Mucosal Immunology

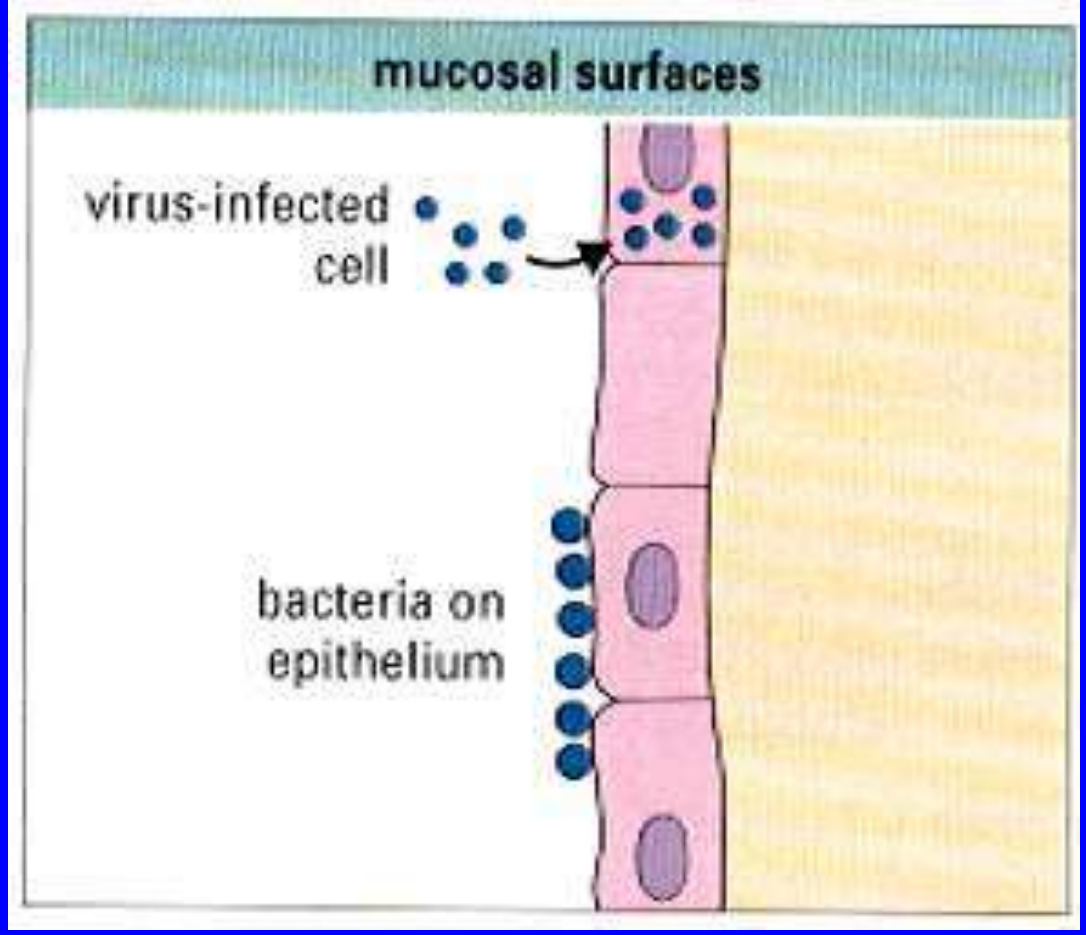
Mucosal Immunology
- Lecture Objectives -

To learn about:

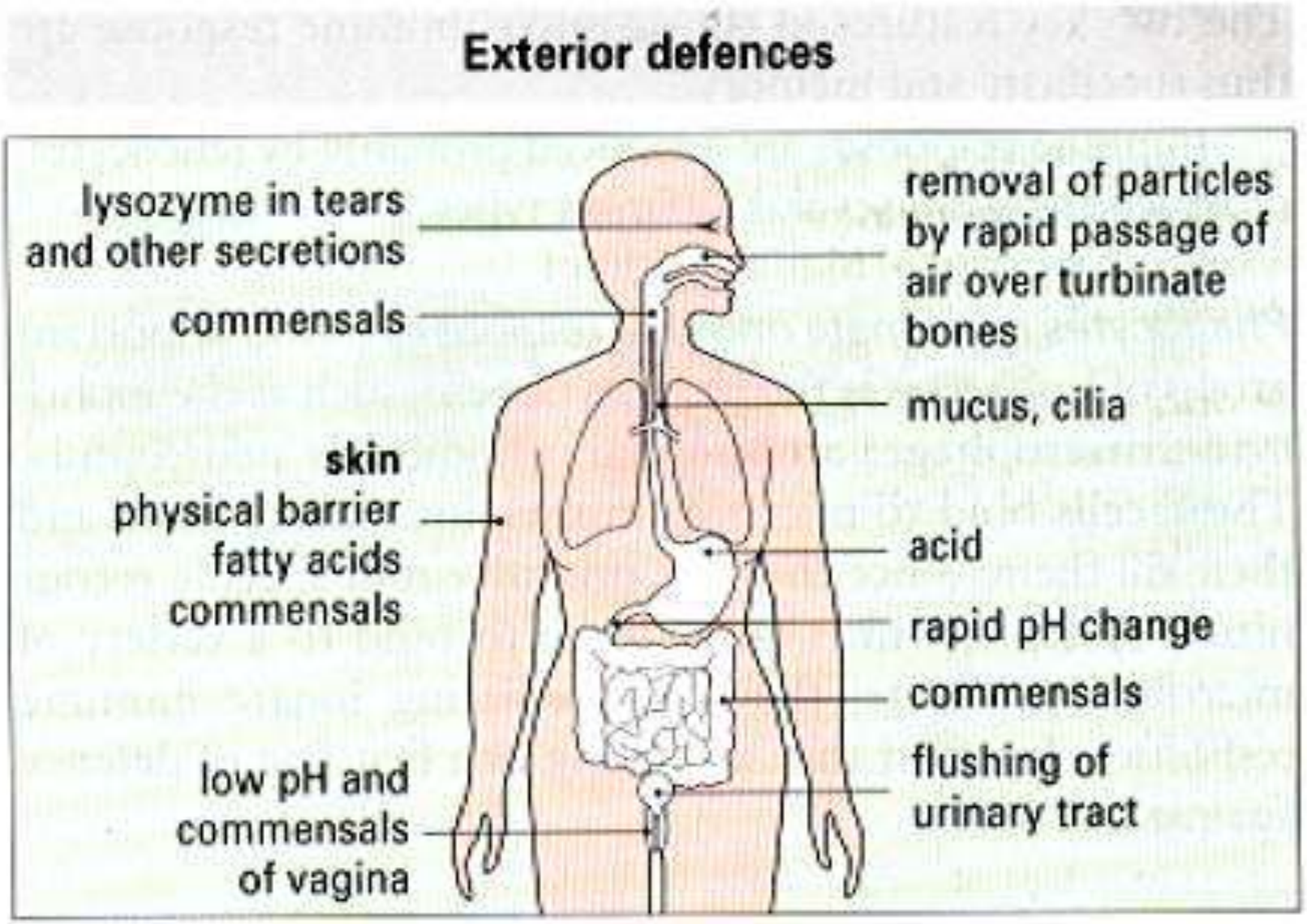
- Common mucosal immunity.
- Cells and structures important to mucosal immunity.
- How mucosal immune responses occur.
- Unique features of IgA immunity.
- Mucosal immunoregulation and oral tolerance.

Mucosal Immunology
- Lecture Outline -

I. Introduction.
II. Mucosa-associated lymphoid tissue (MALT)
III. Induction of mucosal immune responses.
IV. Lymphocyte trafficking and common mucosal immunity.
V. Unique features of IgA immunity
VI. Mucosal T cells.
VII. Oral Tolerance.
VIII. Conclusion



Mucosal surfaces such as the gut are heavily challenged by pathogens. The challenge to host defense: protect against and clear infection; do not respond to harmless antigens (food); effect host defense without damaging the mucosal surface.

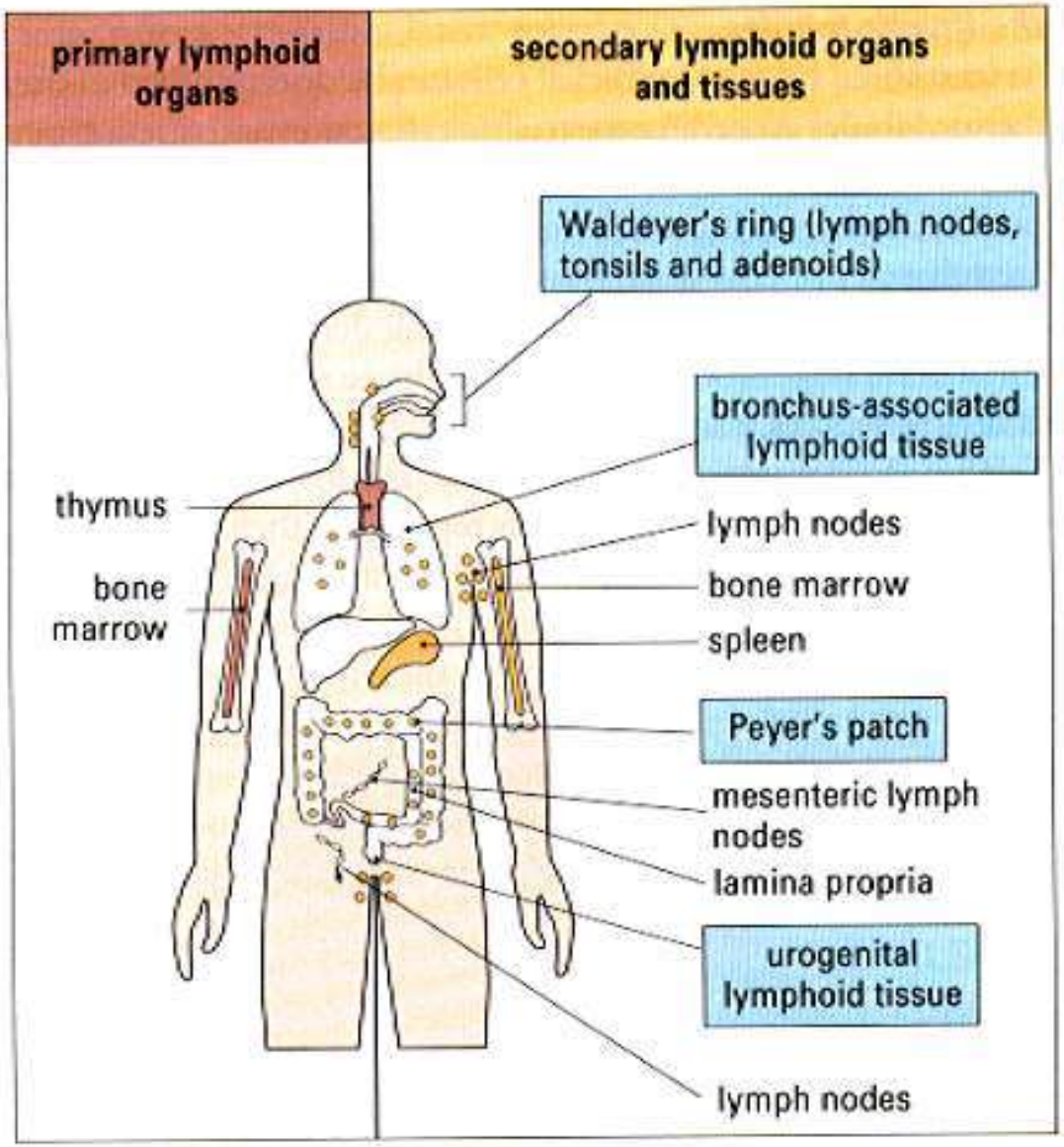


Non-antigen specific mechanisms are important but sometimes insufficient for mucosal host defense.

