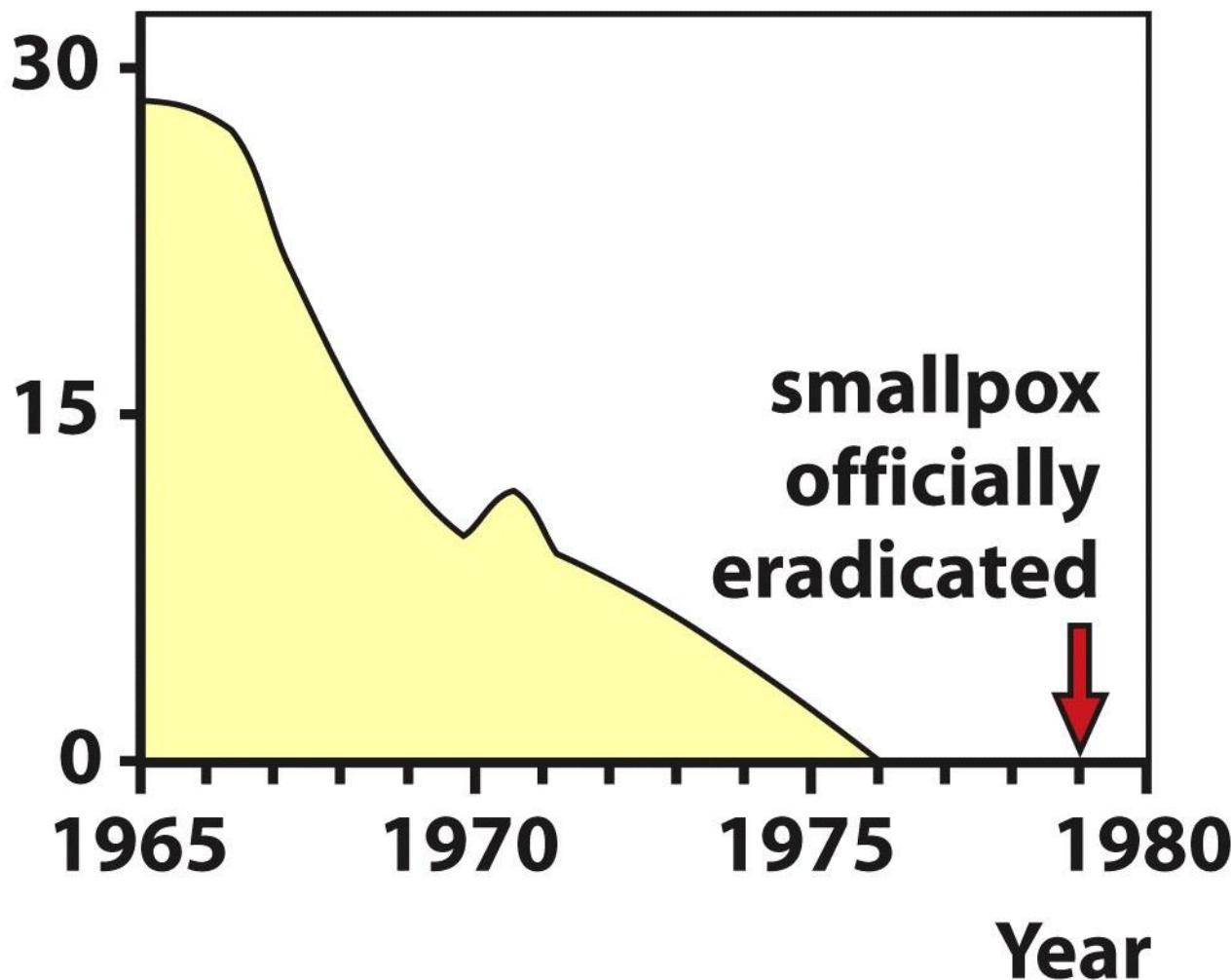


Smallpox infection in Bangladesh girl in 1973



Edward Jenner vaccinating
James Philips against smallpox

**Number of
countries
with one or
more cases
per month**



What is the nature of Immune Response

- ▶ A normal healthy person's body always strives to maintain **homeostasis**, a natural state of balance of all its organs and the nervous and circulatory systems
- ▶ When this homeostasis is disturbed by trauma, pathogens, or the deregulation of body cells (as in cancer), the immune system responds in an attempt to restore balance.

What is infection?

- ▶ **Infection** is defined as the attachment and entry of a pathogen into the host.
- ▶ Once inside the body or cell, the pathogen replicates, generating progeny that spread into the body in a localized or systemic fashion.
- ▶ The manner of this replication determines whether the pathogen is considered extracellular or intracellular.

The establishment of an infection depends on several factors:

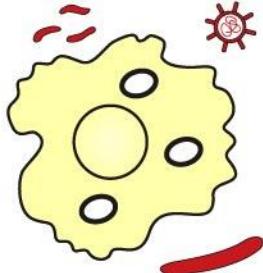
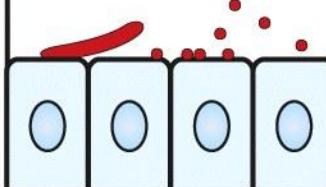
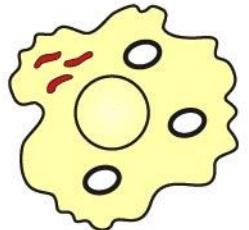
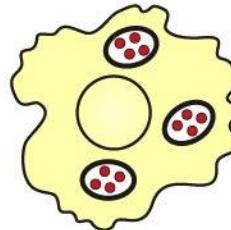
- Characteristics of the microorganism
- Number of organisms
- Mode of transmission (how and where they contact the host)
- Stability of the organism (in and outside of the host)

Extracellular pathogens

- ▶ Certain bacteria and parasites do not need to enter cells to reproduce.
- ▶ After accessing the body, these organisms replicate first in the interstitial fluid bathing the tissues and may then disseminate via the blood.

Intracellular pathogens

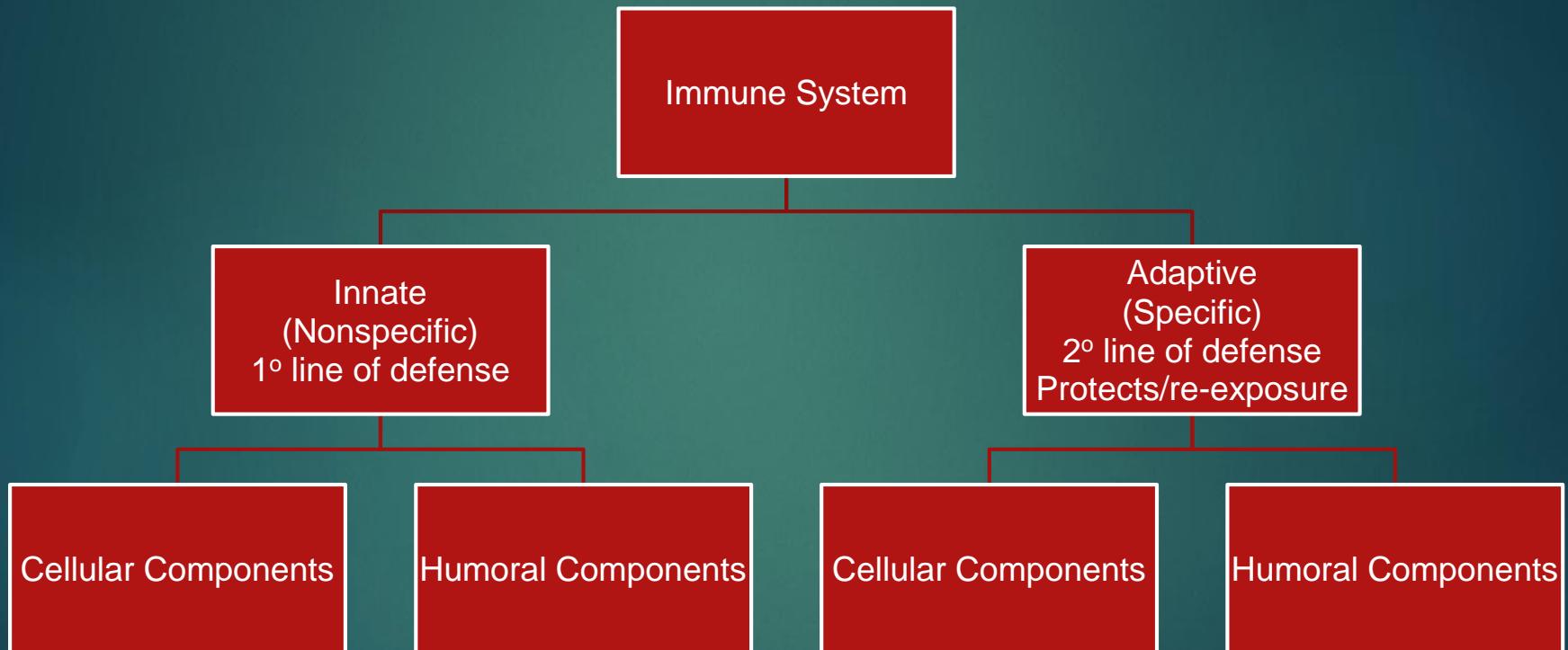
- ▶ Pathogens such as viruses and other bacteria and parasites, enter a host cell, subvert its metabolic machinery, and cause it to churn out new virus particles, bacteria, or parasites.
- ▶ These pathogens may then also travel systemically by entering the blood.

Site of infection	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
				
Organisms	Viruses Bacteria Protozoa Fungi Worms	<i>Neisseria gonorrhoeae</i> <i>Streptococcus pneumoniae</i> <i>Vibrio cholerae</i> <i>Helicobacter pylori</i> <i>Candida albicans</i> Worms	Viruses <i>Chlamydia</i> spp. <i>Rickettsia</i> spp. Protozoa	<i>Mycobacterium</i> spp. <i>Yersinia pestis</i> <i>Legionella pneumophila</i> <i>Cryptococcus neoformans</i> <i>Leishmania</i> spp.
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA	NK cells Cytotoxic T cells	T-cell and NK-cell dependent macrophage activation

The immune system protects against four classes of pathogens

Type of pathogen	Examples	Diseases
Extracellular bacteria, parasites, fungi	<i>Streptococcus pneumoniae</i> <i>Clostridium tetani</i> <i>Trypanosoma brucei</i> <i>Pneumocystis carinii</i>	Pneumonia Tetanus Sleeping sickness <i>Pneumocystis pneumonia</i>
Intracellular bacteria, parasites	<i>Mycobacterium leprae</i> <i>Leishmania donovani</i> <i>Plasmodium falciparum</i>	Leprosy Leishmaniasis Malaria
Viruses (intracellular)	Variola Influenza Varicella	Smallpox Flu Chickenpox
Parasitic worms (extracellular)	<i>Ascaris</i> <i>Schistosoma</i>	Ascariasis Schistosomiasis

Overview of the Immune System



Interactions between the two systems
Most types of blood cell are components of the immune system

Types of Immune Response

- ▶ The mammalian immune system can mount two types of responses:
- ▶ **innate response** is triggered by disruptions to homeostasis caused by either non-infectious or infectious means
- ▶ **adaptive response** that is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth

