“We are All Immunologists Now”

says David Remnick, in The New Yorker, April 13, 2020

Ed Roy, OLLI, Fall, 2021 Assisted by Marie Roy and Mary Kuetemeyer, Class Moderator

COMMENT APRIL 13, 2020 ISSUE

NEW YORK CITY IN THE CORONAVIRUS PANDEMIC

The spectacle of New York without New Yorkers is the result of a communal pact. We know that life now depends on our withdrawal from the city.

By David Remnick

April 5, 2020

“On any person who desires such queer prizes, New York will bestow the gift of loneliness and the gift of privacy,” E. B. White wrote, in the summer of 1948. But these queer prizes are now a public-health requirement. Because New Yorkers are not medieval monks, we mostly chafe at the imposed solitude. We do our best to overcome it through technologies that White would have had a hard time imagining: We text. We Zoom. We send one another links about virology. (We are all immunologists now.)

The Atlantic

HEALTH

Immunology Is Where Intuition Goes to Die

Which is too bad because we really need to understand how the immune system reacts to the coronavirus.

By Ed Yong

- https://www.theatlantic.com/health/archive/2020/08/covid-19-immunity-is-the-pandemics-central-mystery/614956/

There's a joke about immunology, which Jessica Metcalf of Princeton recently told me. An immunologist and a cardiologist are kidnapped. The kidnappers threaten to shoot one of them, but promise to spare whoever has made the greater contribution to humanity. The cardiologist says, "Well, I've identified drugs that have saved the lives of millions of people." Impressed, the kidnappers turn to the immunologist. "What have you done?" they ask. The immunologist says, "The thing is, the immune system is very complicated …" And the cardiologist says, "Just shoot me now."

10 Leading Causes of Death by Age Group, United States – 2007

	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 5,785	**Unintentional Injury 1,588**	**Unintentional Injury 965**	**Unintentional Injury 1,229**	**Unintentional Injury 15,897**	**Unintentional Injury 14,977**	**Unintentional Injury 16,931**	Malignant Neoplasms 50,167	Malignant Neoplasms 103,171	Heart Disease 496,095	Heart Disease 616,067
2	Short Gestation 4,857	Congenital Anomalies 546	Malignant Neoplasms 480	Malignant Neoplasms 479	**Homicide 5,551**	**Suicide 5,278**	Malignant Neoplasms 13,288	Heart Disease 37,434	Heart Disease 65,527	Malignant Neoplasms 389,730	Malignant Neoplasms 562,875
3	SIDS 2,453	**Homicide 398**	Congenital Anomalies 196	**Homicide 213**	**Suicide 4,140**	**Homicide 4,758**	Heart Disease 11,839	**Unintentional Injury 20,315**	Chronic Low. Respiratory Disease 12,777	Cerebro-vascular 115,961	Cerebro-vascular 135,952
4	Maternal Pregnancy Comp. 1,769	Malignant Neoplasms 364	**Homicide 133**	**Suicide 180**	Malignant Neoplasms 1,653	Malignant Neoplasms 3,463	**Suicide 6,722**	Liver Disease 8,212	**Unintentional Injury 12,193**	Chronic Low. Respiratory Disease 109,562	Chronic Low. Respiratory Disease 127,924
5	**Unintentional Injury 1,285**	Heart Disease 173	Heart Disease 110	Congenital Anomalies 178	Heart Disease 1,084	Heart Disease 3,223	HIV 3,572	**Suicide 7,778**	Diabetes Mellitus 11,304	Alzheimer's Disease 73,797	**Unintentional Injury 123,706**
6	Placenta Cord Membranes 1,135	Influenza & Pneumonia 109	Chronic Low. Respiratory Disease 54	Heart Disease 131	Congenital Anomalies 402	HIV 1,091	**Homicide 3,052**	Cerebro-vascular 6,385	Cerebro-vascular 10,500	Diabetes Mellitus 51,528	Alzheimer's Disease 74,632
7	Bacterial Sepsis 820	Septicemia 78	Influenza & Pneumonia 48	Chronic Low. Respiratory Disease 64	Cerebro-vascular 195	Diabetes Mellitus 610	Liver Disease 2,570	Diabetes Mellitus 5,753	Liver Disease 8,004	Influenza & Pneumonia 45,941	Diabetes Mellitus 71,382
8	Respiratory Distress 789	Perinatal Period 70	Benign Neoplasms 41	Influenza & Pneumonia 55	Diabetes Mellitus 168	Cerebro-vascular 505	Cerebro-vascular 2,133	HIV 4,156	**Suicide 5,069**	Nephritis 38,484	Influenza & Pneumonia 52,717
9	Circulatory System Disease 624	Benign Neoplasms 59	Cerebro-vascular 38	Cerebro-vascular 45	Influenza & Pneumonia 163	Congenital Anomalies 417	Diabetes Mellitus 1,984	Chronic Low. Respiratory Disease 4,153	Nephritis 4,440	**Unintentional Injury 38,292**	Nephritis 46,448
10	Neonatal Hemorrhage 597	Chronic Low. Respiratory Disease 57	Septicemia 36	Benign Neoplasms 43	Three Tied* 160	Liver Disease 384	Septicemia 910	Viral Hepatitis 2,815	Septicemia 4,231	Septicemia 26,362	Septicemia 34,828

*The three causes are: Complicated Pregnancy, HIV, Septicema

Source: National Vital Statistics System, National Center for Health Statistics, CDC.

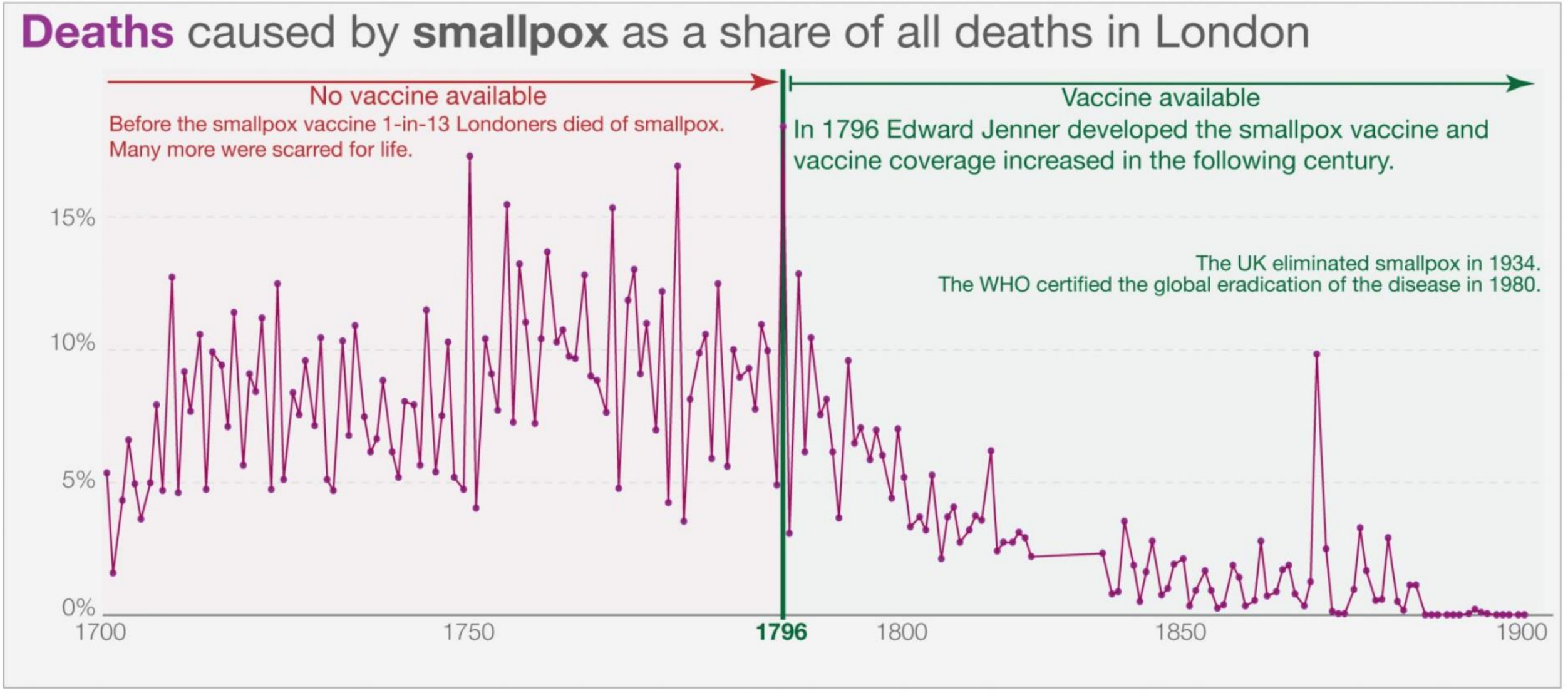
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC.

Immunology’s Finest Accomplishment so far has been Vaccination for prevention of infectious diseases

Disease	Maximum number of cases (year)	Number of cases in 2014
Diptheria	206,939 (1921)	0
Measles	894,134 (1941)	72
Mumps	152,209 (1968)	40
Pertussis	265,269 (1934)	311
Polio (paralytic)	21,269 (1952)	0
Rubella	57,686 (1969)	0
Tetanus	1,560 (1923)	0
Hemophilus influenzae type B infection	~20,000 (1984)	134
Hepatitis B	26,611 (1985)	58

Abbas, 2020, adapted from Ornstein, 2017

Infectious diseases before and after a vaccine became available



Immunology

- Study of defenses against pathogens, microbes such as bacteria, viruses and fungi that cause harm

Learning Objectives for Week 1

- Learn basic features of immunity: barriers, innate and adaptive immunity
- Learn how innate immune cells recognize pathogen associated molecular patterns
- **Appreciate the diversity of antibodies and T cell receptors and understand the role of clonal selection in adaptive immunity**
- Learn about where the immune system is
- Learn how Dendritic cells bridge innate and adaptive immunity, sensing pathogens and activating T cells

We Require Protection from Pathogens

(Microbes that cause harm)

- Bacteria and viruses that can cause damage to your body
- Every organism has a defense system
  - Even bacteria are attacked by viruses, so bacteria have anti-viral responses
- Humans have three levels of defense against pathogens
  - Barriers
  - Innate System
  - Adaptive System

Physical Barriers to Entry

- Squamous cells of skin; dead cells pile up into a protective barrier
- Mucus that lines points of interaction with the outside world, such as respiratory tract and gastrointestinal tract
- Ciliated cells move mucus along

