Imperial College London

Introduction to Immunology

Charles R M Bangham
Department of Immunology
Wright-Fleming Institute
Imperial College

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.**

What happens when the immune system goes wrong?

- persistent or fatal infections
- allergy
- autoimmune disease
- transplant rejection

What is the immune system for?

To identify and eliminate harmful microorganisms and harmful substances such as toxins.

Either by distinguishing ‘self’ from ‘non-self’ proteins

or by identifying ‘danger’ signals (e.g. from inflammation)

- or both.

The immune system has to strike a balance between clearing the pathogen and causing accidental 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

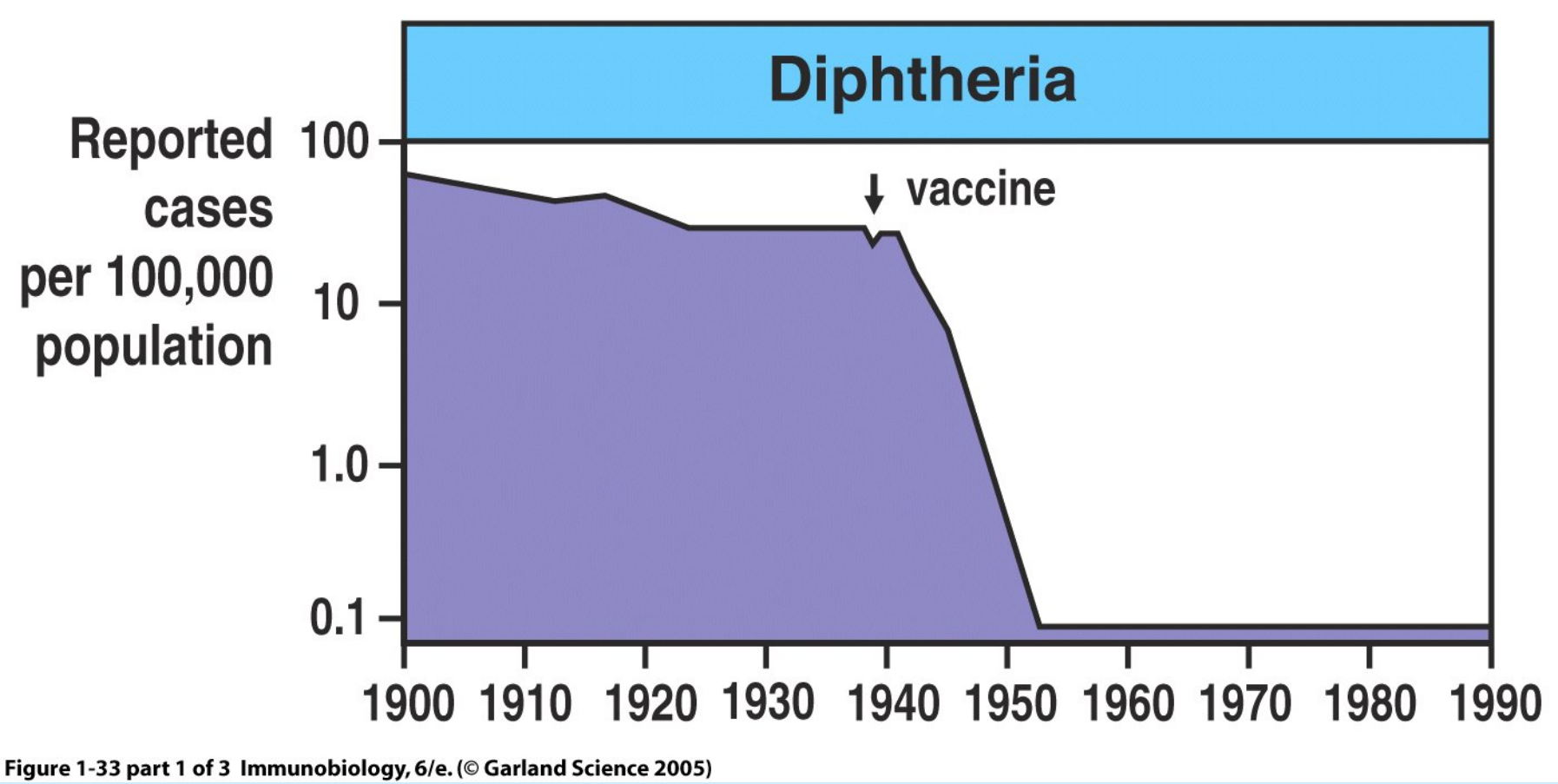


Figure 1-33 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

The impact of vaccination (2)

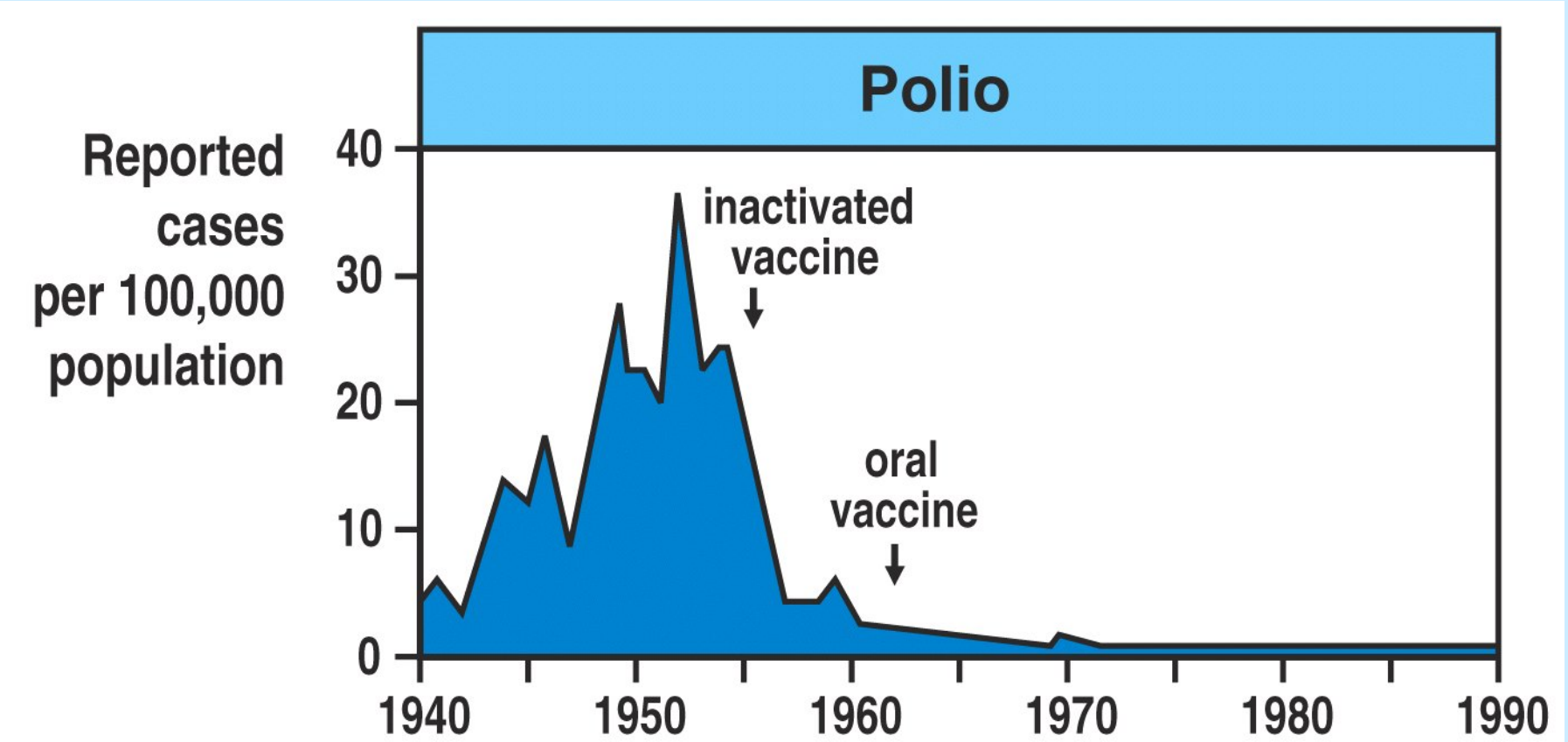
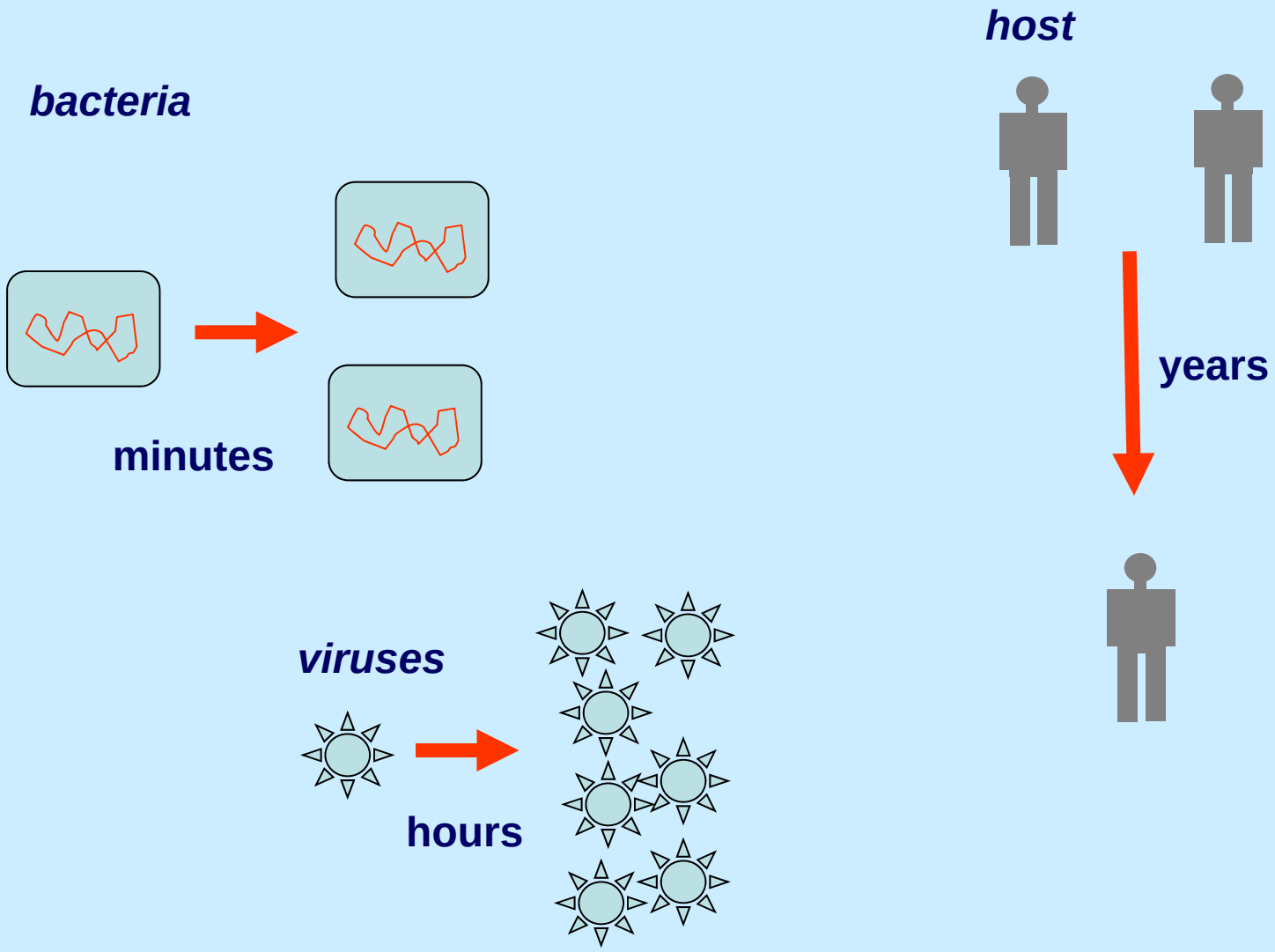


