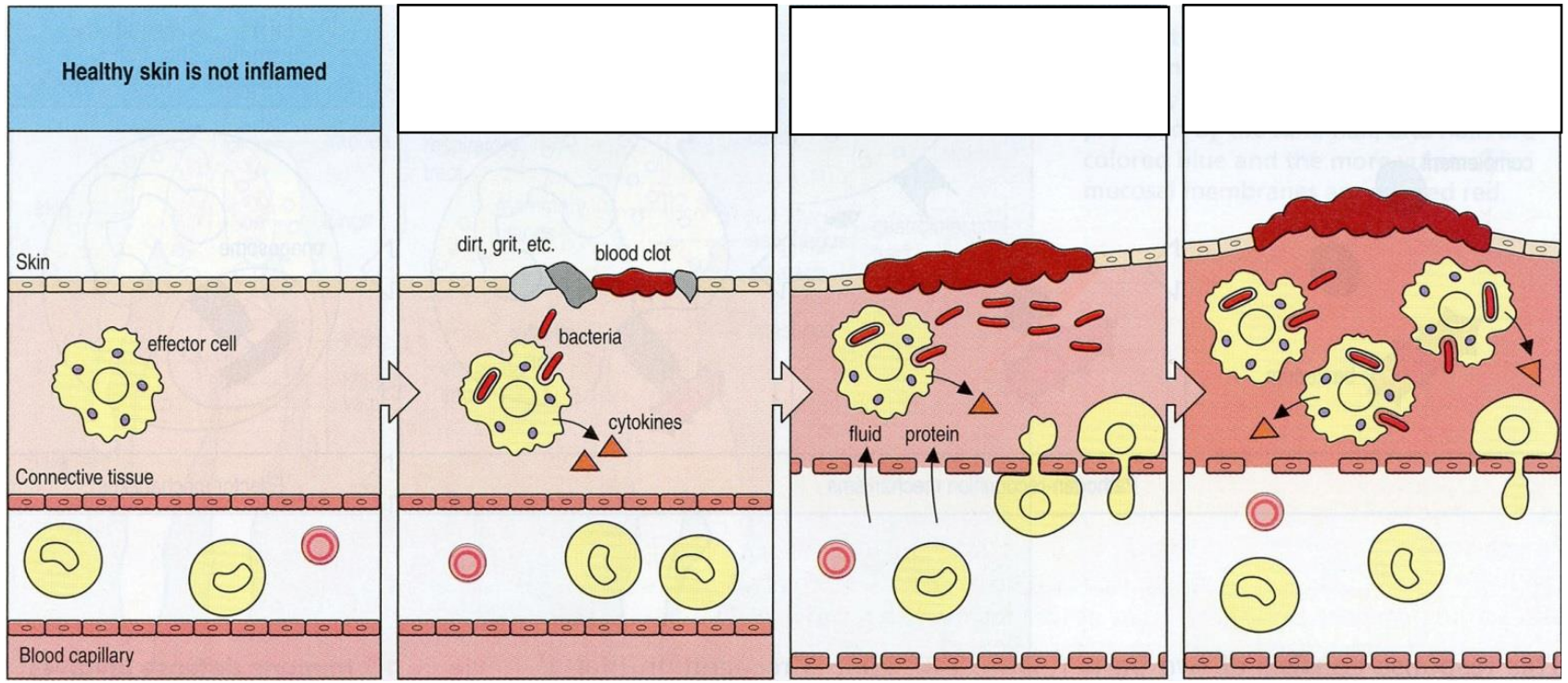
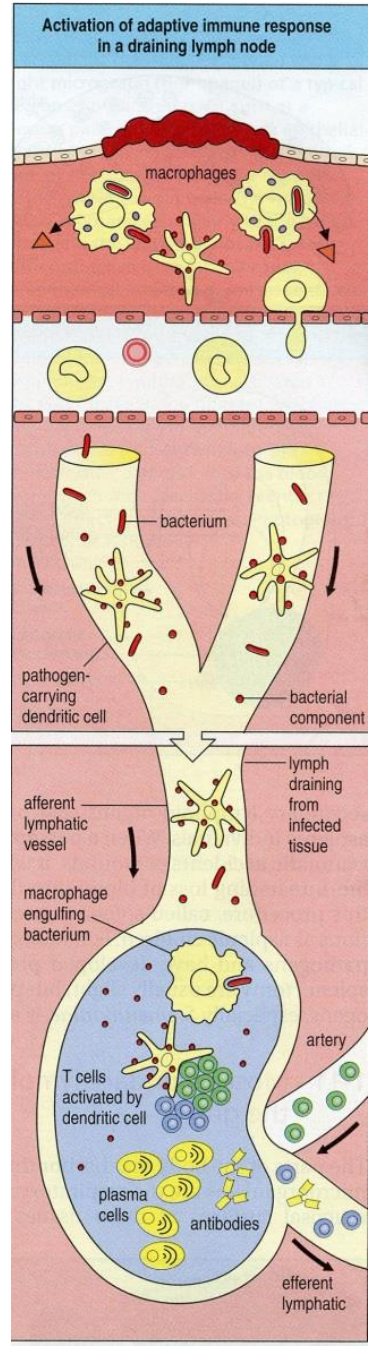
Topic 7 Acquired immunity

Second line of defence: Adaptive immunity

- It is added to the innate immune response.
- Very potent and extremely specific to the pathogen.
- Slow to mount.
- Very long lasting (immunologic memory).


Healthy skin is not inflamed
Skin
effector cell
Connective tissue
Blood capillary
dirt, grit, etc.
blood clot
bacteria
cytokines
fluid
protein


Activation of adaptive immune response in a draining lymph node
macrophages
bacterium
pathogen-carrying dendritic cell
bacterial component
afferent lymphatic vessel
lymph draining from infected tissue
macrophage engulfing bacterium
artery
T cells activated by dendritic cell
plasma cells
antibodies
efferent lymphatic

Adaptive immunity: Primary response

- Selection of lymphocytes expressing specific receptor
  BCR or TCR for the given Ag.

  - Activation and differentiation (clonal expansion)

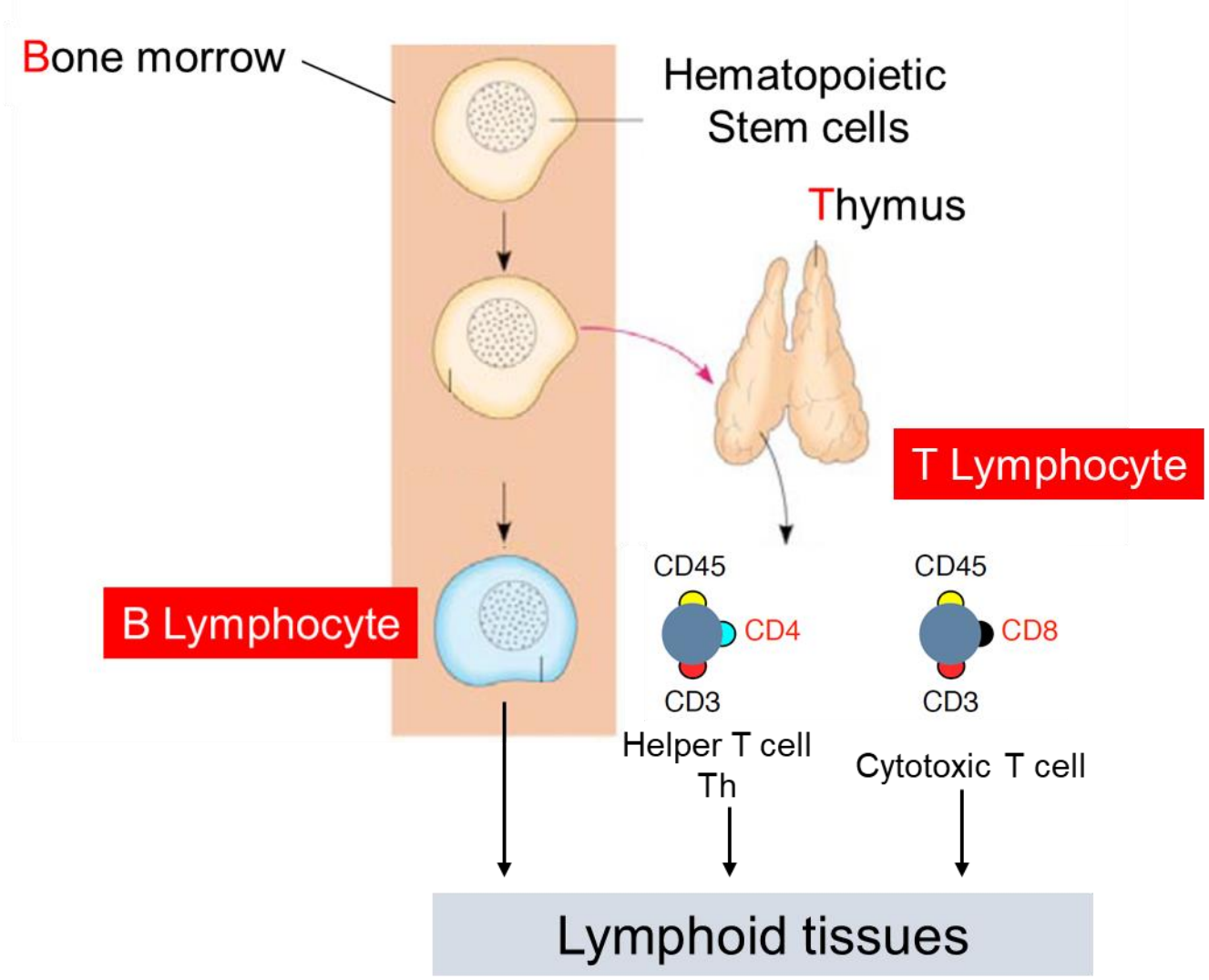
  - Production of large number of specific effector cells

  - Persistence of effector lymphocytes
    (immunologic memory)

From Parham 4th edition

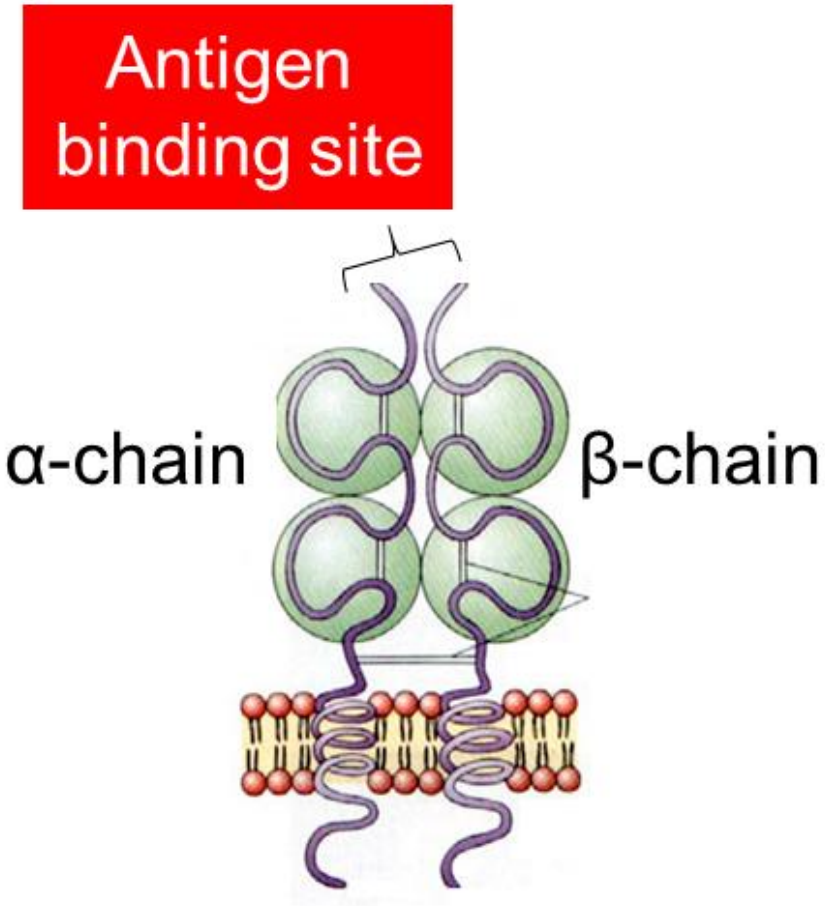
Adaptive immunity:

B and T lymphocyte development and differentiation



Adaptive immunity: T lymphocyte receptor (TCR)

T lymphocytes detect Ag presented on major histocompatibility complex (MHC) molecules.



Adaptive immunity:

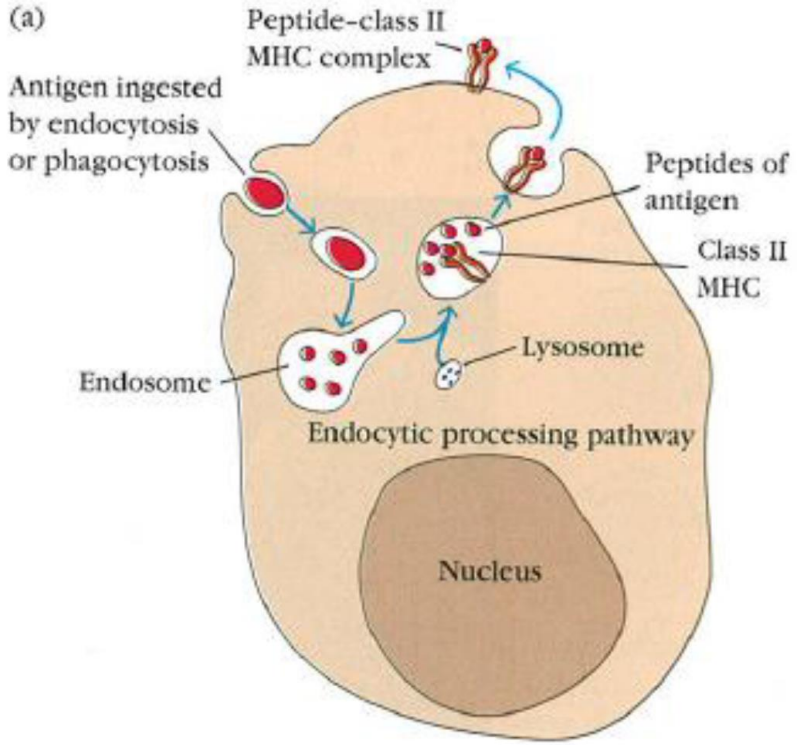
2 types of MHCs:

– **MHC class I** is expressed by all nucleated cells and present Ag to **CD8⁺ lymphocytes**.

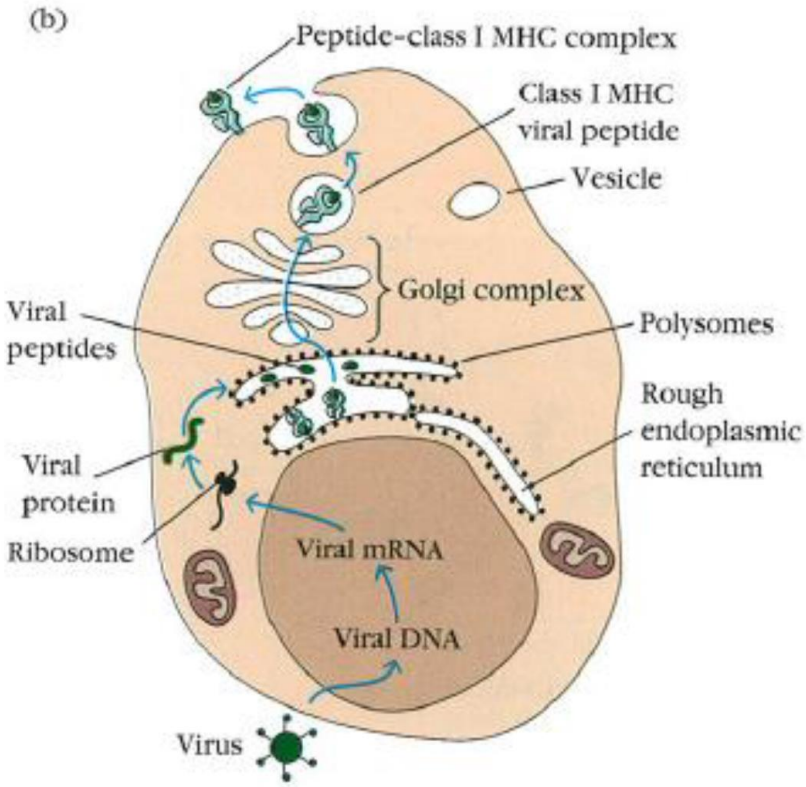
– **MHC class II** is expressed by APC, present Ag to **CD4⁺ helper lymphocytes**.