Mucosal Immunology - Introduction

- Mucosal immunity protects internal epithelial surfaces.
- Components of the mucosal immune system include lymphoid elements associated with internal surfaces of the body (GI, respiratory, urogenital) and exocrine secretory glands linked to these organs, such as the salivary, lachrymal, pancreas, and mammary glands.

Major lymphoid organs and tissues

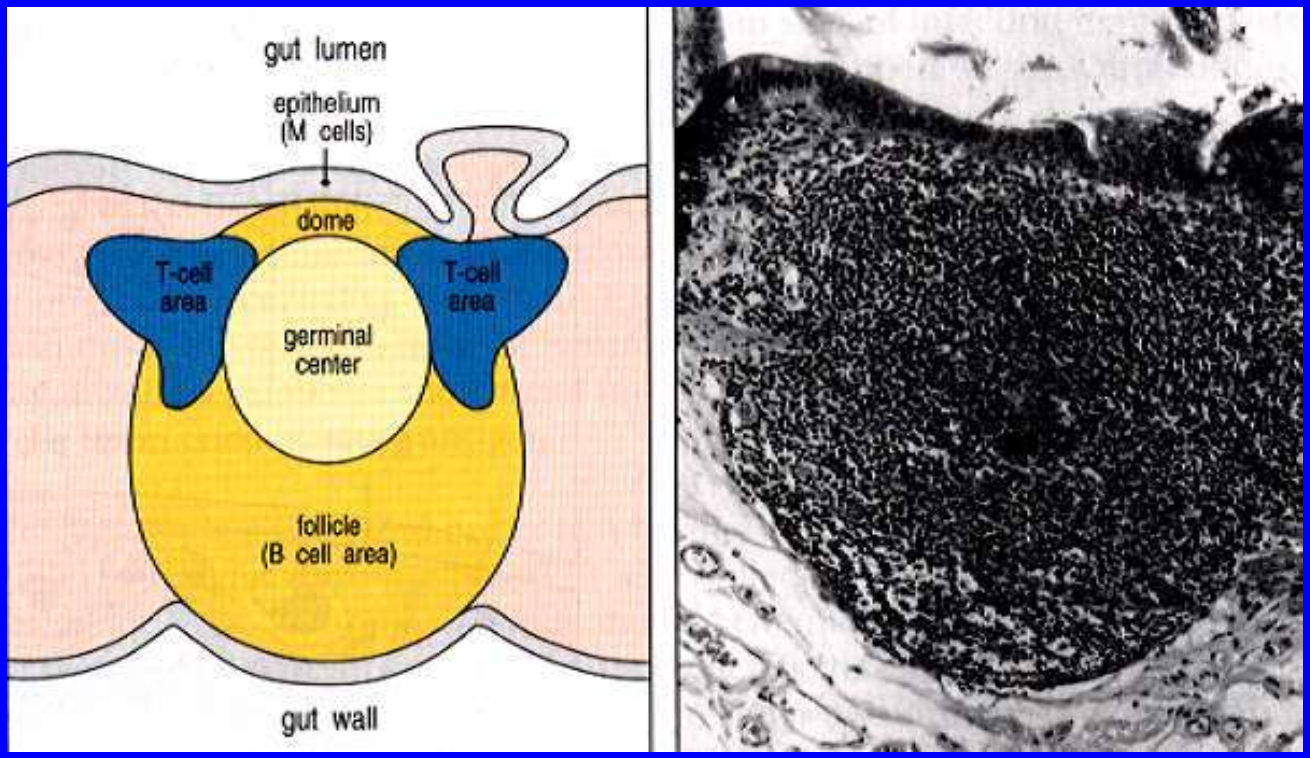


Mucosa-associated lymphoid tissue (MALT)

Examples:

- Nasal-associated lymphoid tissue (NALT).
    - tonsils, adenoids.
- Gut-associated lymphoid tissue (GALT).
    - Peyer's patches.
- Bronchus-associated lymphoid tissue (BALT)

Characteristic features of MALT



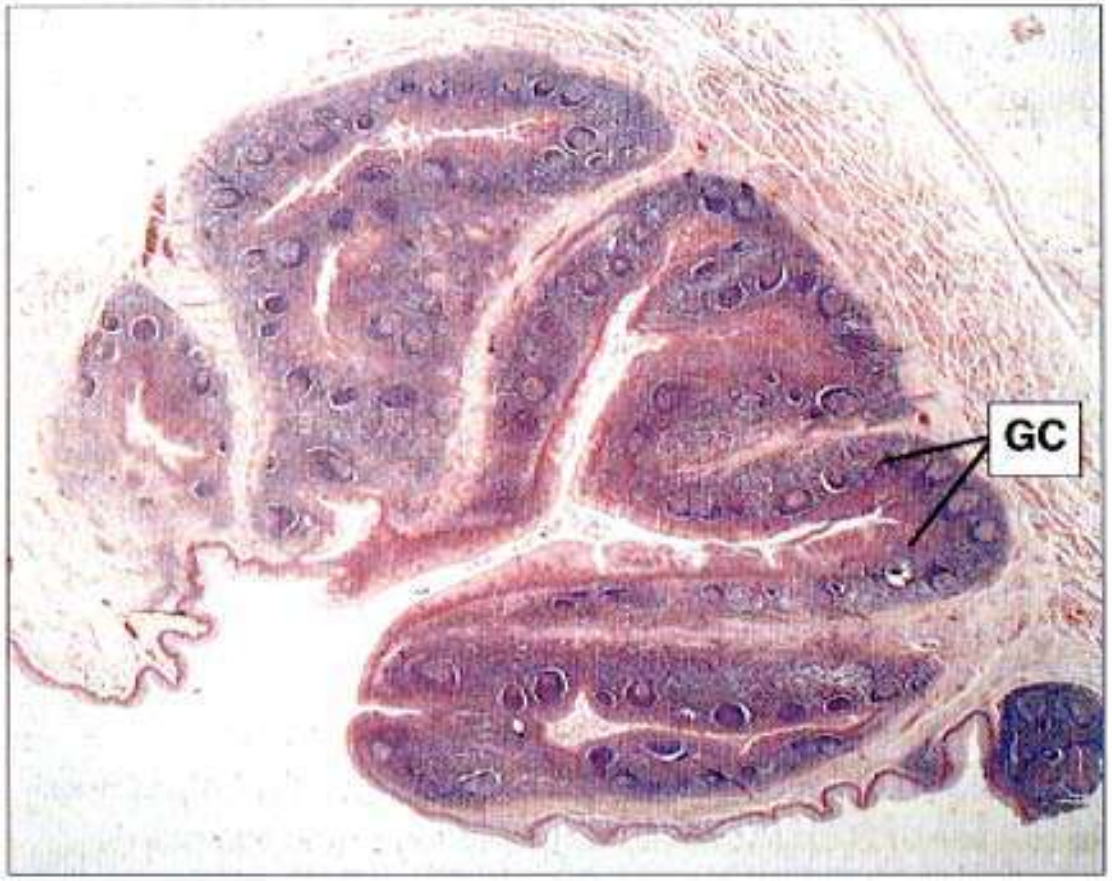


Fig. 3.20 Section of human tonsil showing MALT. This view shows the large number of germinal centres (GC) frequently found in tonsillar lymphoid tissue. H&E stain, ×4. (Courtesy of Mr C. Symes.)