Figure 1-33 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Generation times



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 - and can therefore evolve - millions of times faster than the host.
- 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**

1. Explain the importance of immunology for human health.

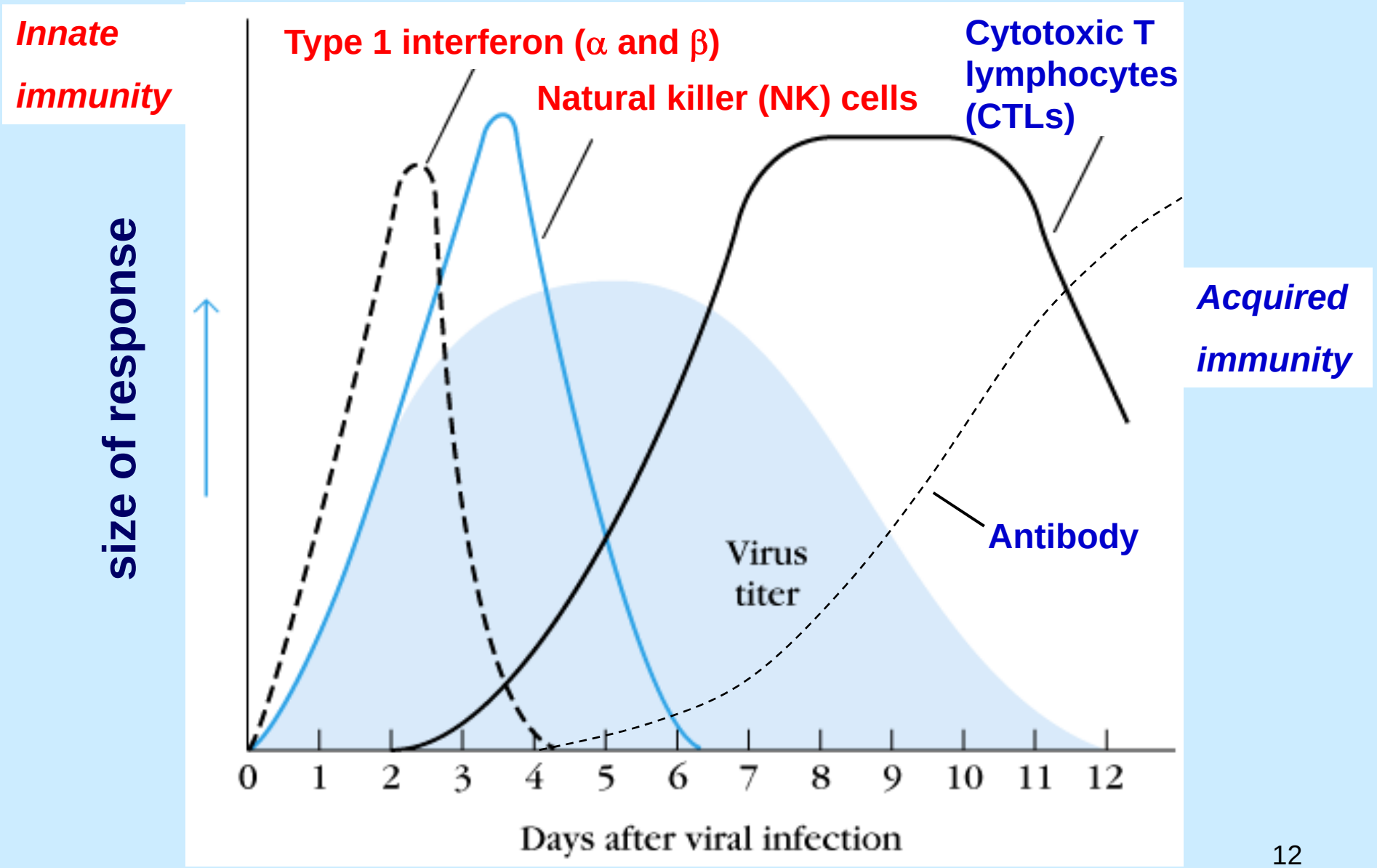
2. **Outline the basic principles of immune responses and the timescales in which they occur.**

3. Define the terms antigen, antibody, B lymphocyte, T lymphocyte, primary and secondary immune responses, and active and passive immunity.

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.

Time-course of primary immune response to a virus



Innate and acquired immunity: basic features

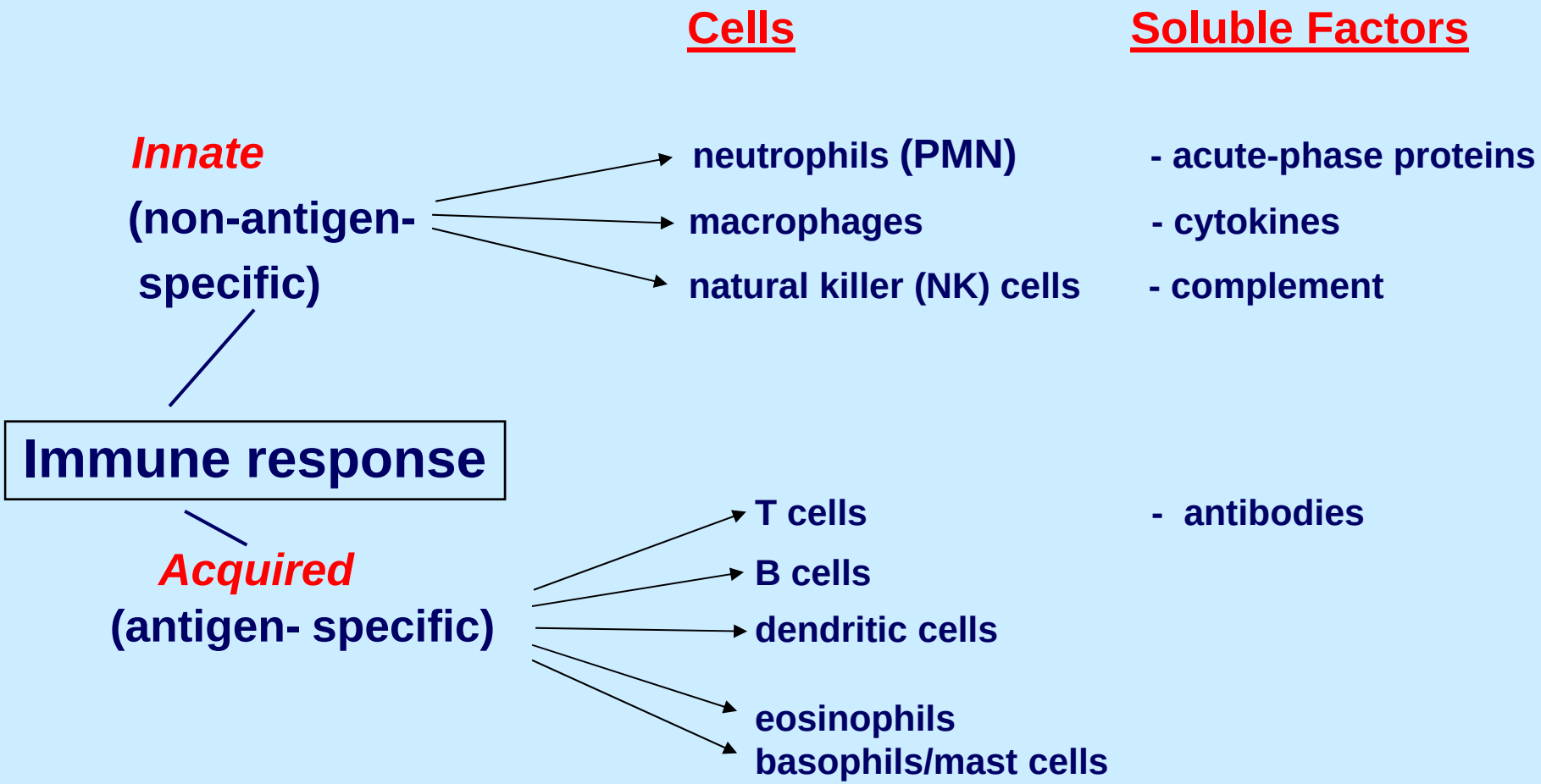
Innate immunity	*Acquired immunity*
• depends on **pre-formed** cells and molecules	• depends on **clonal selection**: i.e. growth of cells or antibodies, selected for antigen specificity
• **fast** (starts in minutes/hrs)	• **slow** (starts in days)
• limited specificity – pattern recognition of '**danger signals**'	• highly **specific** to foreign proteins

Innate Immunity

- ***Anatomical barriers*** - skin is a mechanical barrier; mucus trapping of microbes; cilial propulsion on epithelia

- ***Physiological barriers*** - low pH, secretion of lysozyme, interferons, antimicrobial peptides, complement

Innate and acquired immunity



The innate immune system:

- ***buys time*** **while the acquired immune system is mobilized, and**
- ***stimulates the acquired immune response*****, e.g. through cytokines and complement.**

Innate immune response: Intracellular detection of viruses

Pathogen-associated molecular patterns (PAMPs) are specific types of molecular structures not normally found in the cell.

