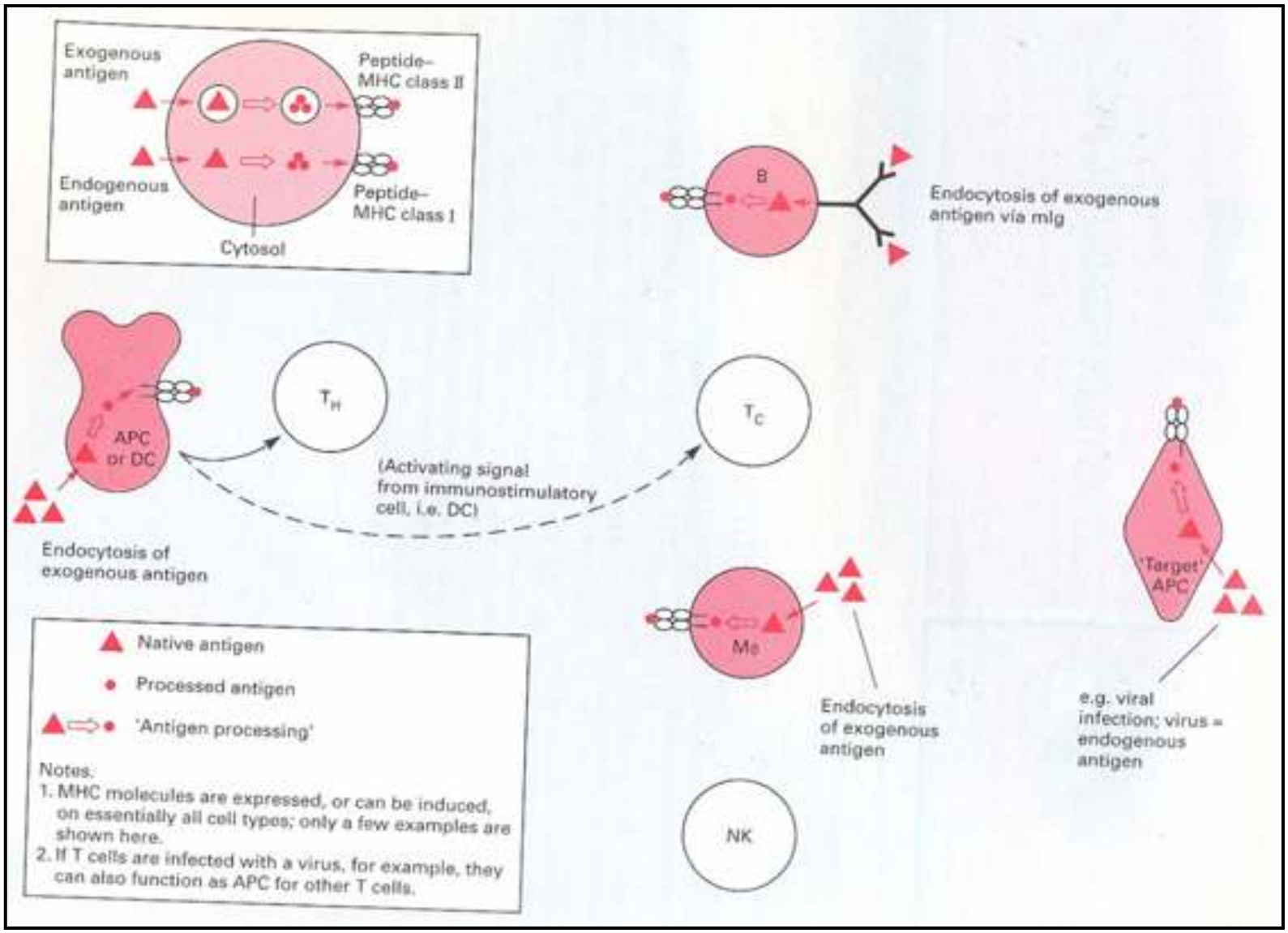
ANTIGEN PRESENTATION.

***Learning Objectives*.**

To be able to learn about:

- T cell recognition of processed antigens.
- Presentation of exogenous antigens by macrophages.
- Presentation of exogenous antigens by B lymphocytes
- Presentation of endogenous antigens by fibroblasts and other cells
- Peptide-MHC interaction.



Scheme of antigen presenting cells.

ANTIGEN PRESENTATION.

Macrophages take up and destroy an immense variety of particles and molecules.

They phagocytose antigens, digest them and then present immunogenic molecules to the lymphocytes.

Hence called antigen presenting cells

- Macrophages express MHC class II molecules that are required for antigen recognition by helper T cells.
- Macrophages also produce cytokine (called lymphocyte activating factor)- also known as IL-1.
- IL-1 can trigger lymphocyte proliferation, by stimulating the secretion of IL-2 from the activated T cells (fig. 2).

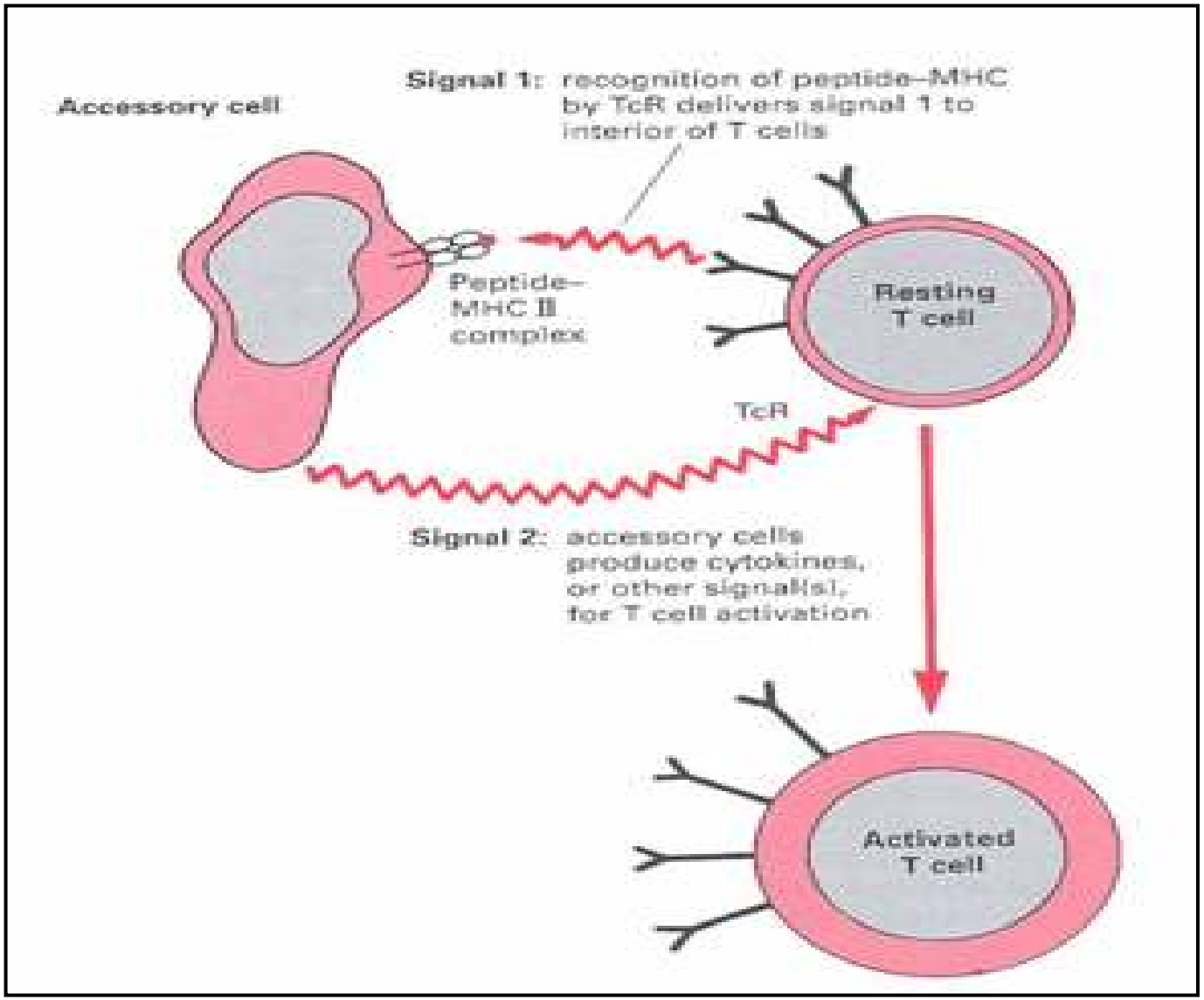


Fig. 2. A "two signal" hypothesis for T cell activation

- Ags are taken up by ag-presenting cells, processed from their native form and presented in association with MHC class II molecules to specific helper T cells.
- This provides the first signal for T cell activation.
- The ag-presenting cells then elaborate one or more soluble molecules (IL-1) that provide the second signal also required for T cell activation.

- Once helper T cells are activated, they can help B cells make antibodies and cytotoxic T cells to develop from their precursors, thus triggering the effector stage of immune response.

NOTE

- The discovery of dendritic cells (*steinman and Cohn 1973*) challenged the above scheme of MΦ as the accessory cells for ag presentation.
- Dendritic cells contained within many adherent MΦ populations from lymphoid tissues (fig.3.) are actually the cells stimulating lymphocyte response to presented antigens.

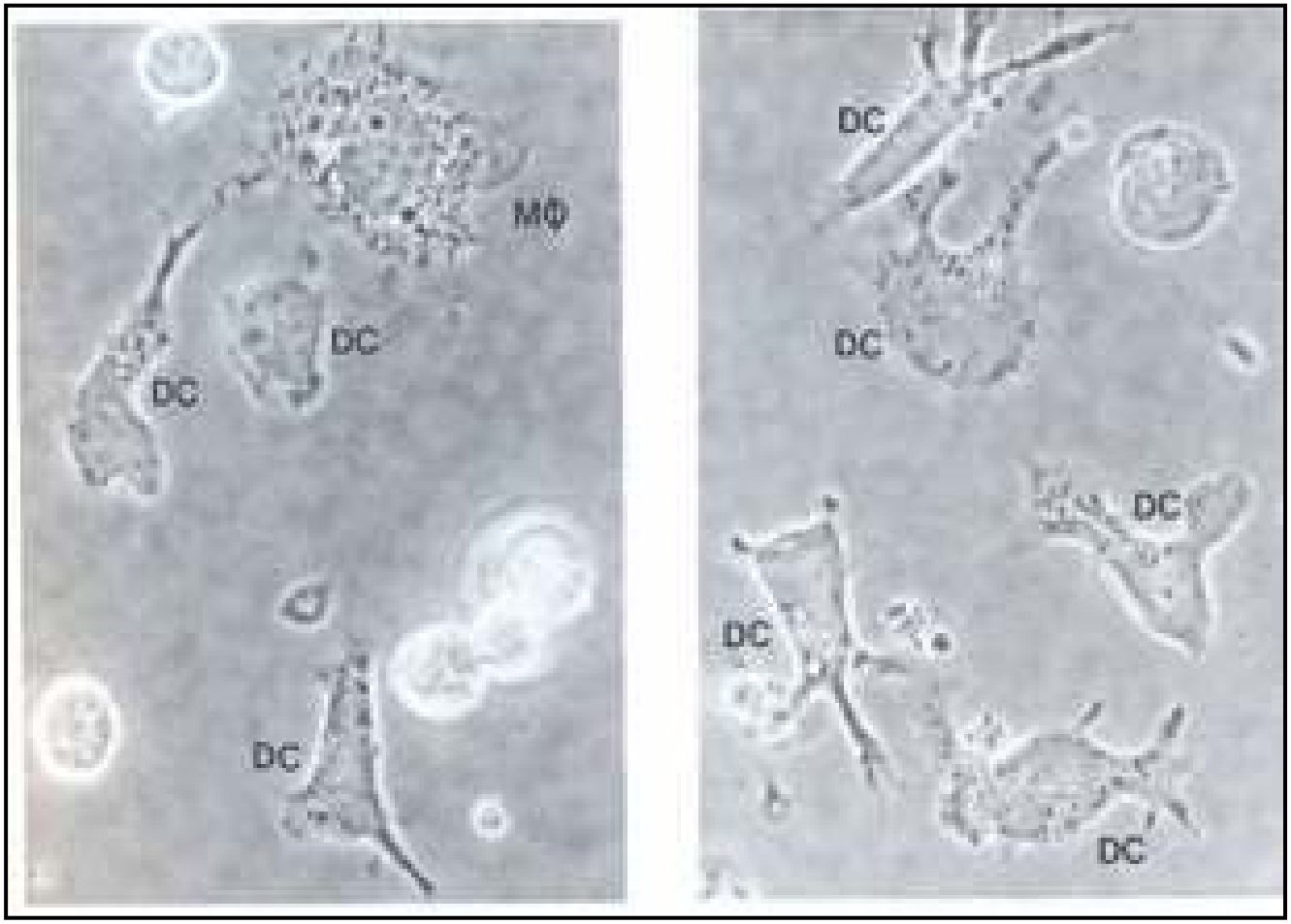


Fig. 3. A population of adherent accessory cells.