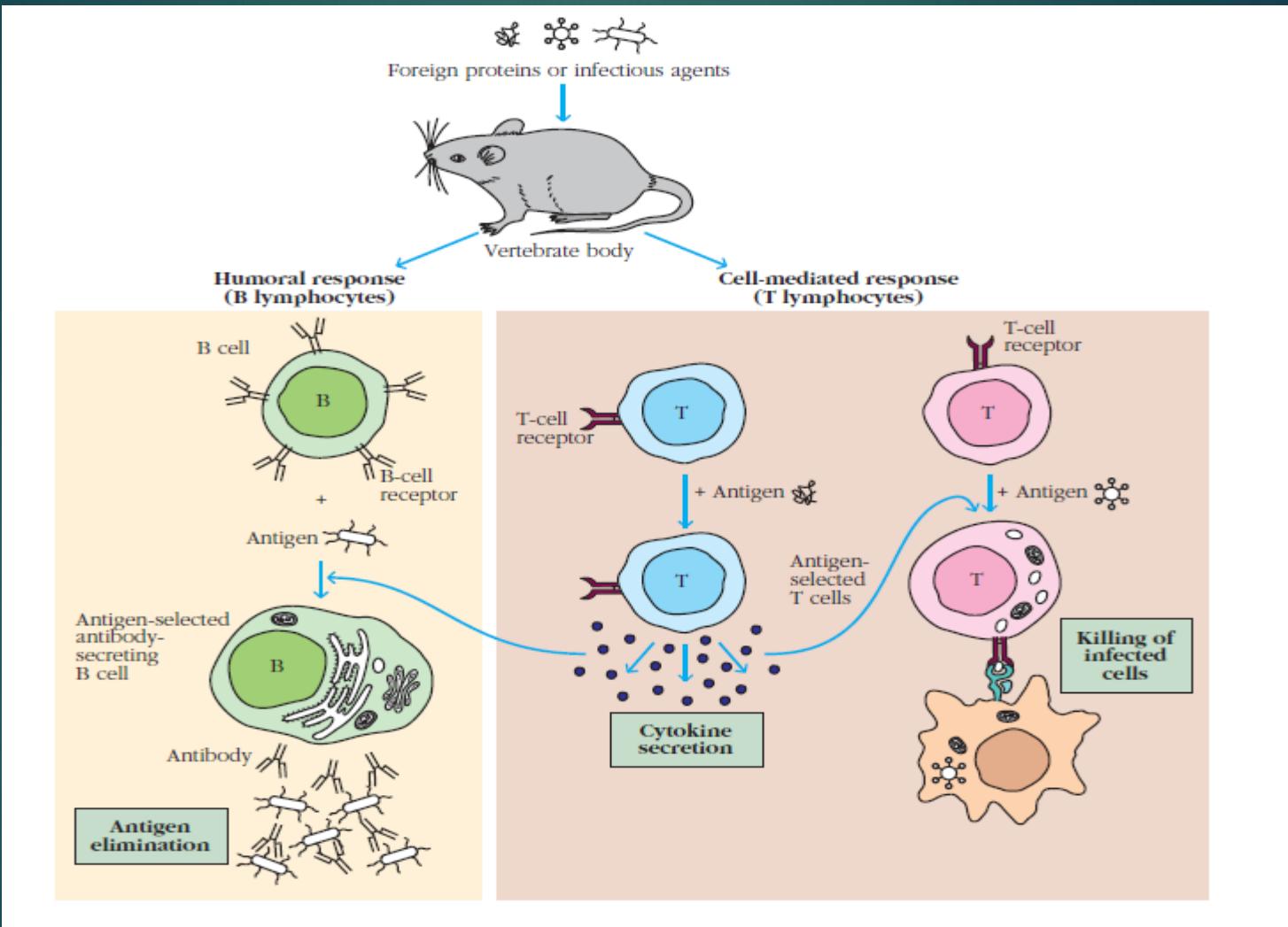
Mechanisms Underlay Immune Responses

- ▶ There were two schools of thought on what mechanisms underlay immune responses.
- ▶ One group of scientists believed that immunity depended primarily on the actions of cells that destroyed or removed unwanted material from the body. This clearance process was referred to as **cell-mediated immunity**.
- ▶ However, another group of researchers was convinced that soluble molecules in the serum of the blood could directly eliminate foreign entities without the need for cellular involvement. In this case, the clearance process was referred to as **humoral immunity**, a term derived from the historical description of body fluids as “humors.”

- ▶ Today, we know that both **cell-mediated** and **humoral responses** occur simultaneously during an immune response and that both are often required for complete clearance of a threat.

- ▶ The cells responsible for cell-mediated immunity are collectively called **leukocytes** or white blood cells.
- ▶ The soluble molecules responsible for humoral immunity are proteins called **antibodies**, and antibodies are secreted by a particular type of leukocyte. In this case a B cell (plasma cell).

Humoral and Cell-mediated Immunity





Introduction to Innate Immune response

Features of Innate Immune Response

- ▶ Barrier Defense
- ▶ Complement Activation
- ▶ Pattern Recognition
- ▶ Inflammation
- ▶ Phagocytosis

Innate immunity:

- Skin, mucous membranes, saliva
- Cough, sneeze, & vomiting reflexes
- Acidic pH of tissues
- Fever
- Interferon and other substances released by leukocytes; several plasma proteins
- Natural killer cells, macrophages; CNS microglia

Components of the Innate Host Defenses

- Anatomical barriers
 - Mechanical factors
 - Chemical factors
 - Biological factors
- Humoral components
 - Complement
 - Coagulation system
 - Cytokines
- Cellular components
 - Neutrophils
 - Monocytes and macrophages
 - NK cells
 - Eosinophils

Anatomical Barriers - Mechanical Factors

System or Organ	Cell type	Mechanism
Skin	Squamous epithelium	Physical barrier Desquamation
Mucous Membranes	Non-ciliated epithelium (e.g. GI tract)	Peristalsis
	Ciliated epithelium (e.g. respiratory tract)	Mucociliary elevator
	Epithelium (e.g. nasopharynx)	Flushing action of tears, saliva, mucus, urine

Anatomical Barriers - Chemical Factors

System or Organ	Component	Mechanism
Skin	Sweat	Anti-microbial fatty acids
Mucous Membranes	HCl (parietal cells) Tears and saliva	Low pH Lysozyme
	Defensins (respiratory & GI tract)	Antimicrobial
	Surfactants (lung)	Opsonin

Anatomical Barriers - Biological Factors

System or Organ	Component	Mechanism
Skin and mucous membranes	Normal flora	Antimicrobial substances Competition for nutrients and colonization

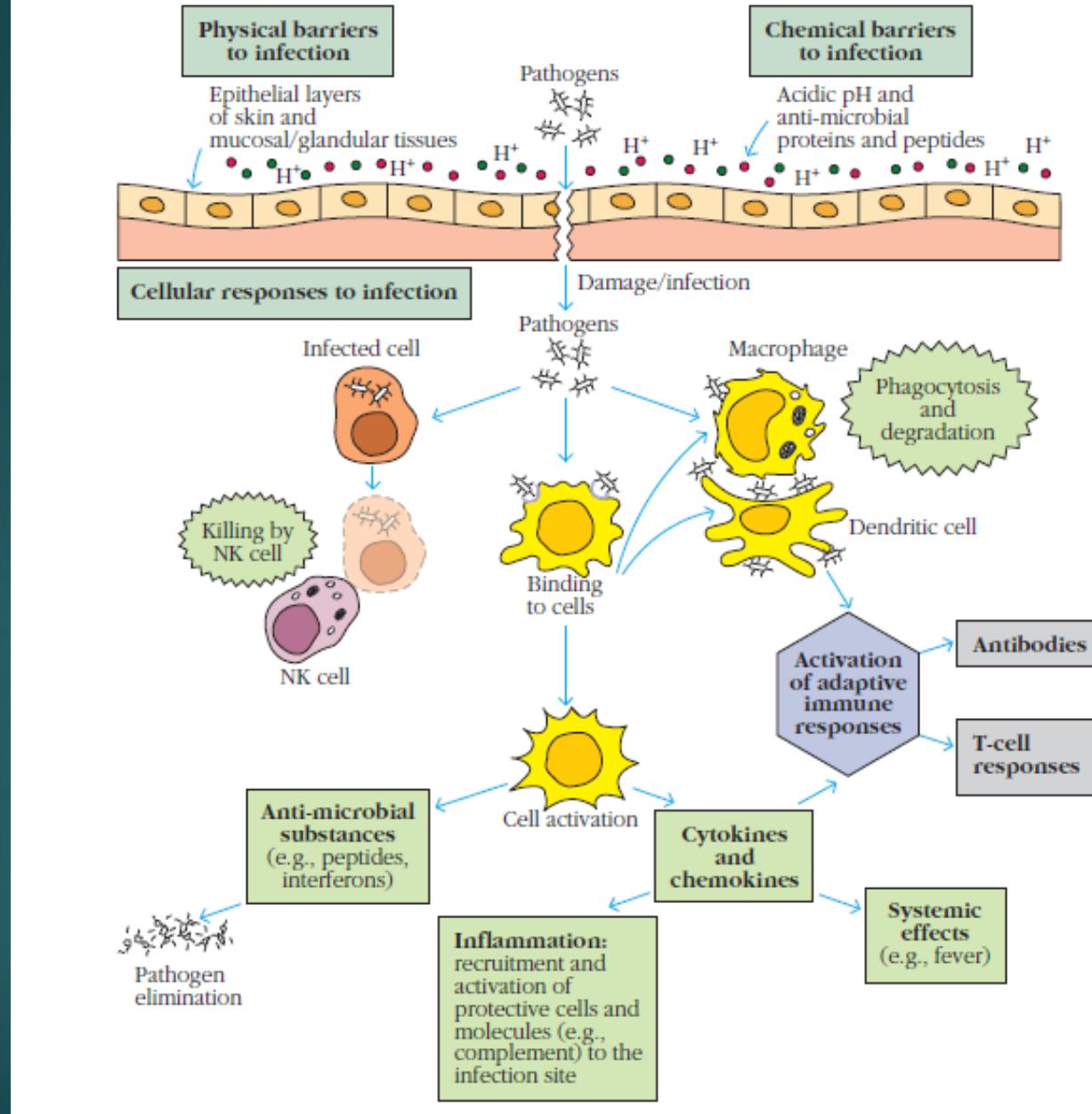
Humoral Components

Component	Mechanism
Complement	Lysis of bacteria and some viruses Opsonin Increase in vascular permeability Recruitment and activation of phagocytic cells
Coagulation system	Increase vascular permeability Recruitment of phagocytic cells
Lysozyme	Breaks down bacterial cell walls
Cytokines	Various effects

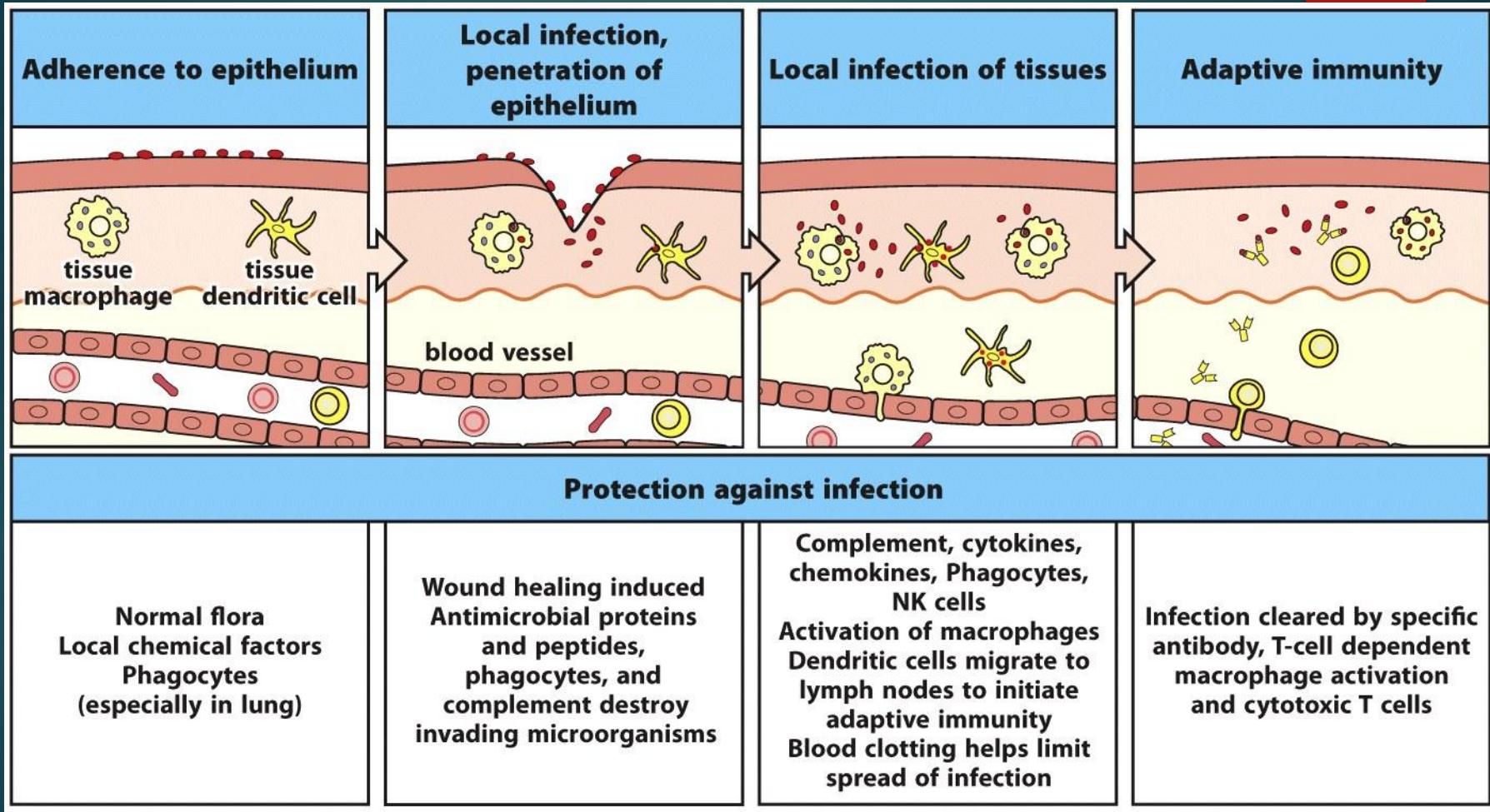
Cellular Components

Cell	Functions
Neutrophils	Phagocytosis and intracellular killing Inflammation and tissue damage
Macrophages	Phagocytosis and intracellular killing Extracellular killing of infected or altered self targets Antigen presentation for specific immune response
NK	Killing of virus-infected and altered self targets
Eosinophils	Killing of some parasites