Adaptive immunity: Antigen processing

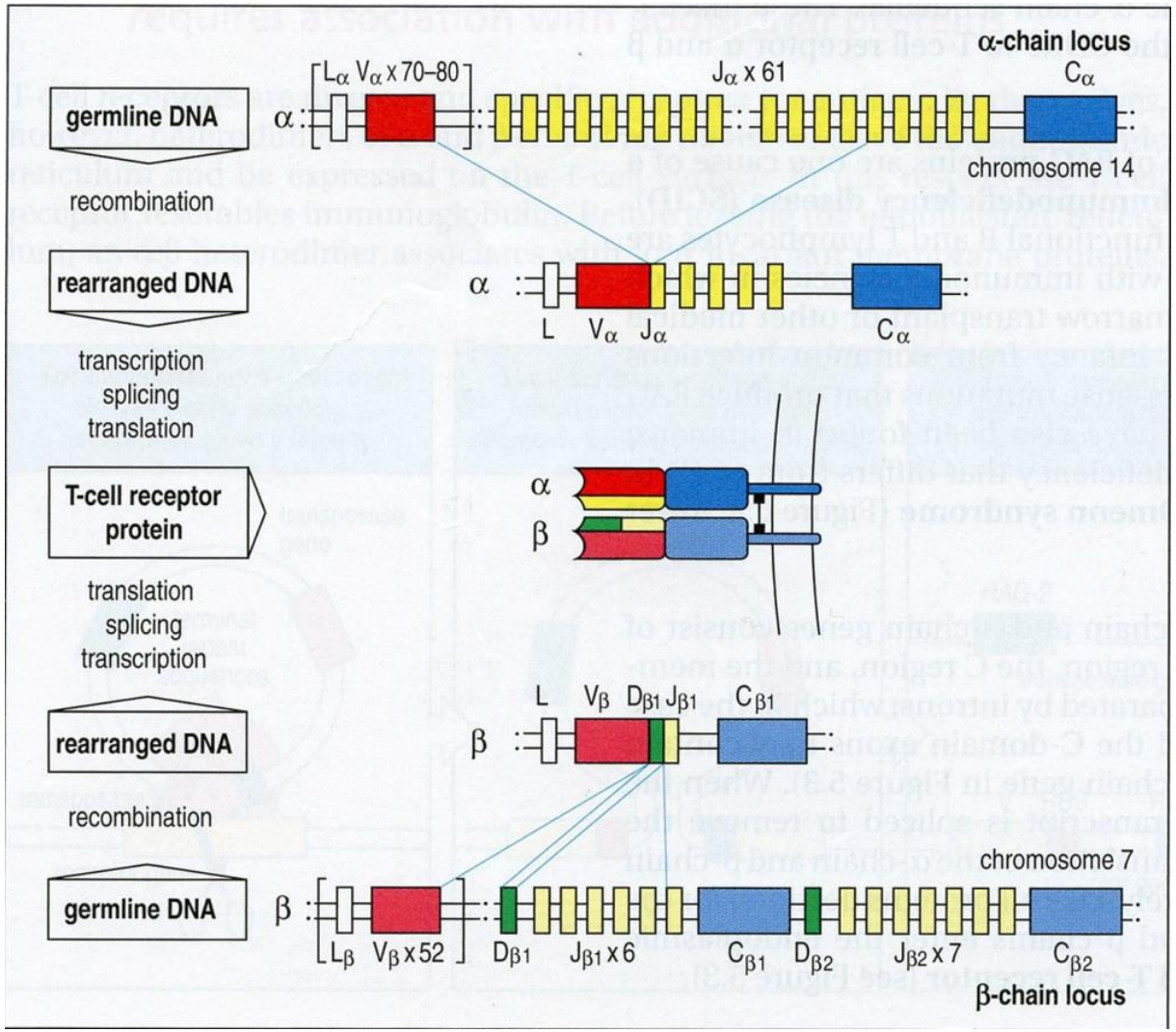
Exogenes Antigen



Endogenes Antigen



Generation of TCR diversity



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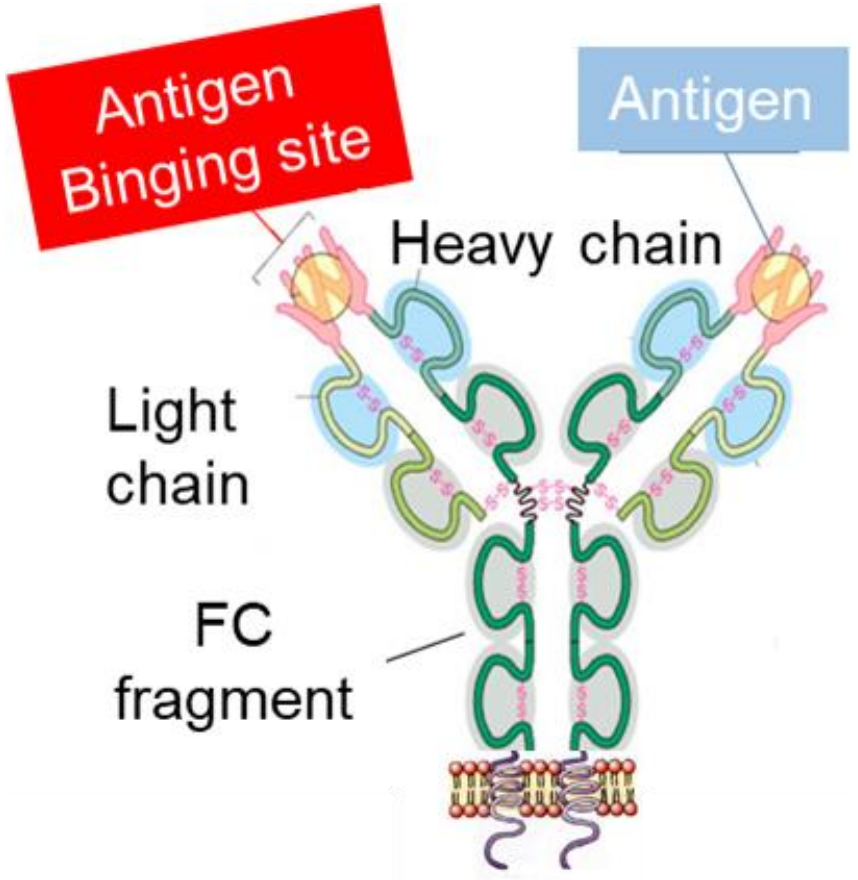
Adaptive immunity:

B Lymphocyte receptor (BCR):

B lymphocytes detect Ag in it native form.



Generation of BCR diversity

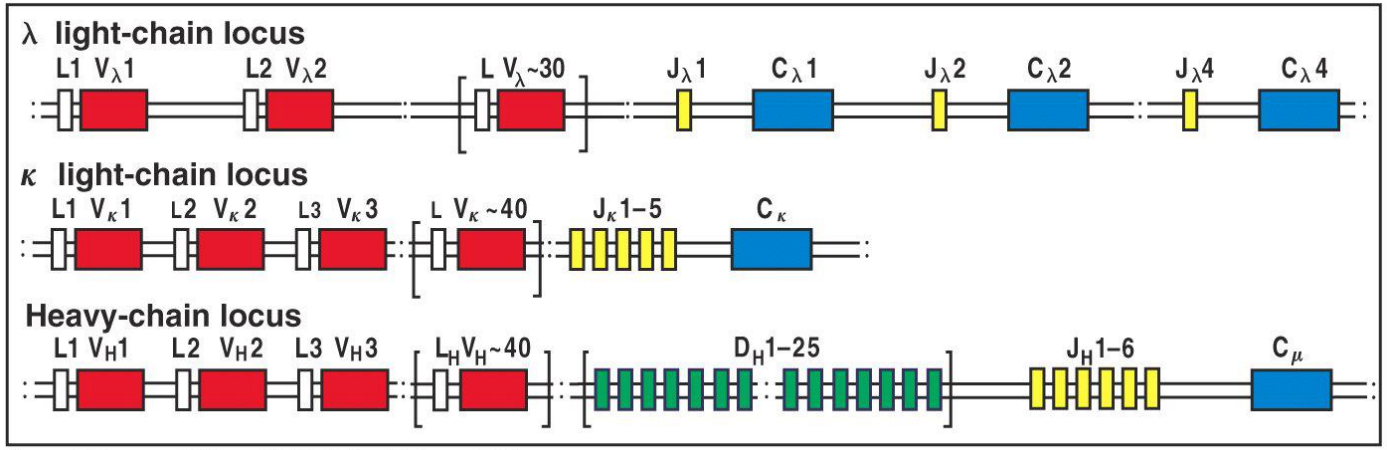


Figure 4-4 Immunobiology, 6/e. (© Garland Science 2005)

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Generation of BCR diversity

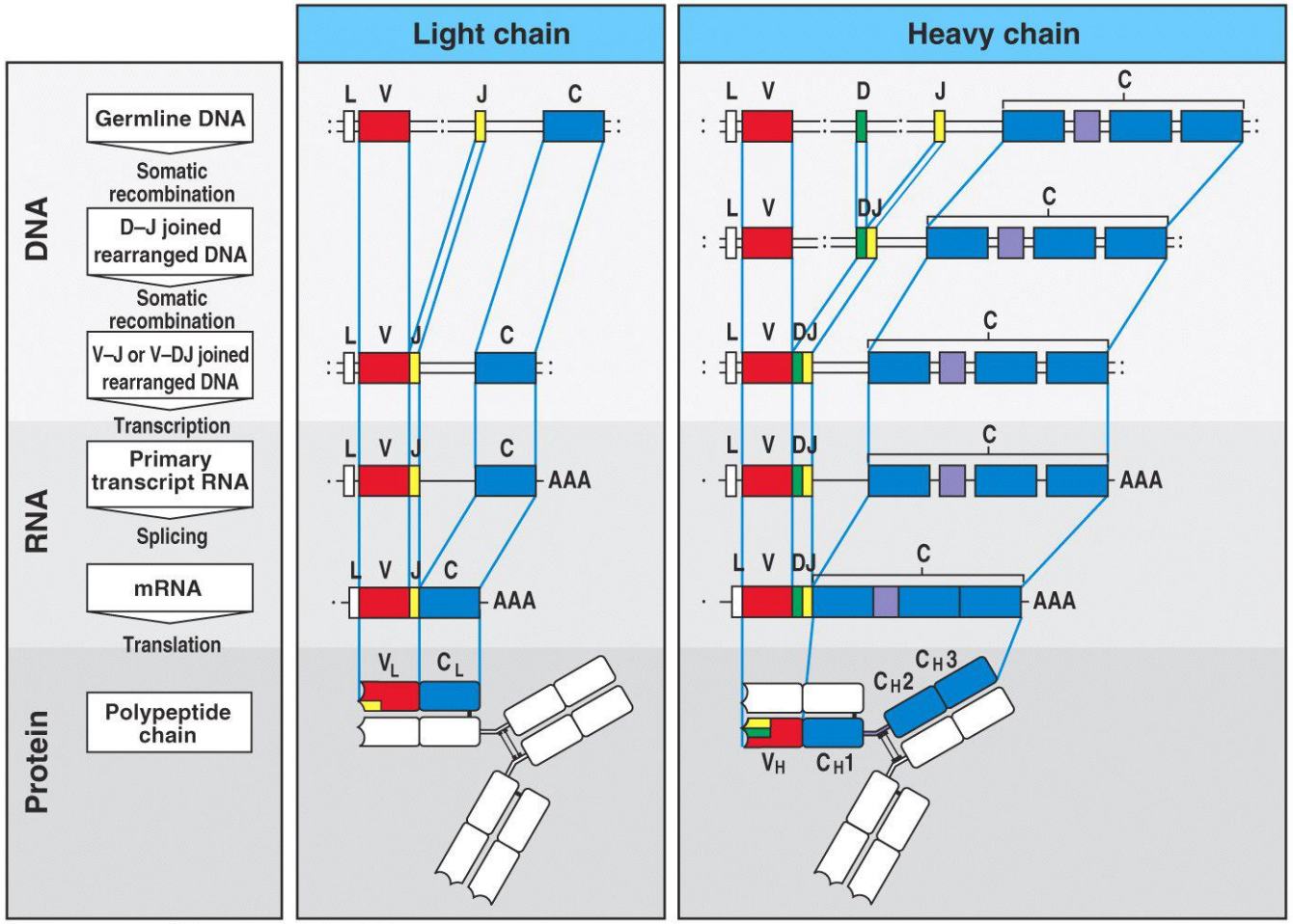

Figure 4-2 Immunobiology, 6/e. (© Garland Science 2005)

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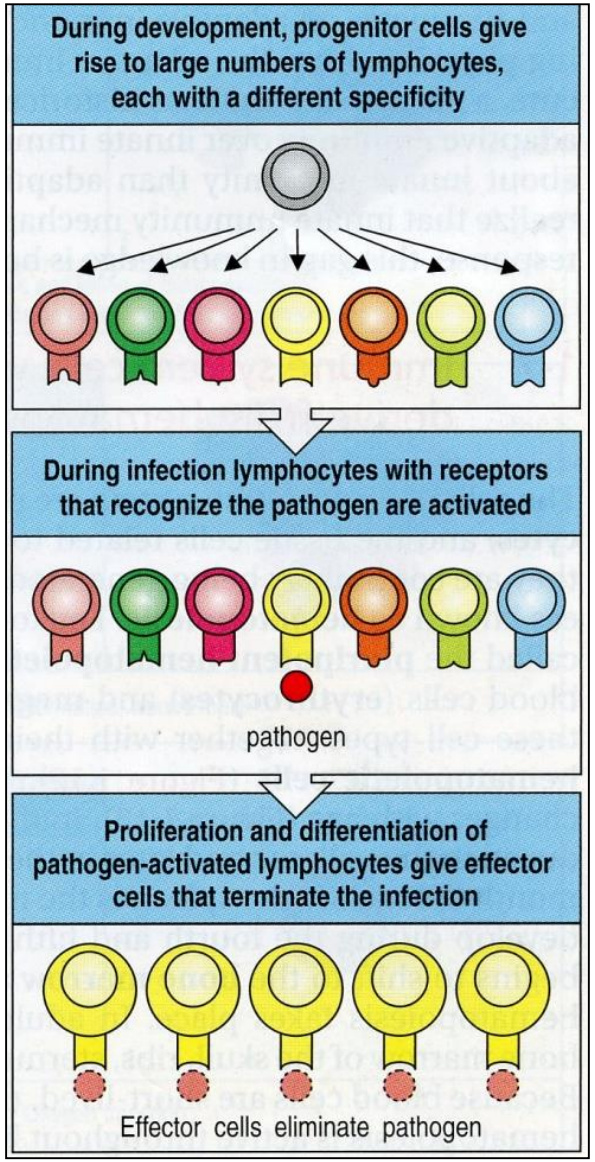
T cell and B cell repertoire diversity

Element	Immunoglobulin		α:β T-cell receptors	
	H	κ+λ	β	α
Variable segments (V)	40	70	52	~70
Diversity segments (D)	25	0	2	0
D segments read in three frames	rarely	–	often	–
Joining segments (J)	6	5(κ) 4(λ)	13	61
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	1.9×10^6		5.8×10^6	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

From Parham 4th edition

Adaptive immunity: Primary response



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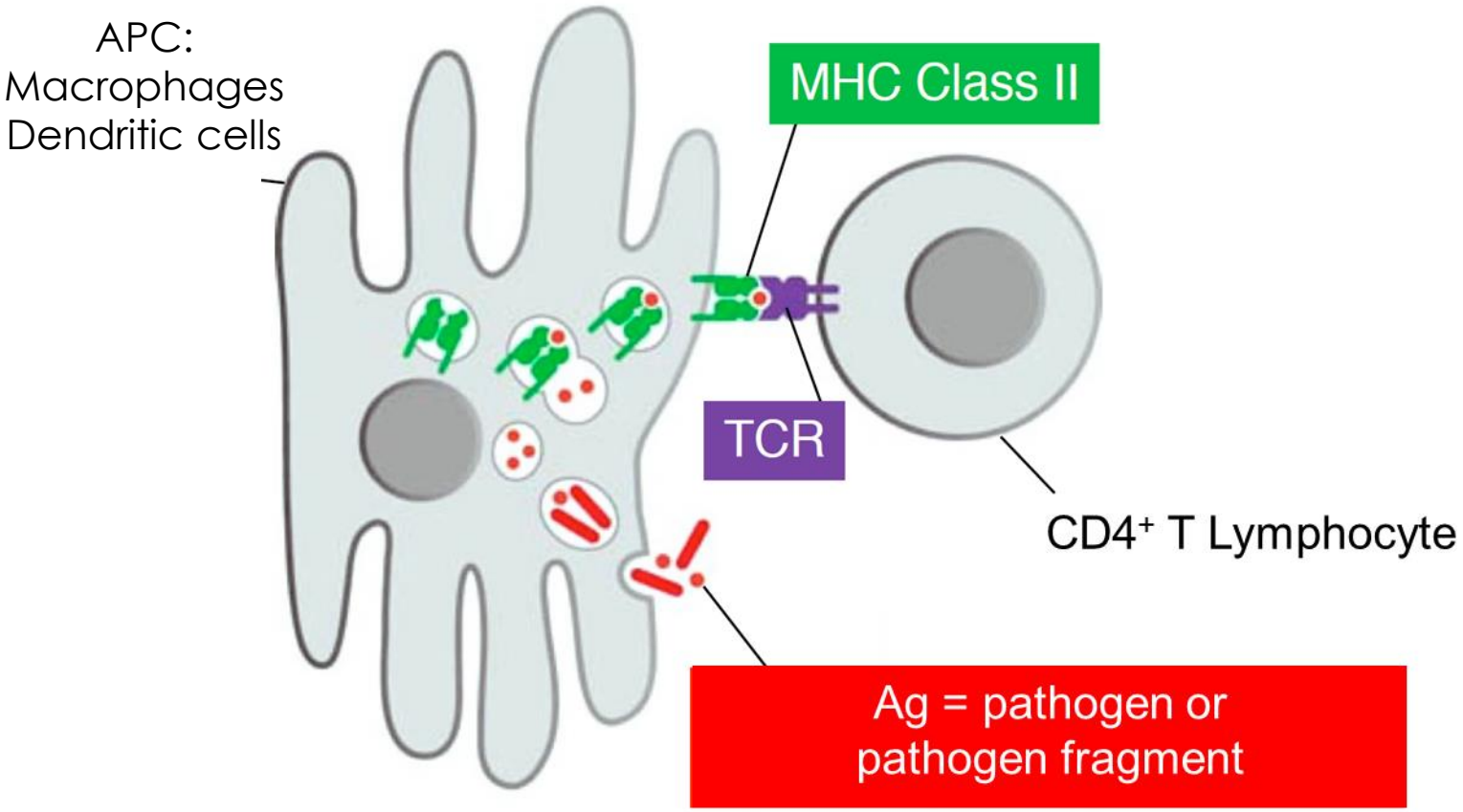
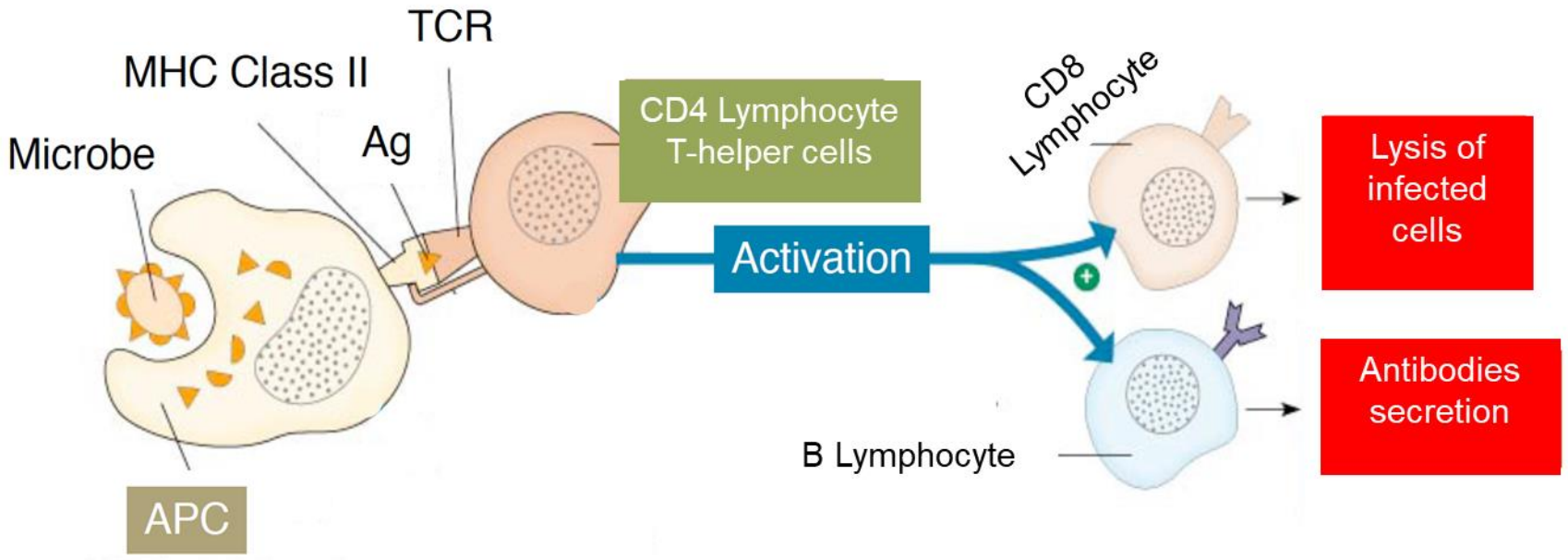
B cells and CD8 T cells need help from CD4 T lymphocytes help to be activated