Potential Sites of Entry for Pathogens

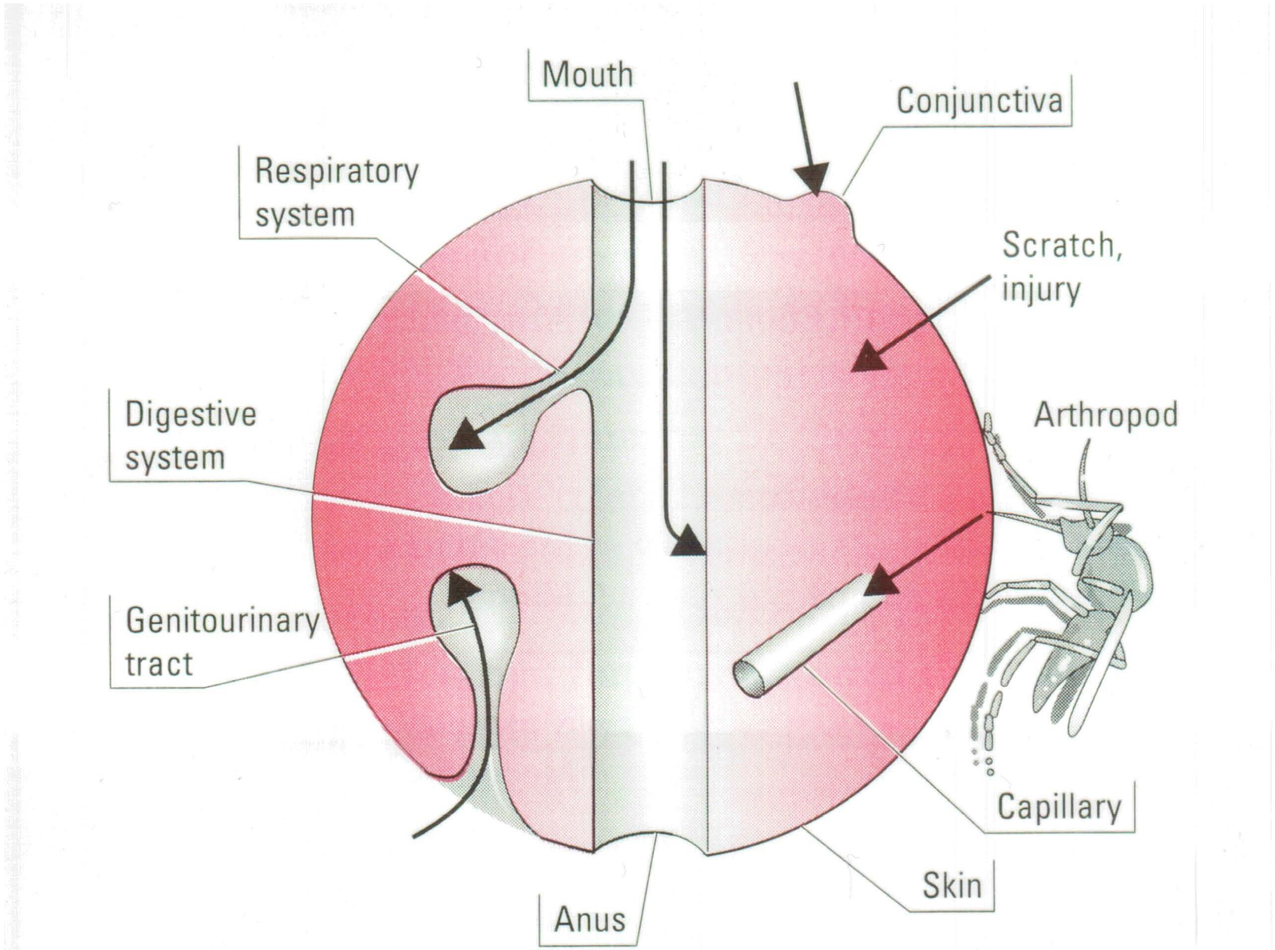
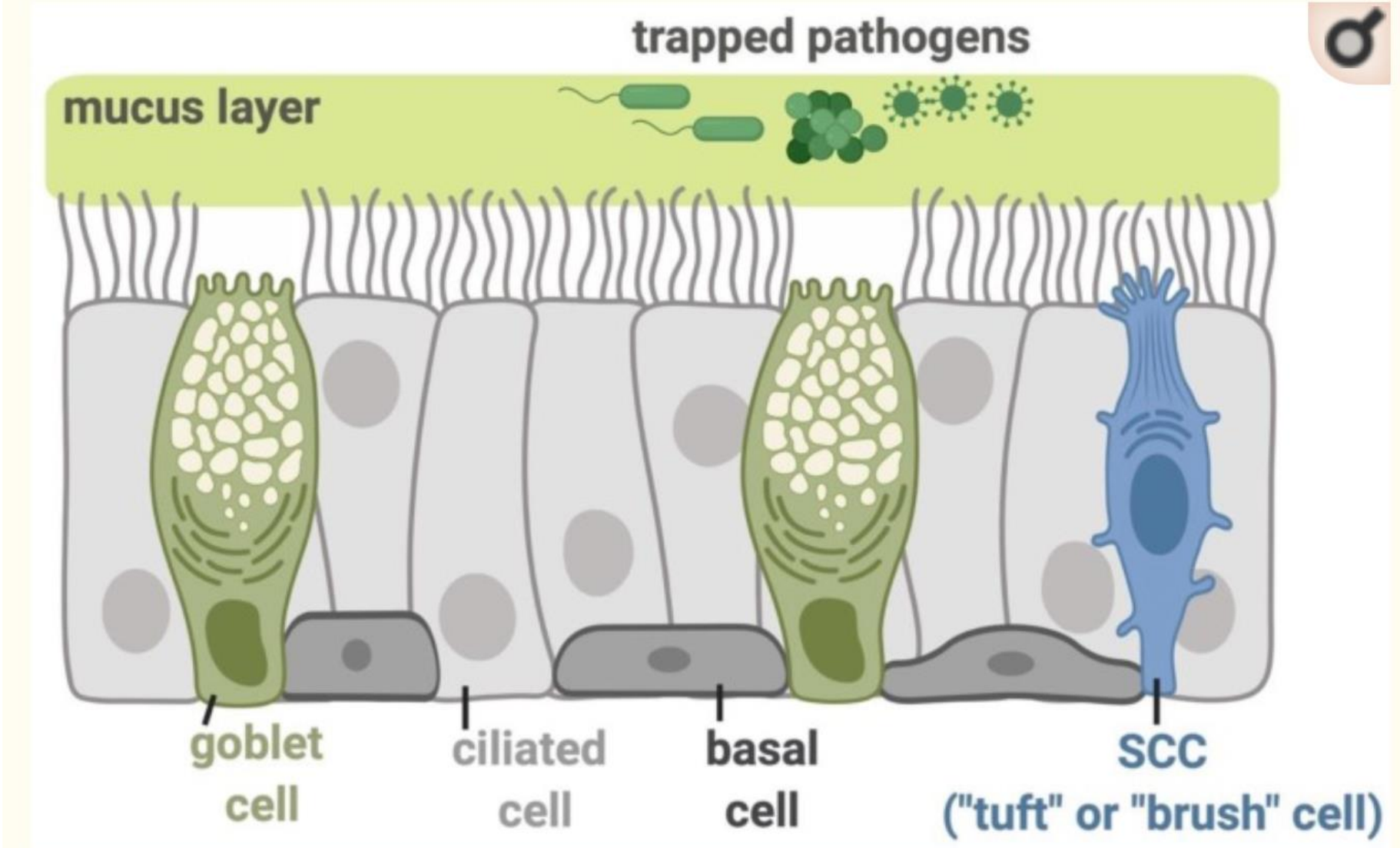


Figure 21.3 Outer and inner body surfaces. Sites of antigen entry are indicated by arrows. (Redrawn from Mims, C. A. (1977) *The Pathogenesis of Infectious Disease*. Academic Press, London.)


trapped pathogens
mucus layer
goblet cell
ciliated cell
basal cell
SCC ("tuft" or "brush" cell)

Two Components of Immune System that attack pathogens that breach barriers, Innate and Adaptive

- Innate: born with it
  - Pathogen recognition and removal components that have evolved against conserved aspects of pathogens
  - **First Responders:** Ready immediately; some sentinel cells in tissues
  - Does not change much on second exposure to pathogen
- Adaptive: changes across one's lifetime
  - Very **specific** for novel aspects of pathogens
  - Takes **time** to develop (5-7 days)
  - Once activated, it retains **memory** and provides "immunity"
- Highly interdependent
  - Innate cells such as dendritic cells and macrophages initiate an adaptive response
  - T cells enhance the effectiveness of macrophages

Innate Responses

Innate = present from birth

- Evolution of responses to conserved features of pathogens across generations
- Pathogen Associated Molecular Patterns (PAMPS) recognized by Pattern Recognition Receptors on immune cells
  - e.g., cell wall components of bacteria recognized by Toll-Like Receptors on macrophages
  - Calls for First Responders, using cytokines to attract neutrophils and macrophages
  - These eat the pathogens and release chemicals that kill pathogens in a very non-specific way, e.g. hydrogen peroxide

Cells of Innate and adaptive immunity

- Innate immunity: "ready to go"; first responders

  Phagocytes:

  Macrophages
  Neutrophils
  Dendritic Cells
  (Natural Killer Cells)

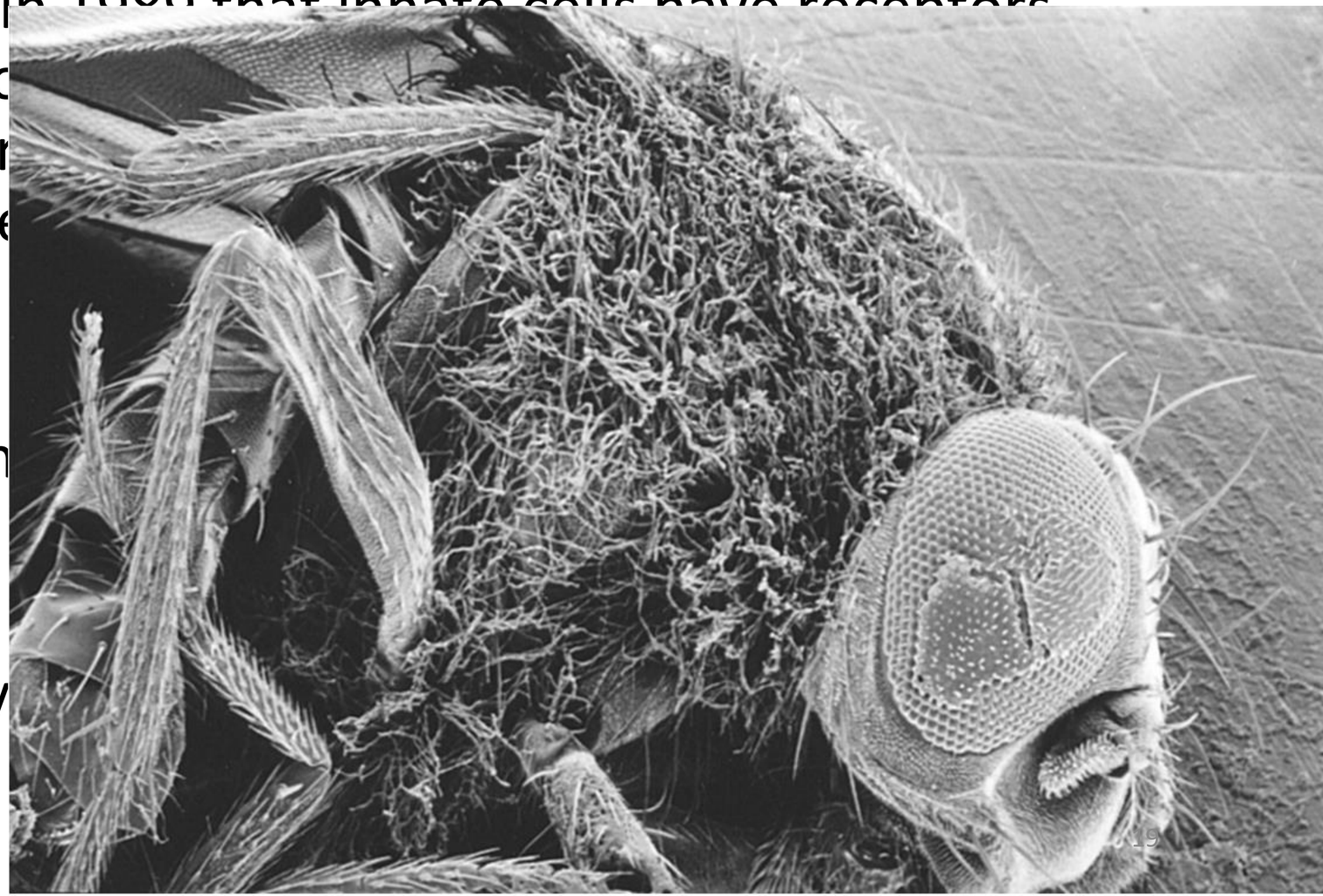
- Adaptive (acquired) immunity: takes time to develop

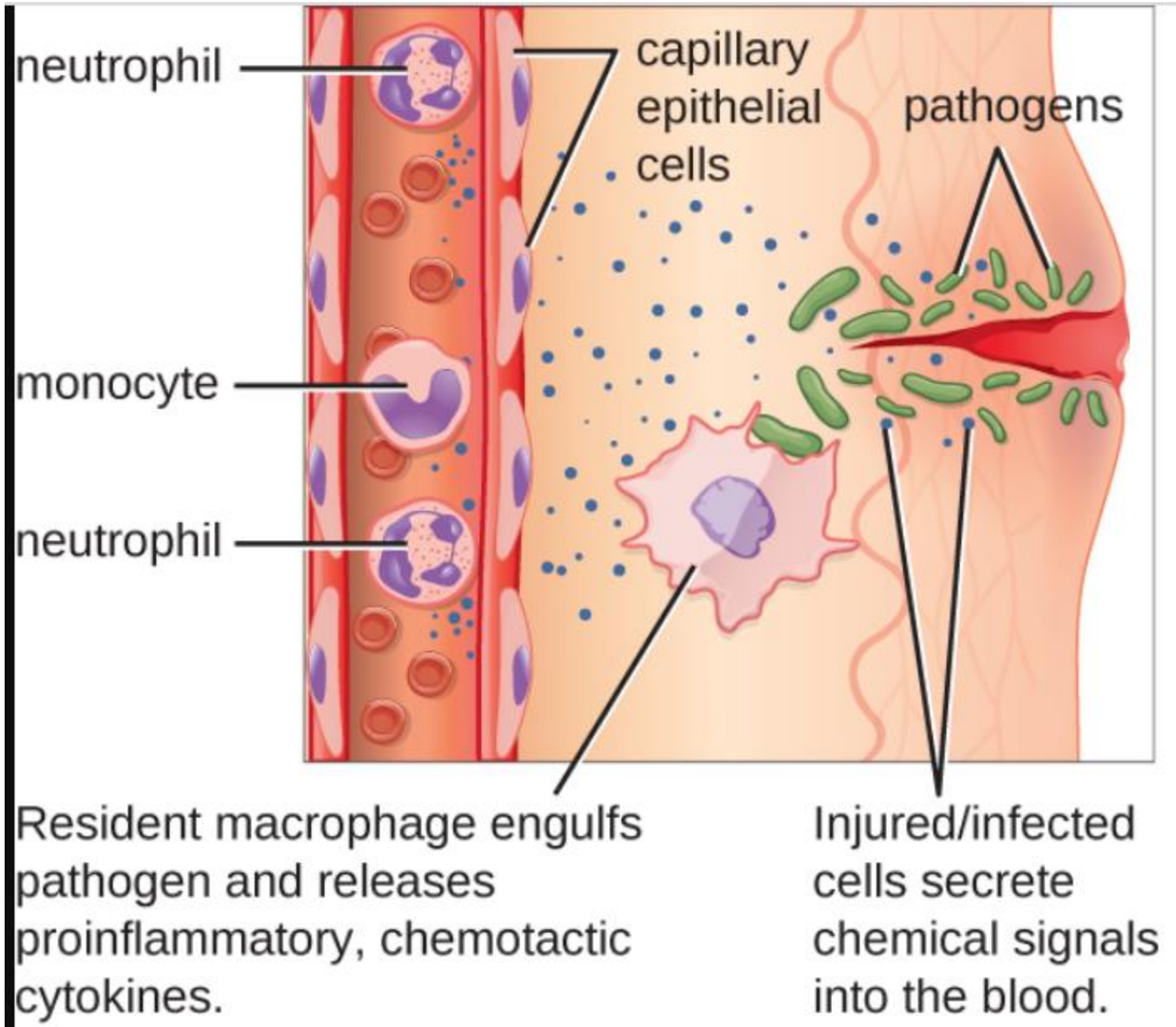
  Lymphocytes:

  B cells
  T cells

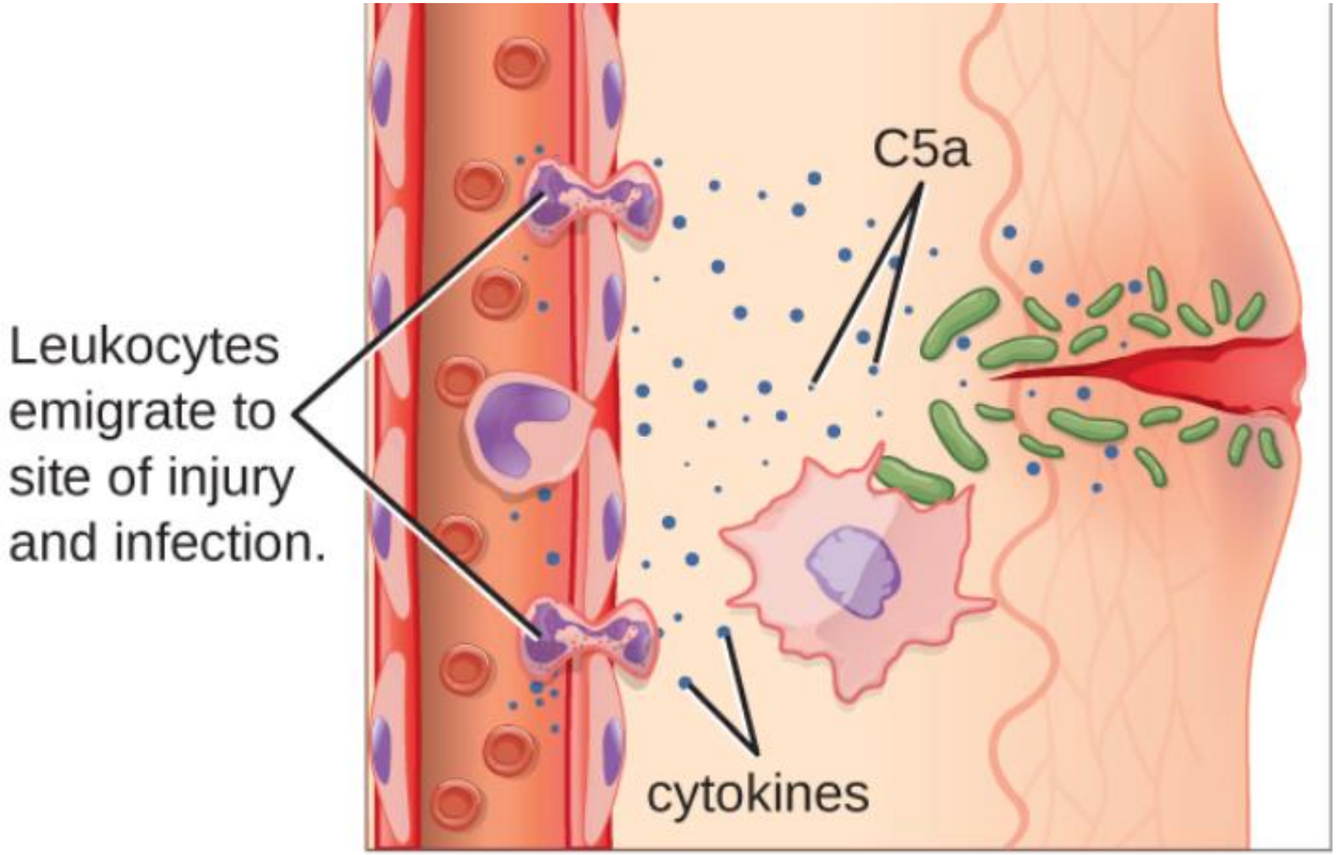
Innate Immune Cells: 2011 Nobel Prize to Beutler/Hoffman for TLRs and Steinman for Dendritic Cells

- Charles Janeway proposed i
  that recognize conserved c
  associated molecular patter
  recognition receptors". Jane
- Jules Hoffmann discovered
  for fighting off fungi, called
  a similar receptor in mice in
  receptors".
- Ralph Steinman discovered
  they coordinate the activity

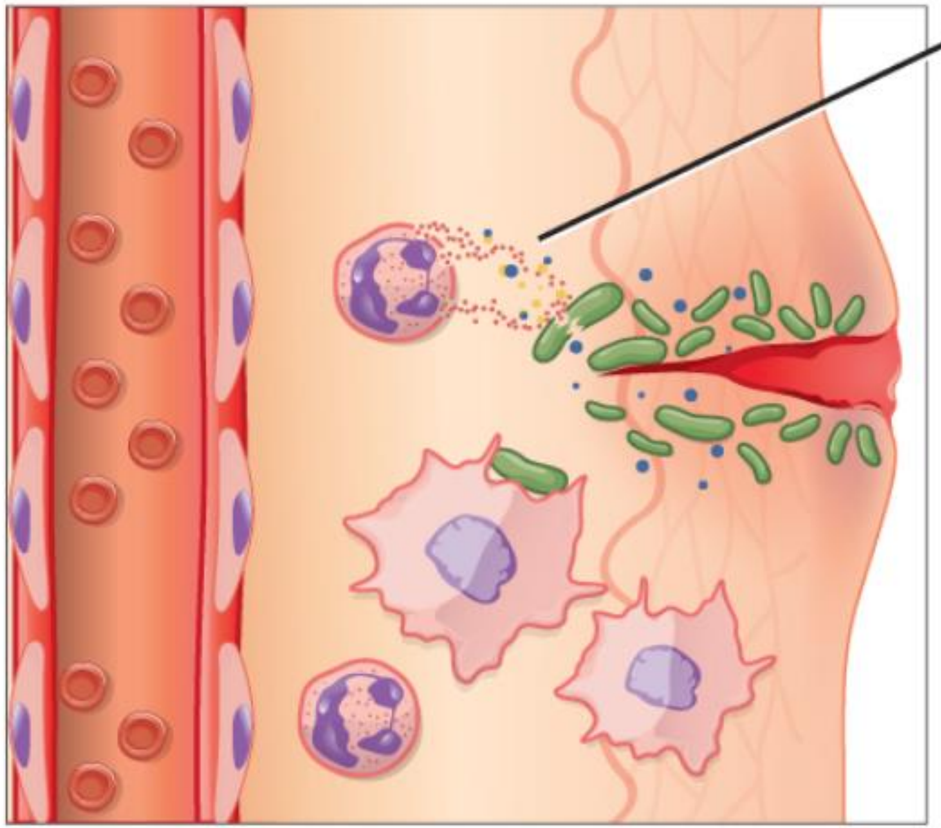




1 Leukocytes in the blood respond to chemical attractants released by pathogens and chemical signals from nearby injured cells.