Innate Immunity

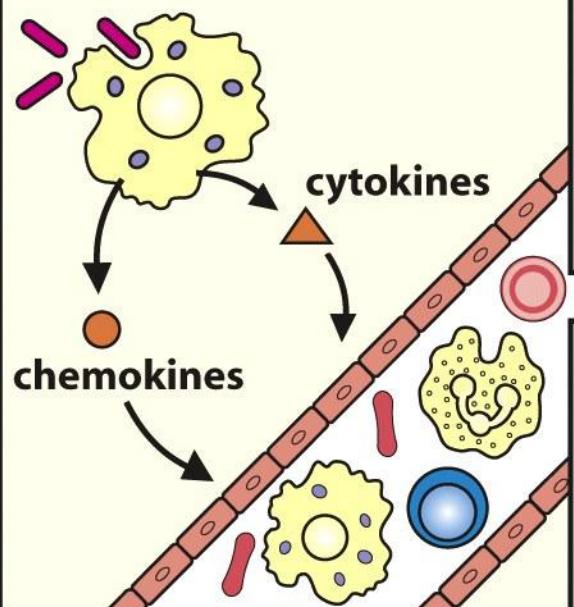


Protection Against Infection

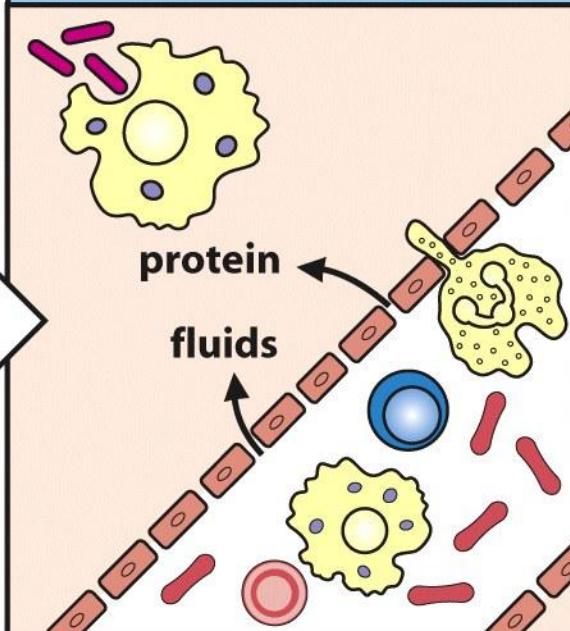


Infection triggers an inflammatory response

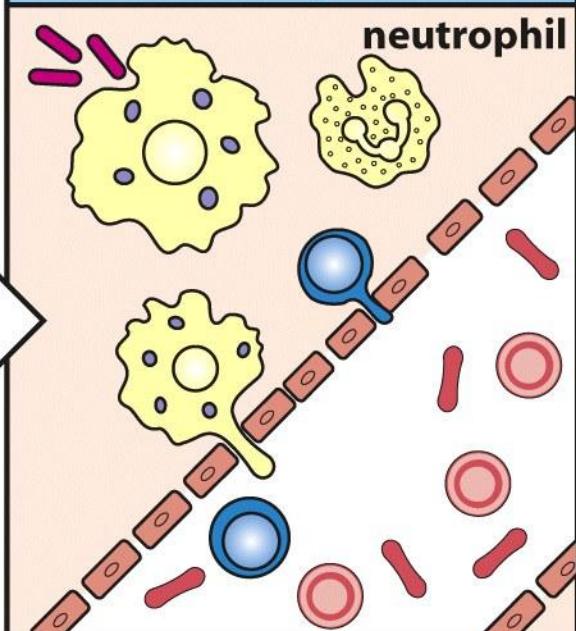
Bacteria trigger macrophages to release cytokines and chemokines



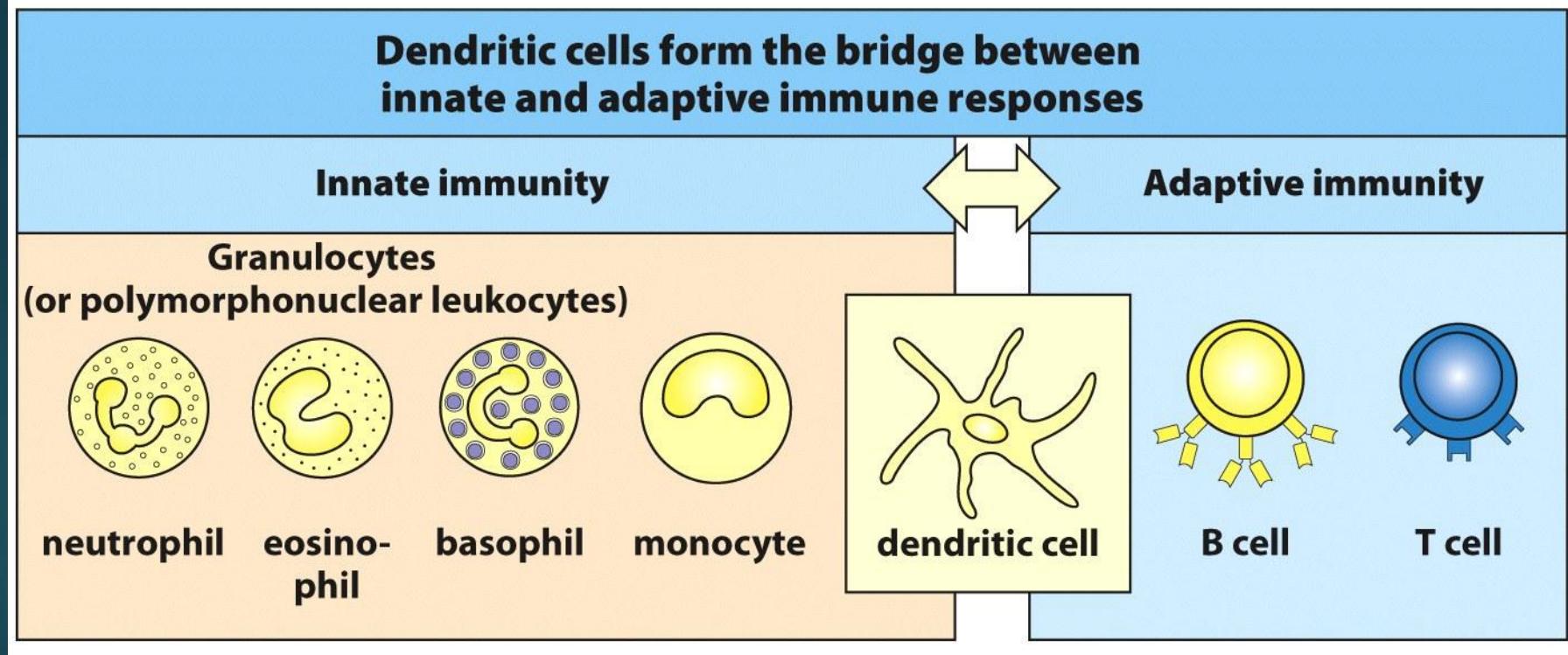
Vasodilation and increased vascular permeability cause redness, heat, and swelling



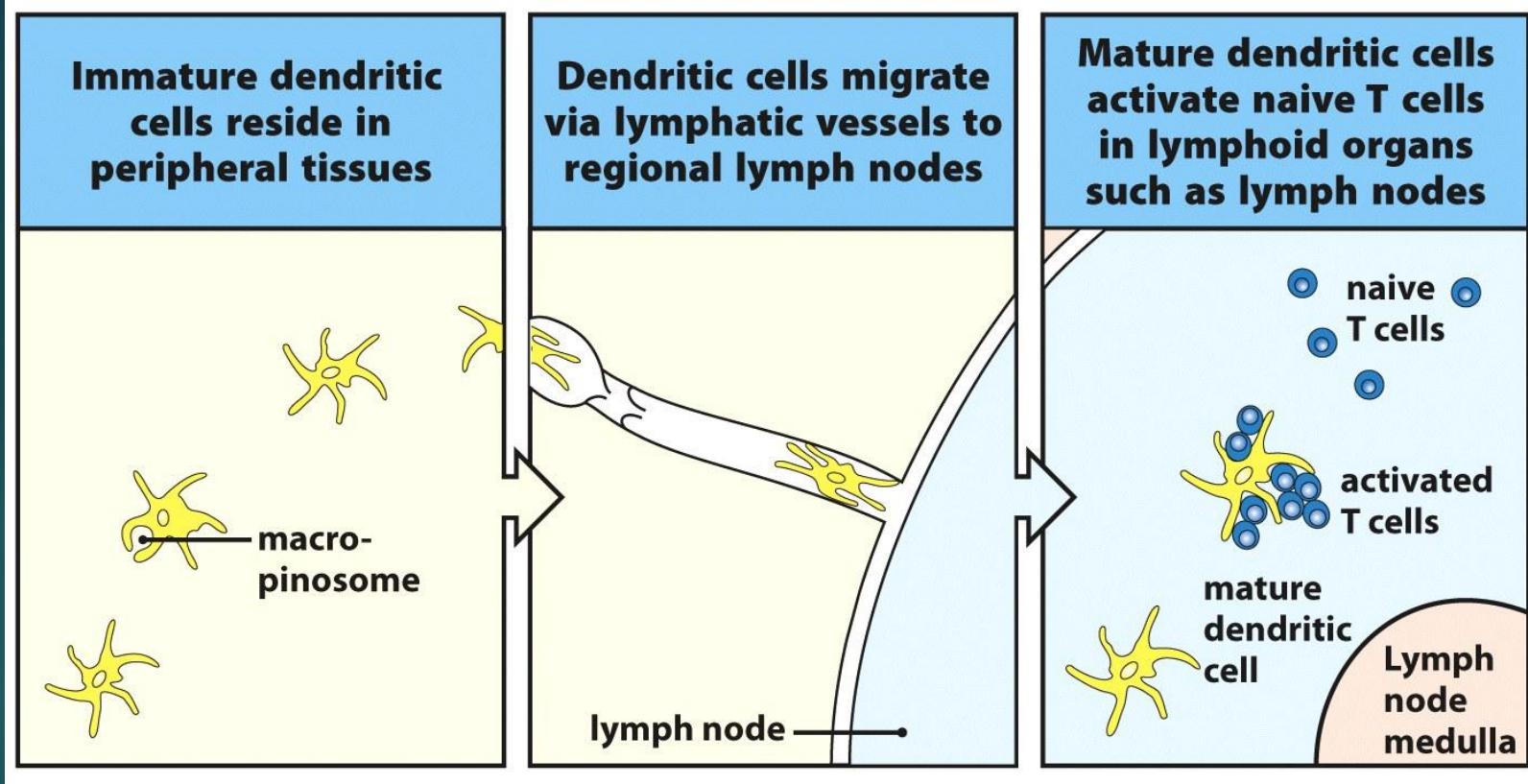
Inflammatory cells migrate into tissue, releasing inflammatory mediators that cause pain



Dendritic cells link the Innate and the Adaptive immune system



Dendritic cells form the bridge between innate and adaptive immune responses



Infection → Activation
Sensing infections (innate function)

Antigen → specific T cell
Activation (adaptive function)

The course of a typical infection and adaptive immune responses can be divided into phases

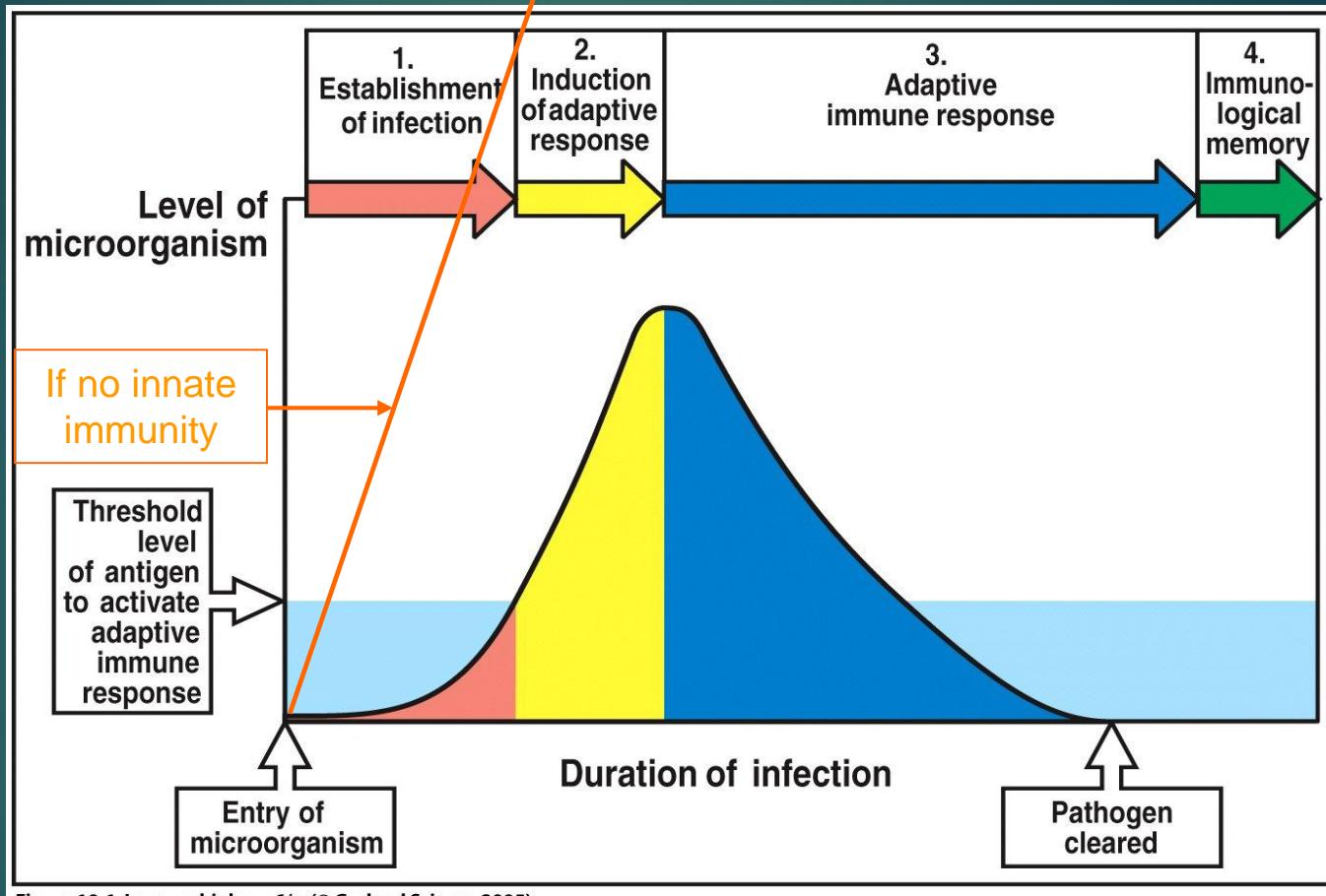


Figure 10-1 Immunobiology, 6/e. (© Garland Science 2005)