- Dendritic cells are required to deliver a particular activation signal(s) to resting T cells that cannot be supplied by most other cell types, as well as being able to present the relevant antigens.

- Once the T cells have been activated, they can respond to any other cell type expressing the same antigen-MHC complex.

- This stimulation of T cells is termed immunostimulation, and dendritic cells are therefore called immunostimulatory cell.

- However, most cells in the body (including dendritic cells) may be able to present antigens to activated T cells and thus act as antigen-presenting cells (fig. 4).

- The term accessory cell can be used for any cell that is required together with antigen to stimulate a lymphocyte response, and it thus encompasses both antigen-presenting cells in general as well as specialized immunostimulatory cells.

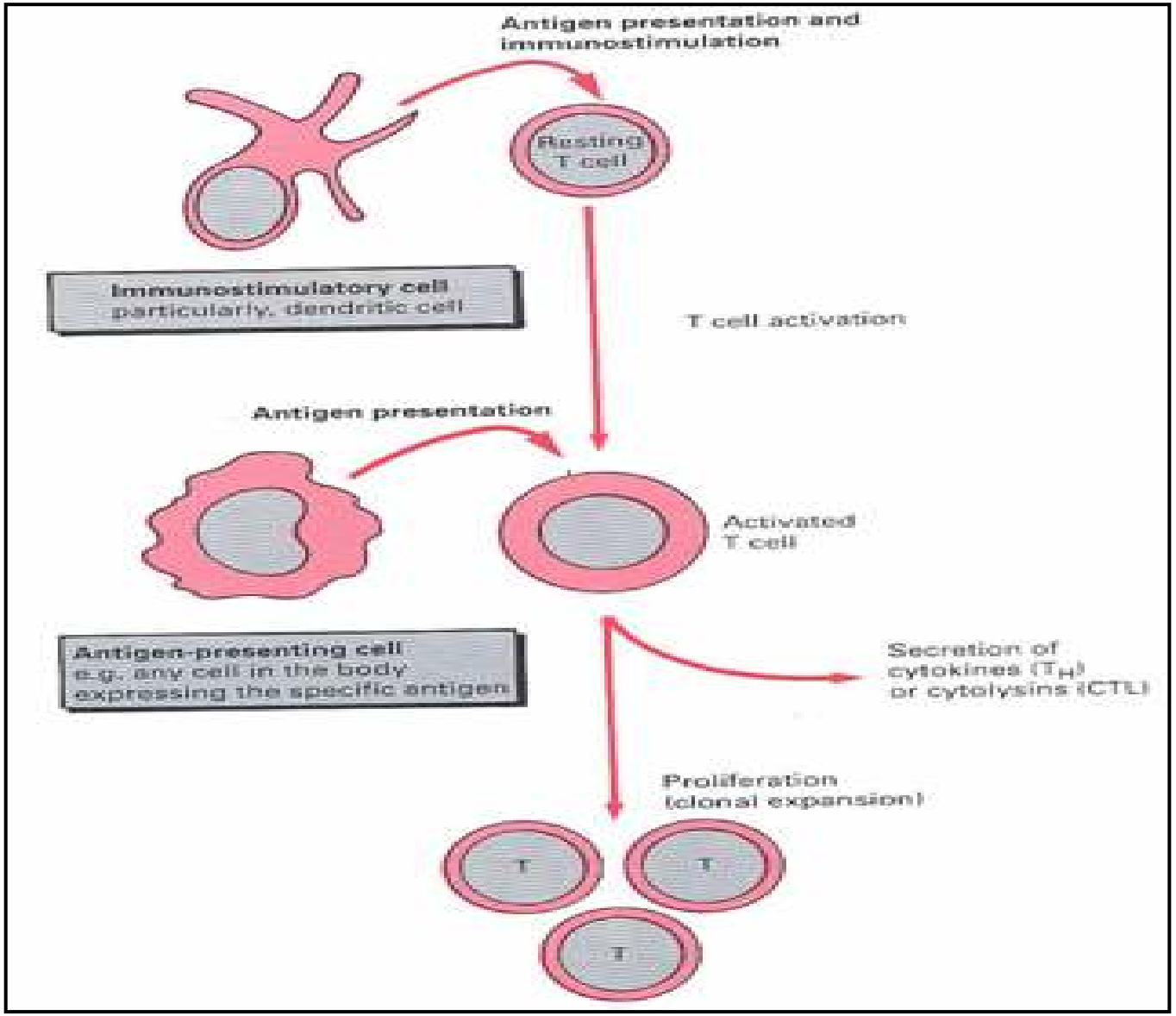


Fig.4. Accessory cells.

Ag-presenting cells.

- Any cell that expresses peptide-MHC complexes that can be recognized by specific T cells.

Ag processing and presentation.

T cell recognition of processed antigens.

- Before it was realized that lymphocytes could be subdivided into T cells and B cells, immune responses had been categorised as 'cellular' and 'humoral' responses.
- Evidence later emerged that different forms of antigen stimulated these two types of response (fig. 5).

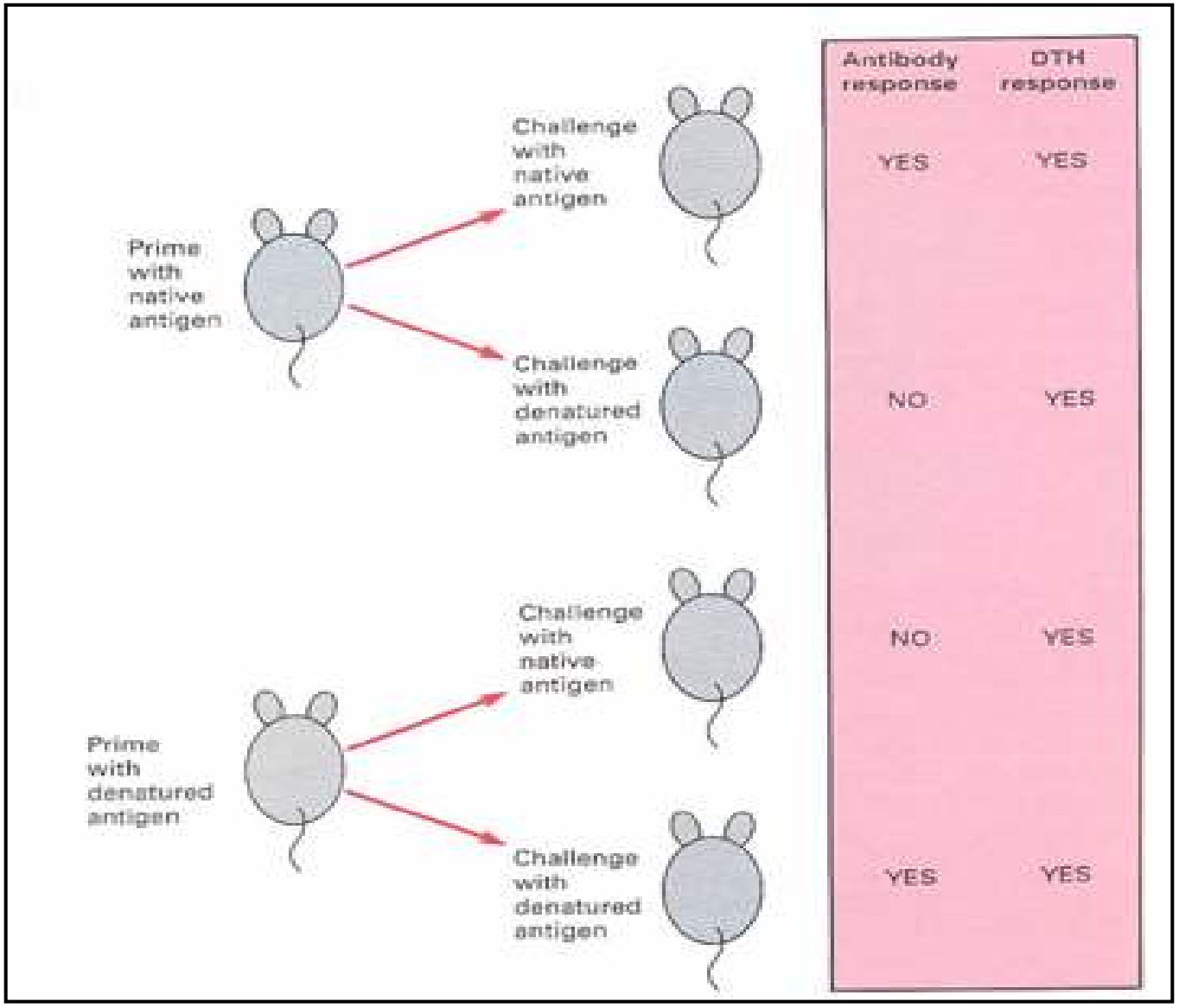


Fig. 5. B and T lymphocytes respond to different forms of antigen.

Therefore:

- Antibody response = humoral immunity- native antigens.
- T cell responses (cellular immunity) = processed antigens.

- Abs., the receptors of B cells, frequently recognize antigenic determinants or epitopes that are directly accessible in the native three-dimensional structure of antigen.
- TCRs recognize epitopes that may be exposed when the molecule is unfolded or degraded (fig.6).

