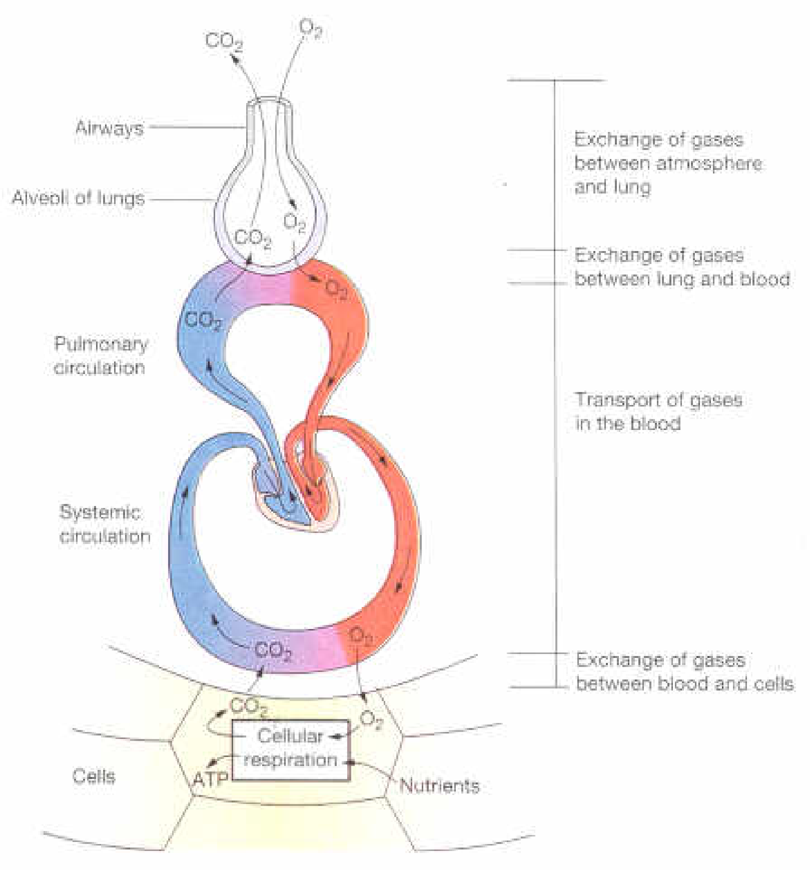
Respiratory System

Asthma & the Immune System

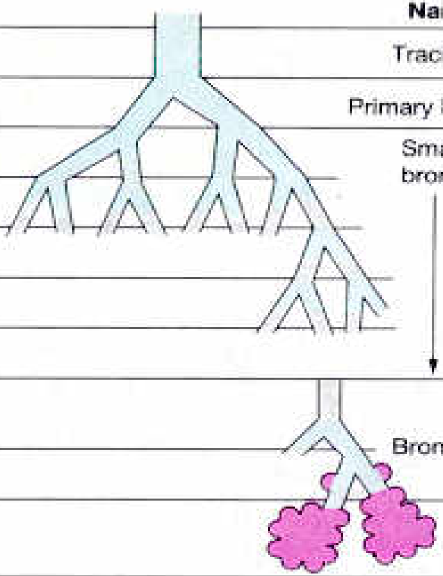
Respiratory System *Physiology*

- Oxygen, nutrients from environment coupled with removal of CO_2 and wastes: diffusion
- Diffusion is limited by distance: we have the circulatory system
- Surface area to volume problem: Area changes as the square of the length (L^2); volume changes as the cube of the length (L^3)
- Large surface area compressed into a small volume



