

Introduction to immunology

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Course code (MBBS) : Immunology 1

Course code (BMS) : IIP-L1

Learning Outcomes

- Microorganisms are abundant in our environment, many with the ability to cause disease, and a functional immune system is essential for human health.
- Historically, immune responses have been termed “innate” and “acquired” or “adaptive”: these two types of response are functional definitions, “innate” responses being present from birth, and “acquired” responses only developing after exposure to foreign “antigen”.
- These two types of response are not independent systems, but work closely together to ensure successful host defence: “innate” responses are initially more rapid (minutes to hours), and help to direct appropriate “acquired” / “adaptive” responses (days to weeks).

Learning Outcomes

- Both types of response depend on soluble factors and specialised cell types.
- Acquired and adaptive immune responses depend on the activation of lymphocytes that express appropriate antigen-specific receptors: binding of antigen to the receptor activates the lymphocyte, causing cell proliferation and production of “effector” cells to fight infection. This is the principle of “clonal selection”.
- Acquired and adaptive responses lead to immunological memory: this forms the basis of vaccination.
- The physical organisation of the immune system is essential for effective immune responses, allowing the appropriate components to access dangerous material.

Learning objectives

- 1. Explain the importance of immunology for human health.**
- 2. Outline the basic principles of immune responses and the timescales in which they occur.**
- 3. Define the terms antigen, antibody, B lymphocyte, T lymphocyte, primary and secondary immune responses, and innate and acquired immunity.**
- 4. Outline the role of clonal selection in immune responses.**
- 5. Understand the role of the *physical organization* of the immune system in its function.**

How does the immune system cause disease?

- immune deficiency → persistent or fatal infections
- allergy
- autoimmune disease
- transplant rejection

What is the normal function of the immune system?

- To identify and eliminate harmful microorganisms and harmful substances such as toxins.
 - by distinguishing 'self' from 'non-self' proteins
 - and**
 - by identifying 'danger' signals (e.g. from inflammation).
- The immune system must strike a balance between clearing the pathogen and causing collateral damage to the host - "immunopathology".

The “defeat” of Infection

1948: US Secretary of State declares
“The conquest of infectious disease is imminent”

1967: US Surgeon General tells White House
that we can “Close the book on infectious diseases”

The impact of vaccination on human health

Figure 1-33 part 1 of 3

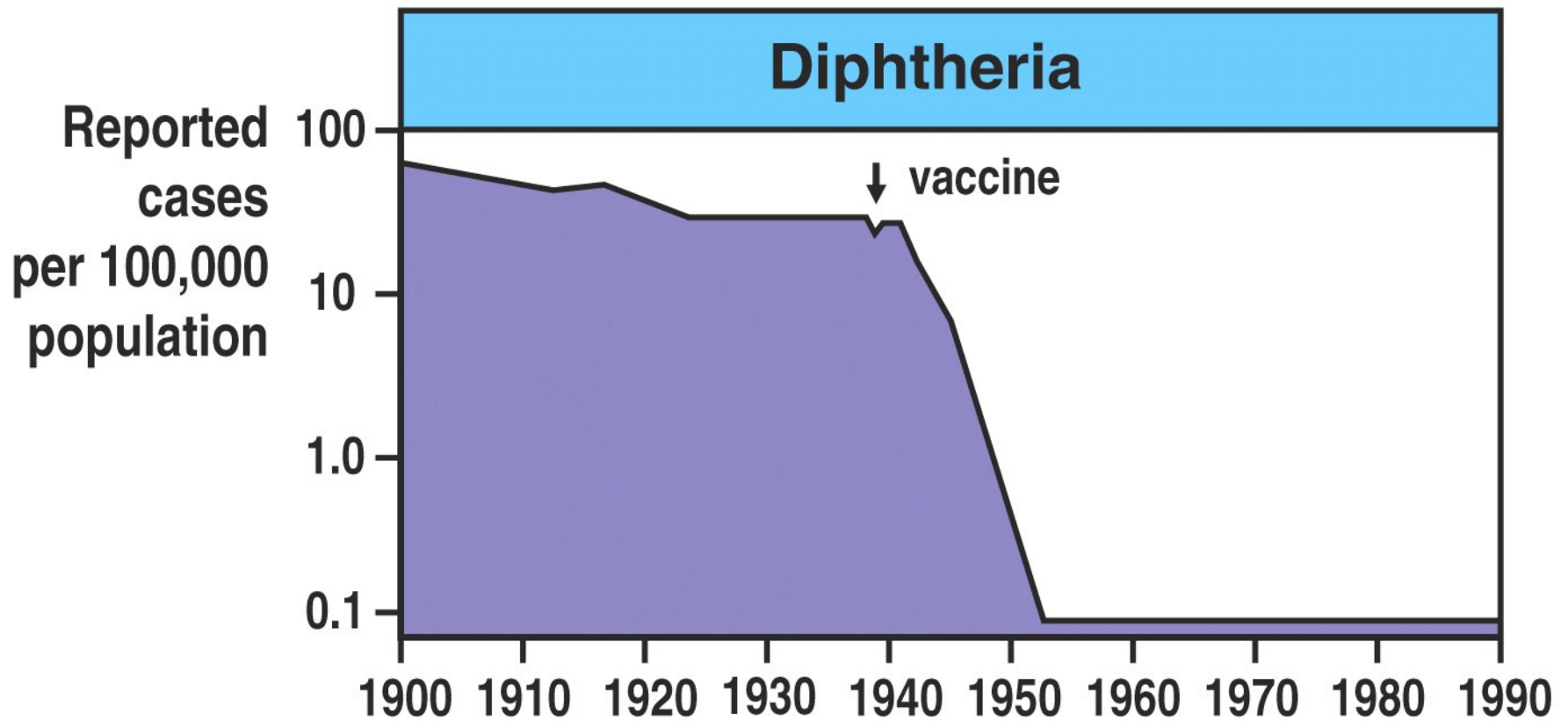


Figure 1-33 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

The impact of vaccination (2)

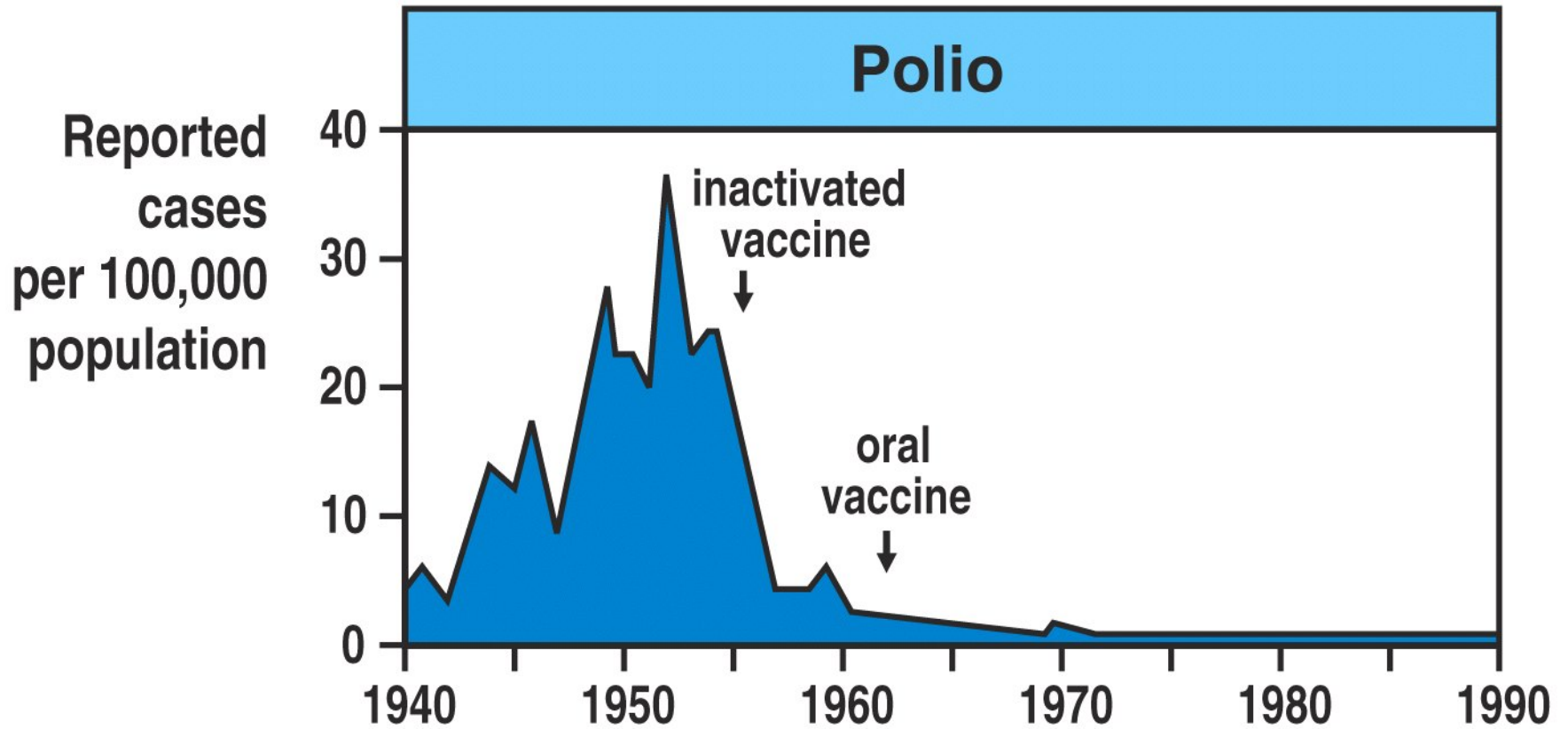
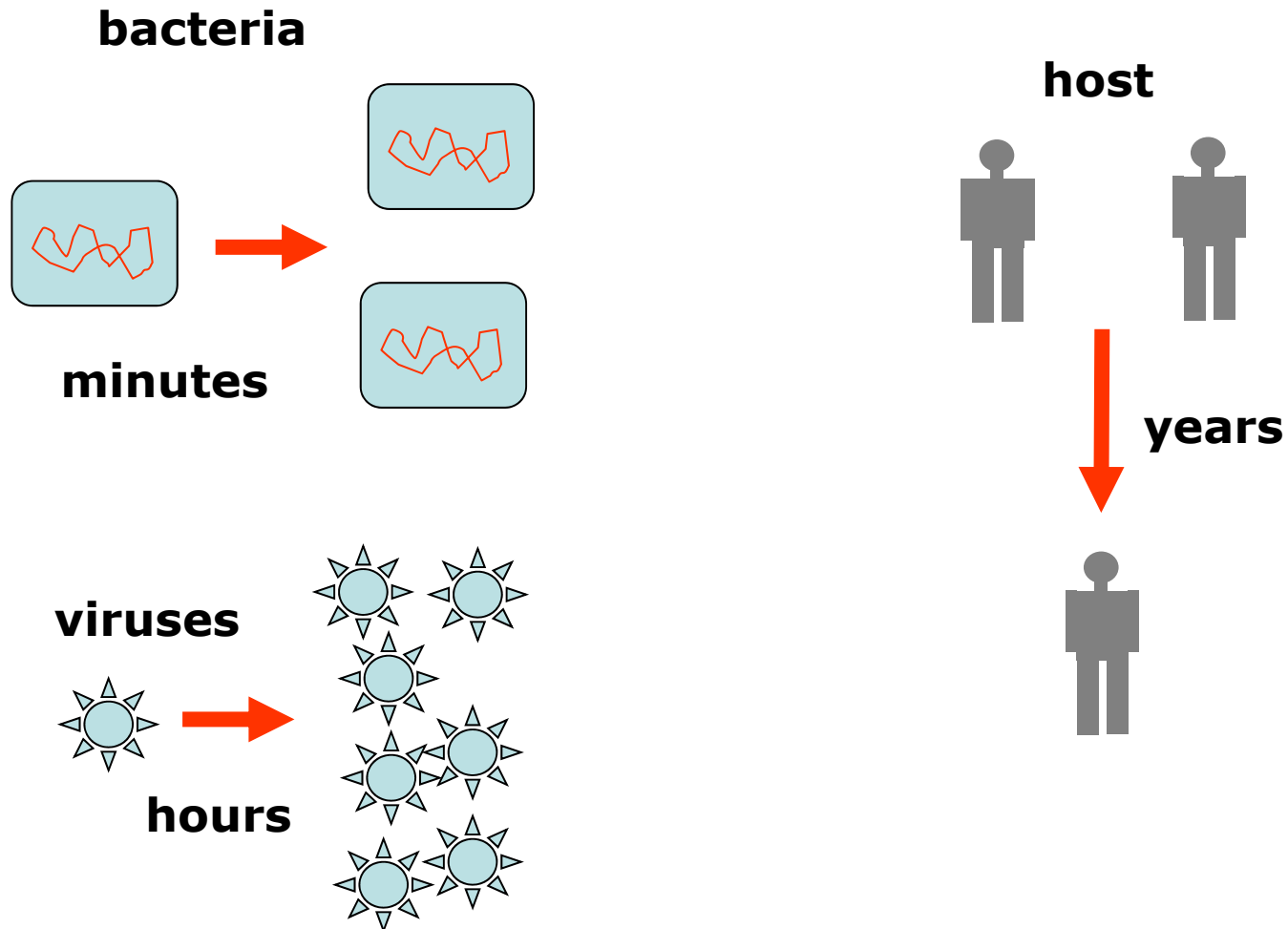