Protective immunity* consists of preformed immune reactants and immunological memory

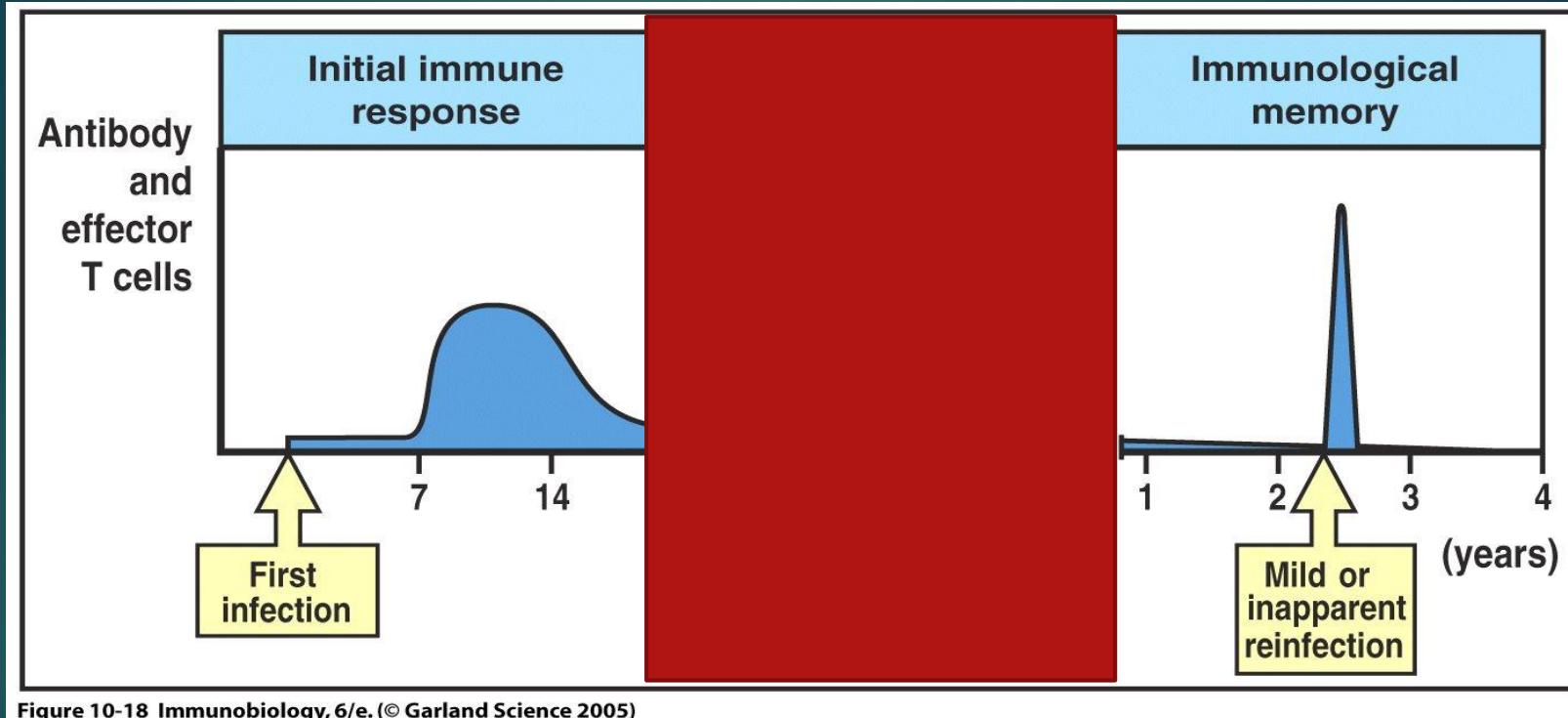
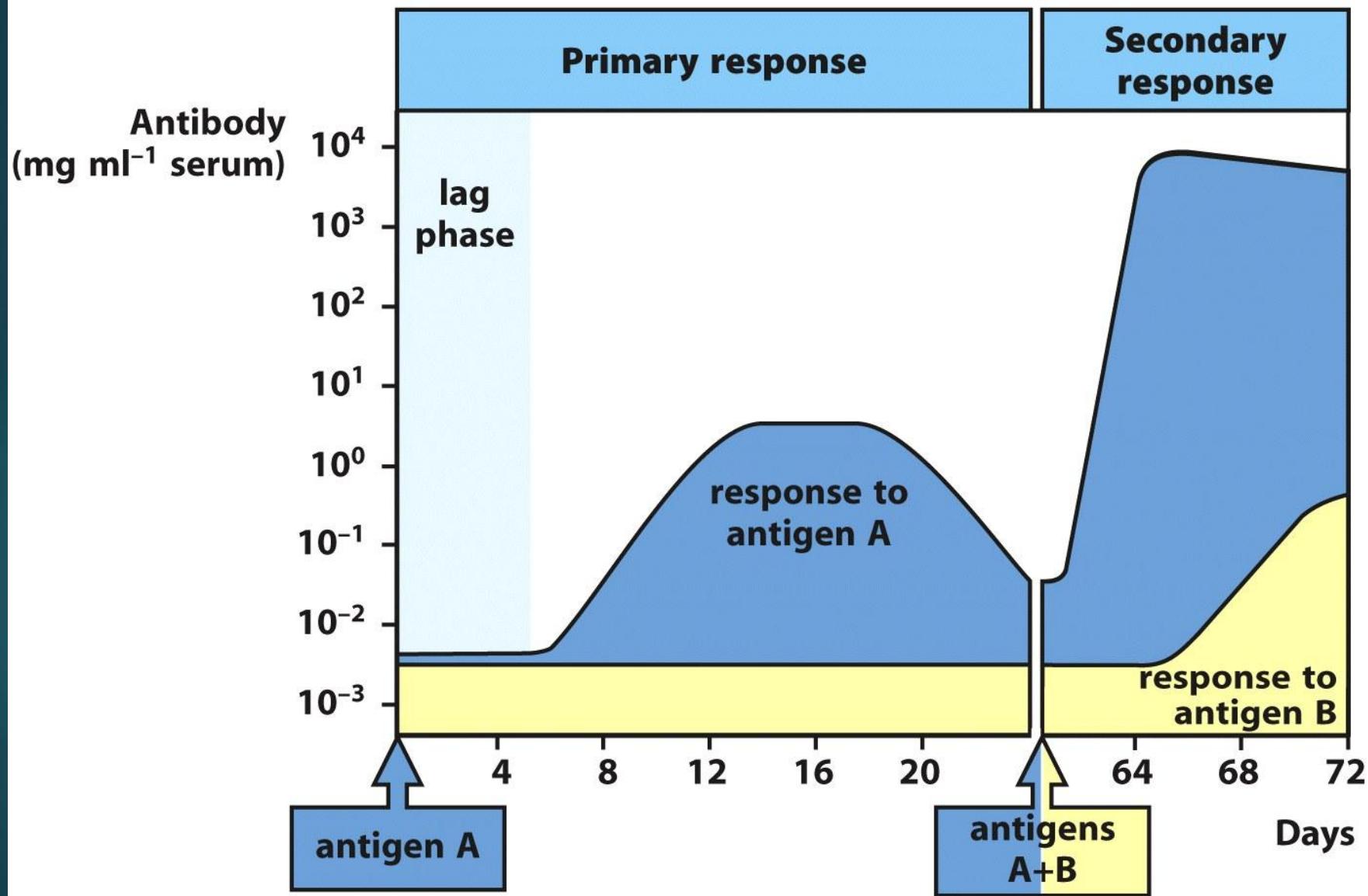


Figure 10-18 Immunobiology, 6/e. (© Garland Science 2005)

*The resistance to specific infection that follows infection or vaccination

The course of a typical antibody response



Infection and Immunity Balance

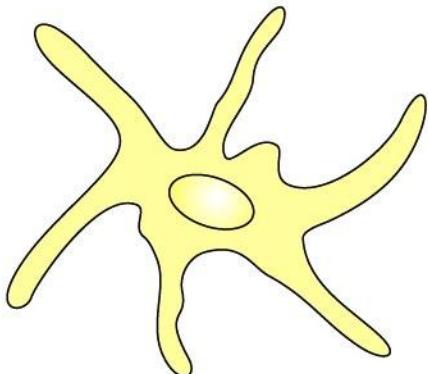
infection

immunity

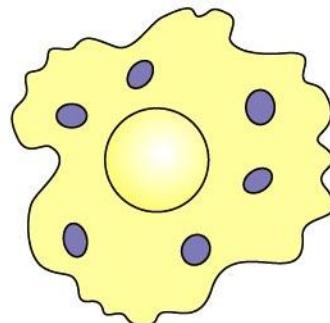


Antigen Presenting Cells

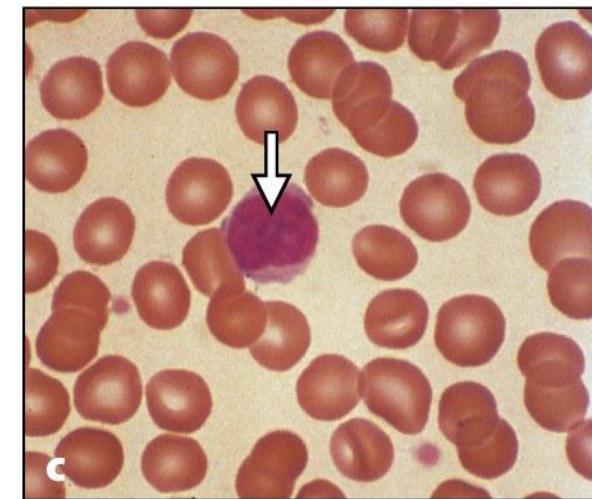
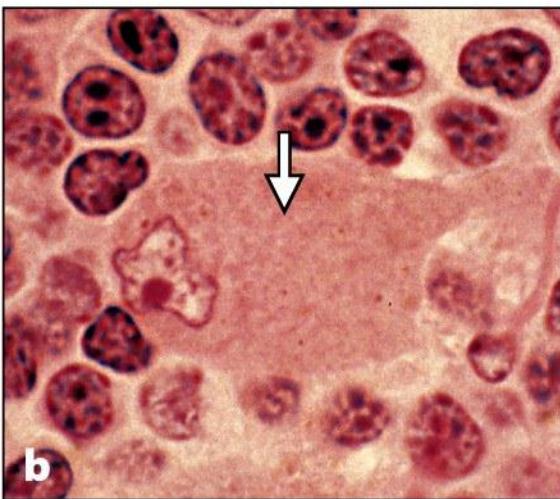
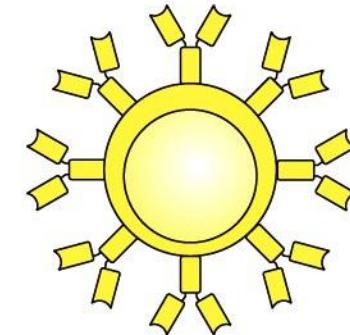
Dendritic cell



Macrophage



B lymphocyte



Acquired immunity

- Present only in vertebrates
- Generally one is born with capacity to respond, but defense is triggered only if organism had prior experience with the invader.
- Discovered by Edward Jenner (18th century):
 - Injected a boy with pus from dairy maid w/ cow pox.
 - Boy later exposed to small pox; he didn't catch it.
 - Vaccination.

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.

Types of Acquired Immunity (Continued)

II. Artificially Acquired Immunity: Obtained by receiving a vaccine or immune serum.

1. Artificially Acquired Active Immunity:

Antigens are introduced in vaccines (**immunization**).

Body generates an immune response to antigens.

Immunity can be lifelong (oral polio vaccine) or temporary (tetanus toxoid).

2. Artificially Acquired Passive Immunity:

Preformed **antibodies** (**antiserum**) are introduced into body by injection.