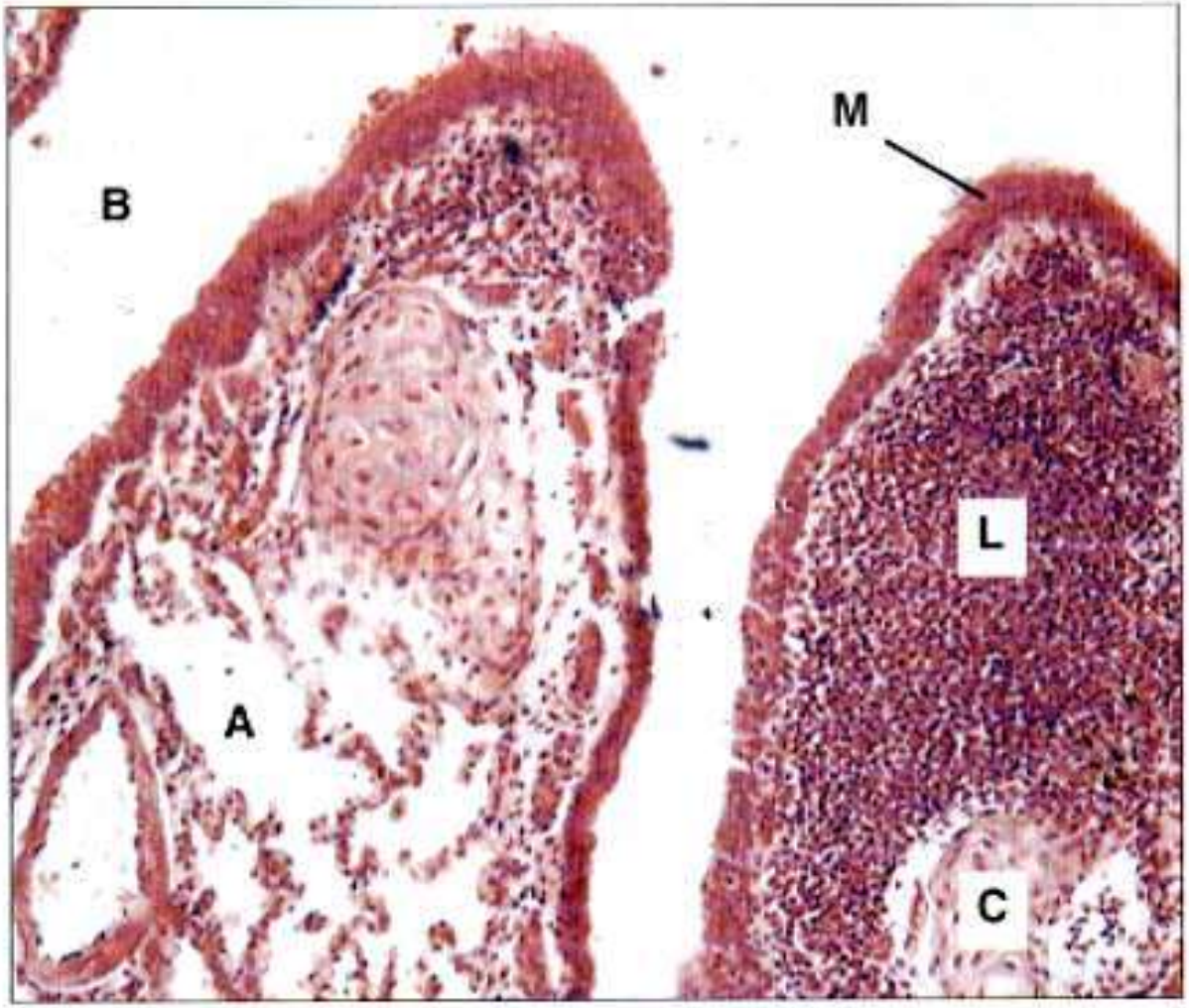
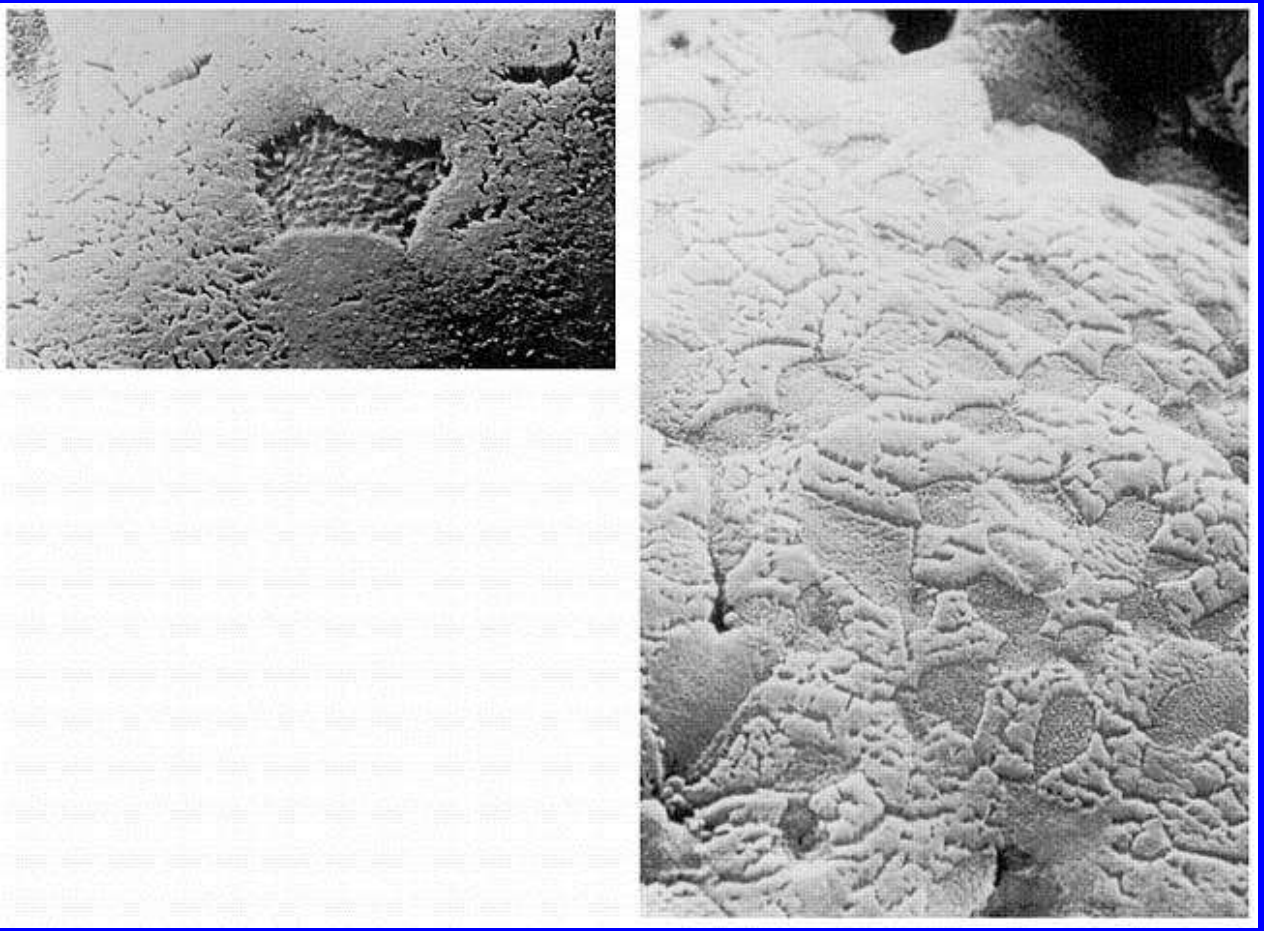
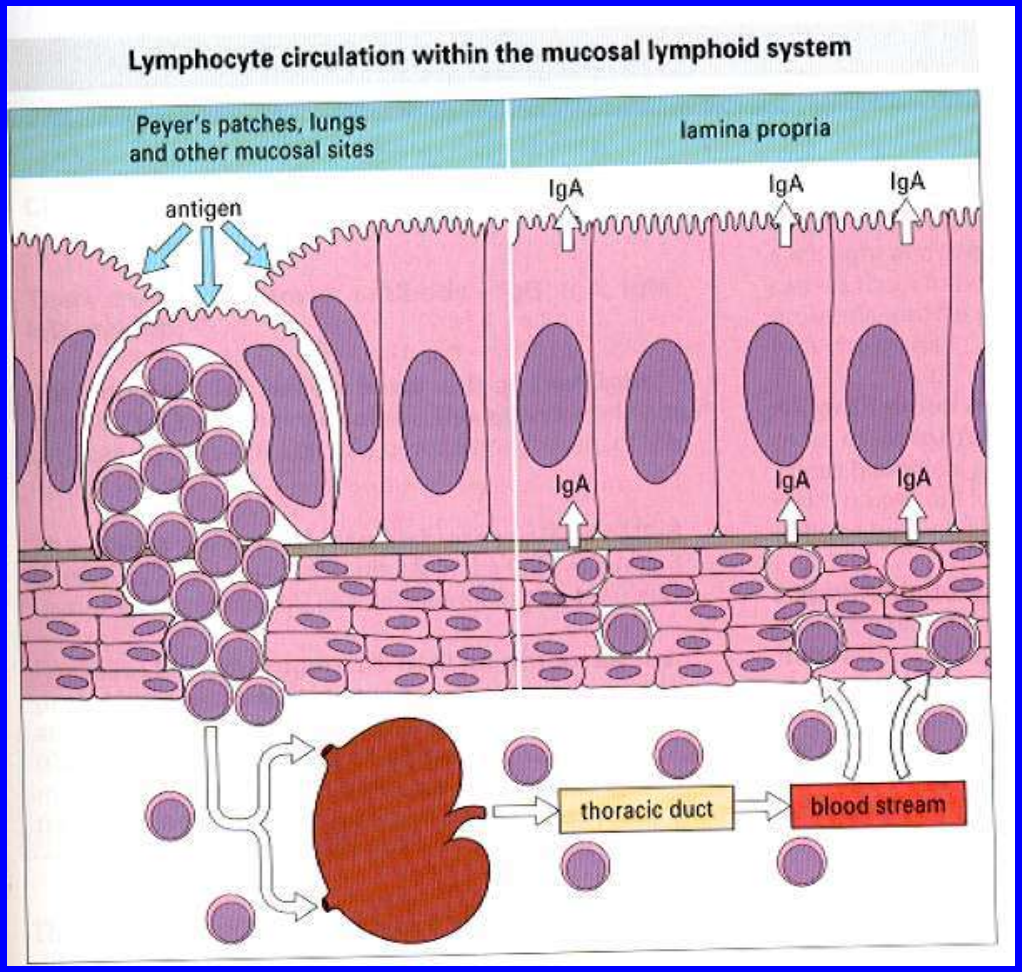


Fig. 3.21 Section of lung showing MALT. This section shows diffuse accumulation of lymphocytes in the bronchial wall. A = alveolar space; B = bronchial lumen; C = cartilage; L = lymphocytes; M = mucosal epithelium. H&E stain, ×40.

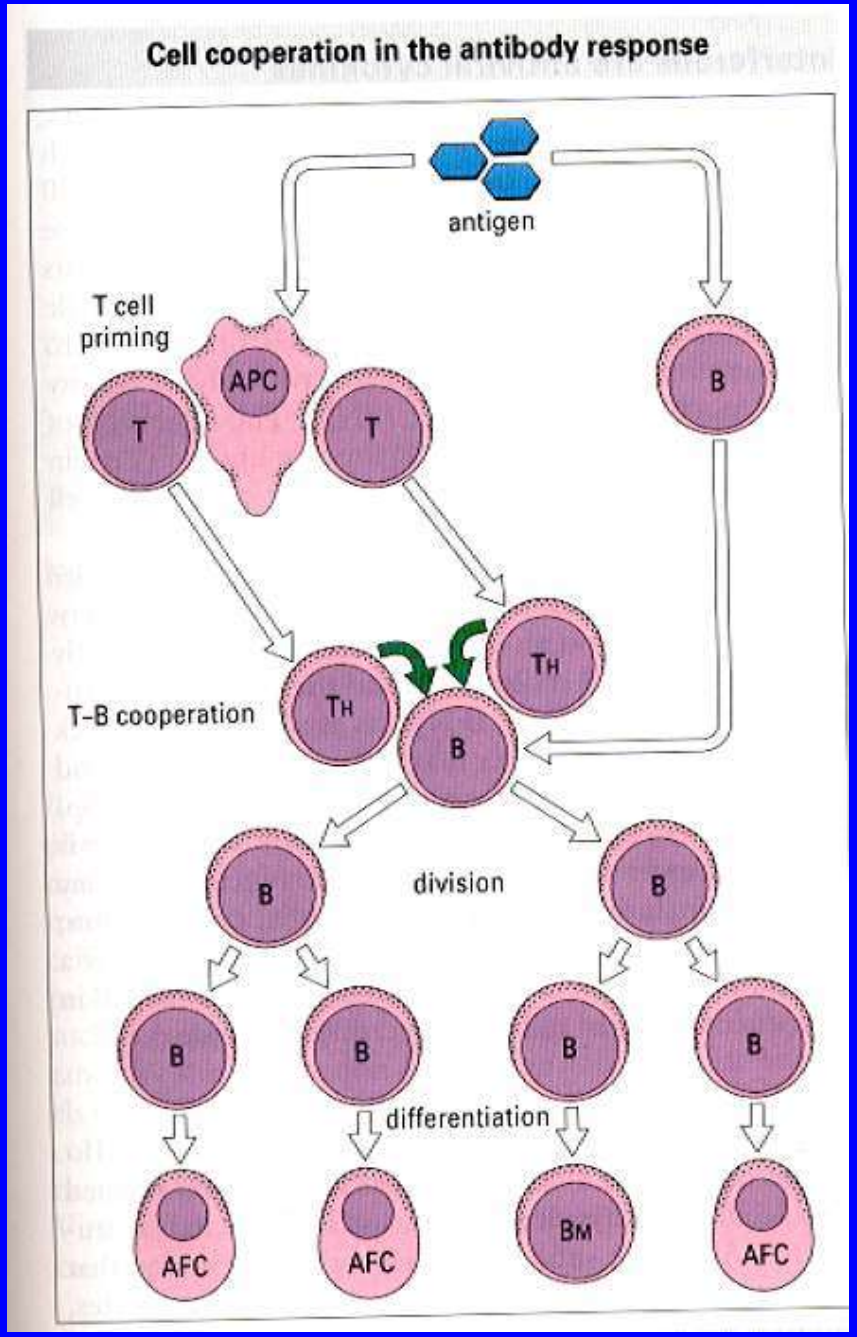
M cells facilitate antigen uptake.