Figure 1-33 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Generation times: how bugs stay ahead of the game



There is an evolutionary 'arms race' between pathogen and host

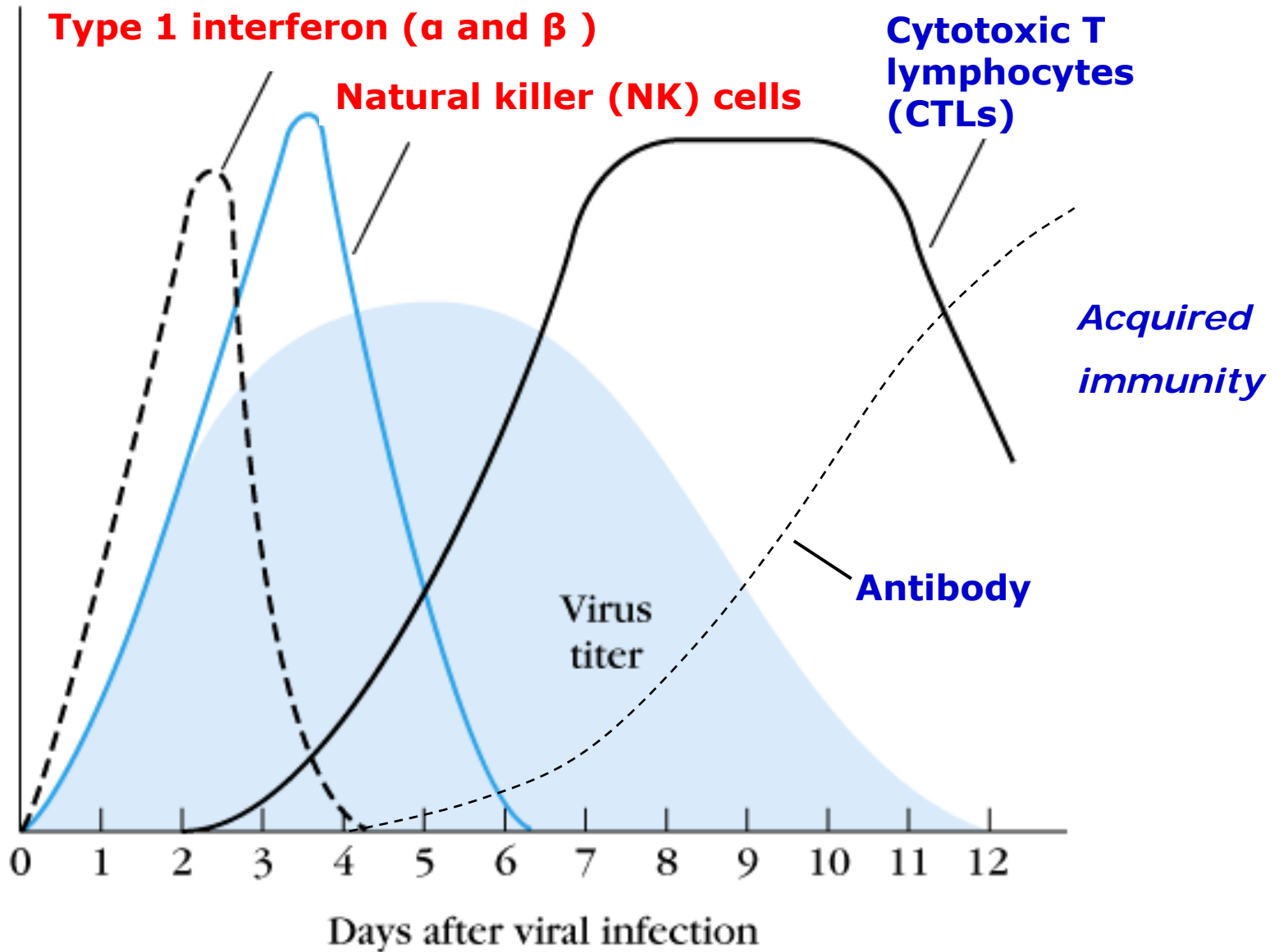
- The host exerts selection on the pathogen; the pathogen exerts selection on the host.
- The pathogen replicates millions of times faster than the host - and so can evolve faster.
- The host therefore relies on a flexible and rapid immune response.
- Our most polymorphic (variable) genes – HLA, KIR – are those that control the immune response: this variation has been **selected by infectious diseases**

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Time-course of primary immune response to a virus

Innate immunity

size of response



Innate and acquired immune response: what's the difference?

Innate

- depends on **pre-formed** cells and molecules
- **fast** (starts in minutes/hrs)
- limited specificity – pattern recognition of '**danger signals**'

Acquired

- depends on **clonal selection**: i.e. growth of cells or antibodies, selected for antigen specificity
- **slow** (starts in days)
- highly **specific** to foreign proteins

Innate Immunity

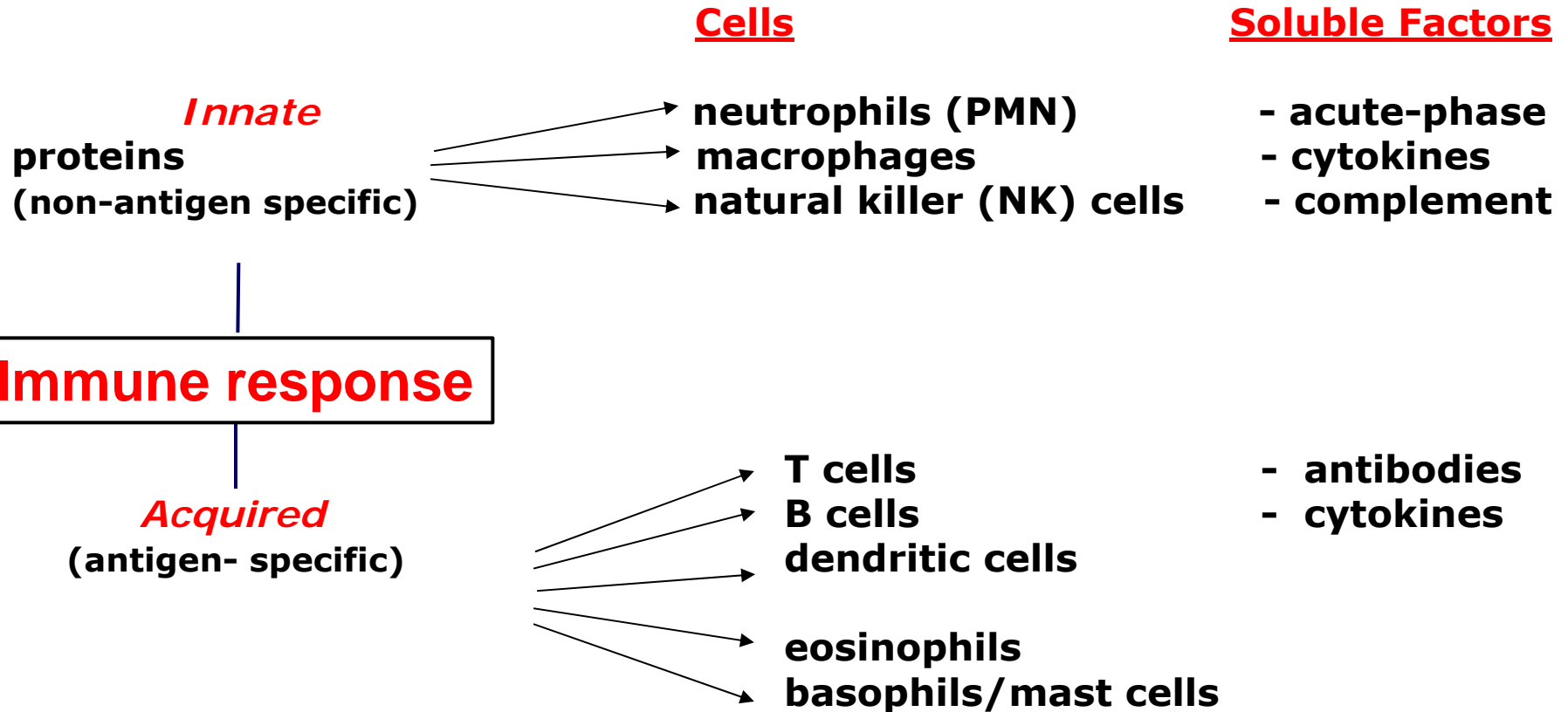
- *Anatomical barriers*

- skin is a mechanical barrier; mucus trapping of microbes; ciliary propulsion on epithelia

- *Physiological barriers*

- low pH, secretion of lysozyme, interferons, antimicrobial peptides, complement

Innate and acquired immune response: main components



The **innate** immune system:

- buys time while the acquired immune system is mobilized, and
- stimulates the acquired immune response

What triggers the innate immune response?

