

BCHEM 471

Immunology

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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 will be presented to give a general overview of functional immunity.
- ▶ Components and systems will be defined to allow an understanding of concepts of innate (always present) and adaptive (inducible and specific) 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***.

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

- ▶ At about the same time, Louis Pasteur applied Jenner's immunization technique for smallpox to the prevention of various animal diseases.
- ▶ Pasteur demonstrated that inoculation with a pathogen that had been weakened in the laboratory could protect against a subsequent exposure to the naturally occurring pathogen.
- ▶ It was Pasteur who coined the term **vaccination** (from the Latin *vaccinus*, meaning “derived from cows”) for this procedure, in honor of Jenner’s work.
- ▶ The research of Pasteur and other investigators spurred the evolution of immunology as a science distinct from (but related to) the established fields of microbiology, pathology, biochemistry and histology



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

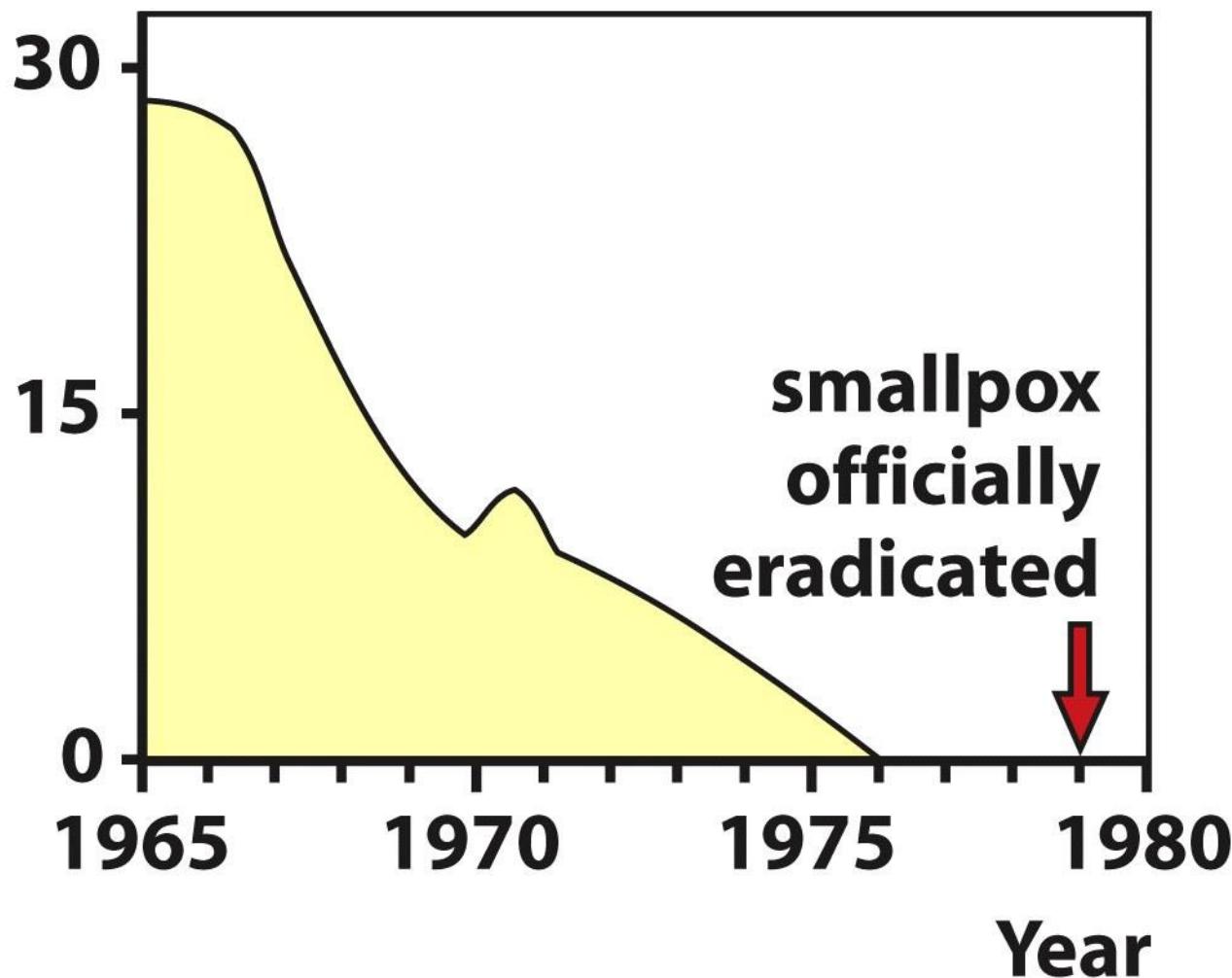


Smallpox infection in Bangladesh girl in 1973



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.

- ▶ At its simplest level, this response involves identifying and clearing damaged and dying cells from the body.
- ▶ More complex responses have evolved to counteract assault on the body by infectious agents, including bacteria, viruses, parasites and fungi.
- ▶ Because these foreign invaders are literally everywhere on Earth and constantly seeking vulnerable hosts, the immune system is constantly occupied with containing attacks.

- ▶ Humans are surrounded by other organisms-in the air, in the soil, in the water, on the skin, and on the **mucosae**, the protective layers of epithelial cells that line the gastrointestinal, urogenital and respiratory tracts.
- ▶ While most of these organisms are harmless and some are even beneficial, some are pathogenic.
- ▶ Like all species, pathogens live to reproduce. In order to reproduce, however, many must penetrate a host's body or one of its component cells.

What is infection?

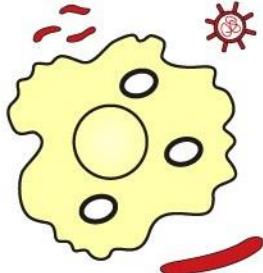
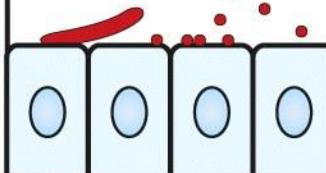
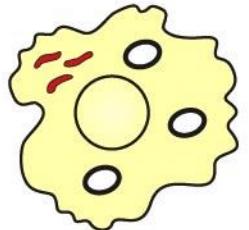
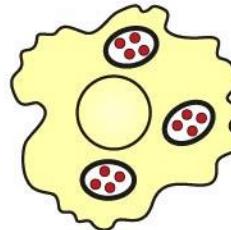
- ▶ **Infection** is defined as the attachment and entry of a pathogen into the host.
- ▶ Once inside the body or cell, the pathogen replicates, generating progeny that spread into the body in a localized or systemic fashion.
- ▶ The manner of this replication determines whether the pathogen is considered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

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

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

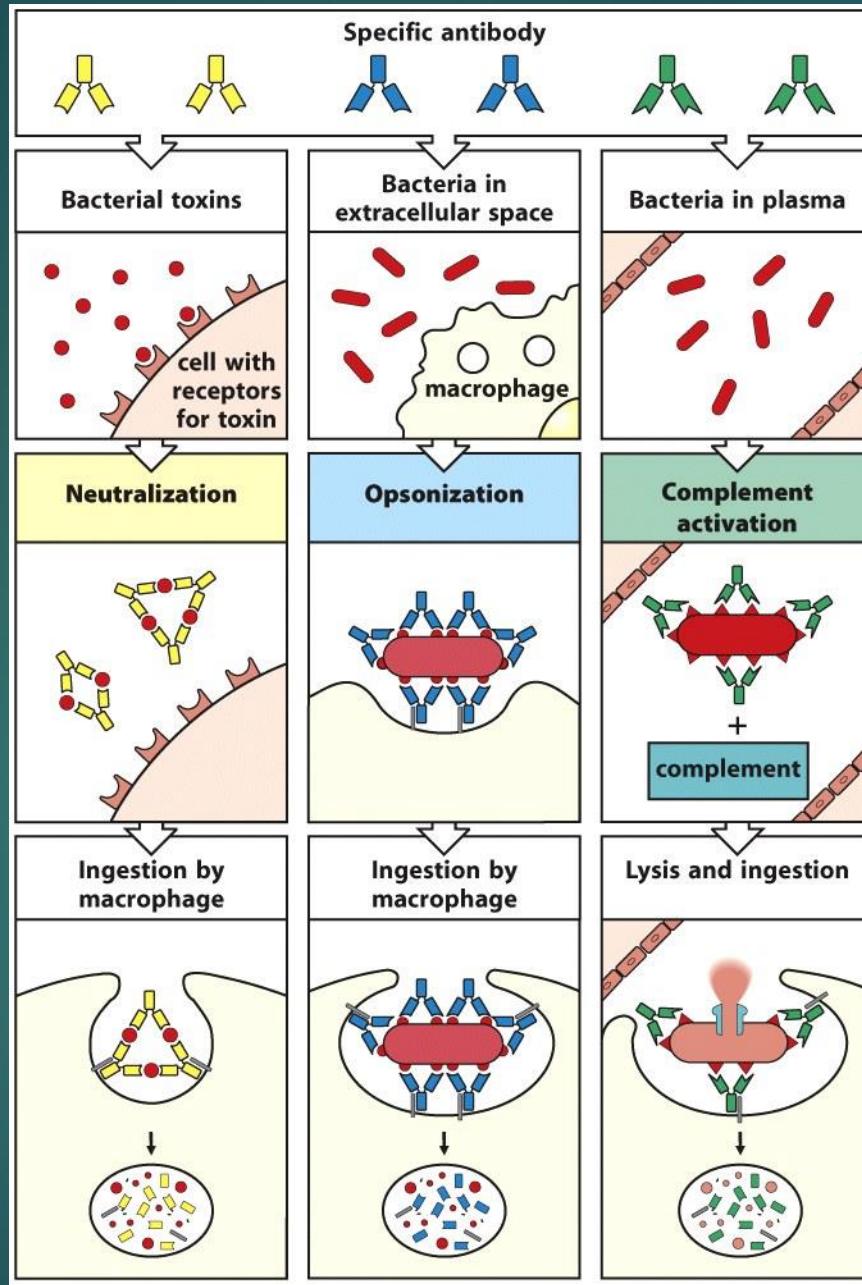
Mechanisms Underlay Immune Responses

- ▶ 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.”