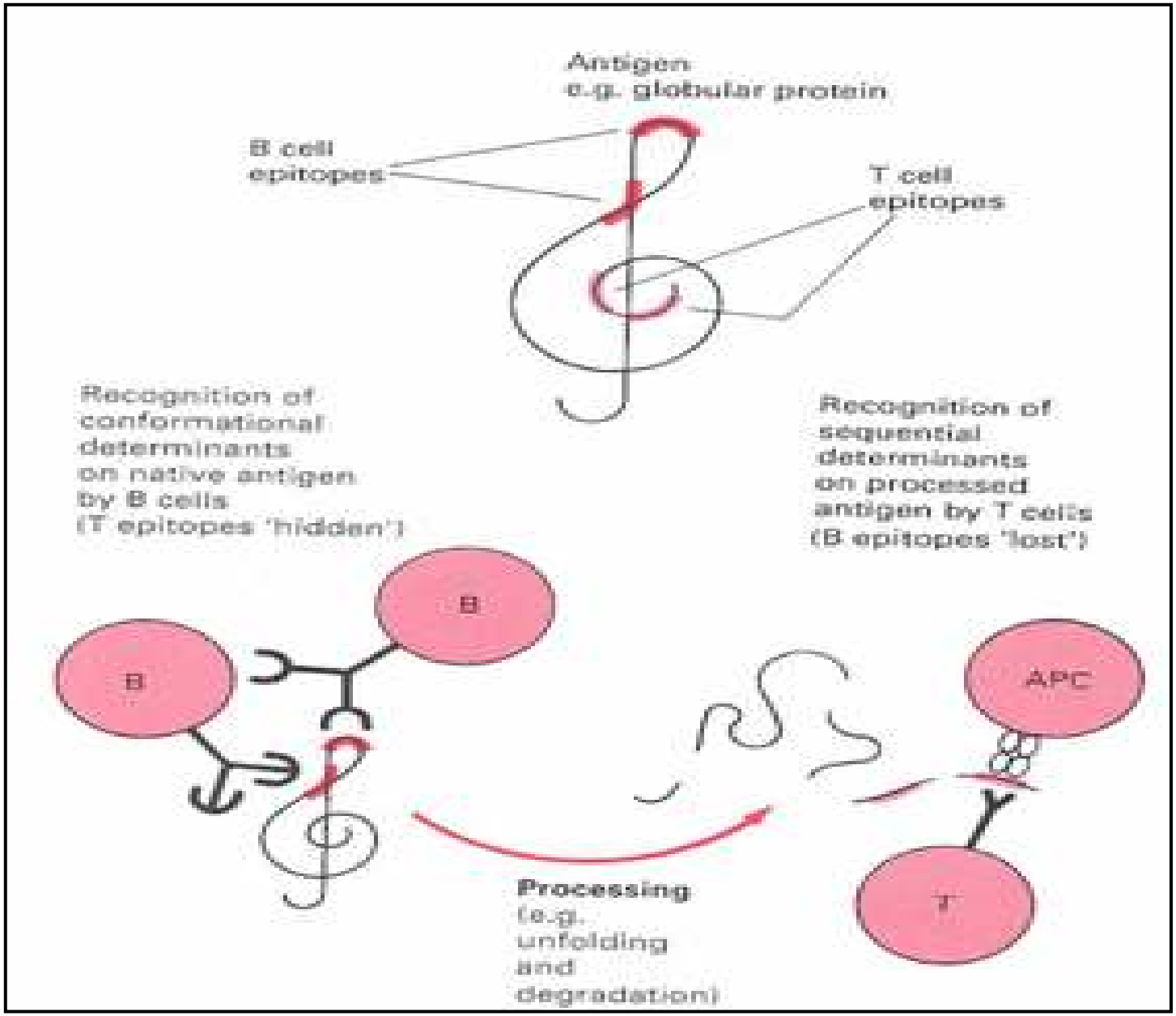


Fig.6. Epitopes for T cells and B cells.

Note.

- T_H cells recognize peptide bound to MHC II molecule on an accessory cell.

- T_C cells also recognize peptide-MHC I complexes, but the cell they recognize is more commonly referred to as a target cell.

- It now seems probable that any cell in the body can process foreign ags into peptides, some of which become bound to MHC molecules, which can then be recognized at the cell surface by T cells (fig. 7).

- Most MHC molecules at the cell surface are normally occupied by self peptides.

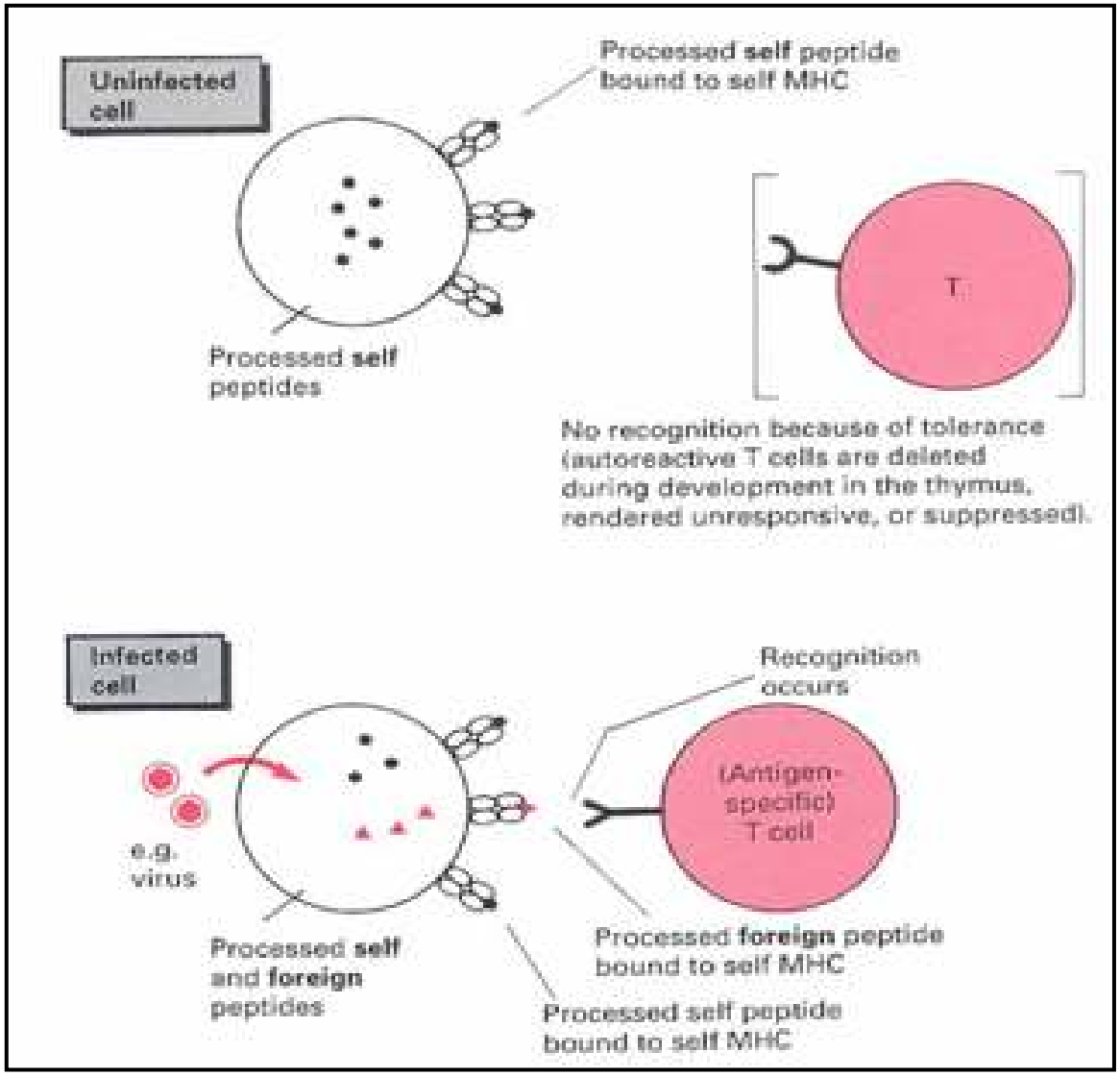


Fig.7. MHC molecules may bind a representative sample of self peptides as well as non-self (foreign) peptides, when present, for perusal by T cells.

Characterization of ags.

- Foreign ags are categorized as exogenous or endogenous, depending on whether they are derived from outside or synthesized within the cell (fig. 8).
- An example of an exogenous antigen would be a protein from a bacterium that is internalized by a cell such as a phagocyte.
- An example of an endogenous antigen is a viral protein that is synthesized within a cell after it has been virally infected.

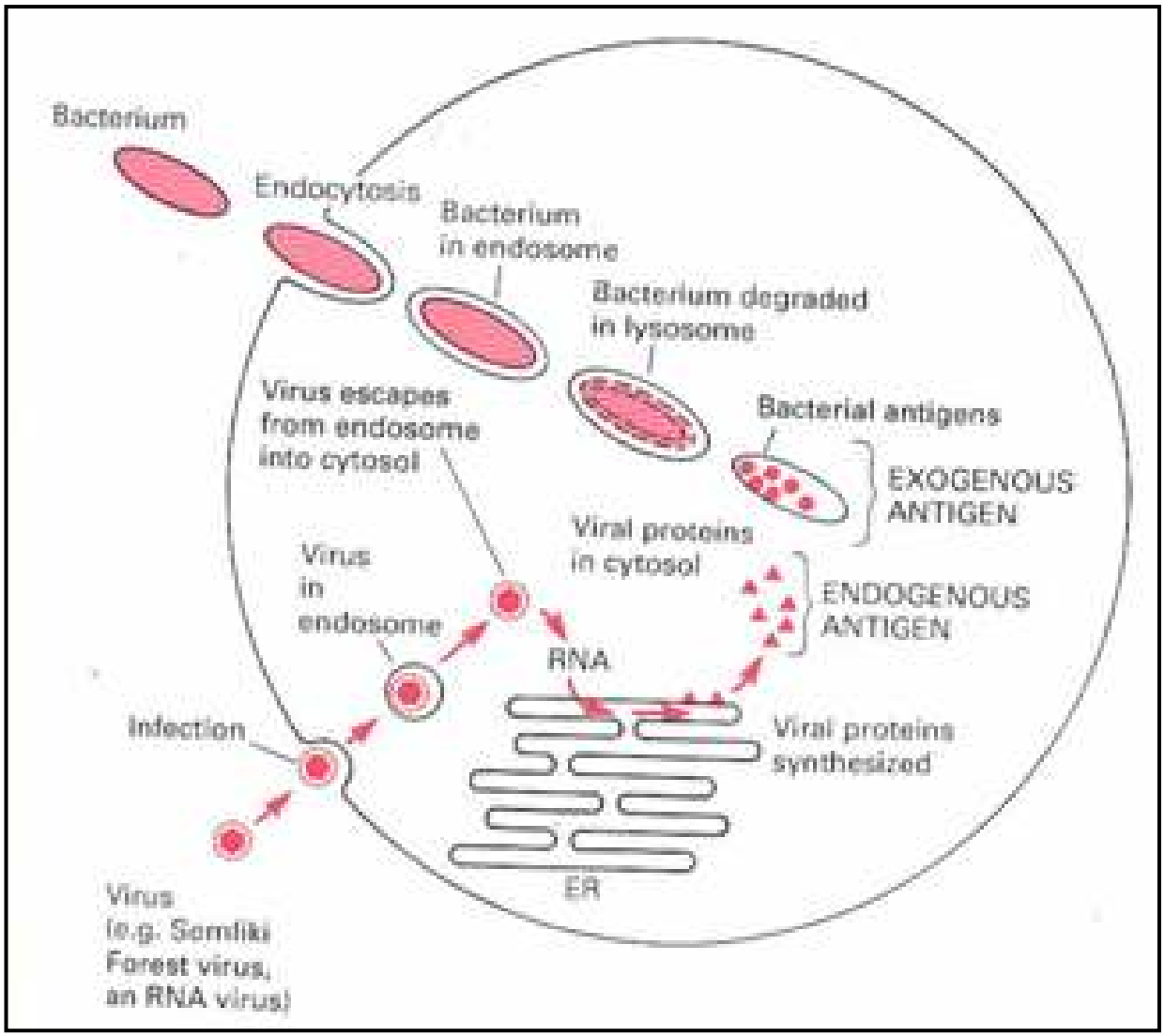


Fig. 8. Exogenous and endogenous antigens.

Ag processing.