Triggers

- PAMPs – pathogen-associated molecular patterns
e.g. dsRNA in cytoplasm;
bacterial cell wall components.
- DAMPs – danger-associated molecular patterns
e.g. monosodium urate;
high extracellular [ATP];
reactive oxygen species (ROS).

Pattern-recognition receptors

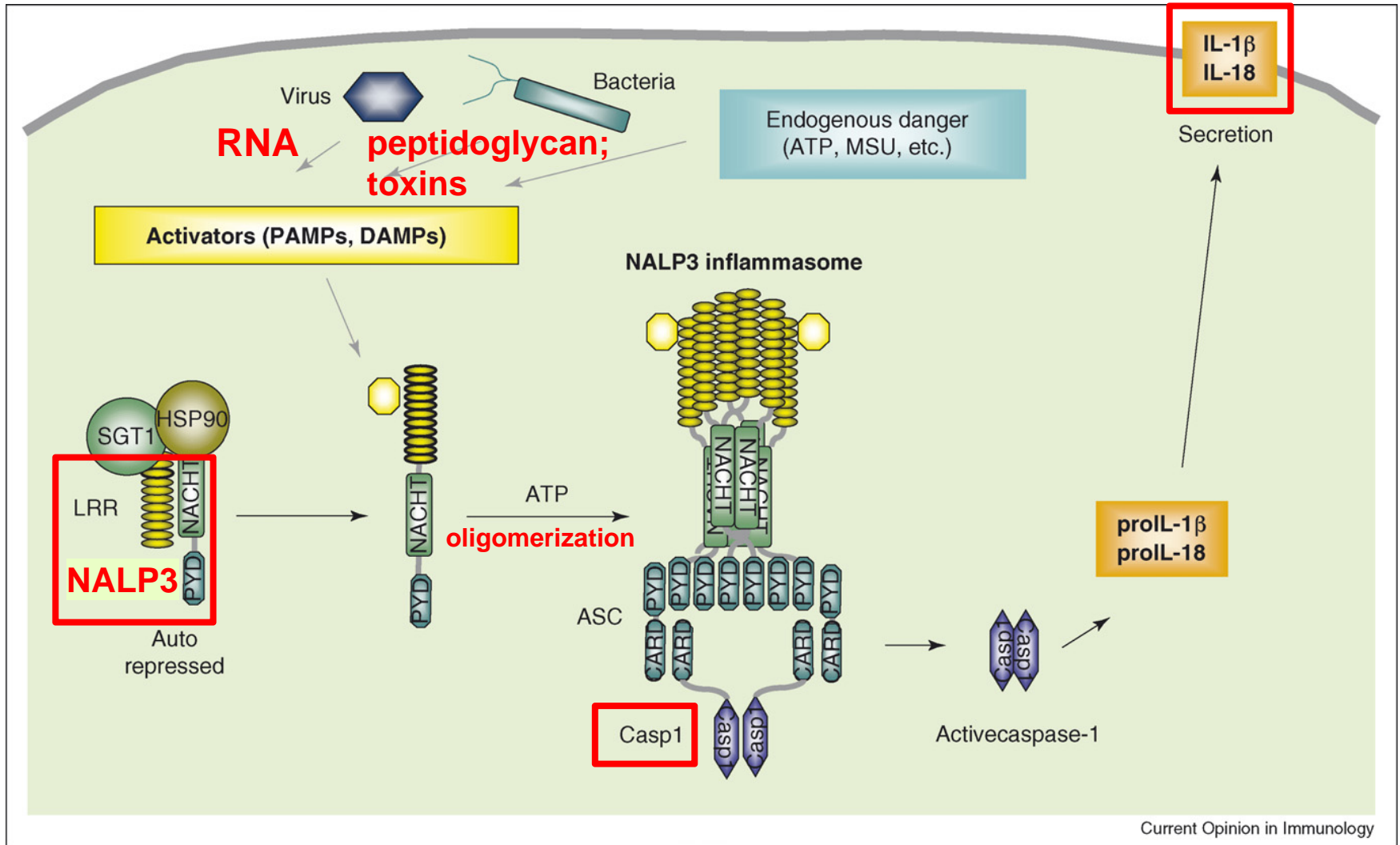
Extracellular danger signals

- TLRs – Toll-like receptors

Intracellular danger signals

- NLRs – NOD-like receptors
- RLRs - RIG-I-like receptors
- AIM2

NALP3 – a NOD-like receptor (NLR)



What does the innate immune response do?

- activates interleukins e.g. IL-1b, IL-18, which in turn activate inflammatory pathways
- elicits type 1 interferons, for antiviral defence
- two main consequences:
 - buys time while the acquired immune response starts
 - kick-starts the acquired immune response

Acute phase inflammatory response (1)

= an *innate* response to tissue damage.

- Rise in body temperature – the fever response.
- Followed by production of “acute phase” proteins by the liver, notably:
 - C-reactive protein
 - serum amyloid protein
 - mannan-binding lectin.

} “Acute phase proteins” or
“reactants”

Acute phase inflammatory response (2)

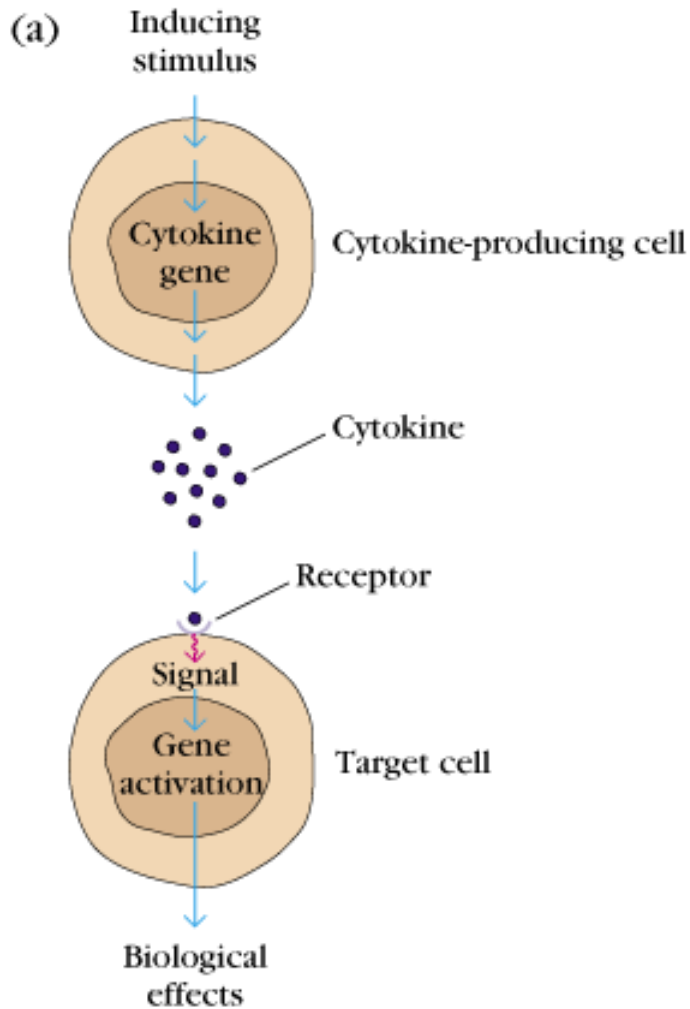
What do acute phase proteins do?

- **C-reactive protein and serum amyloid protein** bind to molecules found on the cell wall of some bacteria and fungi.
- **Mannan-binding lectin** binds to mannose sugar molecules which are not often found on mammalian cells.

These molecules direct phagocytes to identify and ingest the infectious agent.

Cytokines:

small proteins that carry messages from one cell to another



- e.g. to stimulate
activation

OR

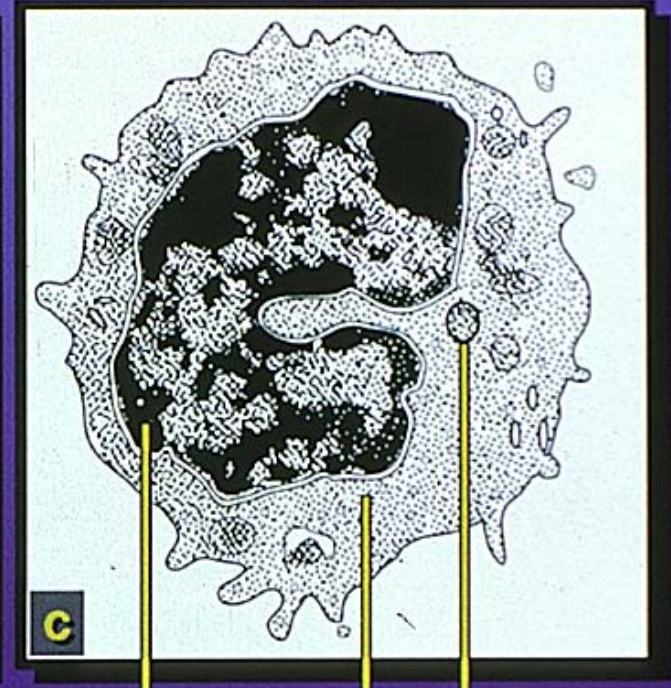
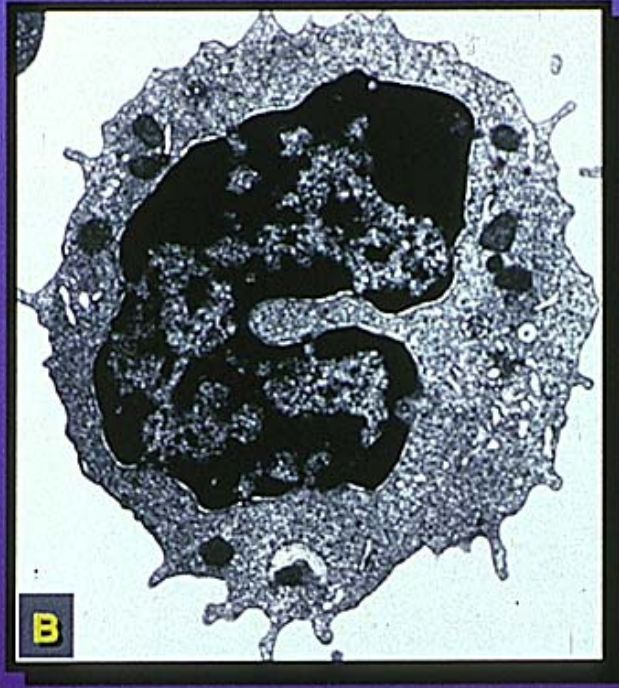
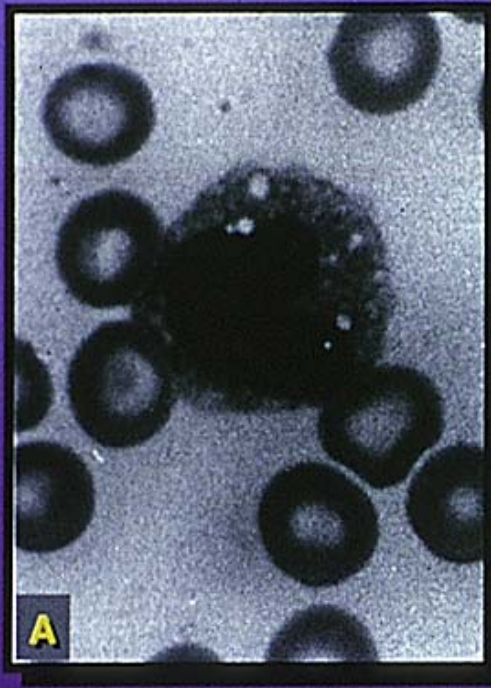
proliferation of lymphocytes.