CD4 Helper T lymphocytes see Ag on MHC class II

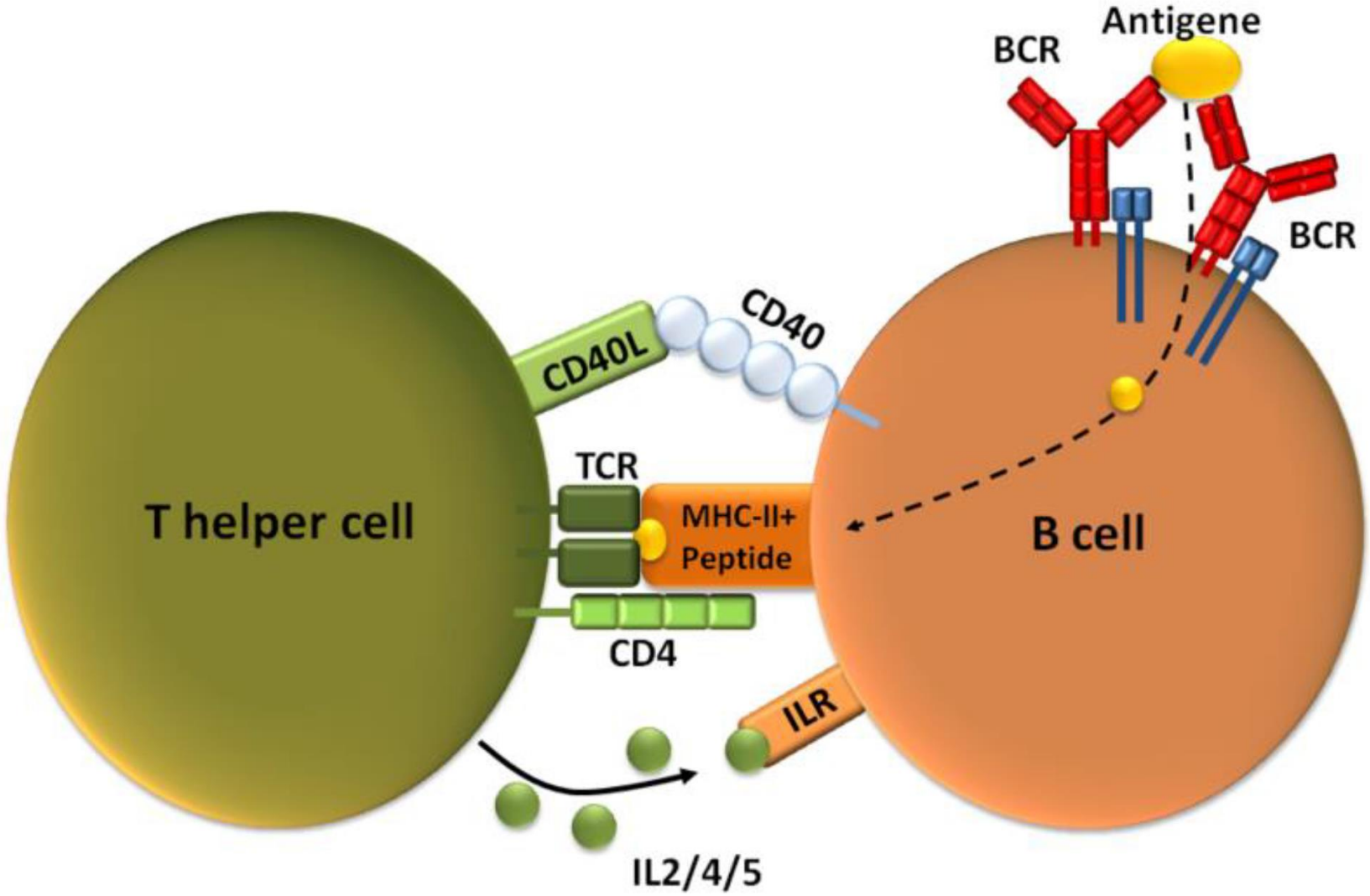


Adaptive immunity: Helper T lymphocytes

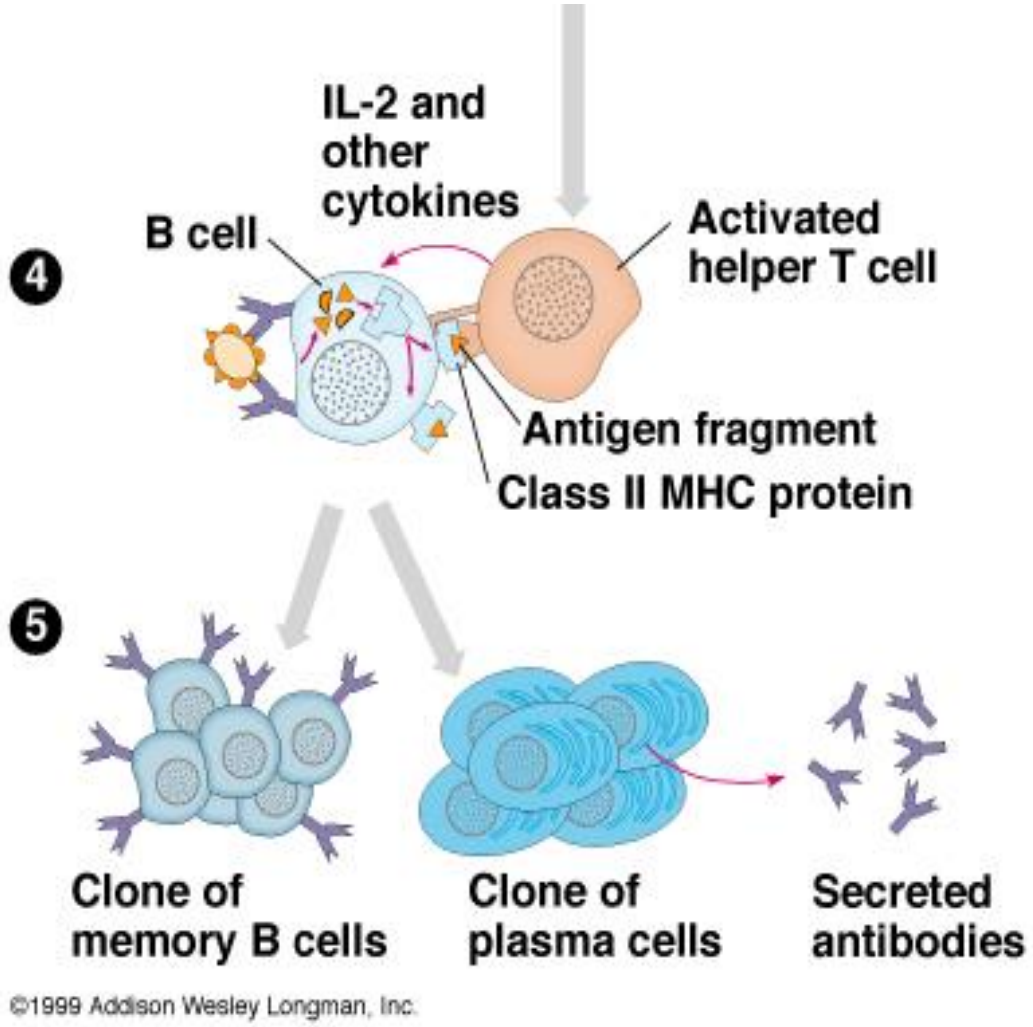


B cells and CD8 T cells that recognize the same Ag/pathogen as the helper T lymphocytes (Th cells) can get help from the Th cells

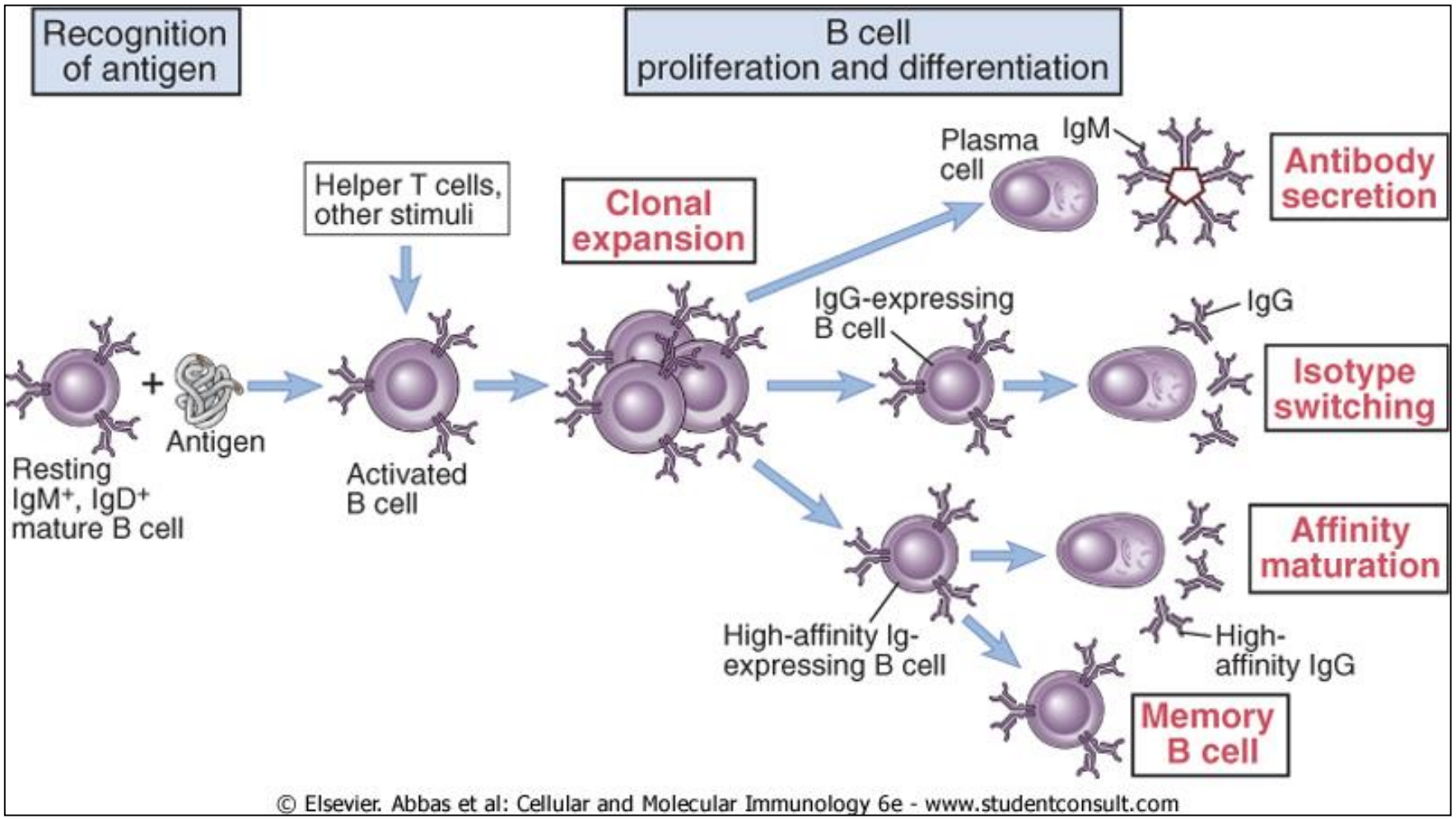
T helper lymphocytes stimulate B cells specific for that particular antigen to become plasma cells



B cells receiving help from CD4 T cells become plasma cells.



Phases of humoral immune response



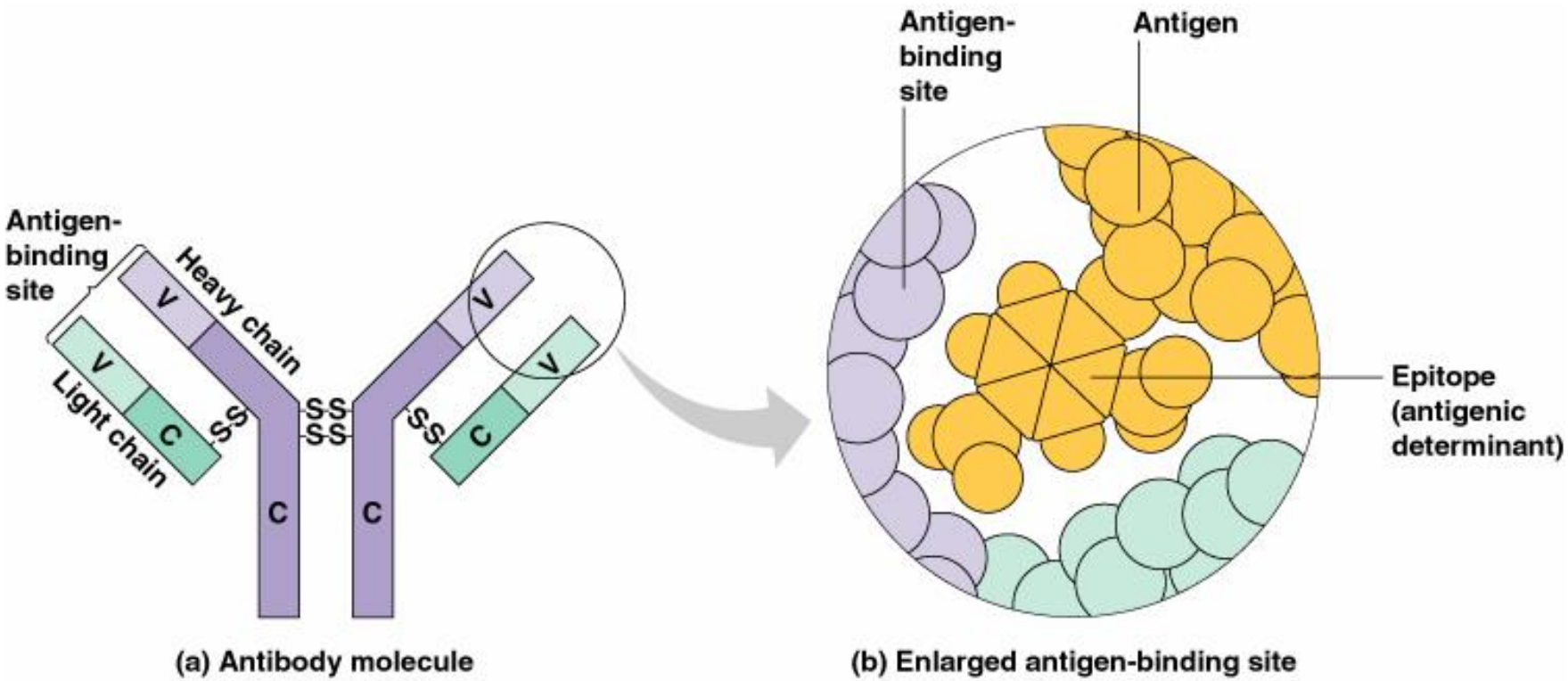
Antibodies

- Antibodies are proteins that recognize and bind a specific antigen with high specificity. They are produced in response to the antigen.

- A virus or a microbe can have various antigenic sites (epitopes) to which different antibodies can bind.

- Every antibody has at least two identical sites that bind an antigen: *antigen-binding sites (paratope)*.

