IMMUNITY - 2

BY
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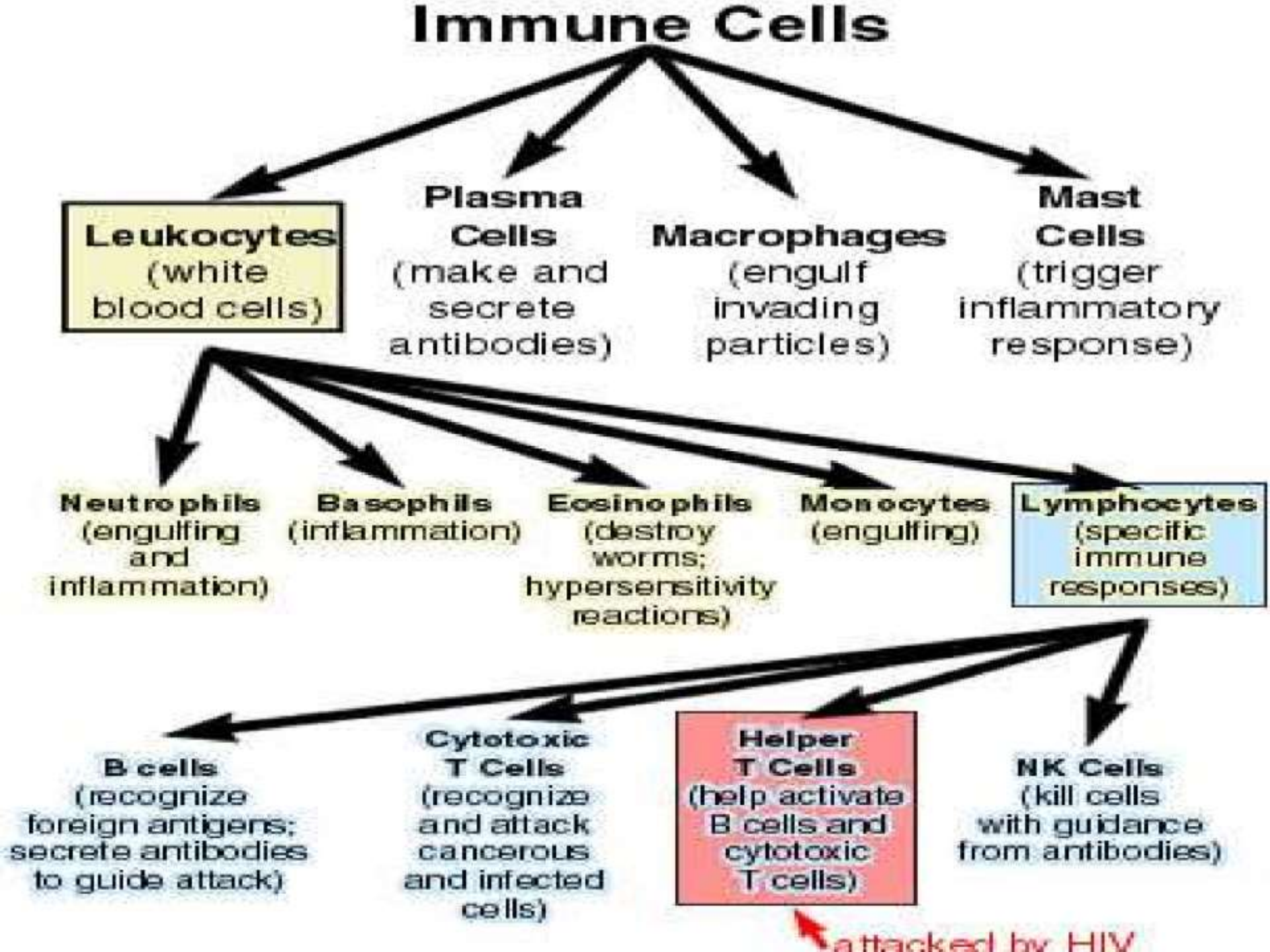
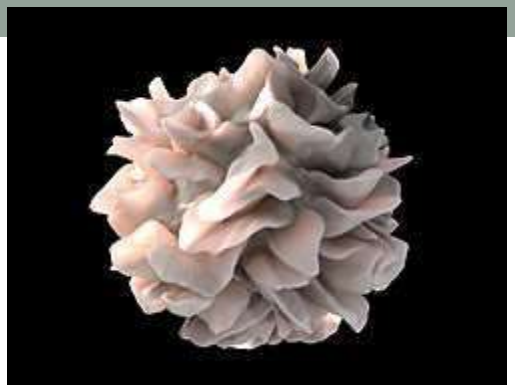
Learning Objectives

- Mechanism of immunity activation
- Types of lymphocytes participating in immunity
- Immunity in both extremes of age
- Immunization and its types


Immune Cells
Leukocytes (white blood cells)
Plasma Cells (make and secrete antibodies)
Macrophages (engulf invading particles)
Mast Cells (trigger inflammatory response)
Neutrophils (engulfing and inflammation)
Basophils (inflammation)
Eosinophils (destroy worms; hypersensitivity reactions)
Monocytes (engulfing)
Lymphocytes (specific immune responses)
B cells (recognize foreign antigens; secrete antibodies to guide attack)
Cytotoxic T Cells (recognize and attack cancerous and infected cells)
Helper T Cells (help activate B cells and cytotoxic T cells)
NK Cells (kill cells with guidance from antibodies)
attacked by HIV

Dendritic cells (DCs)
Accessory cells



- Dendritic cells were first described by Paul Langerhans in the late 19th century.
- Antigen-presenting cells of the mammalian immune system.
- Main function -process antigen material and present it on the cell surface to the T cells.
- Act as messengers between the innate and the adaptive immune systems .

- Dendritic cells are present in those tissues that are in contact with the external environment,

  Eg. skin and the inner lining of the nose, lungs, stomachand intestines. also be found in an immature state in the blood.