Induction of mucosal immune responses.



Antigen presentation and induction of T and B cell responses occurs in MALT in a fashion similar to other sites. MALT is well-equipped with professional APCs such as dendritic cells.



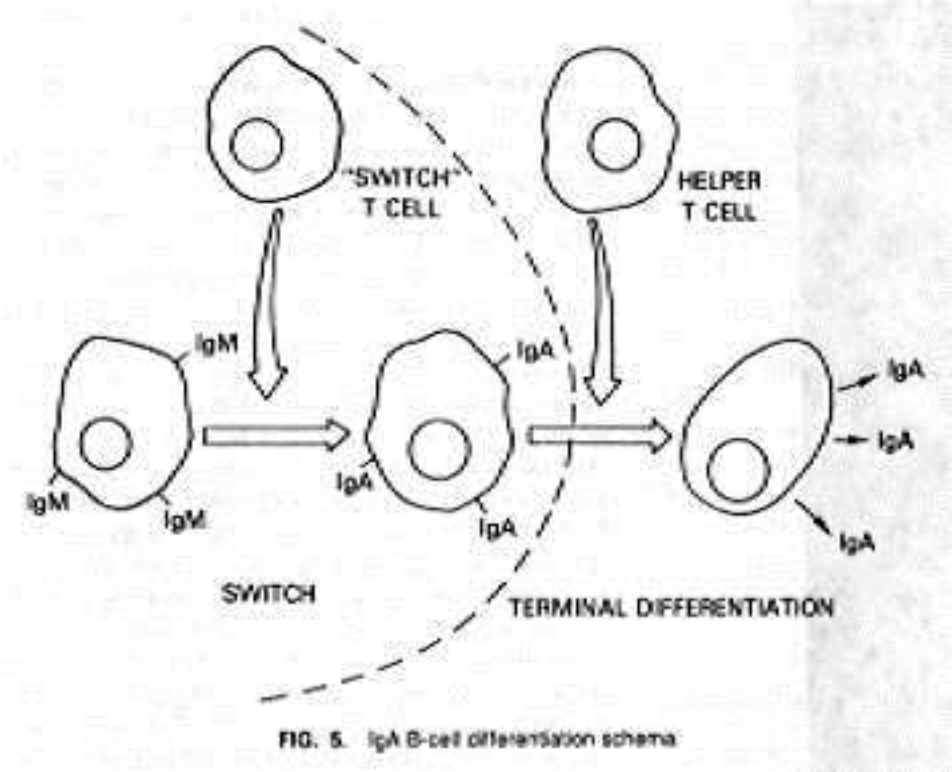
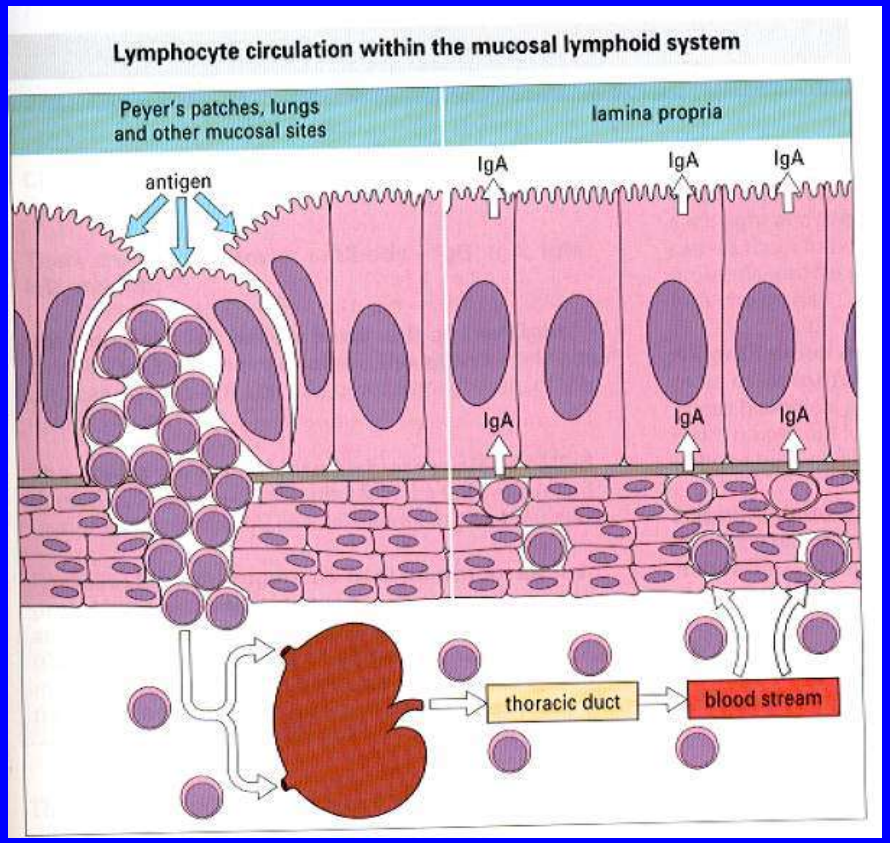


FIG. 5. IgA B-cell differentiation schema

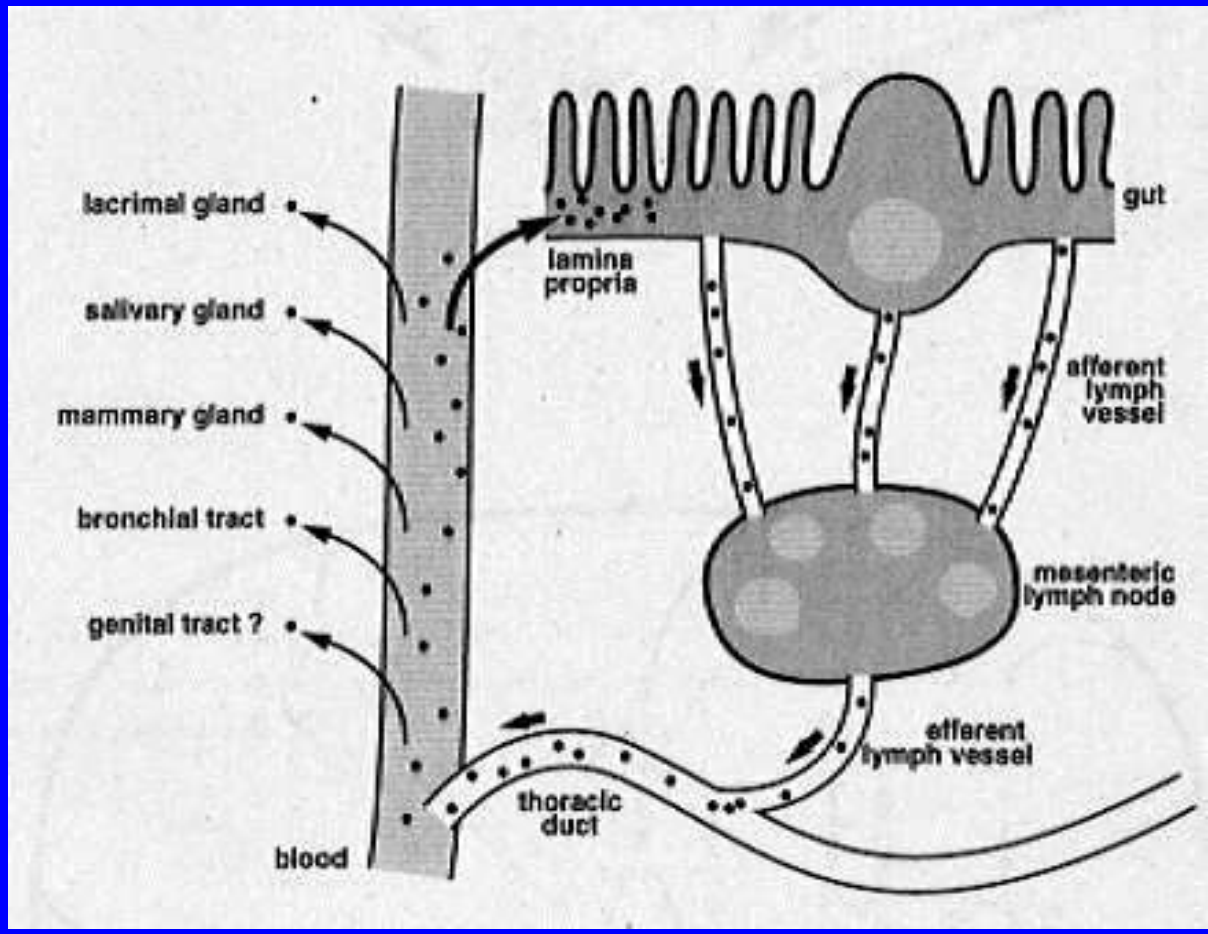
MALT is equipped with T cells preferentially supporting B cell class switch to IgA. TGF-ß and IL-5 are both important in IgA class switching.

Lymphocyte trafficking and common mucosal immunity.

Lymphoblasts generated in MALT preferentially recirculate via the blood to mucosal surfaces. Thus, lymphoblasts generated at one mucosal surface can generalize to other ones.