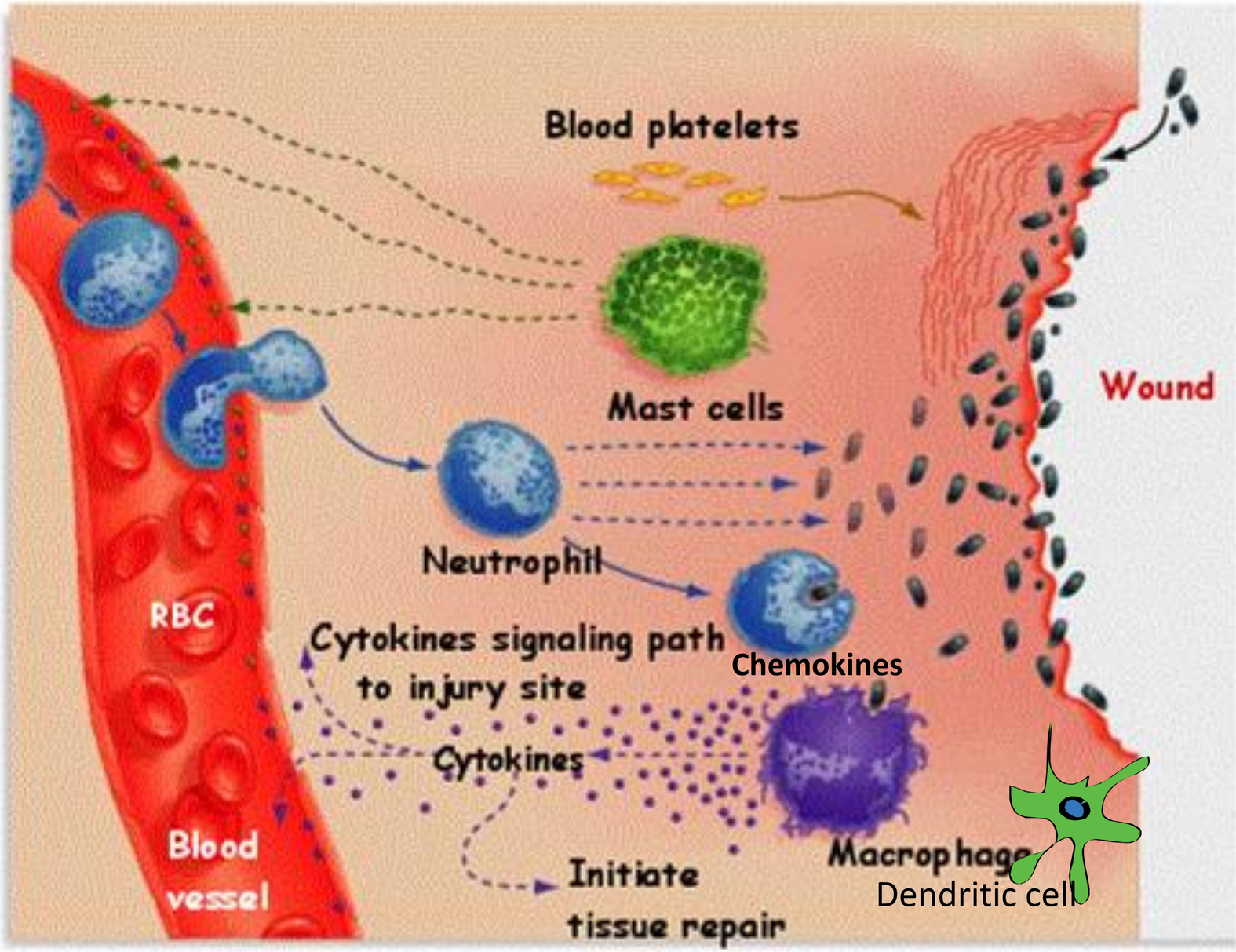


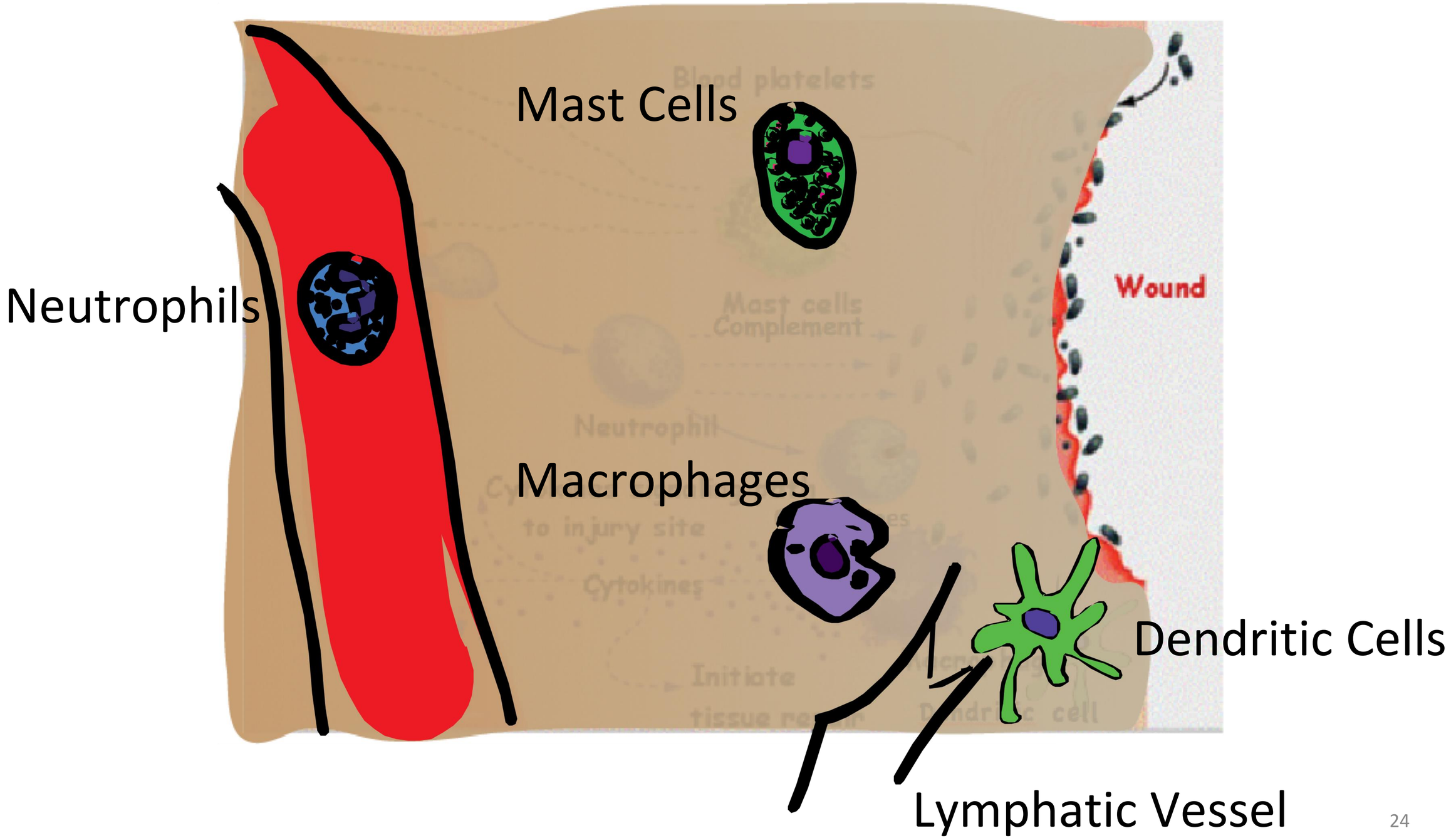
2 The leukocytes squeeze between the cells of the capillary wall as they follow the chemical signals to where they are most concentrated (positive chemotaxis).



3 Within the damaged tissue, neutrophils release chemicals that break apart pathogens. Monocytes differentiate into macrophages. Neutrophils and macrophages phagocytize pathogens and cellular debris.

Tissue resident Macrophages and Dendritic Cells become activated by tissue damage and by microbes to release proinflammatory molecules that cause increased vasodilation and vascular leakage which enables circulating immune components to access the site of infection.




Mast Cells
Neutrophils
Wound
Macrophages
Dendritic Cells
Lymphatic Vessel

Meanwhile back in the lymph node…..

Cells of the Innate System prompt selective expansion of particular lymphocytes of the adaptive system that recognize a piece of pathogen

This process is called Antigen Presentation

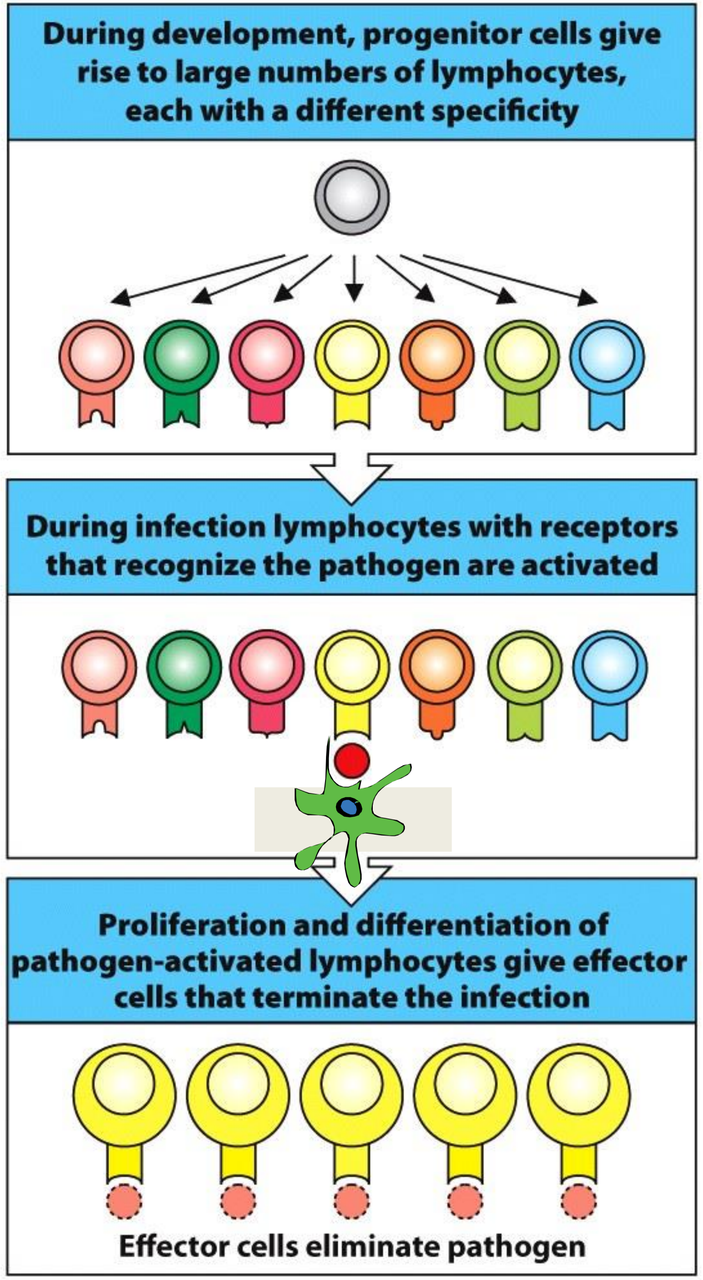


Figure 1.10 The Immune System, 3ed. (© Garland Science 2009)

Where is the immune system?

- In lymphatic organs (bone marrow, thymus, spleen, lymph nodes)
- Circulating in the blood
- Circulating through lymphatic vessels
- In non-immune tissues, either resident or moving through
- At interfaces between inside and outside of body
  - Within skin, in lung, intestines

Immune cells distributed throughout the body but from common origin

- Made up of cells that originate mostly in the **bone marrow**
- **Hematopoietic Stem Cells** in bone marrow give rise to most immune cells (brain microglia are an exception)

Mobility is a Key Aspect of Immune cells

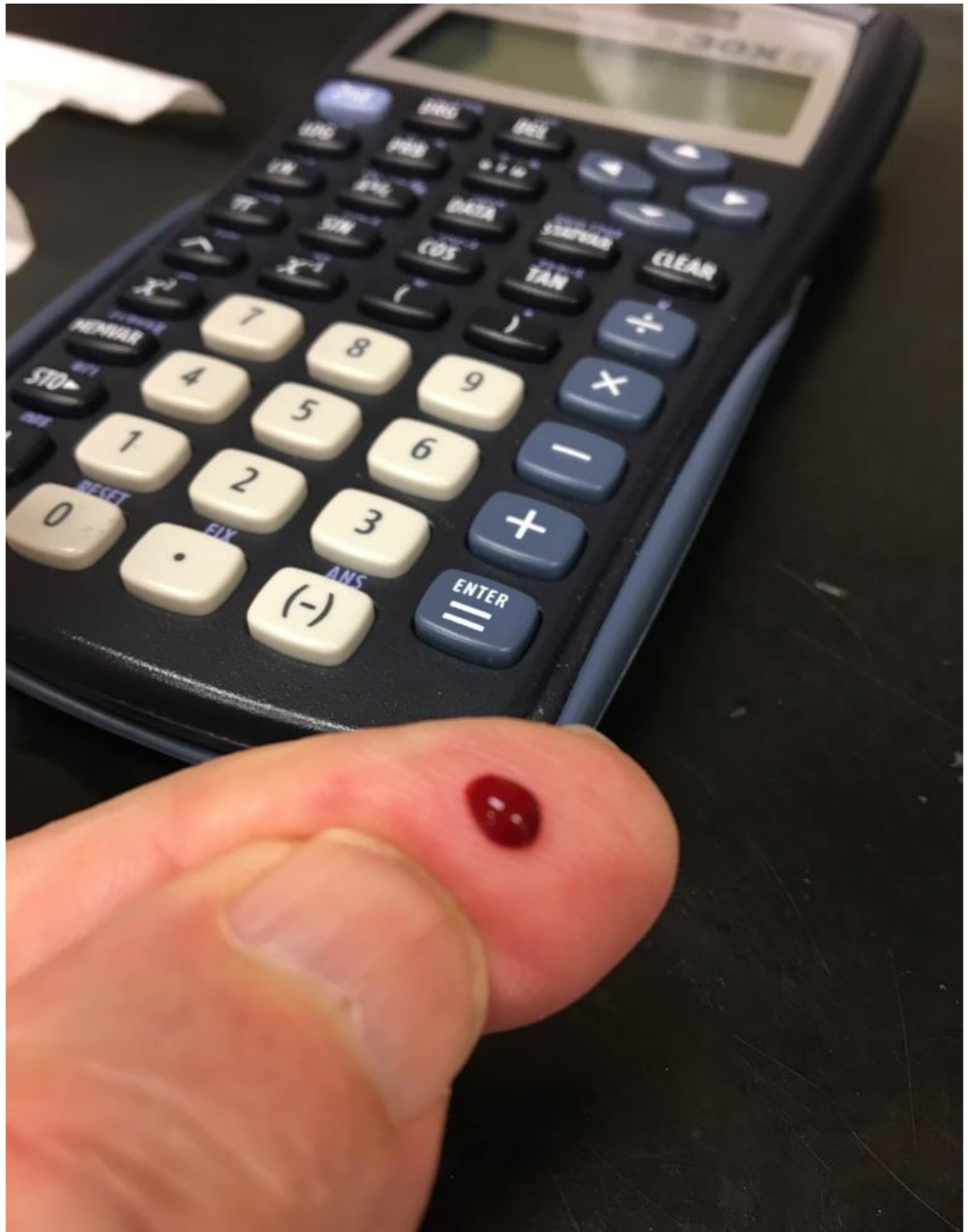
- During development of cells
- Scanning for antigen within lymph nodes
- Looking for infected cells throughout the body

- Sometimes random motion
- Sometimes attracted to a chemical gradient of **chemokines**