Snake anti-venom injection from horses or rabbits.

Immunity is short lived (half life three weeks).

Host immune system does not respond to antigens.

Features of Adaptive Response

- ▶ Specificity
- ▶ Division of Labor
- ▶ Immunological Memory
- ▶ Tolerance (central and peripheral)
- ▶ Faster response

Organs of immune system

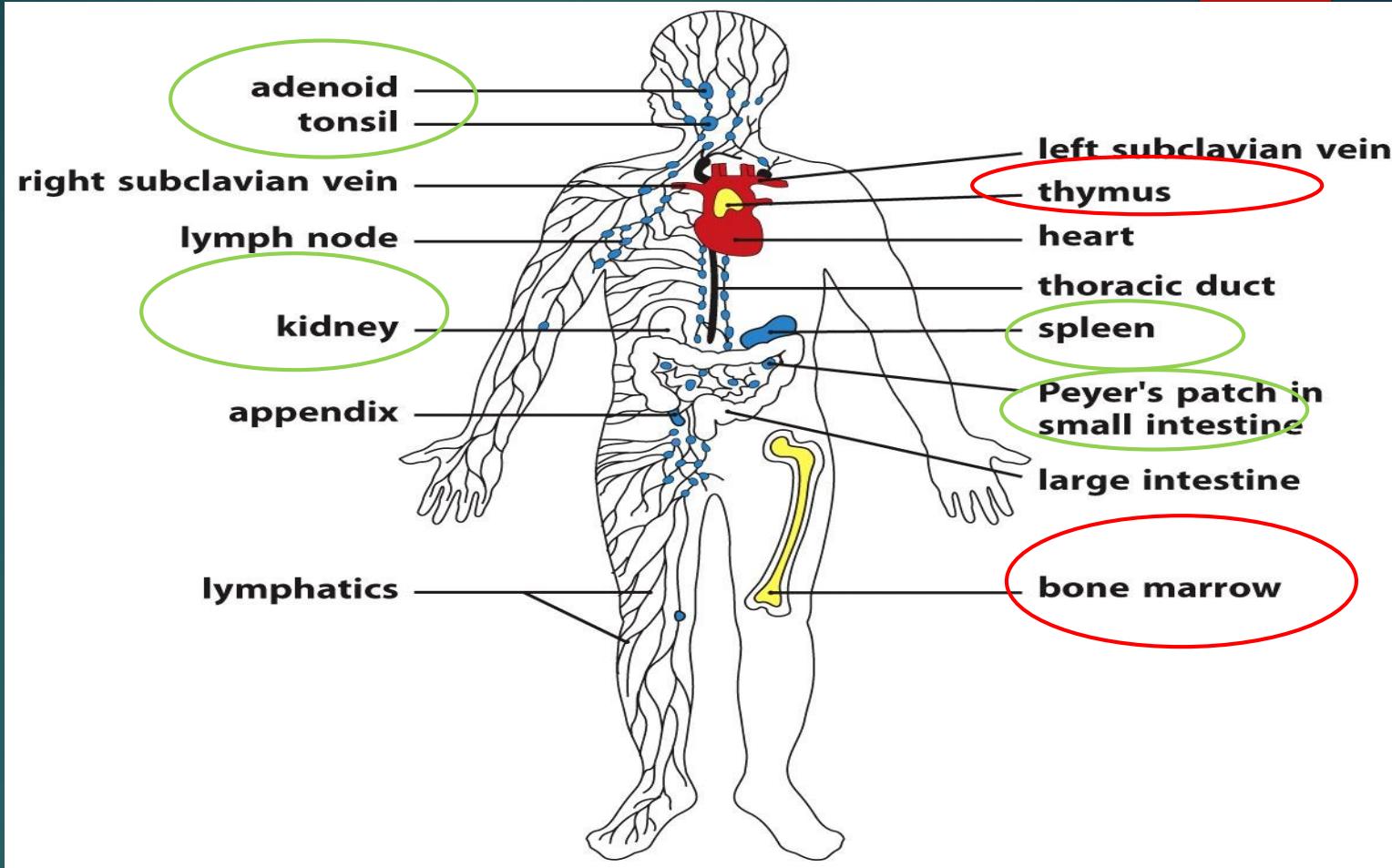
- Thymus: behind sternum (breast bone)
 - Immature T cells mature here. 90% die because they recognize “self” proteins
- Bone marrow: stem cells divide to produce immune system cells

Organs of immune system

- Lymphatic system
 - Transport lymph: interstitial spaces to blood
 - Lymph nodes: enlarged spaces where foreign substances are trapped & phagocytized
- Spleen: upper left abdomen
 - Blood filter, storage for lymphocytes
 - Large phagocytic cells devour old red blood cells, bacteria, cell particles, toxins
 - Antibodies made and released here