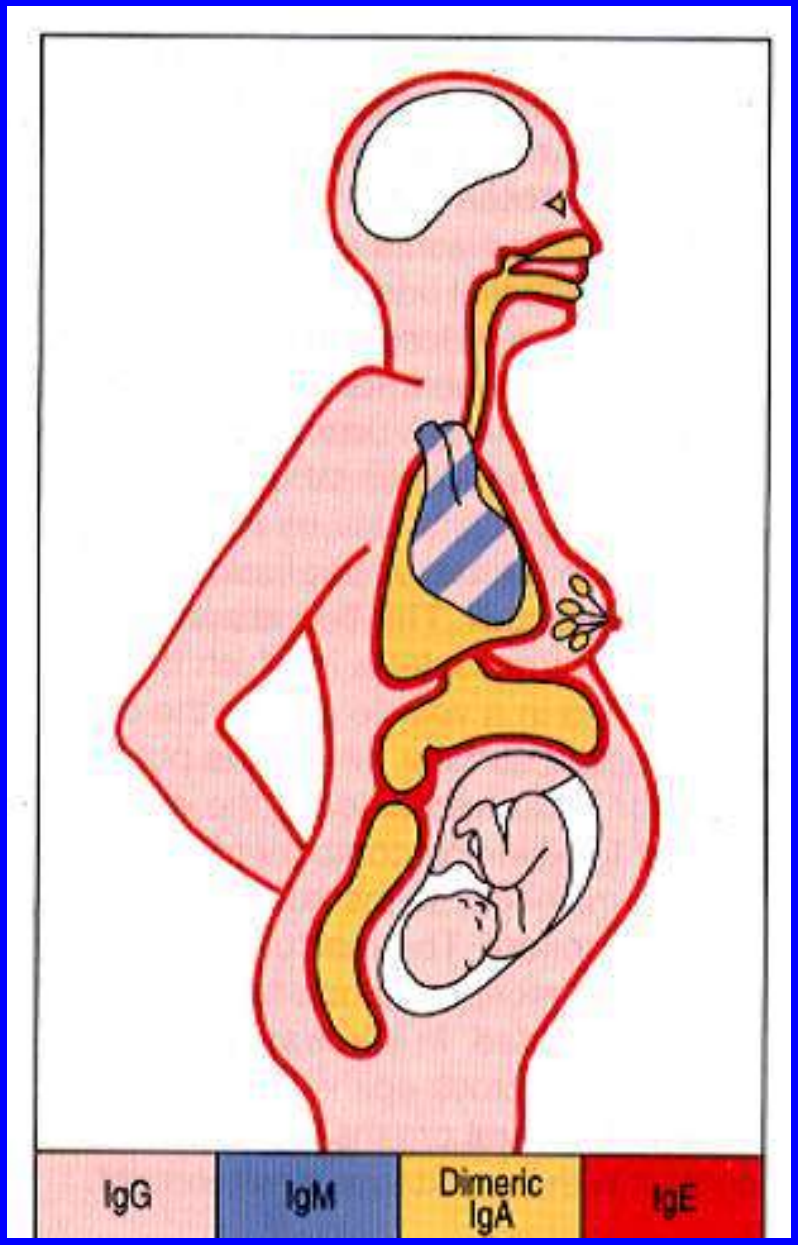
IgA-commited lymphoblasts generated at mucosal surfaces also localize to various exocrine glands. Localization to mammary gland is an important mechanism for maternal transfer of IgA via milk.



Mechanisms for preferential migration of mucosal-derived lymphoblasts to mucosal sites.

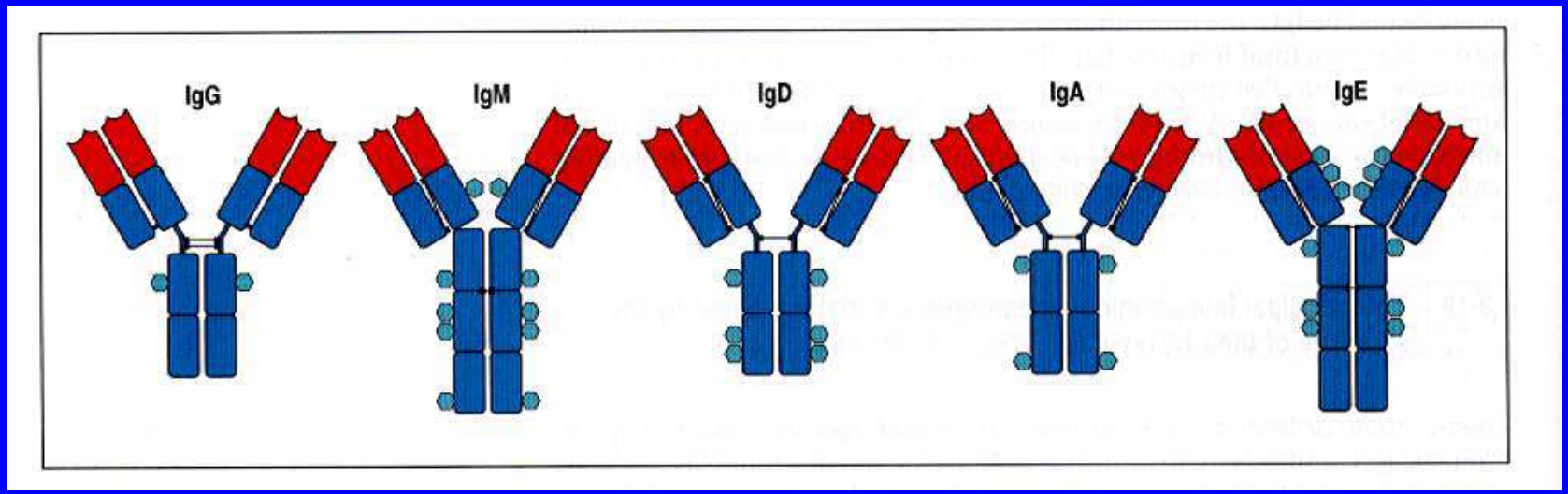
- Preferential migration is believed to result from expression of unique complementary adhesion molecules by mucosal lymphblasts and endothelial cells that target mucosal endothelium for traffic.
- Lymphoblast: $\alpha_4\beta_7$ integrin
- Mucosal endothelium: mucosal addressin cell adhesion molecule (MAdCAM-1).

IgA is the predominant antibody class of the mucosal immune system. Distribution of dimeric IgA is similar to the distribution of mucosal-associated lymphoid tissues.