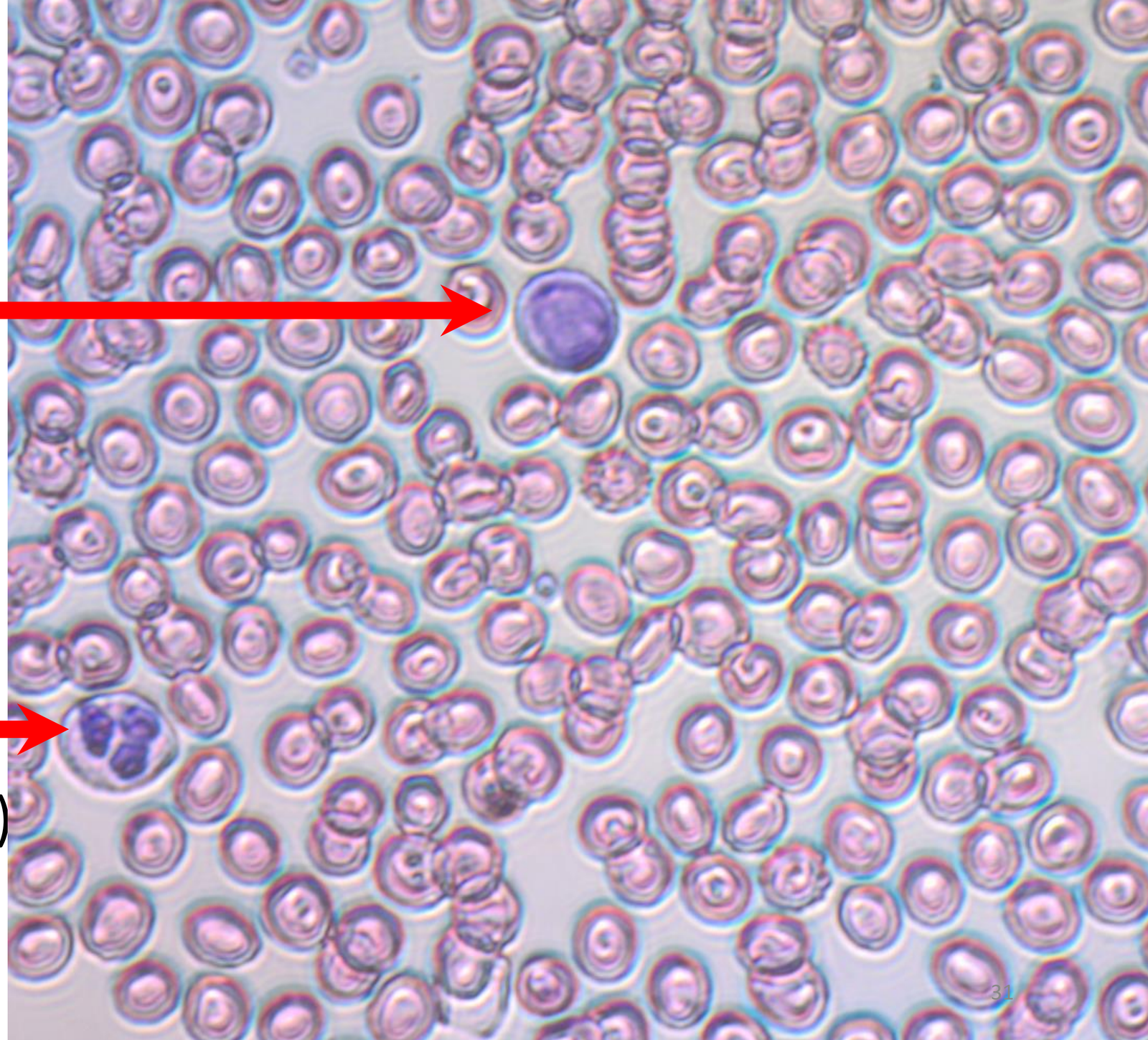
Immune System is unusual in that a substantial number of the cells are not in organs, but are circulating in blood and lymph

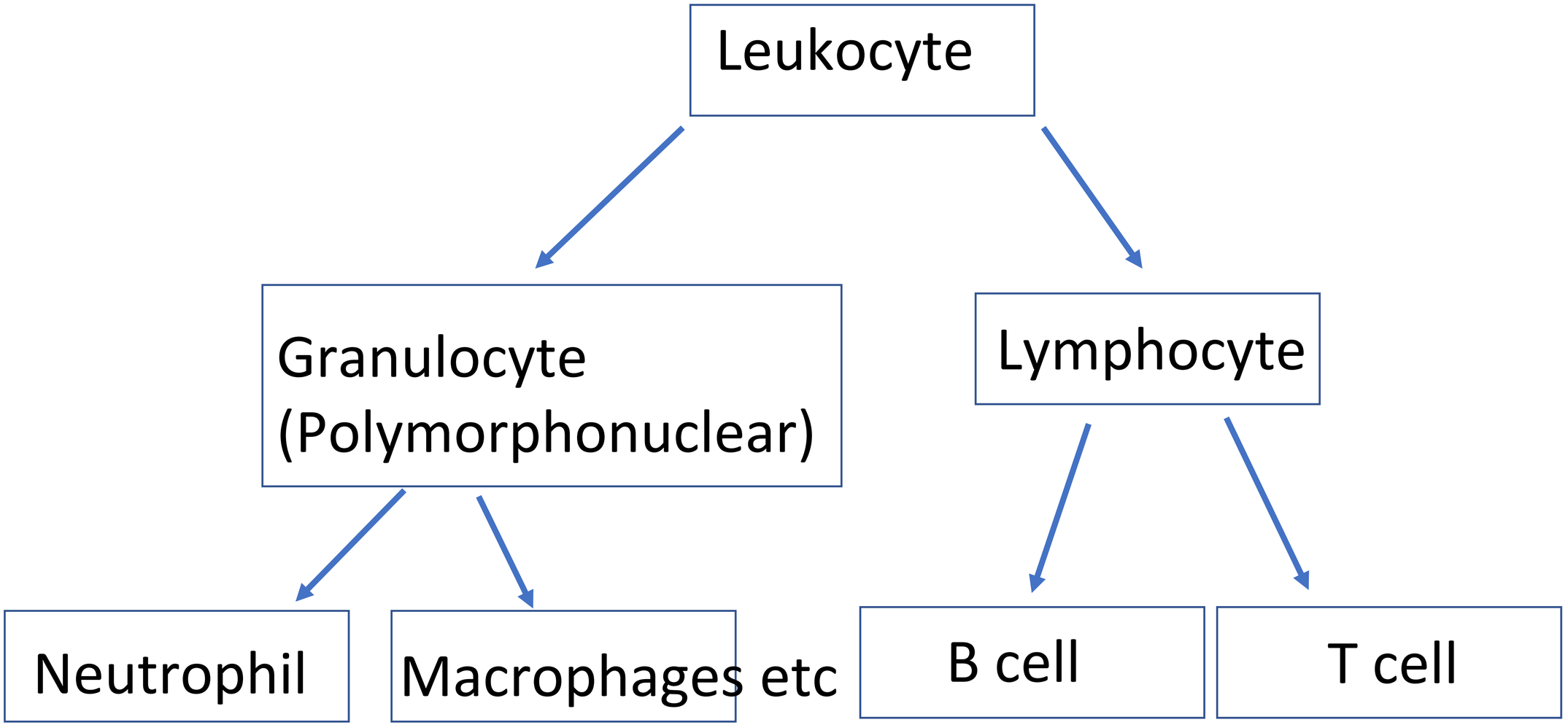
- Easy access to blood has facilitated study of the immune system

Ed’s Blood



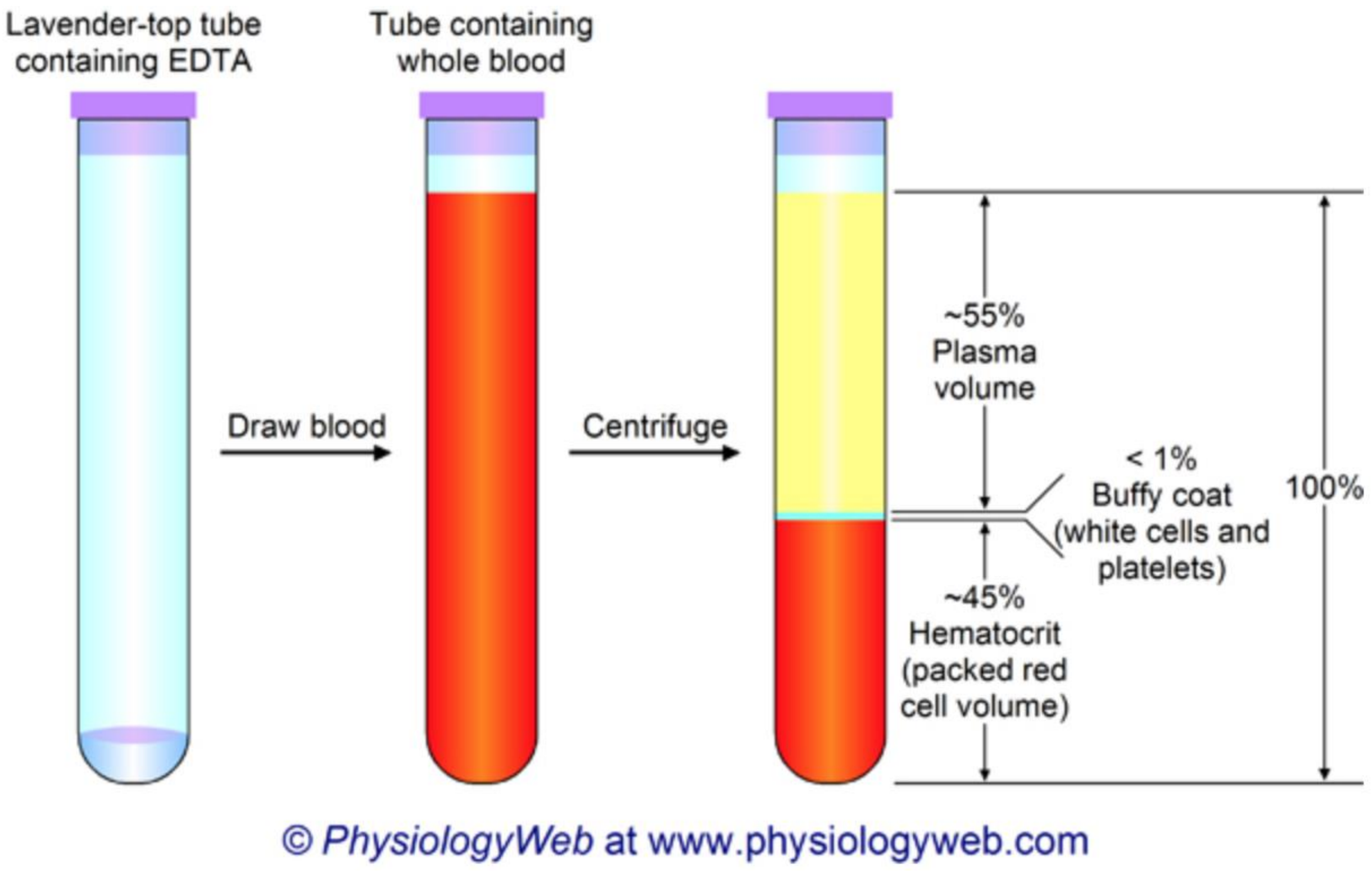
Ed’s Leukocytes (white blood cells)




Leukocyte
Granulocyte (Polymorphonuclear)
Lymphocyte
Neutrophil
Macrophages etc
B cell
T cell
Innate
Adaptive

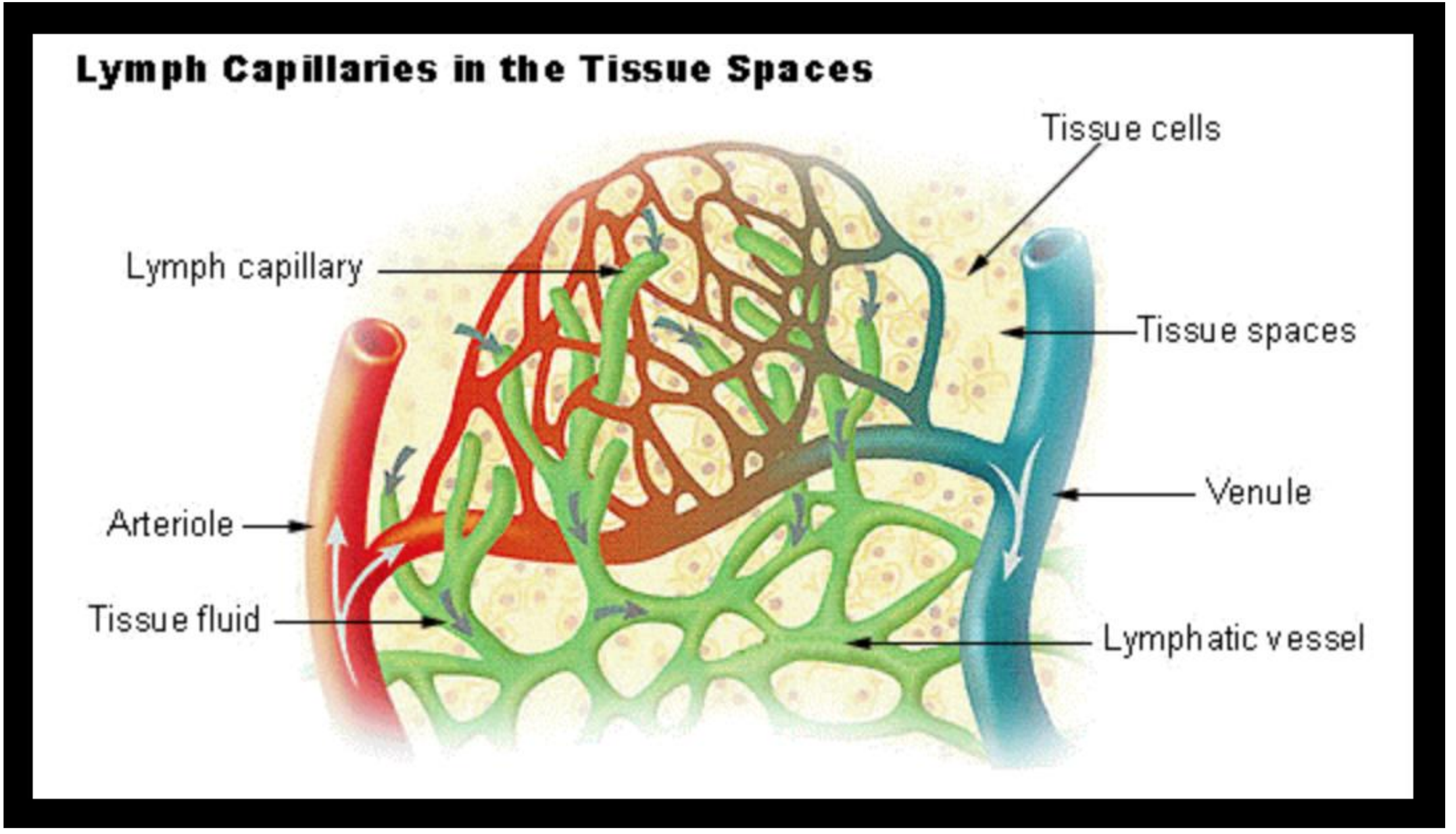
Most Common Leukocytes (White Blood Cells)

