Immunotherapy of Cancer

OLLI, Fall 2020
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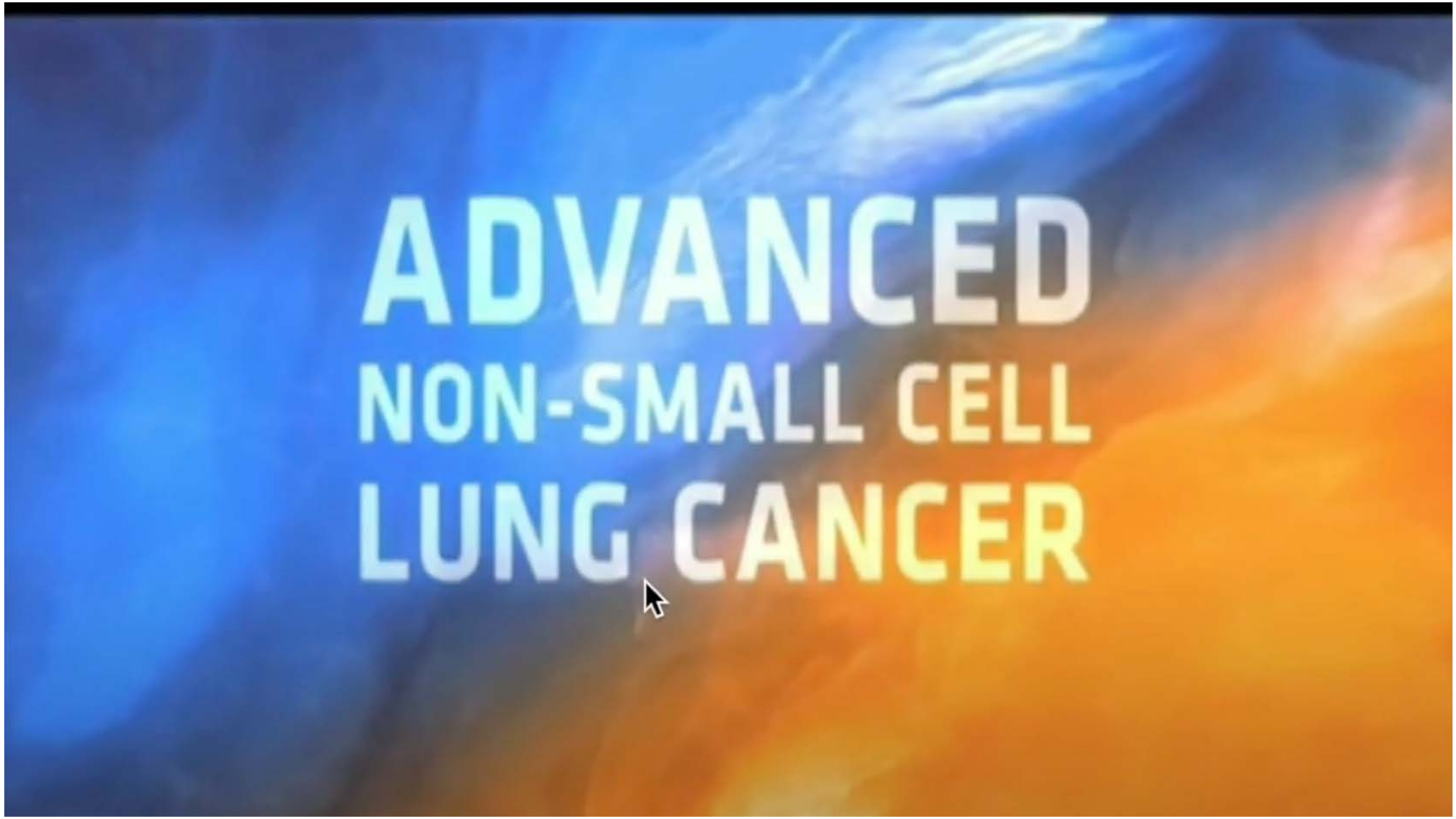
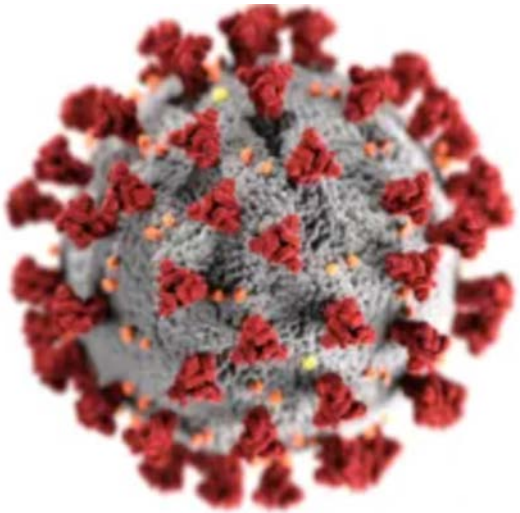
Why learn about immunology?

- Cancer is the second leading cause of death of OLLI-age people (heart disease is slightly ahead of cancer).
- Immunotherapy for cancer has the potential to cure many cancers.

SCIENCE Magazine Breakthrough of 2013

Instead of targeting tumors directly, cancer immunotherapy encourages the immune system to attack tumors.


ADVANCED
NON-SMALL CELL
LUNG CANCER




LOVE YOUR
NEIGHBOR. WEAR
A MASK.


QUIERE A TU
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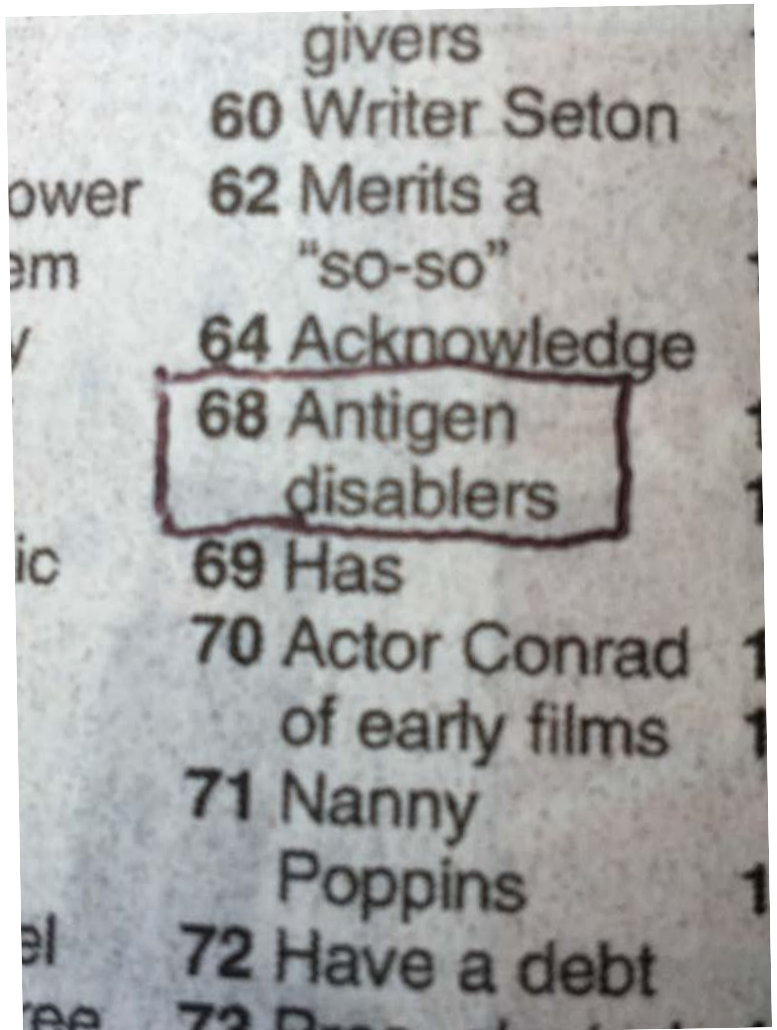
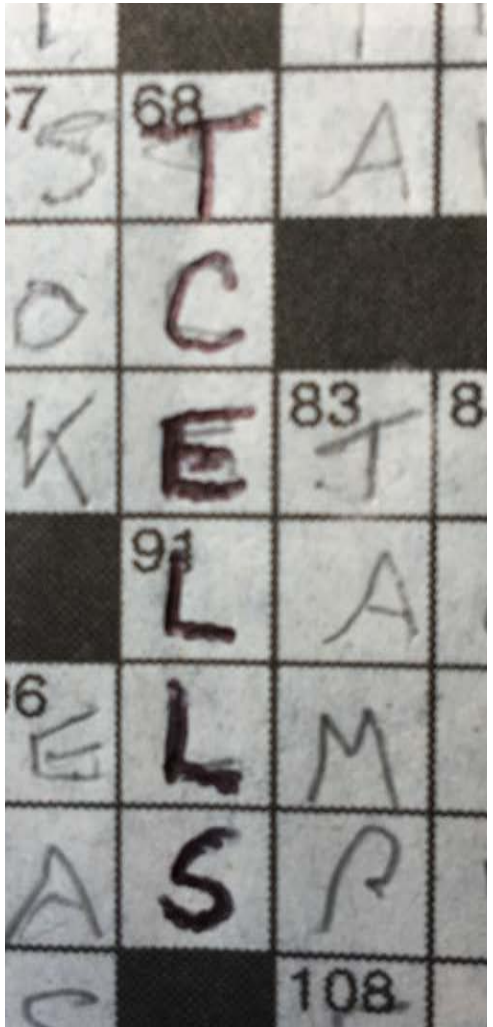
MÁSCARA.

Crossword Puzzle, NewsGazette, October 4, 2020

Antigen disablers





T cells

- “We are all immunologists now”
  - David Remnick, The New Yorker, April 13, 2020

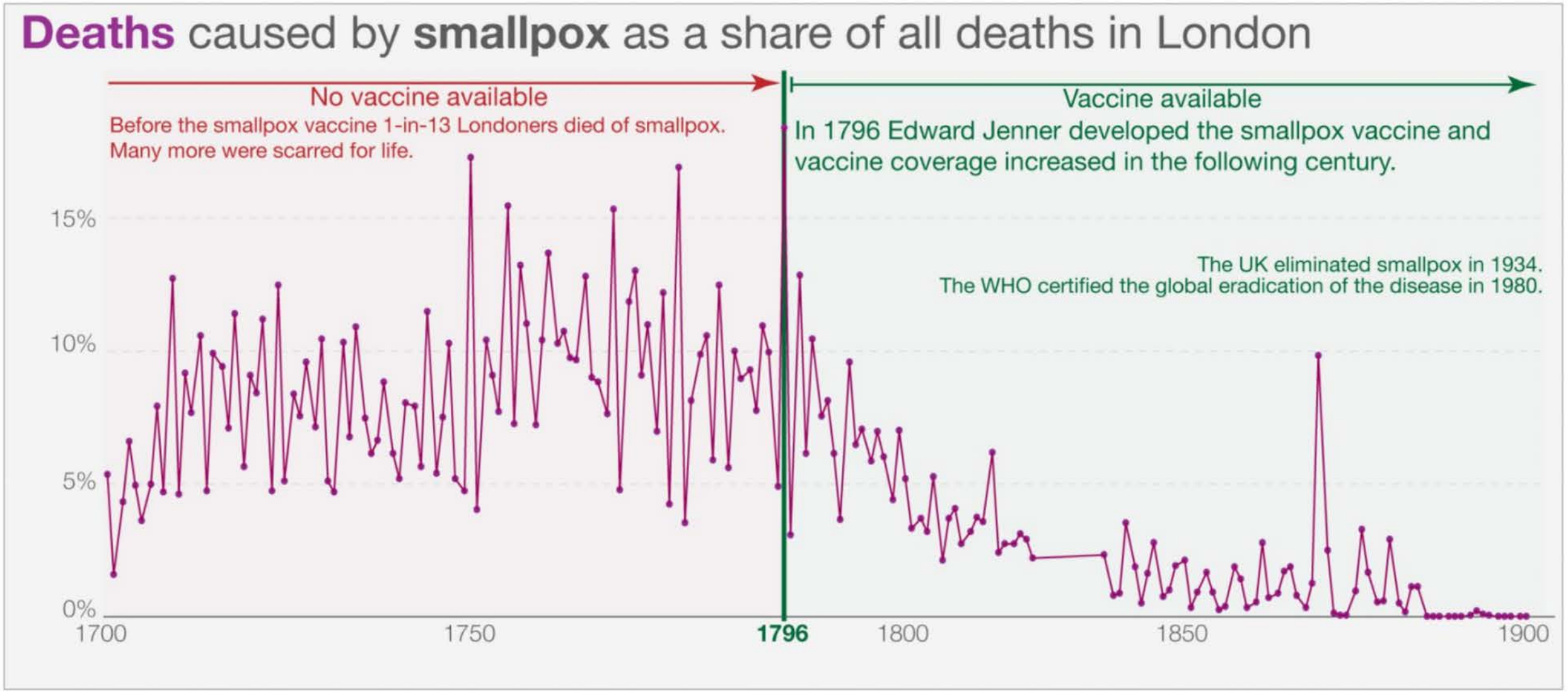
- “The thing is, the immune system is very complicated.”
  - Ed Yong, The Atlantic, August, 2020