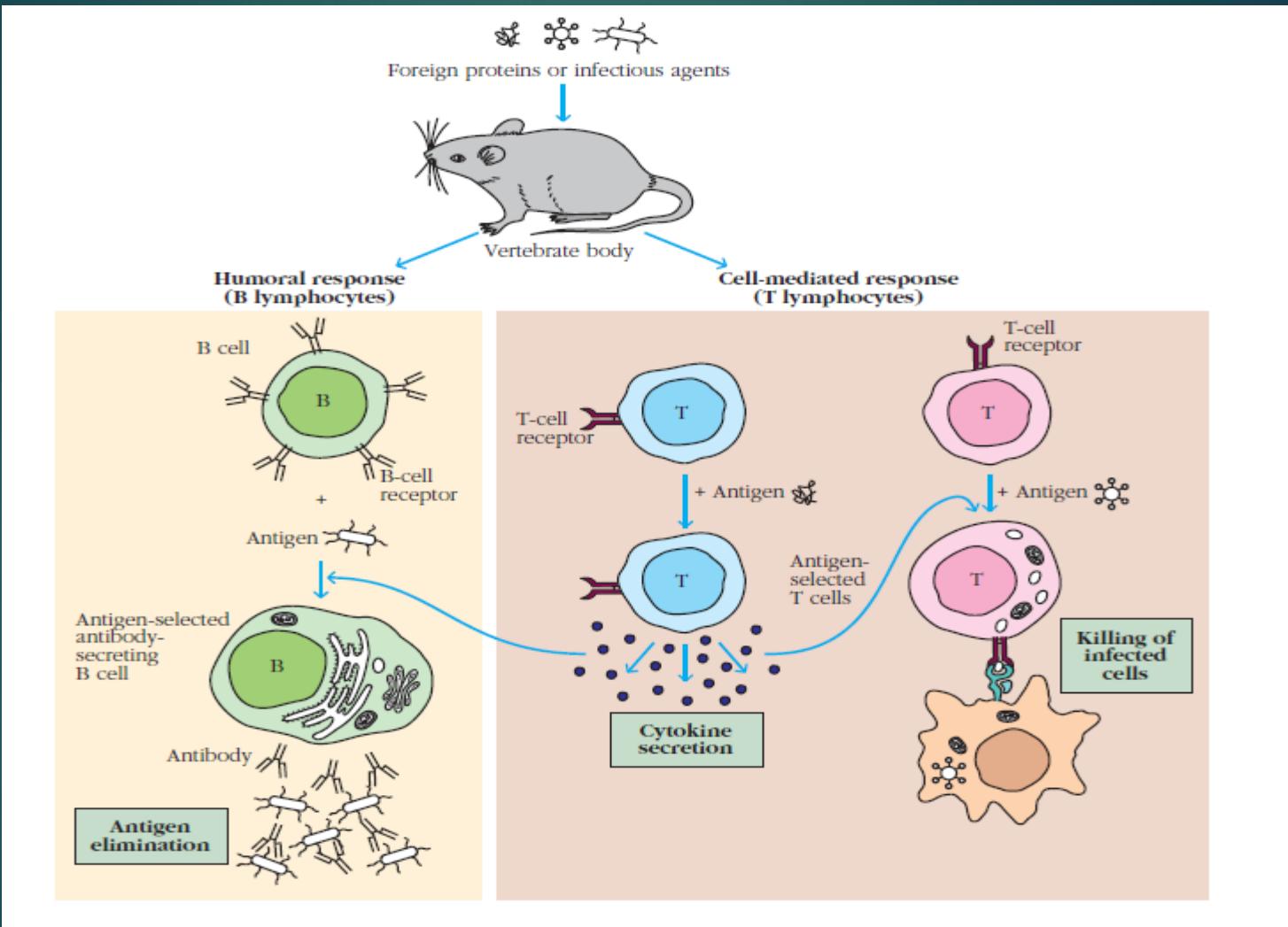
- ▶ Today, we know that both **cell-mediated** and **humoral responses** occur simultaneously during an immune response and that both are often required for complete clearance of a threat.

- ▶ 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).

- Antibodies protect against extracellular pathogens and their toxic products



Humoral and Cell-mediated Immunity



Cells of the Immune System

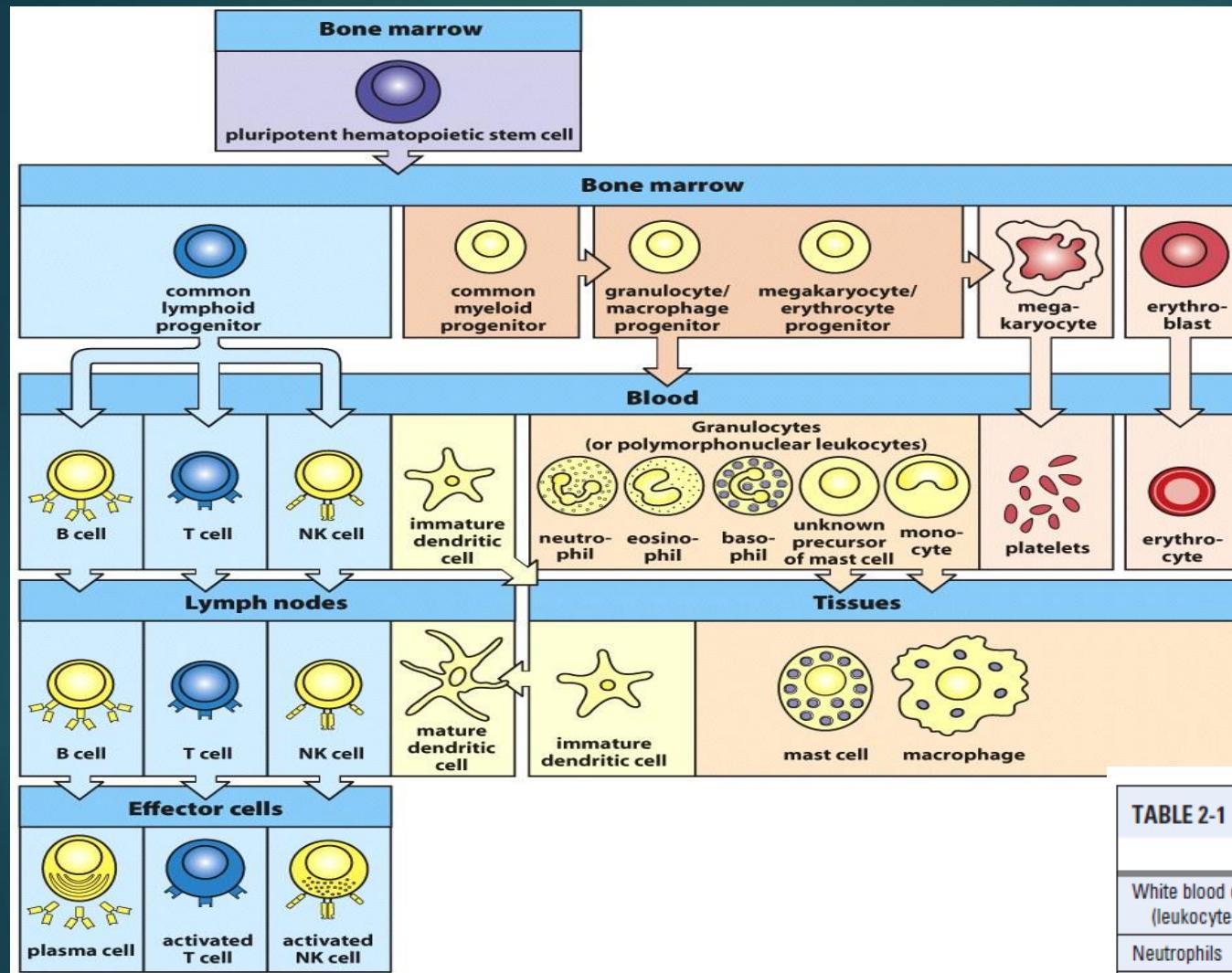
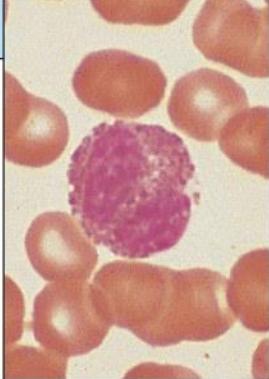
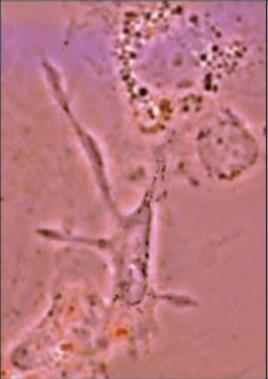
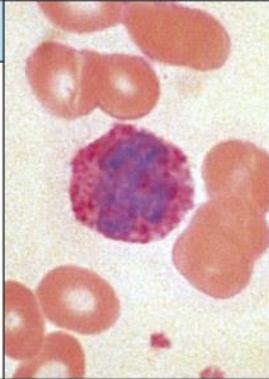
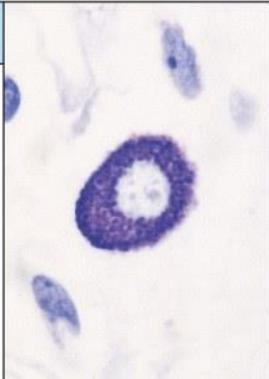