- They belong to a group of serum proteins named immunoglobulins (Igs)



Antibodies structure

- ✓Monomer: a flexible Y-shape molecule with 4 protein chains:

2 identical light chains

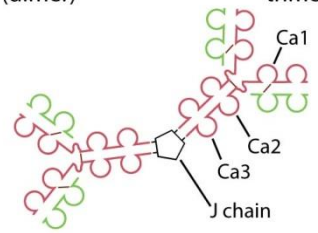
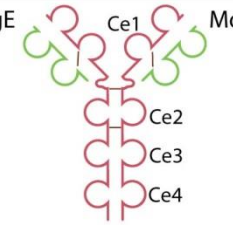
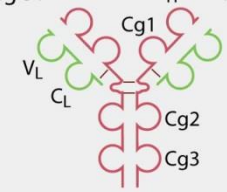
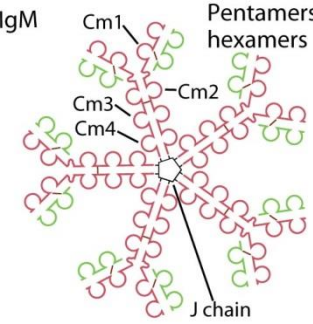
2 identical heavy chains

- ✓Variable regions: two portions at the end of Y arms. It is where the antigen-binding sites are located. They are identical within the same antibody while they differ from one antibody to another.

- ✓Constant regions: stem of the monomer and lower portion of the Y.

- ✓Stem of the monomer: it is important because it can bind either complement components or receptors on cells (e.g. macrophages).

Ig isotypes

Isotype of antibody	Subtypes	H chain	Serum concentr. (mg/mL)	Serum half-life (days)	Secreted form	Functions
IgA	IgA1,2	a(1 or 2)	3.5	6	IgA (dimer) Monomer, dimer, trimer 	Mucosal immunity
IgD	None	d	Trace	3	None	Naive B cell antigen receptor
IgE	None	e	0.05	2	IgE Ce1 Monomer 	Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4	g (1,2,3 or 4)	13.5	23	IgG1 V_H Monomer 	Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None	m	1.5	5	IgM Cm1 Pentamers, hexamers 	Naive B cell antigen receptor, complement activation

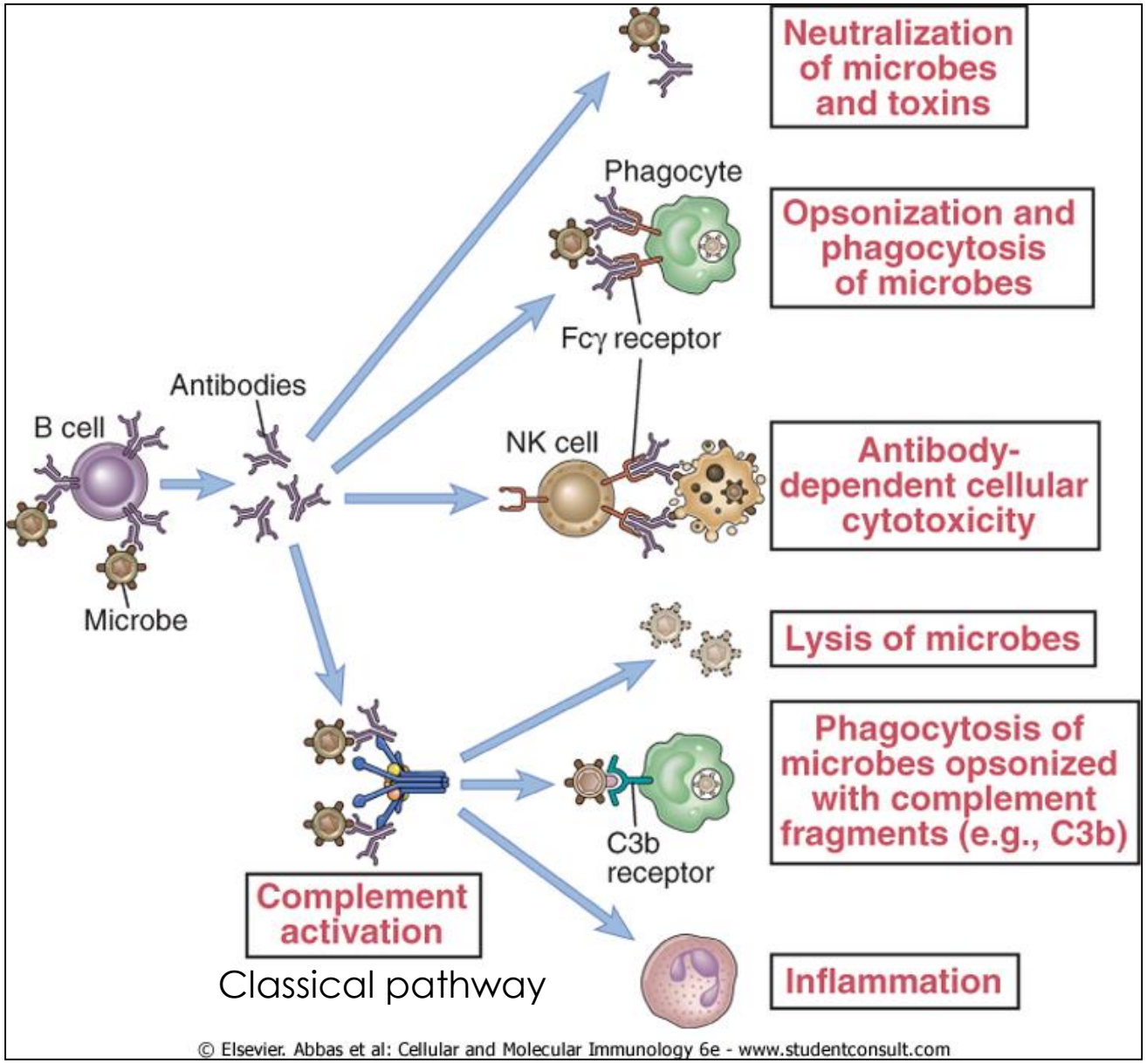
The effector functions of antibodies are discussed in detail in Chapter 14.

Functions of antibody isotypes

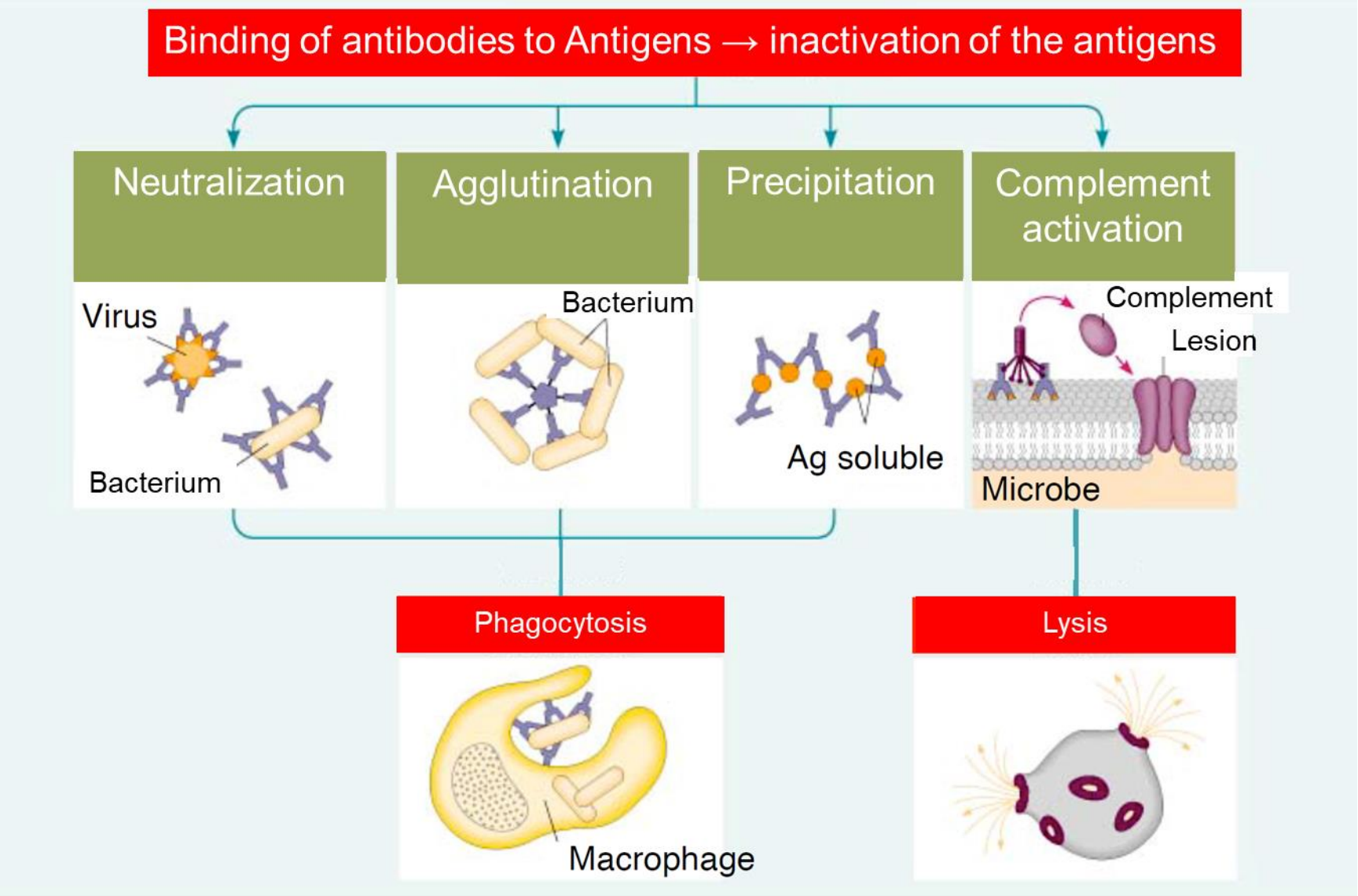
Isotype	Effector functions
IgG	Ag opsonization Activation of complement classical pathway ADCC mediated by NK cells and macrophages Neonatal immunity
IgM	Activation of complement classical pathway Receptor for Ag on naive B lymphocytes
IgA	Mucosal immunity: secretion of IgA into the gastrointestinal and respiratory tracts
IgE	ADCC mediated by eosinophils Mastocyte degranulation
IgD	Receptor for Ag on naive B lymphocytes

Effector functions of Ab

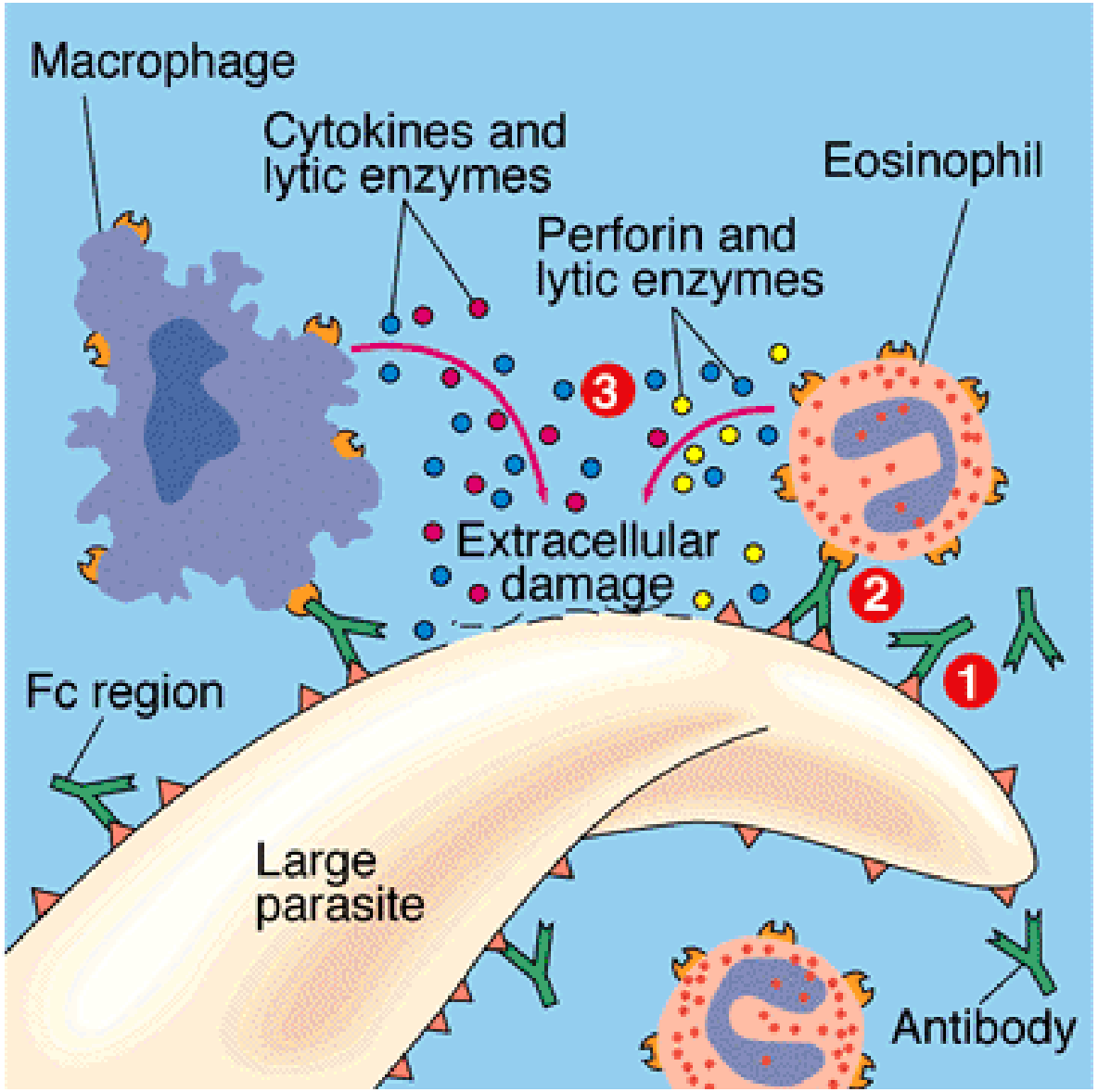
Antibodies mark pathogens and their products