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



- “It is time to close the book on infectious diseases, and declare the war against pestilence won.”
  - attributed to the United States Surgeon General, Dr. William H. Stewart (1965-1969)

Spellberg and Taylor-Blake *Infectious Diseases of poverty* 2013, **2**:3
http://www.idpjournal.com/content/2/1/3

INFECTIOUS DISEASES OF POVERTY

RESEARCH ARTICLE Open Access

On the exoneration of Dr. William H. Stewart: debunking an urban legend

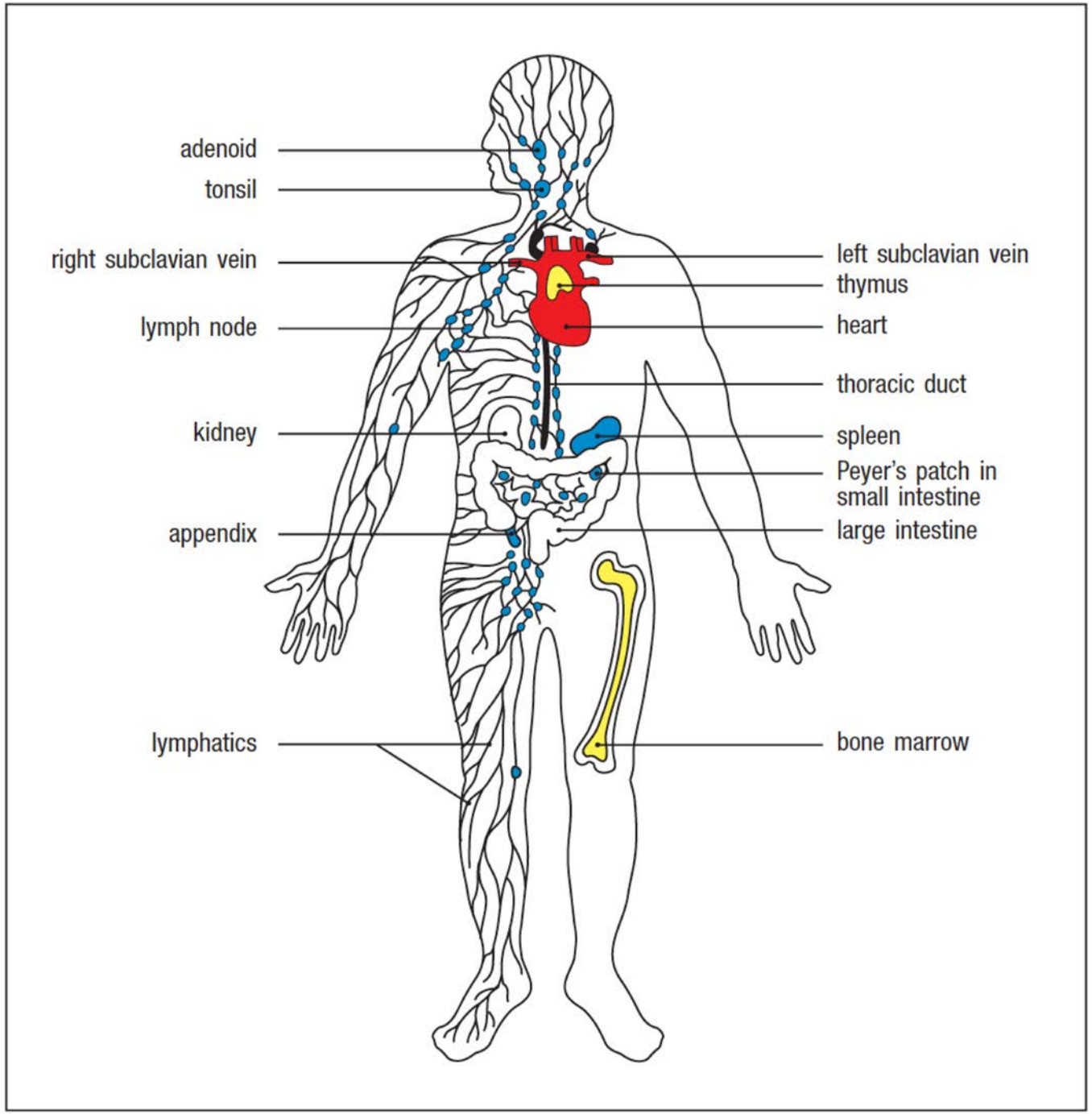
Brad Spellberg[1,2*] and Bonnie Taylor-Blake[3]

Will Immunotherapy have the same impact on Cancer?

- Time will tell…….

Learning Objectives

- Learn a bit about history (William **Coley**)
- Gain a sense of the **size** o pathogens
- Think about what the **imm** components)
- Learn what it means to "**r**
- Learn **where** in the body



Looking Back into history

- Practical manipulation of the immune system predates knowledge of things actually work
- “Immunity” resulting from exposure to a disease agent goes back to Greeks/Chinese
- Biological basis for immunity not understood until twentieth century
- Small components in serum vs cellular defenses
- “Immune system” term first used in 1967

Some progress is possible in the absence of understanding mechanisms

- Inoculation and vaccination (Edward Jenner, 1796)
- Cholera and water (John Snow, 1854)
- Infection and cancer (William Coley, 1893)

William Coley (1862 – 1936)

- Bessie Dashiell, was young friend of John D. Rockefeller, Jr. and a patient of Coley, a young surgeon at Memorial Hospital; she died from a sarcoma on her hand.
- Lead to Coley's experimentation wi
  Rockefeller family's medical philant
- Coley noticed anecdotal reports of
  loss of tumors following bacterial ir
- Fred Stein, a German immigrant sa
  surgical wound infected, and the ca
  disappeared. Coley tracked him do
  was still cancer free.

- Coley tried intentional infection of sarcoma patients with erysipelas, St. Anthony's Fire (streptococcus pyogenes)
- First patient, Zola, an Italian immigrant, responded dramatically, cure lasted 8 years
- First 12 patients, 3 successes, 2 died from treatment

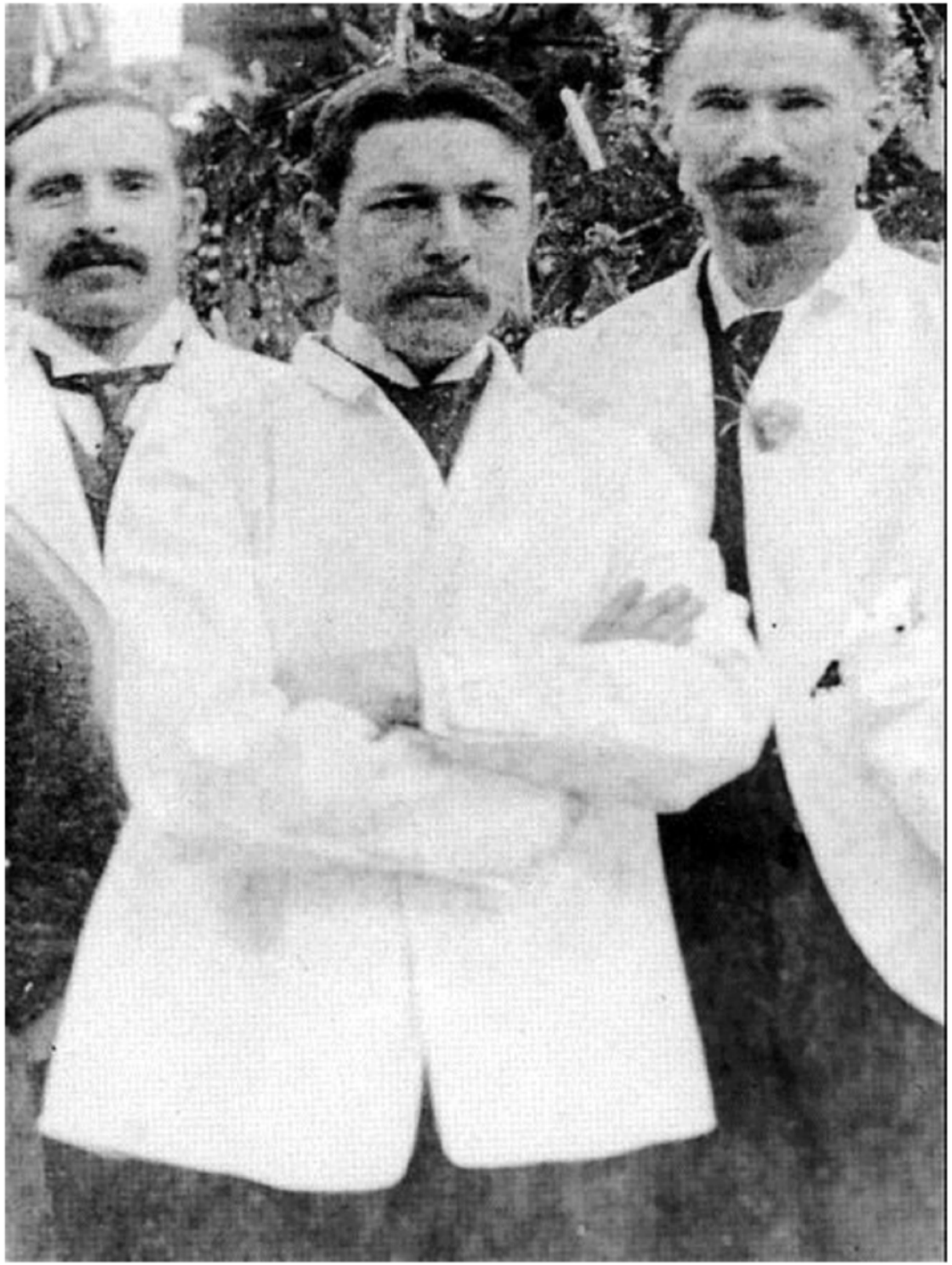
Figure 2

Signor Zola, who survived another 8 years after being treated by Coley in 1891.

Wikipedia

Coley's toxin

- Shifted to toxin extracts. Added *Bacillus prodigiosus* extract, gram negative endotoxin.
- First patient using toxin extract was John Ficken, 16-yr old boy, with enormous intestinal bulge. 1893.
- Increased dose until fever, vomiting, chills.
- Tumor disappeared, remained gone until his death 26 years later from a heart attack.
- Subsequent patients did not respond as dramatically.



ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yesterday that nearly 100 cases of that supposely incurable disease have been cured in this city during the last few years, all through the use of the fluid discovered by Dr. Coley.

Coley claimed 11% cures

NYT, July 29. 1908

Others doing similar experiments before Coley

- C.H.H. Spronck in the Netherlands, first in dogs and then patients, with similar results
- Showed treatment could be effective whether injected into tumor or at a distance from tumor (suggested factor circulating in the blood).

- But the immune system was not understood: Paul Ehrlich and Emil von Behring's antitoxins (antibodies) and Elie Metchnikoff's macrophages just beginning to be explored
- Coley did not even suggest what the mechanism of his occasional successes might be

- Treatment controversial; other physicians had trouble replicating Coley's successes
- Lost out to radiation and later chemotherapy
  - scientific characterization of the agents and political backing
- "Coley initiated his most important series of experiments in an intellectual environment utterly incapable of making scientific sense of them." " -- Stephen Hall, A Commotion in the Blood
- "once a novel therapy acquires the odor of inefficacy or controversy, it becomes extremely difficult to rehabilitate" -- Stephen Hall, A Commotion in the Blood

Was the immune system responsible for Coley's occasional cures of cancer?

If so, what parts of the immune system?