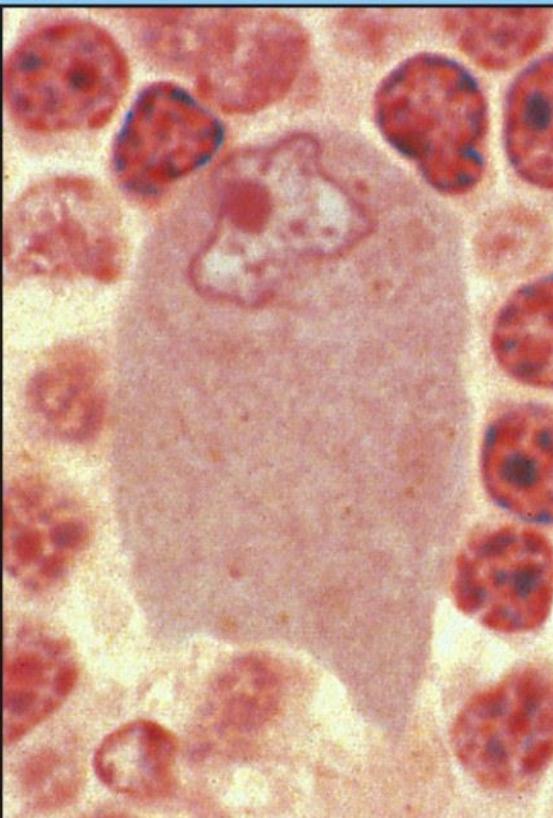
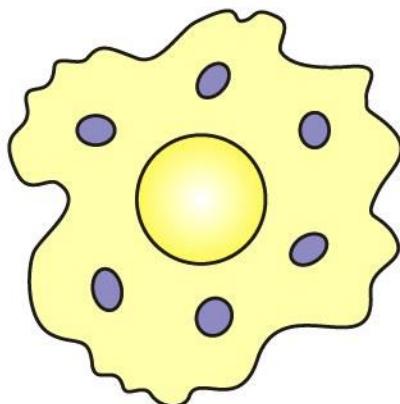
TABLE 2-1 Normal Blood Cell Counts

	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

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

Cell

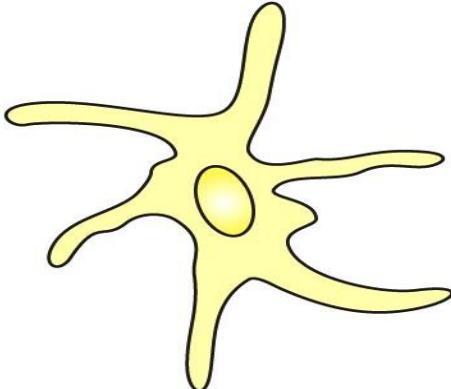
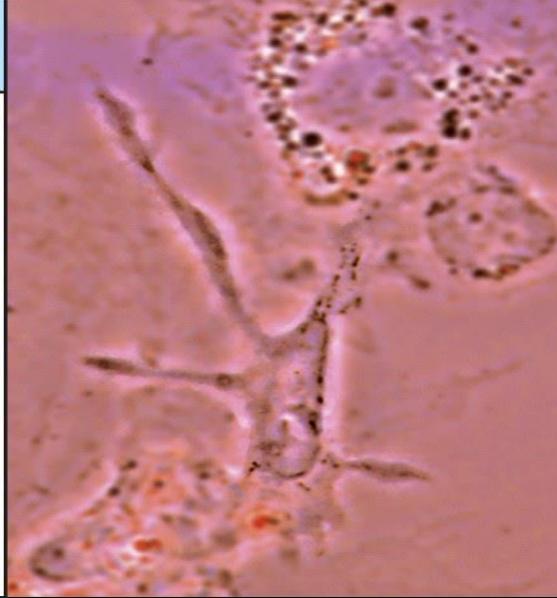
Macrophage



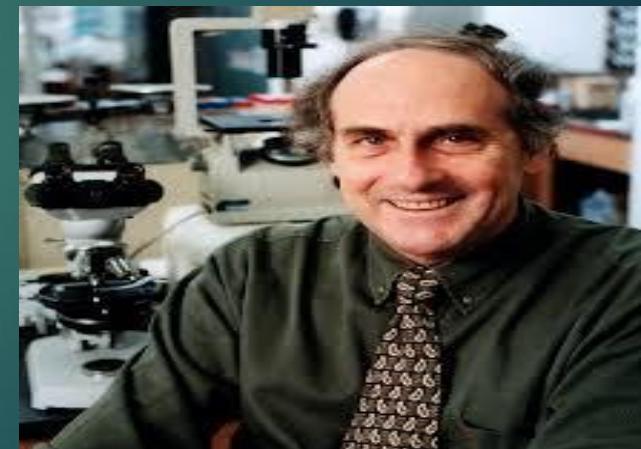
Activated function

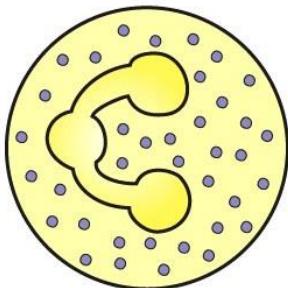
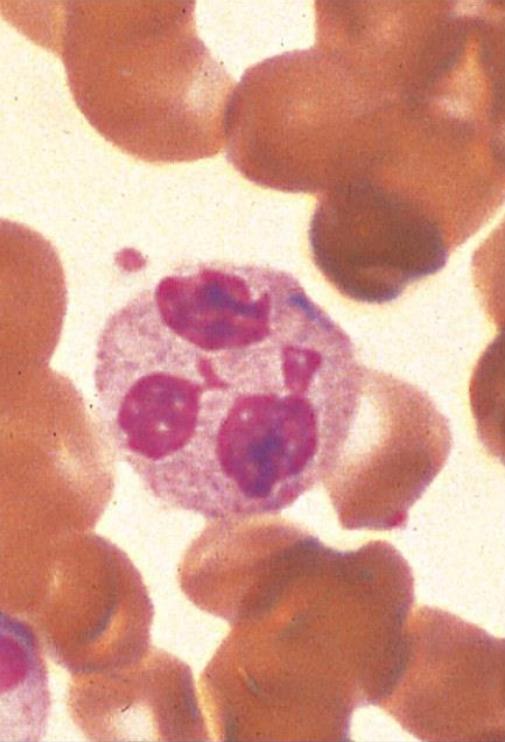
**Phagocytosis
and activation
of bactericidal
mechanisms**

**Antigen
presentation**

Cell	Activated function
Dendritic cell	
	 <p>Antigen uptake in peripheral sites</p> <p>Antigen presentation</p>

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
Neutrophil  	Phagocytosis and activation of bactericidal mechanisms

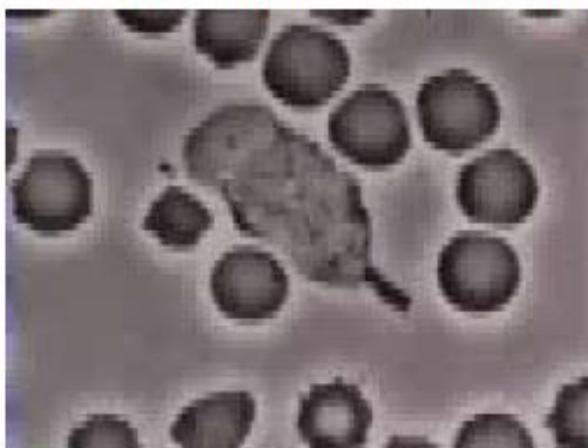
Neutrophils or PMN: polymorphonuclear leukocytes

Cells in blood stream, not in healthy tissues

Become attracted by activated macrophages

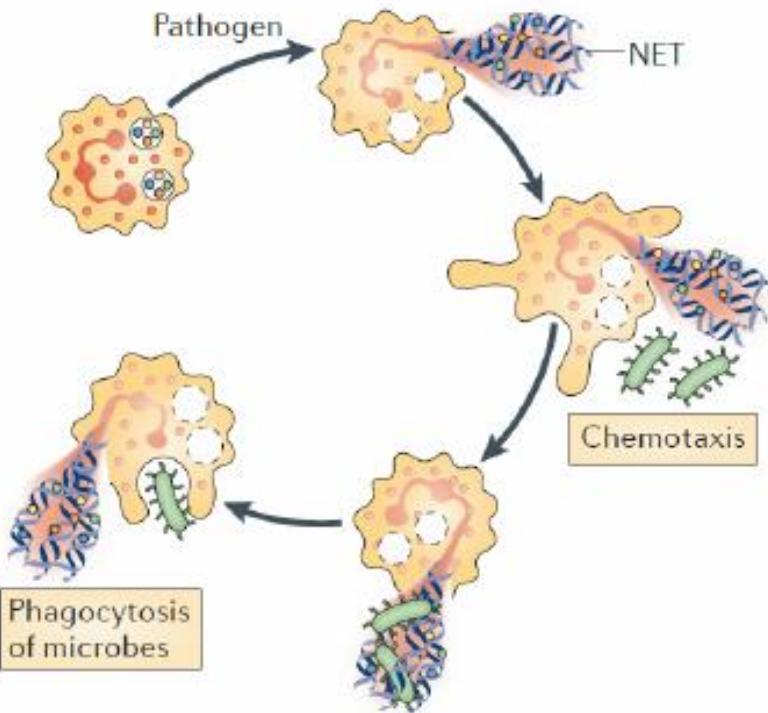
Neutrophil Recruitment

Crawling Neutrophil chasing bacterium

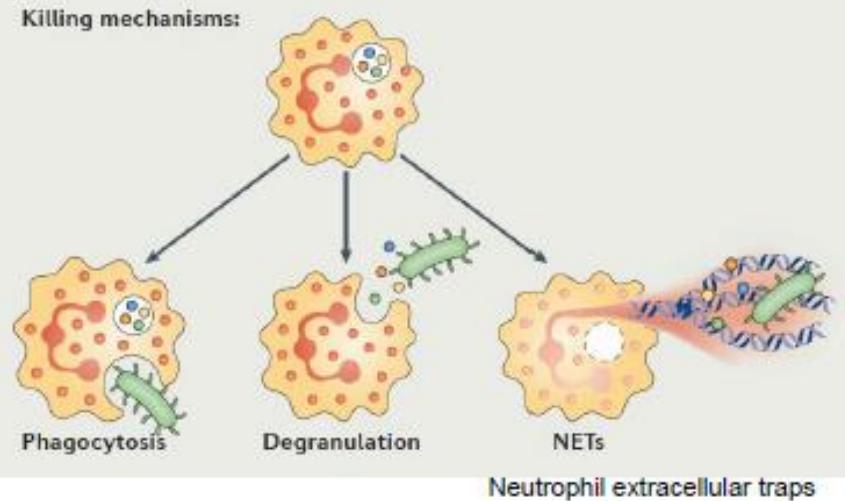


David Rogers, Vanderbilt University

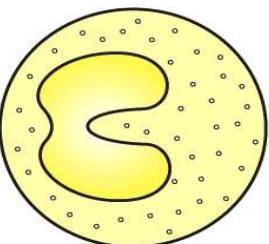
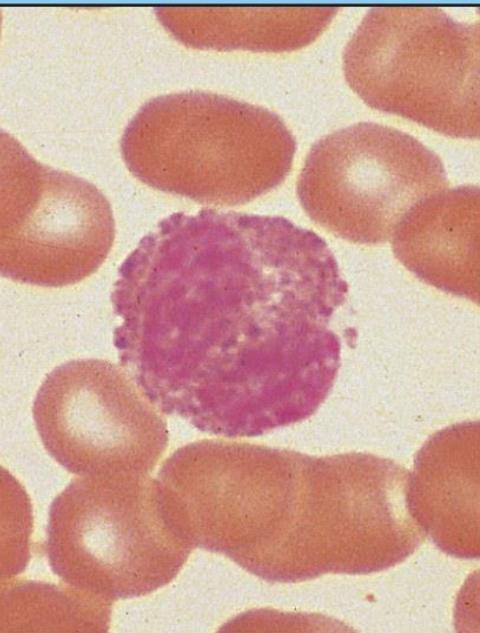
Behaviour of neutrophils that formed NETs *in vivo*