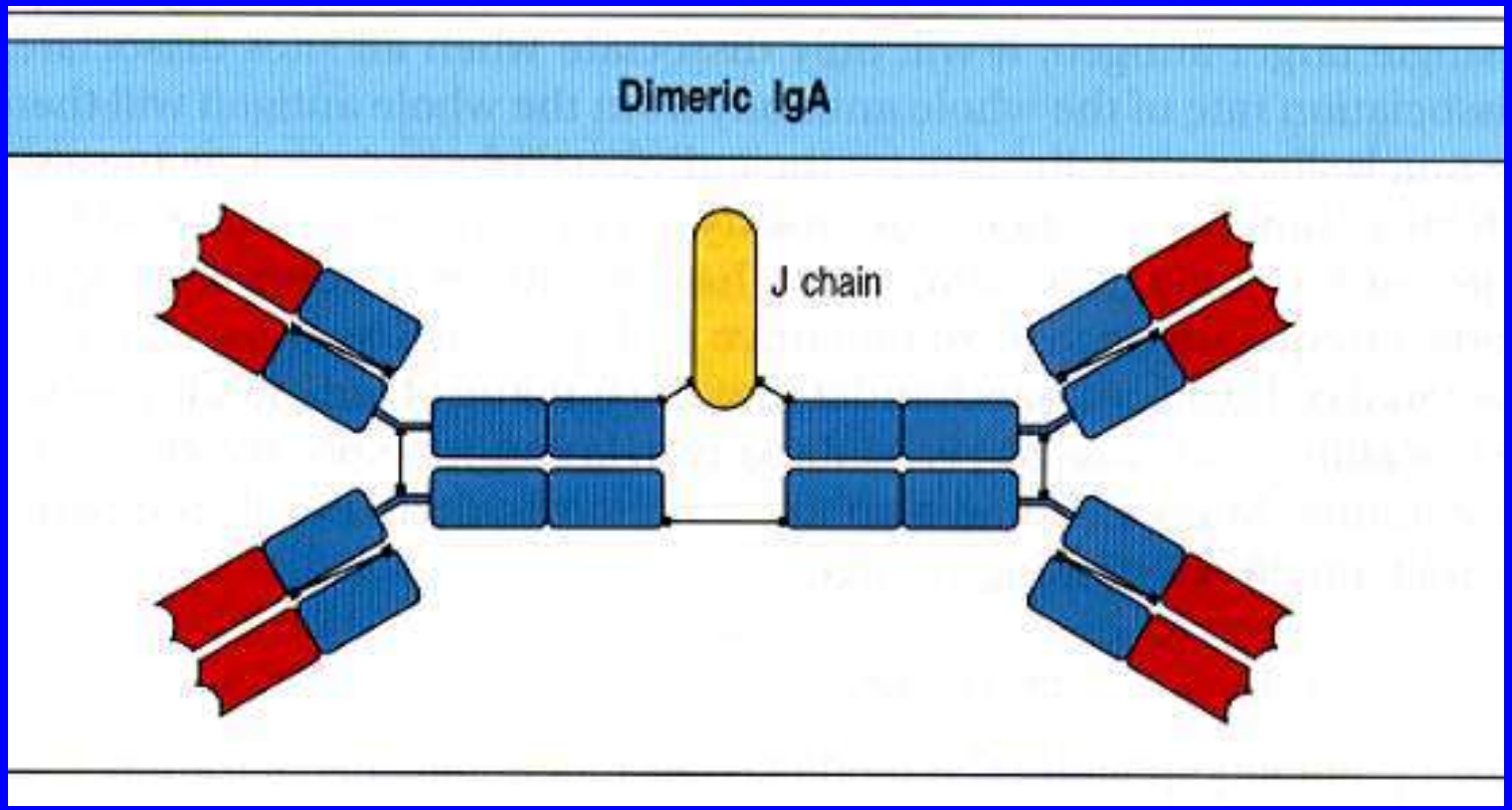


Unique features of IgA immunity

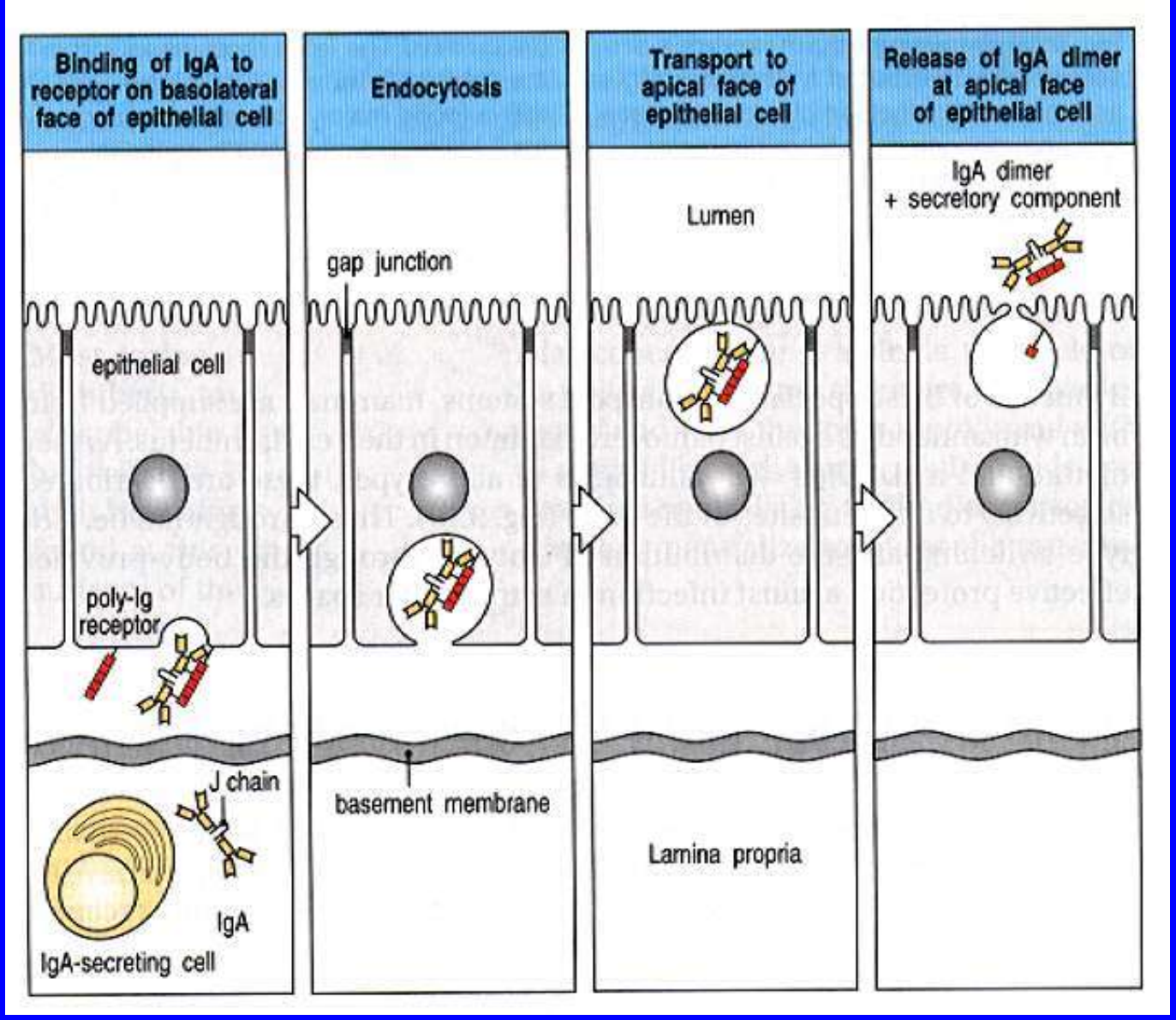
- In the human, IgA is found in both monomeric and dimeric forms.
- Monomeric IgA is produced mostly in bone marrow and found mainly in blood.
- Dimeric IgA is produced mostly in lamina propria of mucosal tissues and found mainly in external secretions.
- Dimeric IgA is actively transported into external secretions via the polymeric immunoglobulin receptor (Pig-R).



Monomeric IgA is structurally similar to monomers of other immunoglobulin classes.



Dimeric IgA consists of two IgA monomers bound by J chain. Individual B cells are committed to secretion of either monomeric or dimeric IgA.



Active transport of dIgA produces secretory IgA.

TABLE 1

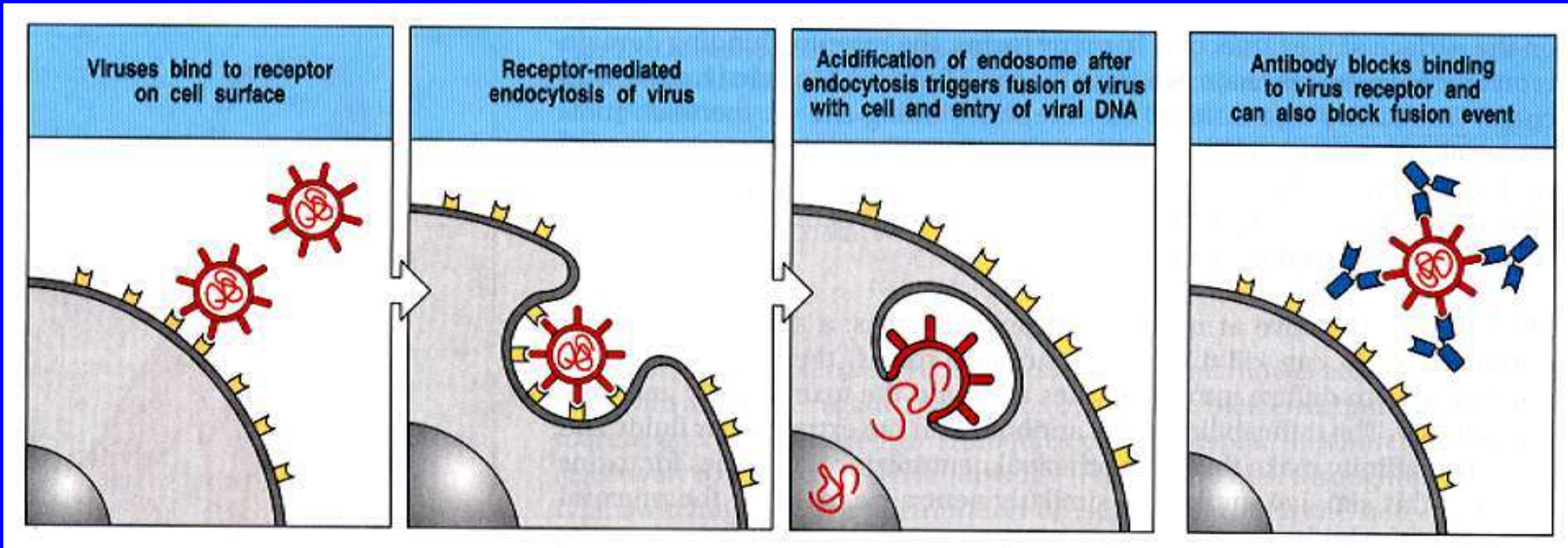
Properties of Secretory and Serum IgA

	Secretory	Serum
Form	Polymer	Monomer
Sedimentation	11S (90%)	7S (90%)
Size	390000	165000
Secretory component	+	-
J chain	+	-
IgA1	50-75%	80-90%
IgA2	25-50%	10-20%

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	–	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

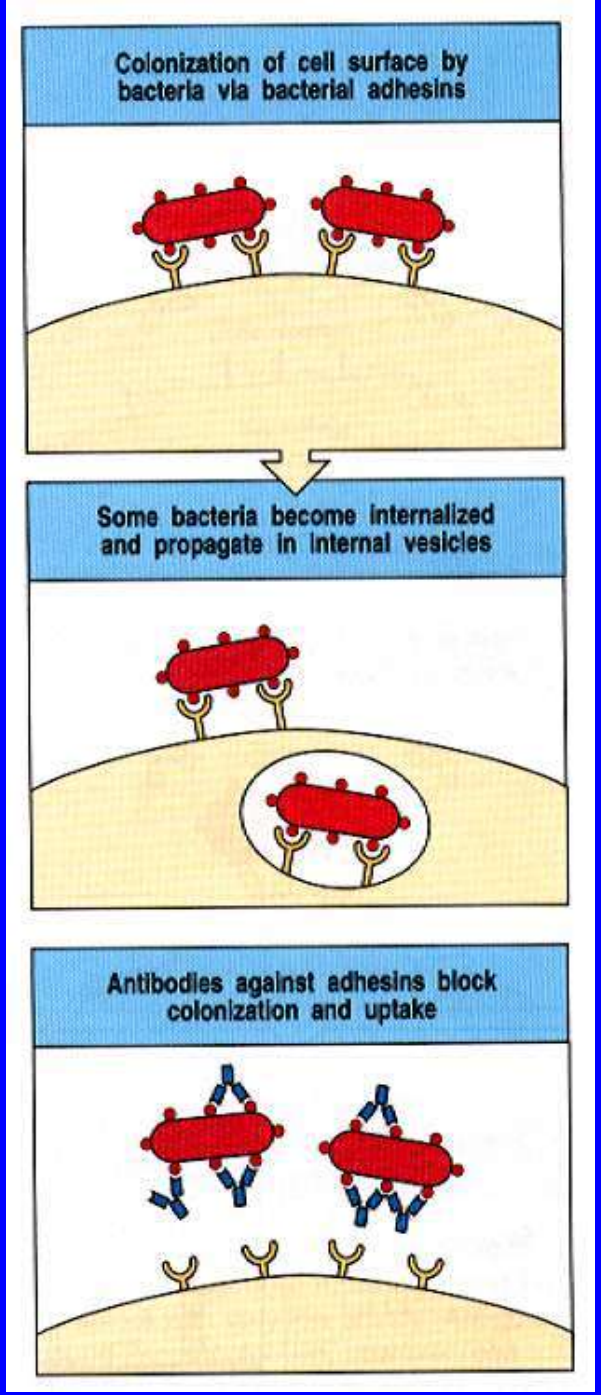
Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	$3x10^{-5}$

Functional activities and distribution of IgA. Note differences relative to IgG.



Role of IgA in host defense against viruses. It can either block entry into epithelium, or directly inactivate virus. Because of its relatively low proinflammatory potential relative to IgG, it is suited for clearance of infection with minimal tissue damage.

IgA and mucosal host defense against bacteria. IgA can act to prevent bacterial adhesion to epithelium, a key first step in infection. Secretory component is believed to provide protection from bacterial proteases. IgA_2 is more protease resistant than IgA_1.