- Is the mechanism by which the native (intact) form of an antigen is degraded to a set of peptides, some of which can bind to an MHC molecule.
- These peptide-MHC molecules may then be presented to T cells (fig 9).

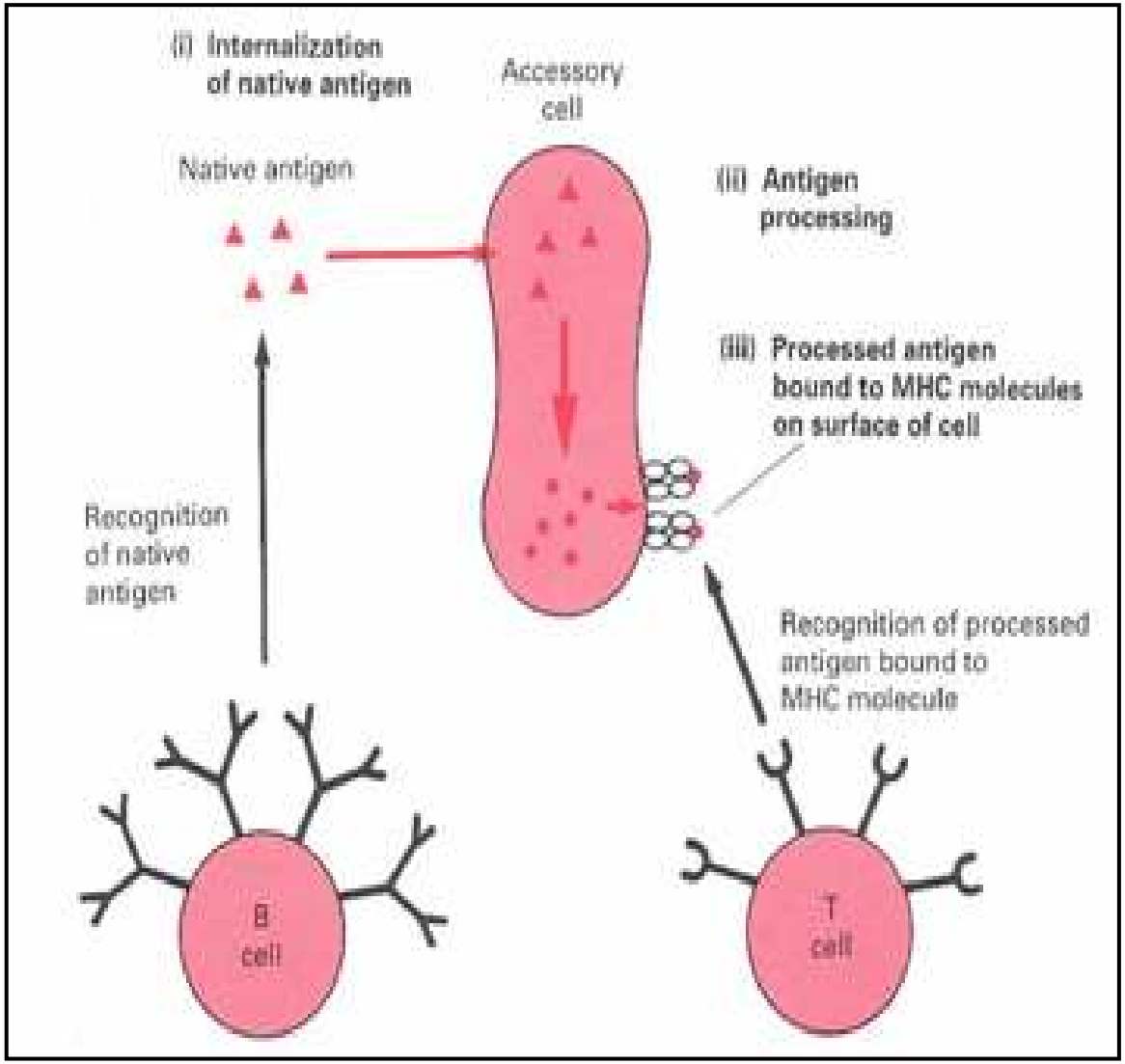


Fig. 9. An outline of antigen processing.

Presentation of exogenous antigens by macrophages.

- Endocytosis in macrophages is one example of how exogenous antigens can be taken up by cells.

Exocytosis and endocytosis:

- During exocytosis, cytoplasmic vescicles transport their contents to the plasma membrane, fuse with it, and discharge their contents to the exterior of the cell (fig.10).

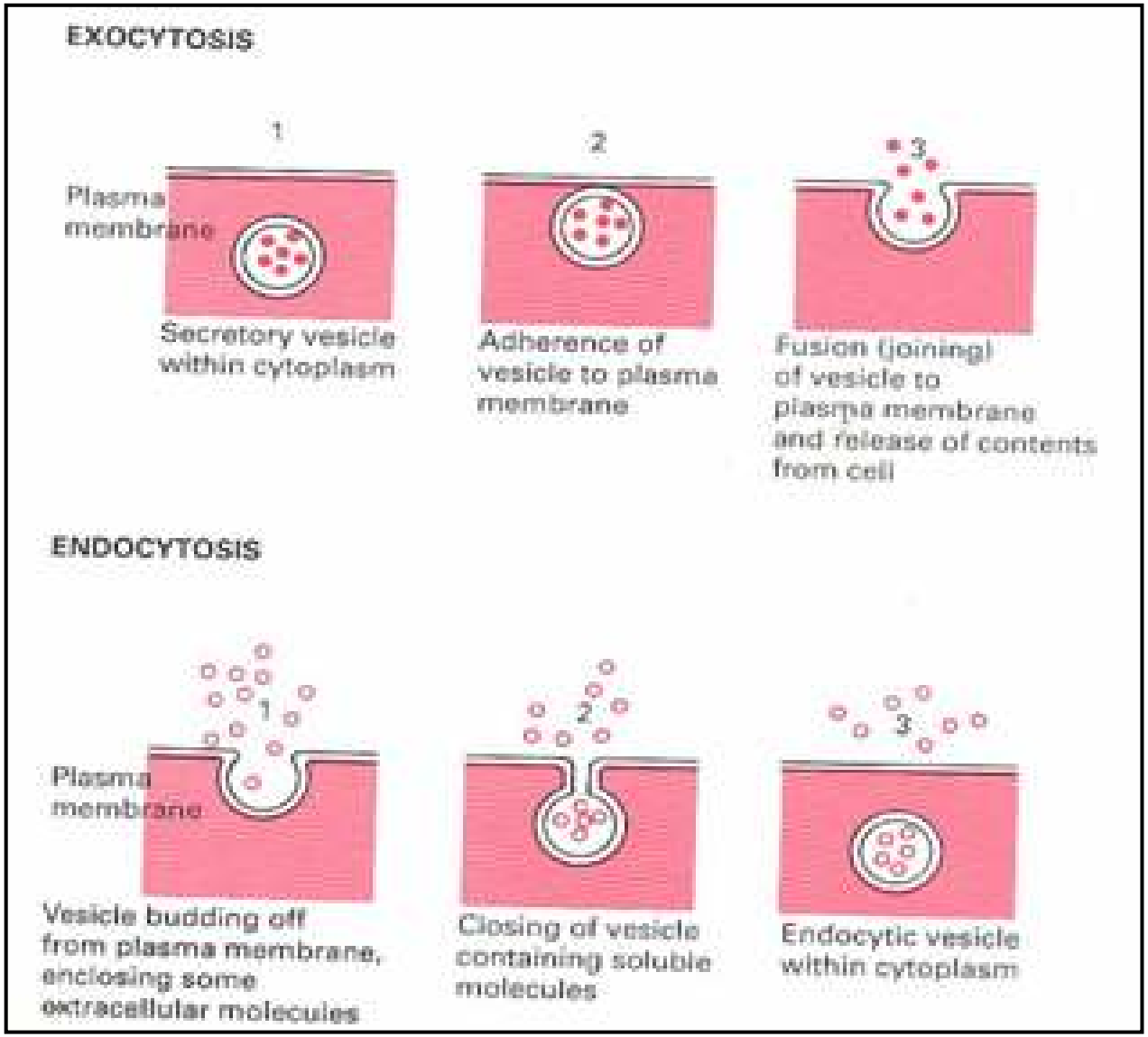


Fig. 10. Exocytosis and endocytosis.

- During endocytosis, particles and macromolecules become surrounded by portions of the plasma membrane which invaginate and pinch off to form vesicles containing the ingested material.
- Endocytosis can be divided into phagocytosis (‘cell eating’) and pinocytosis (‘cell drinking’)

- Phagocytosis occurs in specialized cell types such as macrophages and polymorphonuclear leukocytes, which are therefore called phagocytes.
- During phagocytosis, large particles like micro-organisms and cellular debris are taken into the cell within membrane-bounded phagocytic vacuoles or phagosomes.
- This uptake may be membrane mediated by specific receptors on the plasma membrane of the cell (fig.11).

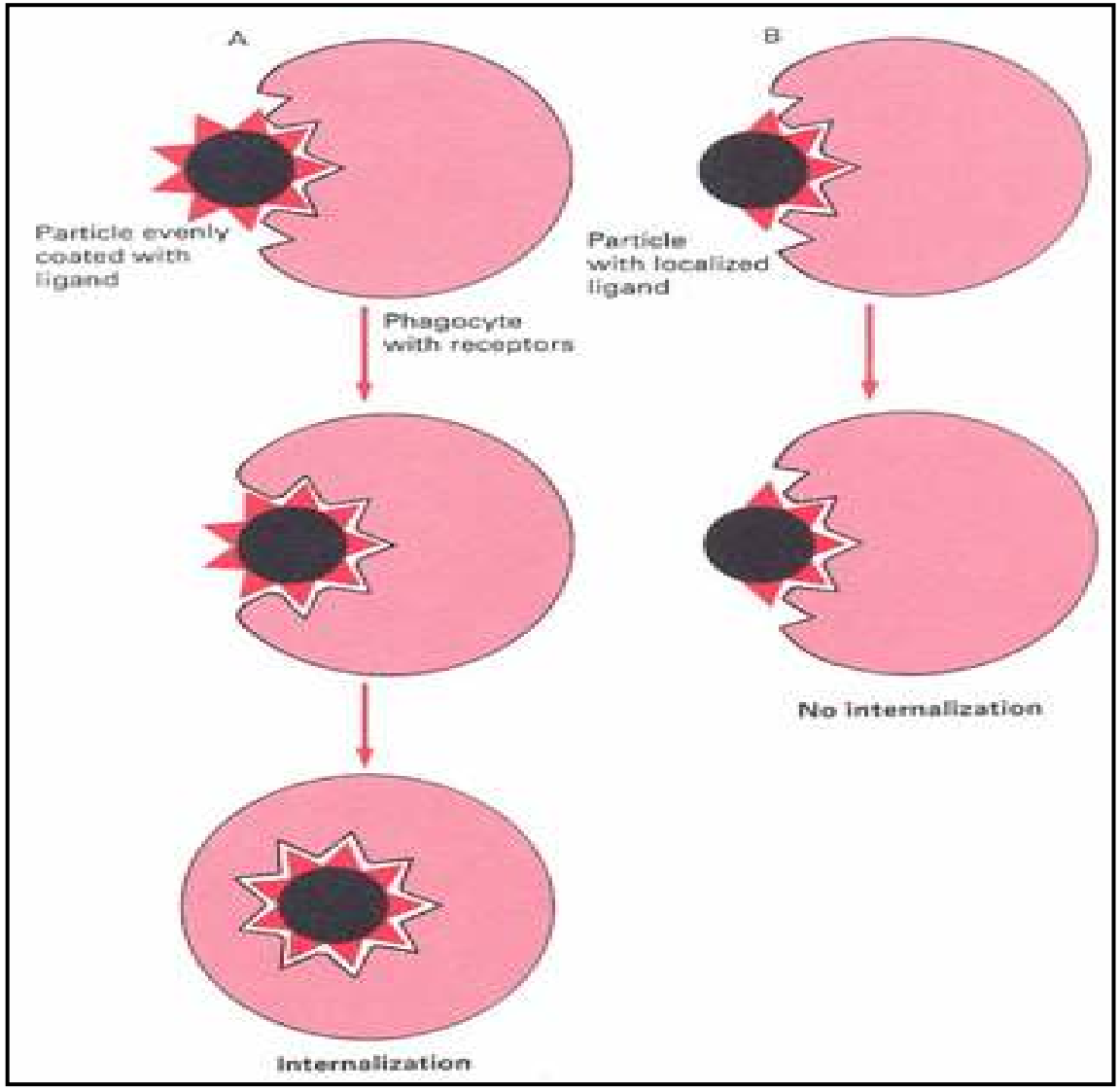


Fig.11. Evidence of a membrane-zippering mechanism of phagocytosis.