Killing mechanisms:



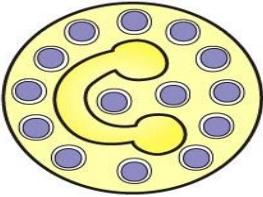
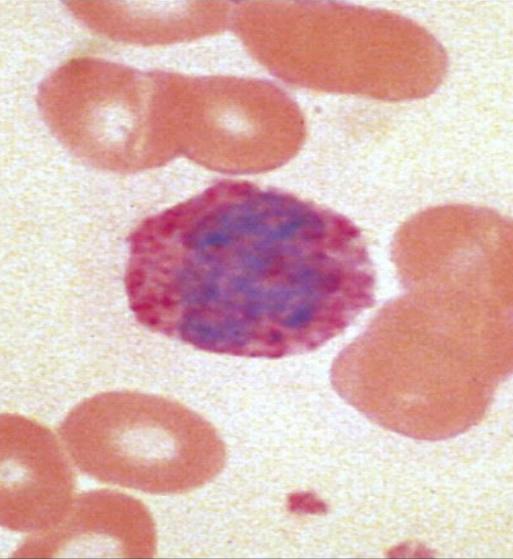
Catching and immobilization
of microbes (possibly directly
killing them)

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>

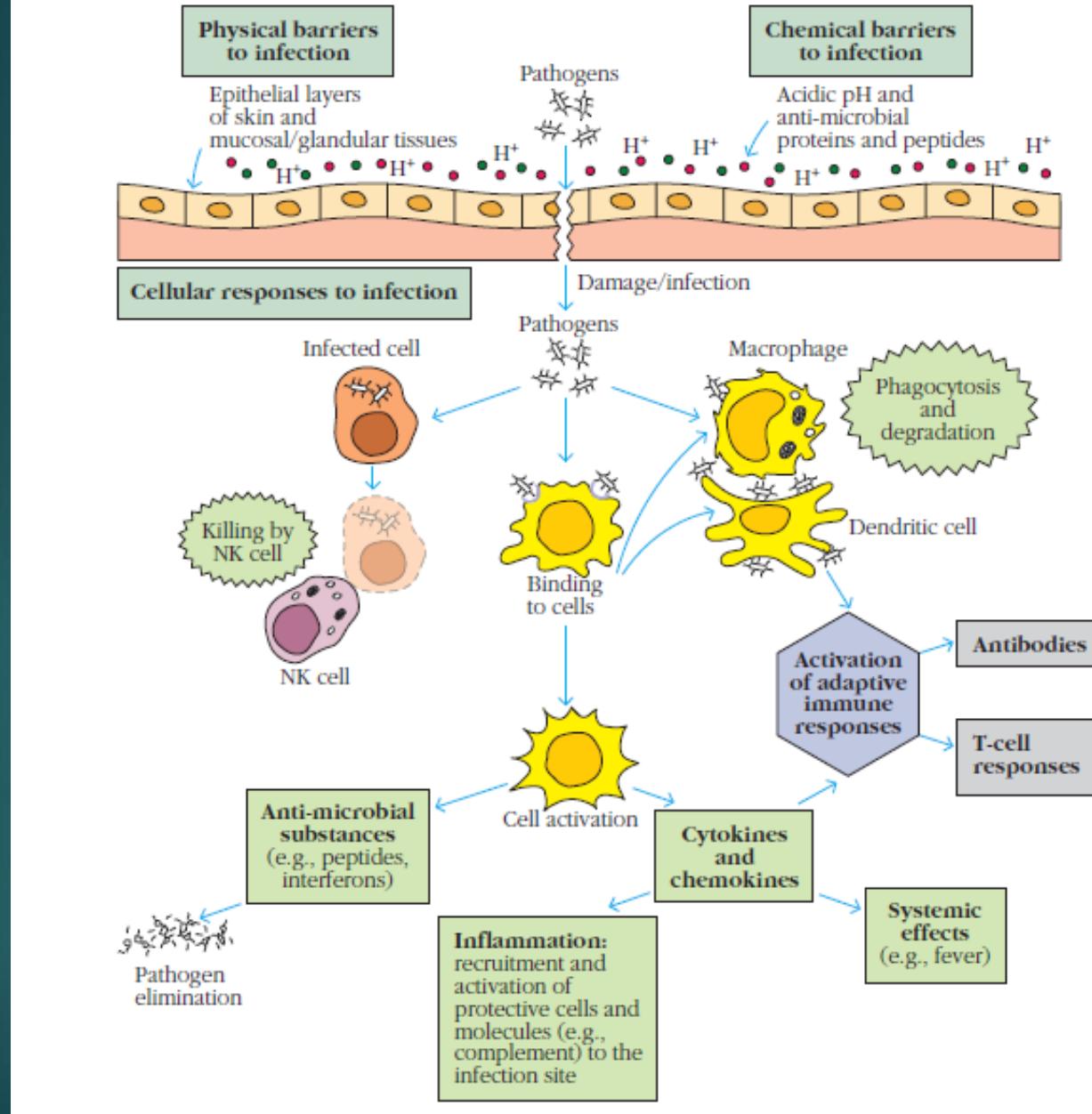
Function similar to Eosinophils (common precursor) but differentiation is mediated by other cytokines (e.g. IL-3)
 low numbers in blood, recruitment and activation by cytokines, Fc receptor
 recognizes Ab-conjugated antigens, secretion of toxic granules

Introduction to Innate Immune response

Features of Innate Immune Response

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

Innate Immunity

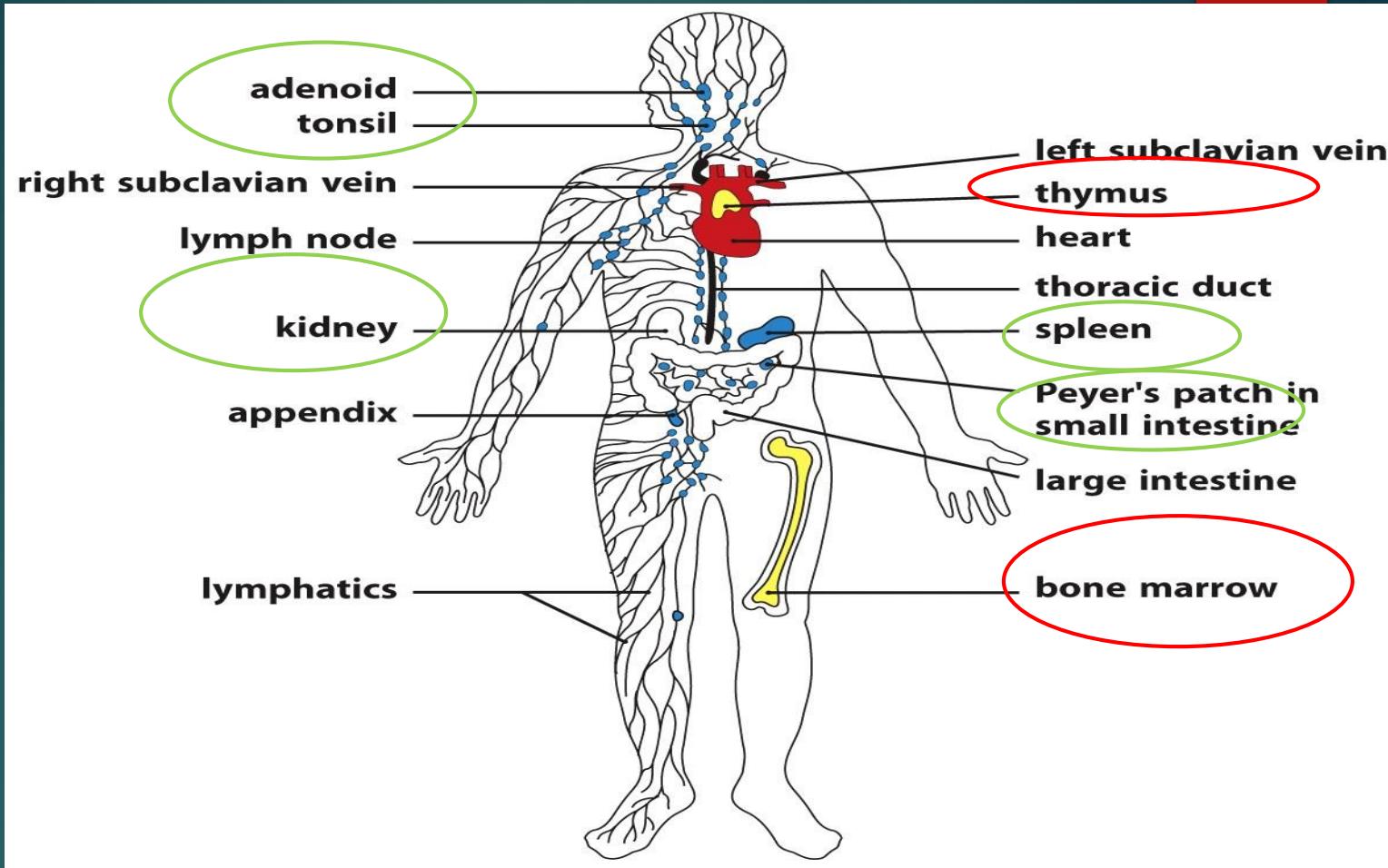


Barriers of the Host Immune System

	Skin	Gut	Lungs	Eyes/nose/ oral cavity
Mechanical	Epithelial cells joined by tight junctions			
Chemical	Fatty acids	Low pH Enzymes (pepsin)	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
	β -defensins Lamellar bodies Cathelicidin	α -defensins (cryptdins) RegIII (lecticidins) Cathelicidin	α -defensins Cathelicidin	Histatins β -defensins
Microbiological	Normal microbiota			