Distribution of lymphoid tissues in the body

The distribution of lymphoid
tissues in the body

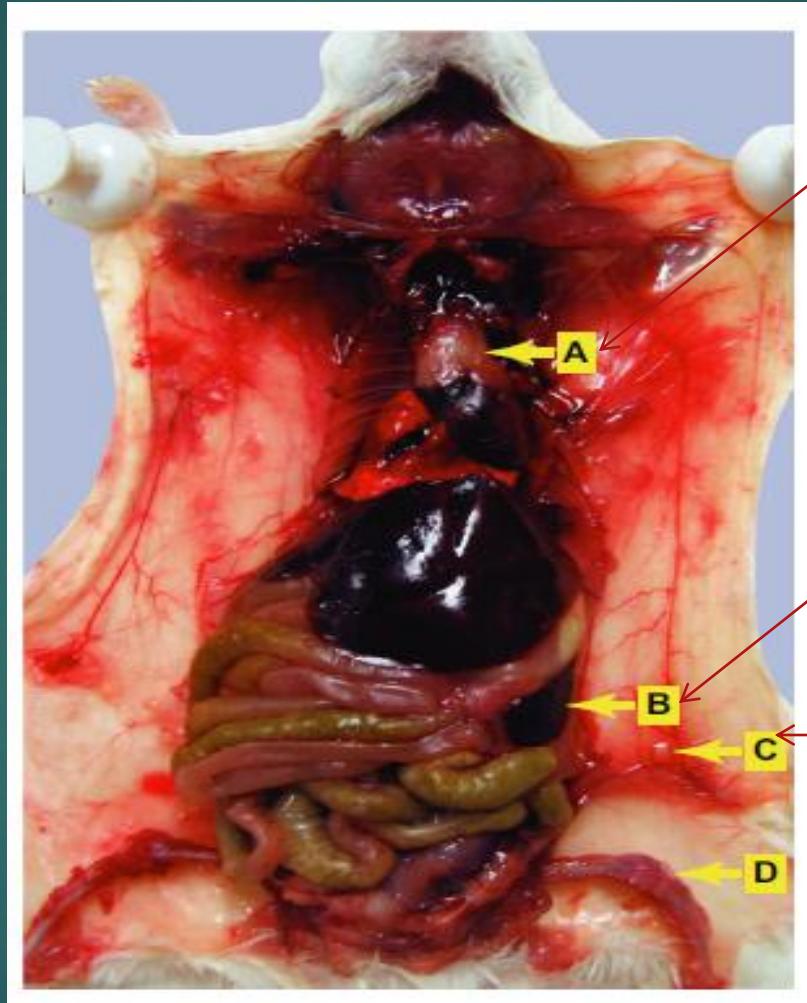


**Primary lymphoid
tissues**

**Secondary lymphoid
tissues**

MALT, BALT
GALT
NALT
SALT

Primary and Secondary Lymph organs



Thymus

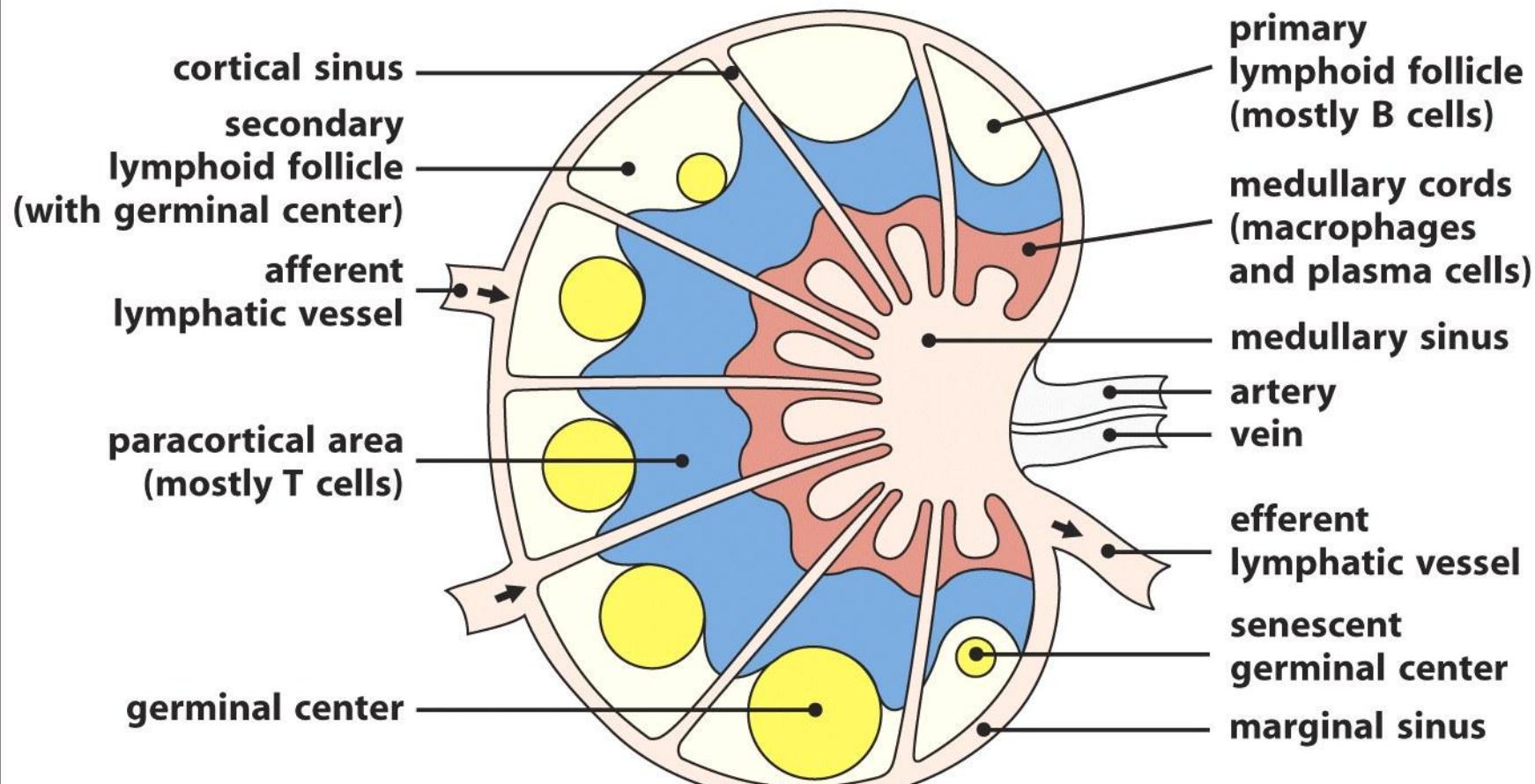
Spleen

Lymph
node

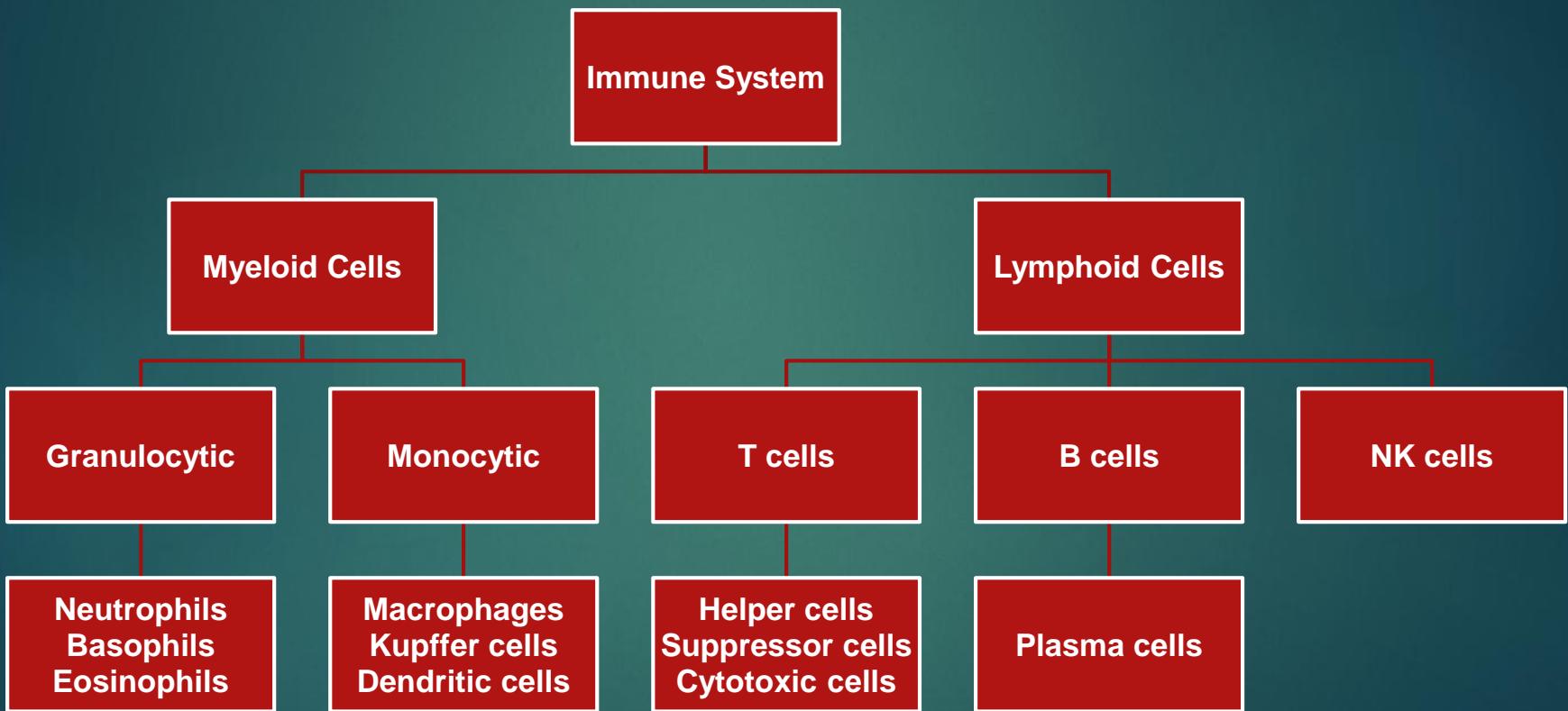
Bone
Barrow

Organization of a lymph node

A lymph node



Cells of the Immune System



Cells of the Immune System

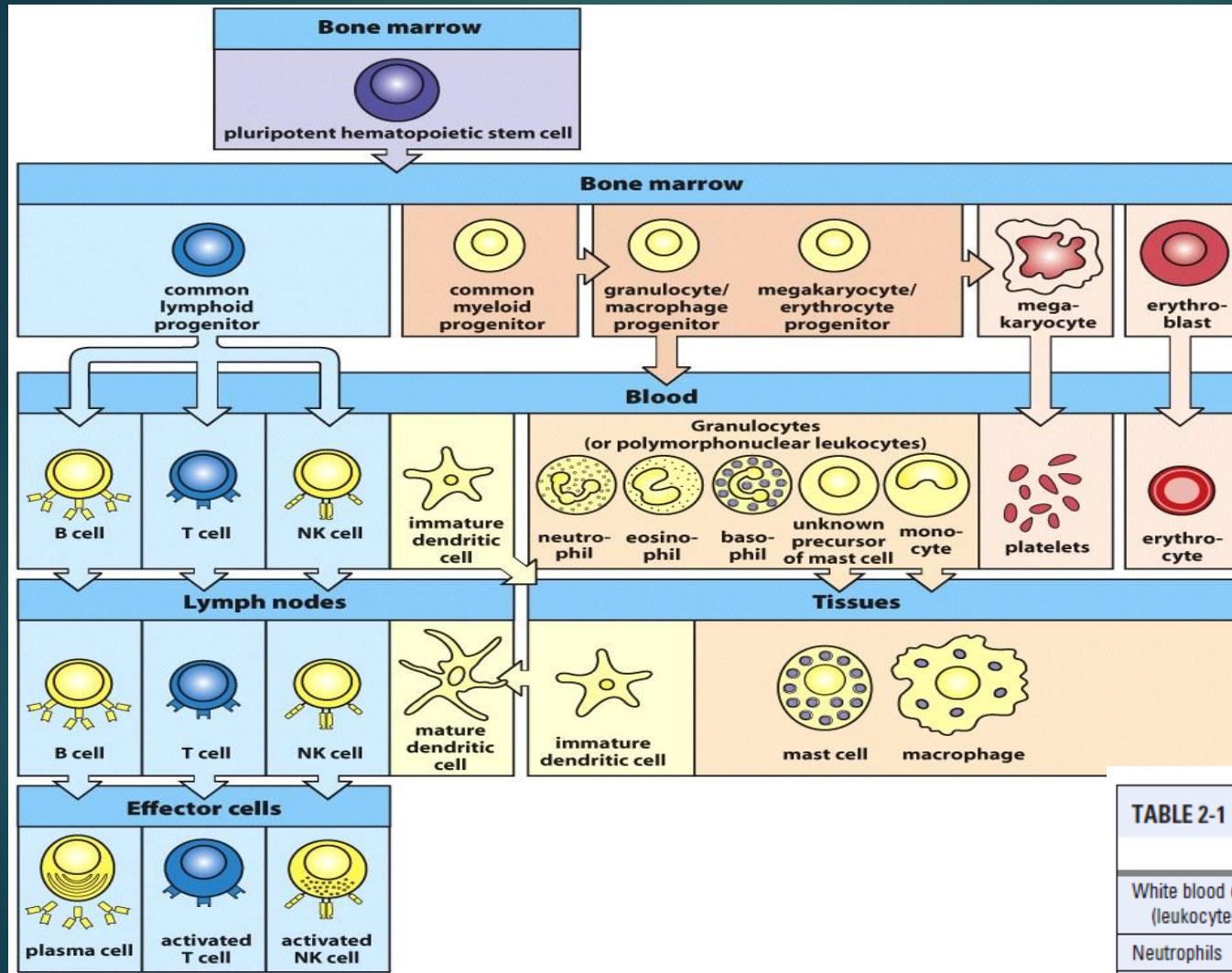
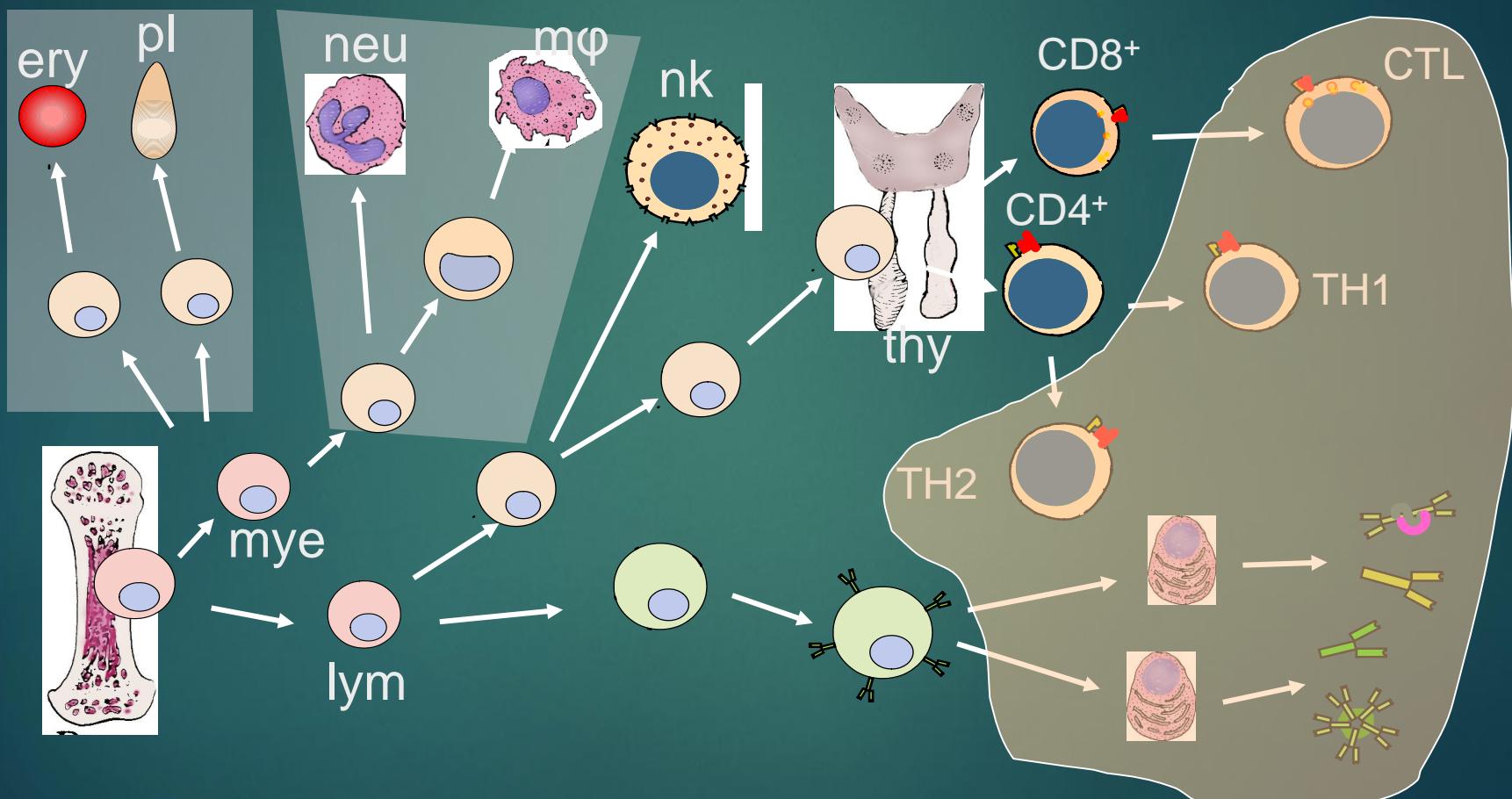
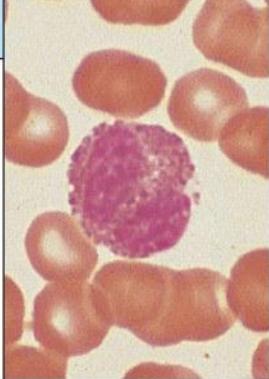
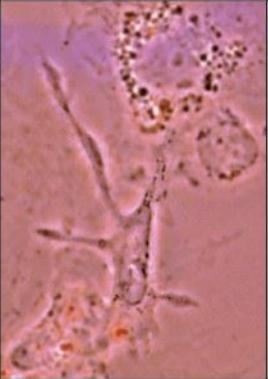
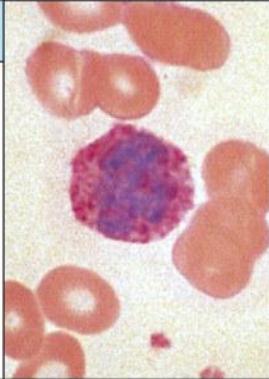
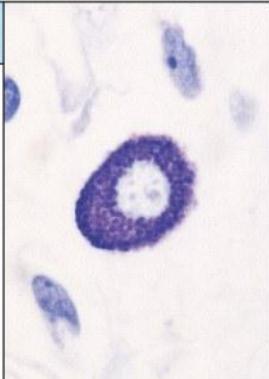


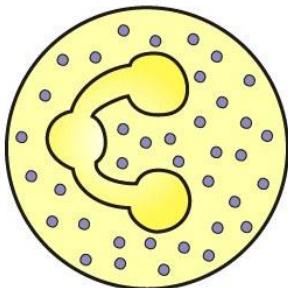
TABLE 2-1 Normal Blood Cell Counts

	Mean Number per Microliter	Normal Range
White blood cells (leukocytes)	7400	4500–11,000
Neutrophils	4400	1800–7700
Eosinophils	200	0–450
Basophils	40	0–200
Lymphocytes	2500	1000–4800
Monocytes	300	0–800

Development of the Immune System



Cell		Activated function	Cell		Activated function
Macrophage		<p>Phagocytosis and activation of bactericidal mechanisms</p> <p>Antigen presentation</p>	Eosinophil		Killing of antibody-coated parasites
Dendritic cell		<p>Antigen uptake in peripheral sites</p> <p>Antigen presentation</p>	Basophil		Promotion of allergic responses and augmentation of anti-parasitic immunity
Neutrophil		Phagocytosis and activation of bactericidal mechanisms	Mast cell		Release of granules containing histamine and active agents

Cell	Activated function
Neutrophil	
	 <p data-bbox="1263 457 1685 731">Phagocytosis and activation of bactericidal mechanisms</p>

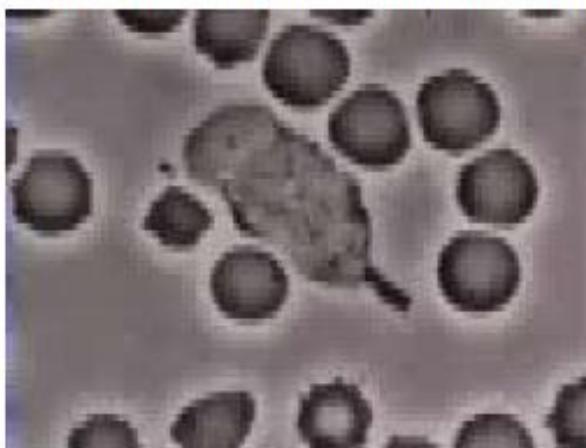
Neutrophils or PMN: polymorphonuclear leukocytes