- Receptor-mediated endocytosis often occurs at specialized regions of the membrane.
- These are called coated pits because they consist of indentations in the plasma membrane that are coated with a thick material on their cytoplasmic face (fig. 12).

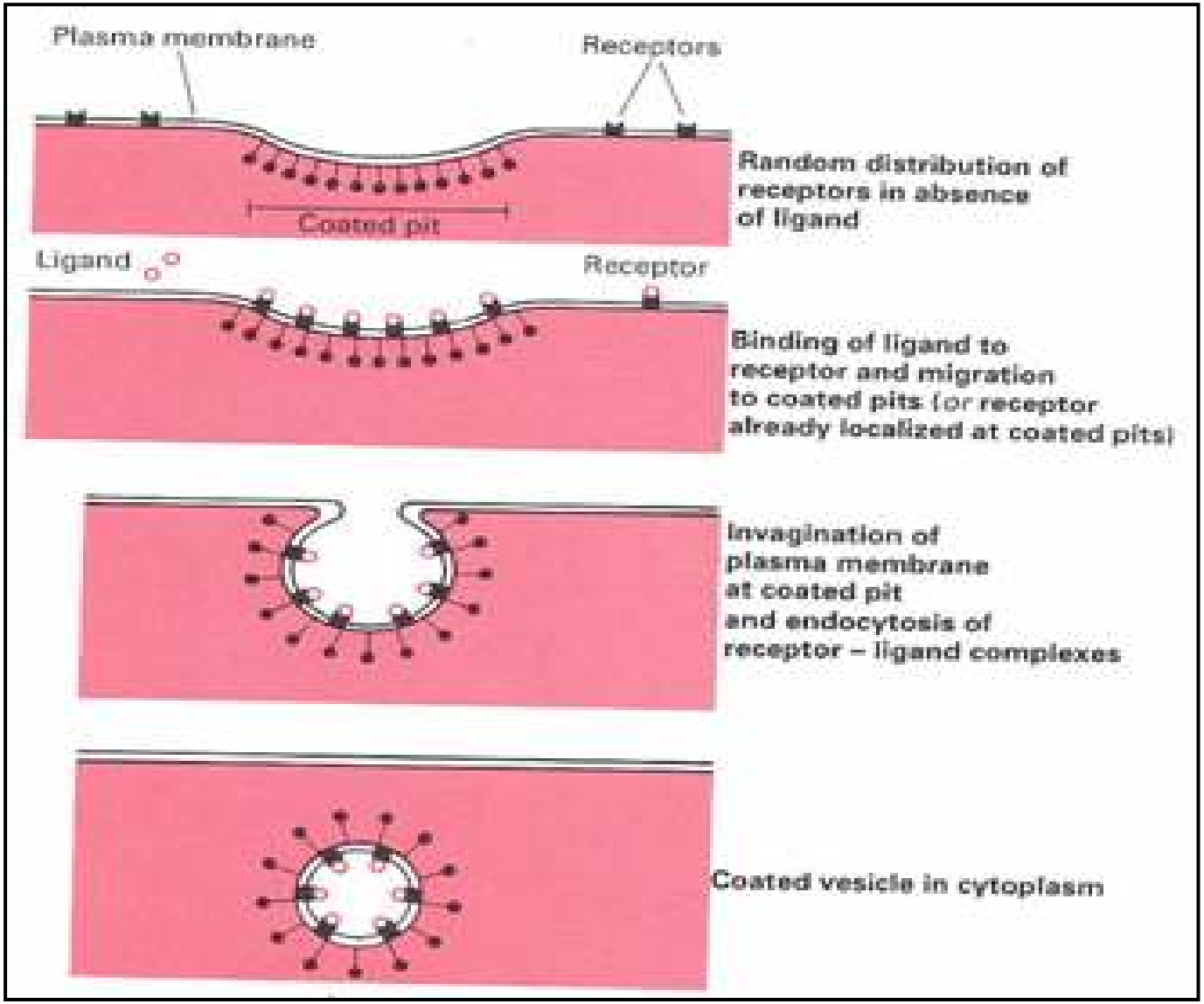


Fig. 12. Endocytosis at coated pits.

- The receptor-ligand complexes are then endocytosed in coated vesicles that are formed as the membrane in the region of the coated pits becomes invaginated.

- Once inside the cytoplasm, the coat is lost from coated vesicles and they fuse with others to form larger vesicles called endosomes (fig. 13).

- Endocytosed contents are transferred sequentially from coated vesicles to early endosomes, late endosomes, and endolysosomes and/or terminal lysosomes.

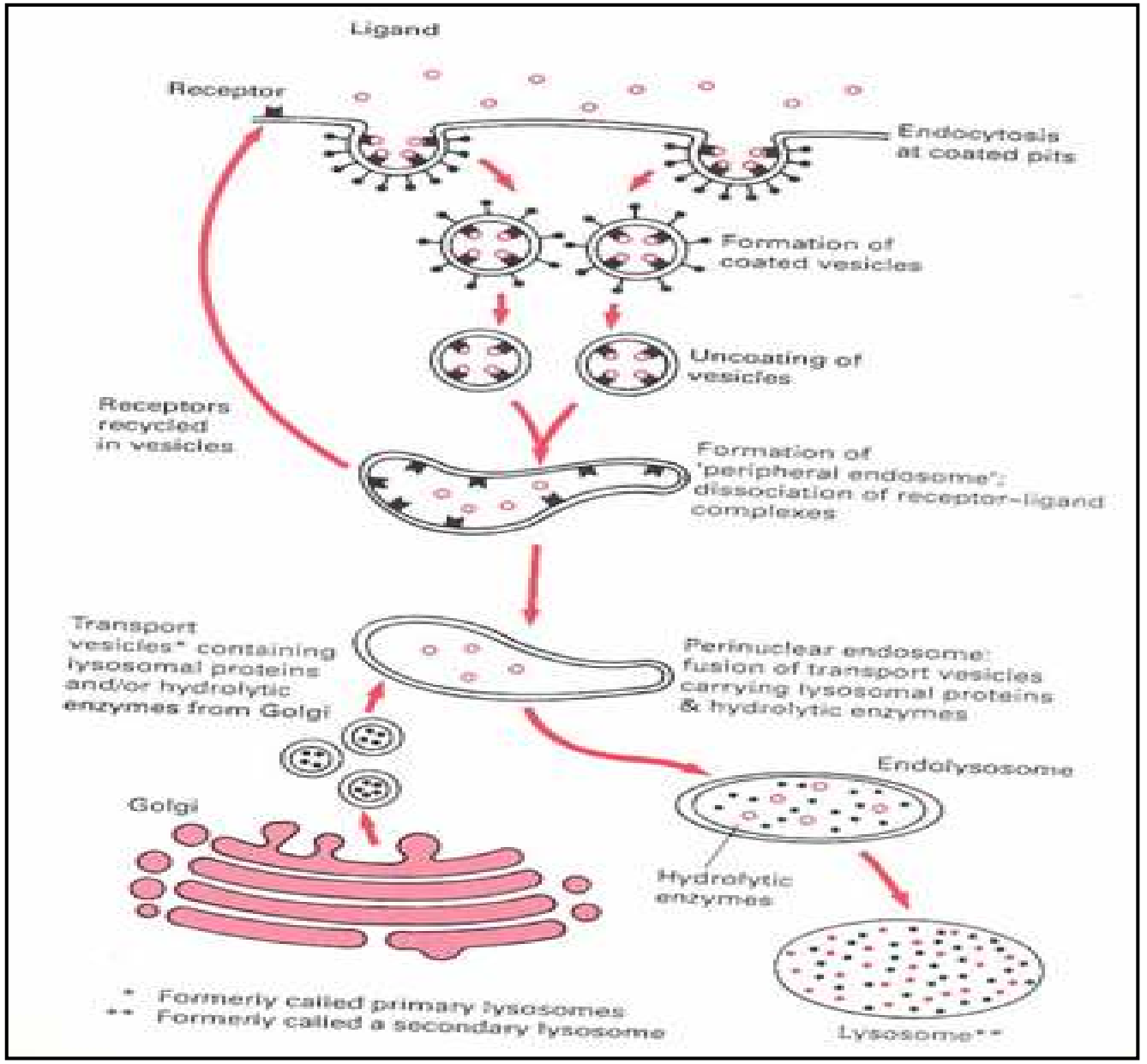


Fig. 13. Endocytosis at coated pits and delivery to lysosomes.

Endocytosis in macrophages.

- MΦs have surface receptors that enable them to internalize particles by receptor-mediated endocytosis (fig. 13).

The receptors involved in this process include:

- Fc receptors- bind particles and ags complexed to certain classes of ab.
- Complement receptors which bind complement-coated particles; and
- Sugar-specific carbohydrate recognition systems, such as the manosyl-fucosyl receptor through which glycoproteins and particles like yeasts can be endocytosed.

Membrane receptors recycled.