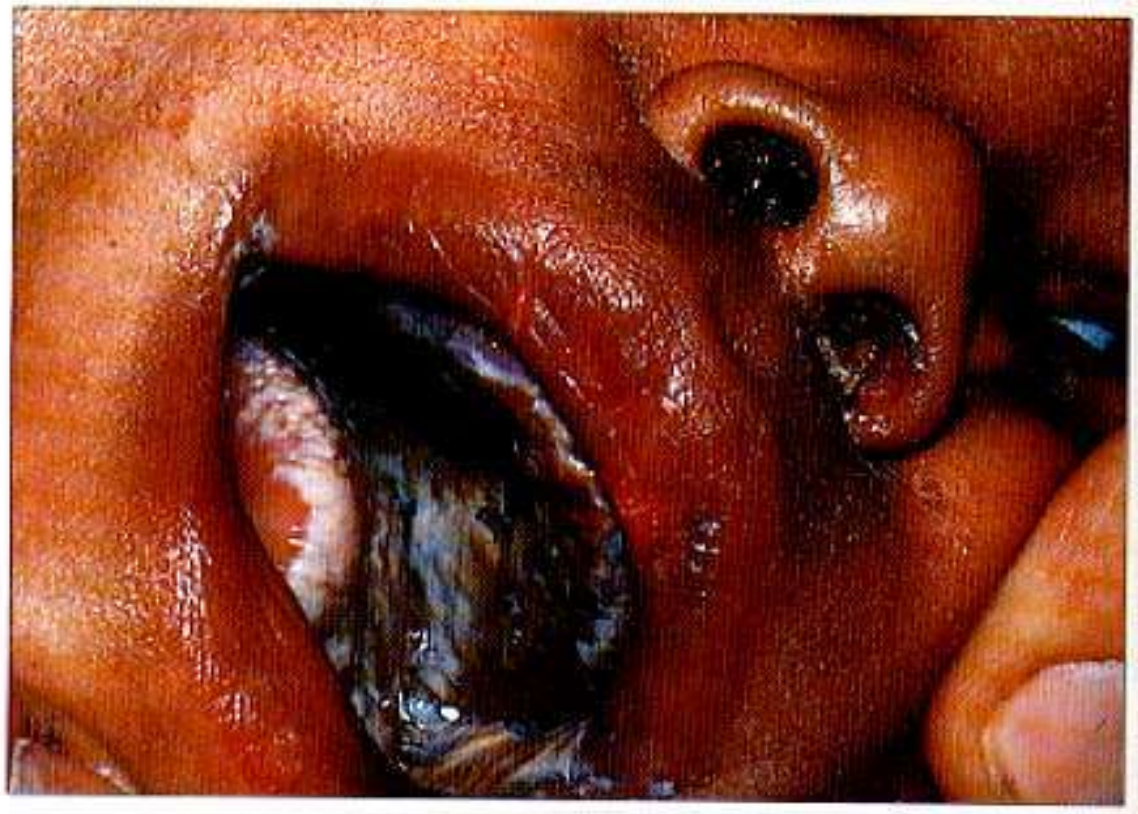
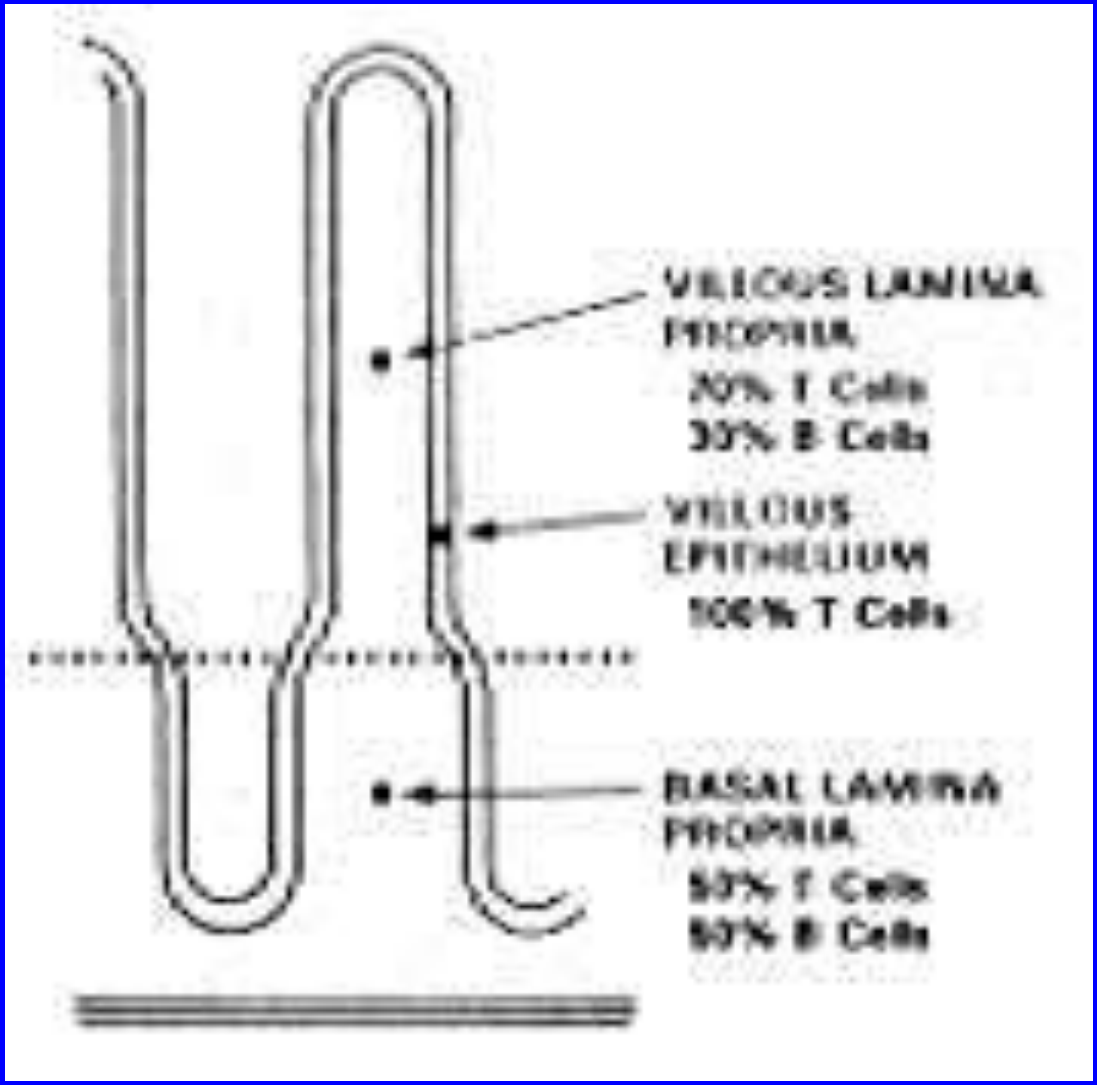


Fig. 21.7 *Candida albicans* in the mouth, in a patient with SCID. This organism grows luxuriantly in the mouth and on the skin of SCID patients.

Cellular (T cell mediated) immunity is also important for the defense of mucosal surfaces.



T cells constitute a large percentage of gut-associated lymphocytes and almost all of the intraepithelial lymphocytes are T cells.

Phenotypic differences between human LPLs and IELs

cell type	TCR αβ	TCR γδ	CD4	CD8
lamina propria lymphocytes	>95%	<5%	70%	30%
intra-epithelial lymphocytes	60–90%	10–40%	<10%	70%

IELs are a unique population of cells with features not found elsewhere. One feature is the prominent presence of ☎✉TCR+,CD8+ cells in the IEL compartment. These cells may play important roles in immunoregulation and epithelial renewal during infection or enteropathy.

Oral Tolerance

- Oral tolerance is the generation of systemic immune unresponsiveness by feeding of antigen. The antigen is usually soluble and without adjuvant or proinflammatory activity.

- Oral tolerance is likely a mechanism for prevention of harmful immune responses to harmless antigens such as foods.

- A number of mechanisms may underlie oral tolerance, including clonal deletion, clonal anergy, or active suppression by T cells (cytotoxic, TH2, or TGF-β producing)

Mechanism for TH1 supression by TH2 cells. Other suppressive T cells might include TGFβ-producing "TH3" cells and CD8+ suppressor/cytotoxic cells.