- Neutrophils (40-75%)
- Lymphocytes (20-50%)

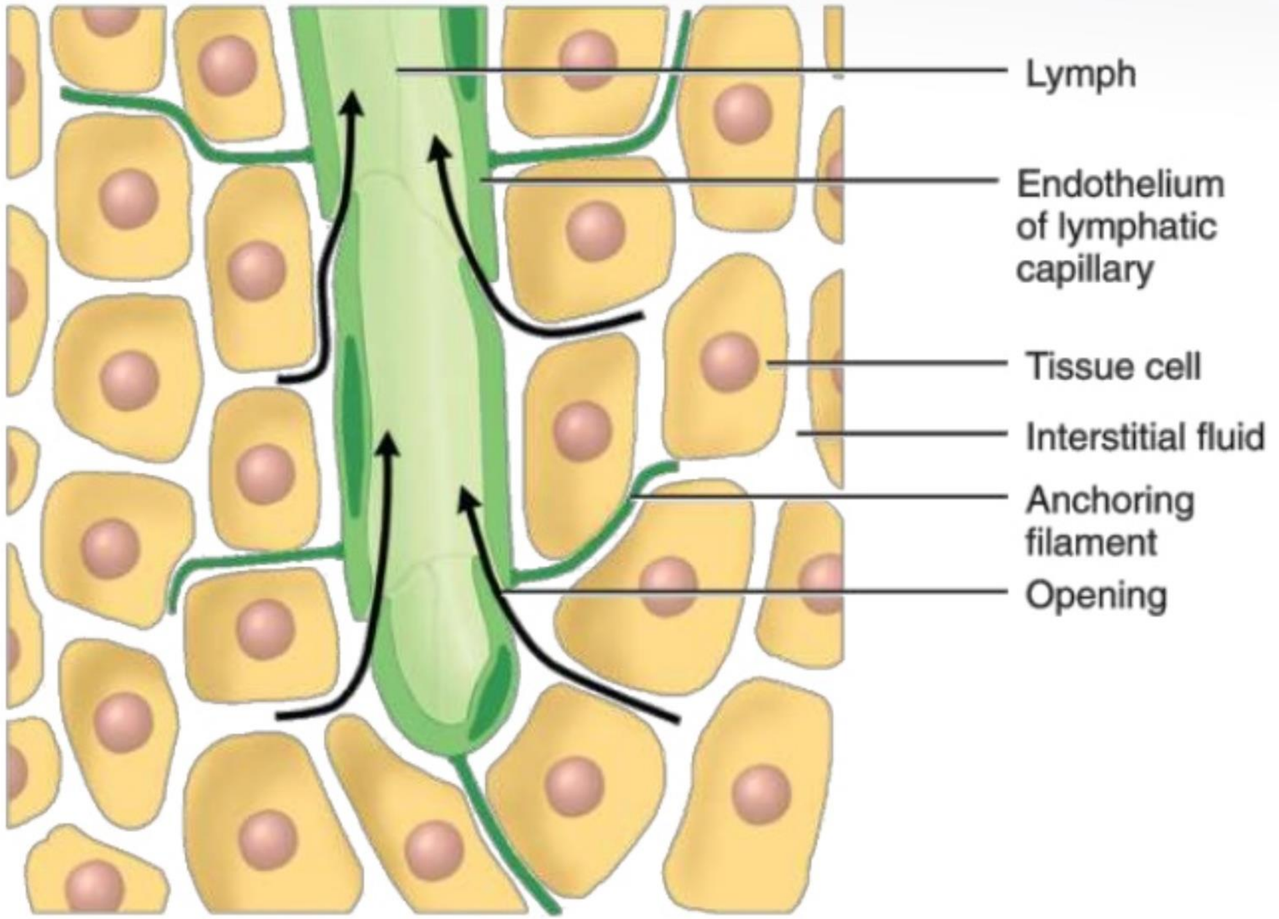

Lavender-top tube containing EDTA
Tube containing whole blood
Draw blood
Centrifuge
~55% Plasma volume
< 1% Buffy coat (white cells and platelets)
~45% Hematocrit (packed red cell volume)
100%
© PhysiologyWeb at www.physiologyweb.com

Where are the cells of the immune system?

- Besides Blood, cells also travel in Lymph
- Cells resident in tissues pick up pathogens and travel to lymph nodes; some pathogens travel in extracellular fluid by bulk flow

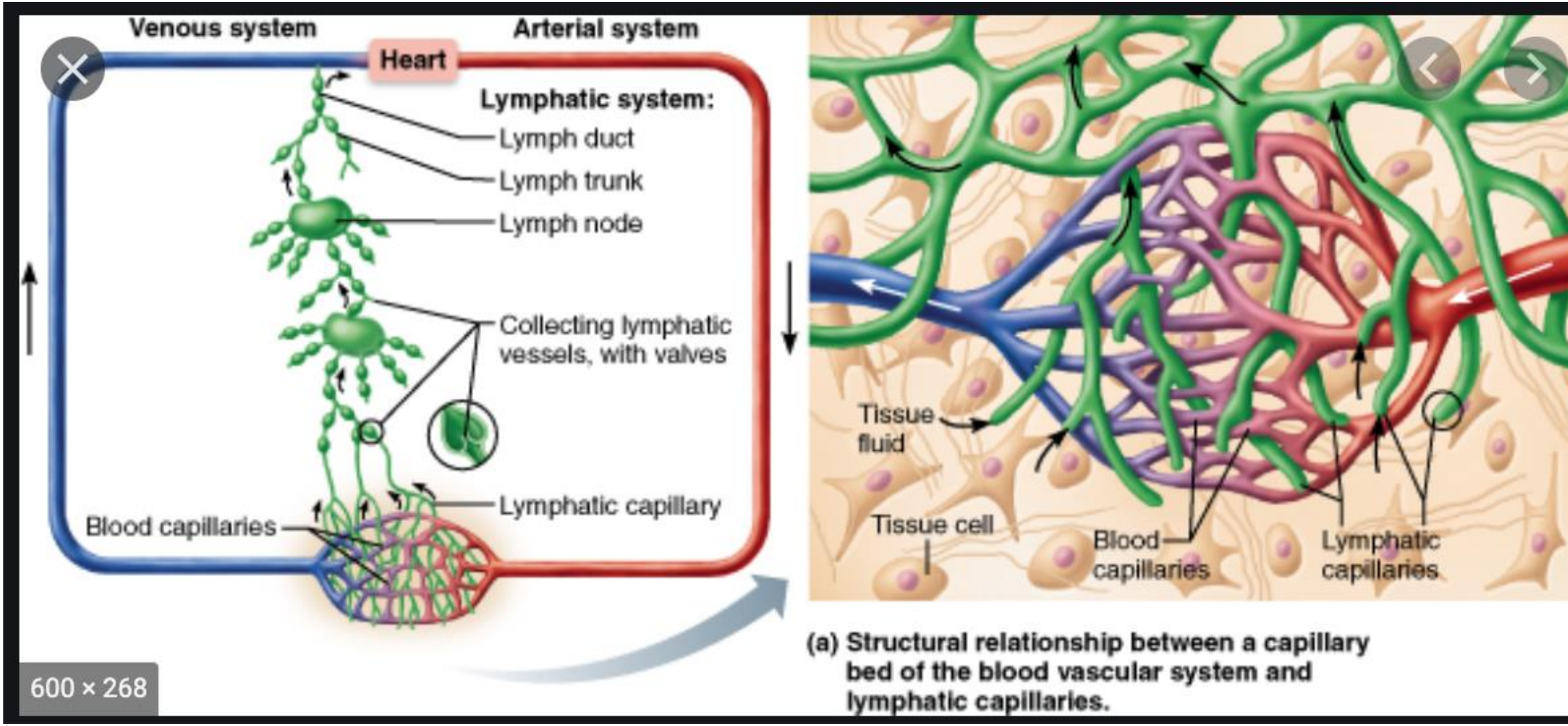

Lymph Capillaries in the Tissue Spaces
Tissue cells
Lymph capillary
Tissue spaces
Venule
Arteriole
Tissue fluid
Lymphatic vessel

Lymphatic Vessels and Fluid



(b) Details of a lymphatic capillary

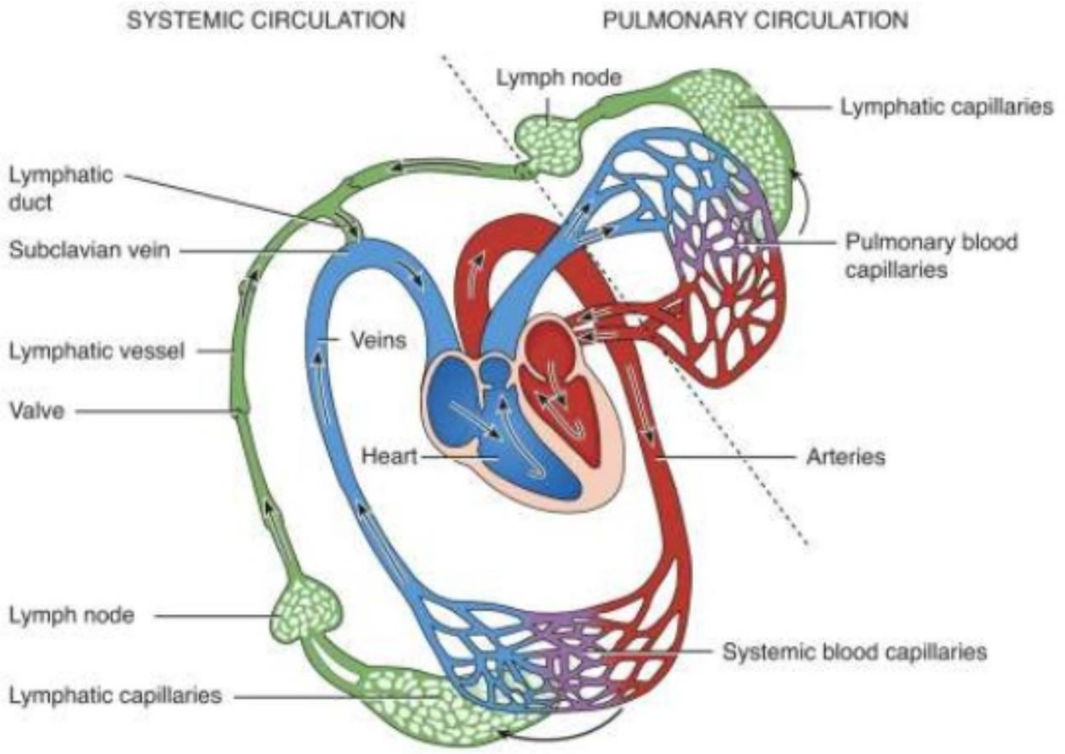
Lymphatic capillaries showing blind ends and one way flow