Cells of the innate immune system (1)

Granular leukocytes

- **Natural killer (NK) cells**
 - identify and kill virus-infected cells & tumour cells
- **Macrophages** ('mononuclear phagocytes')
- **Granulocytes:**
 1. Basophils
 2. Neutrophils
 3. Eosinophils

MONONUCLEAR PHAGOCYTES



Nucleus

Cytoplasm

Phagocytic
vacuole

From Abbas, Lichtman & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1994, Fig. 2-6

Main roles: clearance of debris; presentation of antigens; killing of bacteria

Cells of the innate immune system (2)

- **Neutrophils** - also called polymorphonuclear neutrophils (PMN) because nucleus is multi-lobed; 50-70% of circulating WBC. Phagocytic.
- **Eosinophils** – bi-lobed nucleus, required for immune response to parasites; 1-3% of circulating WBC.
- **Basophils** – not phagocytic, release granules containing histamines, serotonin, prostaglandins; <1% of circulating WBC. Important in T_h2 responses.

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4. Outline the concept of clonal selection and its role in immune responses.
5. Understand the role of the *physical organization* of the immune system in its function.

Acquired or Adaptive Immunity

Characteristics:

- specific to foreign antigens (usually proteins)
- can form memory
- requires priming

Effector arms:

Cellular immunity

- T and B lymphocytes

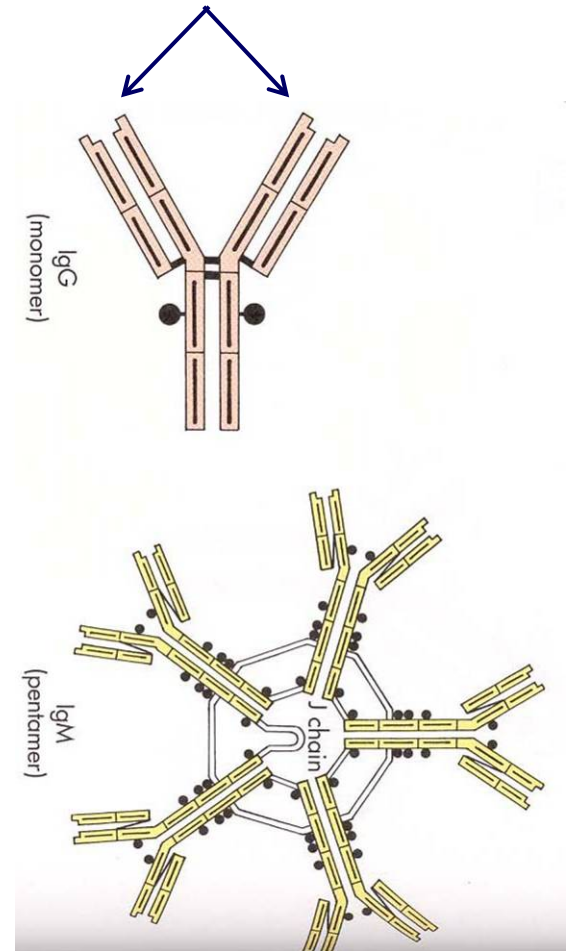
Humoral immunity

- antibodies

Five classes of immunoglobulins (1)

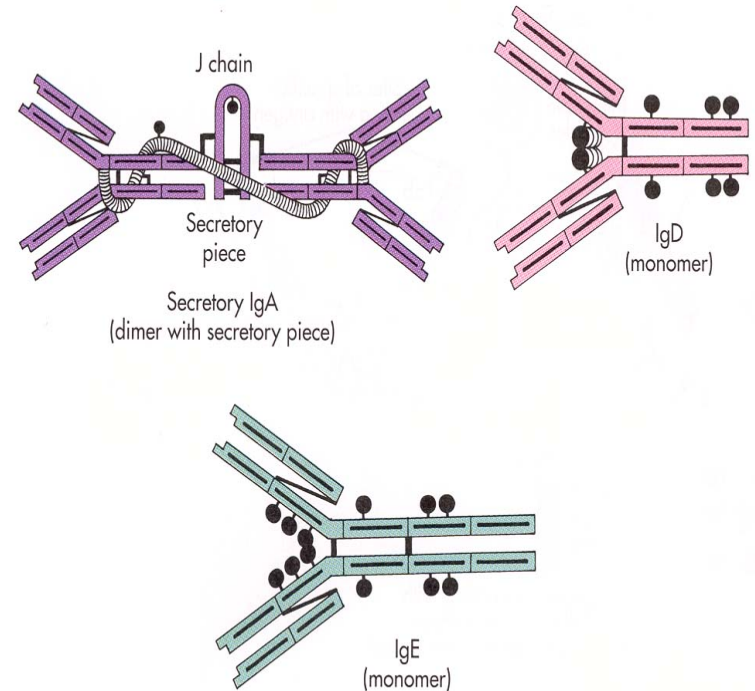
- IgG
 - 75% of our serum Ig
 - Crosses placenta
 - Long half-life in serum
 - Part of secondary immune response
- IgM
 - 10% of total serum immunoglobulin
 - Star-like shape
 - Multivalent antibody (10 binding sites)
 - Important in primary immune response

bivalent: two identical antigen-binding sites

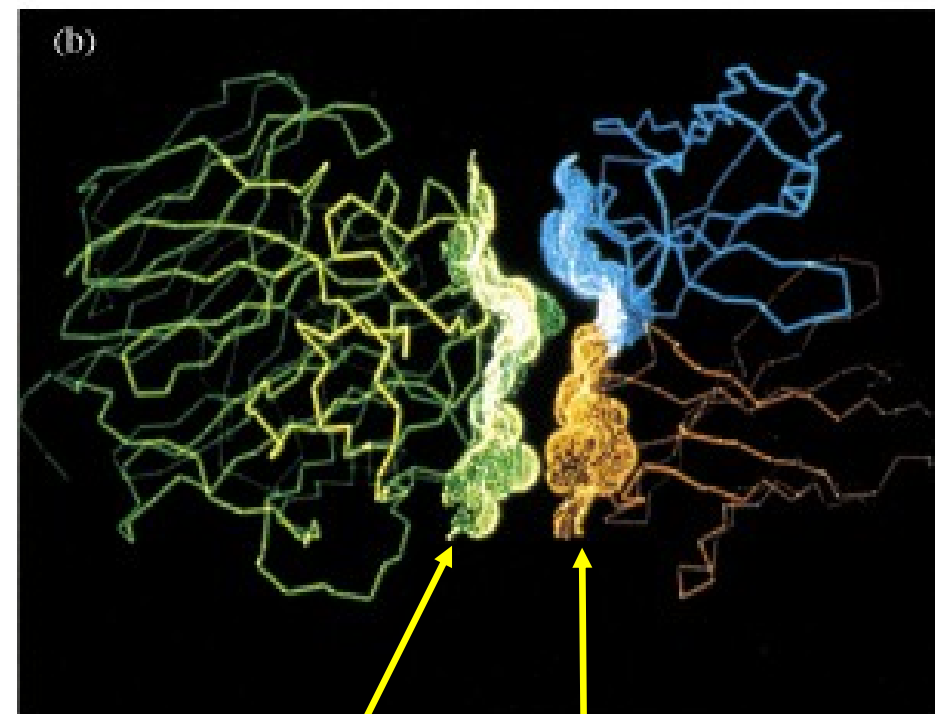
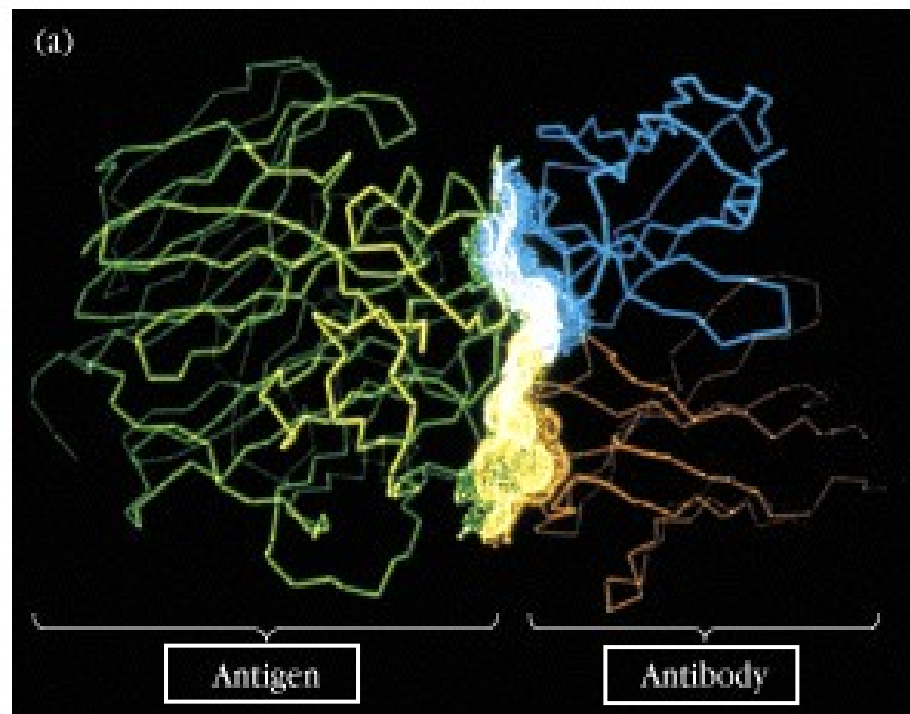


Immunoglobulins (2)

- IgA
 - Found in body secretions
 - Contains a 'secretory component' which protects it from digestive enzymes
- IgE
 - Involved in allergic response
 - Binds to basophils and mast cells
 - Triggers release of histamines
- IgD
 - Complete function not known



An antibody 'recognizes' an antigen because that antibody's binding site makes a perfect fit with a region (epitope) on the antigen



How does an antibody kill a virus?

Four important mechanisms:

- 1) binds to virus and prevents attachment to cell.
- 2) opsonization: virus-Ab complex is phagocytosed by MF.
- 3) complement-mediated lysis of enveloped viruses.
- 4) antibody-dependent cell-mediated cytotoxicity (ADCC), mediated by natural killer (NK)-like cells.