- **Once activated, they migrate to the lymph nodes where they interact with T cells and B cells to initiate and shape the adaptive immune response.**

- **At certain development stages they grow branched projections, the *dendrite* that give the cell its name .**

- **Immature dendritic cells are also called veiled cells, as they possess large cytoplasmic 'veils' rather than dendrites**

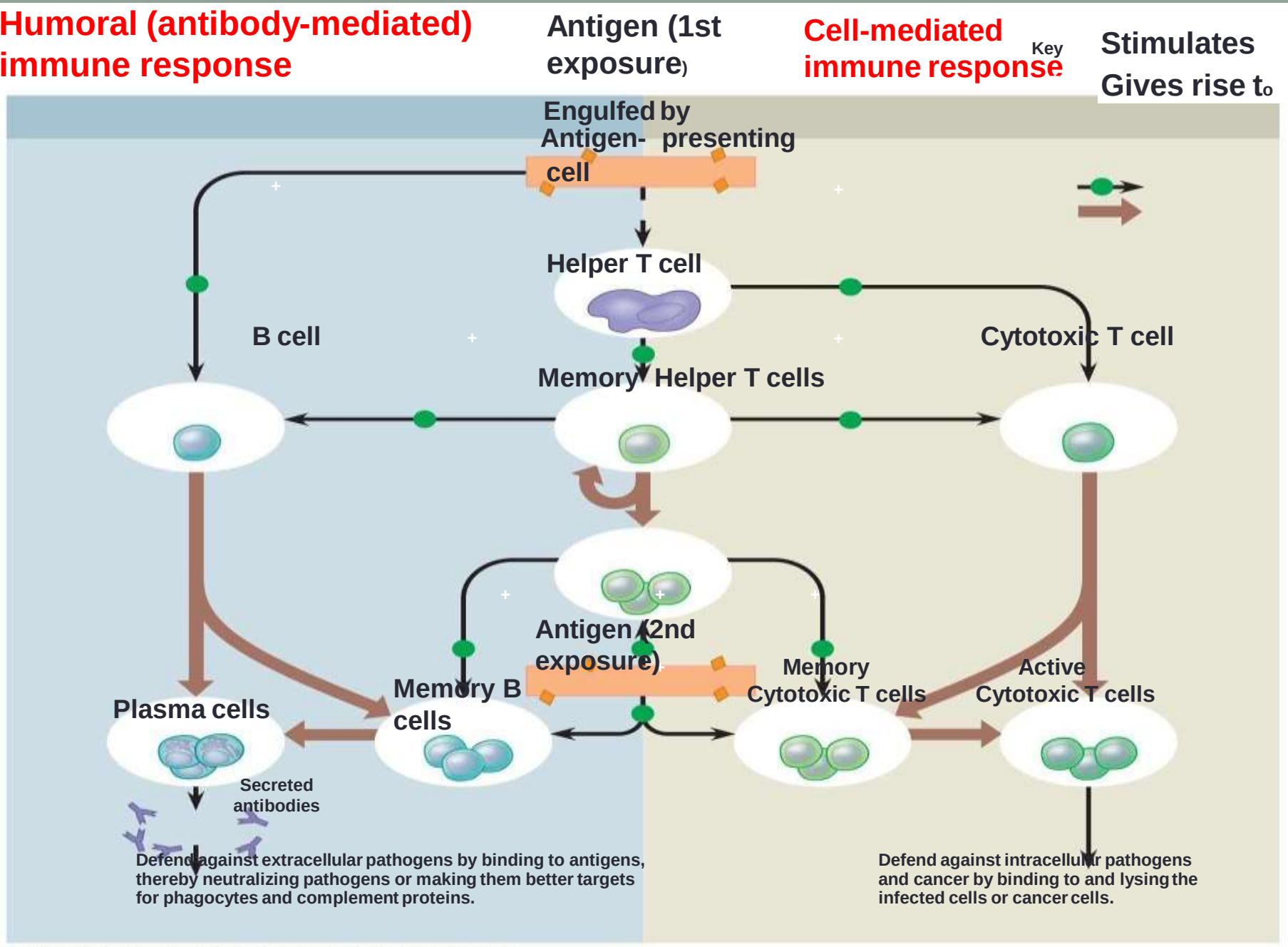


Fig. 43-16a

Humoral (antibody-mediated) immune response

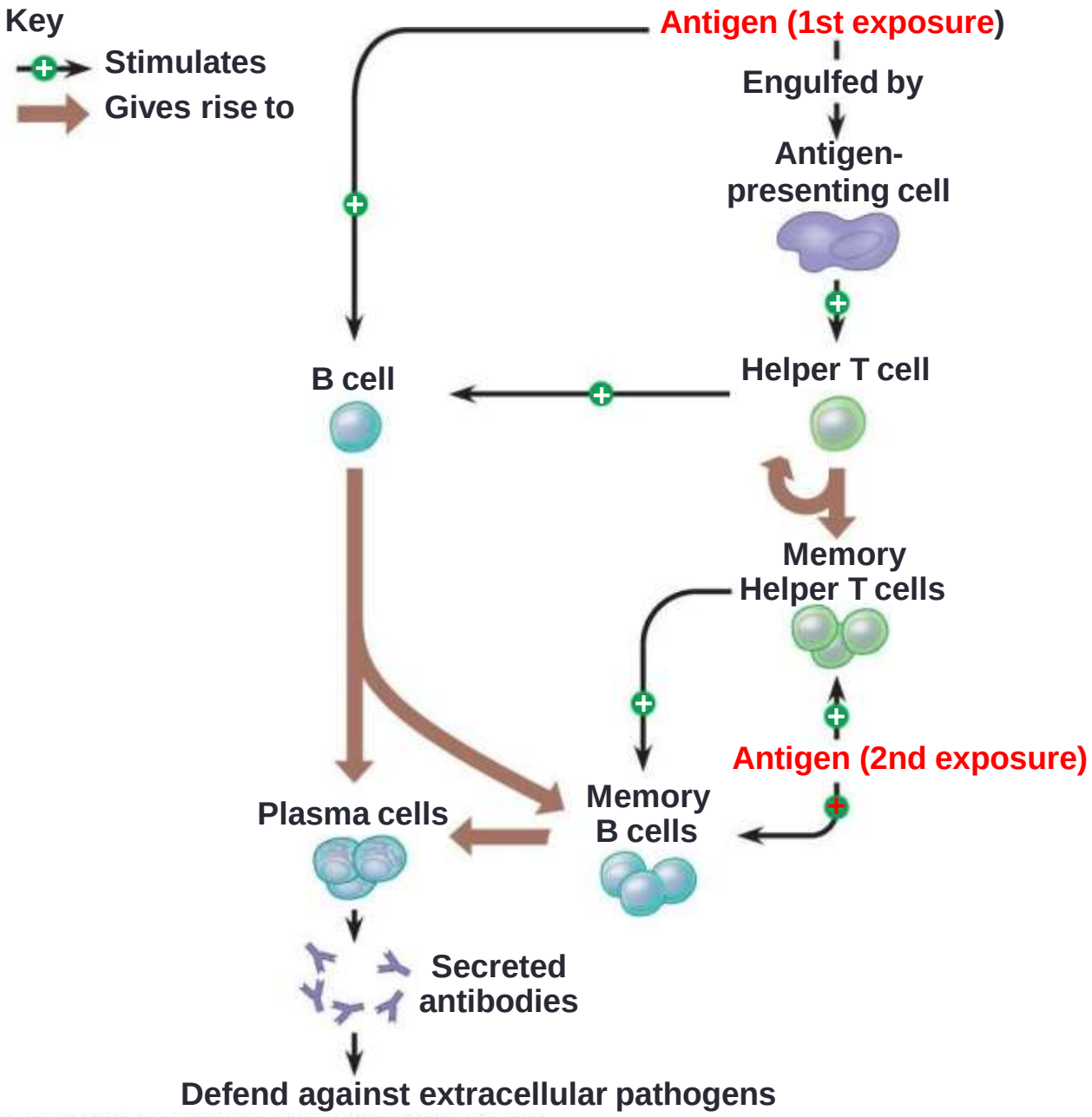
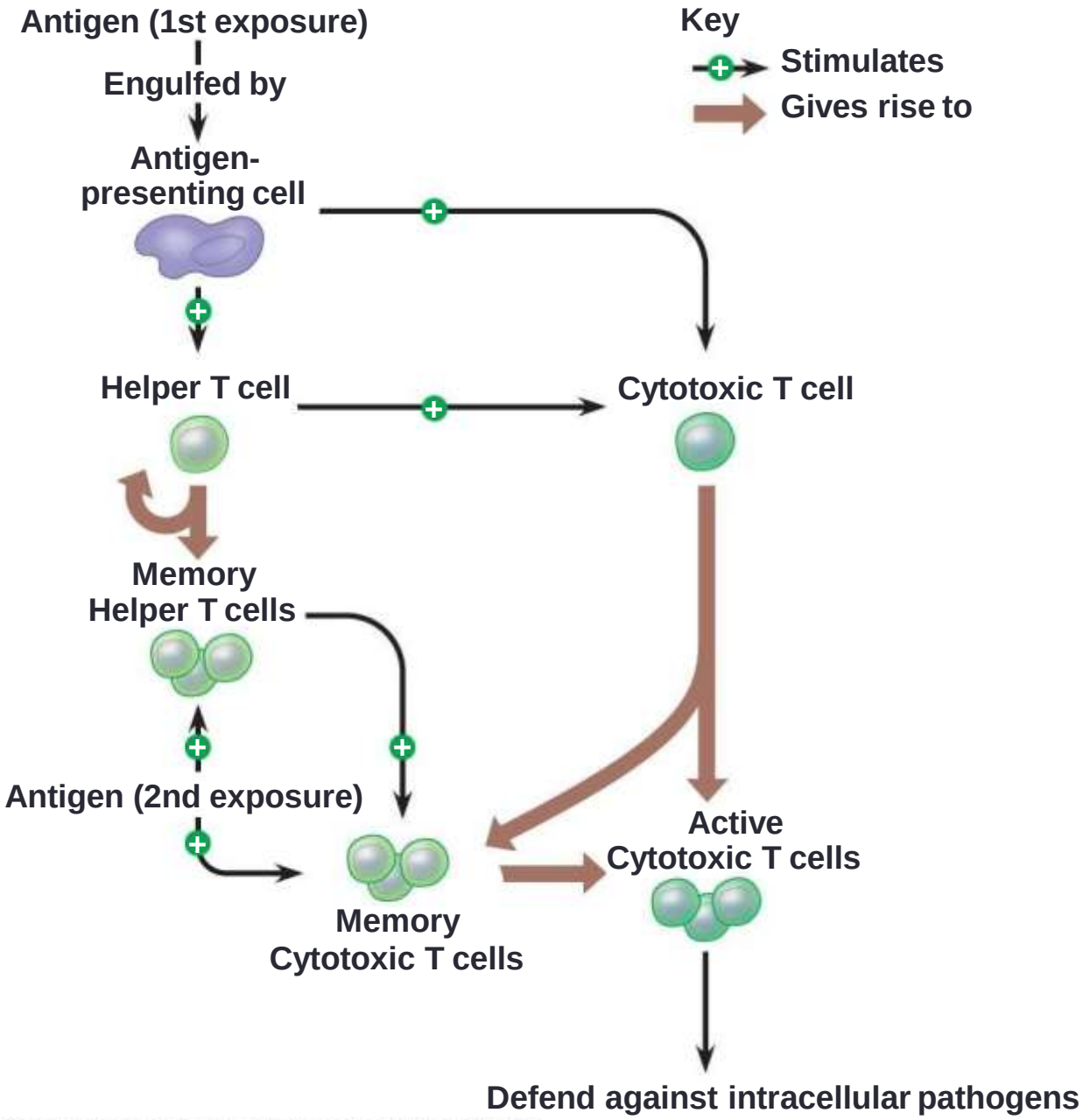