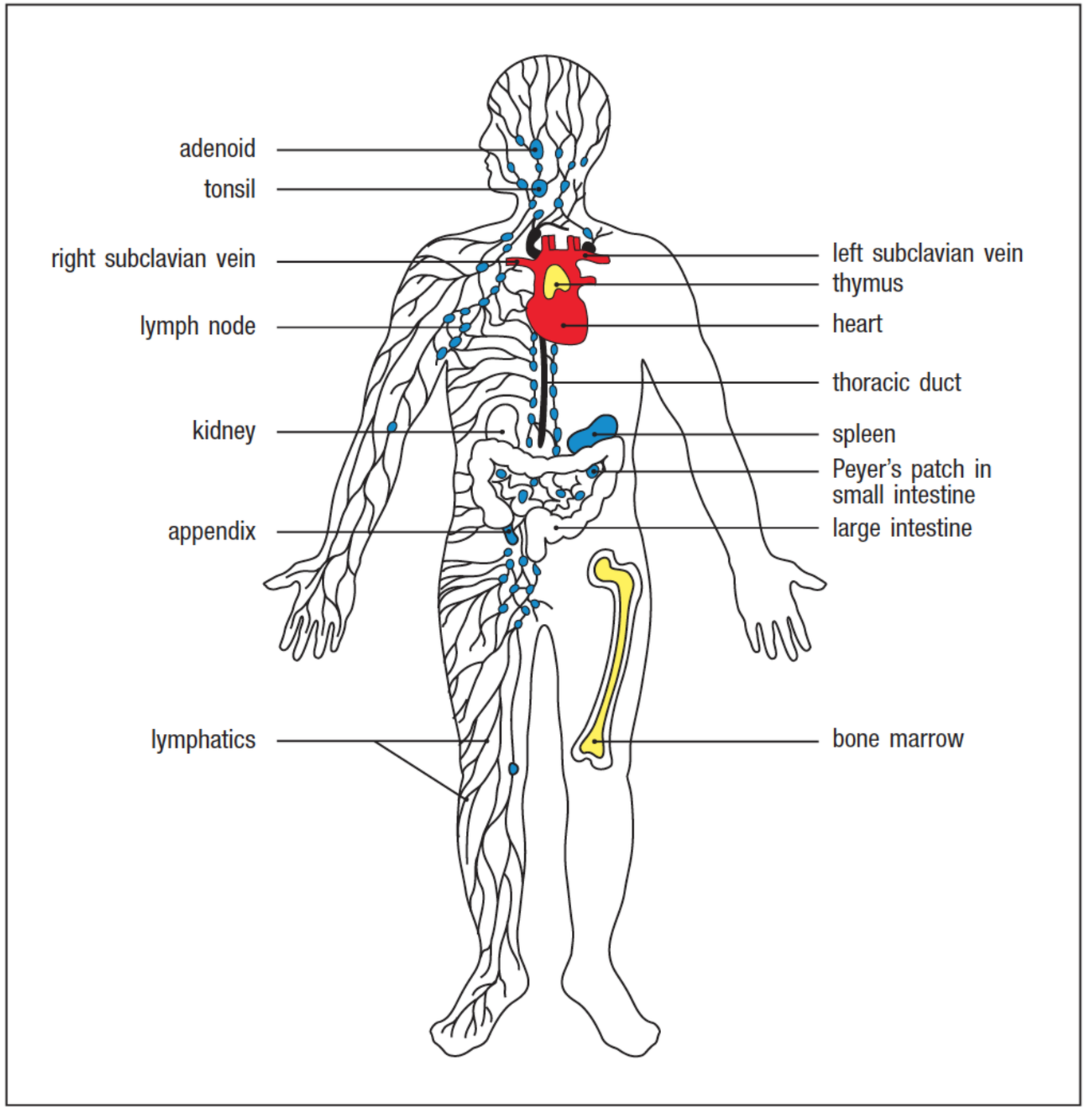


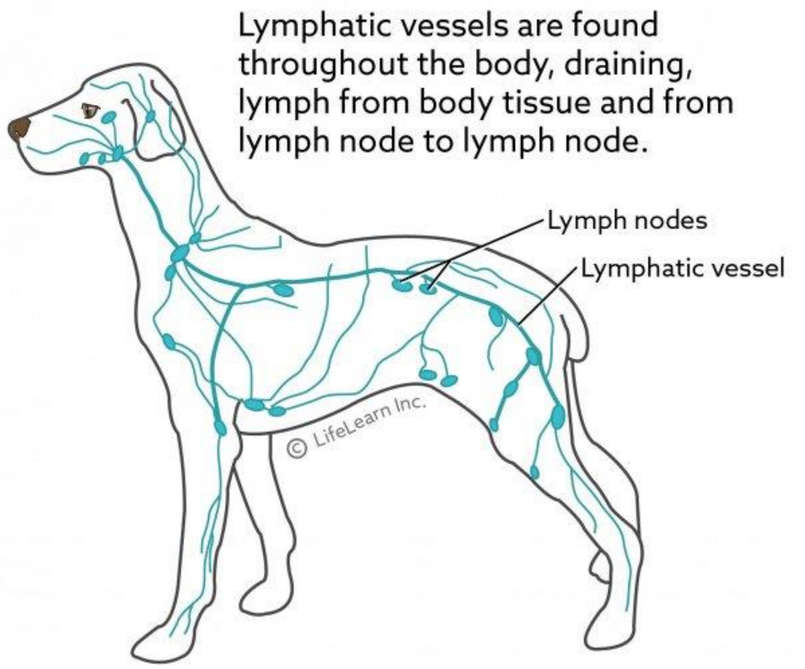
(a) Structural relationship between a capillary bed of the blood vascular system and lymphatic capillaries.

Lymphatic Vessels and Fluid

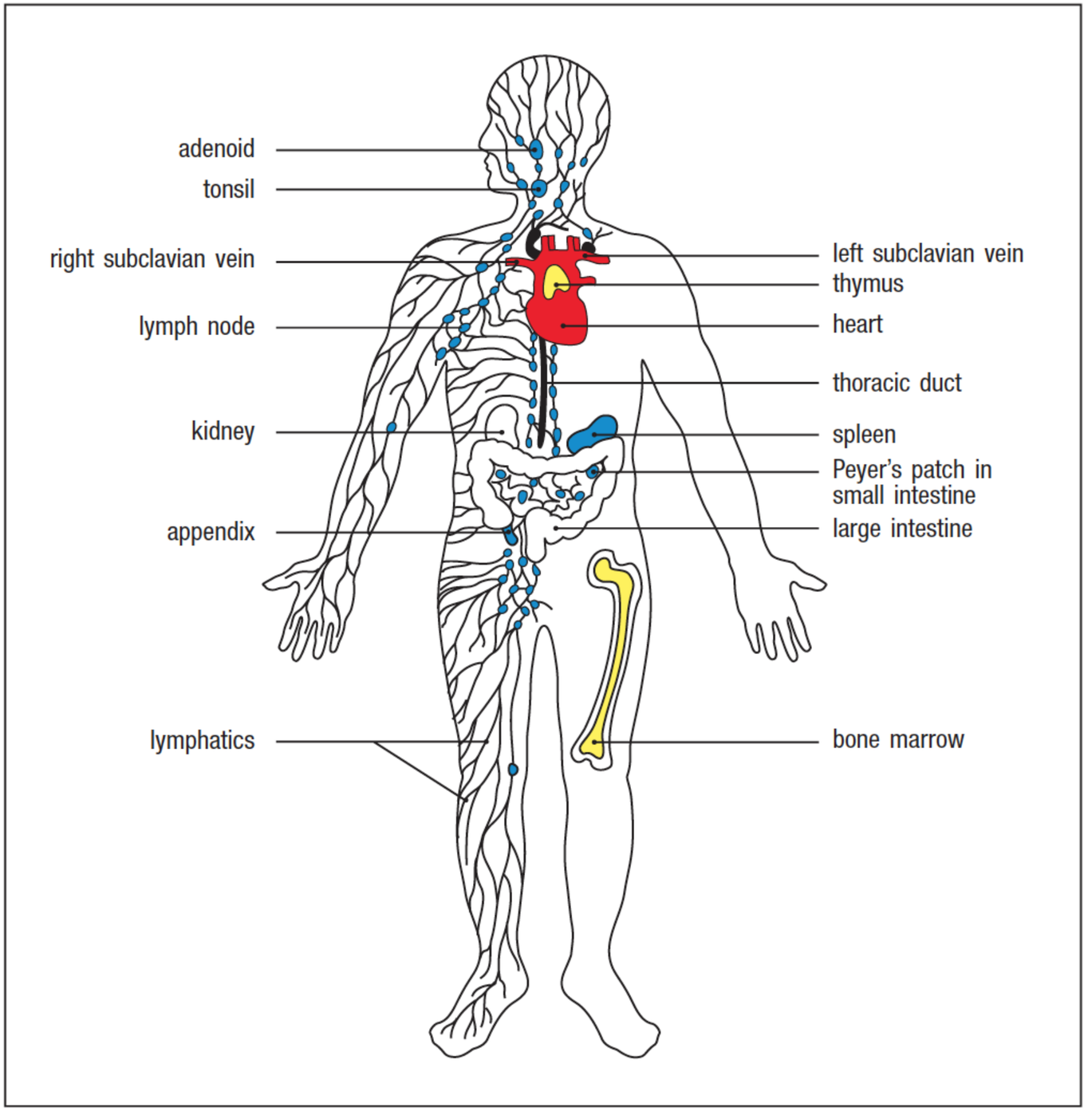
- **Lymphatic fluid is moved** by pressure in the interstitial space and the milking action of skeletal muscle contractions and respiratory movements.
  - An obstruction or malfunction of lymph flow leads to **edema** from fluid accumulation in interstitial spaces.







Janeway, 2017, Fig 1.18,



Janeway, 2017, Fig 1.18,

Lymphocytes: T cells and B cells

- Pieces of pathogen (antigens) are recognized by T cell Receptors (TCRs) and B cell receptors (BCRs)
  - BCRs are initially on the surface of B cells, later secreted into the blood and other fluids as “antibodies”)