Distribution of lymphoid tissues in the body

The distribution of lymphoid tissues in the body

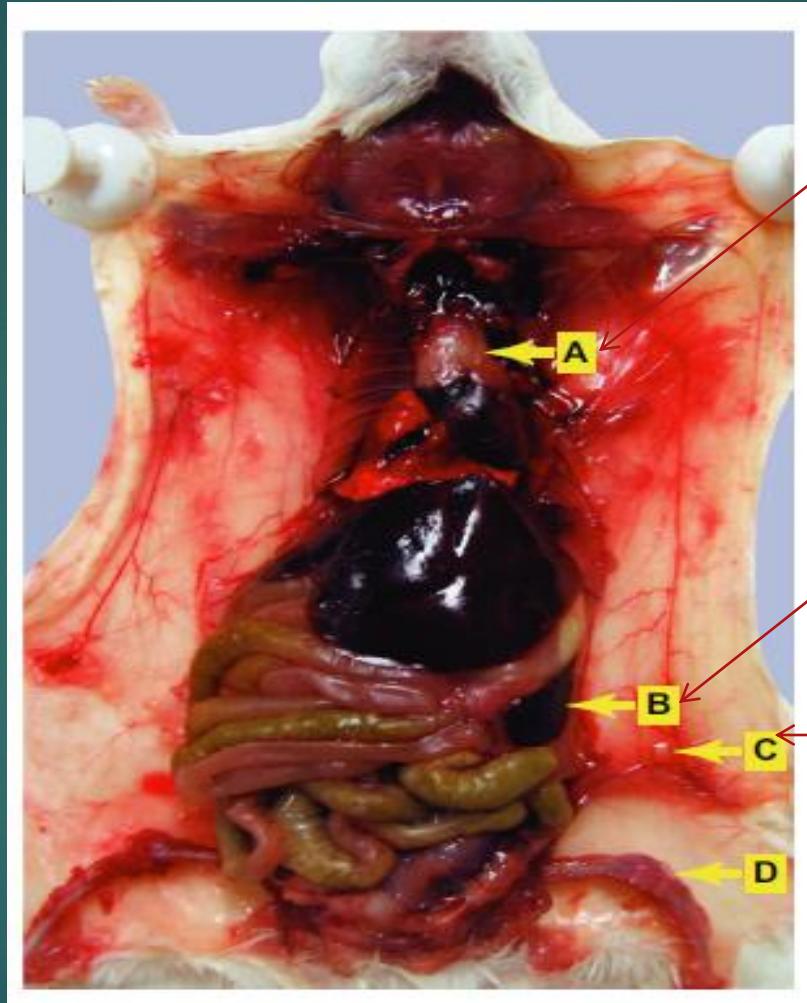


Primary lymphoid
tissues

Secondary lymphoid
tissues

MALT, BALT
GALT
NALT
SALT

Primary and Secondary Lymph organs



Thymus

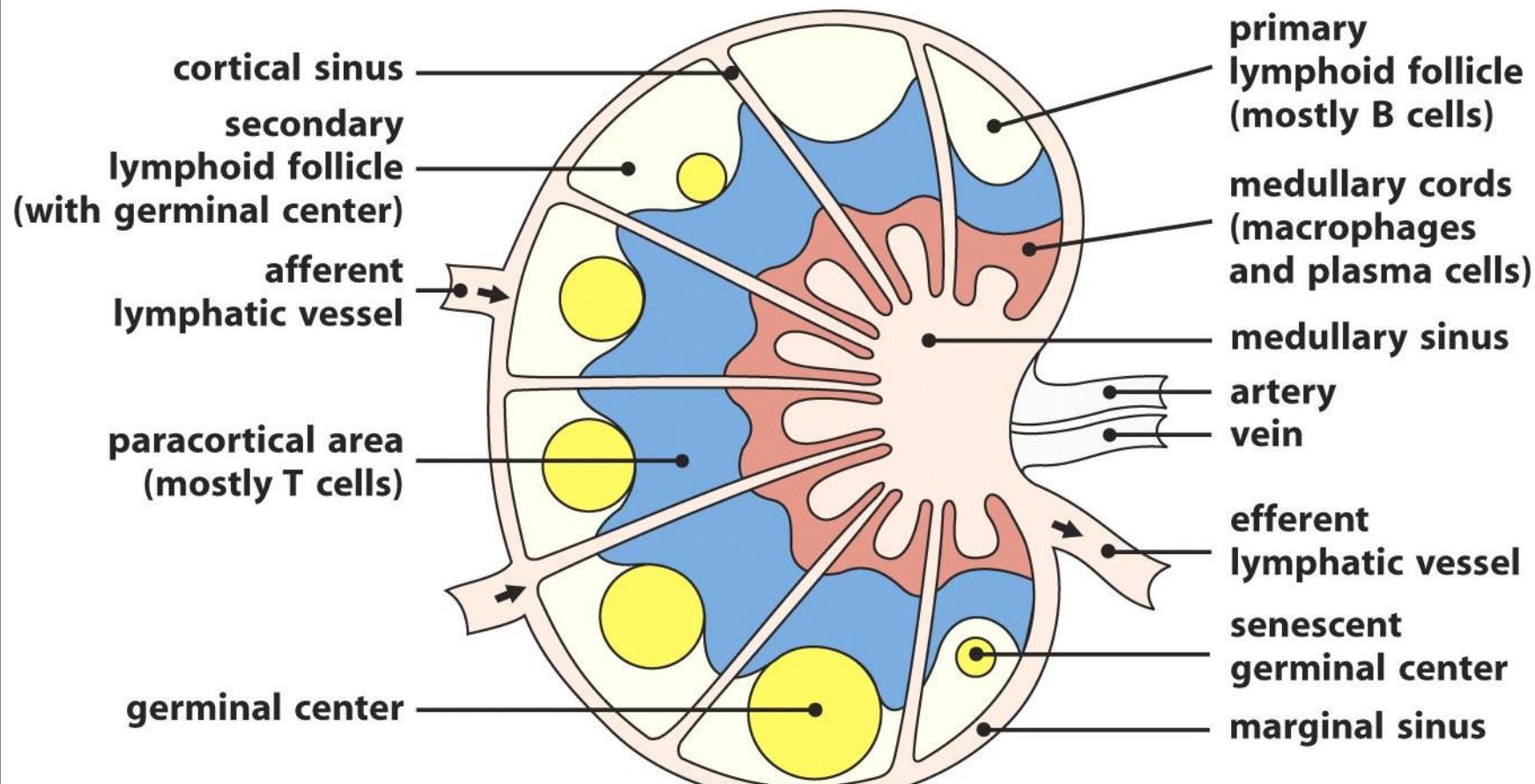
Spleen

Lymph
node

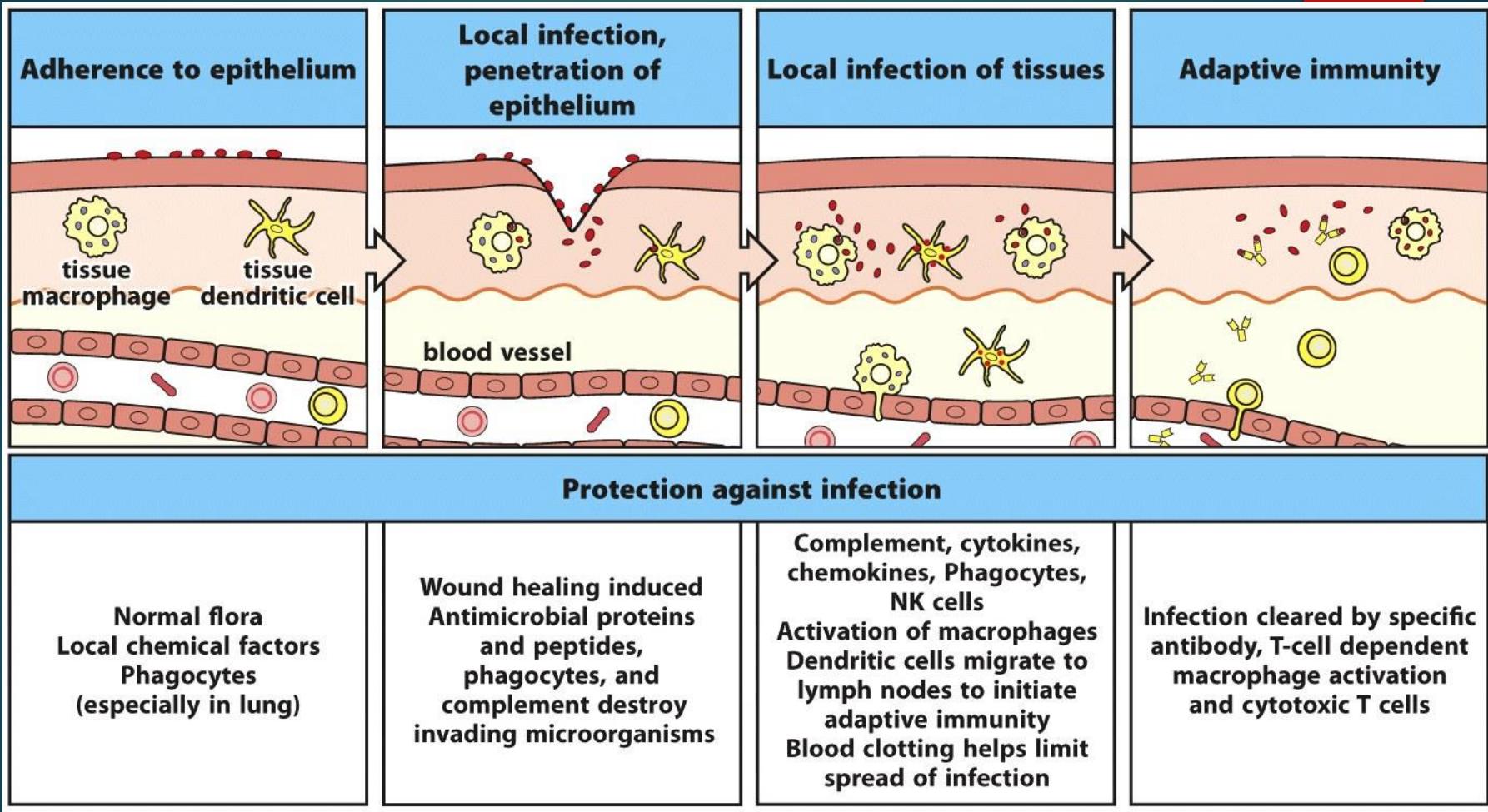
Bone
Barrow

Organization of a lymph node

A lymph node

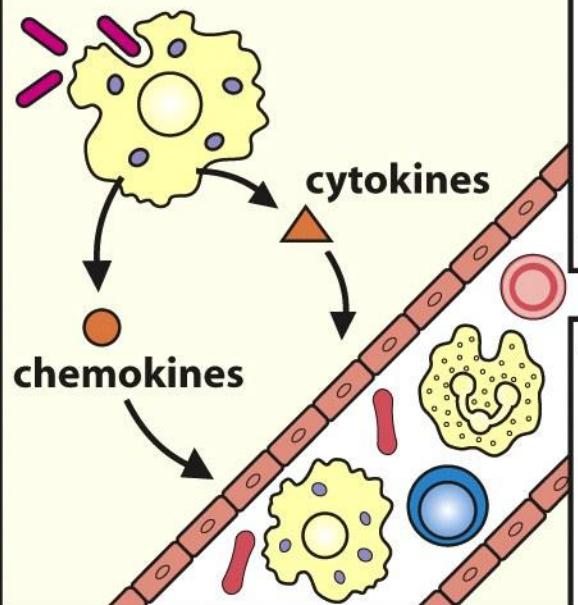


Protection Against Infection

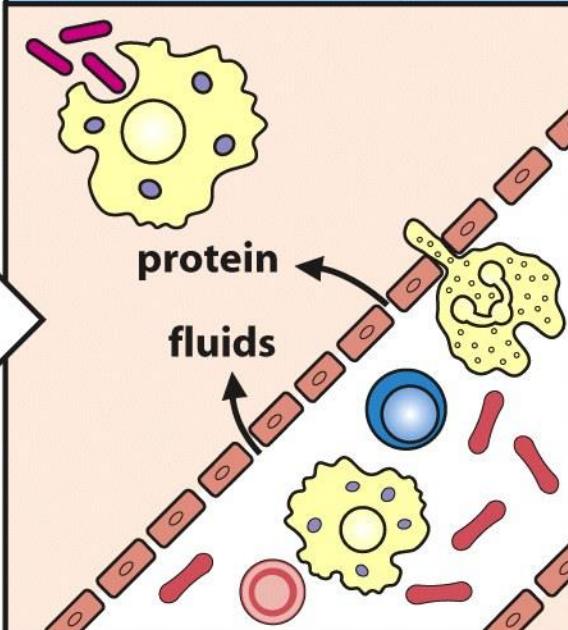


Infection triggers an inflammatory response

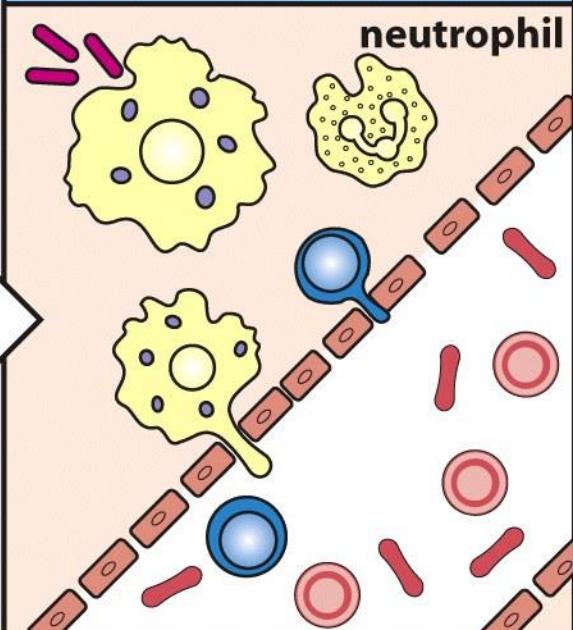
Bacteria trigger macrophages to release cytokines and chemokines



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

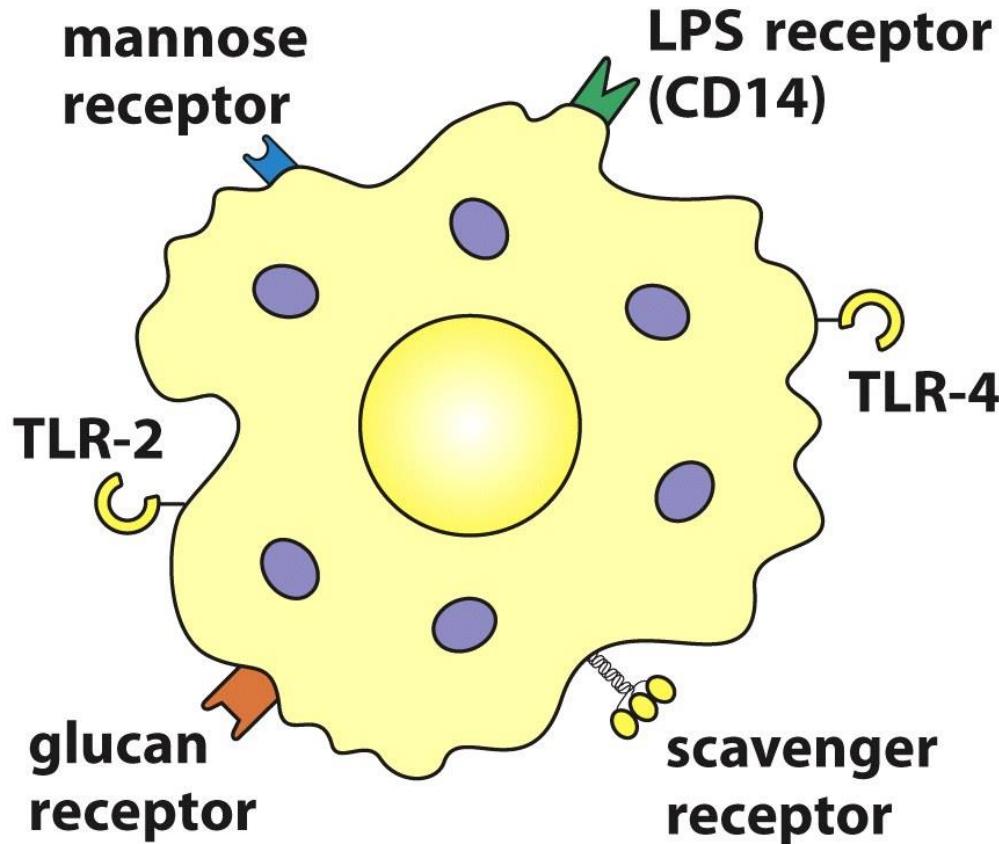


Inflammatory cells migrate into tissue, releasing inflammatory mediators that cause pain