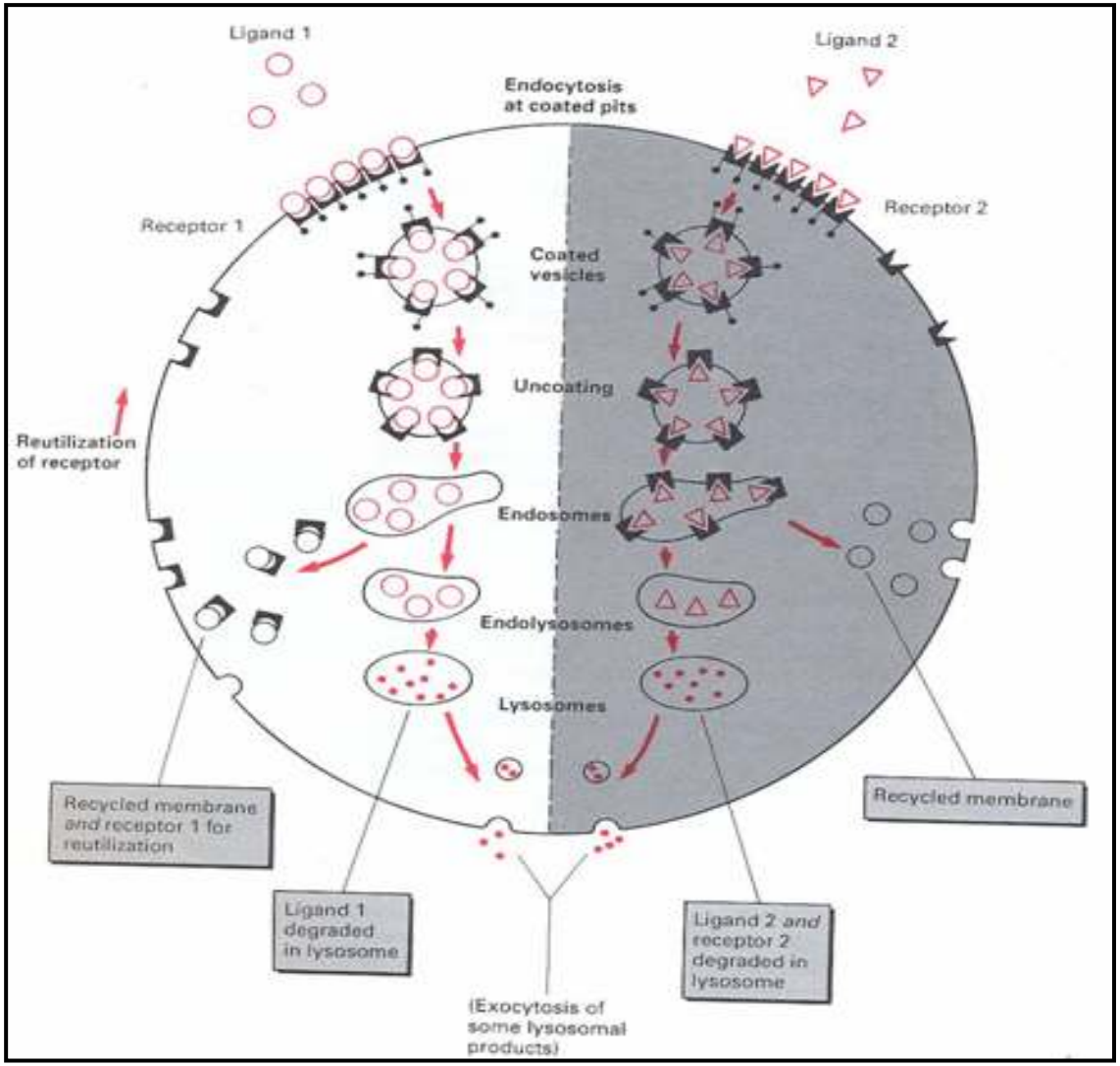


Fig.14 . Recycling of membrane and of some receptors.

Ag presentation by MΦs

- An antigen-dependent and temperature dependent lag phase is required for processing the bacterial ags to a form that could be recognized by the T cells (fig. 15).
- However, denatured antigens or fragments may not need cellular processing (fig. 16).

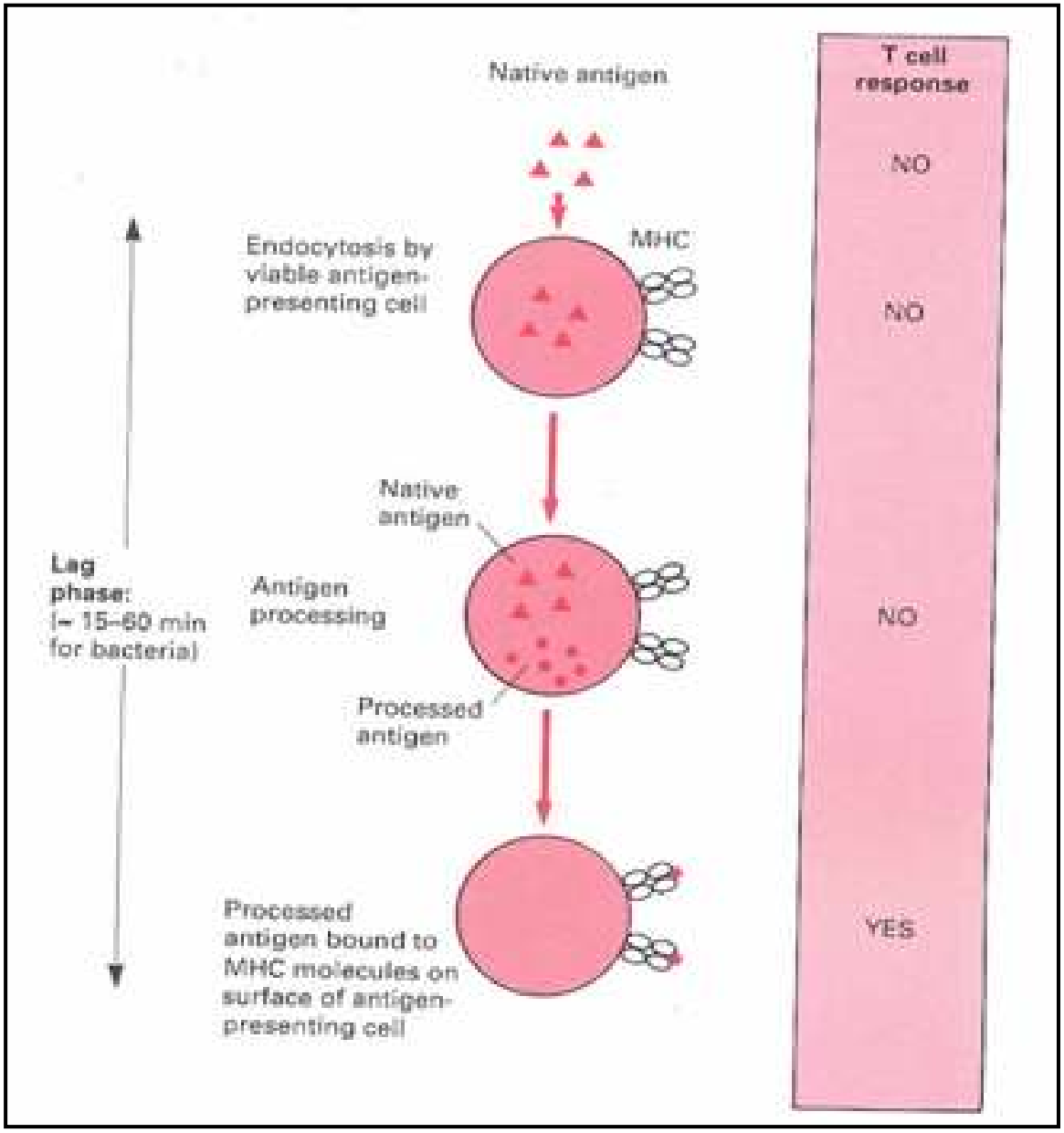


Fig. 15. A 'lag phase' in antigen processing.

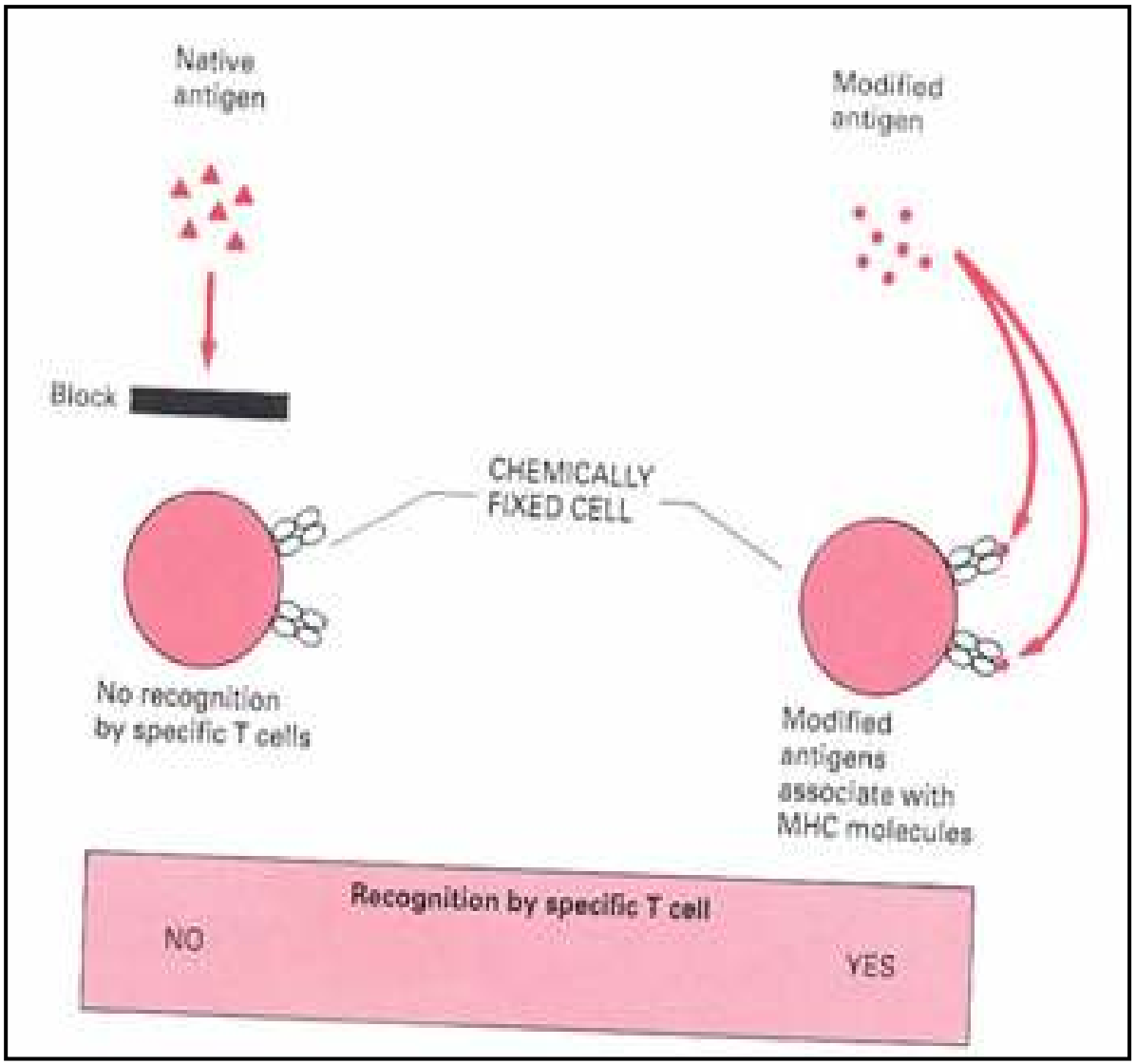


Fig. 16. Fixed accessory cells can present modified (e.g. degraded) forms of antigen, but not the native antigen.

Ag processing by macrophages.

- Exogenous ags are endocytosed and processed intracellularly within an acidic compartment which is lysosomal or perhaps prelysosomal in nature.
- Ag processing results in some degree of unfolding or cleavage of the native molecule, and in most cases almost certainly the production of peptides (fig. 17).
- Some of these peptides become bound to MHC molecules and are transported to the cell surface where they can be recognized by specific T cells.