Break for Questions

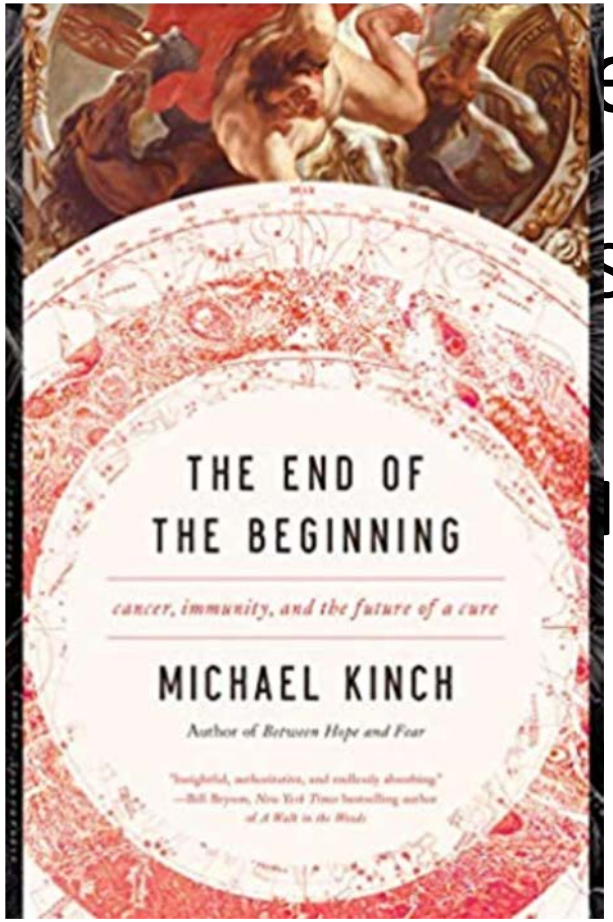
Type your question in the Q&A window

(if no questions, name that tune (song and artist) in the Chat window)

Recommended Texts

- Murphy, K. **Janeway's Immunobiology**, 9th edition, 2017.
- Abbas, AK. **Basic Immunology**, 6th edition, 2020.

ended books



S. **A Commotion in the Blood**, 1998.

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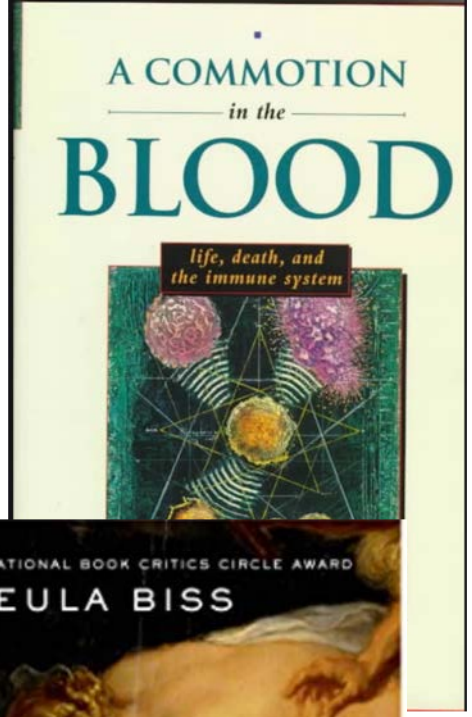
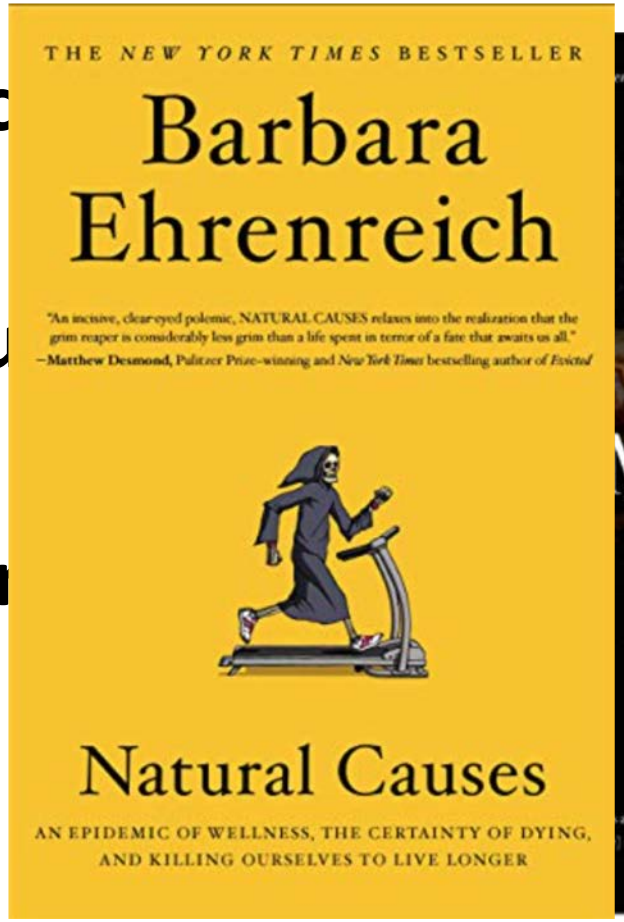
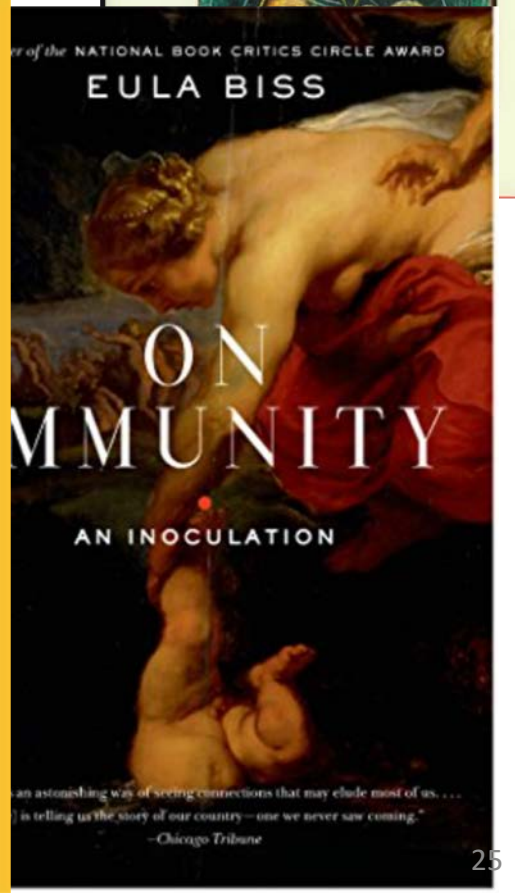






- Kinch, MS. **The End of the Beginn**

Learning Objectives for Today

- Learn a bit about history of immunotherapy for cancer (William **Coley**)
- Gain a sense of the **size** of immune components and pathogens

Metric system terminology

- Meter = 1.09 yards
- Milli 10^{-3} 0.001 meters visible with naked eye
- Micro 10^{-6} 0.000001 meters visible with microscope
- Nano 10^{-9} 0.000000001 meters visible with electron microscope

Relative size (approximate diameter)

• Human hair:	75,000 nanometers	75 microns (micrometers)
• Chemo (small molecule)	1 nanometer	
• Antibody (a protein)	15 nanometers	
• SARS-CoV-2 virus	100 nanometers	
• Bacteria	500 nanometers	0.5 microns
• T cell	10,000 nanometers	10 microns
• Macrophage	20,000 nanometers	20 microns

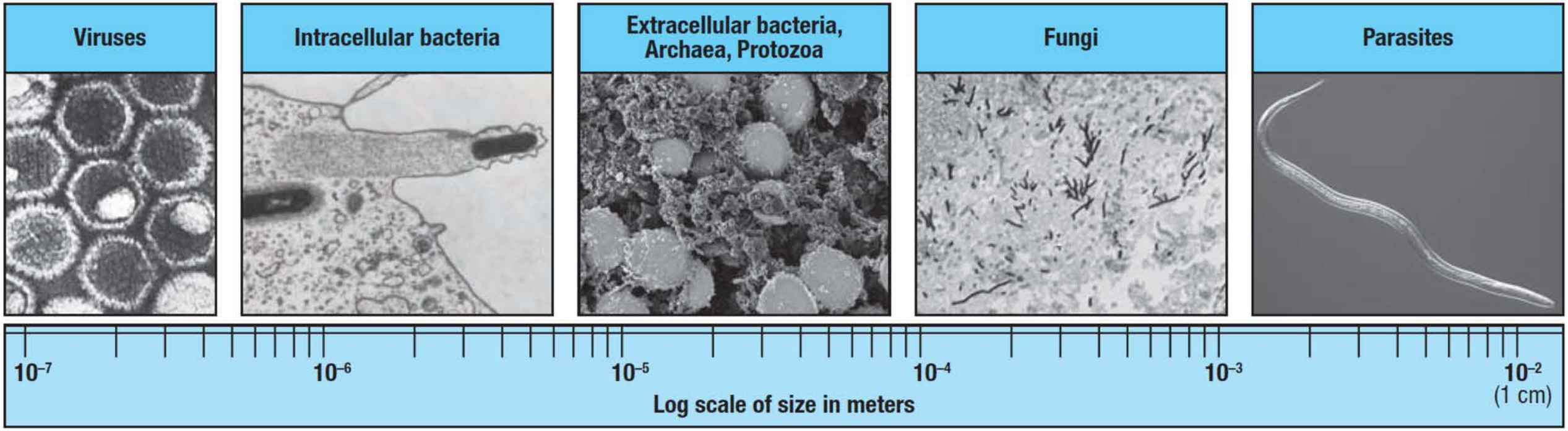


Fig. 1.4 Pathogens vary greatly in size and lifestyle. Intracellular pathogens include viruses, such as herpes simplex (first panel), and various bacteria, such as *Listeria monocytogenes* (second panel). Many bacteria, such as *Staphylococcus aureus* (third panel), or fungi, such as *Aspergillus fumigates* (fourth panel), can grow in the extracellular spaces and directly invade through tissues, as do some archaea and protozoa (third panel). Many parasites, such as the nematode *Strongyloides stercoralis* (fifth panel), are large multicellular organisms that can move throughout the body in a complex life cycle. Second panel courtesy of Dan Portnoy. Fifth panel courtesy of James Lok.

- 20 nm to 2 meters, a nearly billion-fold range in size

Learning Objectives for Today

- Learn a bit about history of immunotherapy for cancer (William **Coley**)
- Gain a sense of the **size** of immune components and pathogens
- Think about what the **immune system** is (**function** and **components**)

The Immune System: What is a “system” in physiology?

- A collection of **cells and molecules** defined as a group by anatomy or function; some in **organs**
- For example, the cardiovascular system circulates blood, the endocrine system consists of various organs that secrete hormones into the blood, the nervous system includes the brain and peripheral nerves that communicate by neurotransmitters
- Communication among cells of the immune system occurs by release of **cytokines** and **chemokines**

Cytokines and Chemokines

- Cytokines and chemokines are protein messengers released by immune cells
- C
  s

way of

New Yorker, May 8, 1989

System consists of molecules in solution and cells: Humoral and Cellular

- Humoral includes soluble proteins like **antibodies** and **cytokines** (messengers between cells)
- Cellular includes a large variety of cells, such as macrophages, B cells, T cells

Humoral and Cellular

- Serum has capability of blocking bacterial toxins
  - Paul Ehrlich's Magic Bullet: "antitoxin" proteins (antibodies)
- Elie Metchnikov's Macrophages engulfing bacteria
  - Neutrophils also phagocytose
- T cells not discovered until 1961
- "Immune System": term first used by Niels Jerne in 1967 by

Systems are not separate

- Immune cells are influenced by **neurotransmitters**
- Neurons are affected by **cytokines**
  - Behavioral effects of cytokines on brain produce “sickness behavior”
- Endocrine **hormones** (like estrogens) affect both immune and nervous systems
- Cytokines are released by cells not usually thought of as “immune cells,” like skin, fat cells,

Is there a single entity that directs all of these systems, a single self?

"This to me is the first lesson of the macrophages that perversely promote lethal cancers. The body – or, to use more cutting-edge language, the "mindbody" – is not a smooth-running machine in which each part obediently performs its tasks for the benefit of the common good. It is at best a confederation of parts – cells, tissues, even thought patterns – that may seek to advance their own agendas, whether or not they are destructive of the whole. What, after all, is cancer, other than a cellular rebellion against the entire organism?"

- Barbara Ehrenreich, Natural Causes

Functions of the Immune System

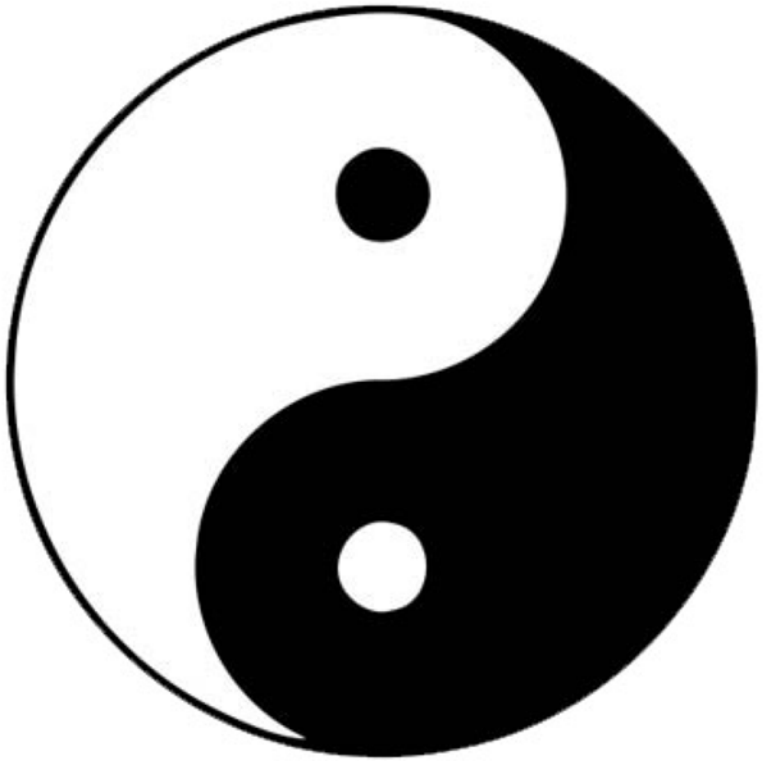
- Protect against Pathogens (microbes that do harm). Pathogens have great diversity and are rapidly evolving.
- Eliminate damaged or altered cells (including cancer)
  - Eliminate extra synapses in the brain
- Coordinate tissue repair
  - Wound healing functions are coopted by cancers

What sets in motion Functions of the Immune System?