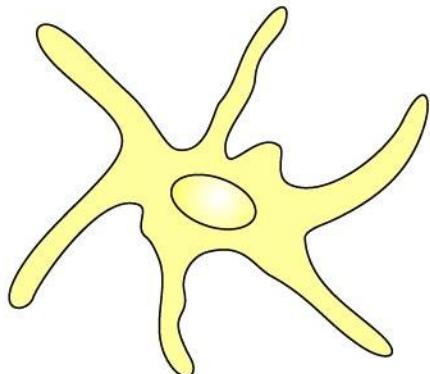
Pathogen Recognition

Macrophages express receptors for many microbial constituents

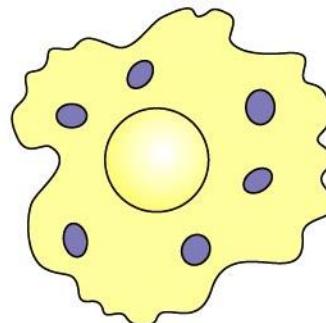


Antigen Presenting Cells

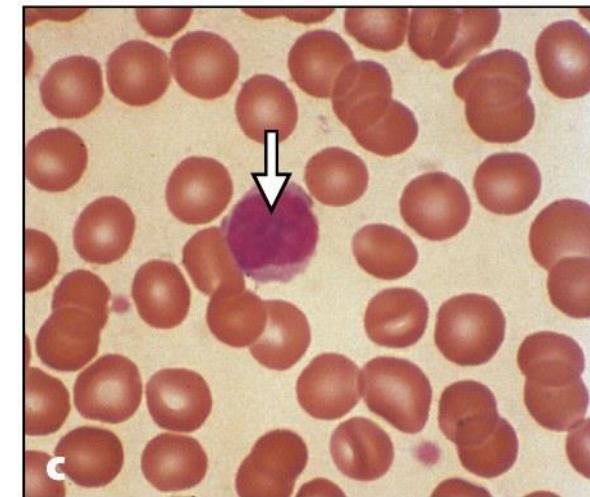
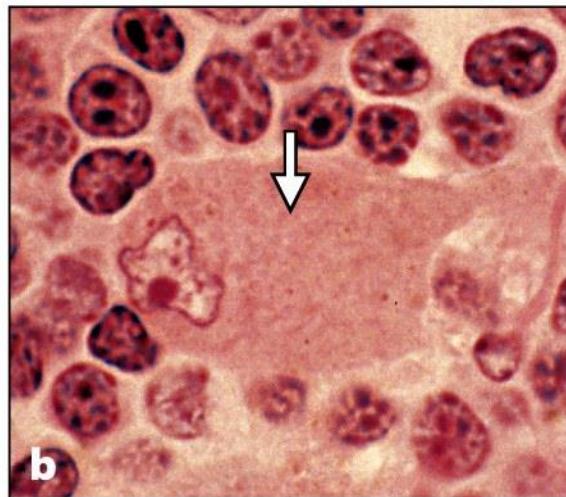
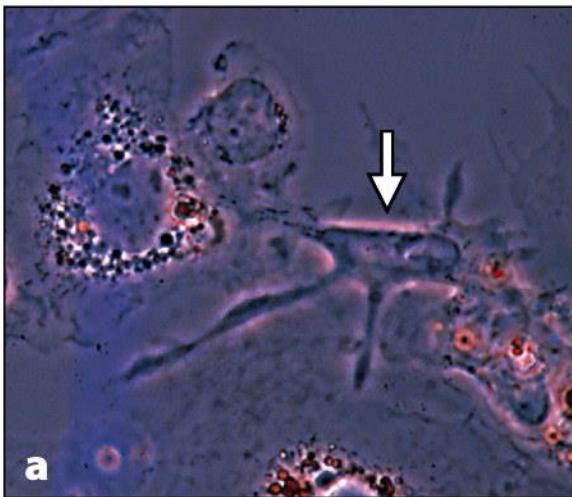
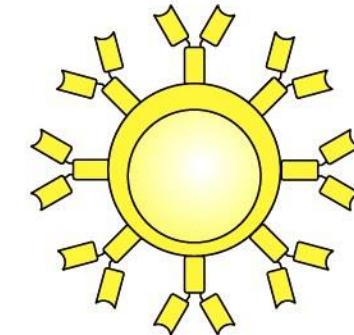
Dendritic cell