Fig. 43-16b

Cell-mediated immune response

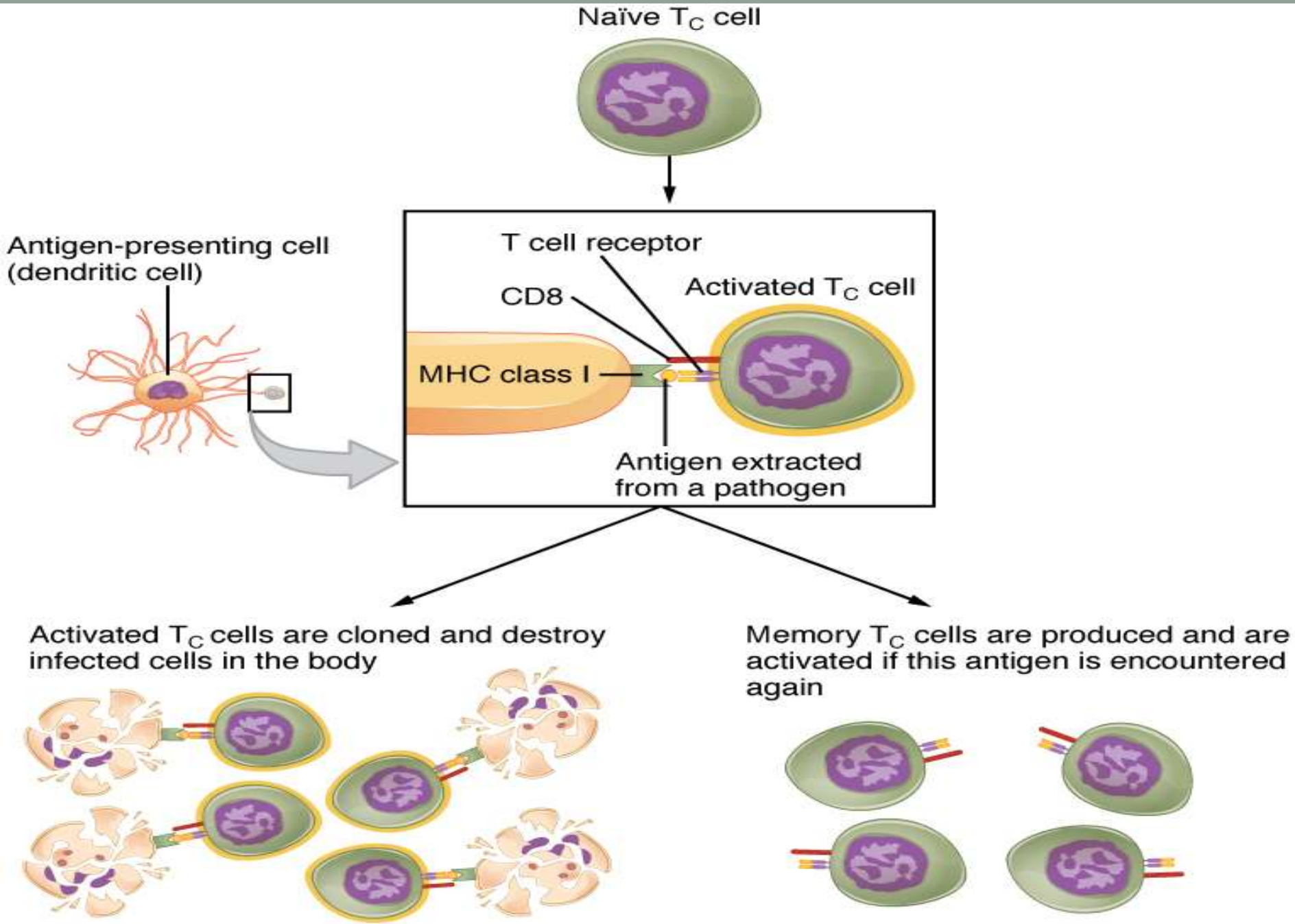


Role of T cells in immunity

Behavior of T Lymphocytes in Defense

- Exposure to Antigen
- Specific clones proliferate
- Activated T cells are released

  (parallel to the antibodies)


Naïve T_C cell
Antigen-presenting cell (dendritic cell)
T cell receptor
CD8
Activated T_C cell
MHC class I
Antigen extracted from a pathogen
Activated T_C cells are cloned and destroy infected cells in the body
Memory T_C cells are produced and are activated if this antigen is encountered again

Behavior of T Lymphocytes in defense

- A few of T cells form memory cell
- Activated T cell Come in the lymphatics and then in circulation and again in lymphatics
- Memory cells act more powerfully on second exposure.

How T cells react

- T cells responds to antigens only when they are bound to MHC (major histocompatibility complex protein)

- Other antigen presenting cells are

(B-cells, macrophages and Dendritic cells)

(i) MHC-1 – presenting antigens to Cytotoxic T cells

(ii) MHC-2- presenting antigens to T Helper cells

Types and functions of T Lymphocytes

1. **T Helper cells**--- (about ¾) secrete Lymphokines i.e (IL2-6, GM-CSF, Inf ϒ)
   - have a major regulatory role in immunity,
   - Especially through IL-2, it increases the growth of cytotoxic and suppressor T cells.

   - Stimulates B cell response, antibodies and plasma cell formation, and activation of macrophage system.
   - IL-2 acts as +ve feedback stimulator on T helper cell activity.