- Frank Macfarlane Burnet (1950's):
  - First distinguish "self" from "non-self" and protect the self from non-self, such as bacteria and viruses
  - Barbara Ehrenreich points out that "s
    arising from Western individualism, a
    scientific concept
  - More recent problem: why does the
    the microbiome, billions of non-self k
    gut?
- Polly Mat
  - To prote (1
  - Danger e i

You do not want a “strong” immune system, you want a **balanced** immune system

Be Tolerant of Self, Innocuous substances, and Commensal Microbes



Turn On and Turn Off

Negative Feedback

Dys-Functions of the Immune System

- Autoimmune Diseases (diabetes, lupus, arthritis, Crohn's disease, multiple sclerosis)
- Allergies
- Inflammatory contributions to Cardiovascular disease, Alzheimer's disease, Parkinson's disease, etc.
- Over-reaction to real threats: "cytokine storm"

Another break for Questions

Questions in Q&A

Name that Tune in Chat

Learning Objectives for Today

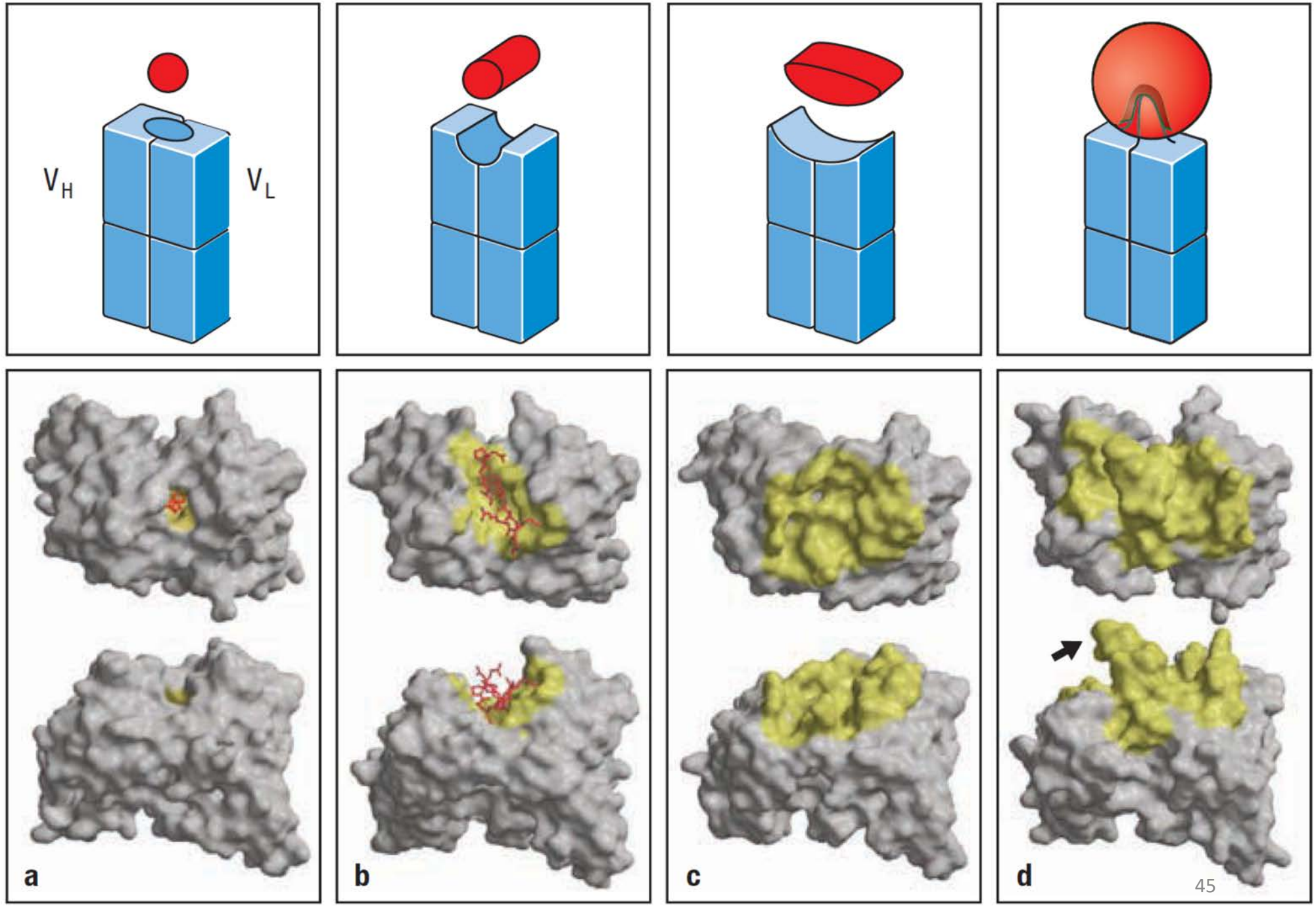
- Learn a bit about history of immunotherapy for cancer (William **Coley**)
- Gain a sense of the **size** of immune components and pathogens
- Think about what the **immune system** is (function and components)
- Learn what it means to "**recognize**" an "**antigen**"

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

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

- The antigen-binding region of the antibody and the antigen have complementary **shape, size, and charge** (or lack of charge) which allows a stable "**binding**" to occur between the two molecules; this constitutes a **molecular attraction**
- The interaction may be loose and transient or tight and stable, "low affinity" or "high **affinity**"
- The interaction may cause a change in the shape of other parts of the antibody protein, thereby transmitting a "**signal**"


V_H
V_L
a
b
c
d

Antigen Recognition by Antibodies and T cell antigen receptors (TCRs)

- The binding interaction can be exquisitely **specific**: modifying a single atom in the antigen can eliminate binding of a particular antibody to a particular antigen
- This **specificity** is the power of immunotherapy: mutated cancer cells can be targeted by antibodies and T cells
- Picking the right target is essential

Questions about protein recognition of molecules?
(if no questions, name that tune)

Learning Objectives for Today

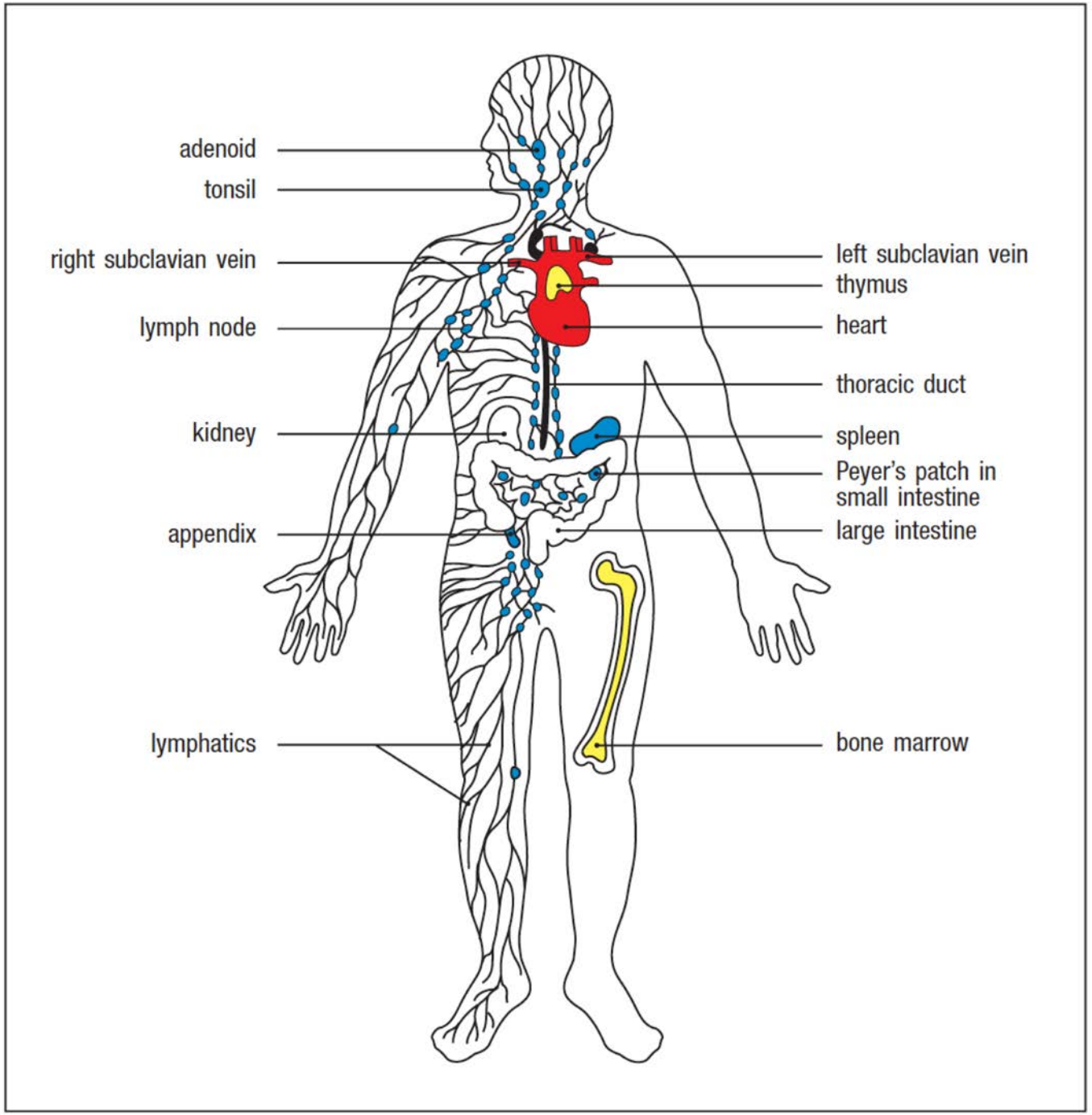
- Learn a bit about history of immunotherapy for cancer (William **Coley**)
- Gain a sense of the **size** of immune components and pathogens
- Think about what the **immune system** is (function and components)
- Learn what it means to "**recognize**" an "**antigen**"
- Learn **where** in the body the immune system is

Where is the Immune System?

- Some Cells are in Central and Peripheral Immune Organs
  - Central: Bone Marrow and Thymus
    - Early development of cells
  - Peripheral: Lymph Nodes and Spleen
    - Sites of antigen presentation and activation of cells

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



Janeway, 2017, Fig 1.18,

Topological View of the Body

- What is inside and what is outside?