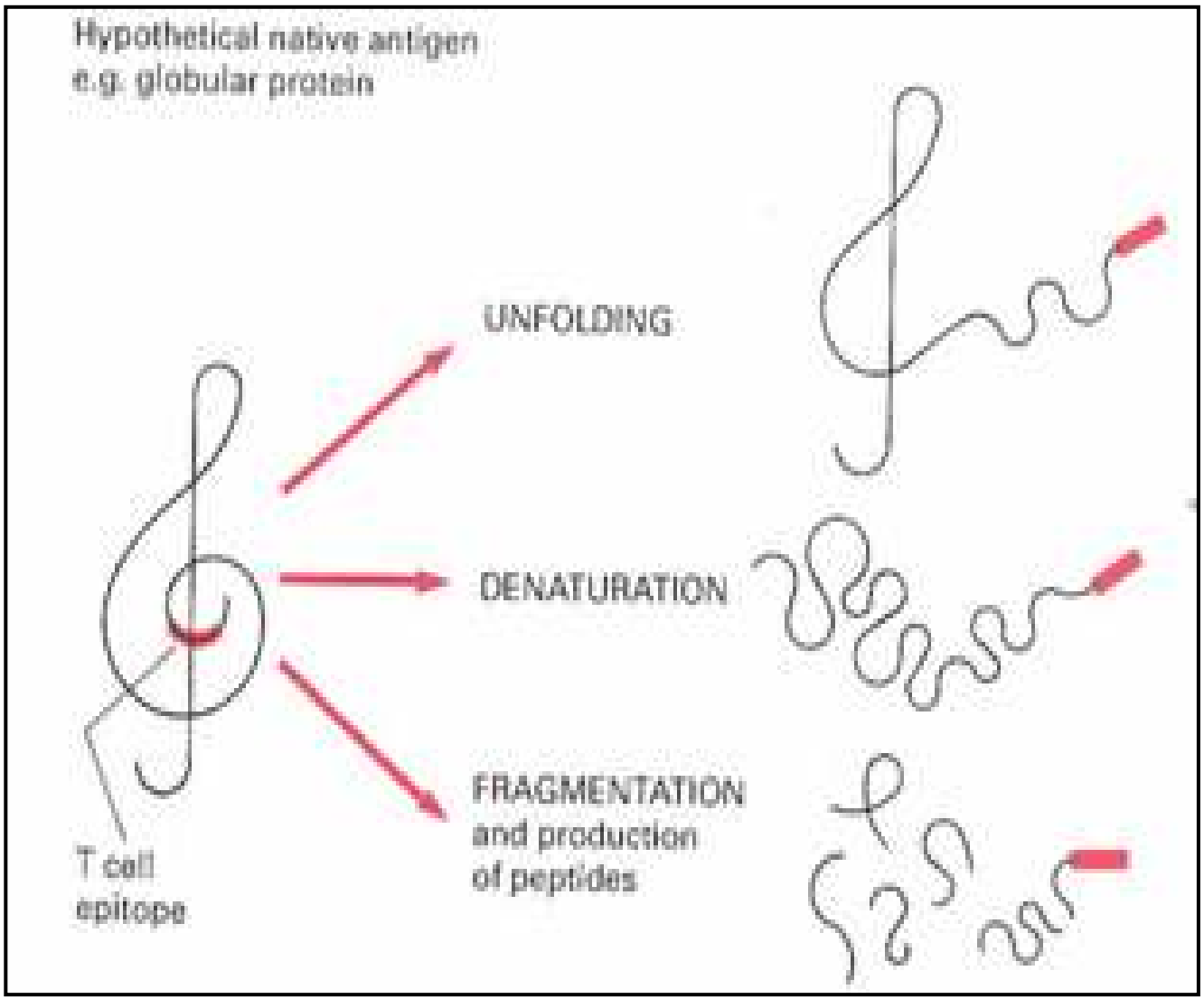


Fig. 17. Presumed conformational changes during antigen processing.

Processing and presentation of exogenous ags by B lymphocytes.

- Although B cells are non-phagocytic, there are two or more routes by which they can endocytose ags. (fig.18).

➢ Via non-specific pinocytosis and,

➢ Via their specific antigen receptors (membrane-bound abs; Igs)

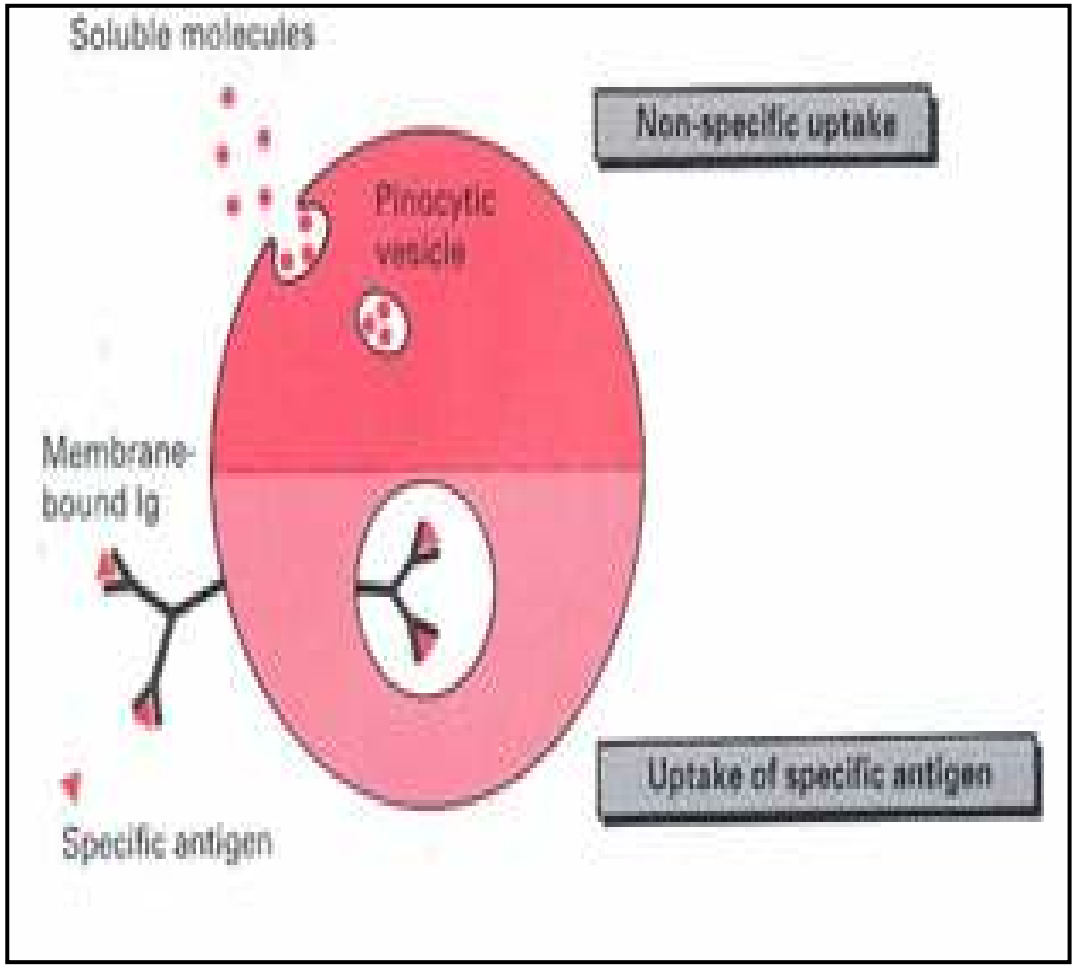


Fig.18. Two pathways for endocytosis of antigens in B lymphocytes.

NB:

- The function of membrane-bound abs on B cells is to bind antigen, which then is internalized and processed within the B cell (fig. 19).
- The expression of abs on the membrane of a B cell may thus be viewed as a means of capturing and concentrating antigen within the cell.
- The processed ag is subsequently re-expressed on the surface of the B cell as peptides, bound to MHC molecules, in a form that can be recognized by the T cells.

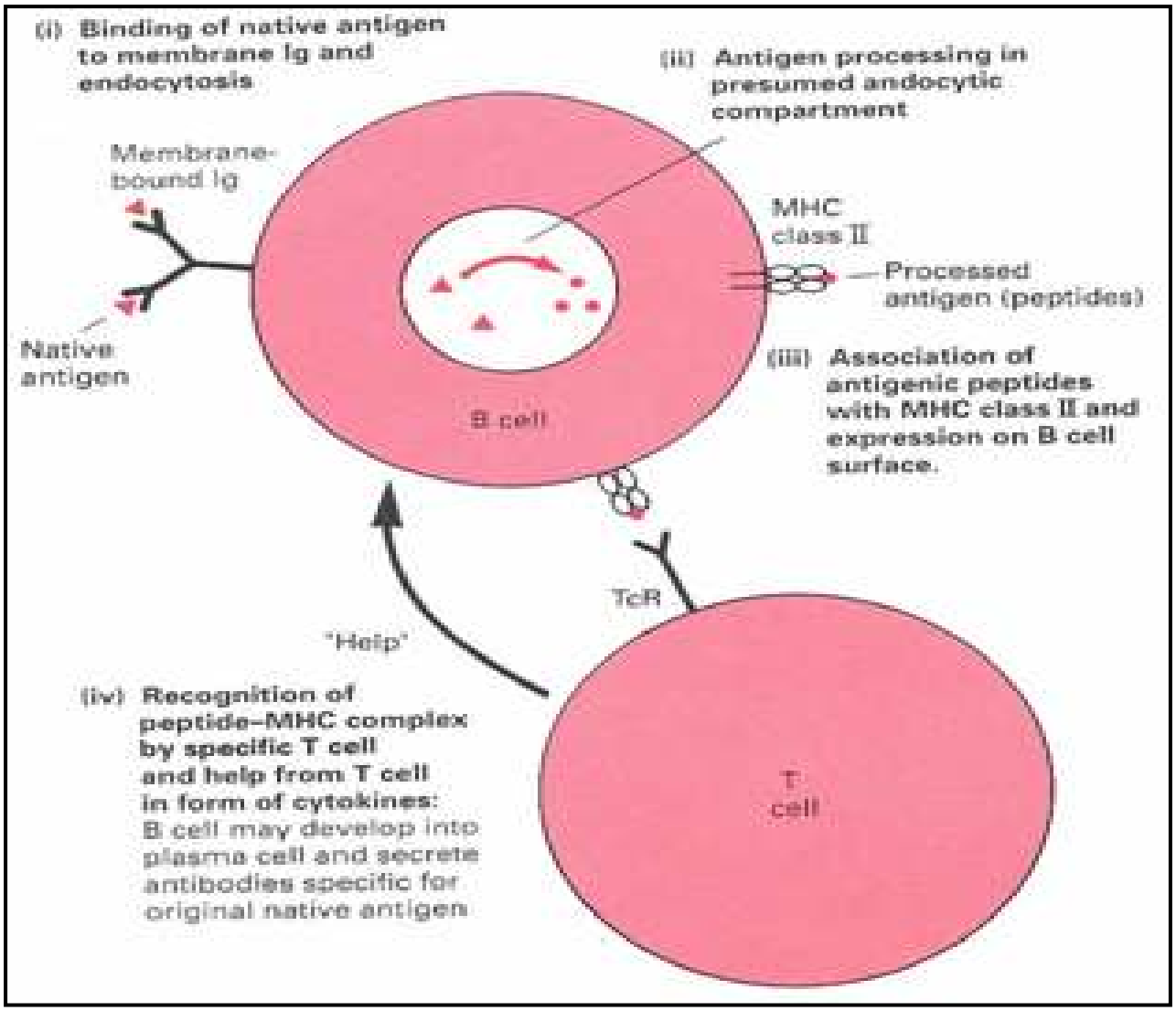


Fig. 19. Antigen processing and presentation by B cells.

Presentation of endogenous ags by fibroblasts and other cells.

- Helper T cells proliferate or secrete IL-2 when they recognize processed antigens in the form of peptide-MHC complexes.

- T_c cells recognize peptide-MHC complexes and can kill fibroblasts infected with virus, as well as uninfected fibroblasts that have been incubated with pre-formed viral peptides (fig. 20).