Types and functions of T Lymphocytes

2. **Cytotoxic or T killer cells**

   Attach to the antigens--- secretes *perforins* - holes formation– swelling of cells– death of cells.

3. **T- Suppressor cells**

- **Regulate T helper and cytotoxic T cells activity,**
- **Maintain the tolerance to immunity and**
- **Protect the self tissue from cytotoxic activity.**

Tolerance of the Acquired immunity system to own body tissue

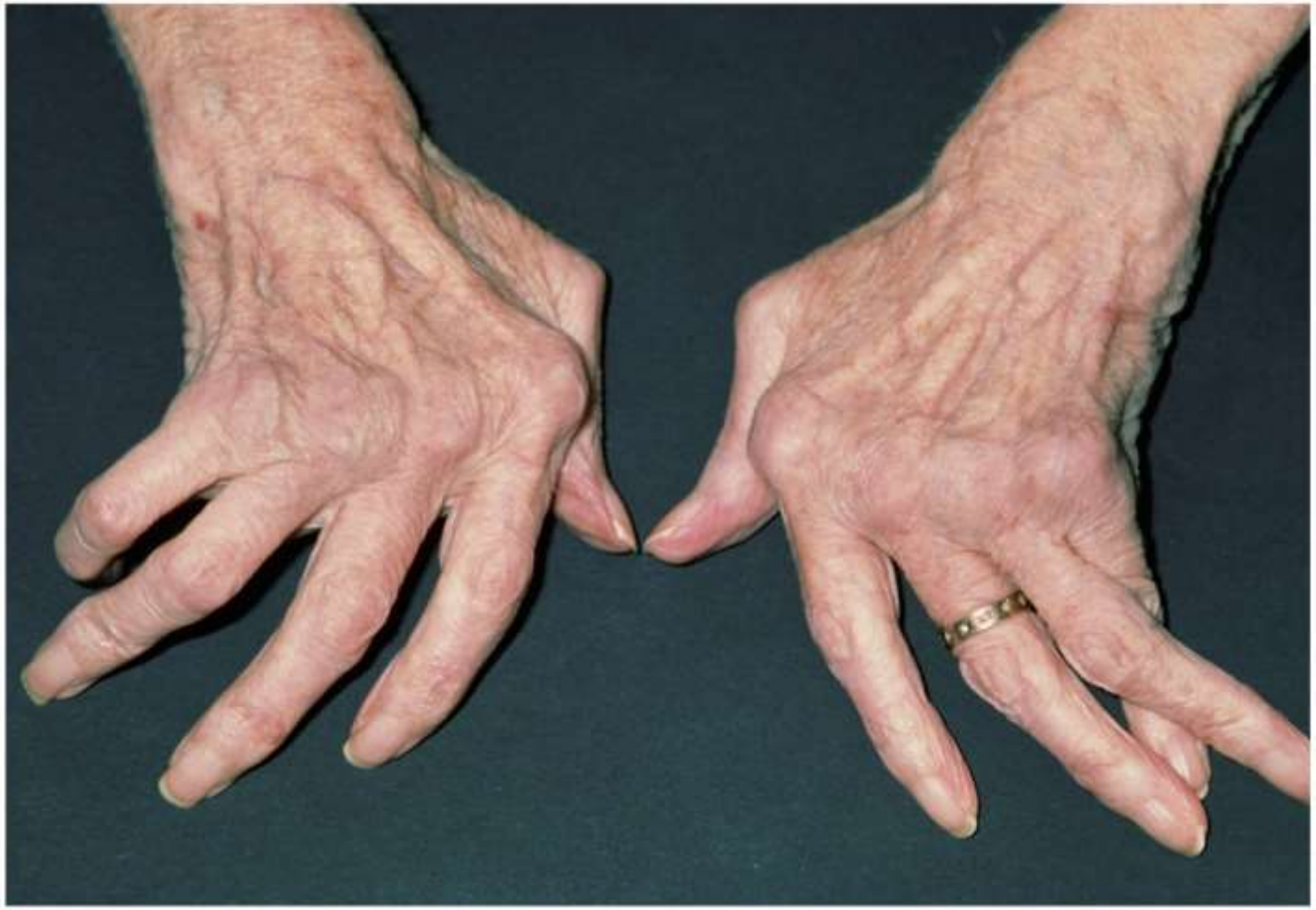
- This is the role of pre-processing in the Thymus and bone marrow
- Recognition of own body tissue in pre-processing normally
- When some lymphocytes are refusing to recognize own body tissue, they are destroyed in thymus or bone marrow

  (T or B lymphocytes)