Potential Sites of Entry for Pathogens

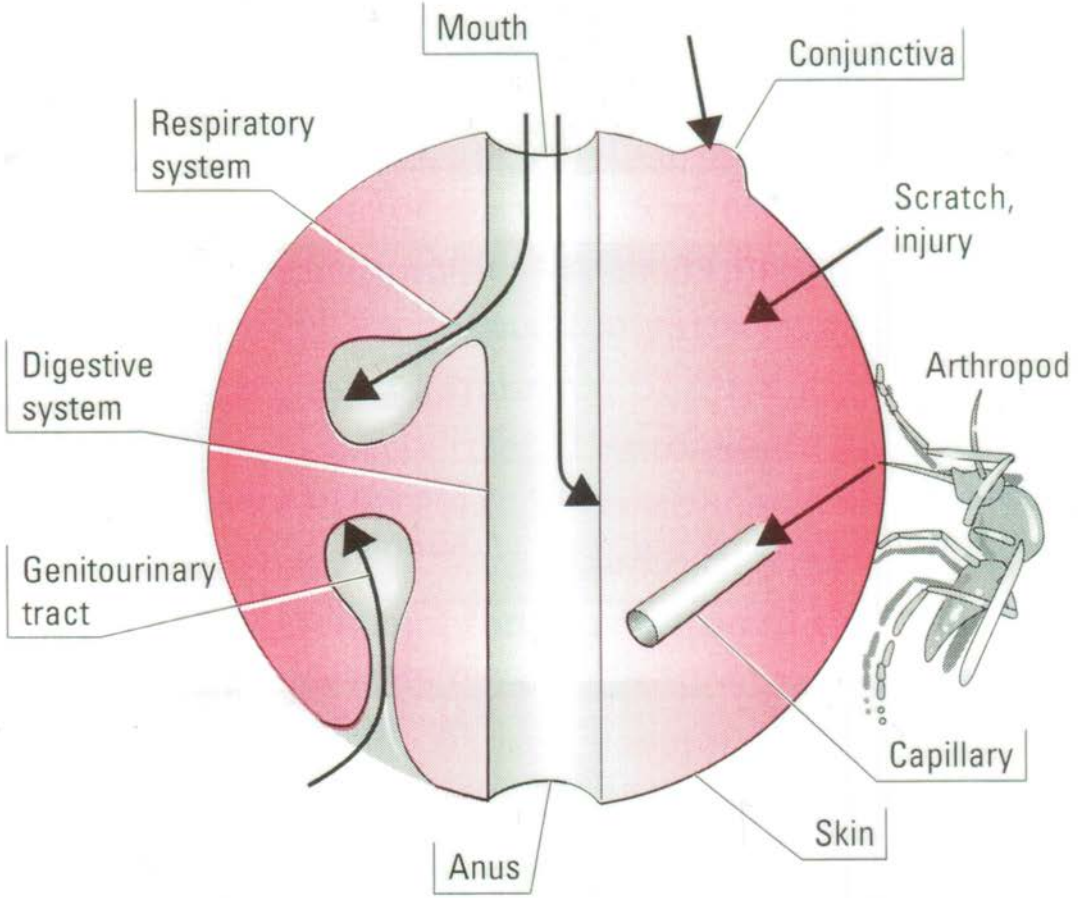
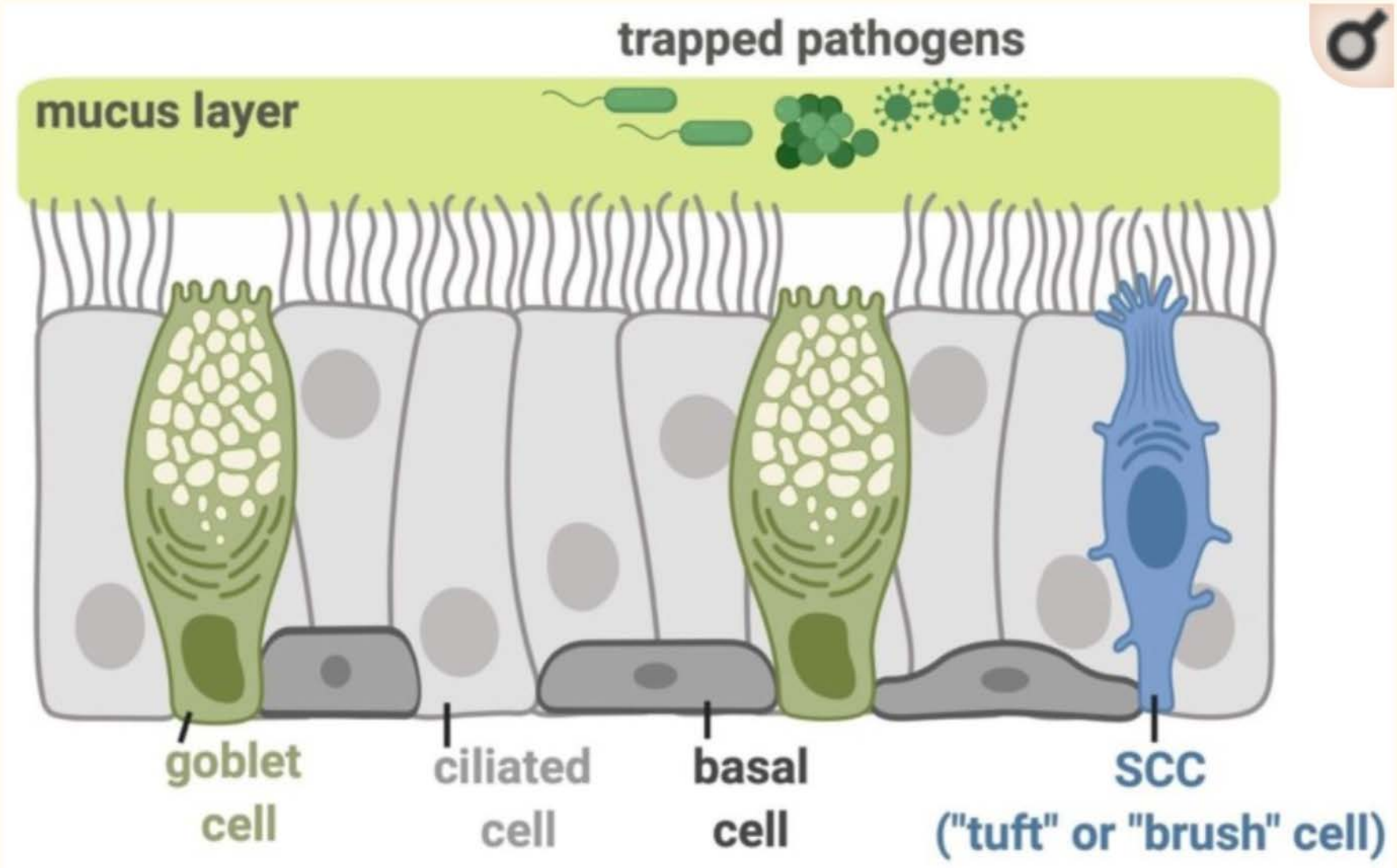


Figure 21.3 Outer and inner body surfaces. Sites of antigen entry are indicated by arrows. (Redrawn from Mims, C. A. (1977) *The Pathogenesis of Infectious Disease*. Academic Press, London.)

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


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

Immune cells distributed throughout the body but from common origin

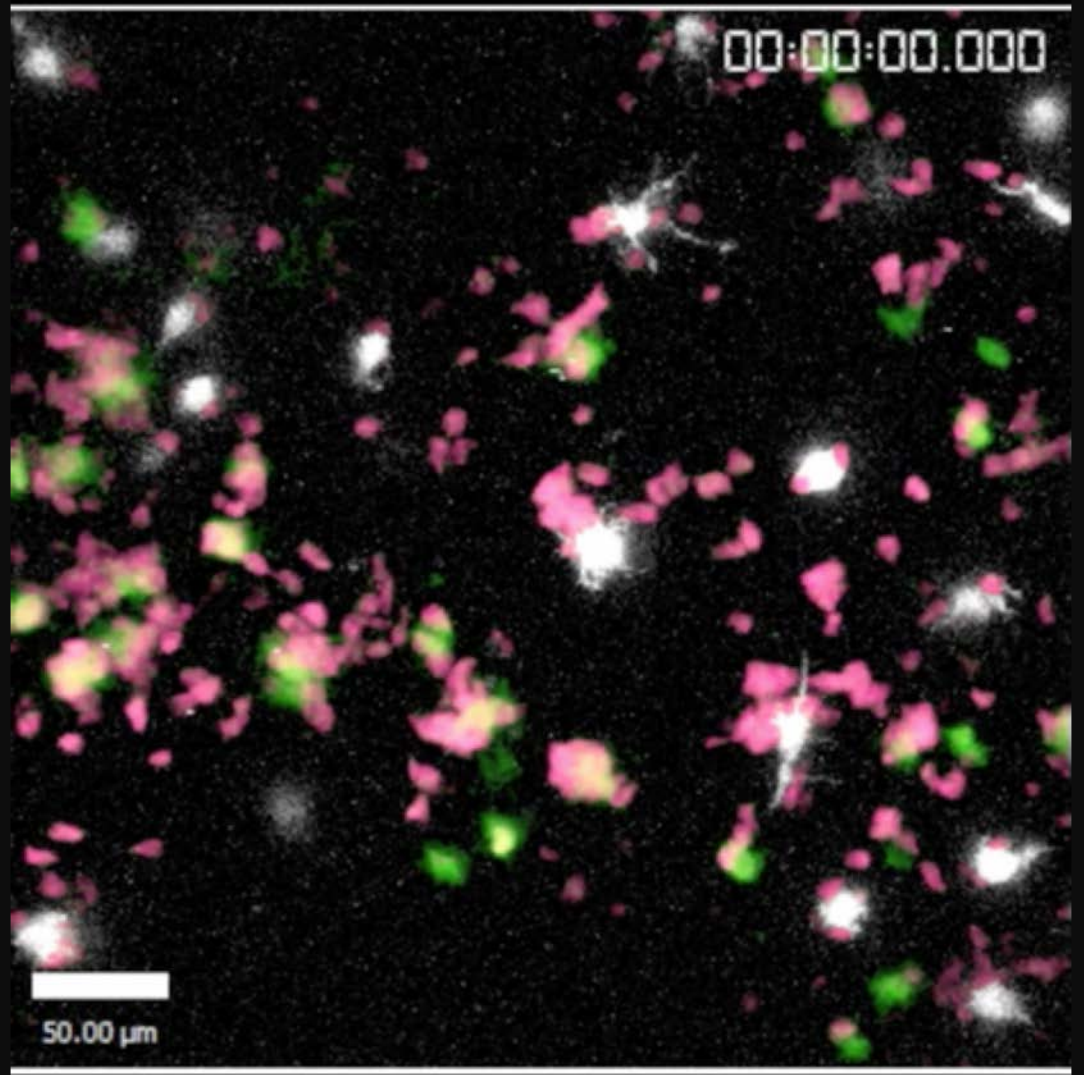
- Made up of cells that originate mostly in the **bone marrow**
- **Hematopoietic Stem Cells** in bone marrow give rise to most immune cells (brain microglia are an exception)

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**

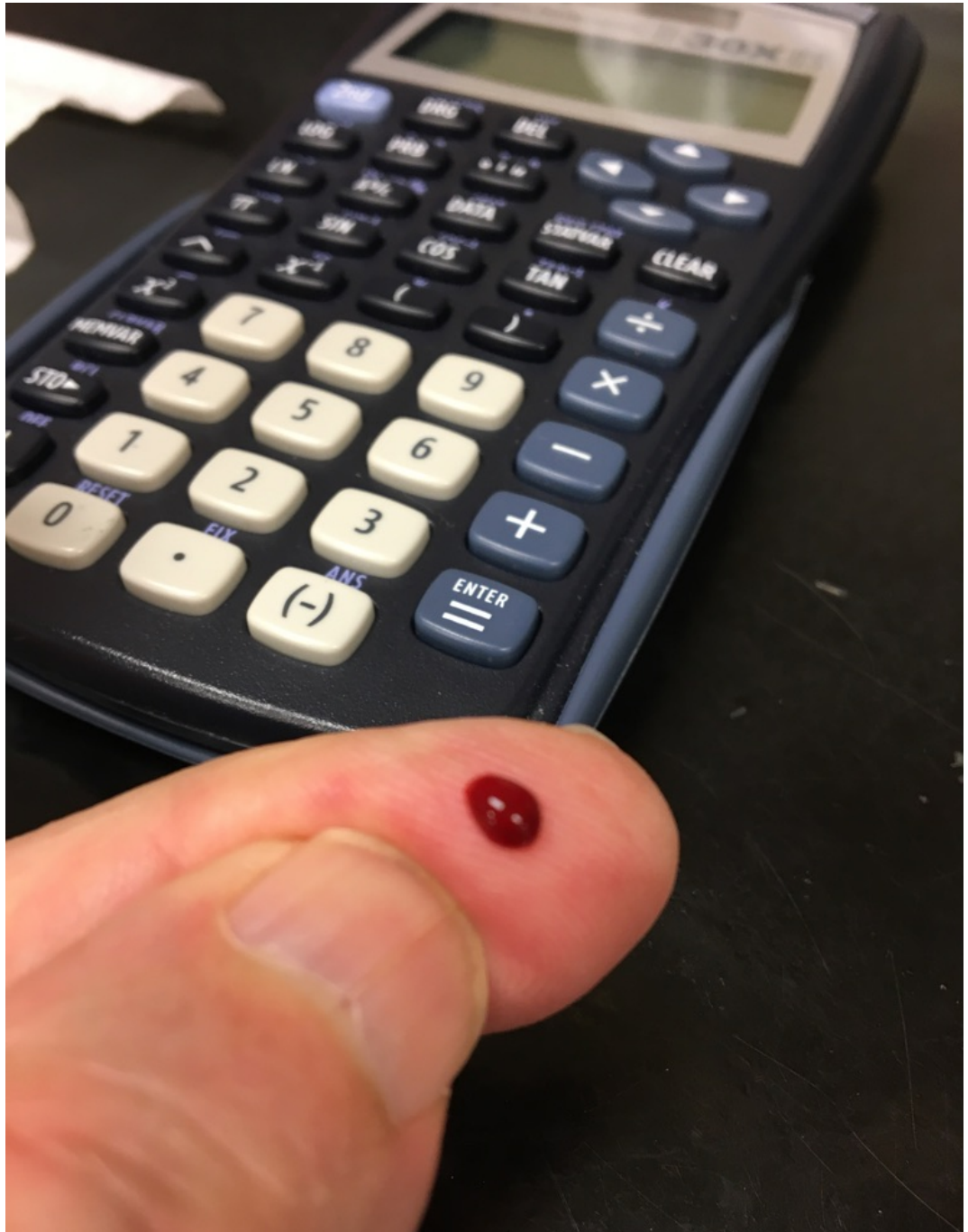
LFA1^{-} DCs migrate to LN and promote Ag specific clustering