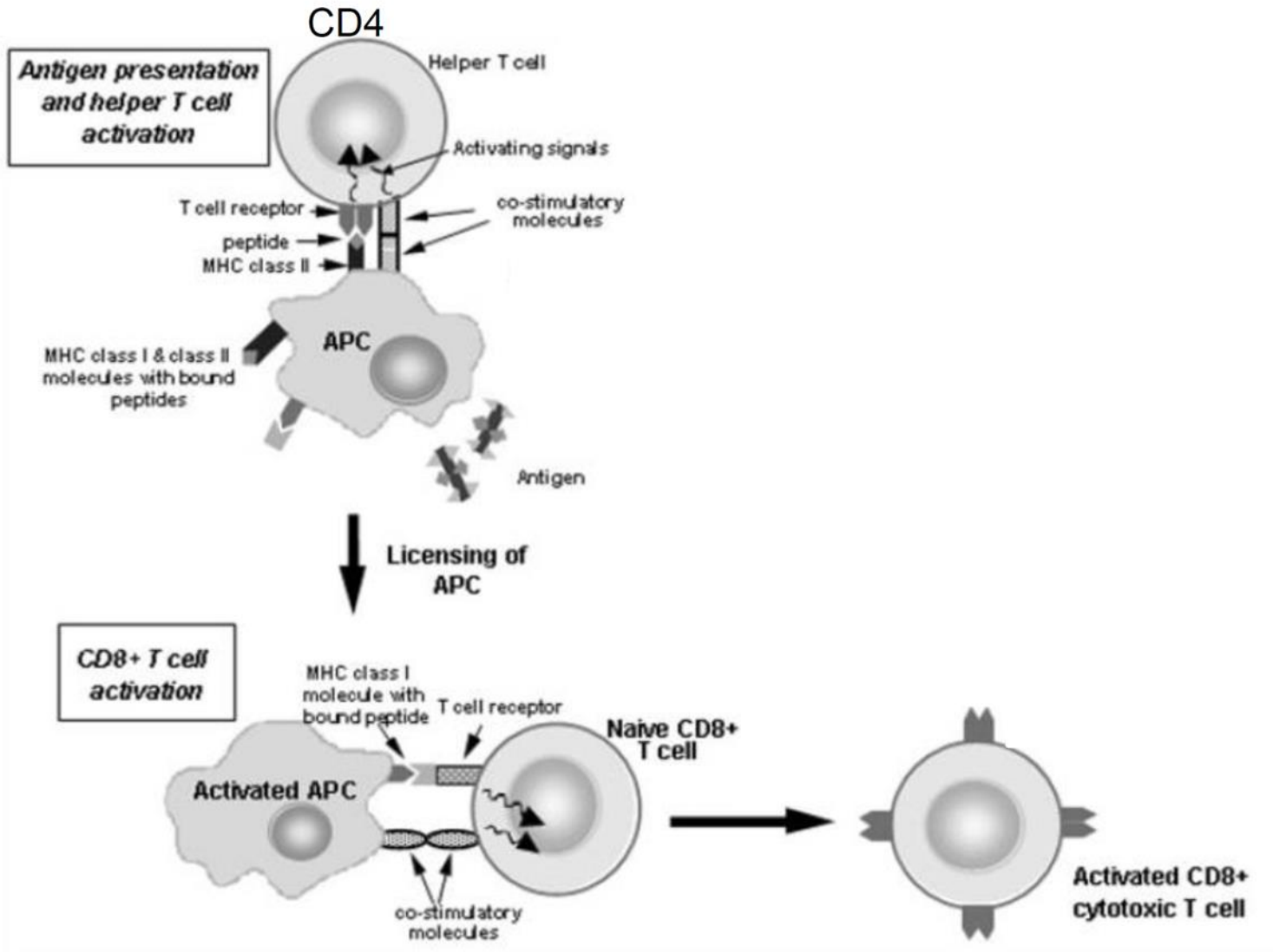
Adaptive immunity: Antibody function



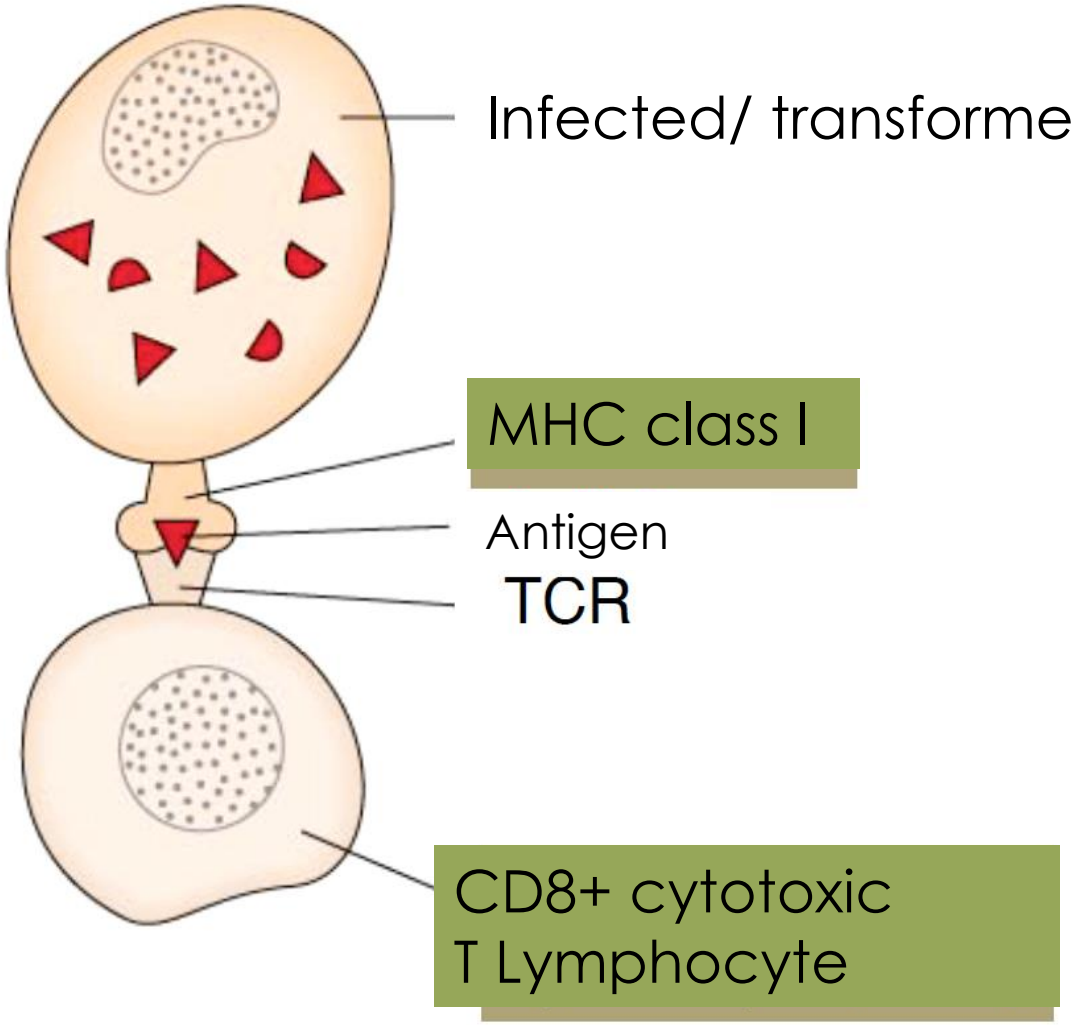
Antibodies mediate the destruction of big parasites by innate immunity



Adaptive immunity: CD8+ Cytotoxic T Lymphocyte



Adaptive immunity: $CD8^+$ Cytotoxic T Lymphocyte

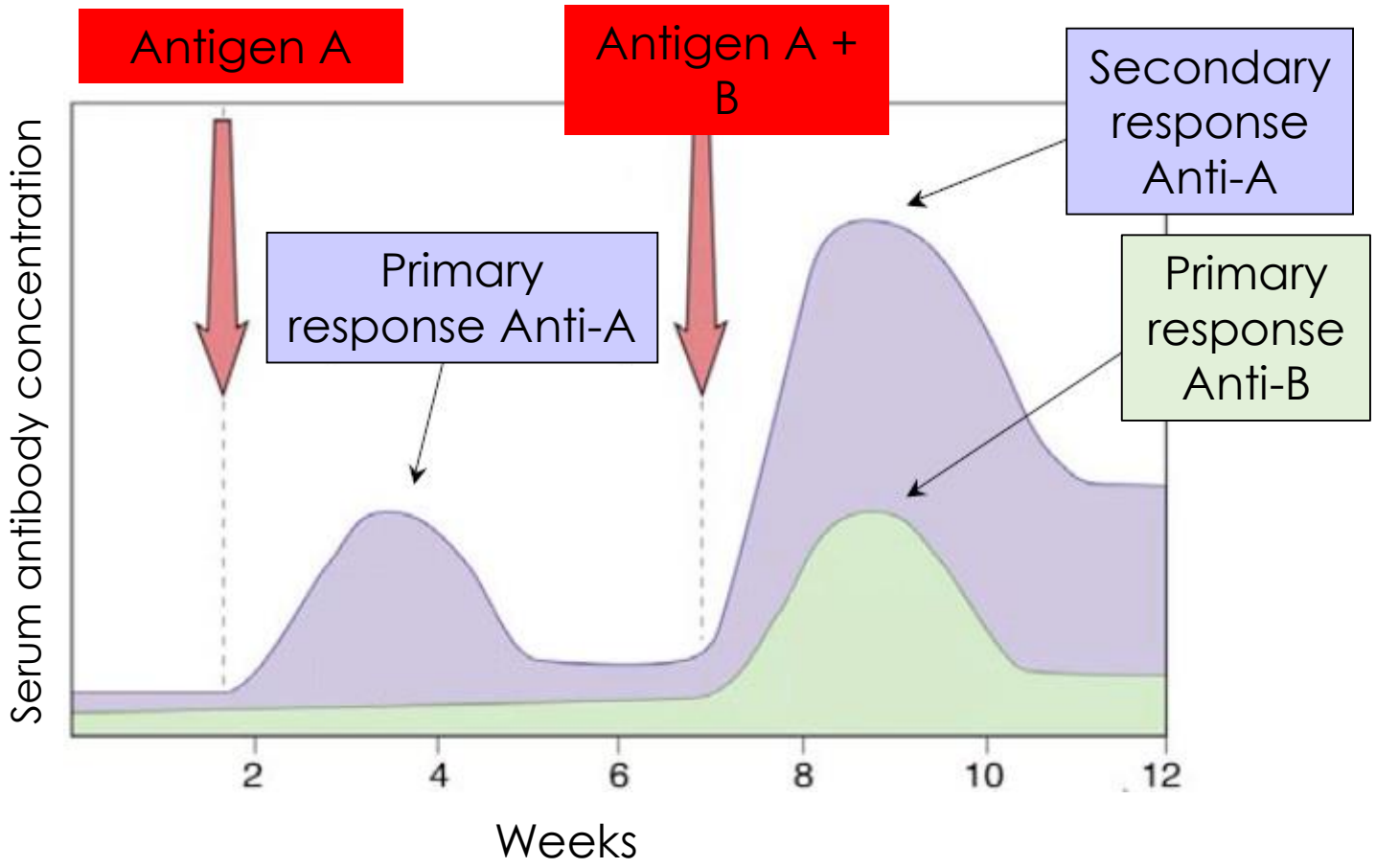


Adaptive immunity: Secondary response

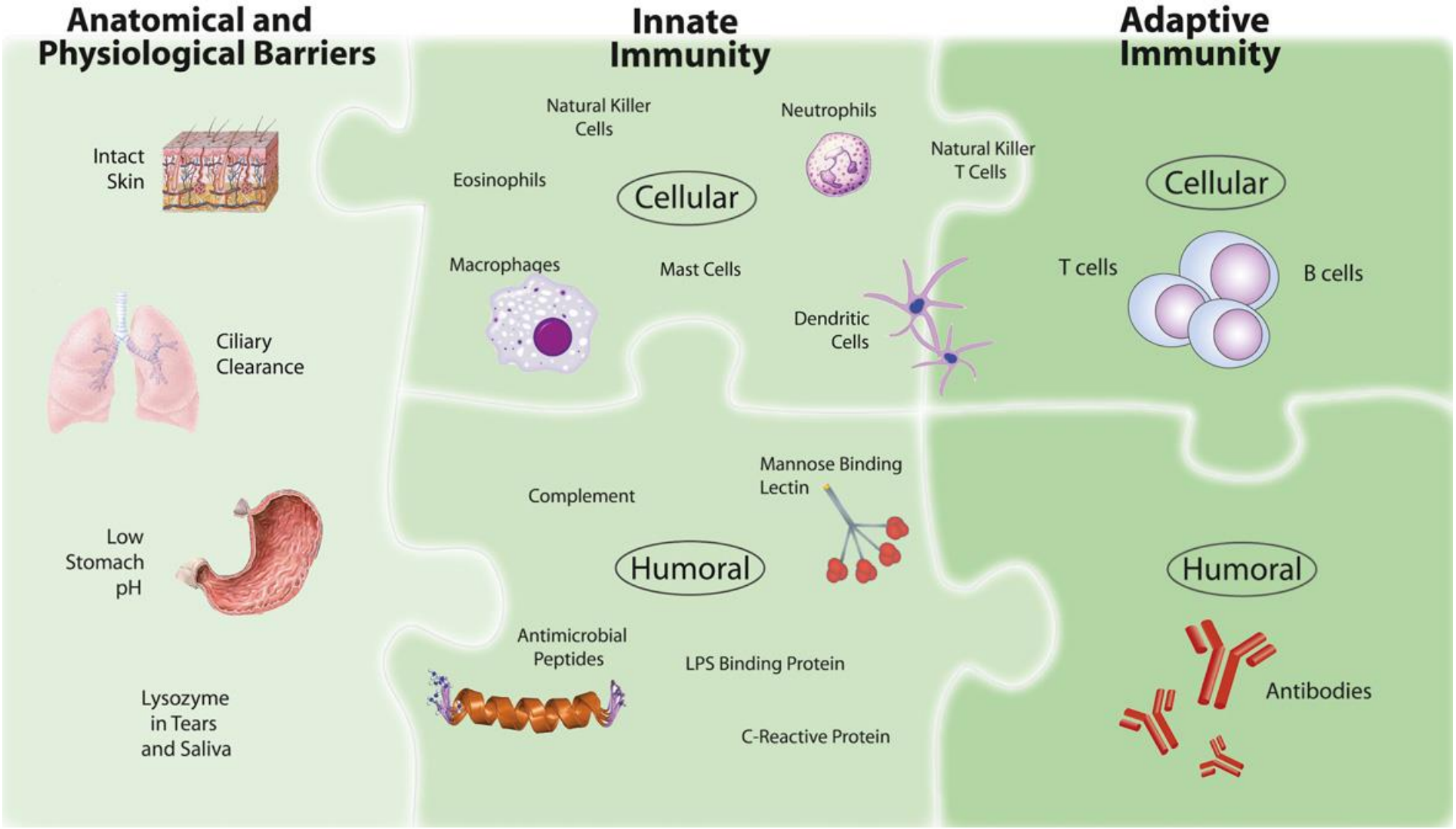
- Second or subsequent encounter with the same Ag.
    - reactivation of the memory effector cells.
    - Faster than primary response
    - More potent than the primary response

- Principle of vaccination
- generate immunological memory before real encounter with pathogen

Specificity and memory of the immune response



The effectors of immunity



From Turvey, S. E. 2010 American Academy of Allergy

Conclusion

- The immune cells are generated in the primary lymphoid organes
  - Bone morrow
    - Hematopoiesis
    - B cell development
    - Host the plasmocytes
  - Thymus
    - T cell development and differentiation

- The secondary lymphoid orgarns
  - Lymph nodes
  - Mucosa-associated lymphoid tissues (MALT)
    - Concentrate at sites in contact with pathogens
    - Provide the microenvirnment for lymphocyte activation
  - The spleen
    - Immune filtration of the blood

Conclusion

The immune system protects from pathogens and abnormal host cells

- Discriminate self from non self.
  - Self must be tolerated
    - Host cells
    - Commensal microorganisms (macrobiota)
  - Non self must be rejected
    - Exogenous cells (pathogens, organ transplant)
    - Exogenous substances (toxins, venoms, allergens)
    - Modified self (cancer)

- Two defence mechanisms:
  - Innate immunity
  - Adaptive immunity
    - Anatomical barriers, humoral and cellular components

$$\text{Antigen (Ag)} = constant$$

The immune response is a double-edged sword

Benefic

- Protection against pathogens (non self)
- Elimination of altered self (cancer)

Harmful

- Discomfort (inflammation)
- Alteration of sefl (auto-immunity)

Topic 8 Immune system diseases

Hypersensitivities or allergic reactions

An over-reaction of the immune system to innocuous environmental antigens causing both local and systemic damage.

The mechanisms are the same used against pathogenic **antigen.**

- Etiology
- Intensity of reaction
- Final outcome (tissue damage)

Hypersensitivity reactions are classified based on the mechanisms underlying the pathology

Genetics predisposition: 40 % of Caucasian population

Epidemic of allergy

Antigens or allergens

Exogenous environmental antigens

- Dust
- Medications
- Microbes,
- Chemicals,
- Bood derivatives
- Food

Autologous antigens (self): autoimmune diseases

Four types of hypersensitivity reactions

Classification is based on the mechanisms underlying the immune reaction involved.

Type I,
Type II
Type III
Type IV

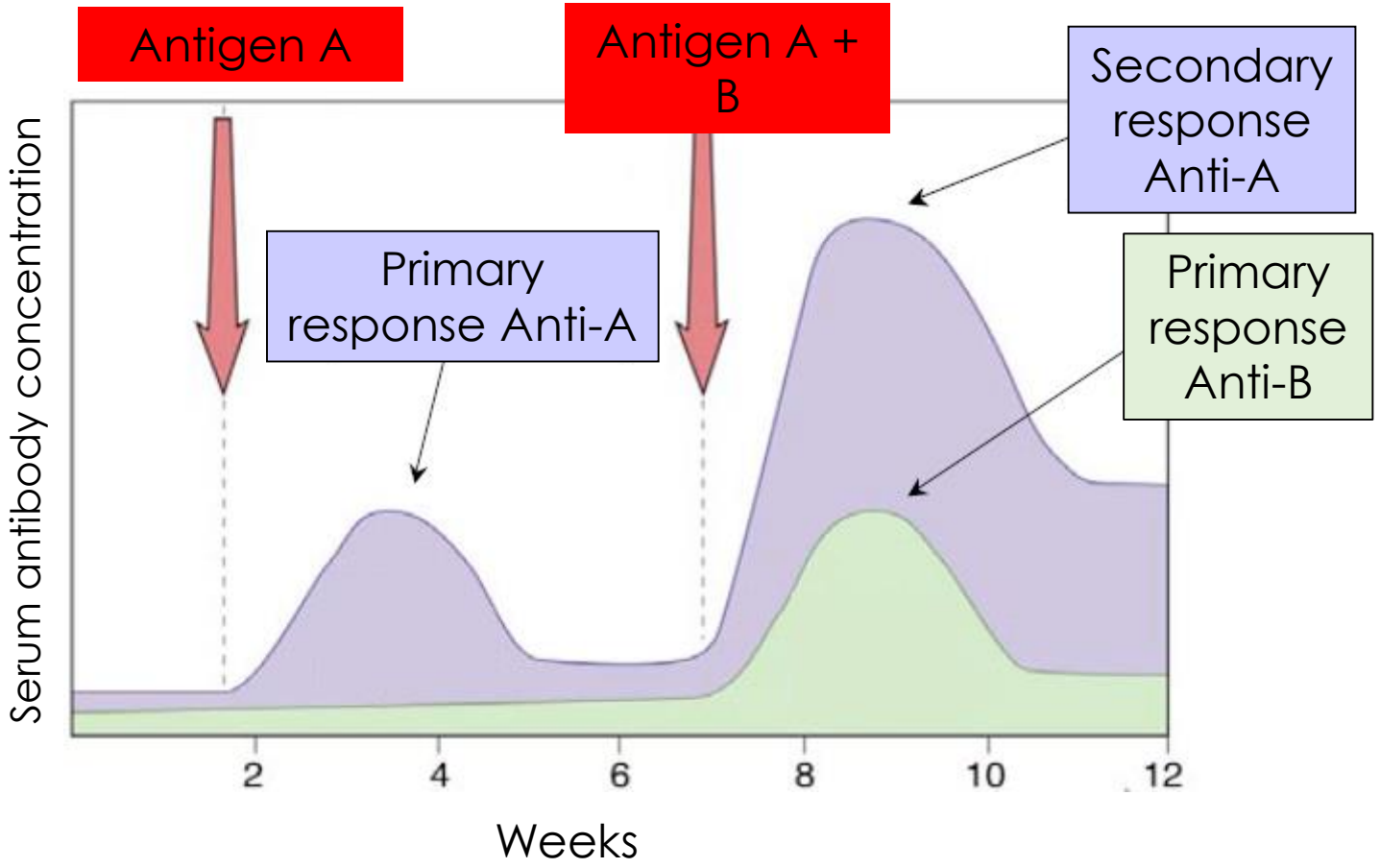
Type I Hypersensitivity: Immediate IgE-Mediated