Cells of the acquired immune system

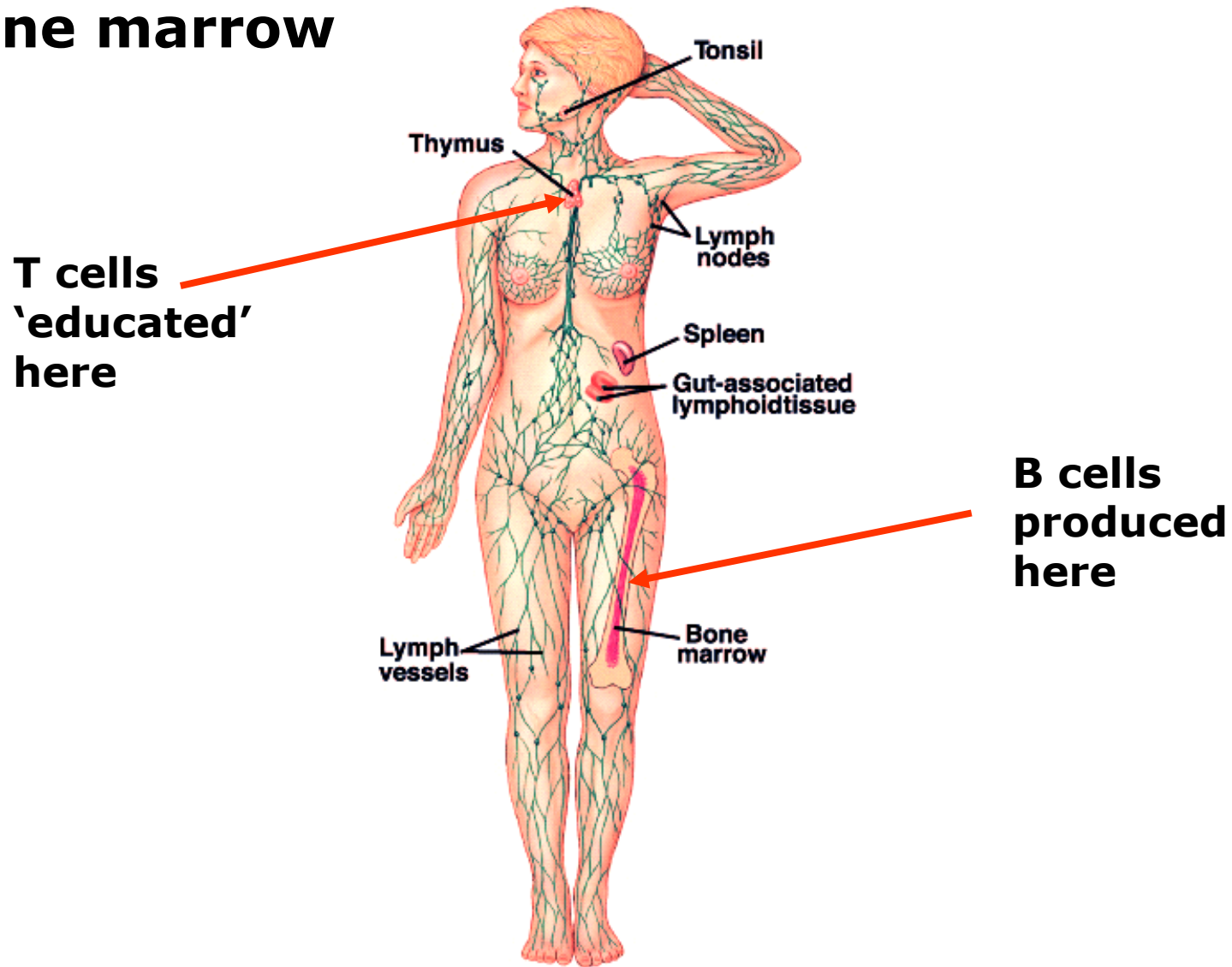
Lymphocytes (agranular leukocytes)

20-40% of the circulating WBCs, 99% of the cells in lymph

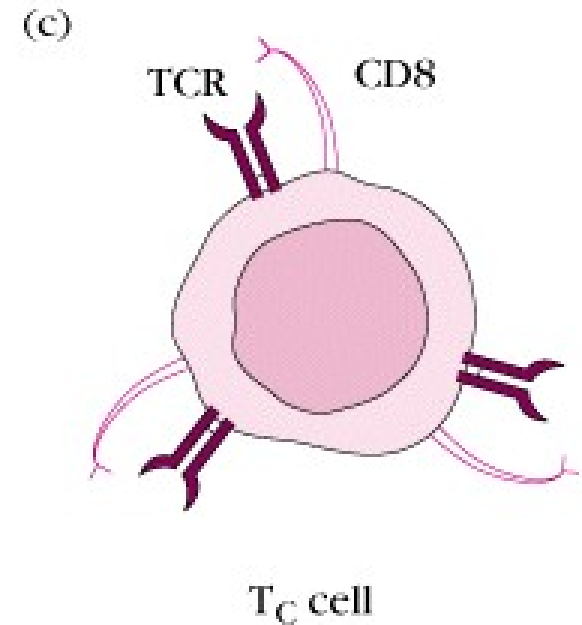
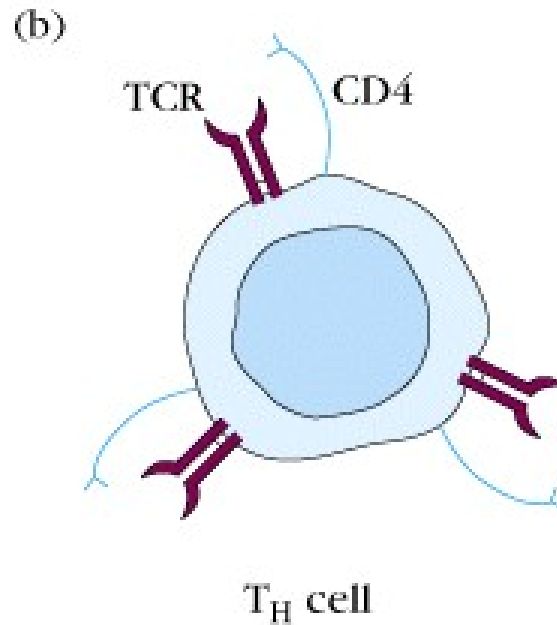
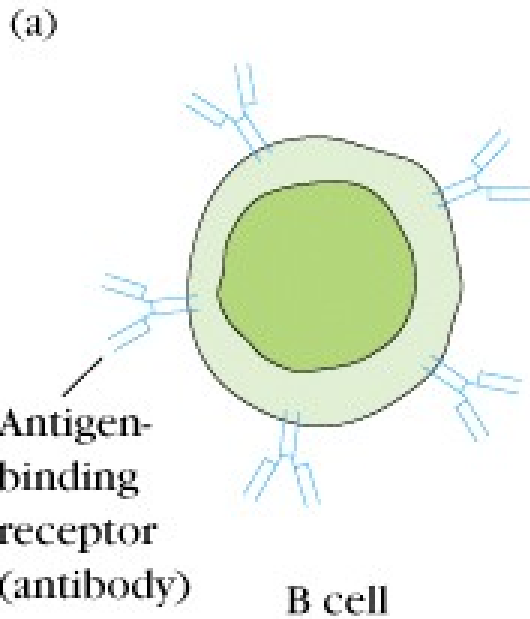
- T (**T**hymus-derived) cells
- B (**B**one marrow-derived) cells
- NK (**N**atural **K**iller) cells

Each subset has distinct cell-surface molecules
e.g. CD4 on helper T-cell.

Lymphocyte precursors are produced in haematopoietic tissue – bone marrow



Three types of antigen-specific lymphocyte



alias: helper T-cell

**cytotoxic T-cell
(CTL)**

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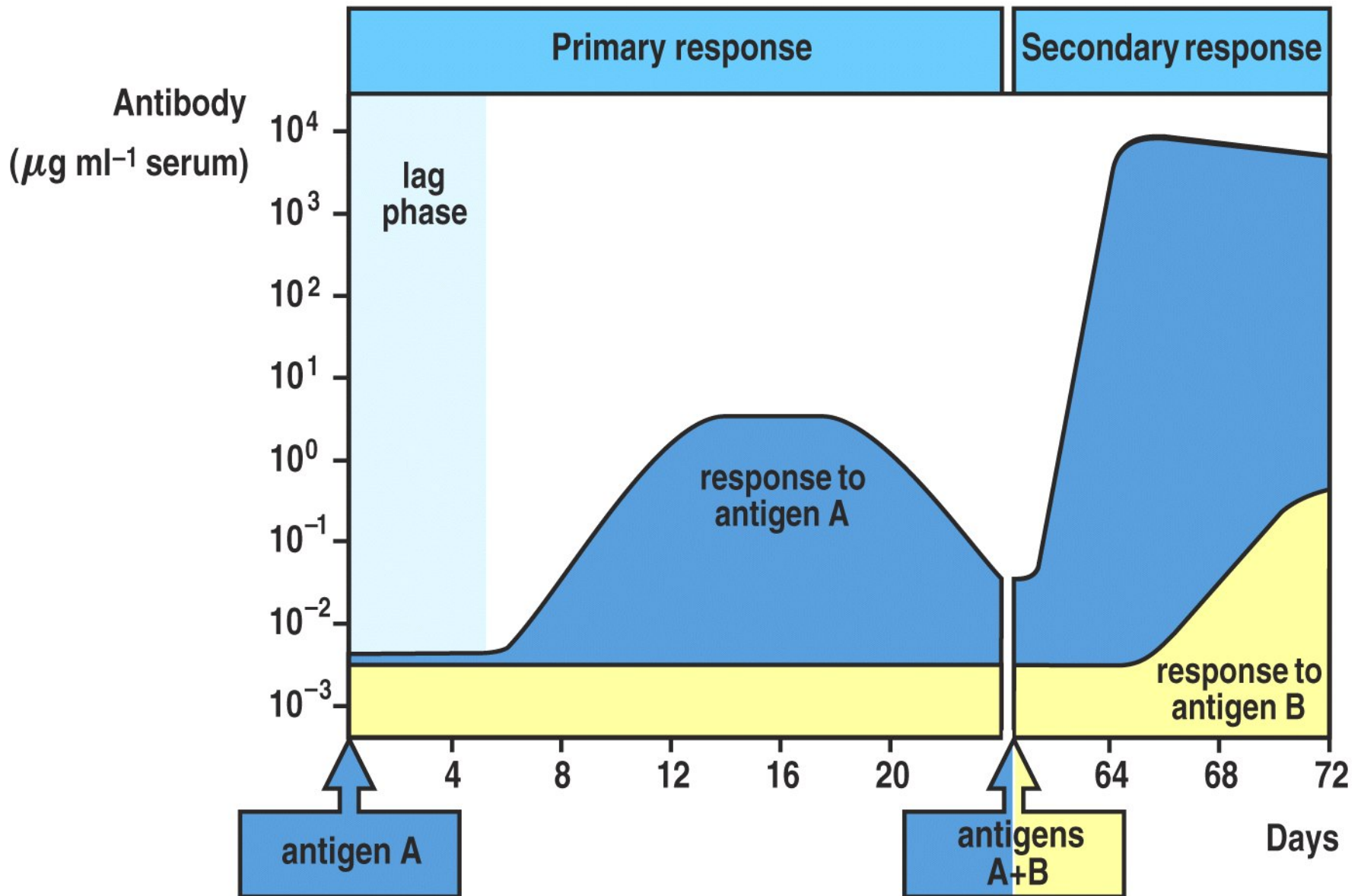
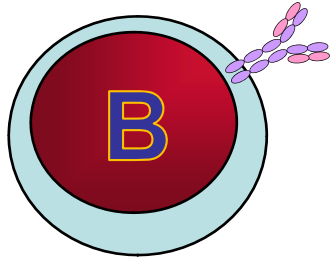


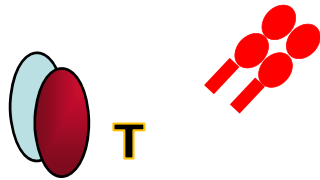
Figure 1-20 Immunobiology, 6/e. (© Garland Science 2005)

Lymphocyte antigen receptors



The B cell antigen receptor is a membrane-bound antibody
i.e a **surface immunoglobulin**

- binds **intact** antigens.