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

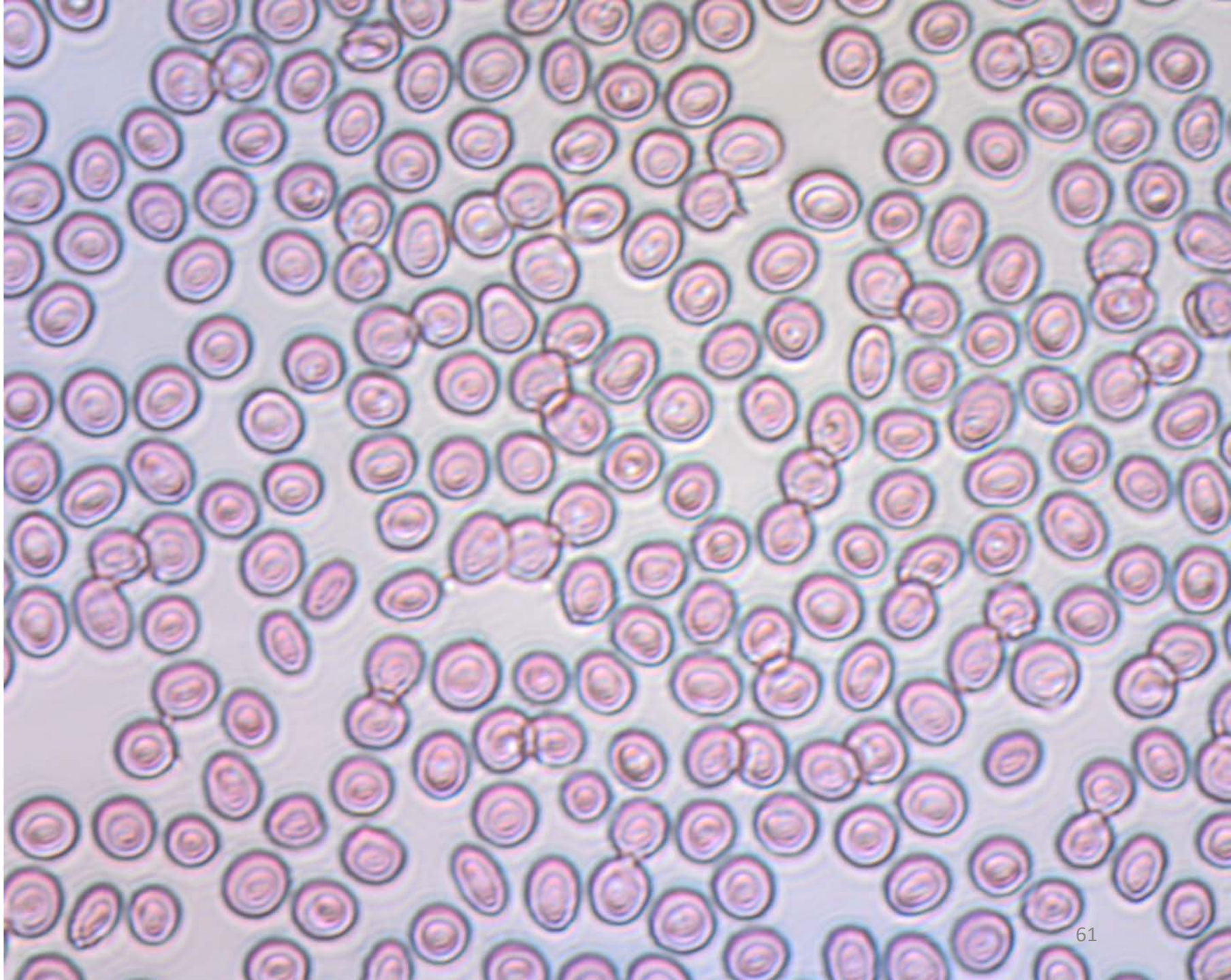
- Easy access to blood has facilitated study of the immune system