- examples of PAMPs include dsRNA & certain carbohydrates

PAMPs bind to sensors (receptors) on the surface or in the cytoplasm:

- Toll-like receptors (TLR) (cell surface; intracellular)
- RIG-I-like receptors (RLR) (cytoplasmic)
- Nucleotide-binding domain, leu-rich repeat-containing proteins (NLR)
- C-type lectin receptors (CLR)

(different cell types use different receptors to detect viruses)

The receptor elicits a signalling cascade, resulting in anti-viral responses

- Interferon type 1 ⟶ enzymes that degrade viral nucleic acid
- Interferon type 3 & retroviral restriction factors

Acute phase inflammatory response (1)

= an ***innate*** response to tissue damage.

- Rise in body temperature – the fever response.
- This is followed by increased production of a number of proteins, mainly by the liver. Notable amongst these are:
  - C-reactive protein
  - serum amyloid protein
  - mannan-binding lectin.

  } "Acute phase proteins" or "acute phase reactants"

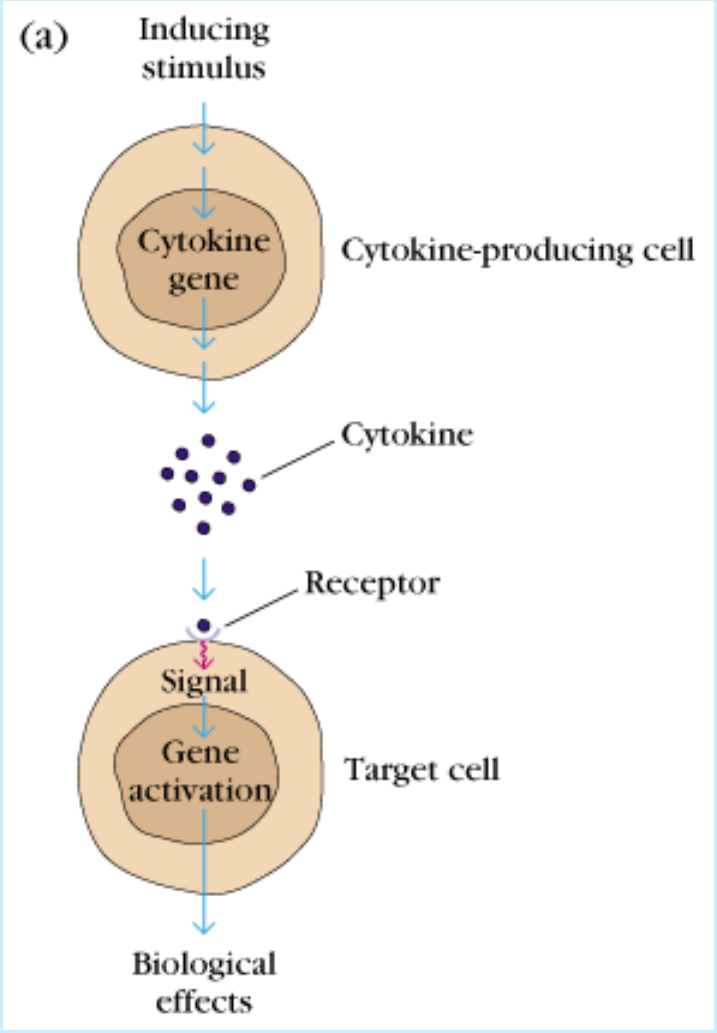
Acute phase inflammatory response (2)

How do the acute phase proteins act?

- 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

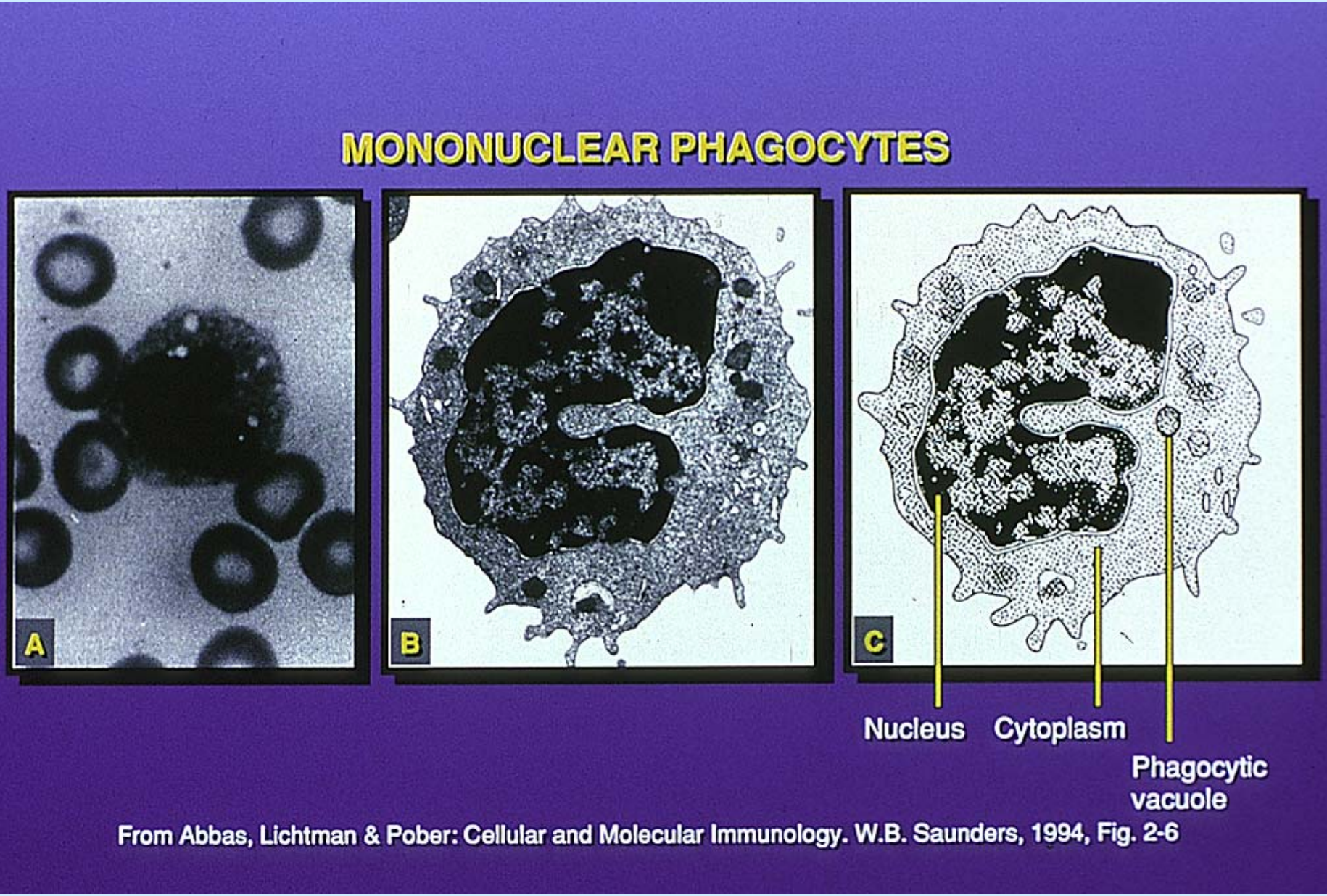


- e.g. to stimulate **activation** or **proliferation** of lymphocytes.

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



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.

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 active and passive immunity.**
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 (usu. proteins)
- can form memory
- requires priming

Effector arms:

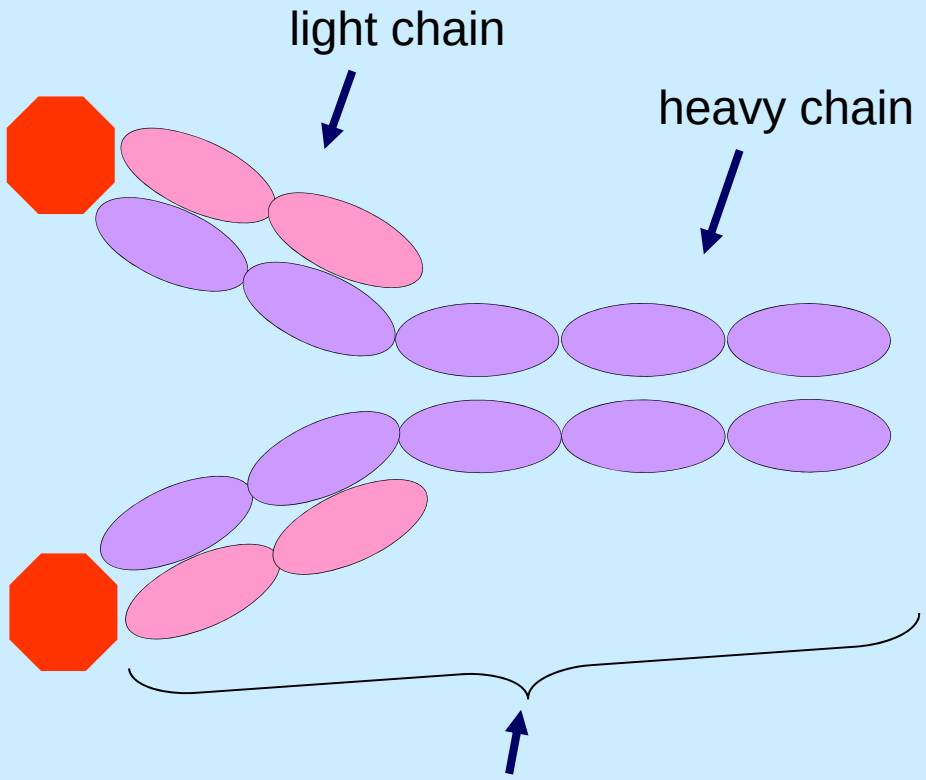
Cellular immunity
- T and B lymphocytes

Humoral immunity
- Antibodies

Definition of terms: antigen, immunogen, antibody

Antigens are molecules which react with antibodies or T cells.