Expressed on the T cell surface are 2 protein
chains (α and β) which together make the

T cell antigen receptor (TCR)

- binds **digested** ('processed') antigen
fragments.

1. Each antigen receptor binds to a particular site – an **epitope** – on a different antigen.
2. Each clone of B cells or T cells has a unique receptor, specific to one antigen; each cell carries many copies of this receptor on the cell surface.

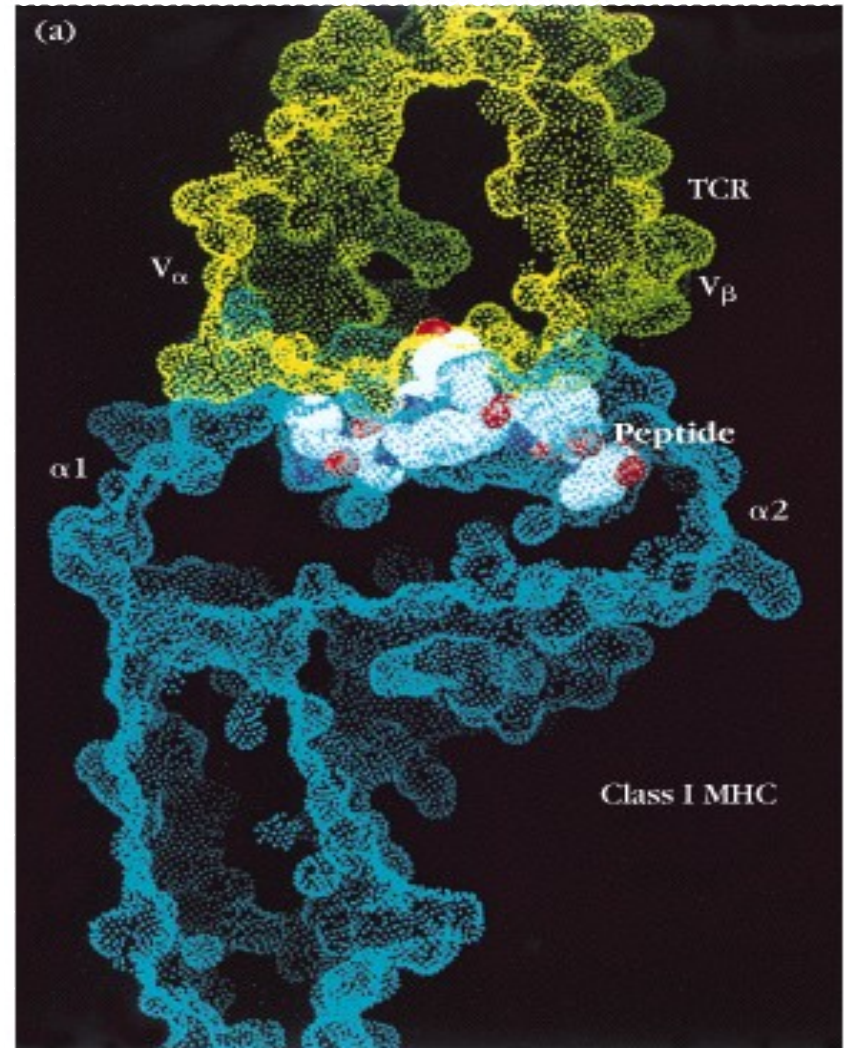
How does the T-cell receptor (TCR) recognize an antigen?

TCR recognizes a complex of:

antigen peptide +
HLA (MHC) molecule

MHC denotes the
Major
Histocompatibility **C**omplex -
also known as
Human **L**eukocyte **A**ntigens
(HLA)

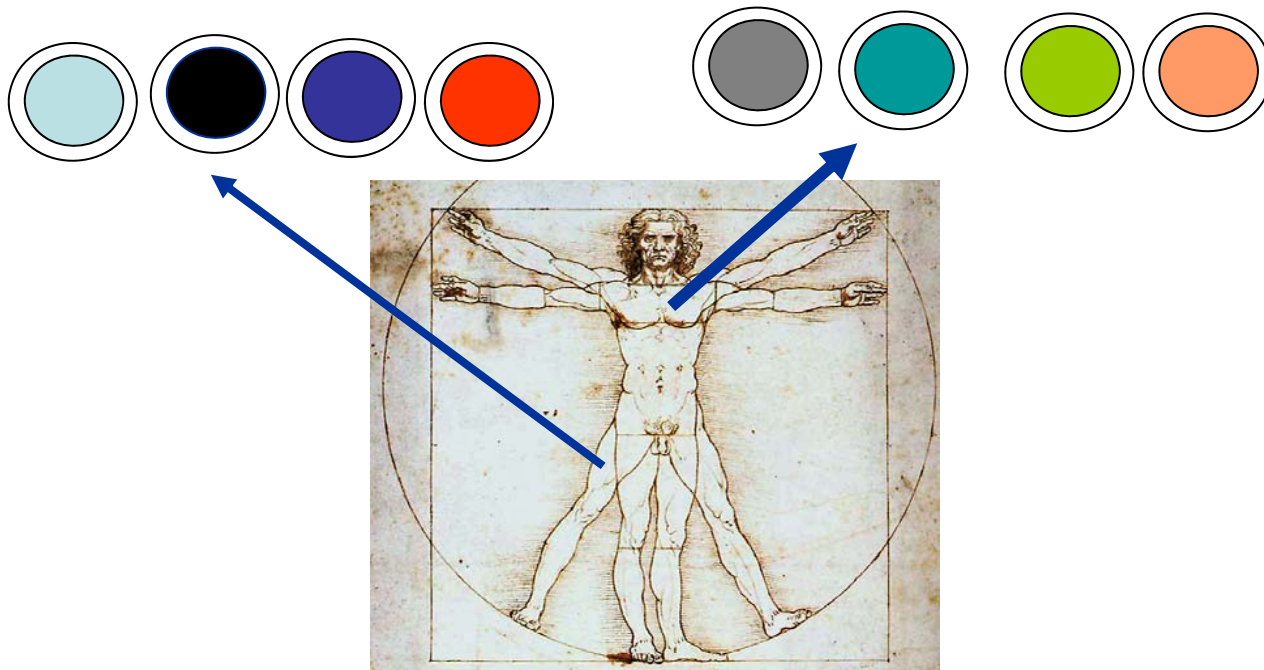
MHC molecules display fragments of intracellular proteins on the cell surface for immune surveillance.



Generation of clonal diversity in lymphocytes

During B and T cell development, **random genetic recombinations** occur within each cell among multiple copies of immunoglobulin genes (B cells) or TCR genes (T cells).

These processes generate the diversity of clones of lymphocytes: each clone is **specific to a different antigen**.



Clonal nature of the adaptive immune response

Each lymphocyte carries a single, unique antigen receptor.

There are millions of lymphocytes in the body, and thus millions of different antigen receptors.

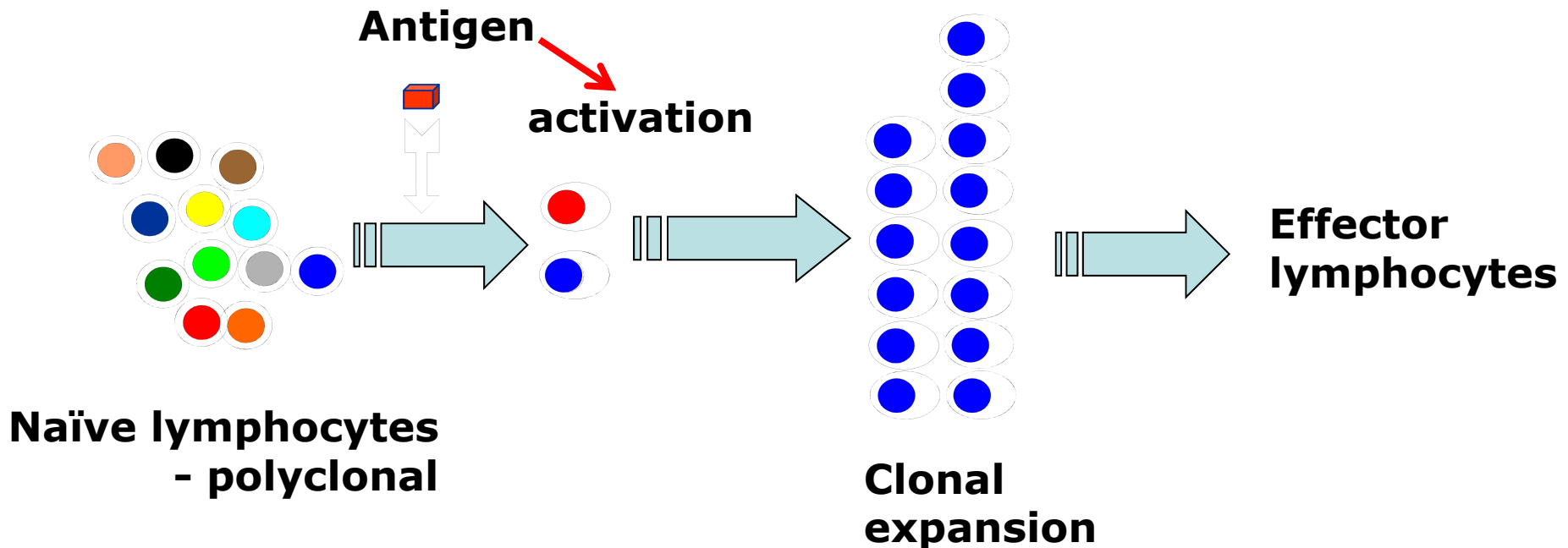
Lymphocytes that meet an antigen they recognize will proliferate and survive.

The huge majority of lymphocyte clones will die out.

Primary immune response: clonal selection

A typical antigen is recognized by 1 in $\sim 10^5$ naive T cells.

98% of T cells are in the lymph circulation and organs; 2% in blood.



Antigen binds to surface receptor on the B cell (Ig) or the T cell (TCR) and causes selective expansion of that clone.

What happens when the antigen is removed?