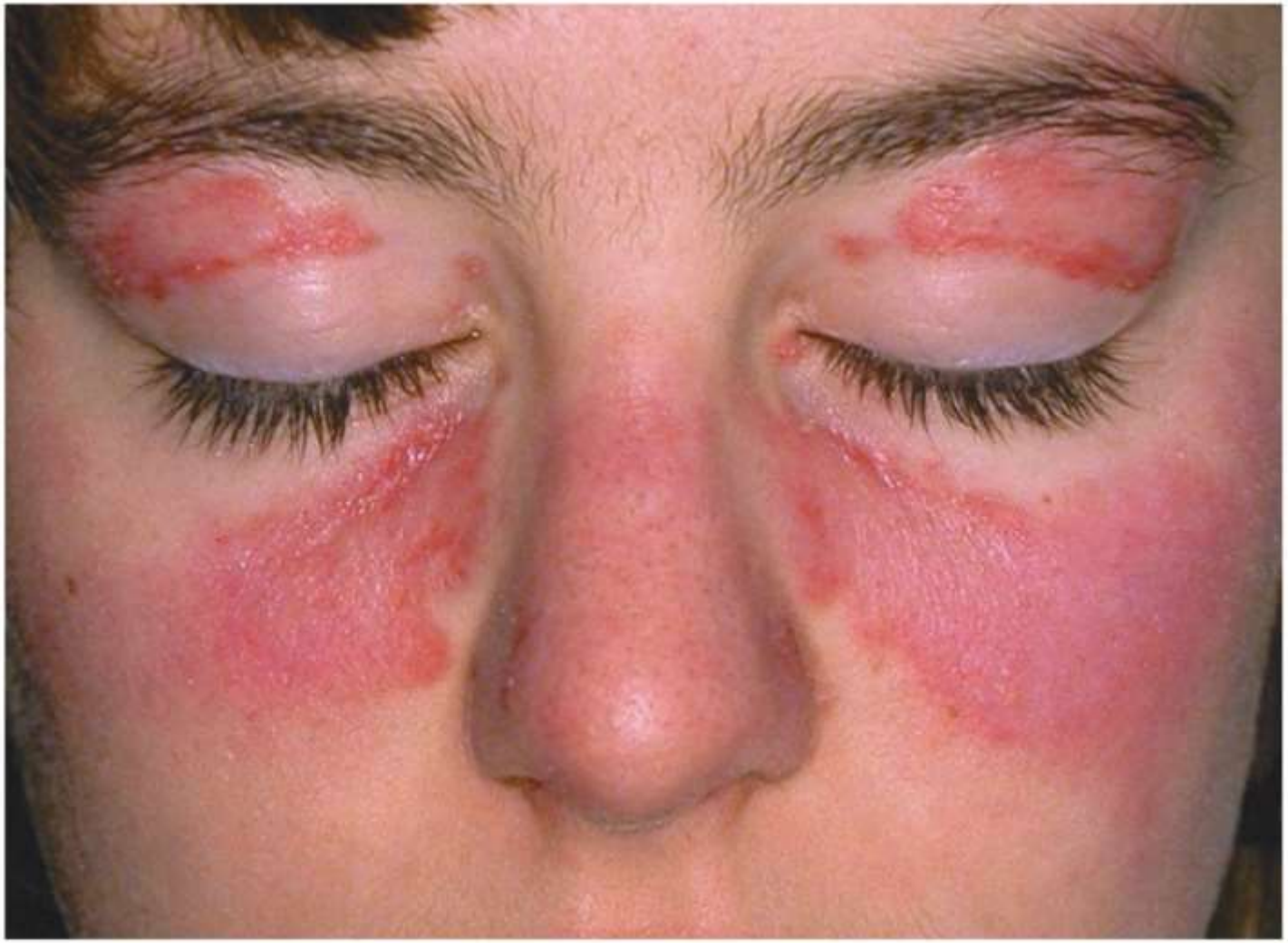
Failure of tolerance examples

- Rheumatic fever
- Glomerulonephritis (Good pasture syndrome)
- Myasthenia gravis
- Systemic lupus erythematosus

The crippling distortion of joints characteristic of rheumatoid arthritis



The characteristic facial rash of systemic lupus erythematosus



IMMUNITY AT THE EXTREMES OF AGE

WHAT IS IMMUNOSENESCENCE

- **Immunosenescence** refers to the gradual deterioration of the immune system brought on by natural ageing process.
- Progressive deterioration in the ability to respond to infections.
- This age-associated immune deficiency is common

ROLE OF THYMUS AND BONE MARROW TO TOLERATE ACQUIRED IMMUNITY

- In Thymus the T-Cells are trained to recognize own body tissue
- In thymus if T-Cells start action against antigen in thymus, soon they are destroyed by thymus endothelium
- If any lymphocyte, refusing to recognize own body tissue during pre-processing, then they are destroyed by thymus or bone marrow.

Failure of tolerance,, the Immunity problems in extremes of age

Rheumatic fever & Rheumatic heart disease

Glomerulonephritis

Myesthenia gravis

SLE , Systemic sclerosis,

Rheumatoid arthritis etc

Immunity in early age

- Physiologically slow immunity

(before birth and after birth, mother health SLE)

- Pathologically increased exposure to antigen
- Genetic disorders
- Inherited from mother

CONSEQUENCES OF AGING

- Atrophy of the thymus.
- Changes in the innate immunity
- Changes in the function of both B and T cells.
- Changes in both the total numbers and subsets of lymphocytes
- Changes in the patterns of secretion of cytokines and growth factors.
- Disruption of intracellular signaling.

IMPACT OF ADVANCING AGE ON INNATE IMMUNITY

Aged phagocytes include a reduced expression of Toll-like receptors on macrophages.

There is a decline in the phagocytic capacity and reduced superoxide anion production (ROS) in macrophages and neutrophils in the aged.

Activation of neutrophils by formyl-methionyl-leucyl-phenylalanine (fMLP) is impaired in old compared to young , linked to a reduction of intracellular Ca^{2+}mobilization.

INFLAMM-AGEING

Ageing is associated with the increased production of pro-inflammatory cytokines(IL-1 and $TNF-\alpha$) by macrophages and fibroblasts.

For example.

Elevated levels of these mediators are responsible for the age-associated diseases such as diabetes, osteoporosis and atherosclerosis hence called Inflammatory Pathogenesis.

The emerging evidence suggests that the balance between pro- and anti-inflammatory cytokines i.e (IL-4, IL-6, IL-10, IL-11, and IL-13) is disturbed.

Natural Killer cells:

- Impaired NK-cell cytotoxicity and reduced production of cytokines and chemokines by activated NK cells.

- Expansion of different NK-cell subsets because there are reports that in the elderly there is an increased proportion of the $CD56^-$ NK-cell subset compared to more abundant $CD56^+$ NK-cell subset.