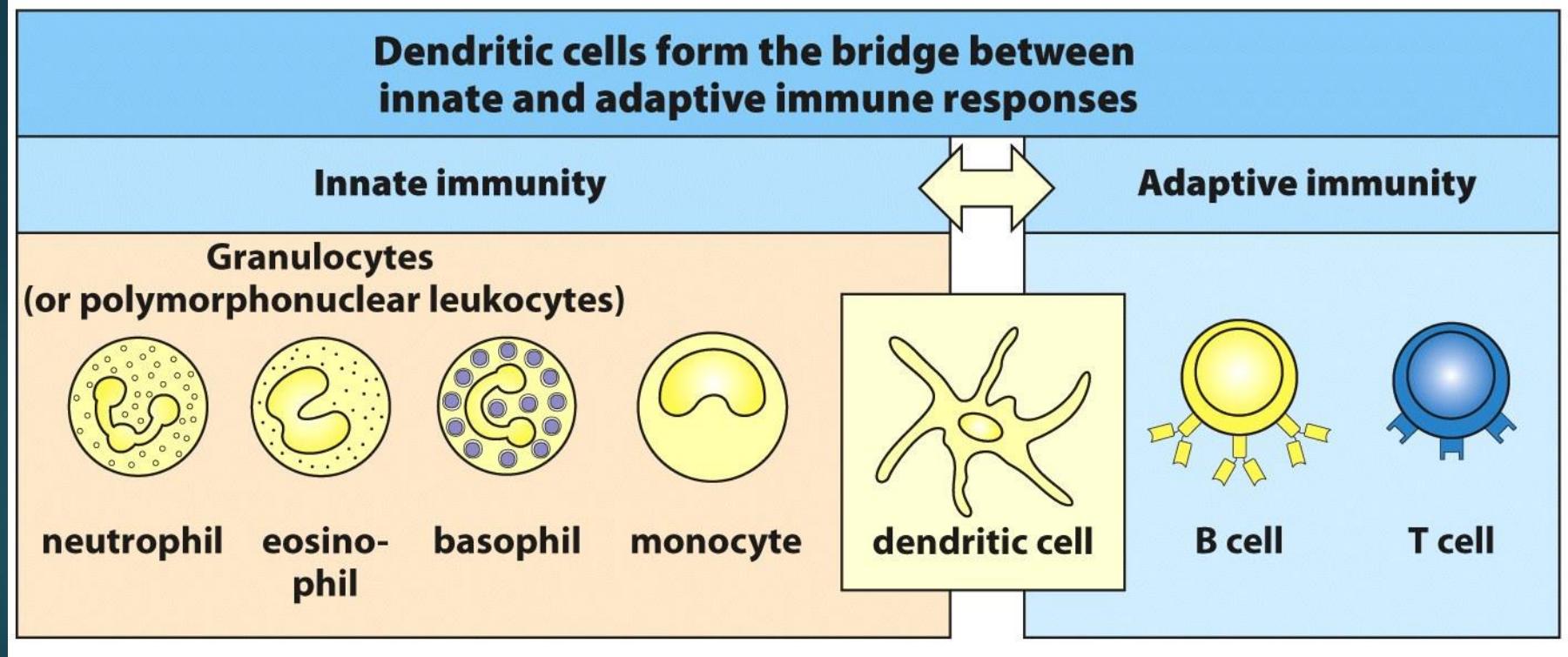
Macrophage



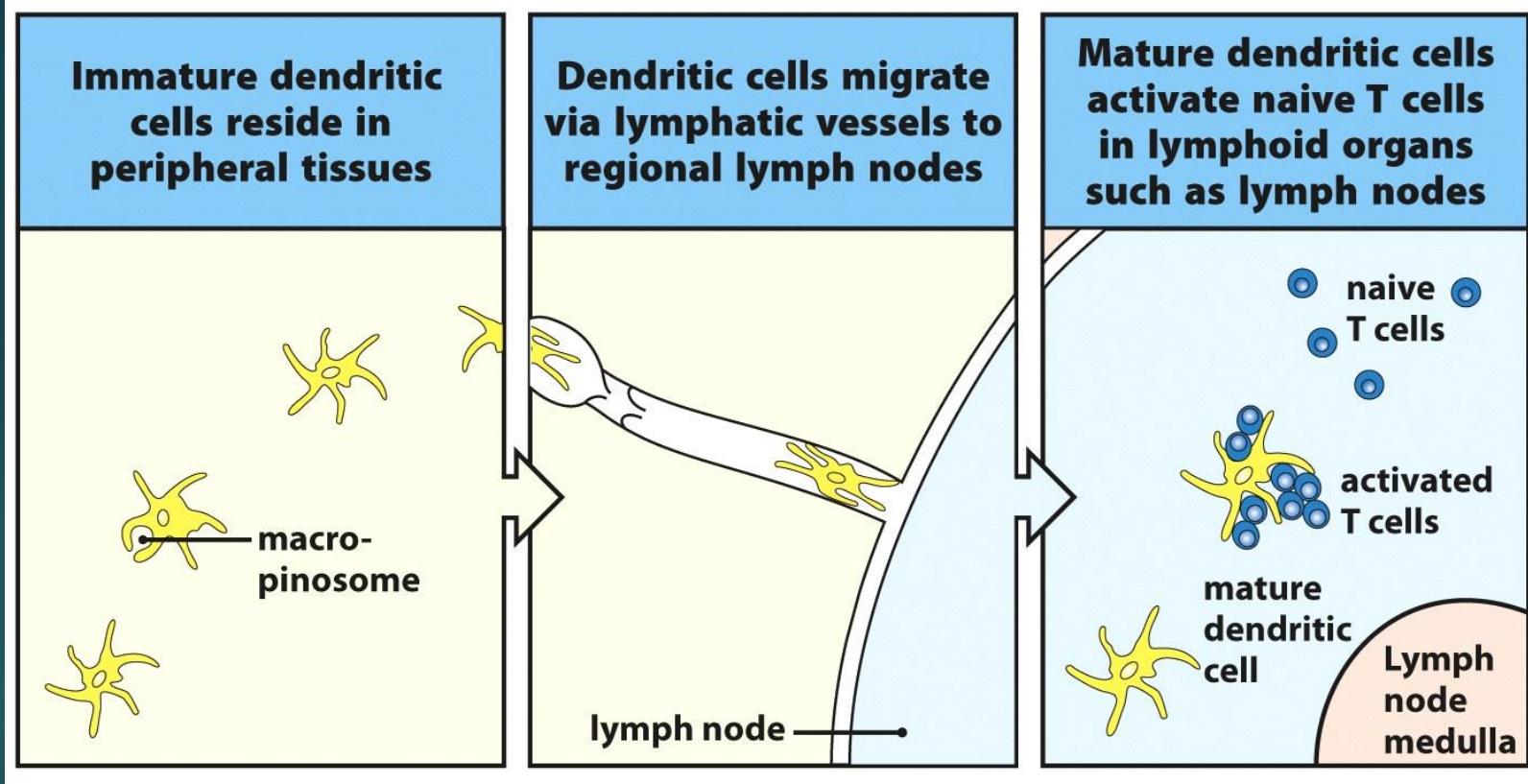
B lymphocyte



Dendritic cells link the Innate and the Adaptive immune system



Dendritic cells form the bridge between innate and adaptive immune responses



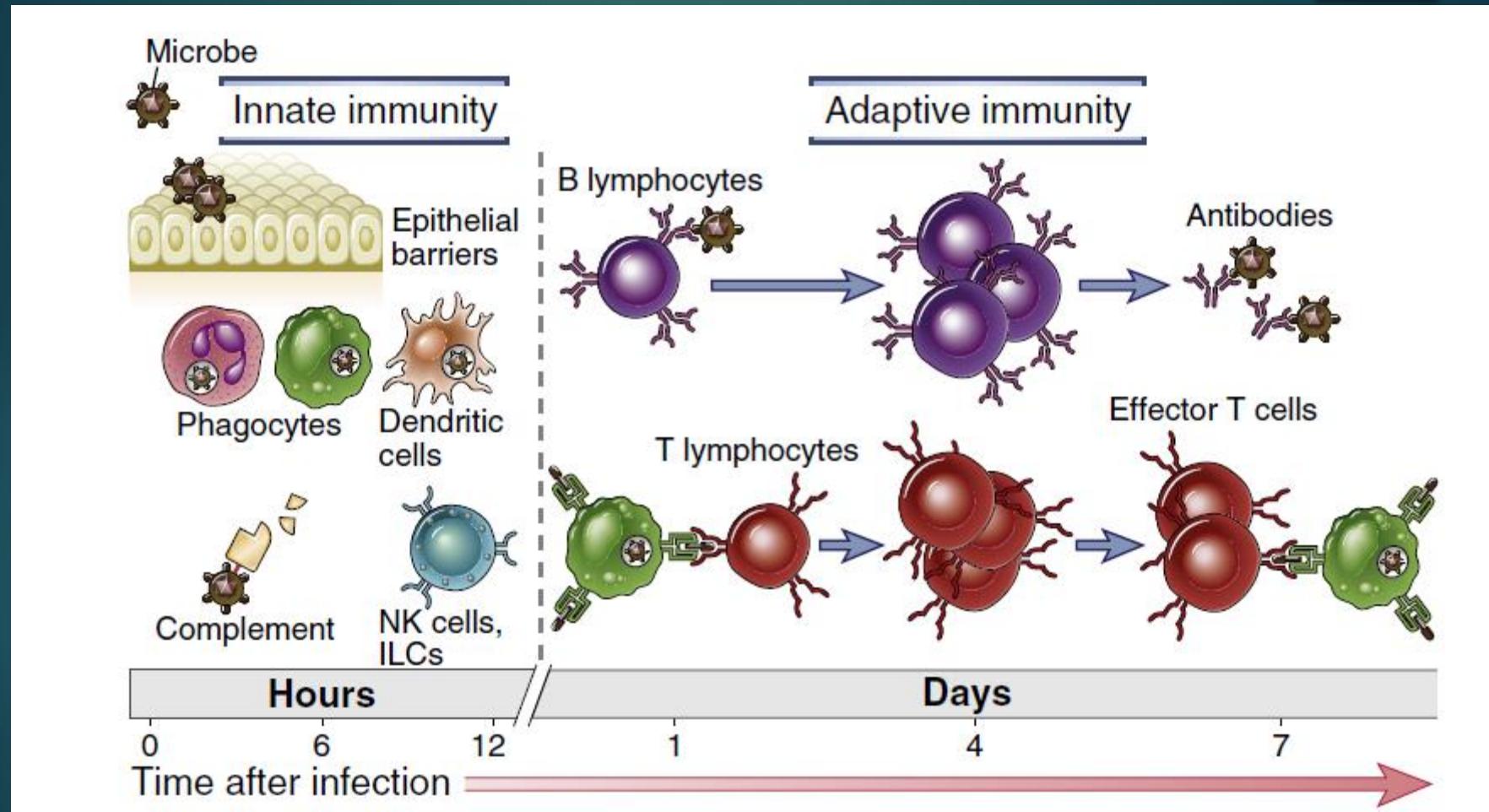
Infection → Activation
Sensing infections (innate function)

Antigen → specific T cell
Activation (adaptive function)

Features of Adaptive Response

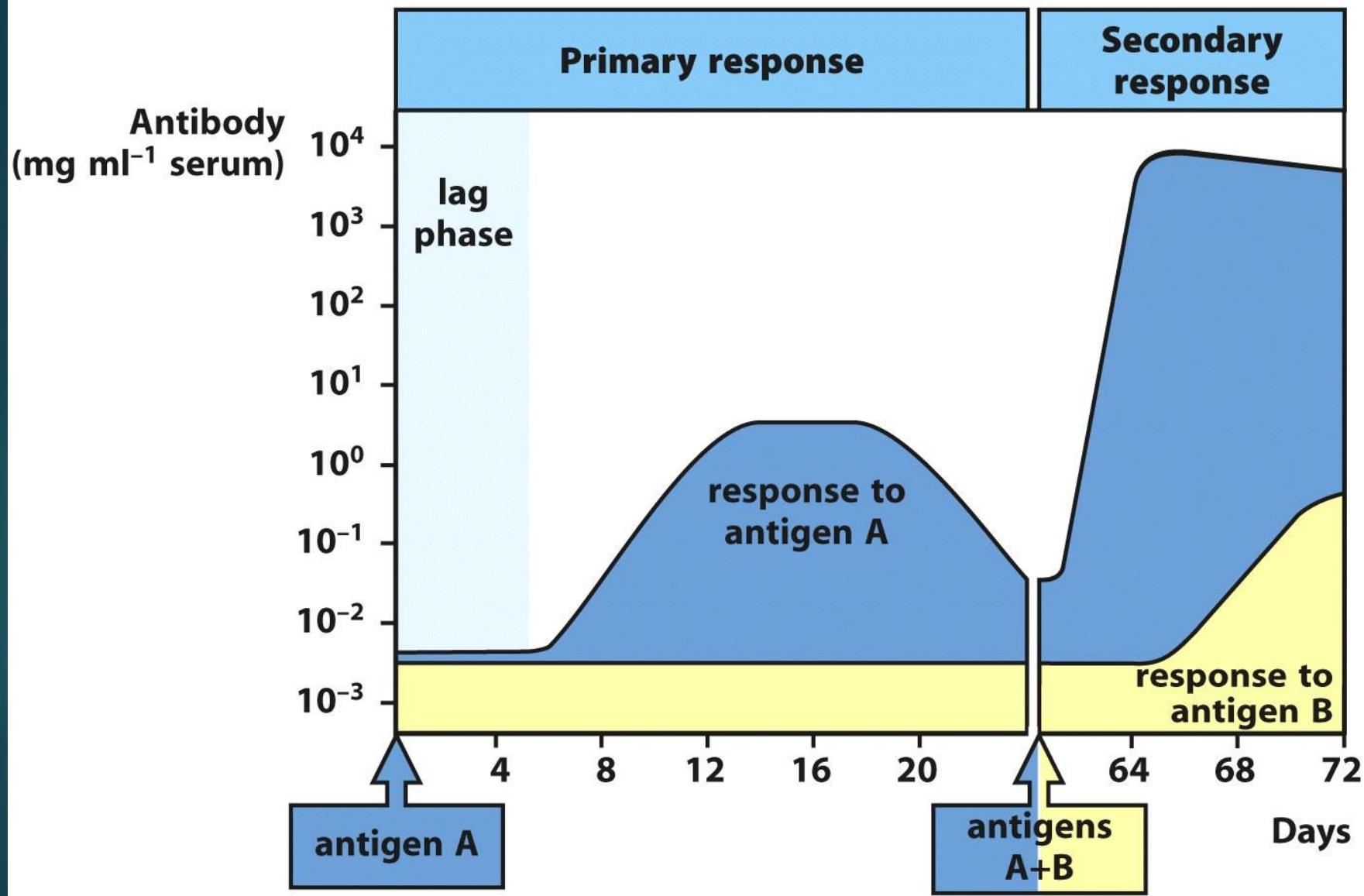
- ▶ Specificity
- ▶ Division of Labor
- ▶ Immunological Memory