Cells in blood stream, not in healthy tissues

Become attracted by activated macrophages

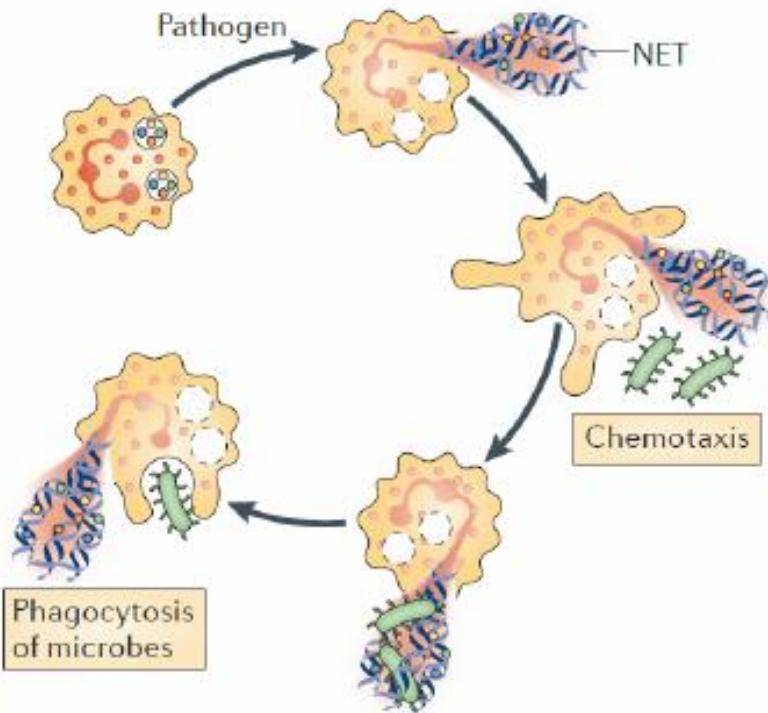
Neutrophil Recruitment

Crawling Neutrophil chasing bacterium

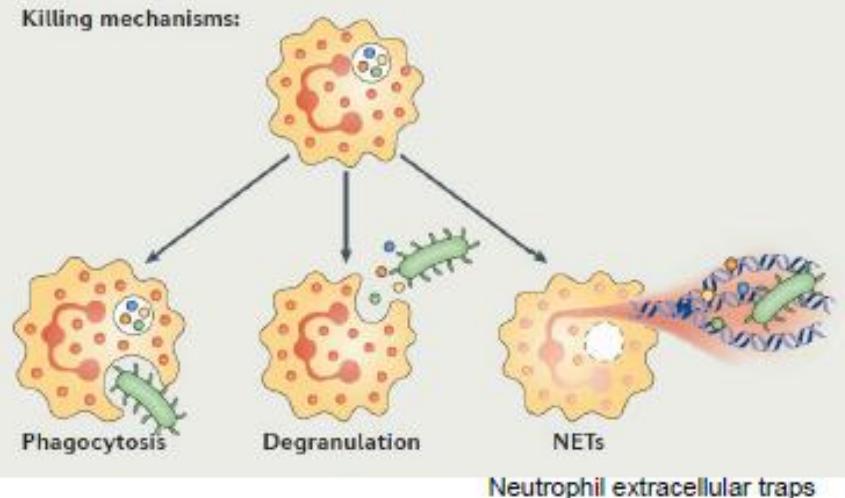


David Rogers, Vanderbilt University

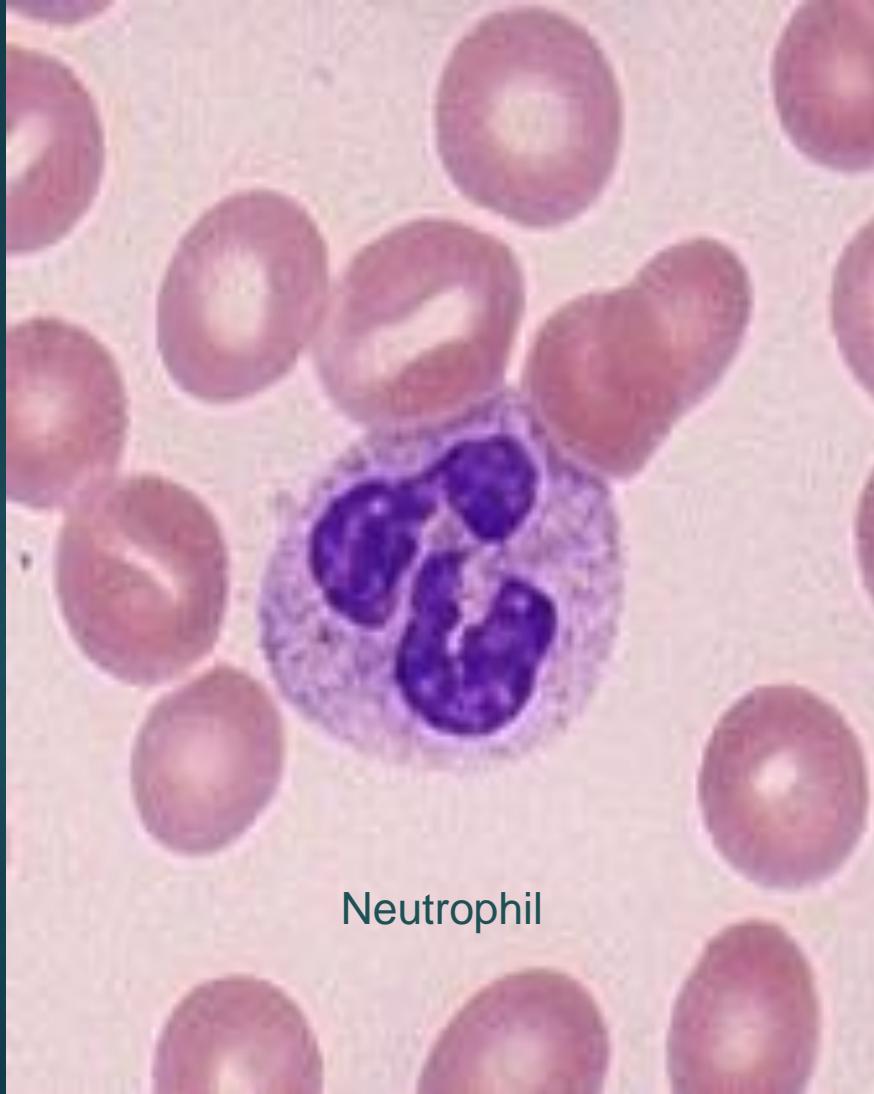
Behaviour of neutrophils that formed NETs *in vivo*



Killing mechanisms:



Catching and immobilization
of microbes (possibly directly
killing them)

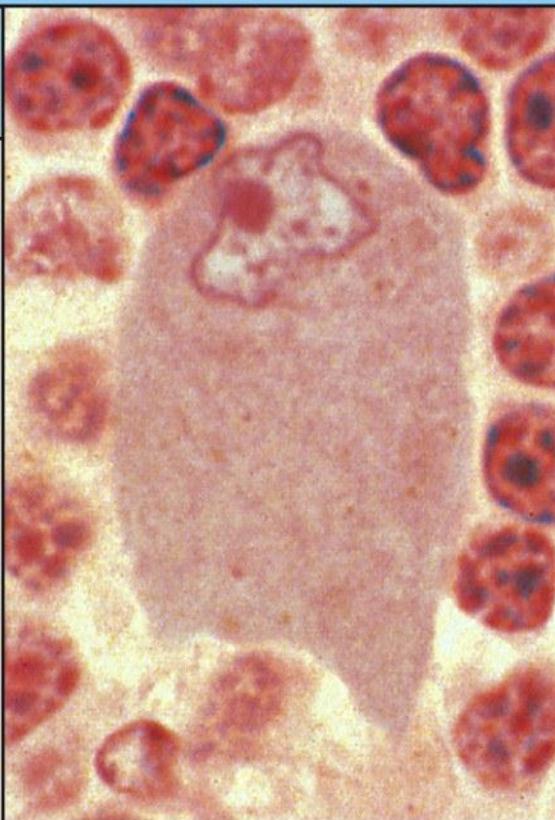
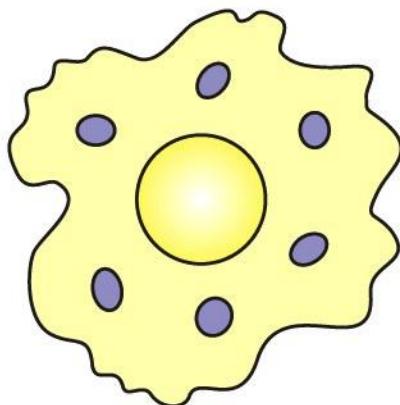


Neutrophils

- polymorphonuclear leukocytes
- 4 to 10 million per ml of blood
- Main role is to get to the site of infection rapidly and ingest microorganisms
- Infection activates the bone marrow to produce more (20 million/ml of blood) through cytokine stimulation
- After taking up microorganisms the neutrophil will die.

Cell

Macrophage



Activated function

**Phagocytosis
and activation
of bactericidal
mechanisms**

**Antigen
presentation**

Monocytes

0.5 to 1 million monocytes per ml of blood

Migrate into the tissues and differentiate into
Macrophages

Phagocytose microorganisms

Differentiate to macrophages

Present antigens to T cells

The name of monocyte-derived cells depends
upon the tissue they reside in:

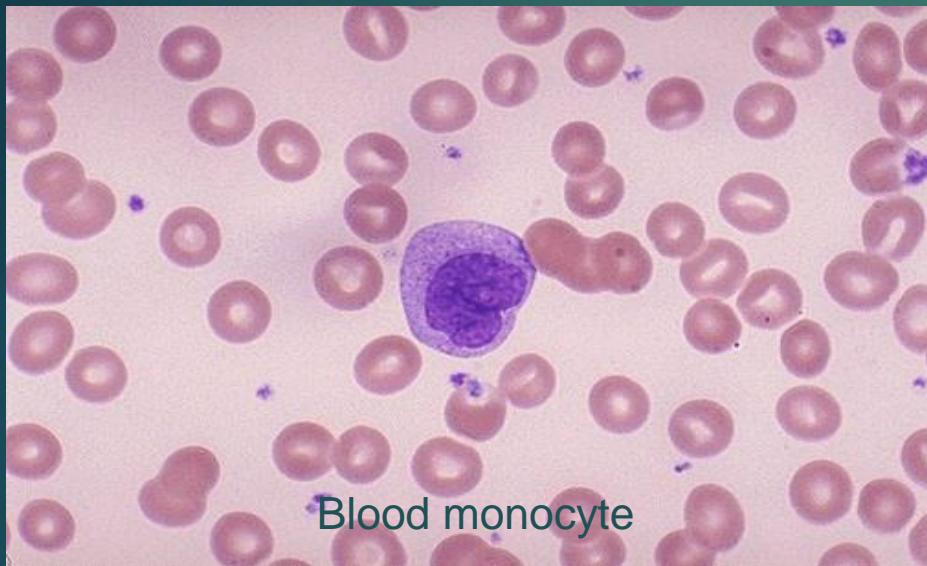
Liver - Kupffer cells

Lung - Alveolar macrophages

CNS - Microglial cells

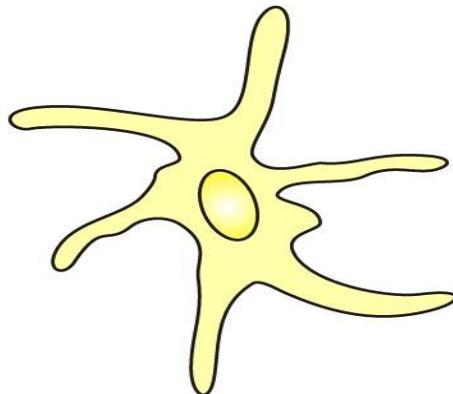
Bone - Osteoclasts

Human Macrophage ingesting yeast



Cell

Dendritic cell

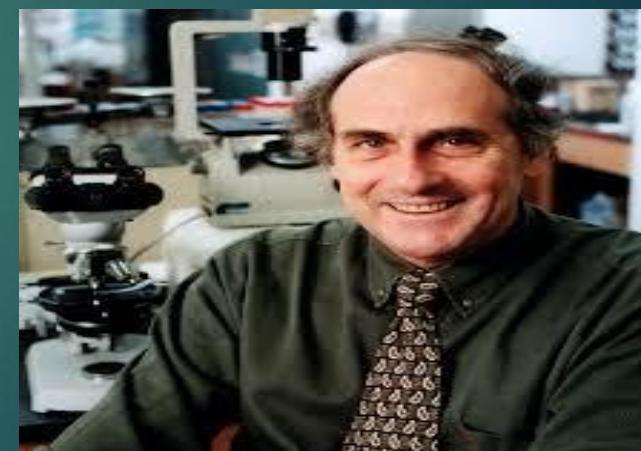


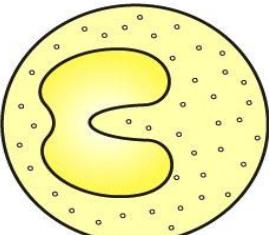
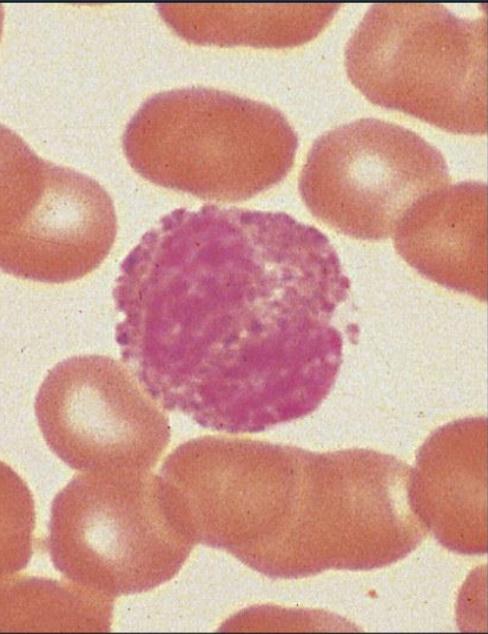
Activated function

Antigen uptake in peripheral sites

Antigen presentation

DCs were first characterized by Ralph Steinman. Dr. Steinman was awarded a share in the 2011 Nobel Prize in Physiology or Medicine for his seminal work.