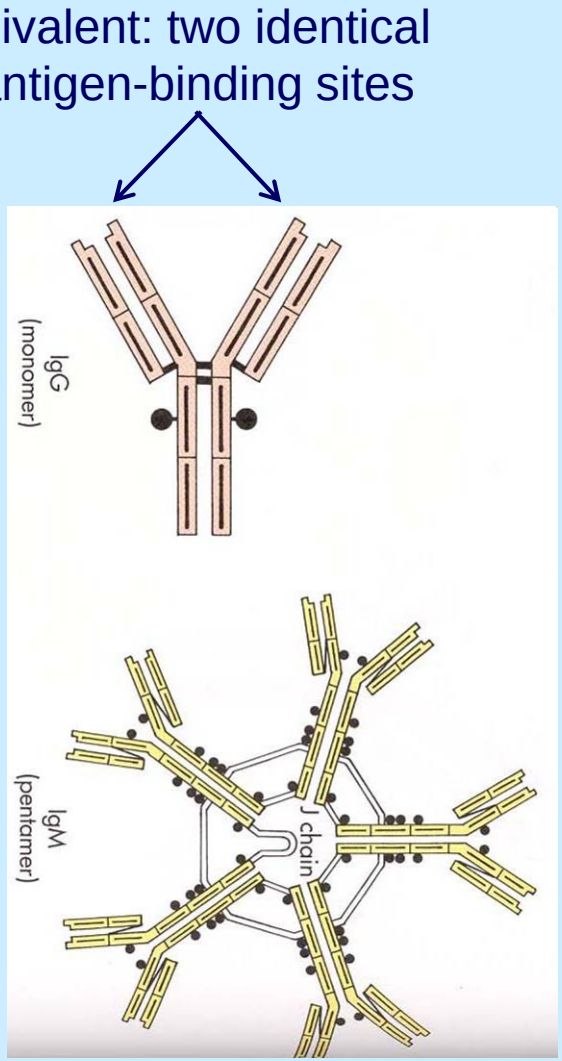
But not all antigens can *initiate* an immune response - those that can are ***immunogens***.



An antibody is an immunoglobulin molecule in the bloodstream and body fluids which binds specifically to an antigen. The antibody response is the *acquired* part of the *humoral* (soluble) immune response.

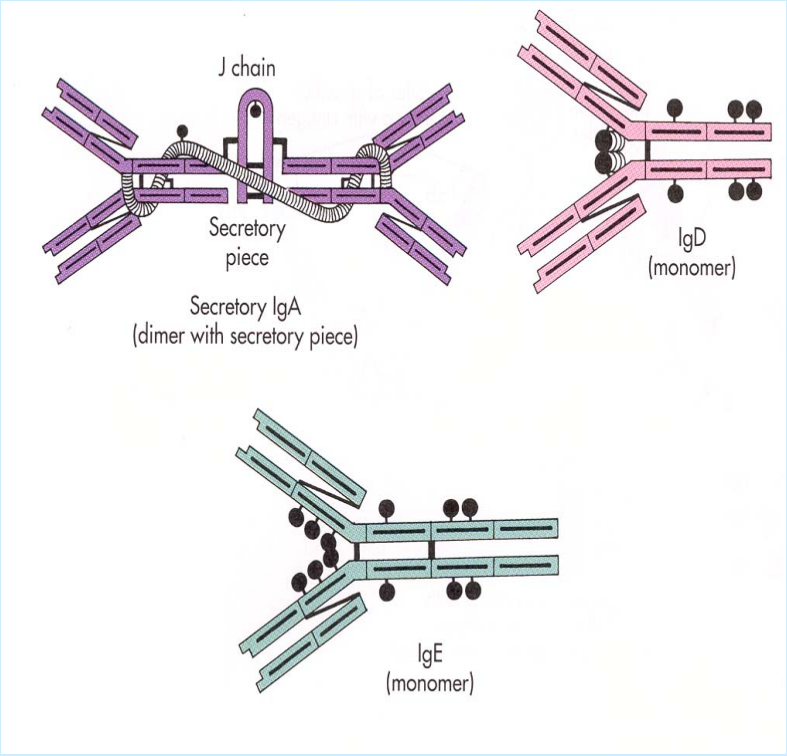
Five classes of immunoglobulins (1)

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

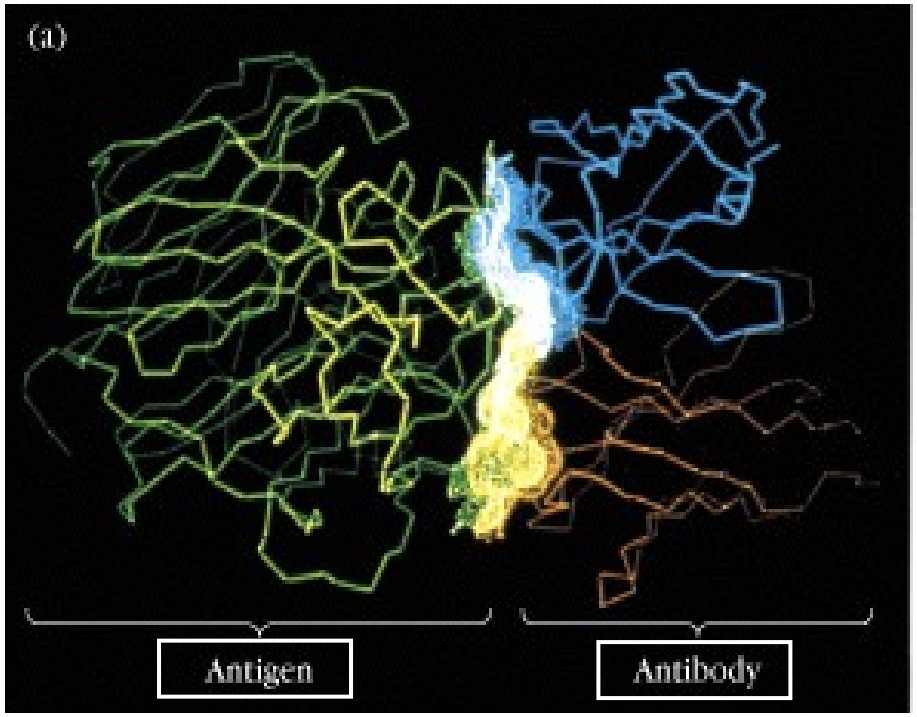


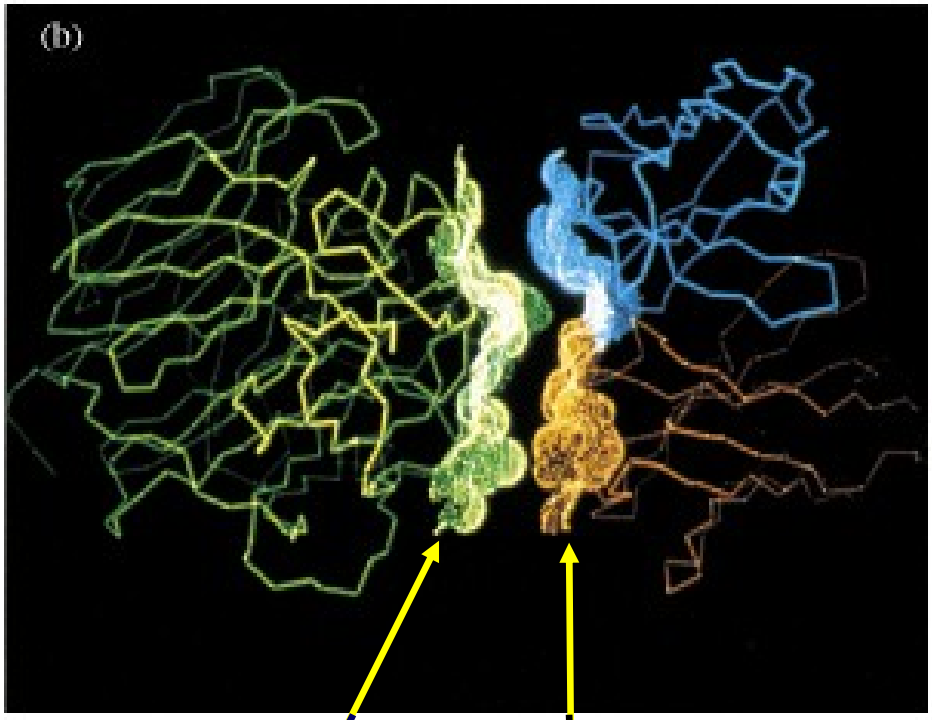
Immunoglobulins (2)

- 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



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





epitope

Ab binding site

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 MΦ.
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)

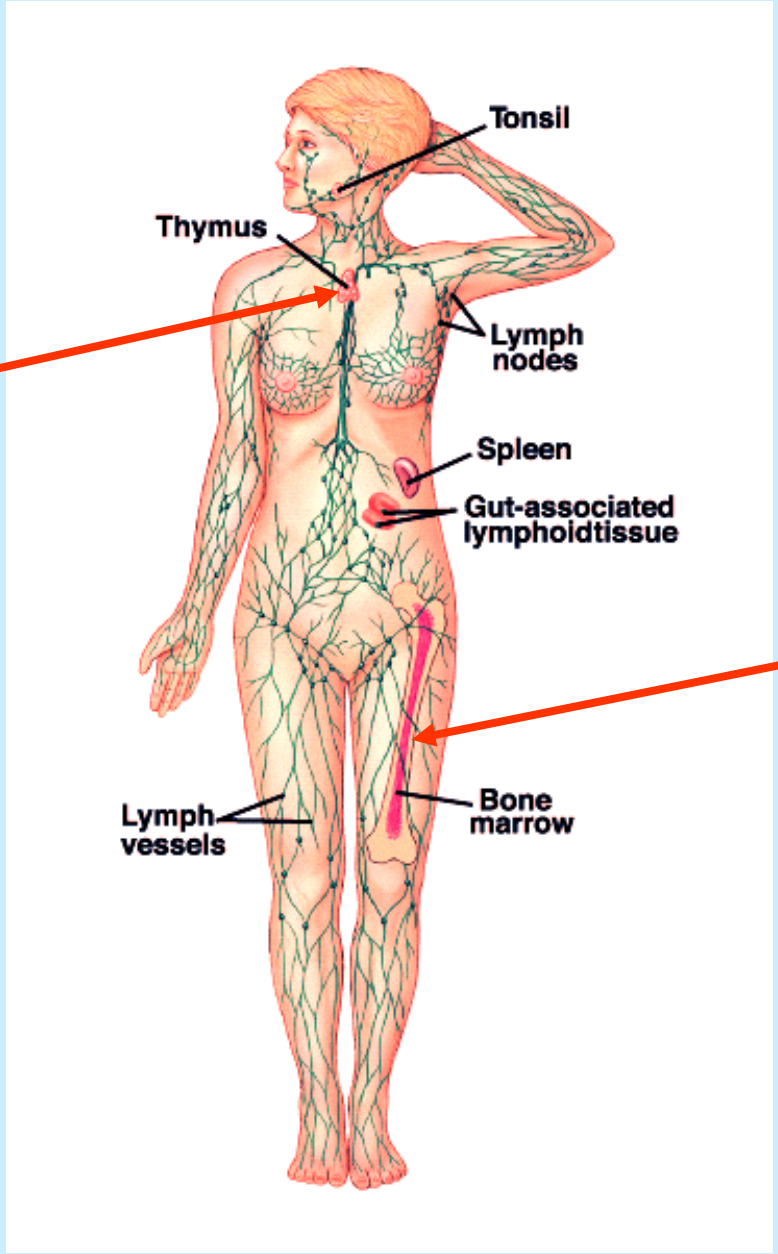
20-40% of the circulating WBCs, 99% of the cells in lymph

- 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.