- ▶ Tolerance (central and peripheral)
- ▶ Faster response

Innate and Adaptive Immunity



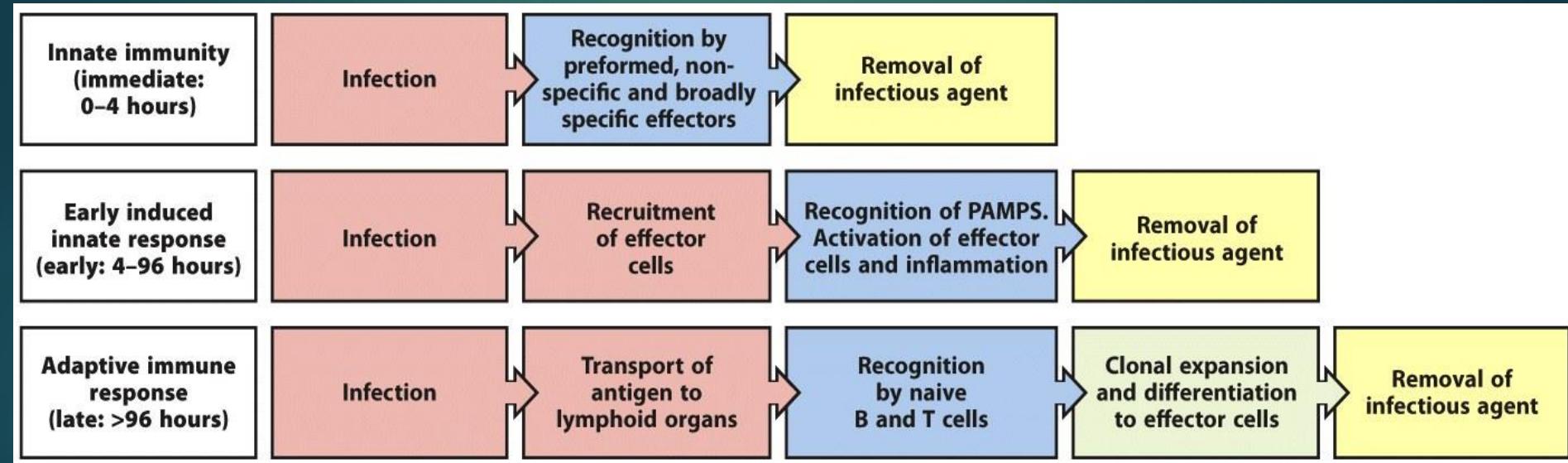
Phases of Immune Response

The course of a typical antibody response



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

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?

References

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2. Kaufmann, S.E., Sher, A. and Ahmed, R. (Eds): Immunology of Infectious Diseases. Washington, DC: ASM Press, 2001.
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