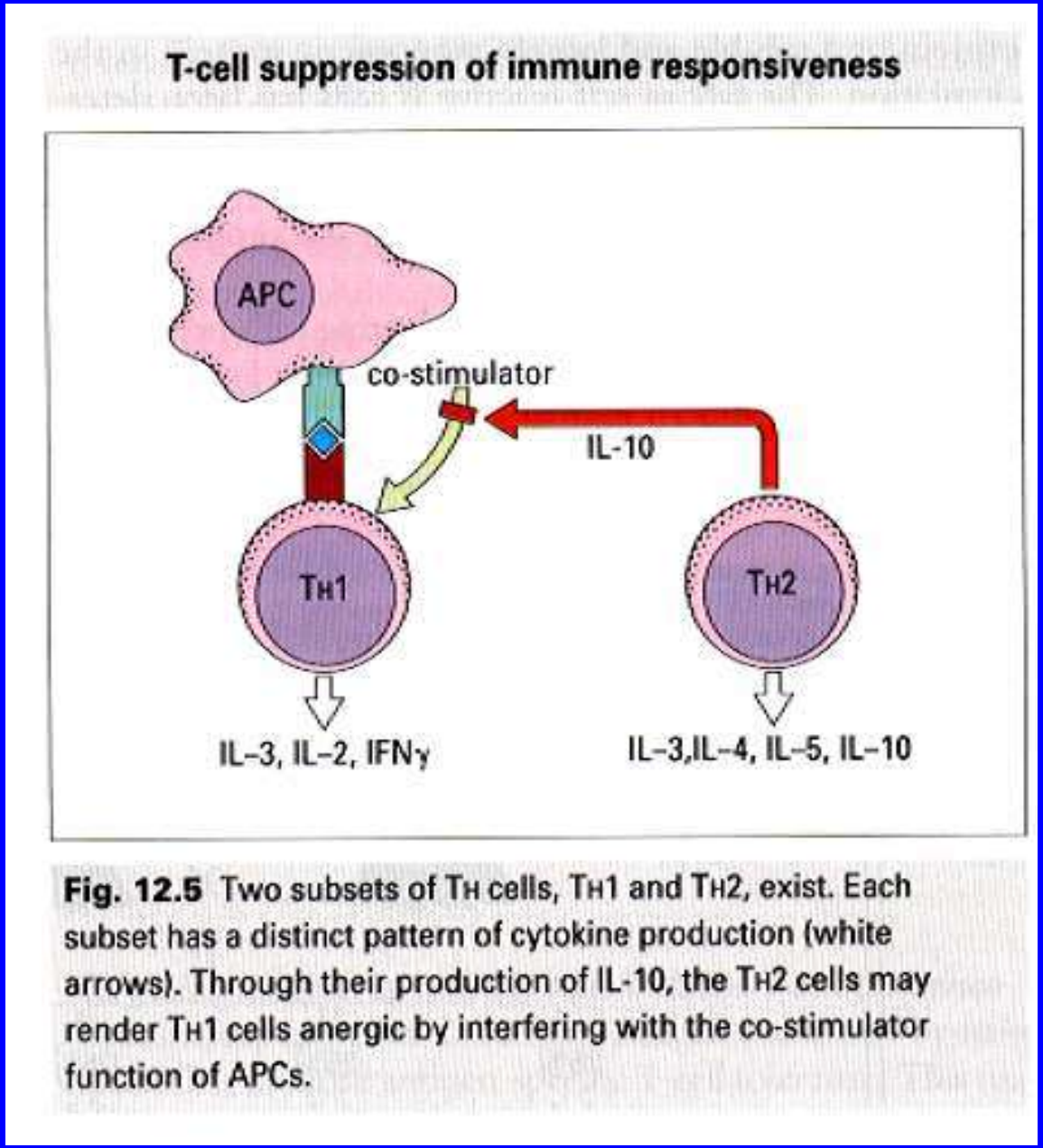
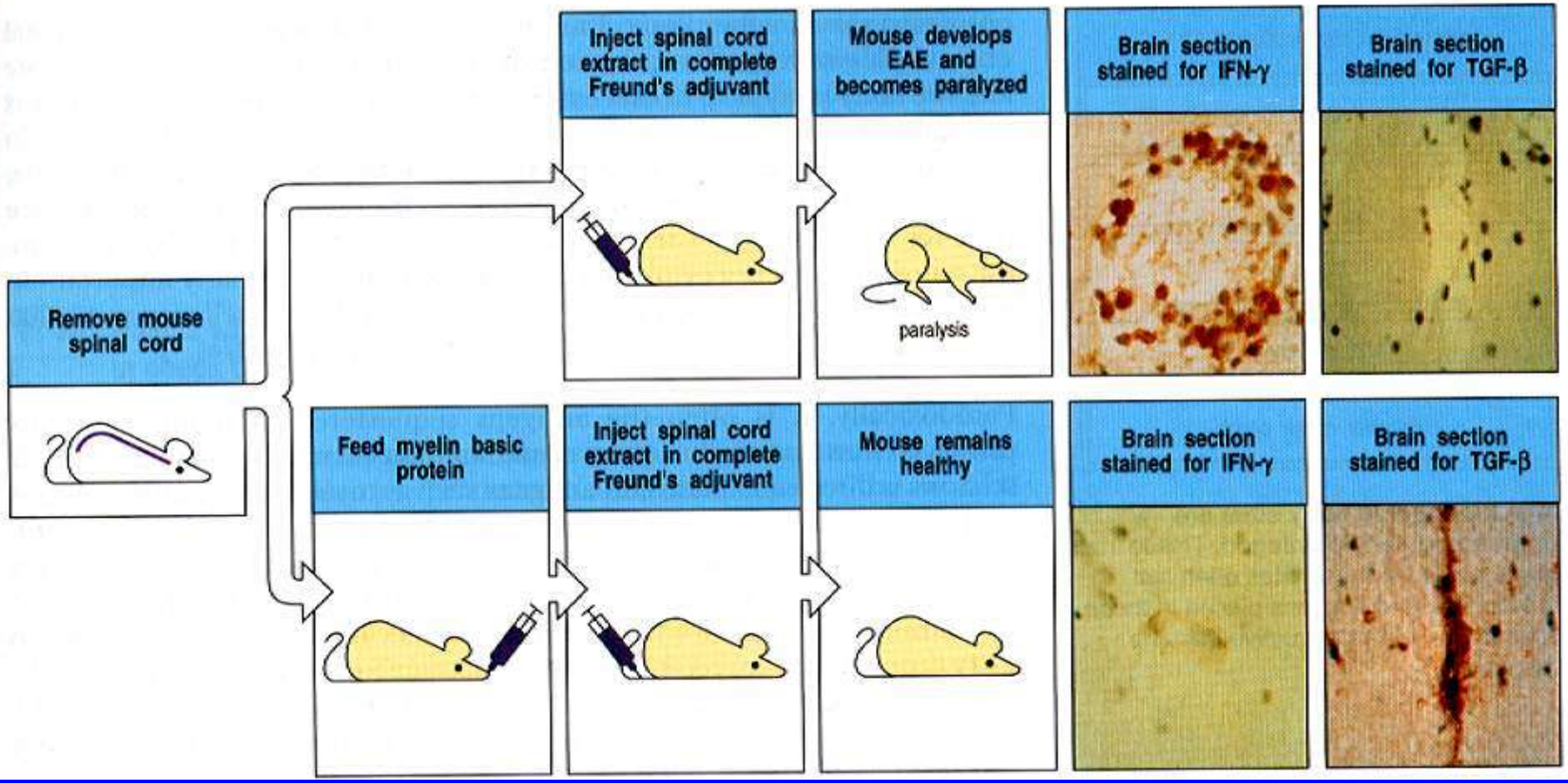
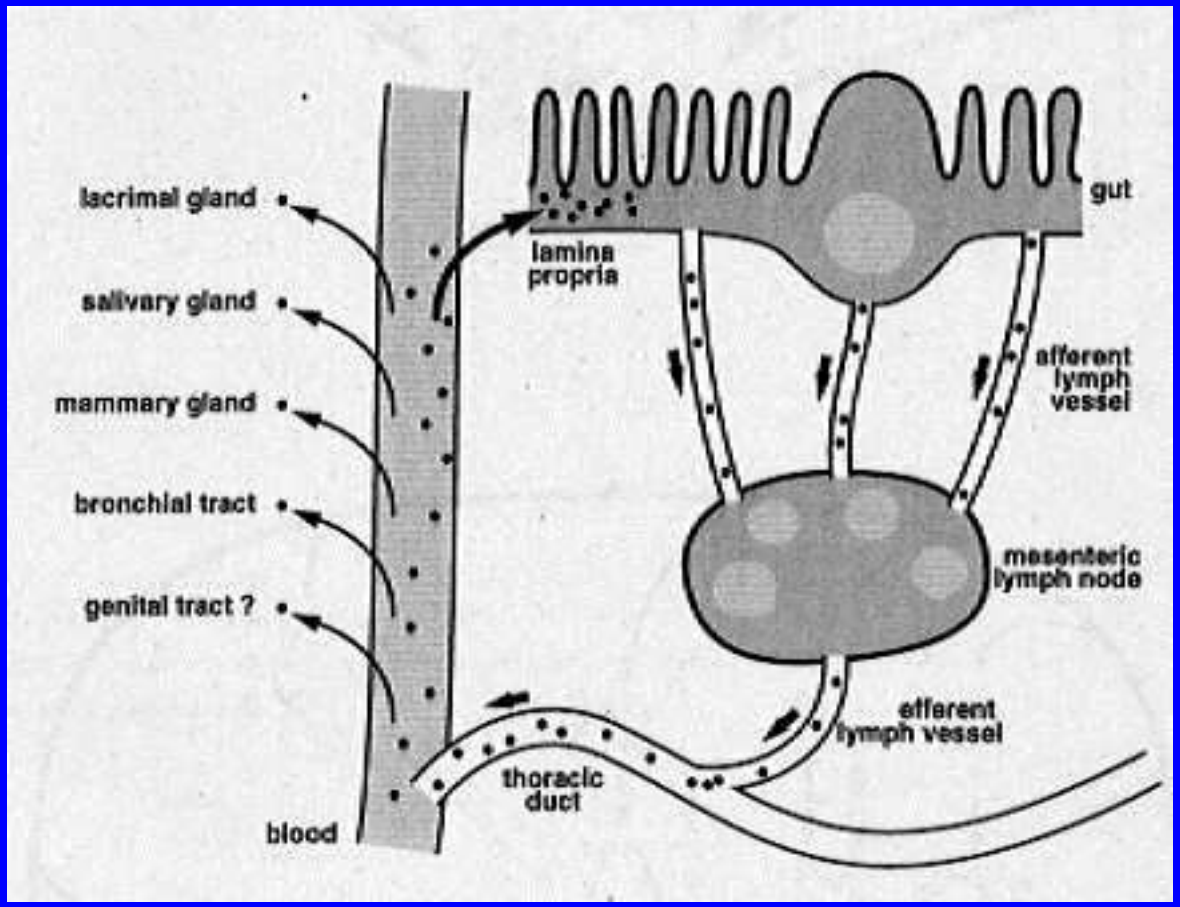
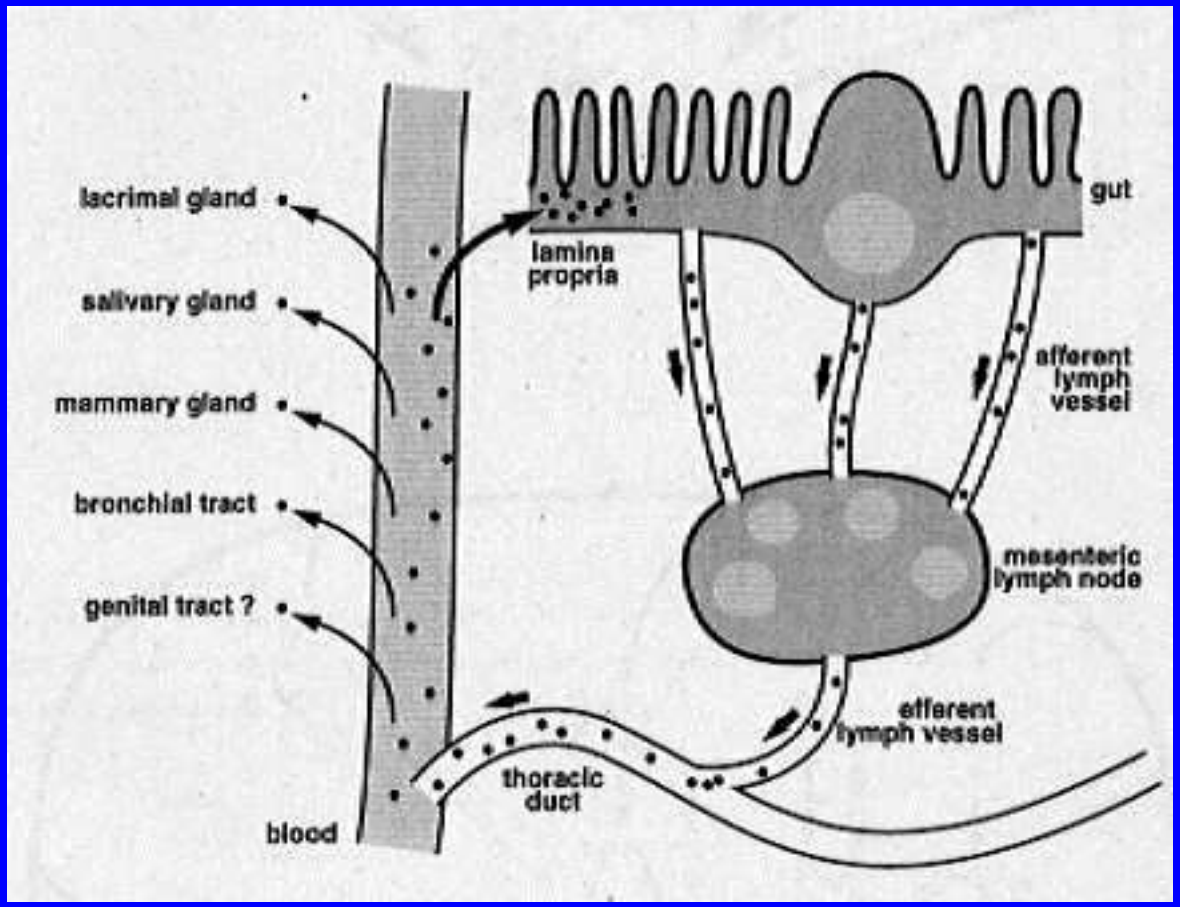


Fig. 12.5 Two subsets of TH cells, TH1 and TH2, exist. Each subset has a distinct pattern of cytokine production (white arrows). Through their production of IL-10, the TH2 cells may render TH1 cells anergic by interfering with the co-stimulator function of APCs.



Oral tolerance as a treatment for experimental allergic encephalomyelits. Induction of oral tolerance is being studied for use clinically.


lacrimal gland
salivary gland
mammary gland
bronchial tract
genital tract ?
blood
lamina propria
gut
efferent lymph vessel
mesenteric lymph node
efferent lymph vessel
thoracic duct



Overview: sequence of events leading to an IgA response.

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