Within minutes after exposure

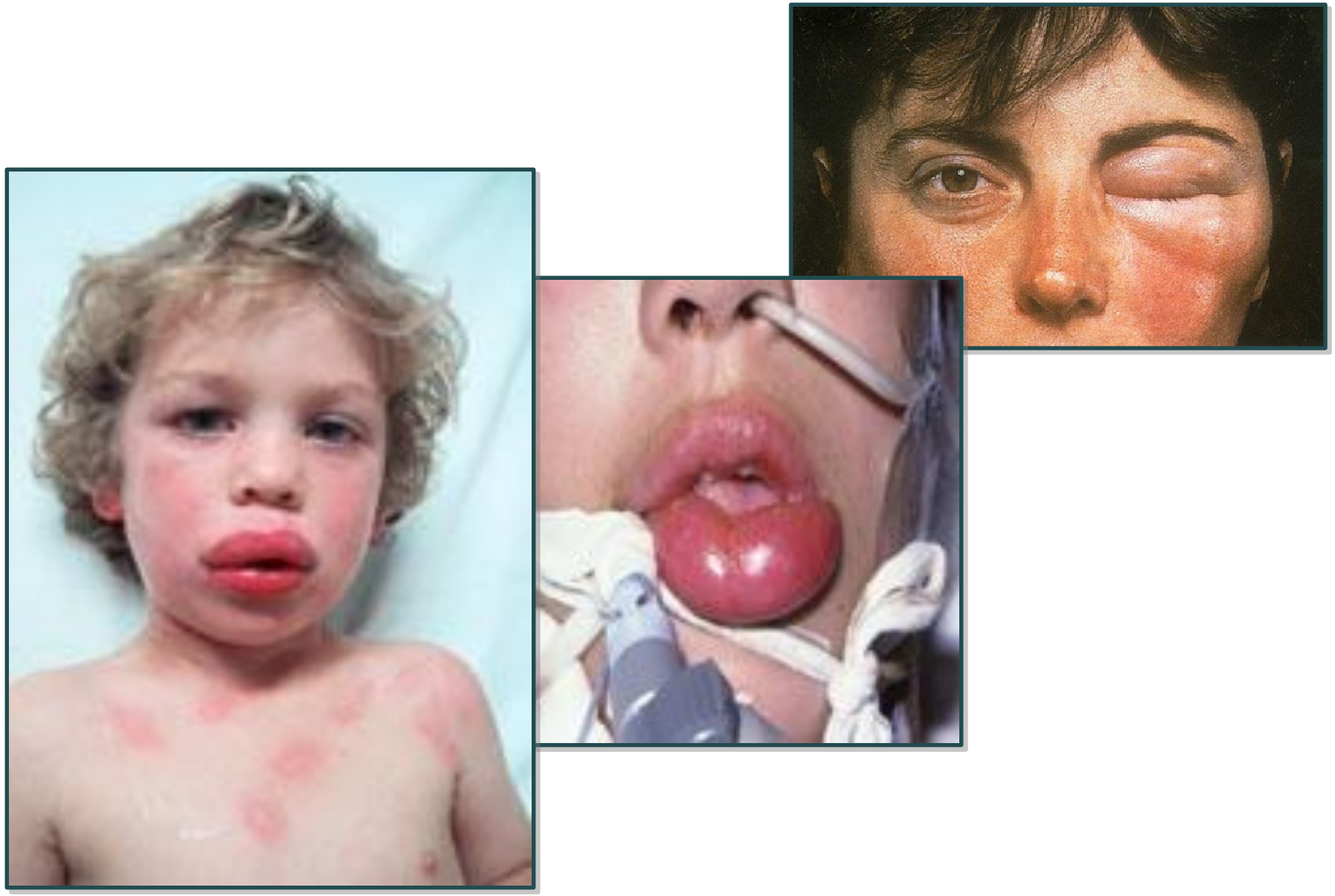
Type I hypersensitivities occur when an individual who has already produced IgE antibodies against a harmless antigen/allergen (pollens) comes into contact again with the same antigen.

Characterized by immediate reaction of the sensitized individual, generally within minutes of exposure.

Primary and secondary immune responses

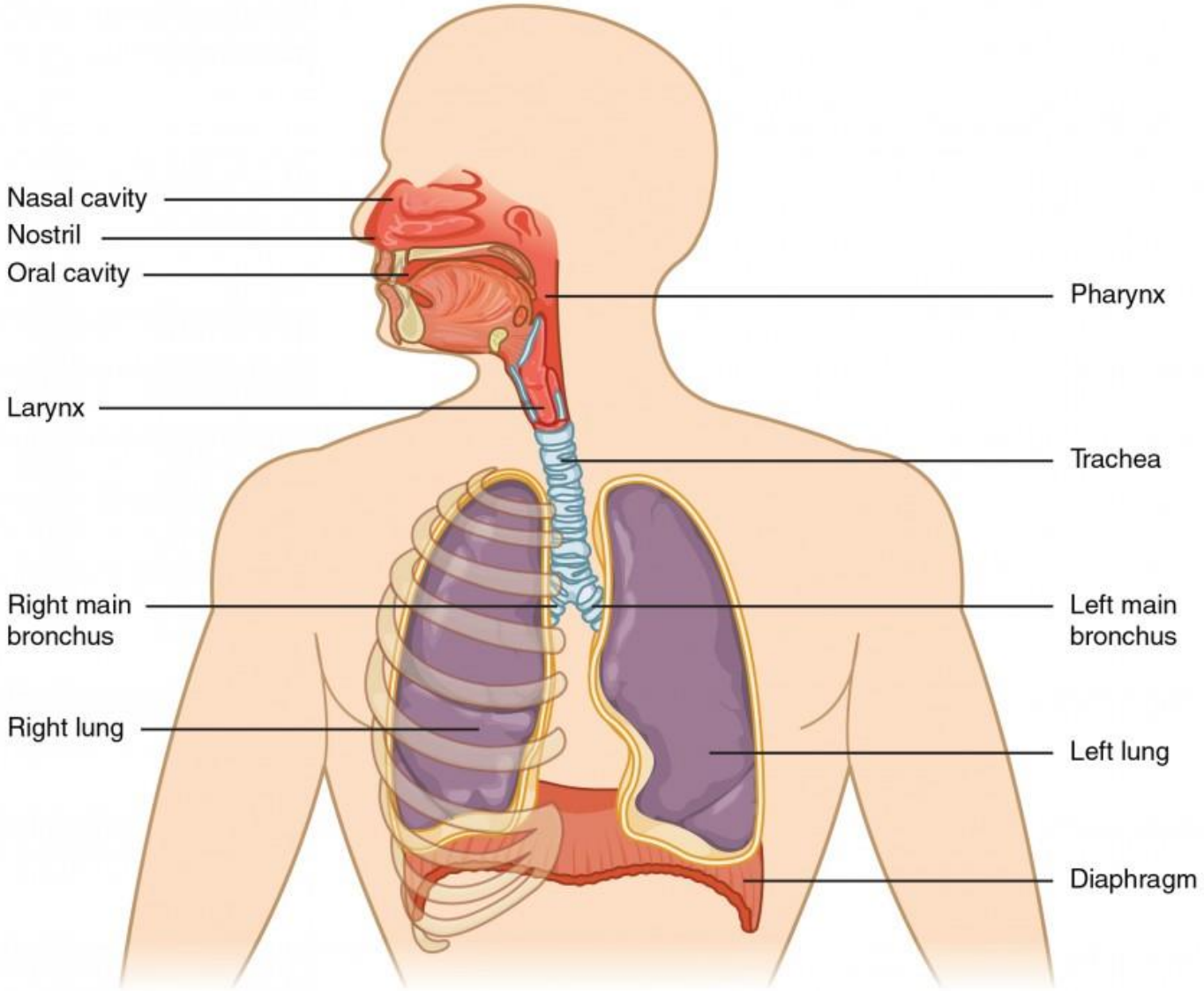


Anaphylaxis



The Respiratory System

Organs and Structures of the Respiratory System



The respiratory system can be divided into a conducting zone and a respiratory zone.

The function of the respiratory system:

1. Provide oxygen to body tissues for cellular respiration
2. Remove the waste product carbon dioxide
3. Help to maintain acid-base balance.

Portions of the respiratory system are also involved in non-vital functions:

1. Sensing odours
2. Speech production
3. Straining during childbirth
4. Coughing

Respiration

Exchange of O_2 and CO_2 between the atmosphere and the body cells.

Events of Respiration:

- **Pulmonary ventilation**- Air move in and out of the lungs
- **External respiration**- exchange of O_2 and CO_2 between the air and blood in the lungs. O_2 diffuses in blood while CO_2 move to the lungs.
- **Transport**- O_2 move from lungs to body cells, CO_2 does the opposite, accomplished by the cardiovascular system.
- **Internal respiration-** O_2 diffuses from blood to body cells and CO_2 does the opposite.

Conducting Zone

- Provide a route for incoming and outgoing air.
- Remove debris and pathogens from the incoming air.
- Warm and humidify the incoming air.
- Several structures within the conducting zone perform other functions as well.
  - Sensing odours
  - Metabolize some airborne carcinogens.

The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system.

1. The external nose.
    1. Consists of the surface and skeletal structures forming the nose outward appearance and contribute to its numerous functions.

The Nose and its Adjacent Structures

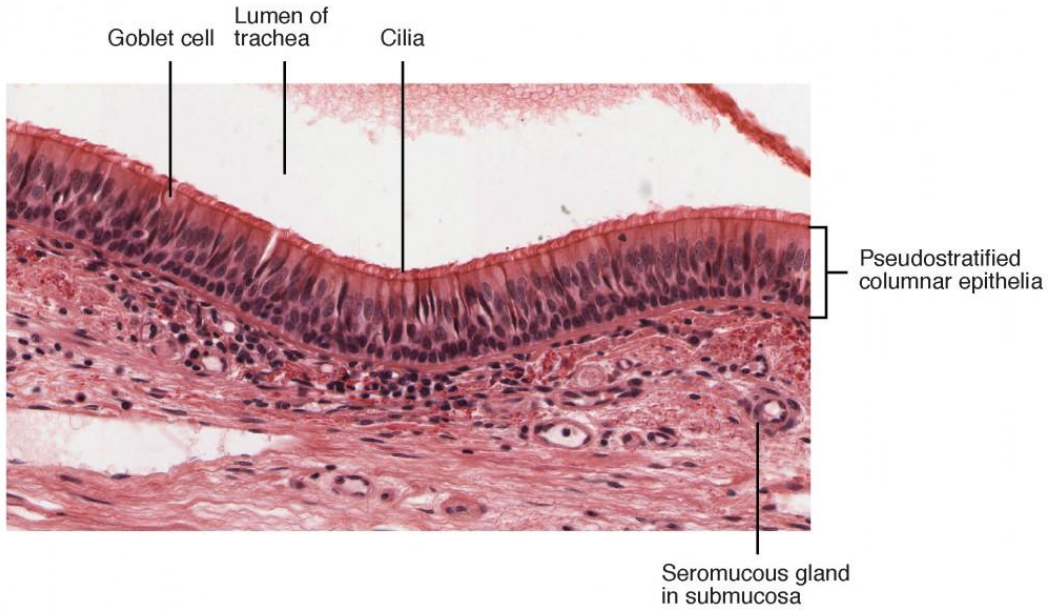
1. The internal nose (nasal cavity).
    - The nares open into the nasal cavity.
    - Each lateral wall of the nasal cavity has three bony projections: the superior, middle, and inferior nasal conchae.
    - Conchae increase the surface area of the nasal cavity and disrupt the air flow causing air to bounce along the epithelium, where it is cleaned and warmed.

    - The conchae and meatuses trap water during exhalation and prevent dehydration of the nasal epithelium.
    - Air exits the nasal cavities via the internal nares to moves into the pharynx.
    - Several bones forming the walls of the nasal cavity have air-containing sinuses to warm and humidify incoming air. Sinuses are lined with a mucosa. The sinuses produce mucus and lighten the weight of the skull.

The conchae, meatuses, and paranasal sinuses are lined by respiratory epithelium: pseudostratified ciliated columnar epithelium.

- Goblet cells that produce mucus to trap debris and pathogens.
  - Secrete the lysozyme enzyme and defensins.
  - The cilia with a constant beating motion remove the mucus and debris from the nasal cavity. Material is swept towards the throat to be swallowed.
- Cold air slows the movement of the cilia, resulting in accumulation of mucus: runny nose during cold weather.
- This moist epithelium warms and humidifies incoming air.
  Capillaries located beneath the nasal epithelium warm the air by convection.

- Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.



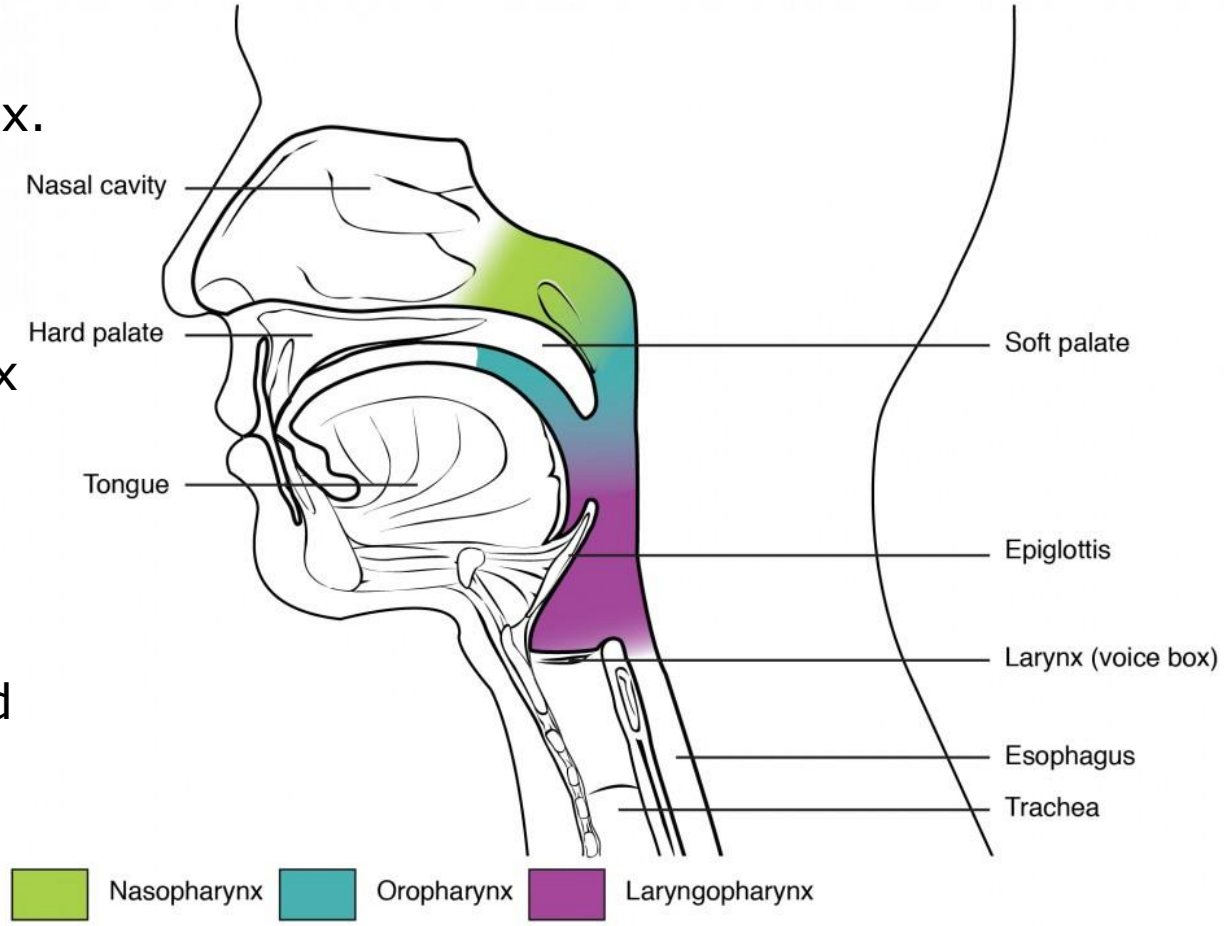
Pharynx: muscular passage from nasal cavity to larynx

1. Nasopharynx – superior region behind nasal cavity.
2. Oropharynx – middle region behind mouth.
3. Laryngopharynx – inferior region connects to larynx.

- Auditory tubes open into the nasopharynx
- Tonsils of the pharynx

1. Pharyngeal tonsils (adenoids) – in the nasopharynx
2. Palatine tonsils – each side of the oropharynx
3. Lingual tonsils – at the base of the tongue

The pharynx is a tube formed by skeletal muscle lined by mucous membrane that is continuous with that of the nasal cavities.

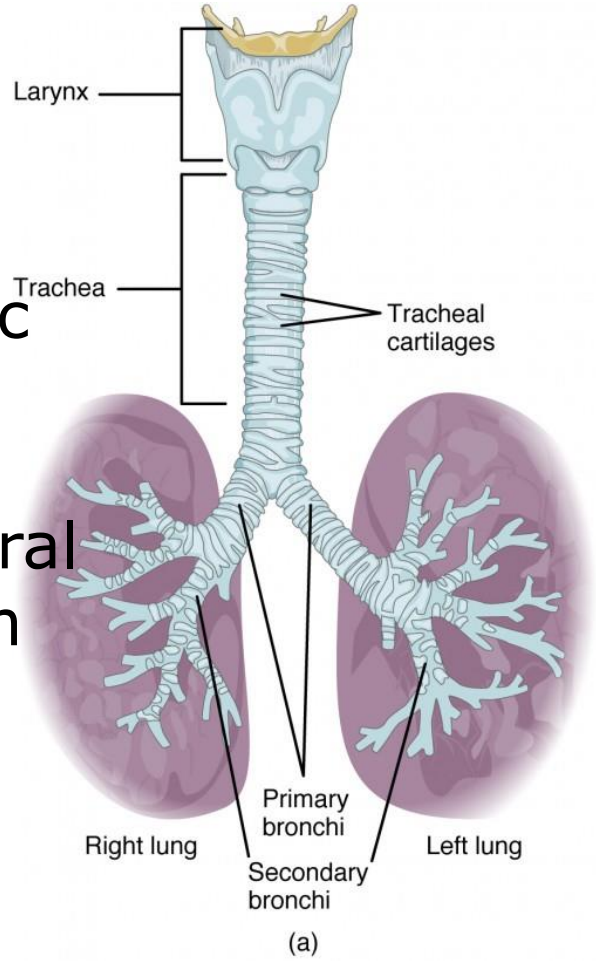


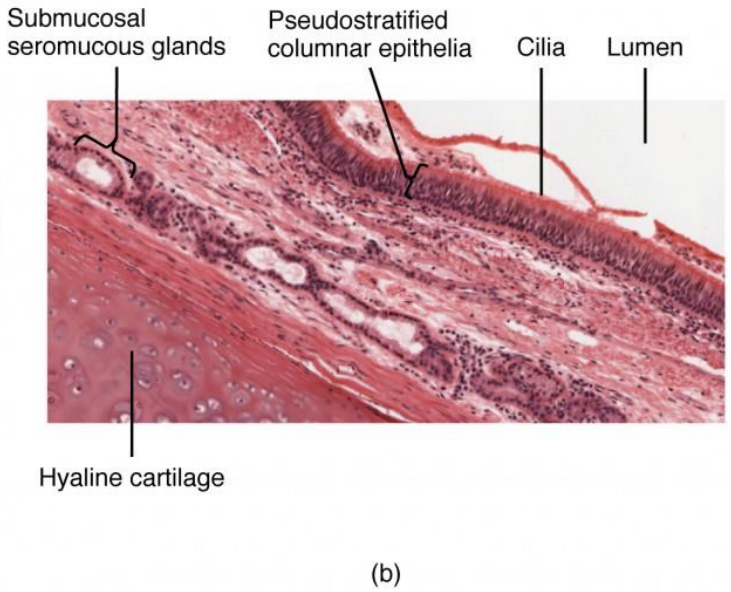
The trachea (windpipe) is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage connected by dense connective tissue.