Ed’s Blood

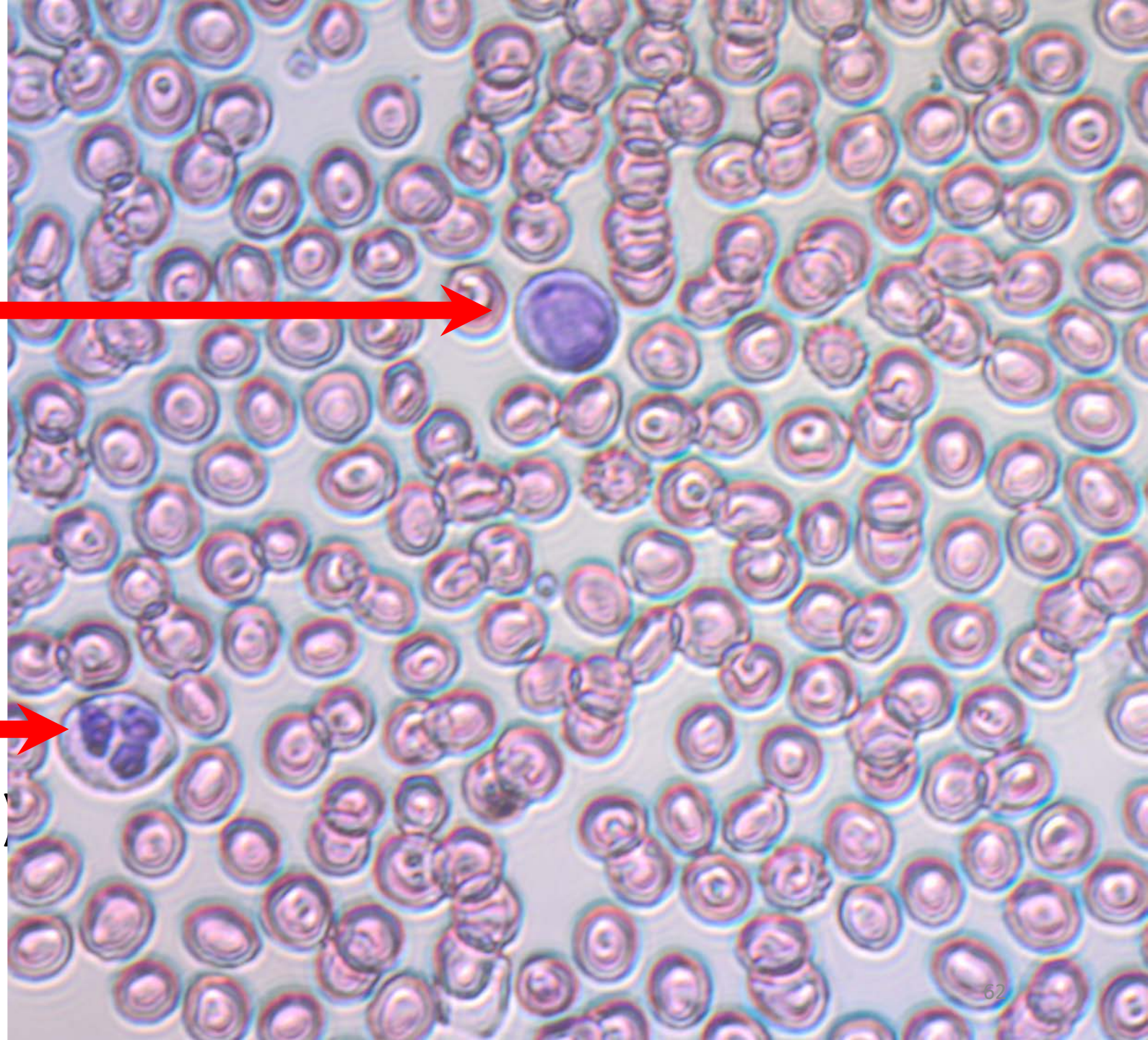


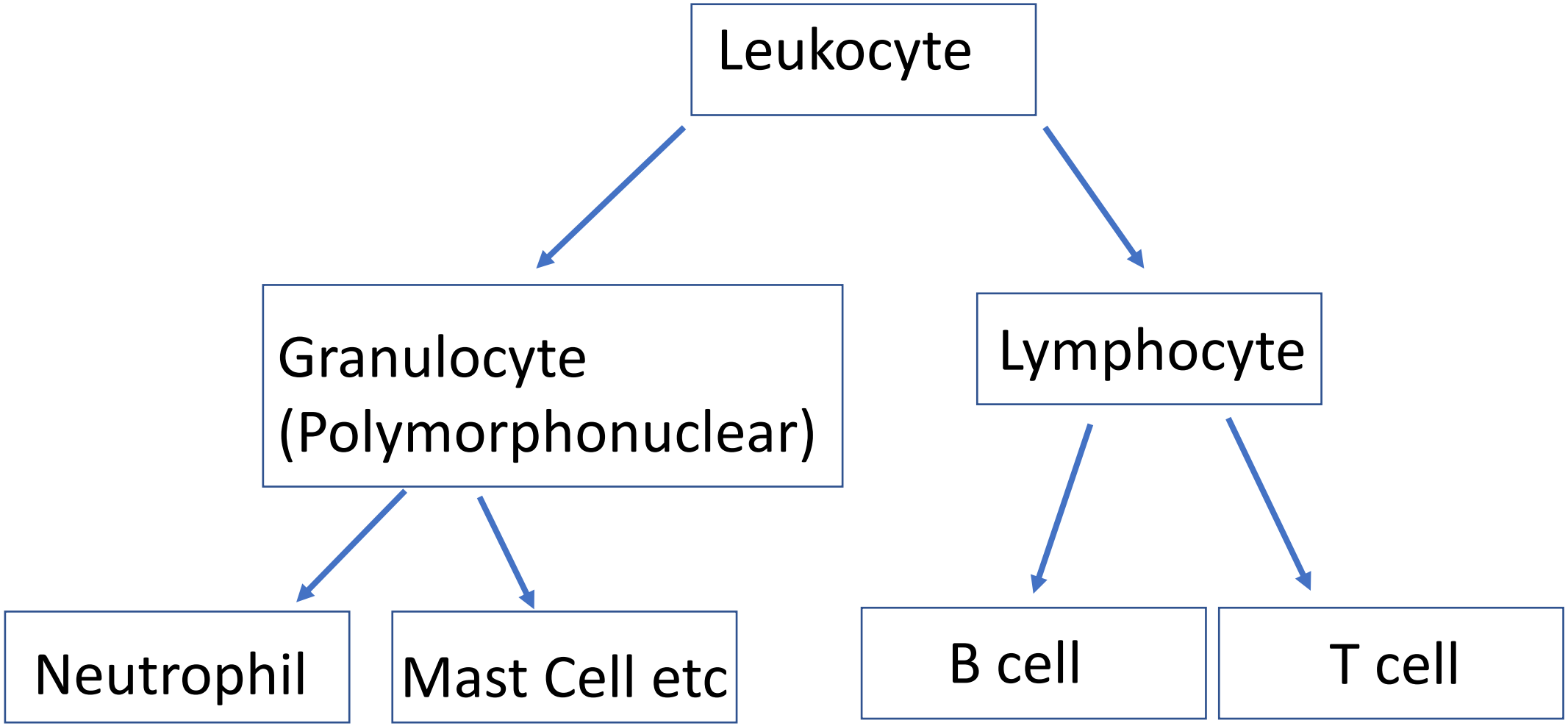
Ed’s Blood

Mostly Red
Blood Cells



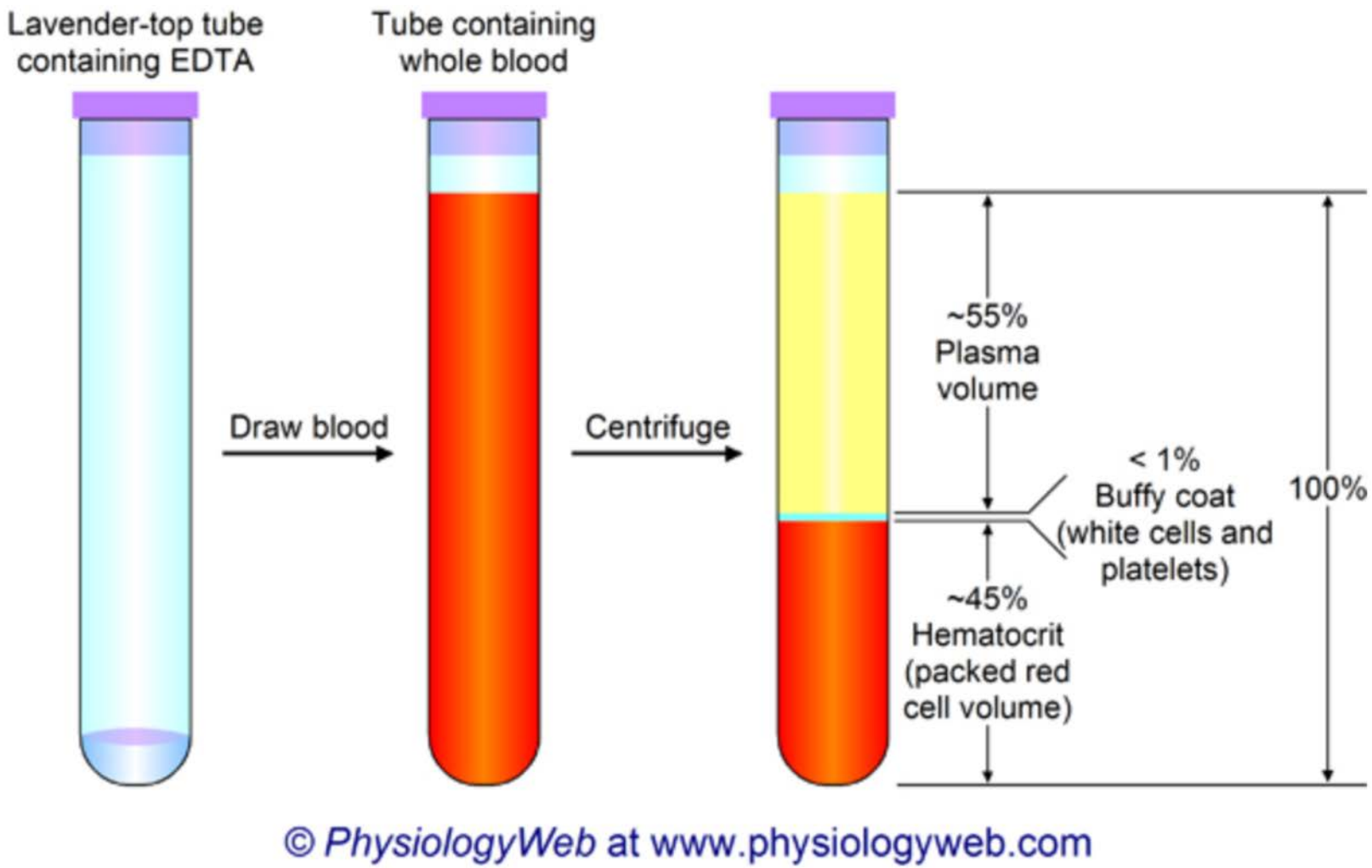
Ed's Leukocytes (white blood cells)




Leukocyte
Granulocyte (Polymorphonuclear)
Lymphocyte
Neutrophil
Mast Cell etc
B cell
T cell

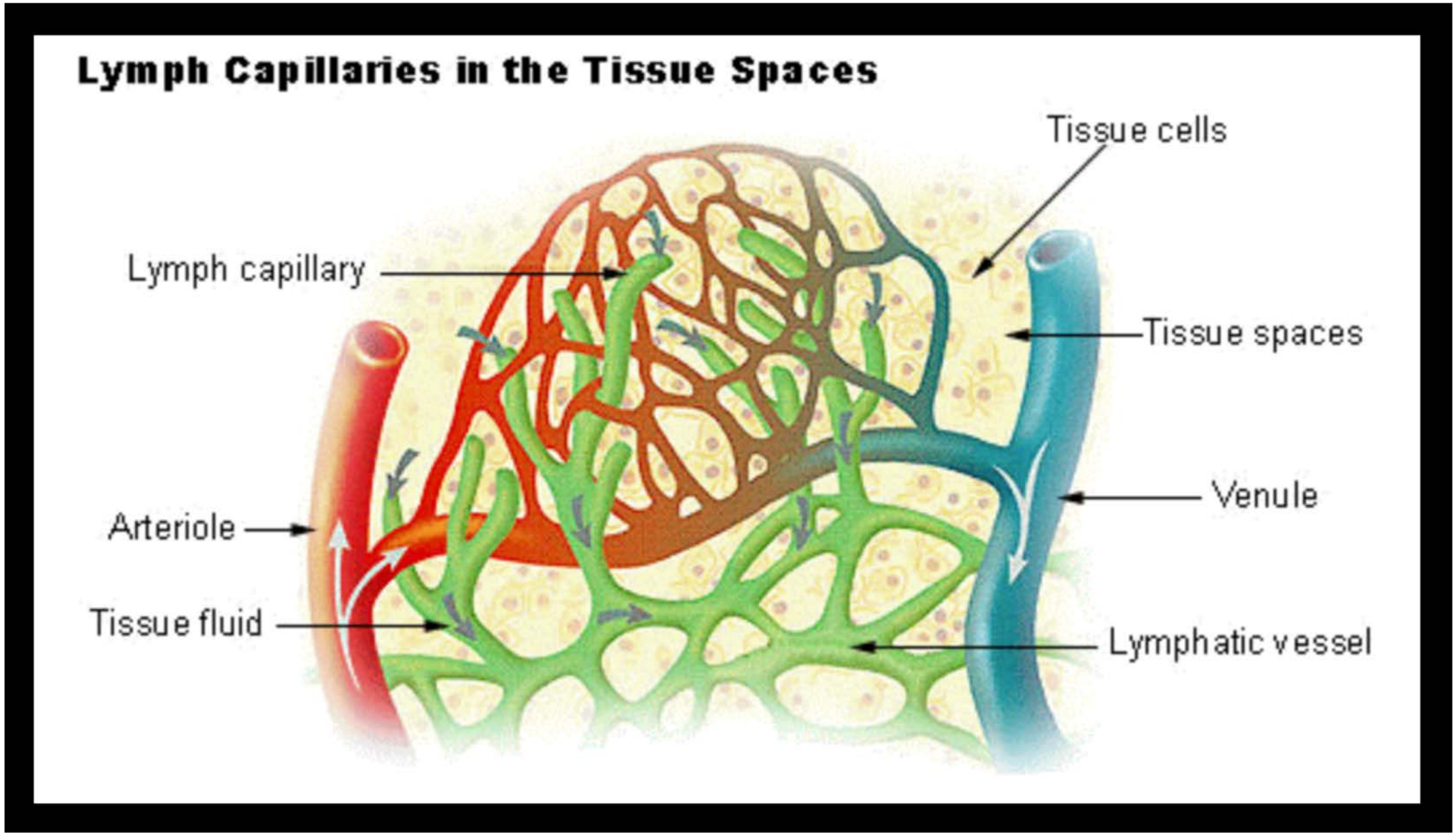
Most Common Leukocytes (White Blood Cells)

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

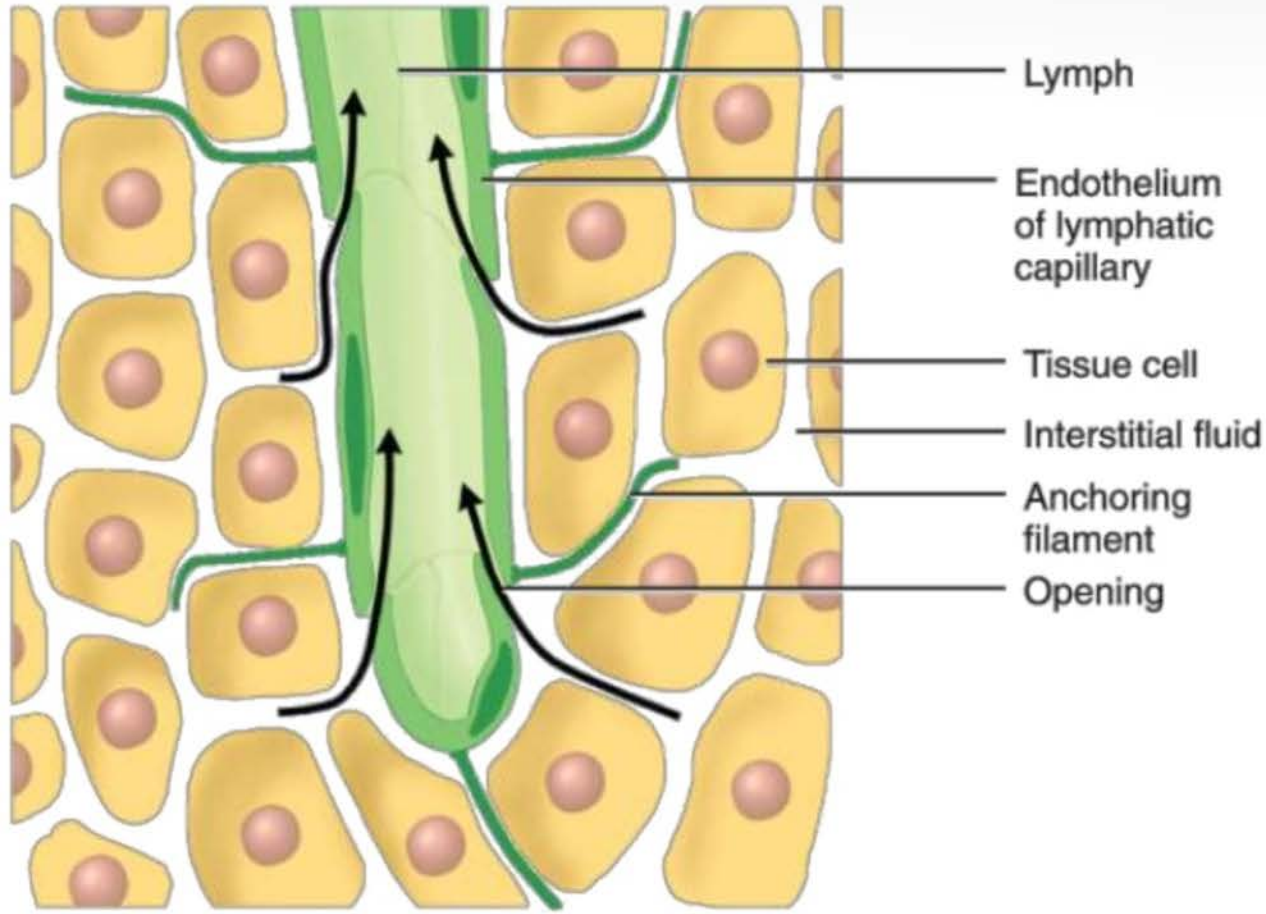

Lavender-top tube containing EDTA
Tube containing whole blood
Draw blood
Centrifuge
~55% Plasma volume
< 1% Buffy coat (white cells and platelets)
~45% Hematocrit (packed red cell volume)
100%
© PhysiologyWeb at www.physiologyweb.com