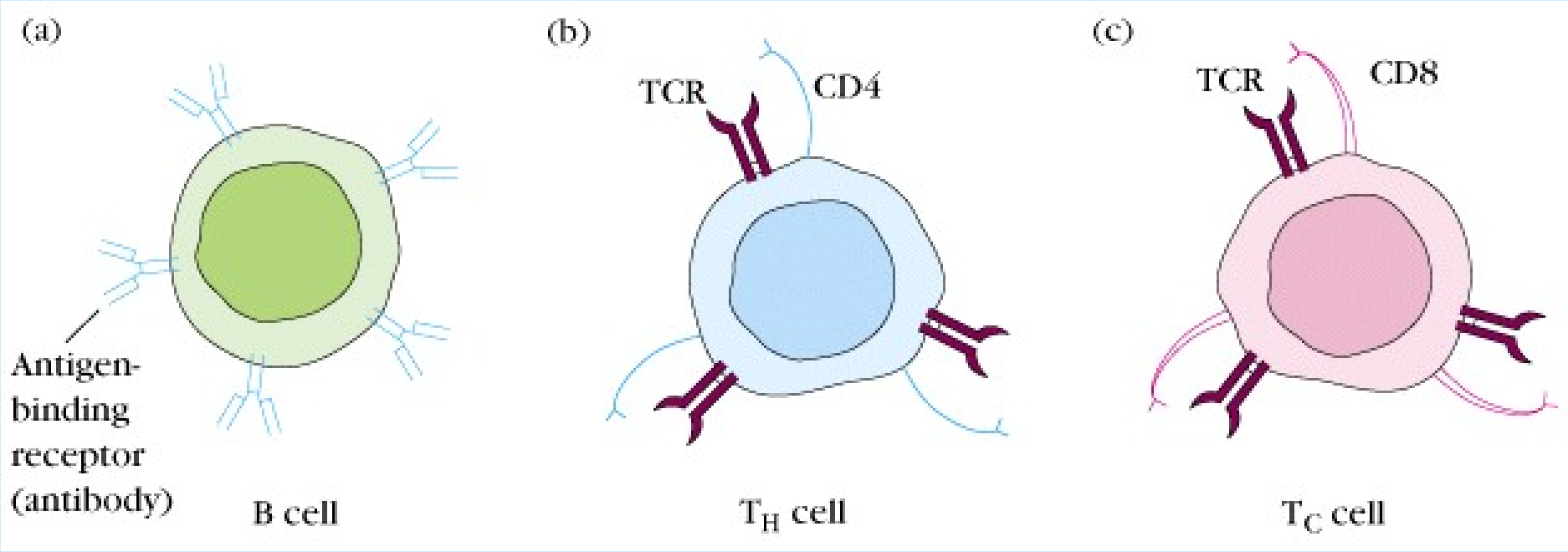
Lymphocyte precursors are produced in haematopoietic tissue – bone marrow

T cells 'educated' here



B cells produced here

Three types of antigen-specific lymphocyte



***alias*:** **helper T-cell** **cytotoxic T-cell (CTL)**

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 active and passive immunity.
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.

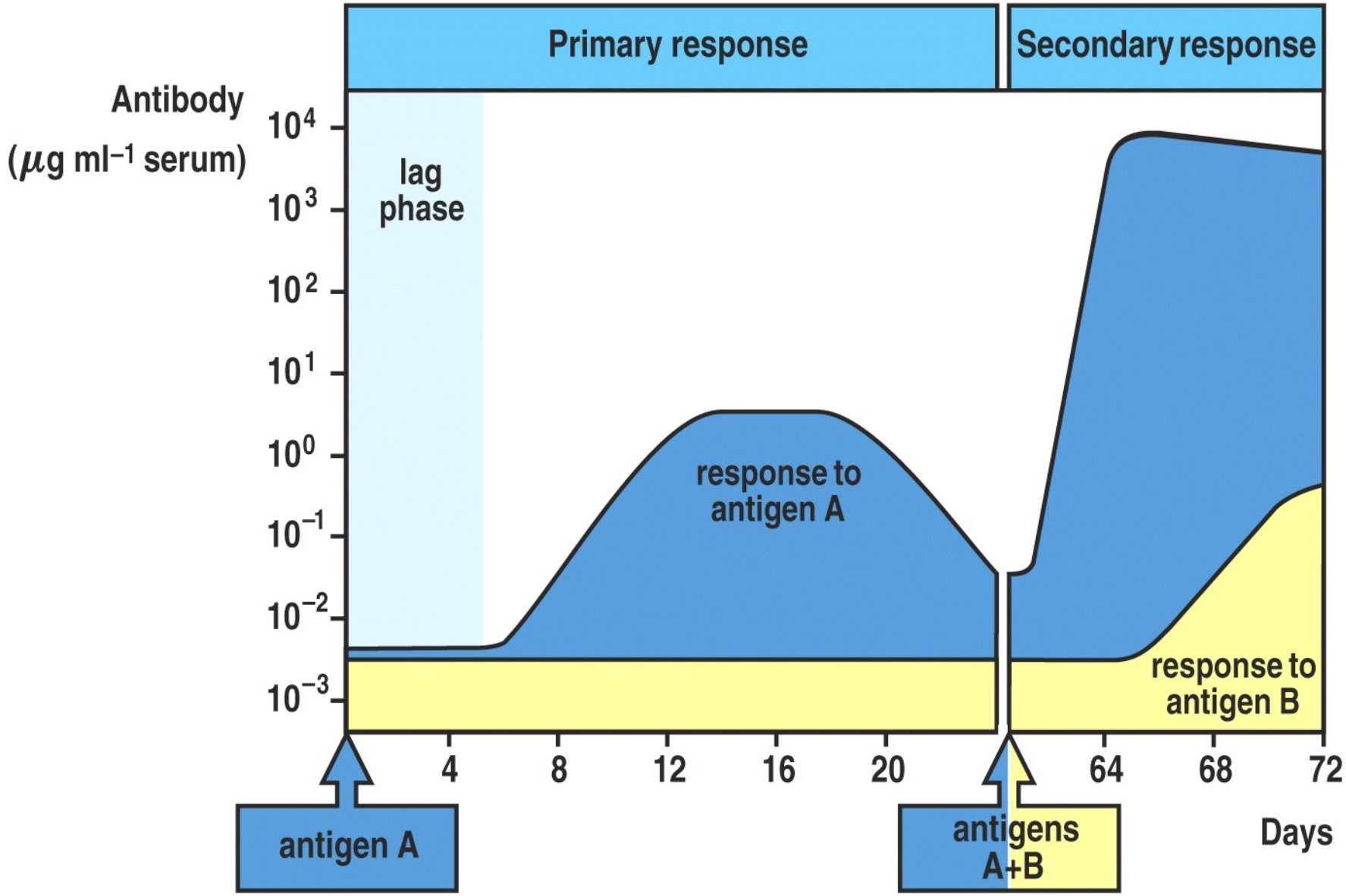
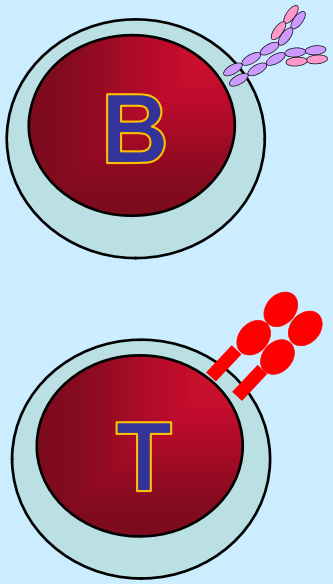


Figure 1-20 Immunobiology, 6/e. (© Garland Science 2005)

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 cell has a unique receptor, specific to one antigen; there are many copies of this receptor on the cell surface.

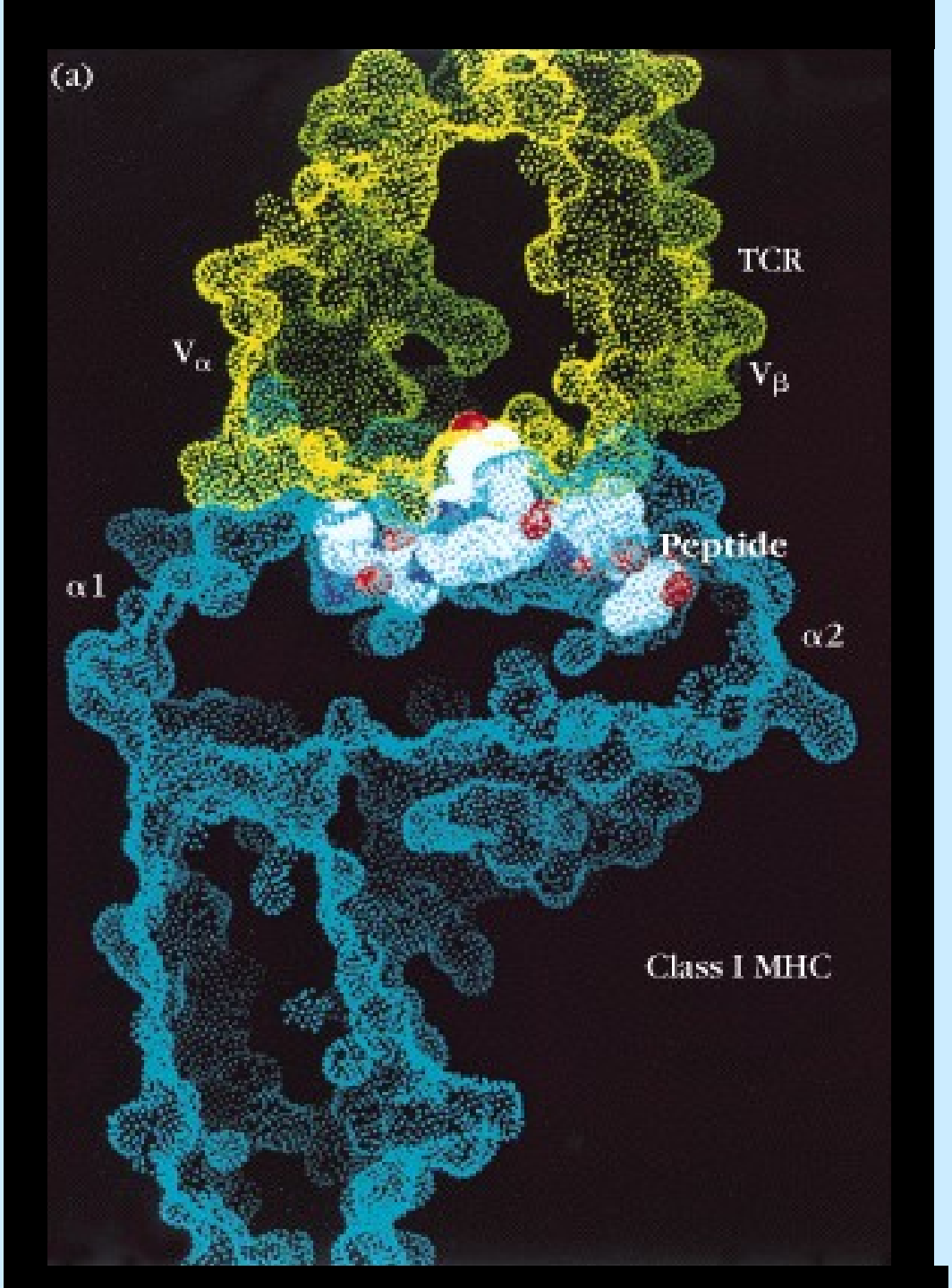
The T-cell antigen receptor (TCR) recognizes a complex of