The trachealis muscle and elastic connective tissue form the fibroelastic membrane (for stretching).

The rings of cartilage provide structural support and prevent the trachea from collapsing.

The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx.



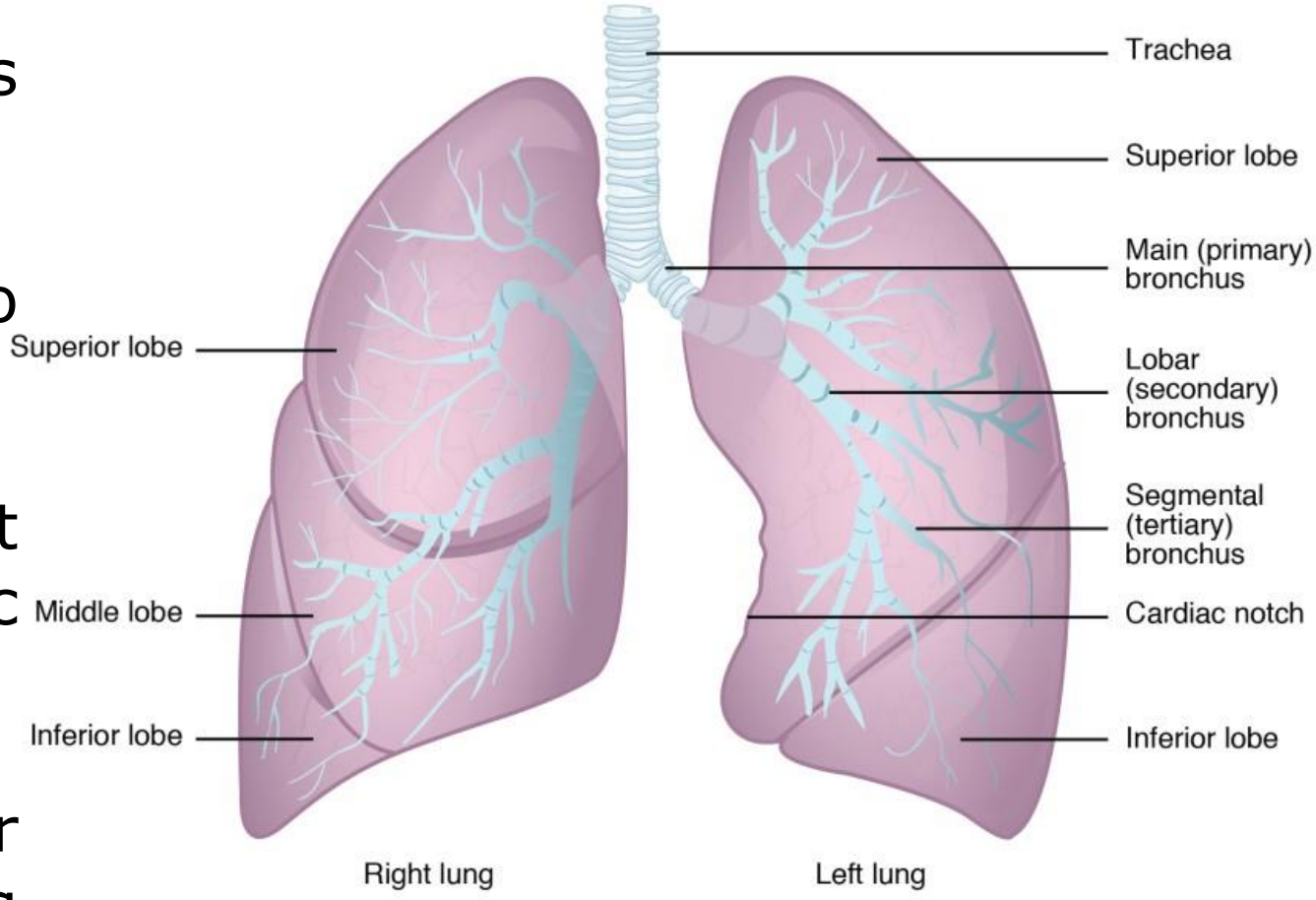


Gross Anatomy of the Lungs

Pyramid-shaped paired organs connected to the trachea by the bronchi.
Enclosed by the pleurae attached to the mediastinum.

The diaphragm is a flat muscle at the base of the lungs and thoracic cavity.

The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right.



Each lung is composed of smaller units called lobes. Each lobe houses multiple bronchopulmonary segments.

Blood Supply and Nervous Innervation of the Lungs

Blood Supply

- Plays an important role in gas exchange and transport.
- The pulmonary artery bring deoxygenated blood to the lungs where erythrocytes are loaded with oxygen.
- Branches multiple as it follows the bronchi.
- One arteriole and an accompanying venule supply and drain one pulmonary lobule. Pulmonary arteries ramify to become the pulmonary capillary network.
- Capillary wall meets the alveolar wall, creating the respiratory membrane. Oxygenated blood drains from the alveoli through multiple pulmonary veins which exit the lungs through the hilum.

Nervous Innervation

- Both the parasympathetic and sympathetic nervous systems control constriction and dilation of the airway. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. The nerves follow the bronchi and branch to innervate muscle fibers, glands, and blood vessels.

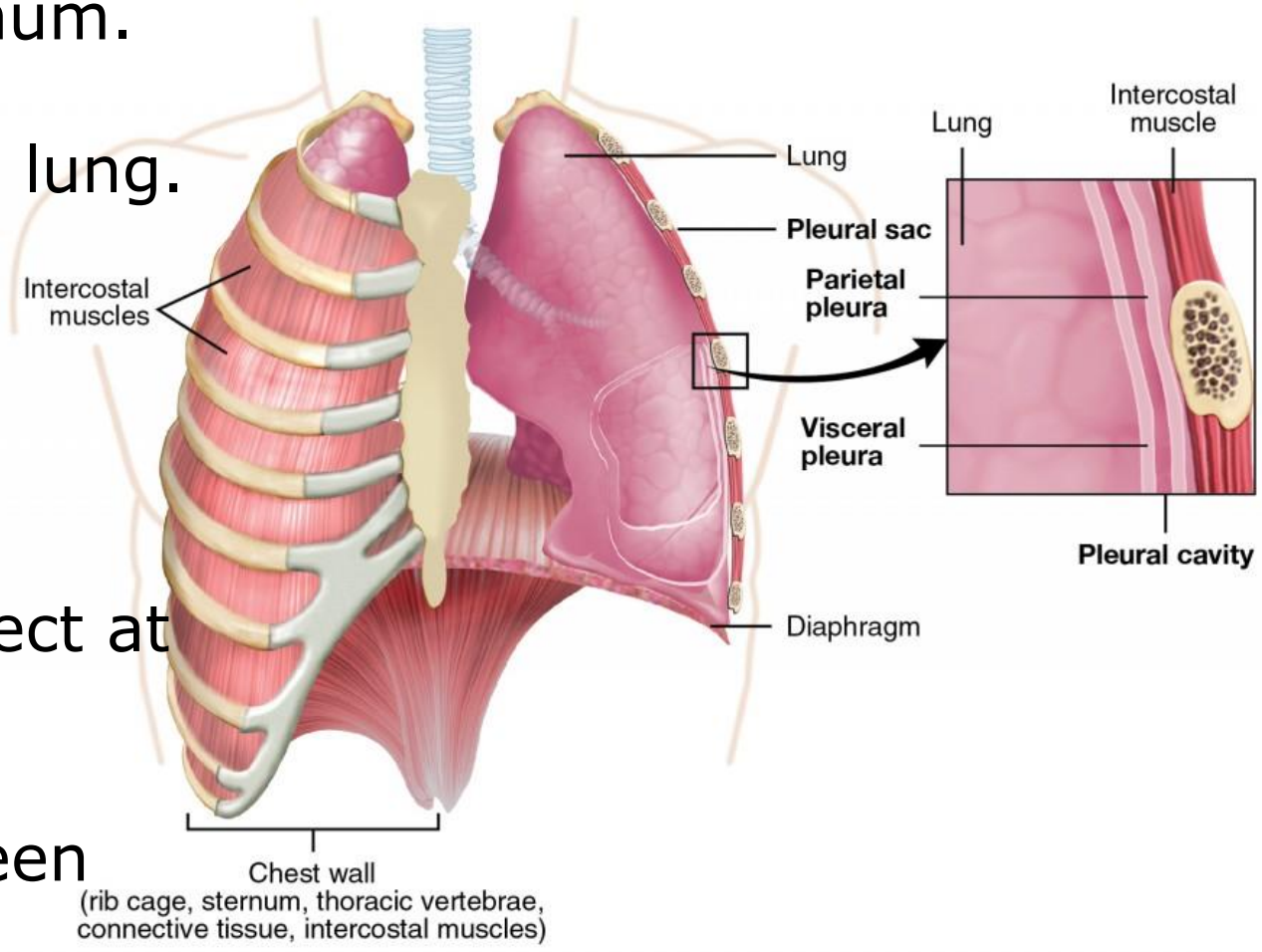
Each lung is enclosed within a cavity surrounded by the pleura, a serous membrane separated by the mediastinum.

Visceral pleura is the layer lining the lung.

Parietal pleura is the outer layer connecting to the thoracic wall, the mediastinum, and the diaphragm.

The visceral and parietal pleurae connect at the hilum.

The **pleural cavity** is the space between the visceral and parietal layers.



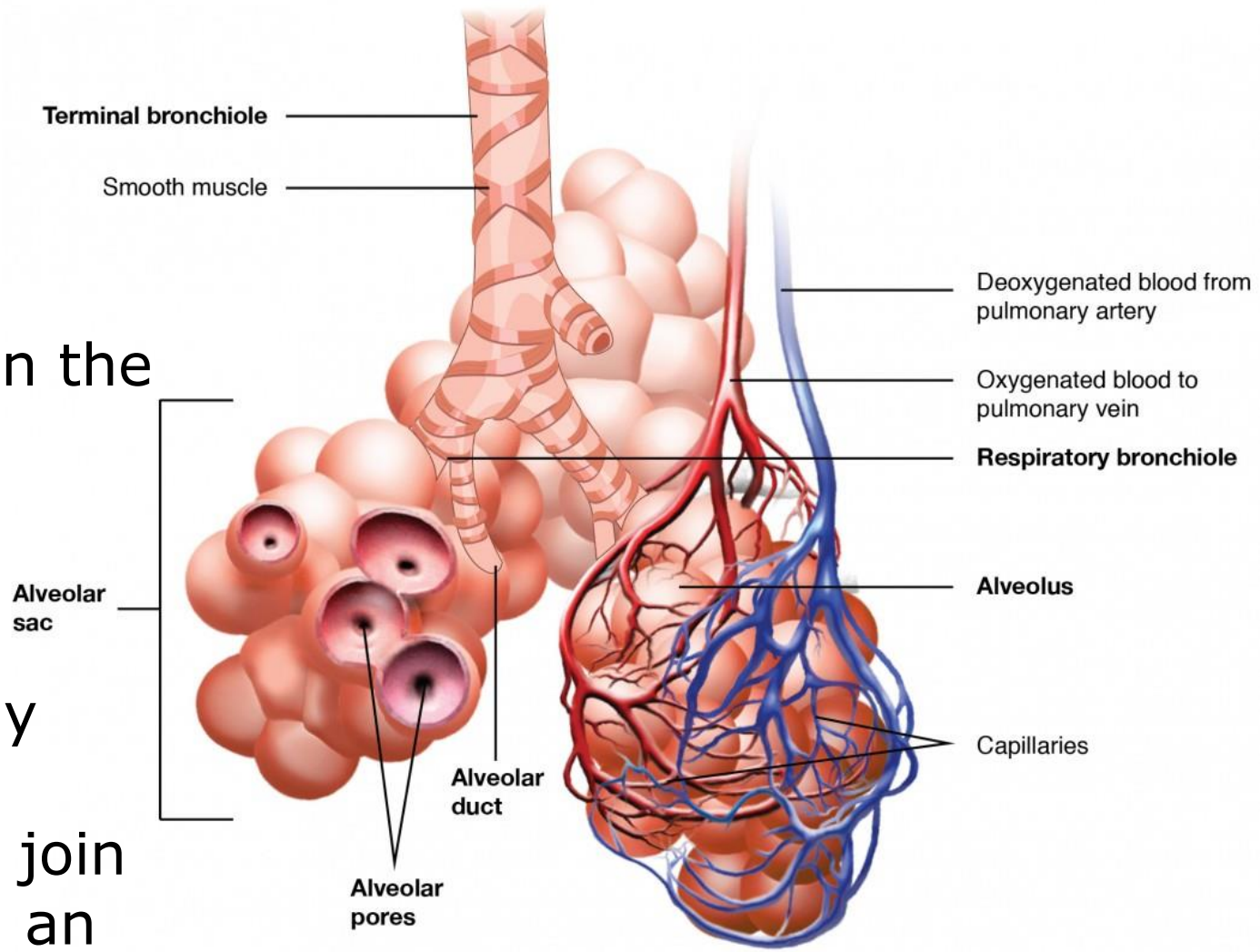
The lungs: Each lung is divided into lobes by fissures – deep grooves

- Left lung – 2 lobes
- Right lung – 3 lobes

Pleural fluid – serous fluid between the 2 layers that reduces frictions.

Respiratory Zone

Includes structures that are directly involved in gas exchange.
Begins where terminal bronchioles join a respiratory bronchiole connected an alveolar duct which reach a cluster of alveoli.



Alveoli

Alveolar duct: tube composed of smooth muscle and connective tissue.

An alveolar sac is a cluster of many individual alveoli (gas exchange).

Alveoli are approximately 200 μm Ø small sac with elastic walls, attached to the alveolar ducts.

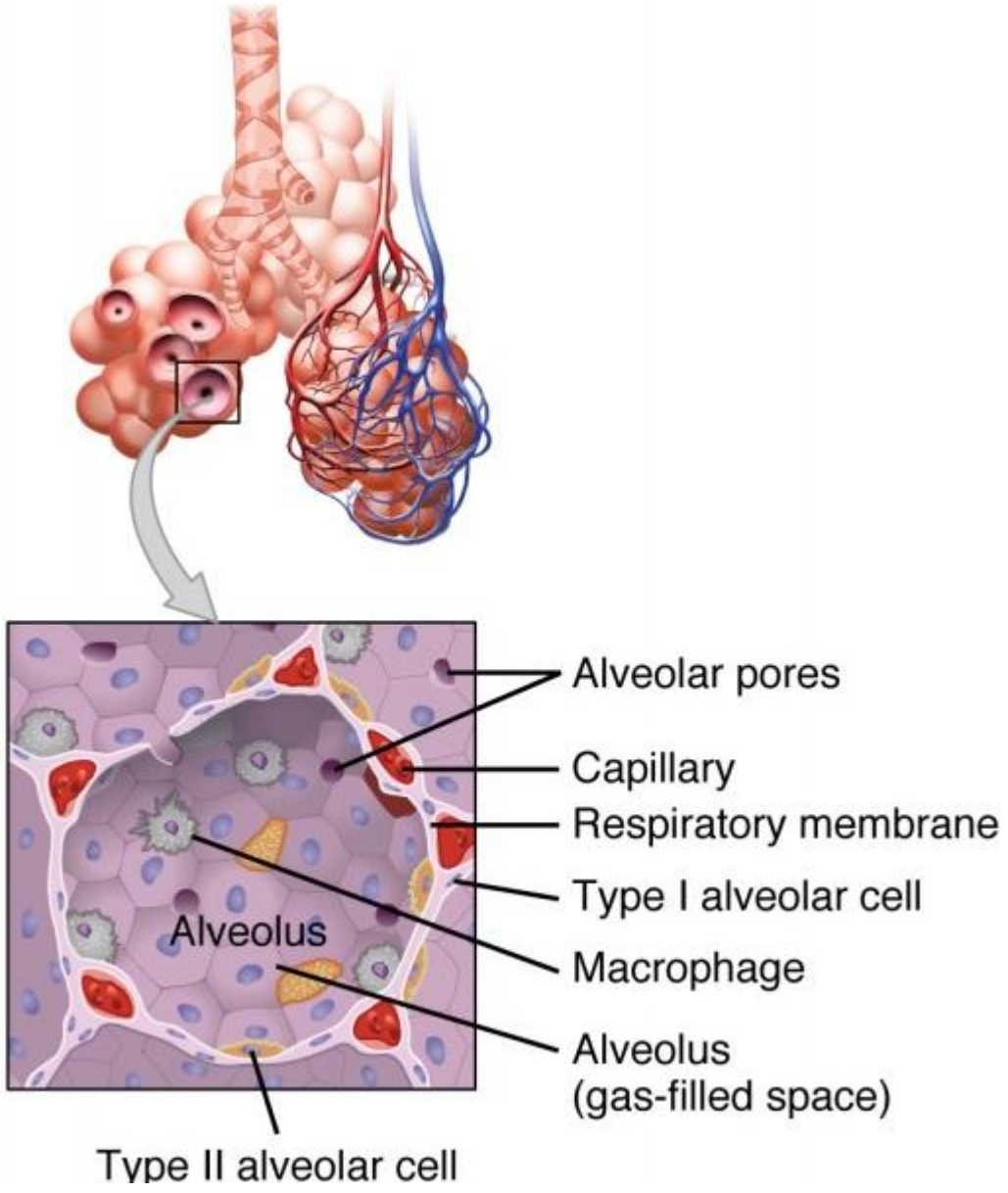
Alveoli are connected to their neighbors by alveolar pores, which help maintain equal air pressure throughout the alveoli and lung.