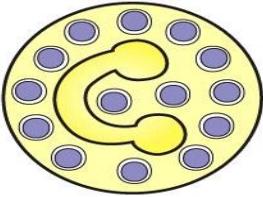
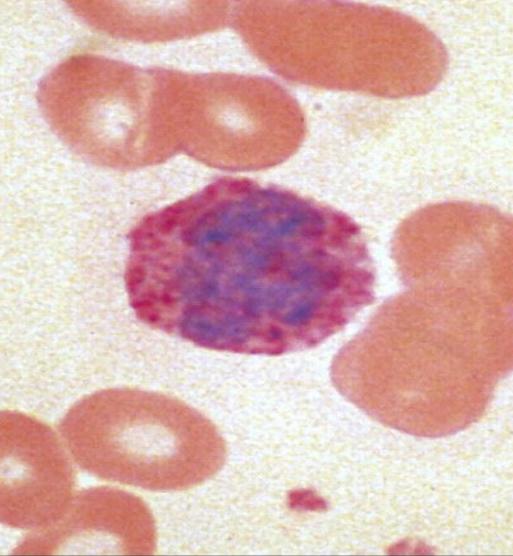


Cell	Activated function
Eosinophil	  <p>Killing of antibody-coated parasites</p>

Contain granula with argini-rich basic proteins, which can be stained by eosin

In peripheral tissue, low numbers in blood

After activation, they release granula with toxic substances that kill microorganisms esp. parasites but can also damage host in allergy; release cytokines to attract other cells

Cell	Activated function
Basophil	
	 <p>Promotion of allergic responses and augmentation of anti-parasitic immunity</p>

Function similar to Eosinophils (common precursor) but differentiation is mediated by other cytokines (e.g. IL-3)
 low numbers in blood, recruitment and activation by cytokines, Fc receptor
 recognizes Ab-conjugated antigens, secretion of toxic granules

Natural Killer (NK) cells

Non-T, non-B cells

No classical antigen receptors

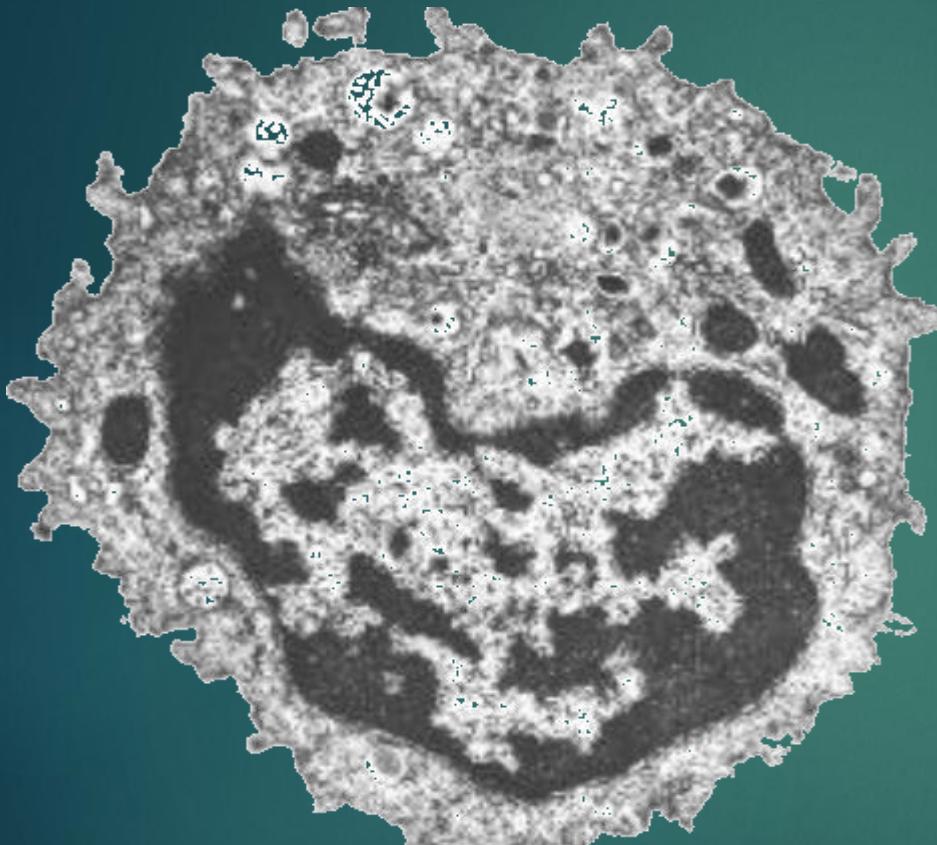
Part of the innate immune system

Recognise and kill abnormal cells such as
tumour cells

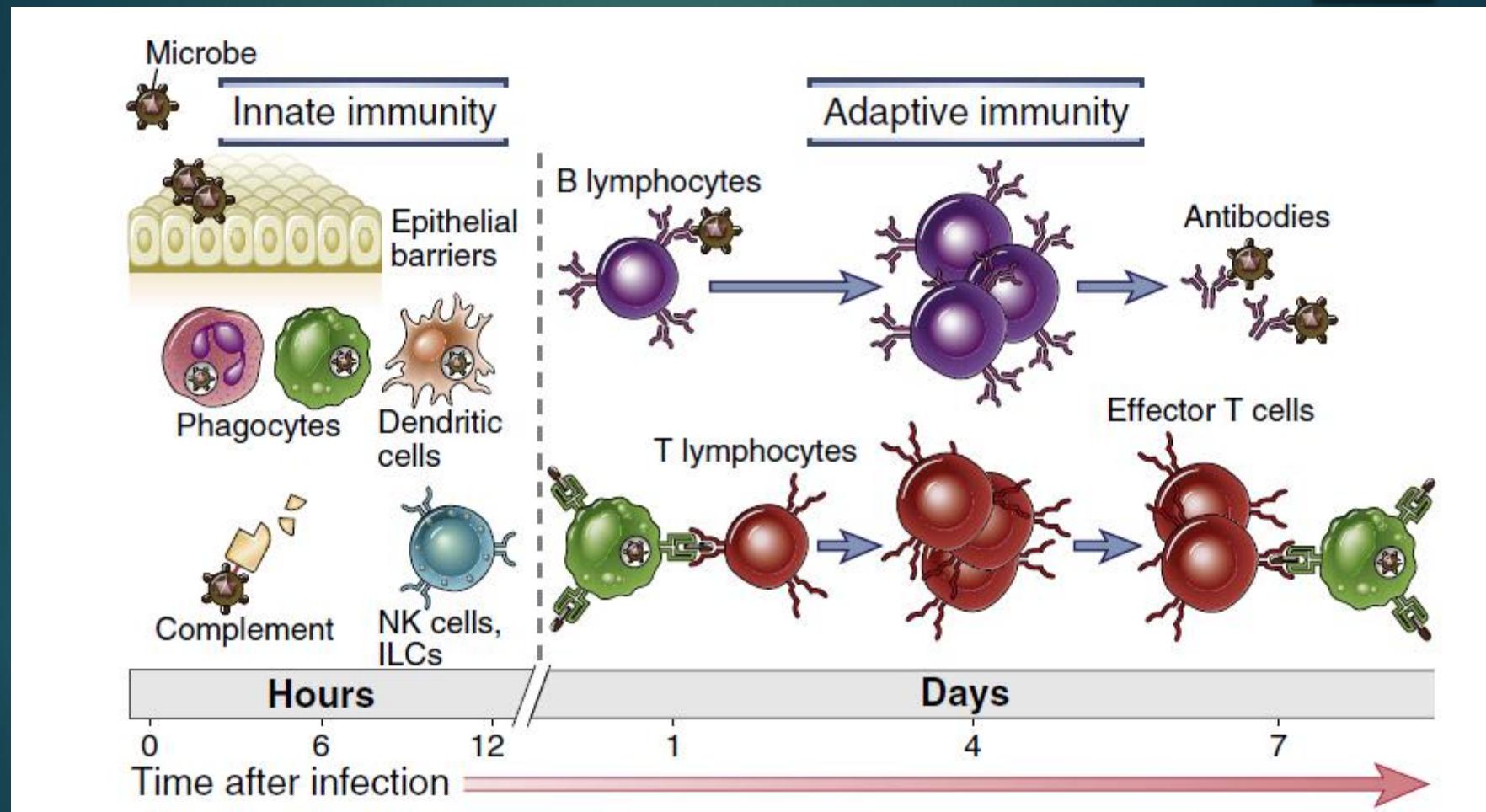
Directly induce apoptosis in virus infected
cells by pumping proteases through pores
that they make in target cells

Similar cytolytic mechanisms to cytotoxic T
lymphocytes (CTL)

Involved in antibody-dependent cellular
cytotoxicity (ADCC)



Innate and Adaptive Immunity



Phases of the immune response			
Response		Typical time after infection to start of response	Duration of response
Innate immune response	Inflammation, complement activation, phagocytosis and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Effector cells and antibodies eliminate the pathogen	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Comparison of Innate and Adaptive Immunity

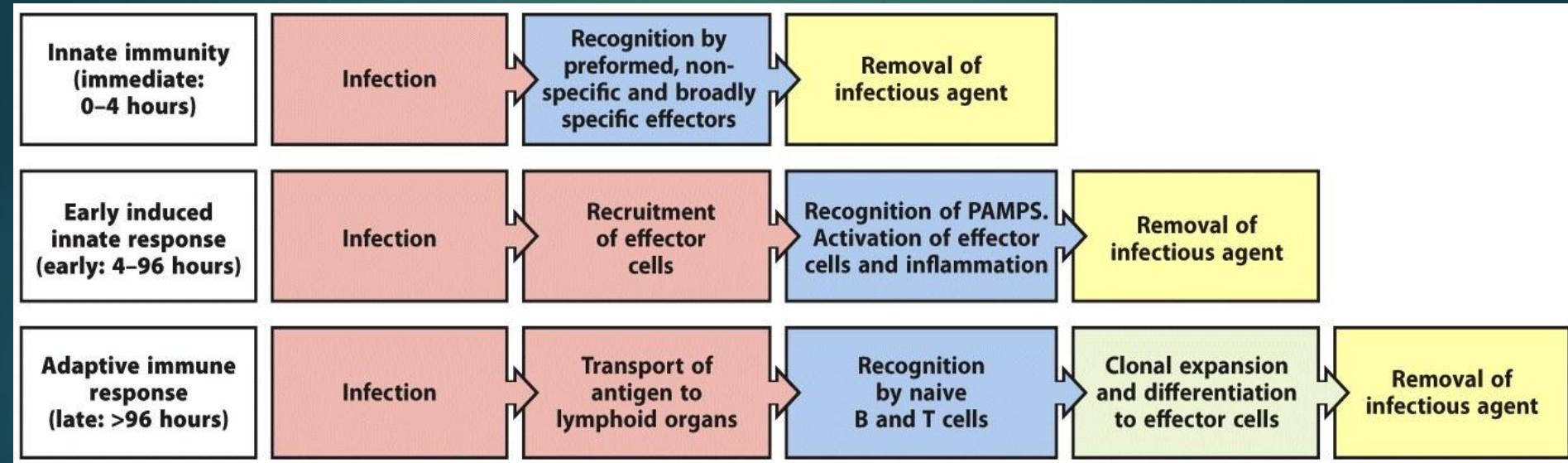
Innate Immunity

- No time lag
- Not antigen specific
- No memory

Adaptive Immunity

- A lag period
- Antigen specific
- Development of memory

Summary



Questions

- ▶ What is the difference between infection and disease
- ▶ What is the major difference between extracellular and intracellular pathogens?
- ▶ Distinguish between cell-mediated and humoral immunity
- ▶ Describe 3 important features of adaptive immunity
- ▶ What are the two stages of tolerance ?
- ▶ Distinguish between PAMPs and PRR
- ▶ Is inflammation good or bad, and why?

Quiz I (15.09.2016)

- ▶ 1. Name the two types of immune response
- ▶ 2. List the 2 mechanisms underlying host immune responses
- ▶ 3. List two examples of intracellular pathogens
- ▶ 4. In your own words define immunity?
- ▶ 5. The second line of defense of the immune response is referred to as.....
- ▶ 6. Give two features of adaptive immune response