Cellular Immunity in the Elderly

- Altered T cell phenotype
  - ↓ naïve T cells; ↑ memory T cells

- Reduced T cell responses
  - ↓ response to TCR stimulation
  - ↓ T cell proliferation
  - ↓ expression of IL2-R
  - ↓ IL2 production

IMPAIRED B CELL DEVELOPMENT

HSC in the bone marrow give rise to early B cells through common lymphocyte precursors.

These common lymphocyte precursors become Pro-B cells in the bone marrow by immunoglobulin heavy-chain gene rearrangements and subsequently differentiate into Pre-B cells.

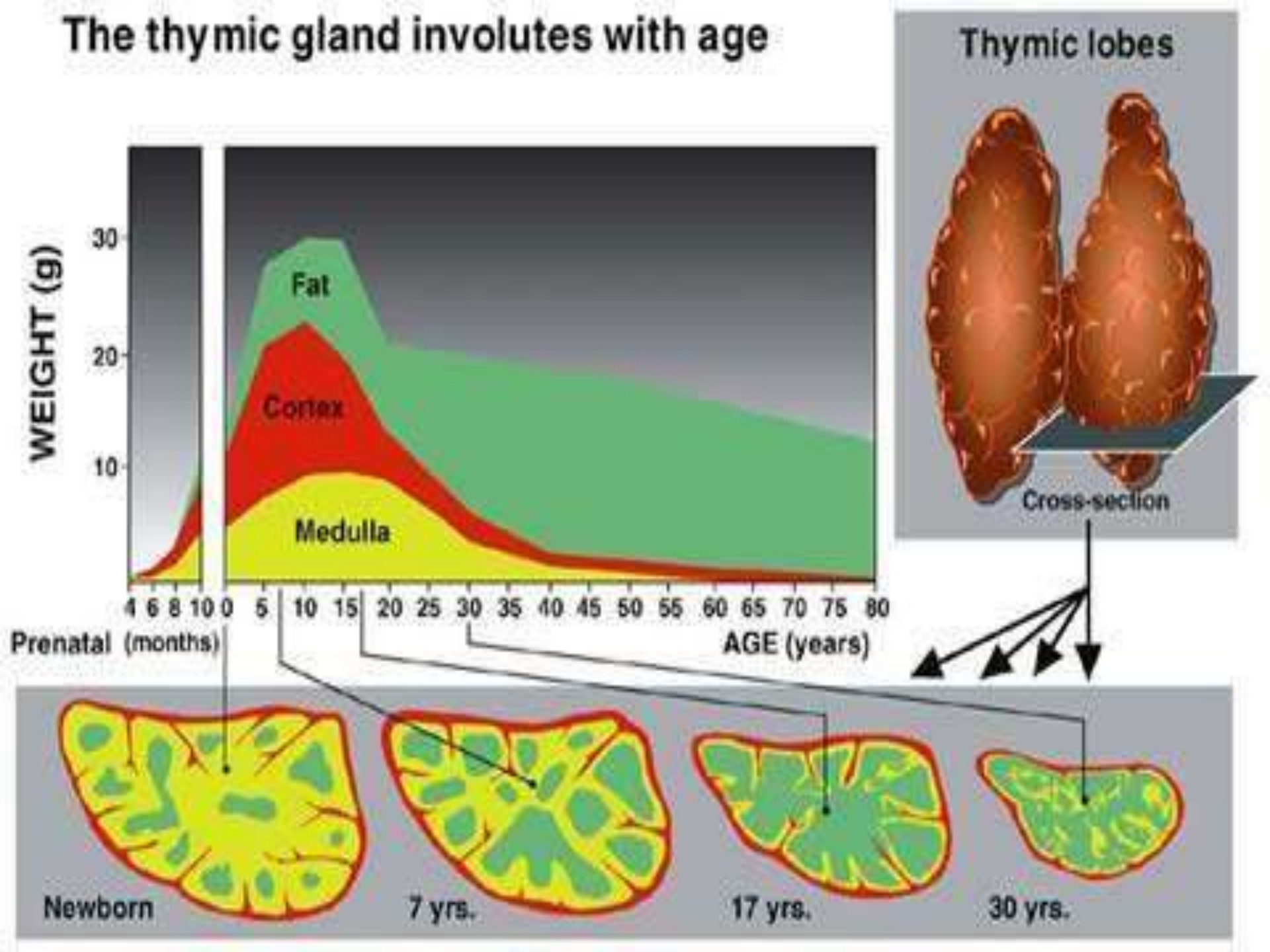
Transition to Pro-B cell and Pre-B cell stages are dependent upon the activity of recombination activating gene (*RAG1* and *RAG2*).

Which are defective in old age.

THYMIC INVOLUTION

Thymic involution the shrinking of the thymus with age, resulting in changes in the architecture of the thymus and a decrease in tissue mass.

The thymic gland involutes with age



TREATMENT

- One successful therapy is Bone Marrow Transplantation(BMT).
- Hormone therapies for innate age-associated dysfunctions,

  for example DHEAS supplements (*Dehydroepiandrosterone - DHEA*)are able to enhance superoxide production in neutrophils and can increase NK-cell activity
- Gene therapy can treat immunological disorders in old and immunodeficient individuals.
- Blocking IL-1 or TNF has been highly successful in patients with rheumatoid arthritis, inflammatory bowel diseases.Agents such as TNF-neutralizing antibodies, soluble TNF receptors, and IL-1 receptor antagonist have been infused into > 10,000 patients.

Conclusions

- Immunosenescent changes particularly affect T cell populations and function
- Immunosenescence affects the response to vaccines
- Vaccine-induced antibody responses wane rapidly in the elderly
- Better vaccine efficacy in the elderly may require (i) improved immune responsiveness and (ii) changes to vaccine formulation
- Herd immunity applies to the elderly as well as to the young

What can be done to better protect the elderly?

- Immunosenescence is not a random deteriorative phenomenon, rather it appears to inversely repeat an evolutionary pattern.

- Immunosenescence can also be sometimes happen as the result of the continuous unavoidable exposure to a variety of antigens such as viruses and bacteria.