Type I alveolar cells, squamous epithelial cells, 25 nm thick, highly permeable to gases. Represents 97% of the alveoli surface.

Type II alveolar cells dispersed among the type I, secretes pulmonary surfactant (mixture of phospholipids and proteins) that reduces the surface tension of the alveoli. Formed an extremely thin simple squamous epithelium attached to a thin, elastic basement membrane.

They are bordered by the endothelial membrane of capillaries to form the respiratory membrane (approximately 0.5 mm thick), allows gases to cross by simple diffusion.

Alveolar macrophages: phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.



The Process of Breathing

Pulmonary ventilation: Movement of air in and out the lungs.

1. Atmospheric pressure (Patm)
2. Alveolar pressure (Palv)
3. Intrapleural pressure (Pip)

Inspiration-Active

1. diaphragm and external intercostal muscles contract volume of thoracic cavity increases.
2. Increase in lungs volume lowers intra alveolar pressure.
3. Atmospheric pressure higher than the pressure in the lungs: air is pulled into the lungs.

Expiration-Passive

1. Diaphragm and intercostal muscles relax.
2. Volume of thoracic cavity decreases.
3. Decrease in the volume of the lungs raises intra-alveolar pressure.
4. Intra-alveolar pressure higher than atmospheric pressure: Air is pushed out.

Control of Breathing

1. The respiratory centre in the brain stem control breathing in response to CO2 levels.
2. Medulla Oblongata sets the basic rhythm of breathing (pacemaker).
3. Pons smooths out respiratory rate and influence depth and length of respiration.

Factors Influencing Breathing

Chemical factors:

CO_2, H^+ and O_2 are the most important factors that regulate respiration.

Chemoreceptors located the respiratory center, the carotid arteries and aorta detect CO_2, H^+, and O_2 levels in the blood.

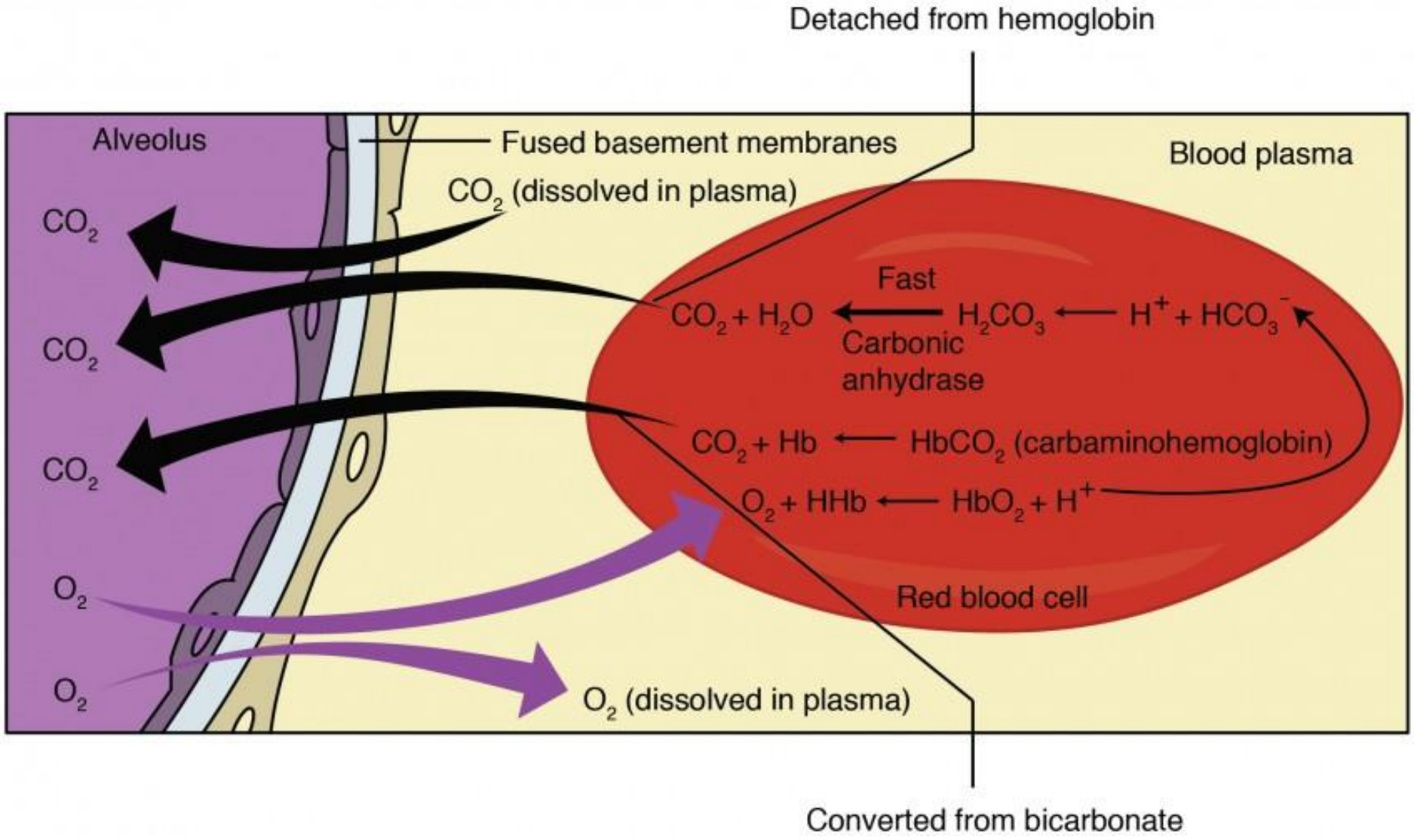
- CO_2 increase the rate and depth of breathing.
- O_2 levels only affect breathing when dangerously low.

Stretch receptors in the visceral pleura are sensitive to the degree of stretching of the lungs.

Higher brain centers- (the cerebrum) control voluntary altering of breathing.
Body temperature- increase in body temperature such as during exercise or fever increases respirations.

External respiration

Uses partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.

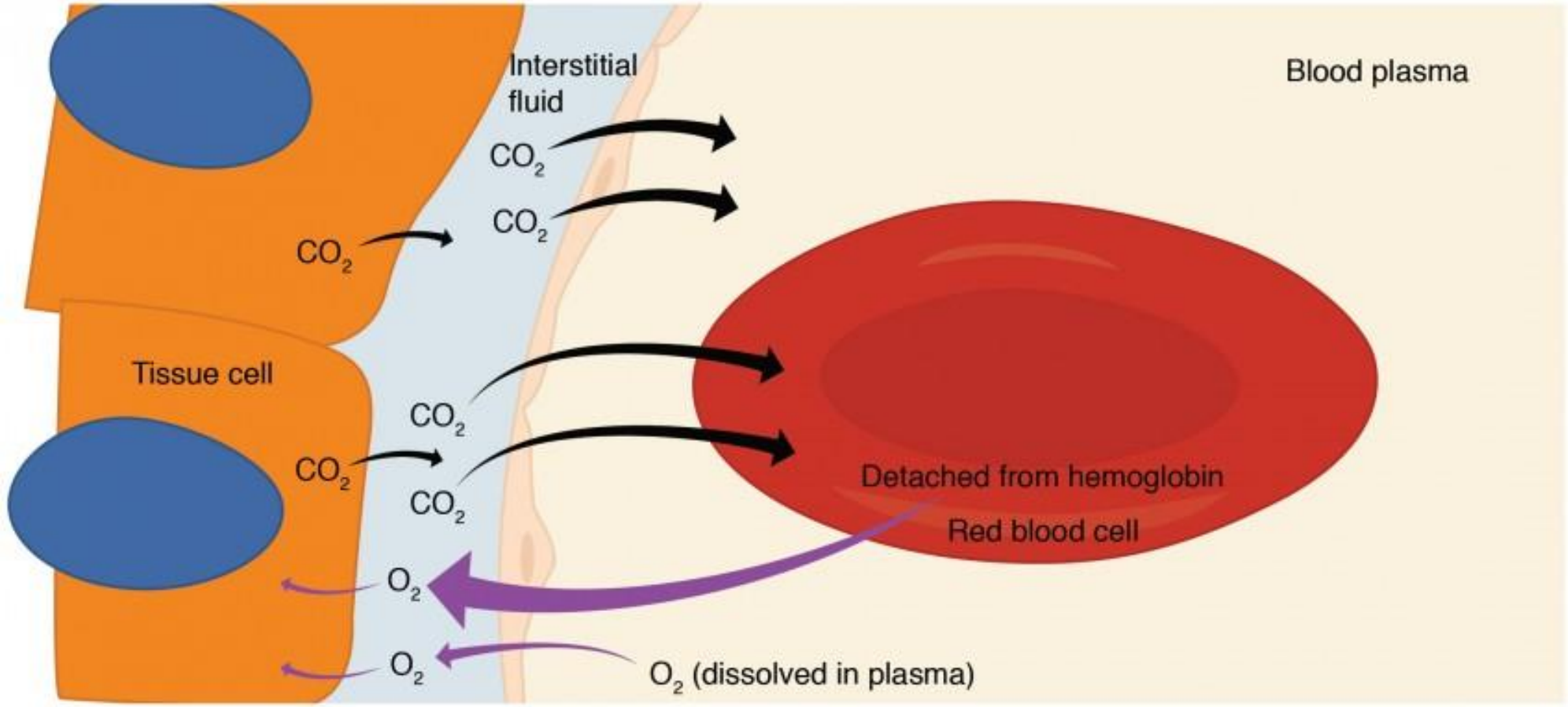


Internal respiration

Partial pressure of O_2 in tissues is about 40 mm Hg while it is about 100 mm Hg in oxygenated blood.

The resulting pressure gradient causes O_2 to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue.

CO_2 partial pressure higher in tissue than in blood causing CO_2 to diffuse out of the tissue, cross the interstitial fluid, and enter the blood.



Pathophysiology of COVID-19

SARS-CoV-2 virus is β coronaviruses, enveloped positive-sense ~30 kb single-stranded RNA virus.

Enter host cells through endocytosis or membrane fusion.
Four structural proteins;

- Spike (S): transmembrane trimetric glycoprotein determines host tropism
  activated by proteolysis transmembrane protease serine 2 (TMPRSS2).
- Membrane (M),
- Envelop (E)
- Nucleocapsid (N)

Angiotensin converting enzyme 2 (ACE2) is the host receptor for the virus.

The symptom ranges from minimal symptoms to severe respiratory failure with multiple organ failure.

Primarily affects the respiratory system, although other organ systems are also involved.

Lower respiratory tract infection related symptoms:

- Fever,
- Dry cough and
- Dysphnea
- Headache,
- Dizziness,
- Generalized weakness,
- Vomiting and
- Diarrhea

Respiratory symptoms of COVID-19 are extremely heterogeneous, ranging from minimal symptoms to significant hypoxia with ARDS.

DCs and macrophages serve as innate immune cells to fight against viruses till adaptive immunity is involved.

In the draining lymph node DC and macrophages activates CD4 and CD8 T cells.

Patients with severe diseases showed lymphopenia (the reduction in peripheral blood T cells).

Patients with severe diseases were reported to have increased plasma concentrations of proinflammatory cytokines.

Compensation with interleukin (IL)-10 (immunomodulatory cytokine)

- Immunoparalysis

T cell have exhaustion phenotype.

Epidemiological studies have shown that mortalities are higher in elder population while the incidence is much lower in children.

Mean incubation period was 5.2 days.

Older age associated risk factors:
higher sequential organ failure assessment (SOFA) score
Higher d-dimer>1 μg/mL (marker of cell stress)

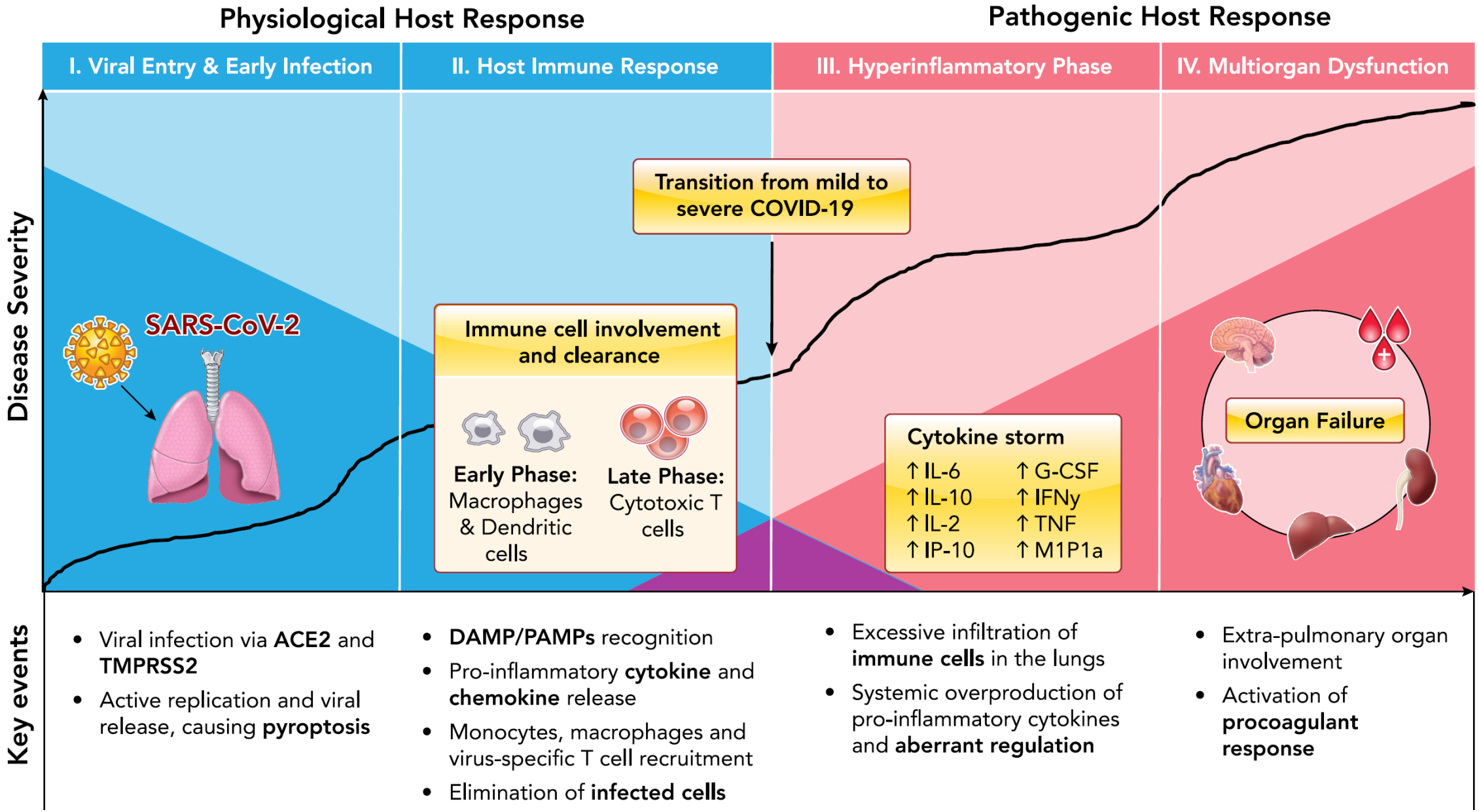
Comorbidity increase the likelihood to have sever disease:
coronary artery disease
Diabetes
Hypertension

Main difference between children and elderly could depend on the difference of ACE2 expression.
ACE2 gene is located on the X-chromosome. ACE2 levels higher in men than in women (responsible for the difference in severity and mortality between men and women both in the adult and the pediatric population.

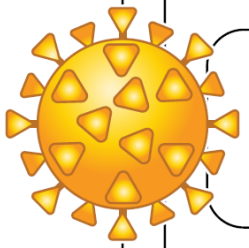
Children may have a qualitatively different response to the SARS-CoV-2 virus than adults.

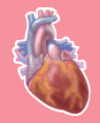
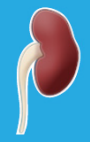
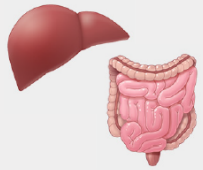
With ageing there is a shift in T cell subset distribution from naïve T cells to central memory T cells, effector T cells and effector memory T cells.

SARS CoV-2 infection course



Extrapulmonary involvement in COVID-19



	Laboratory/Clinical Profile	Key Potential Mechanisms
	• Headache, dizziness • Confusion, epilepsy • Ataxia, anosmia, ageusia etc.	• Direct viral infection • Systemic inflammation and cerebral edema • Pulmonary hypoxia, metabolic acidosis
	↑ Cardiac troponins ↑ NT-proBNP, BNP	• Direct viral infection • Systemic inflammation • Myocarditis • Stress-induced cardiomyopathy
	↑ Serum creatinine ↑ Urea • Proteinuria	• Direct viral infection • Systemic inflammation
	↑ ALT & AST ↑ Lipase, amylase ↑ Albumin • Vomiting, nausea	• Direct viral infection • Systemic inflammation, IL-6 pleiotropic effects • Drug-induced liver injury • Hypoxic-mediated dysfunction
	↑ Prothrombin time ↑ D-dimer ↑ Fibrinogen ↑ aPTT	• SARS-CoV-2-mediated endothelial dysfunction • Systemic inflammation (e.g. cytokine, complement pathways)
	↑ Ferritin ↑ C-reactive protein ↑ ESR • Lymphopenia, fever	• Systemic inflammation