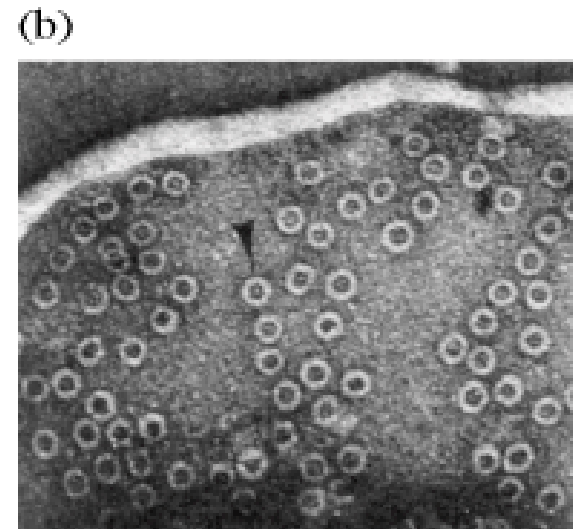
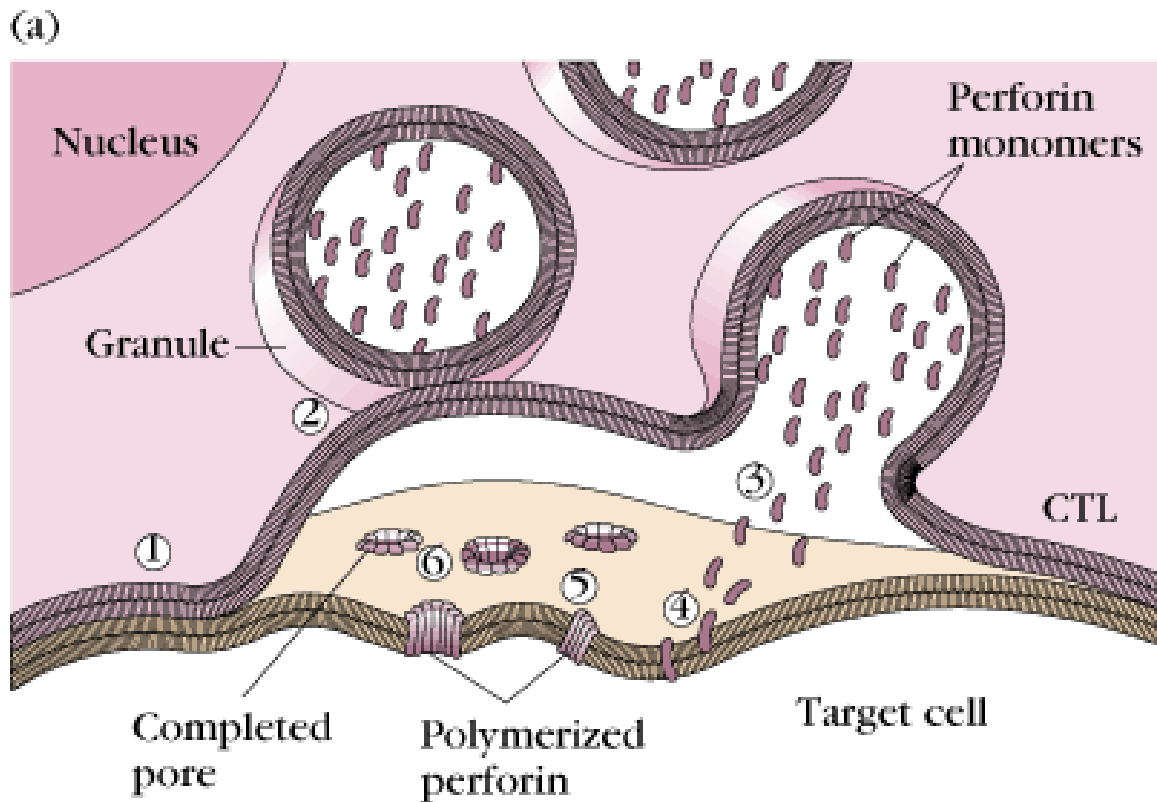
Most lymphocytes that have proliferated recently will *die* after fulfilling their function.

Some survive as *memory cells*.

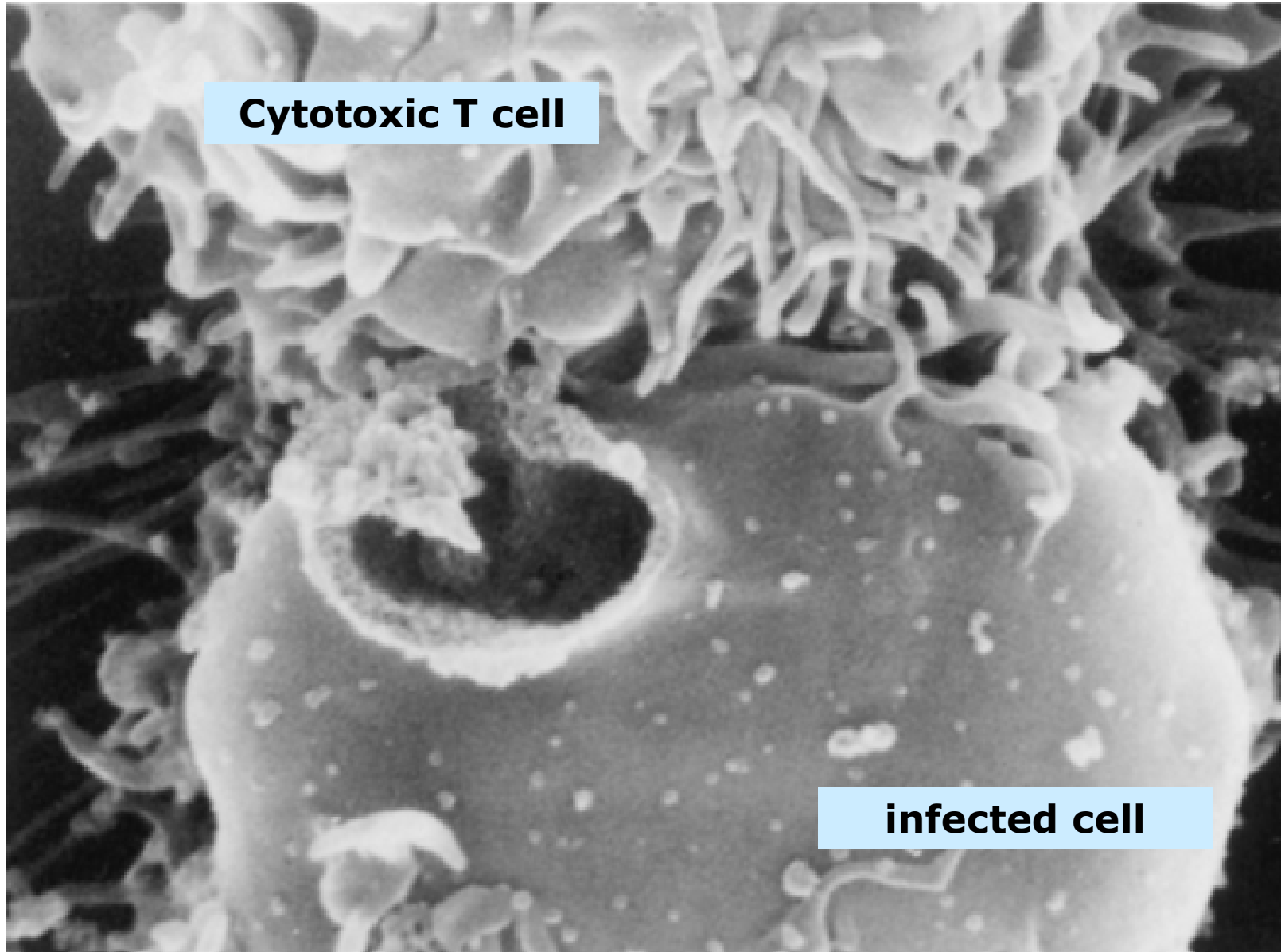
How does the immune response actually clear a pathogen?

- Cytotoxic T lymphocytes (CTLs) kill infected cells
- Antibodies bind to pathogens: the complex is destroyed or ingested by cells.

Cytotoxic T lymphocytes destroy infected cells by injecting lethal enzymes



Infected cell killed by cytotoxic T cell

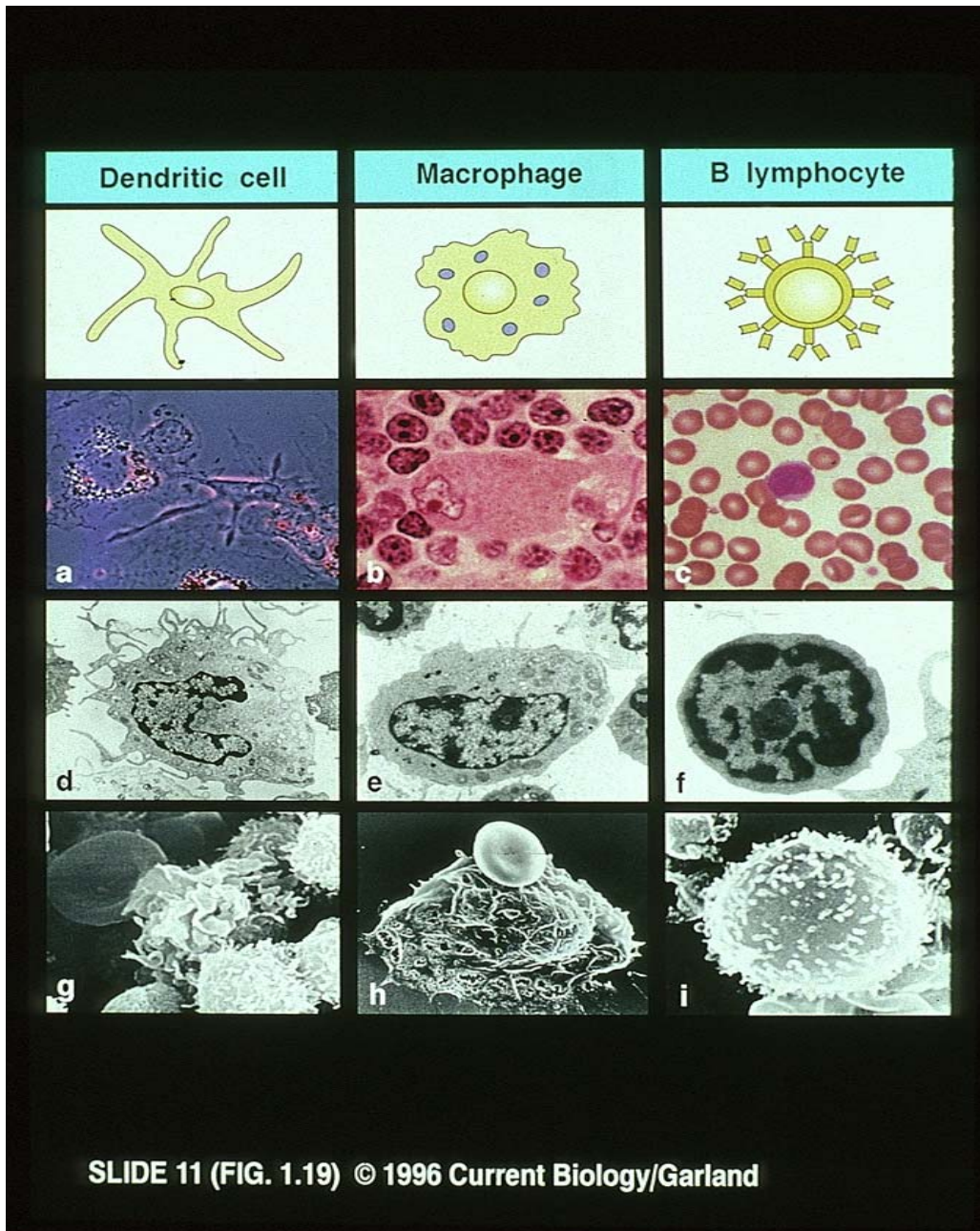


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How does a T cell meet its antigen?