***antigen peptide* +**

HLA (MHC) molecule

MHC denotes the *Major Histocompatibility Complex* - also known as Human Leukocyte Antigens (HLA)

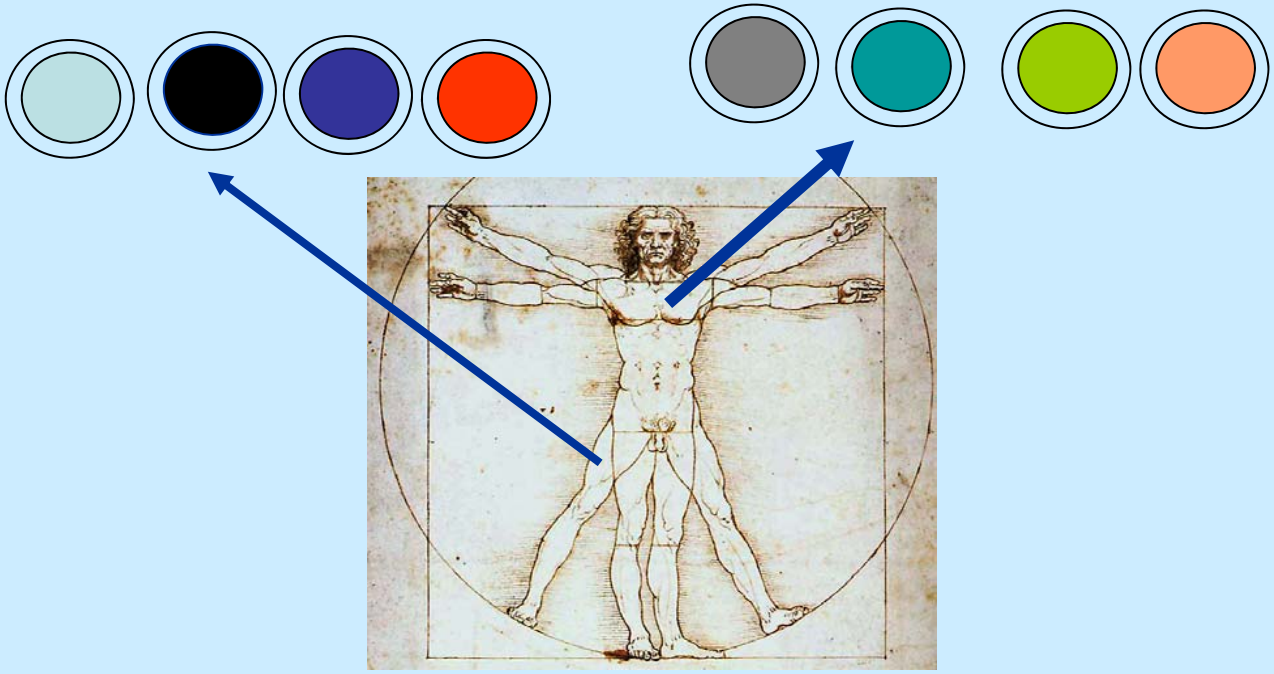
MHC molecules display fragments of intracellular proteins on the cell surface for immune surveillance.



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.

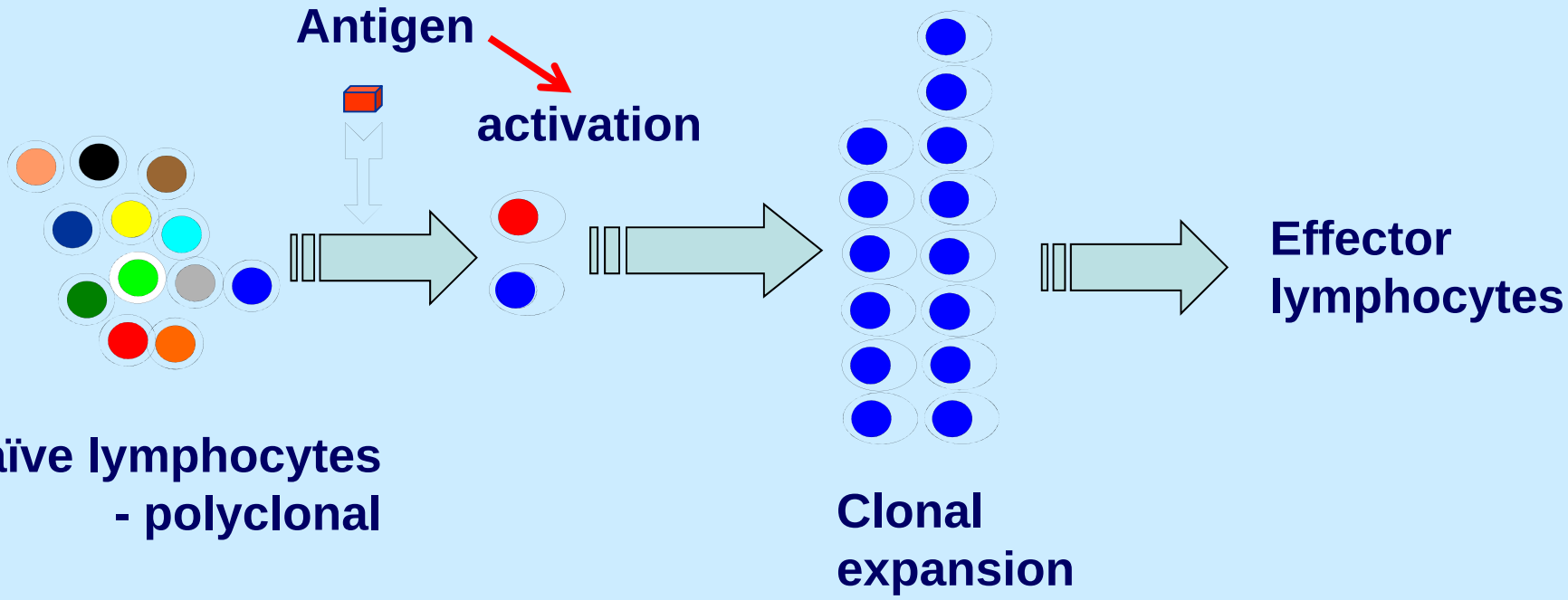
Lymphocytes that meet an antigen they recognize will proliferate and survive.

The huge majority of lymphocyte clones will die out.

Primary immune response: clonal selection

A typical antigen is recognized by 1 in ~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?

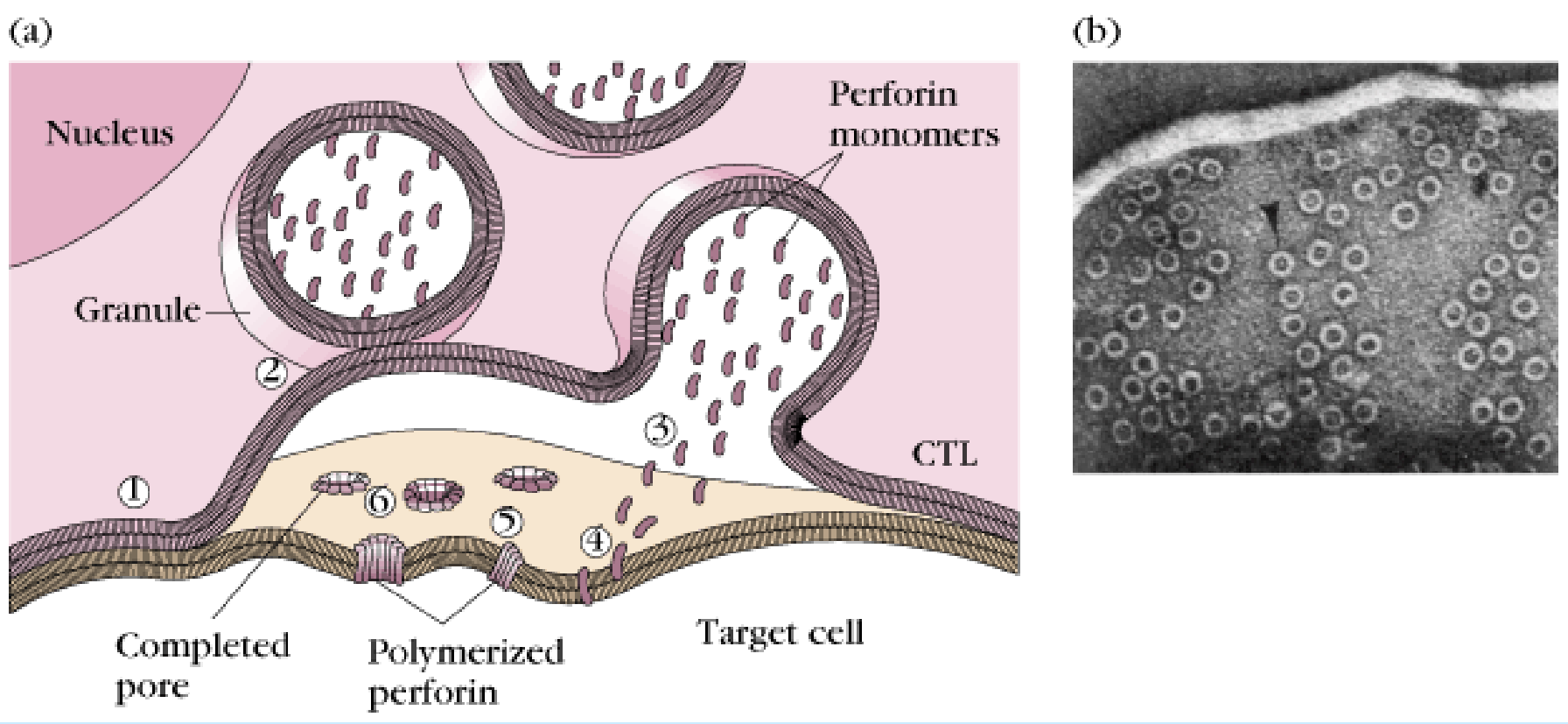
Most lymphocytes that have proliferated recently will *die* after fulfilling their function.