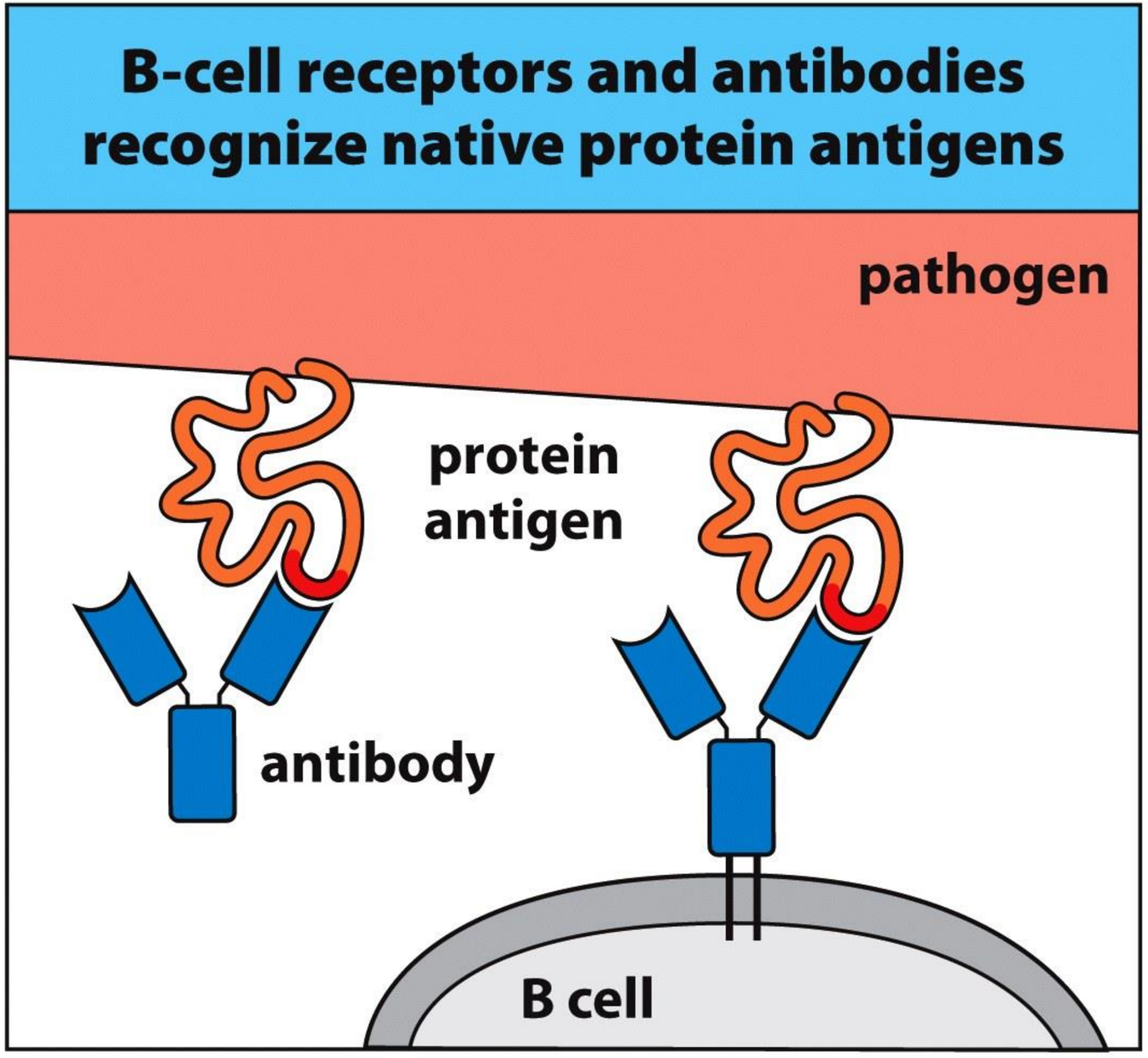
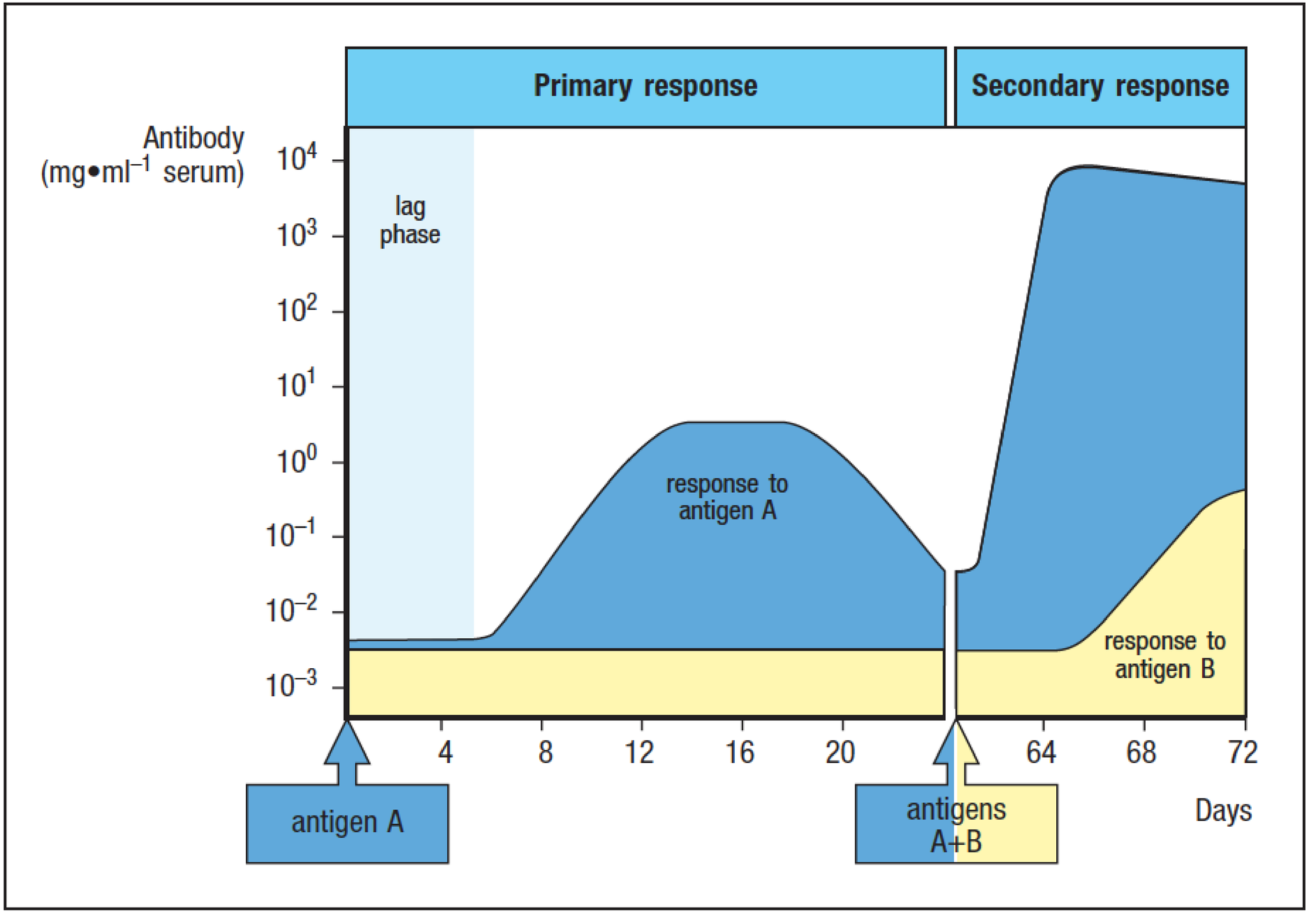


Figure 3.12 The Immune System, 3ed. (© Garland Science 2009)

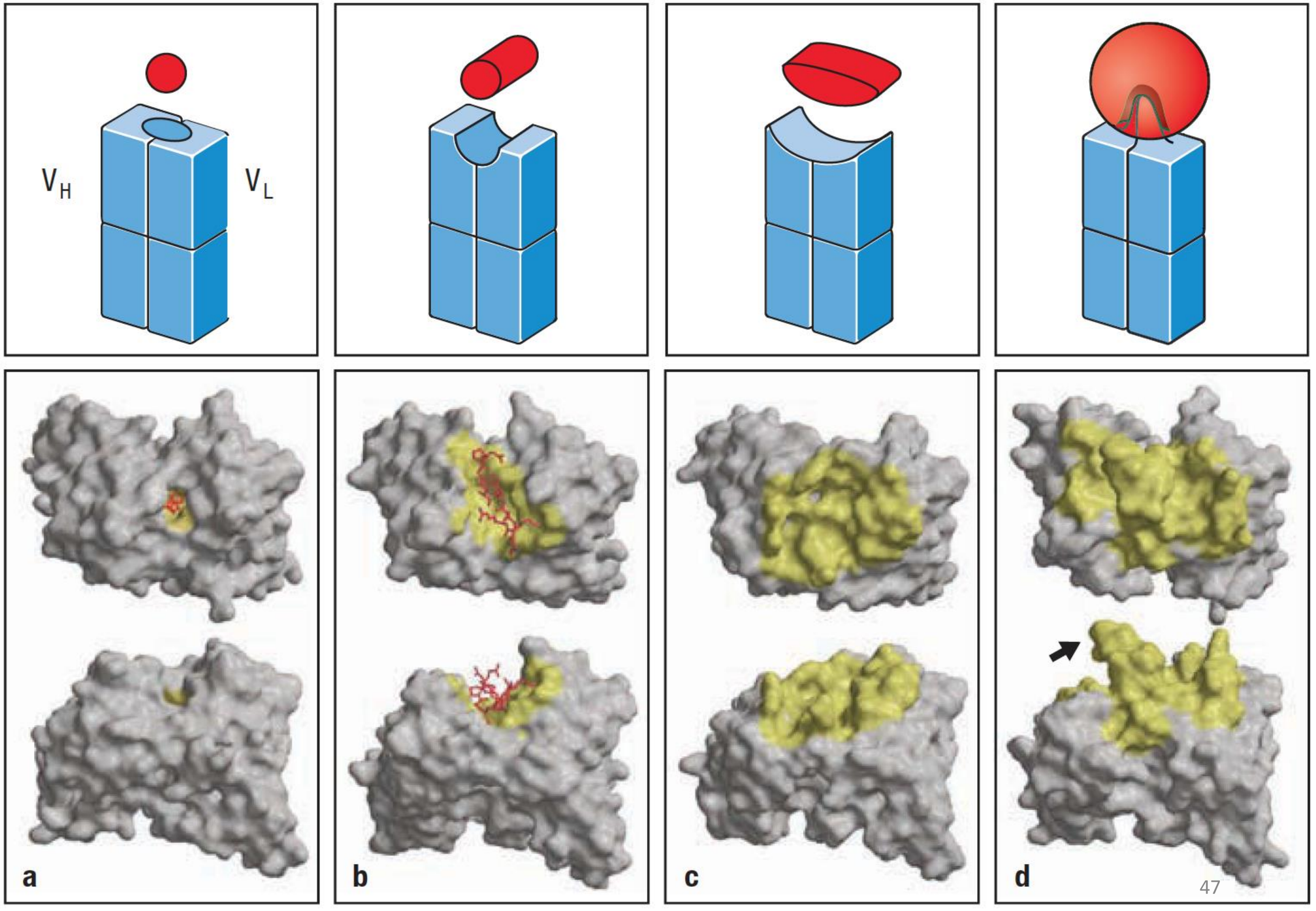
Adaptive

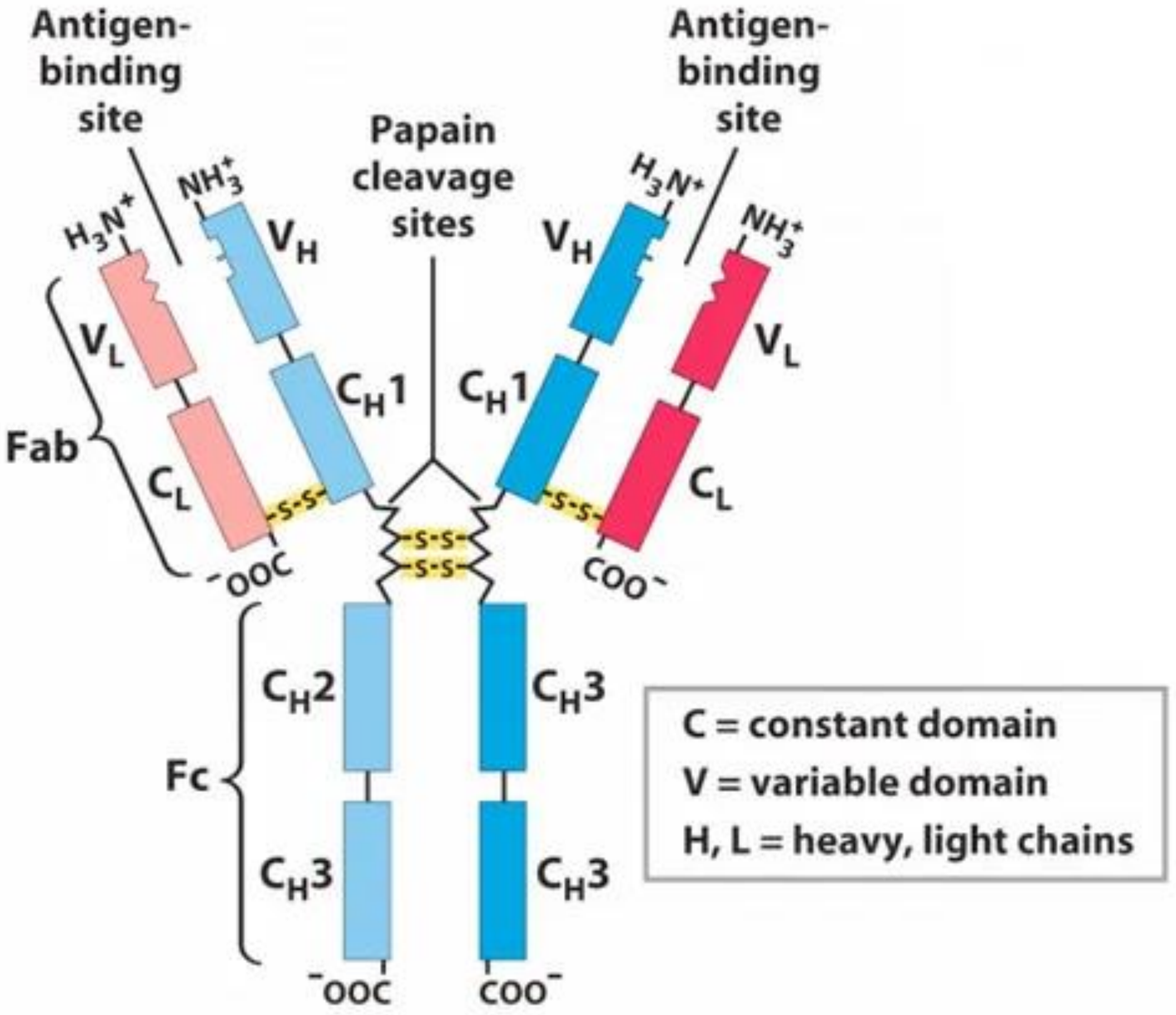
- B cells and T cells
- Requires time to become effective
- Constantly generating random diversity by gene rearrangements
- Cells whose receptors bind to an antigen proliferate in response to binding pathogens (clonal selection)
- Retains memory of pathogen: Second exposure response is higher faster stronger
  - This memory is what we call “immunity”


Primary response
Secondary response
Antibody
(mg•ml−1 serum)
10^4
10^3
10^2
10^1
10^0
10^−1
10^−2
10^−3
lag
phase
response to
antigen A
response to
antigen B
4
8
12
16
20
64
68
72
Days
antigen A
antigens
A+B

What does it mean to "**recognize**" something? E.g., an **antibody** recognizes an **antigen**?

- **Recognition** occurs at molecular level
- An **antibody** is a protein, made up of amino acids linked together
- The antibody's strand of amino acids takes on a particular 3-dimensional **shape**
- An **antigen** is anything that stimulates an immune response, often a small piece of a pathogen
- The antigen binding region of the antibody is a small region on the tips of two arms


V_H
V_L
a
b
c
d


Antigen-binding site
Antigen-binding site
Papain cleavage sites
H_3N^+
NH_3^+
V_H
V_L
C_H1
C_L
Fab
^-OOC
COO^-
C_H2
C_H3
Fc
C = constant domain
V = variable domain
H, L = heavy, light chains

Pause for Questions