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

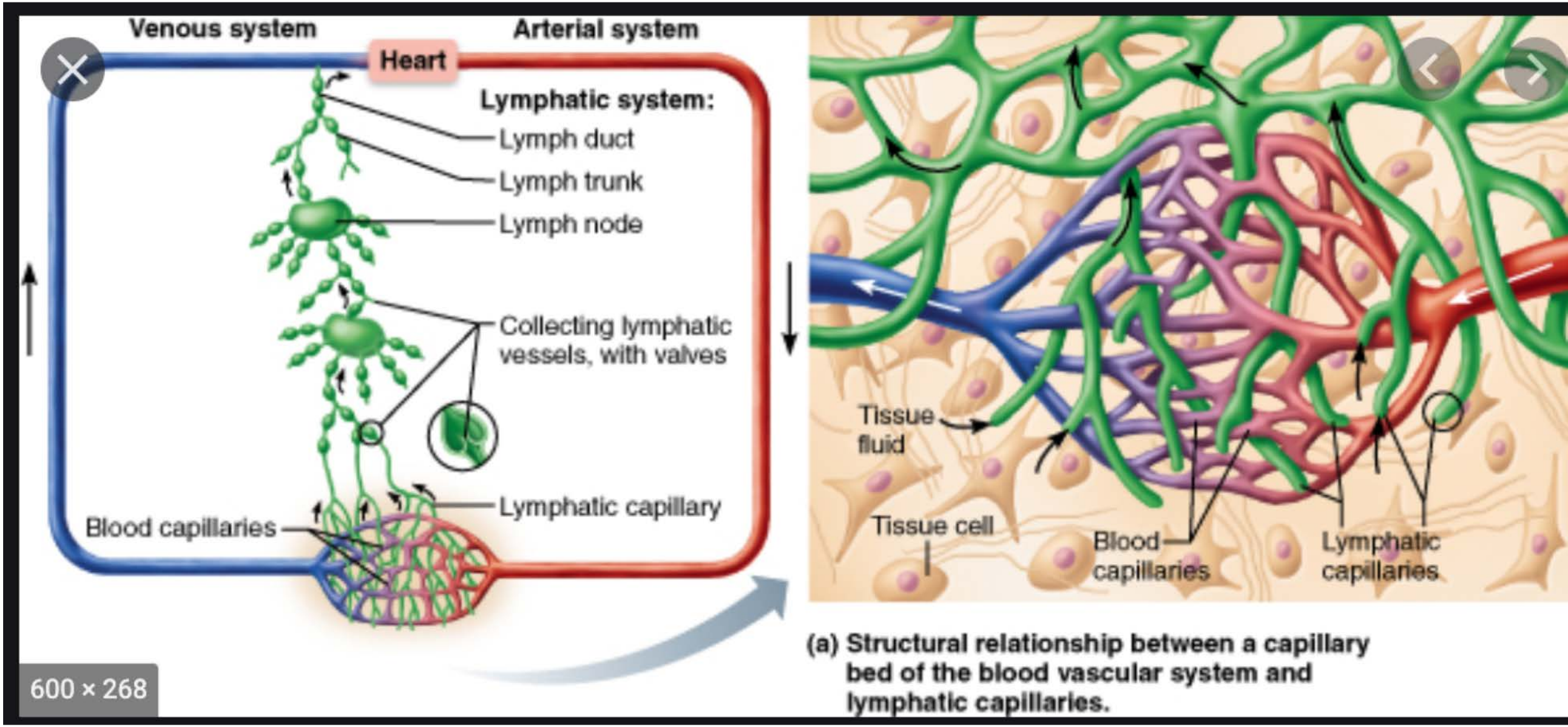

Lymph Capillaries in the Tissue Spaces
Tissue cells
Lymph capillary
Tissue spaces
Venule
Arteriole
Tissue fluid
Lymphatic vessel

Lymphatic Vessels and Fluid



(b) Details of a lymphatic capillary

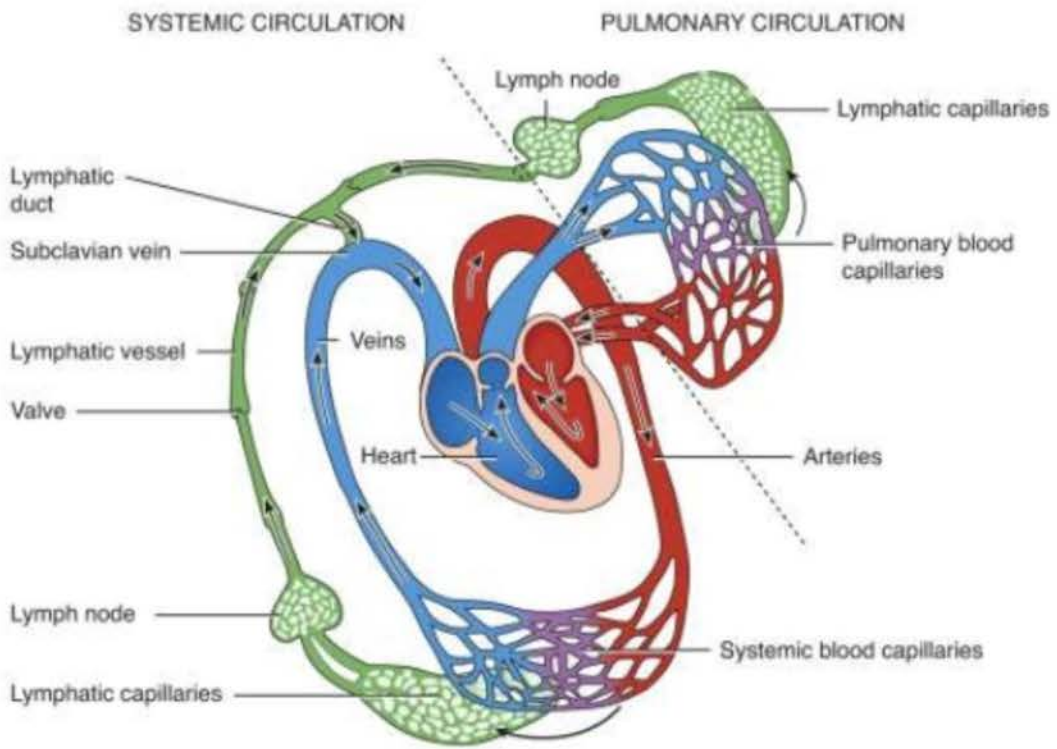
Lymphatic capillaries showing blind ends and one way flow

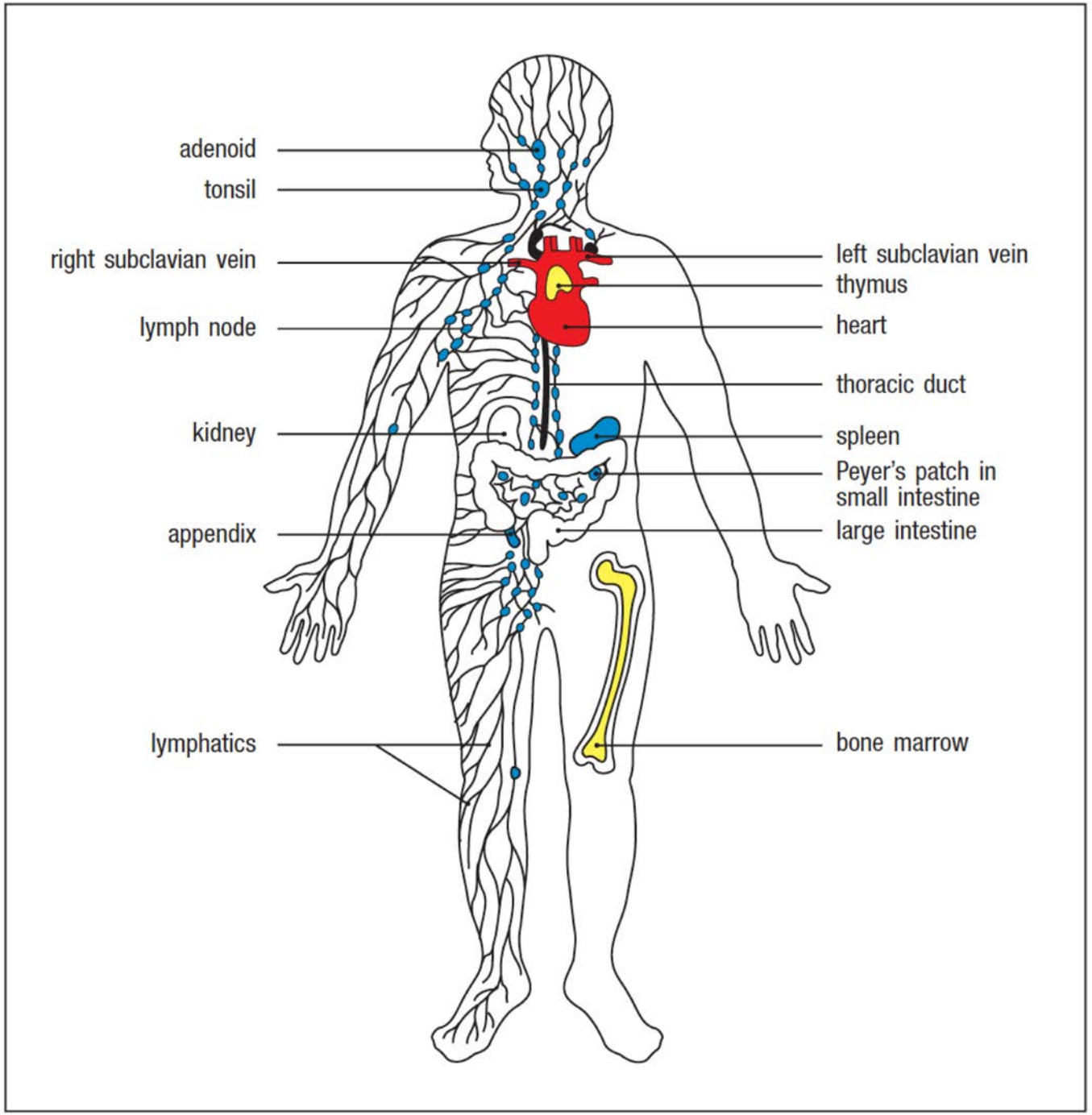


(a) Structural relationship between a capillary bed of the blood vascular system and lymphatic capillaries.

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,

Tissue	Number of lymphocytes	
Spleen	70×10^9	17%
Lymph nodes	190×10^9	43%
Bone marrow	50×10^9	11%
Blood	10×10^9	2%
Skin	20×10^9	6%
Intestines	50×10^9	12%
Liver	10×10^9	2%
Lungs	30×10^9	7%

Final Question Session

- This Tune is a preview of next week, when we start with the innate immune response and inflammation: Fever

10 Leading Causes of Death by Age Group, United States – 2018

	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 4,473	Unintentional Injury 1,226	Unintentional Injury 734	Unintentional Injury 692	Unintentional Injury 12,044	Unintentional Injury 24,614	Unintentional Injury 22,667	Malignant Neoplasms 37,301	Malignant Neoplasms 113,947	Heart Disease 526,509	Heart Disease 655,381
2	Short Gestation 3,679	Congenital Anomalies 384	Malignant Neoplasms 393	Suicide 596	Suicide 6,211	Suicide 8,020	Malignant Neoplasms 10,640	Heart Disease 32,220	Heart Disease 81,042	Malignant Neoplasms 431,102	Malignant Neoplasms 599,274
3	Maternal Pregnancy Comp. 1,358	Homicide 353	Congenital Anomalies 201	Malignant Neoplasms 450	Homicide 4,607	Homicide 5,234	Heart Disease 10,532	Unintentional Injury 23,056	Unintentional Injury 23,693	Chronic Low. Respiratory Disease 135,560	Unintentional Injury 167,127
4	SIDS 1,334	Malignant Neoplasms 326	Homicide 121	Congenital Anomalies 172	Malignant Neoplasms 1,371	Malignant Neoplasms 3,684	Suicide 7,521	Suicide 8,345	Chronic Low. Respiratory Disease 18,804	Cerebro-vascular 127,244	Chronic Low. Respiratory Disease 159,486
5	Unintentional Injury 1,168	Influenza & Pneumonia 122	Influenza & Pneumonia 71	Homicide 168	Heart Disease 905	Heart Disease 3,561	Homicide 3,304	Liver Disease 8,157	Diabetes Mellitus 14,941	Alzheimer's Disease 120,658	Cerebro-vascular 147,810
6	Placenta Cord. Membranes 724	Heart Disease 115	Chronic Low. Respiratory Disease 68	Heart Disease 101	Congenital Anomalies 354	Liver Disease 1,008	Liver Disease 3,108	Diabetes Mellitus 6,414	Liver Disease 13,945	Diabetes Mellitus 60,182	Alzheimer's Disease 122,019
7	Bacterial Sepsis 579	Perinatal Period 62	Heart Disease 68	Chronic Low Respiratory Disease 64	Diabetes Mellitus 246	Diabetes Mellitus 837	Diabetes Mellitus 2,282	Cerebro-vascular 5,128	Cerebro-vascular 12,789	Unintentional Injury 57,213	Diabetes Mellitus 84,946
8	Circulatory System Disease 428	Septicemia 54	Cerebro-vascular 34	Cerebro-vascular 54	Influenza & Pneumonia 200	Cerebro-vascular 567	Cerebro-vascular 1,704	Chronic Low. Respiratory Disease 3,807	Suicide 8,540	Influenza & Pneumonia 48,888	Influenza & Pneumonia 59,120
9	Respiratory Distress 390	Chronic Low. Respiratory Disease 50	Septicemia 34	Influenza & Pneumonia 51	Chronic Low. Respiratory Disease 165	HIV 482	Influenza & Pneumonia 956	Septicemia 2,380	Septicemia 5,956	Nephritis 42,232	Nephritis 51,386
10	Neonatal Hemorrhage 375	Cerebro-vascular 43	Benign Neoplasms 19	Benign Neoplasms 30	Complicated Pregnancy 151	Influenza & Pneumonia 457	Septicemia 829	Influenza & Pneumonia 2,339	Influenza & Pneumonia 5,858	Parkinson's Disease 32,988	Suicide 48,344

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

- https://www.theatlantic.com/health/archive/2020/08/covid-19-immunity-is-the-pandemics-central-mystery/614956/?utm_source=newsletter&utm_medium=email&utm_campaign=atlantic-daily-newsletter&utm_content=20200824&silverid-ref=NjE5NzA0NDY3NzA4S0