Some survive as *memory cells.*

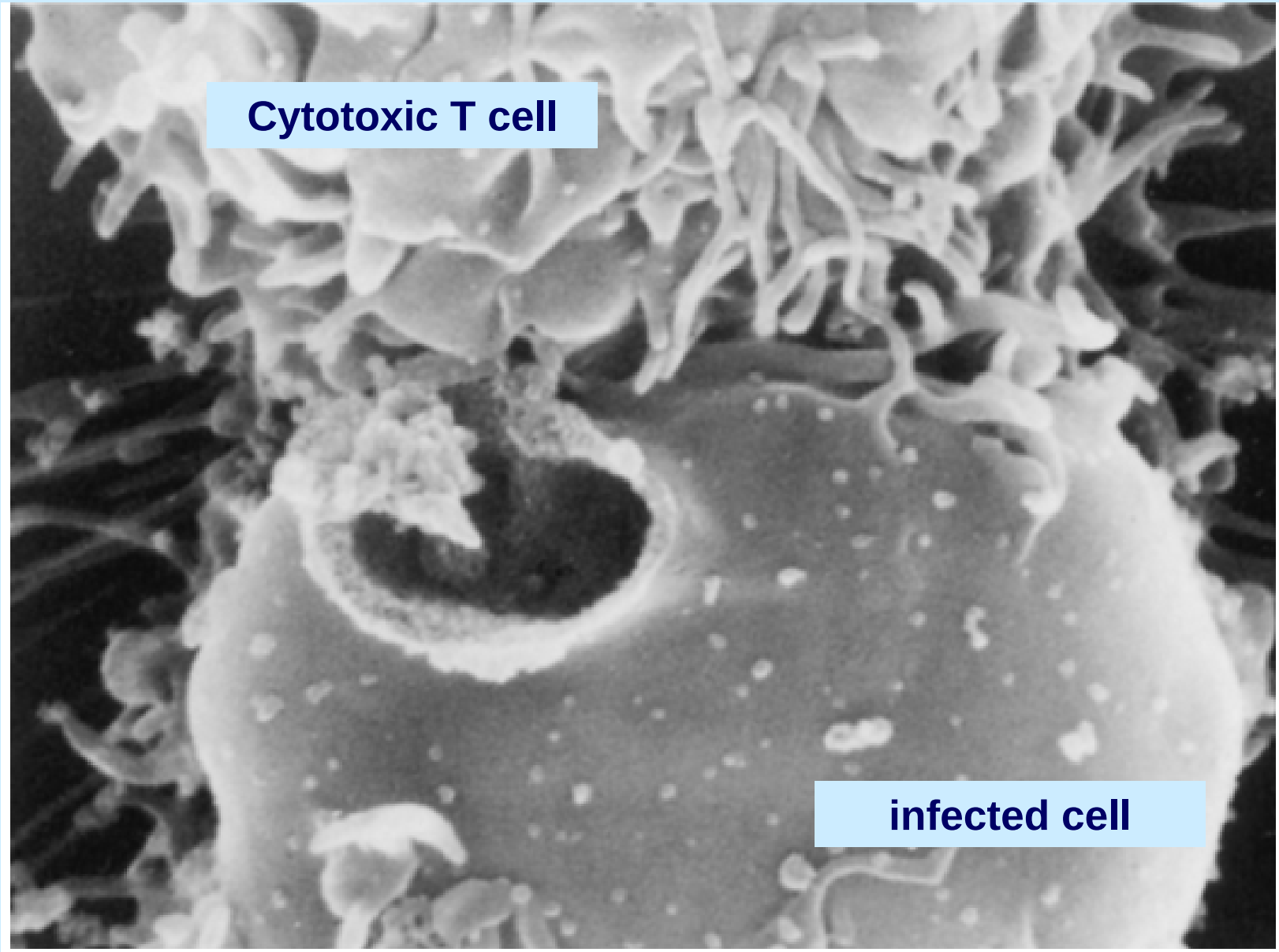
How does the immune response actually clear a pathogen?

- 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

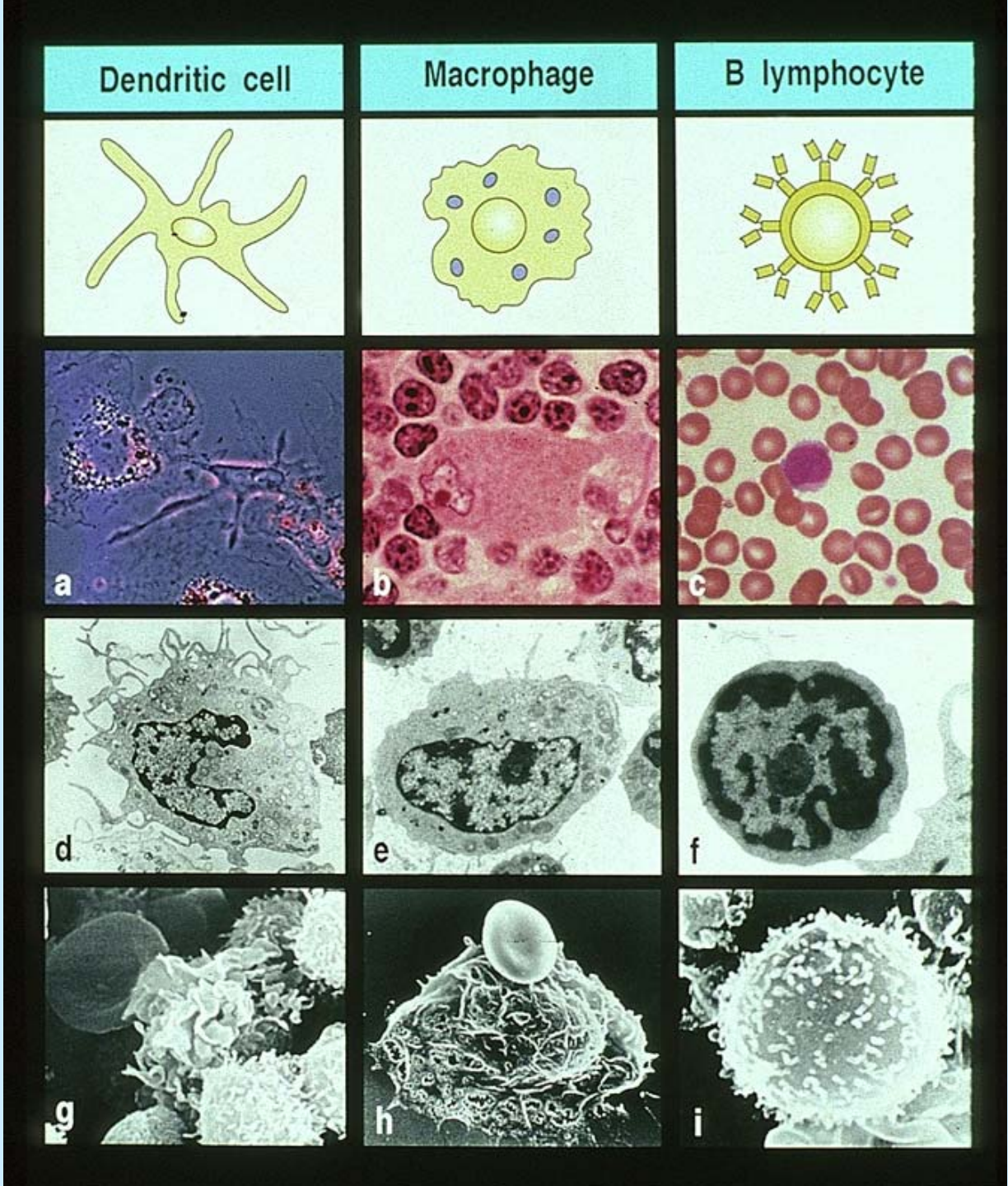


1. Explain the importance of immunology for human health.
2. Outline the basic principles of immune responses and the timescales in which they occur.
3. Define the terms antigen, antibody, B lymphocyte, T lymphocyte, primary and secondary immune responses, and active and passive immunity.
4. Outline 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.**

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

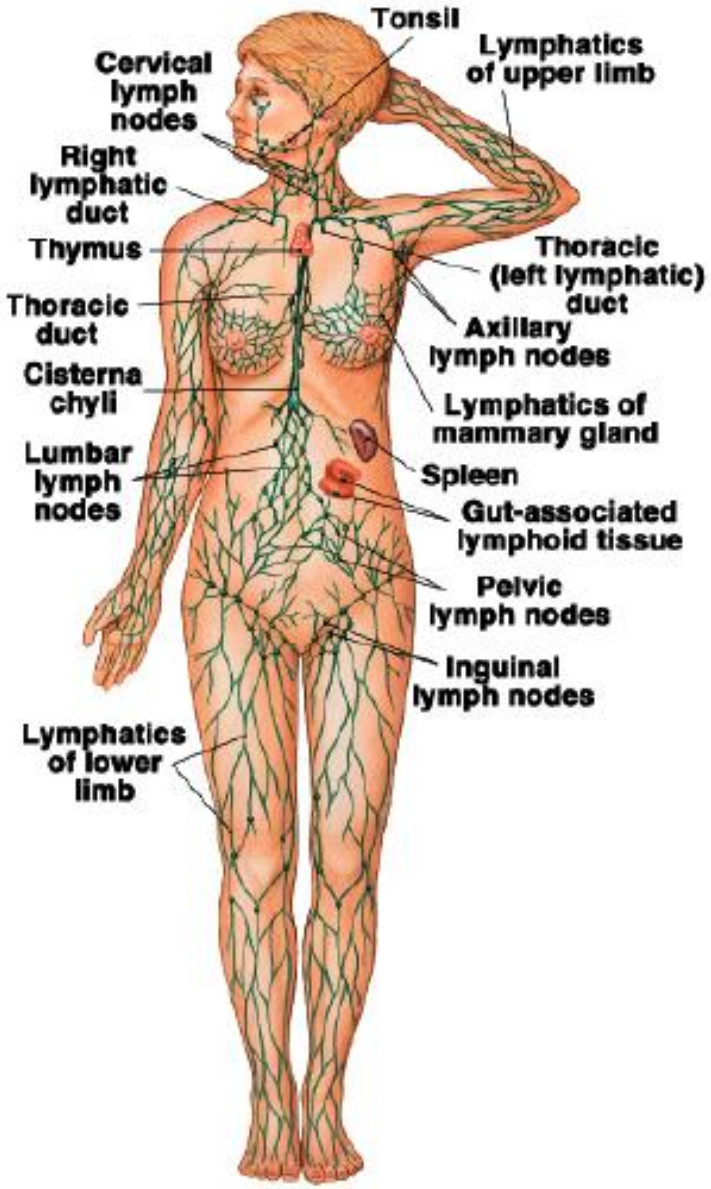
Spleen (white pulp)