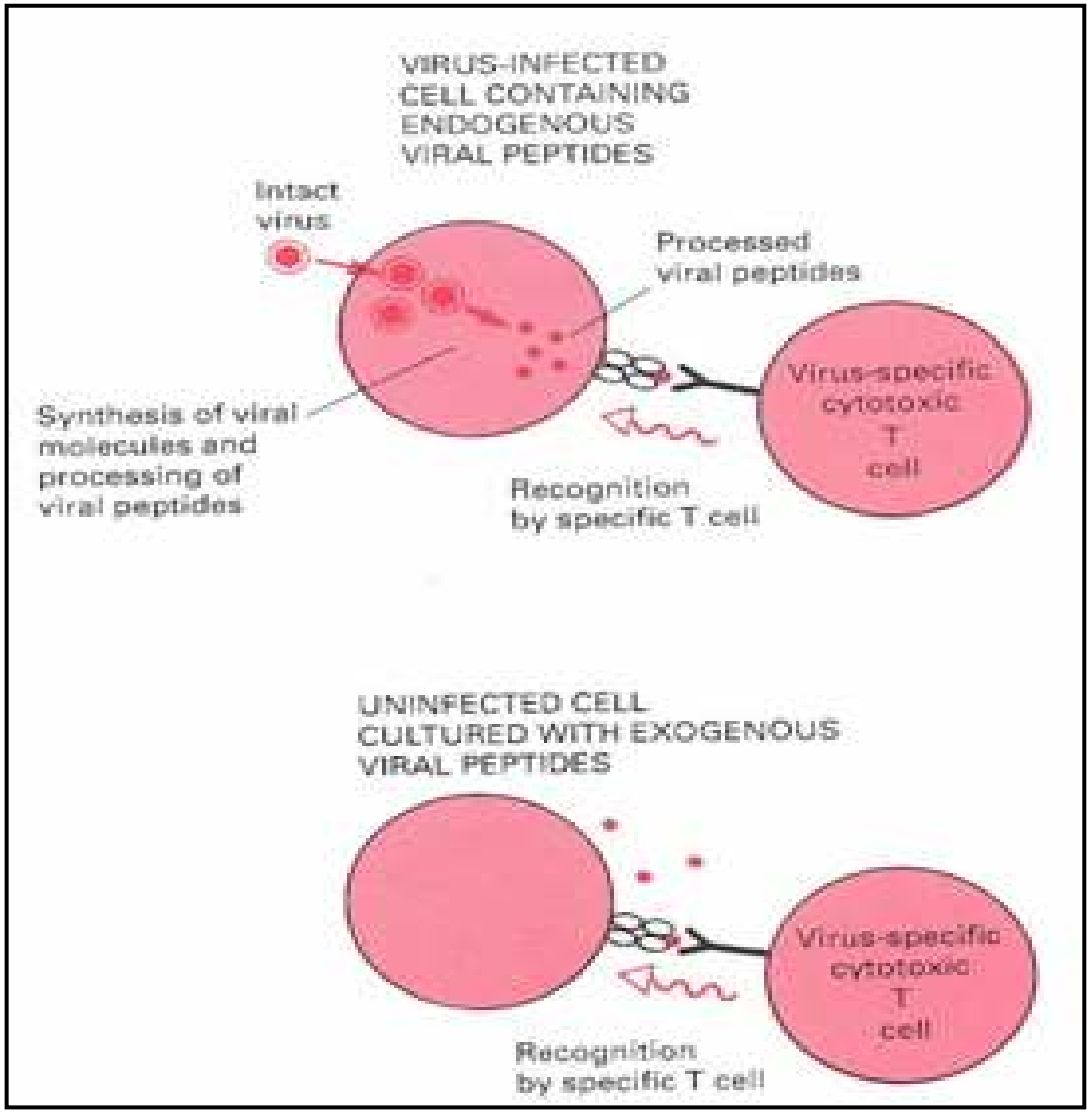


Fig. 20. Tc cells can recognize virus-infected cells as well as uninfected cells that have been cultured with preformed viral peptides.

Note.

- The precise pathway(s) for processing of endogenous ags within the cytoplasm has not been fully defined.
- One route may involve ubiquitin-dependent proteolysis within the cytoplasm (fig.21); which is also normally involved in the regulation of turnover of cellular proteins, including those that may be incorrectly folded after biosynthesis or which have been routed to an incorrect cellular compartment.

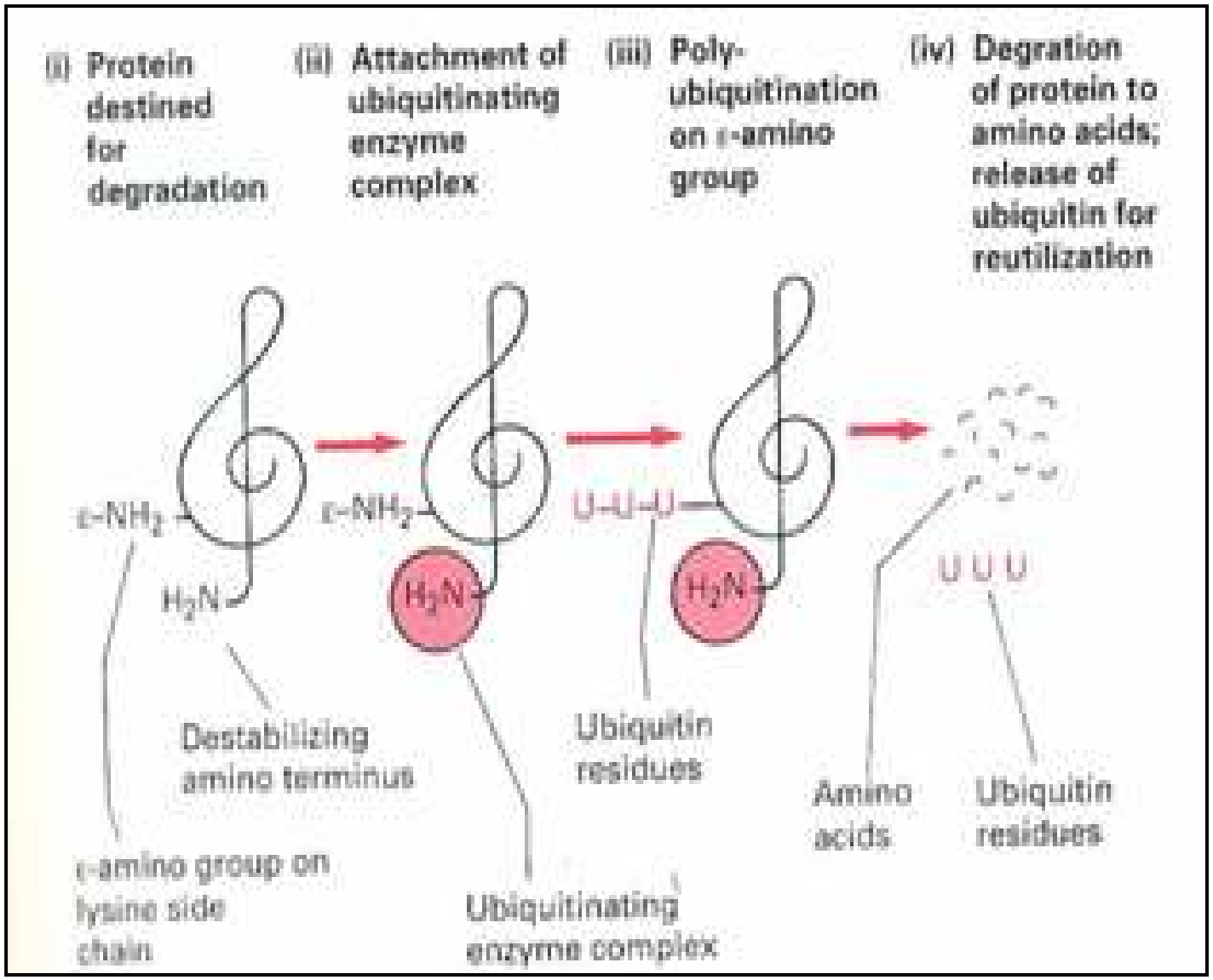


Fig. 21. Ubiquitin-dependent proteolysis.

Summary: Peptide-MHC interactions

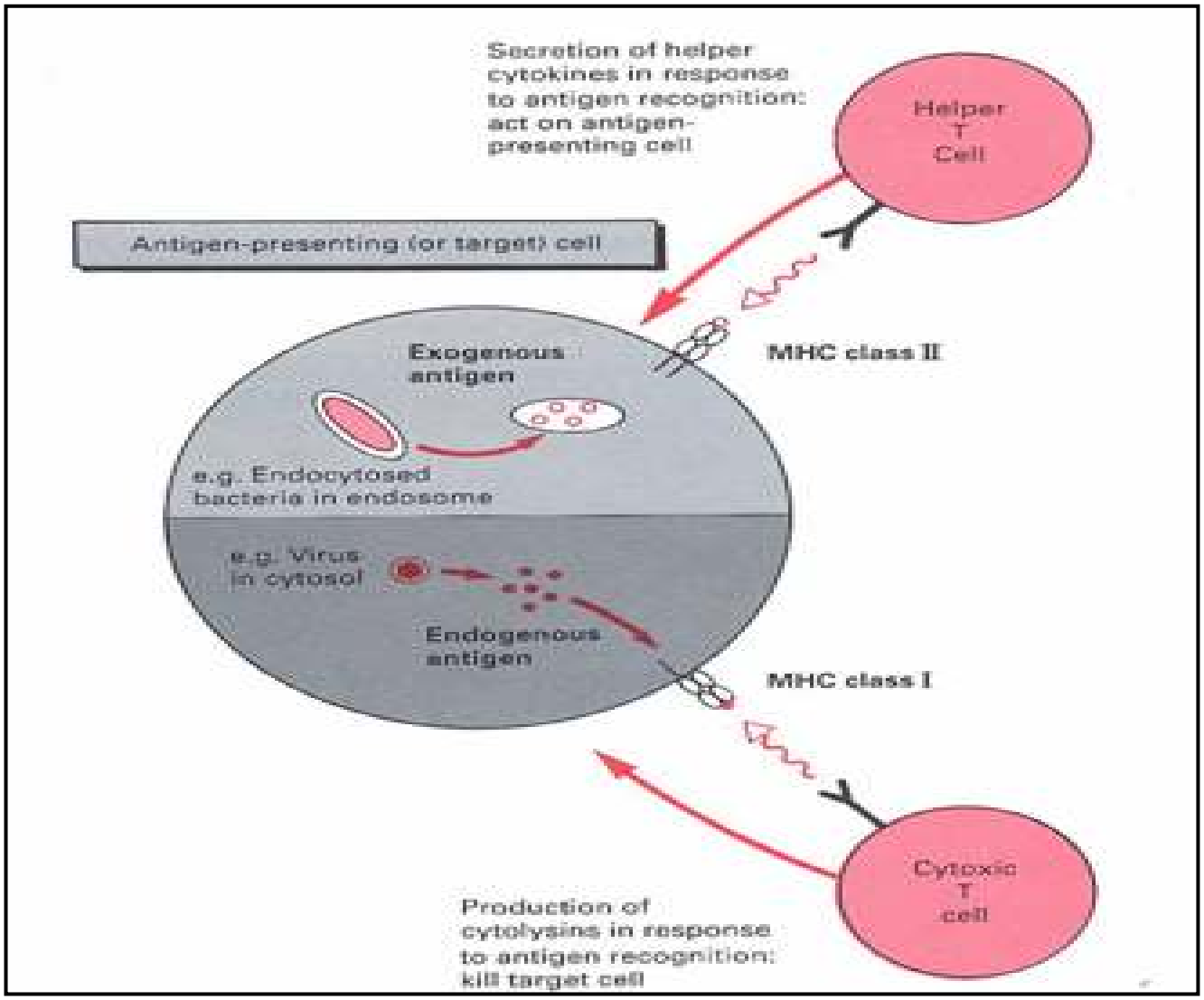


Fig. 22. Exogenous and endogenous antigens tend to associate with different classes of MHC molecules.