Antigens are taken up by specialized *antigen-presenting cells* and transported from the tissues into secondary lymphoid organs, where they meet T cells.

Immune responses are **initiated** by 'professional' antigen-presenting cells



Lymphoid organs

Organized tissue in which lymphocytes interact with non lymphoid cells
Sites of initiation & maturation of adaptive immune responses.

Primary lymphoid organs:

Thymus – T cell maturation

Bone marrow – B cell maturation

Secondary lymphoid organs:

Lymph nodes

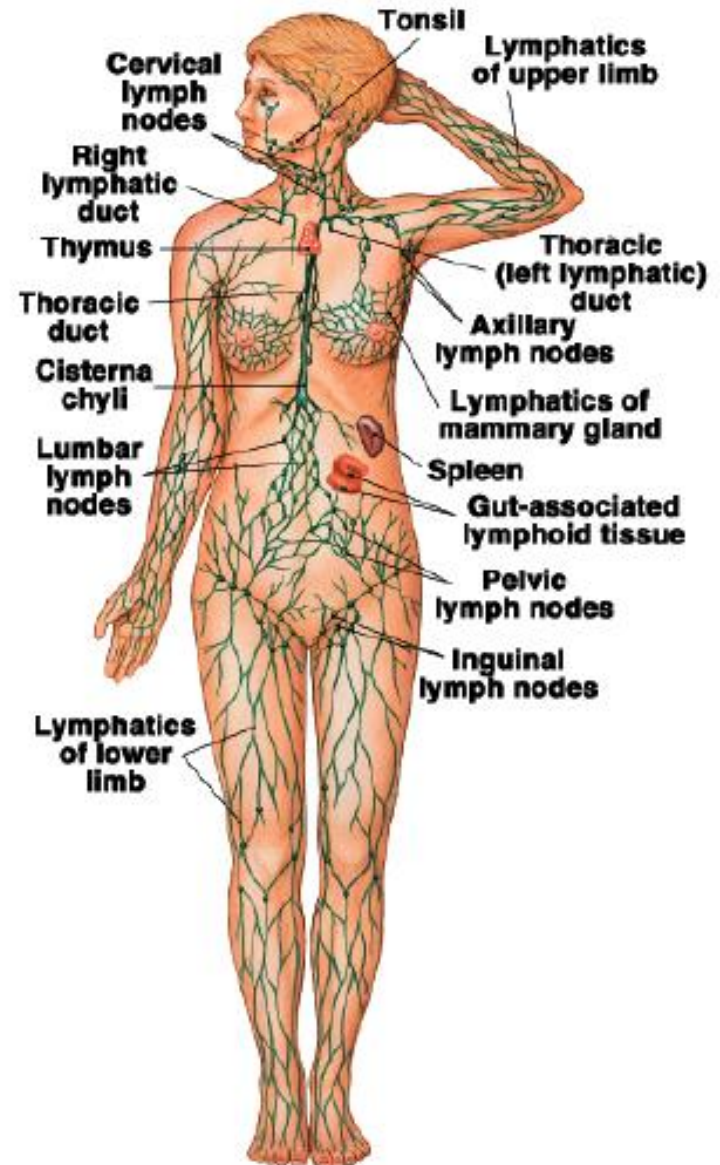
Spleen (white pulp)

Mucosa-associated lymphoid tissue (MALT)

II. Organization of the Lymphatic System

System includes:

- **Lymphatic vessels**
 - Venules
 - Veins
 - Ducts
- **Lymphatic tissues**
 - Nodules
 - Nodes
 - Tonsils
 - Peyer's Patches
- **Lymphatic organs**
 - Spleen
 - Thymus

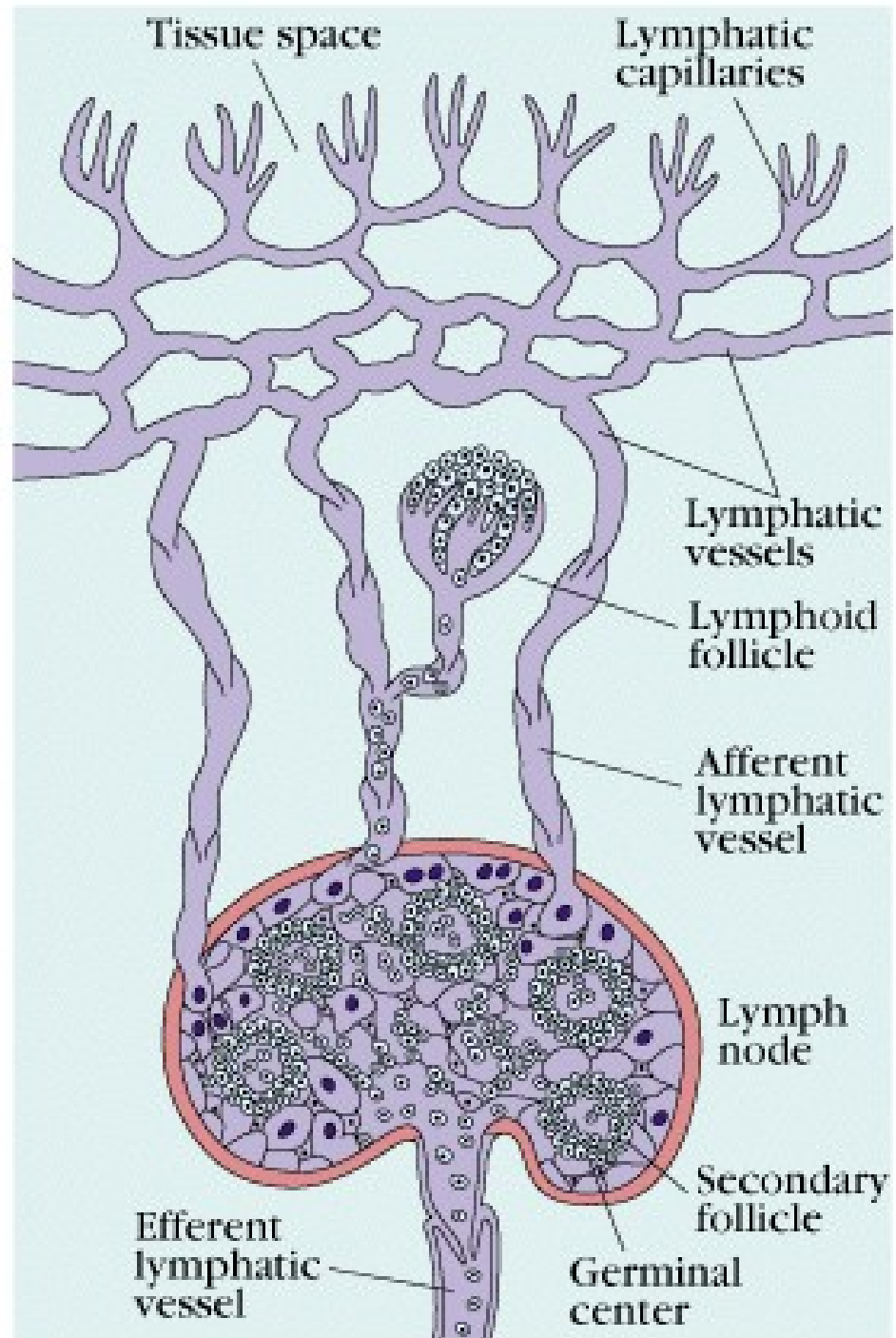


Lymphocytes and antigen-presenting cells recirculate through lymphatic vessels:

from tissues

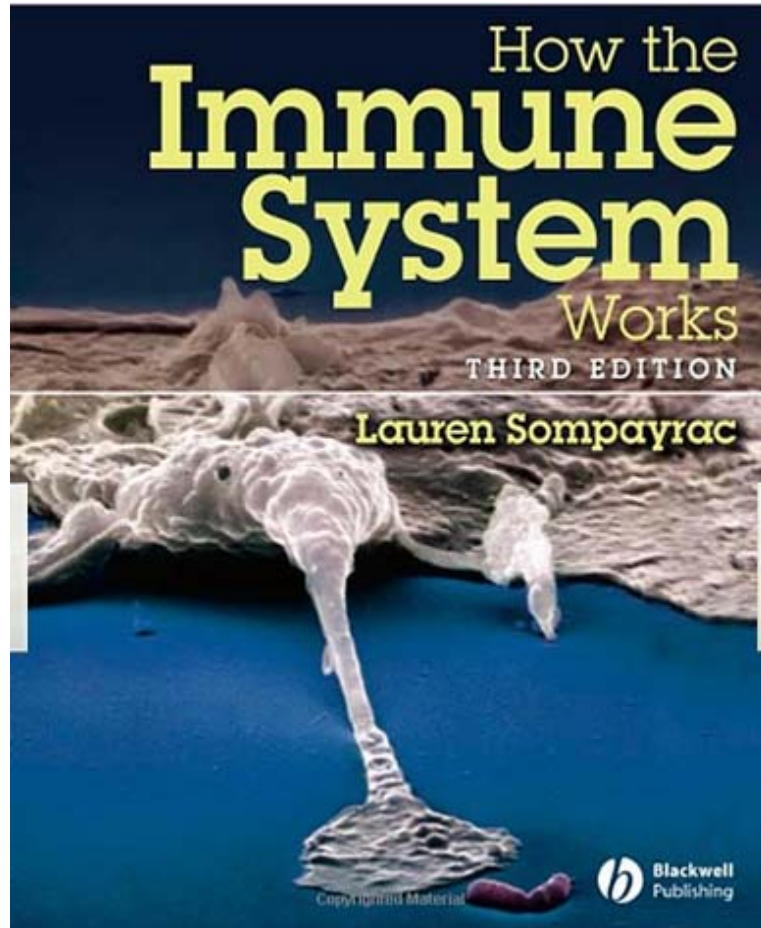
via lymph nodes or spleen

into the blood.



Summary: what I want you to remember

- Role of immune system in maintaining health
- Innate and acquired immune responses
- Major actors – ‘effectors’ – in the immune response
- Clonal nature of the acquired immune response
- Role of *physical organization* in the immune system



Recommended reading