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

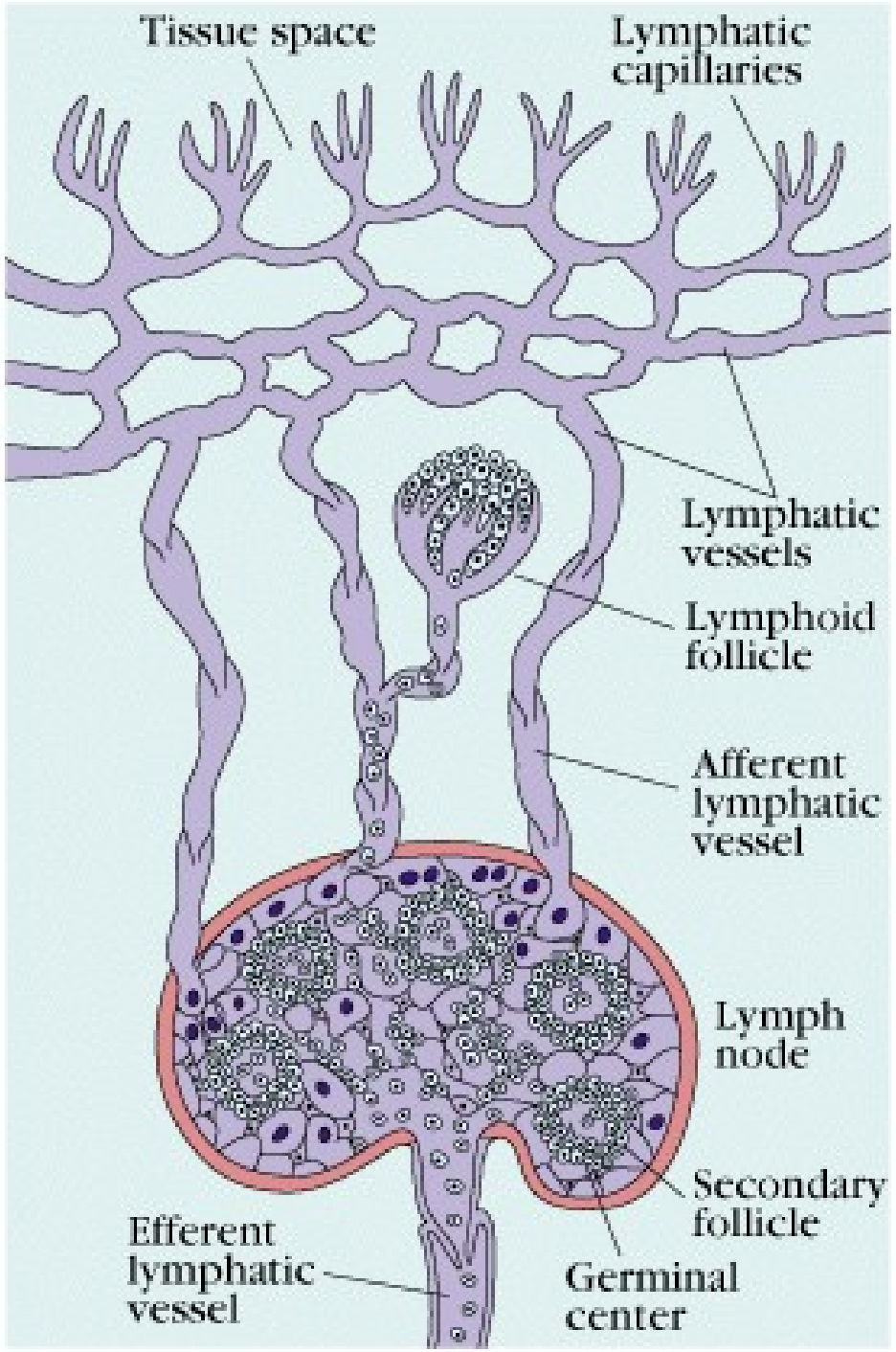


Lymphocytes and antigen-presenting cells recirculate through lymphatic vessels:

from *tissues*

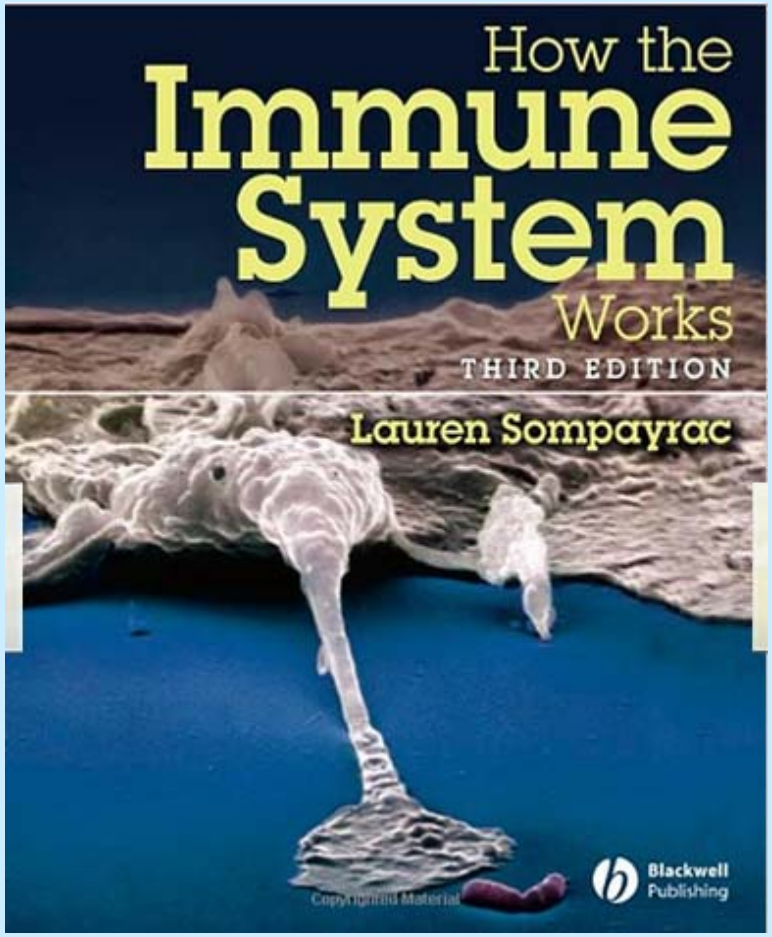
via *lymph nodes or spleen*

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

The impact of vaccination (3)

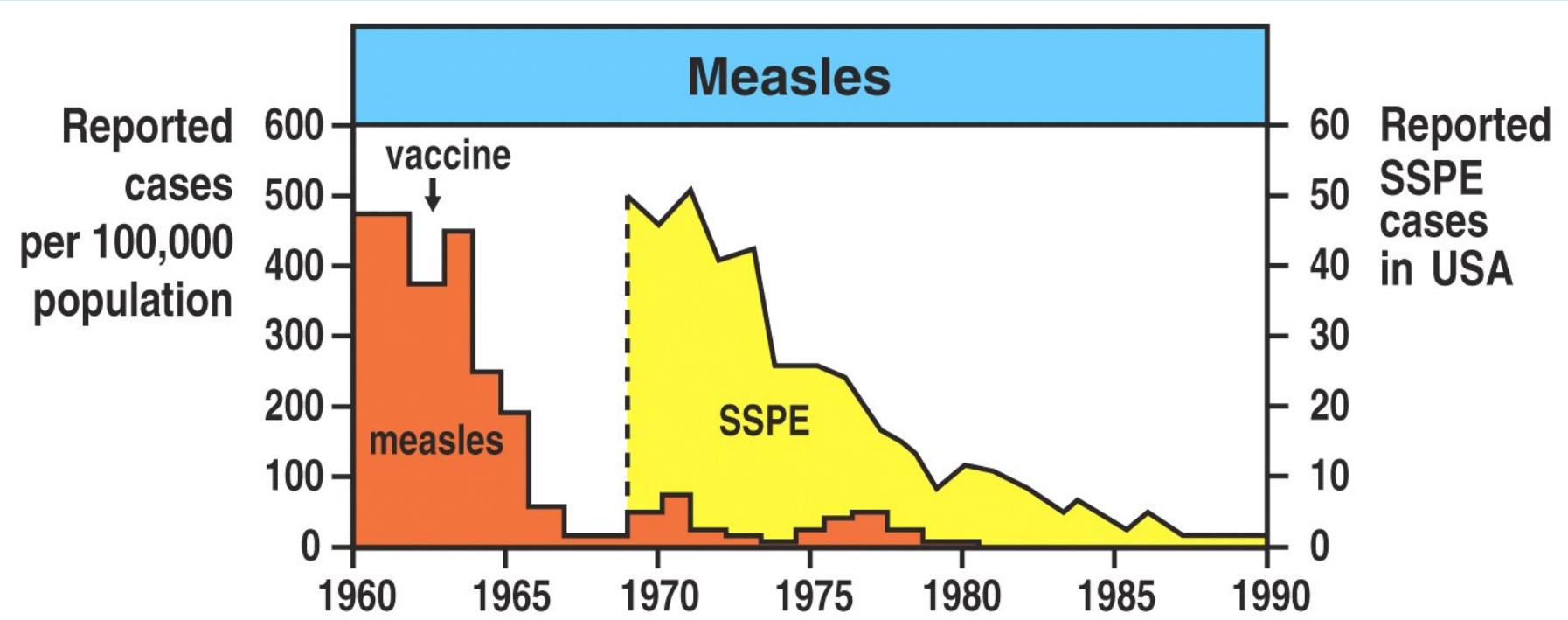


Figure 1-33 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)