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Imbalance between ***inflammatory and anti inflammatory*** materials in old age.

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Natural Killer cells:

Impaired NK-cell cytotoxicity and reduced production of cytokines and chemokines by activated NK cells.

Impared B-Cells development and reduced production of antibodies, which depends on recombinant activating genes *(RAG-1 and RAG-2) Recombinant antigen gene 1 & 2*

TWO MECAHNISMS RESPONSIBLE FOR IMPAIRMENT

1) Decreased production of long-term immunoglobulin-producing B lymphocytes because of intrinsic and microenvironmental defects in bone marrow.

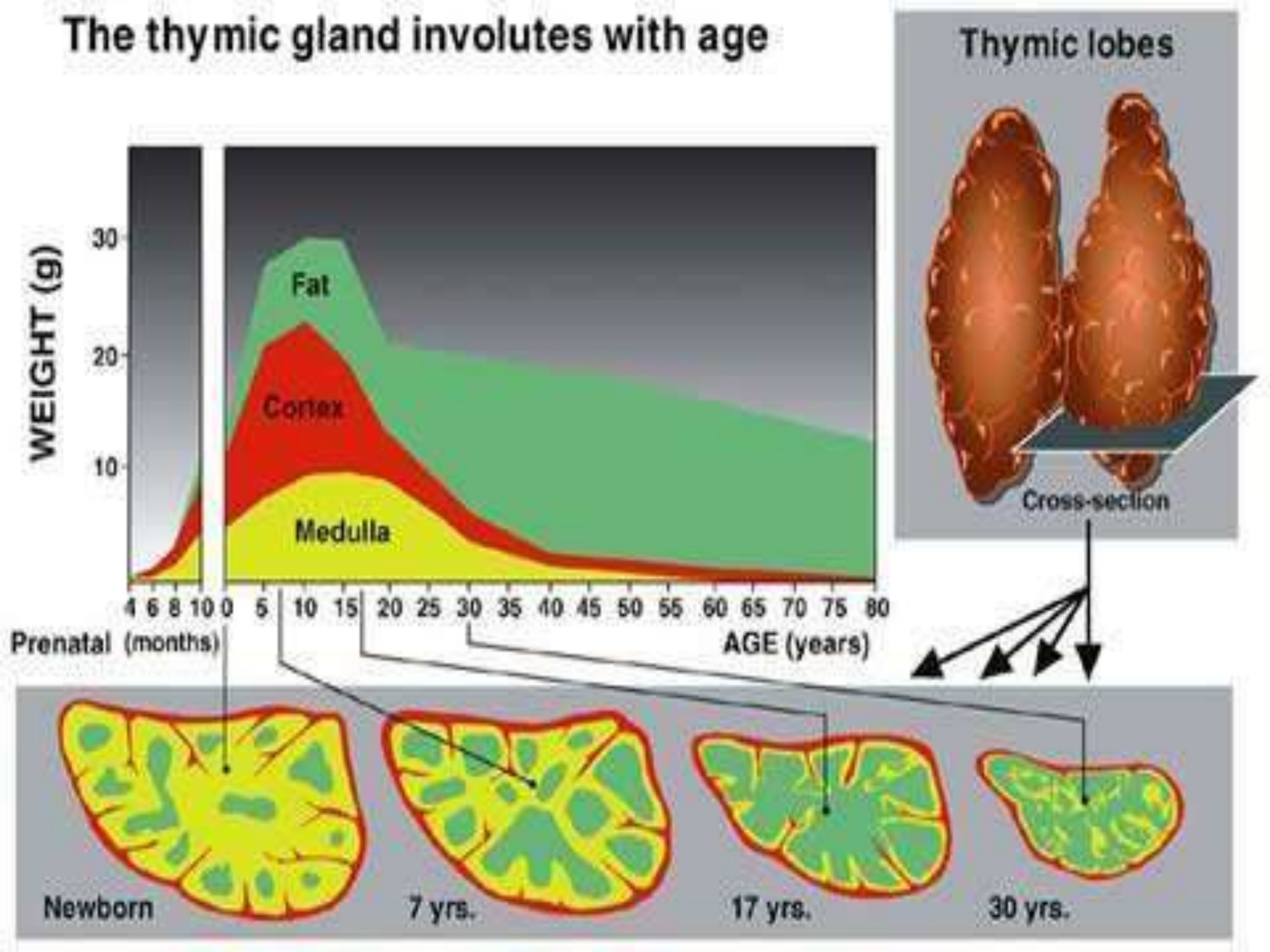
(2) The loss of immunoglobulin diversity and affinity. Reduced activity of trancription factor

THYMIC INVOLUTION

Thymic involution

the shrinking of the thymus with age contribute to weaker immunosurveillance of the elderly

The thymic gland involutes with age



T Cell defects in ageing

- General decline in T cell immunological functions
- Decreased T cell response to infections
- Decline in new cell formation
- Disturbed proportion in Memory cell, active and native cells
- Defective apoptosis and accumulation of senescent T cells

IMMUNIZATION AND VACCINATION

Immunization

- To establish an immunity through primary, secondary and tertiary exposure through a processed specific antigens, by injections or oral

May be natural or artificial

- **Active immunization**
- **Passive immunization**

Active Immunization

A. Natural (any specific infection)
B. Artificial, by injection or oral

1. Living but attenuated organisms
   (small pox,measles, polive etc)
2. Dead and non pathogenic organisms
   (typhoid, whooping cough, dephtheria)
3. Inactivated toxins
   (Tetanus, botulism)

Passive Immunization

A. Natural from mother to baby

B. Transfusion of pre-formed antibodies or T Lymphocytes to a person for temporary protection is called passive immunization

These a/b or T cells are taken from another person or animals and give protection for 2, 3 weeks to 8,10 weeks.

THANK YOU