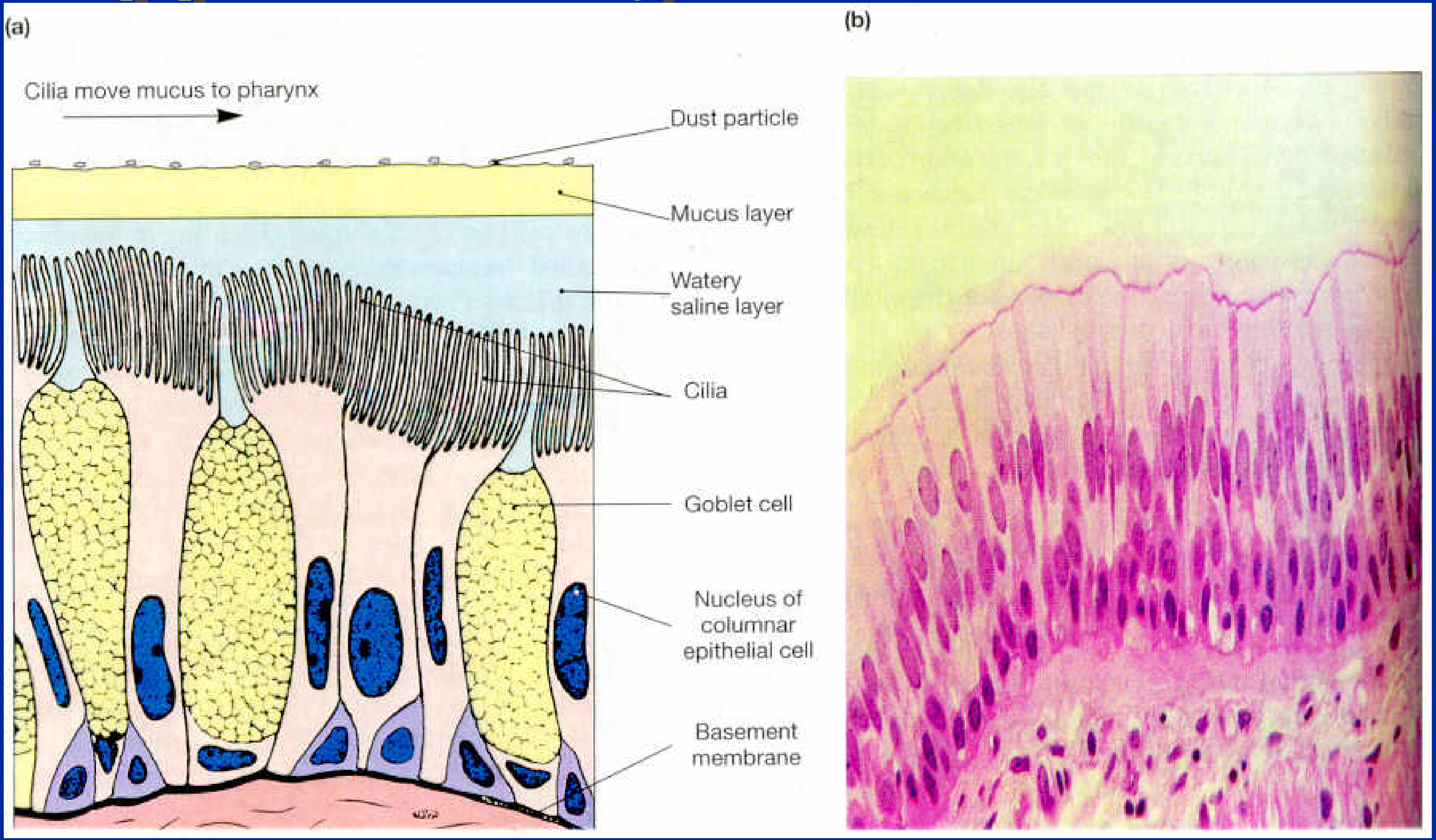
Squash court 75 meter sq. in a 3 liter soda bottle

Architecture



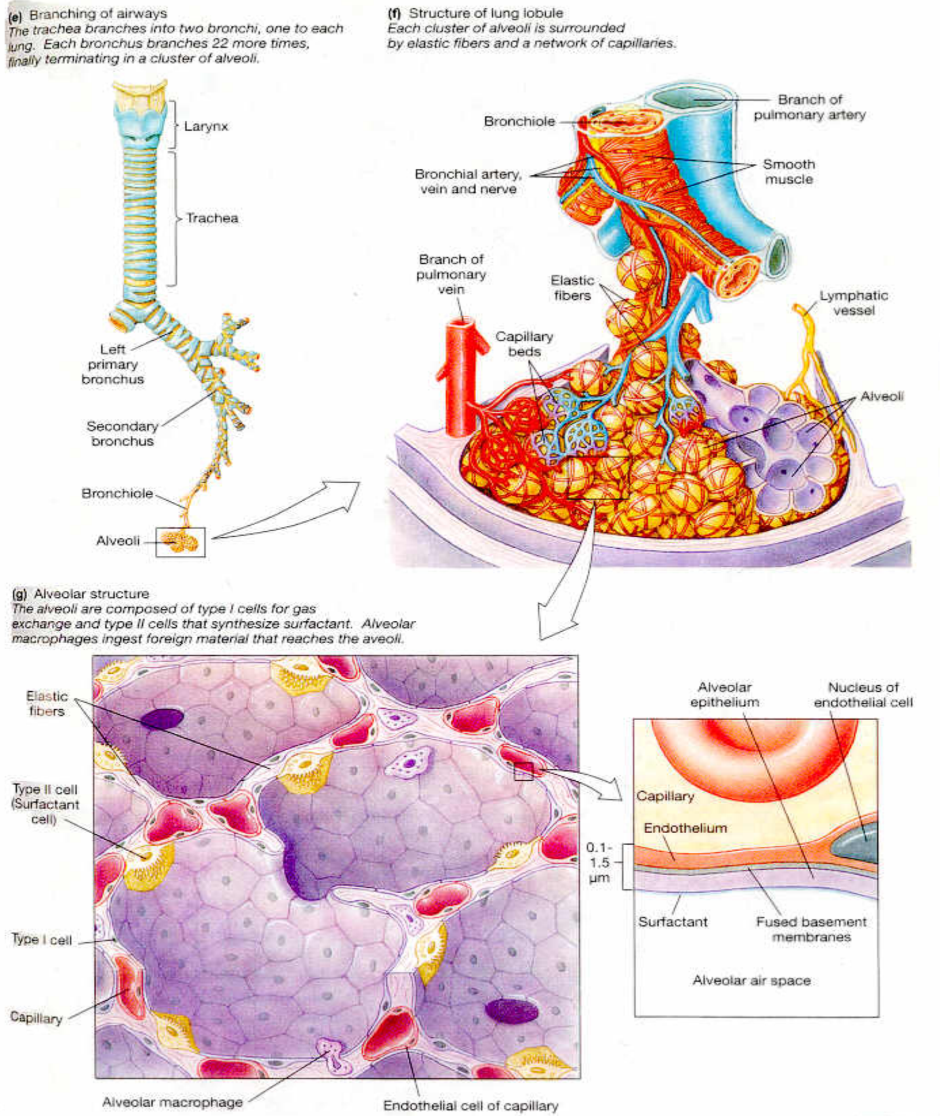
	Name	Division	How many?	Cross-sectional area (cm)
Conducting system	Trachea	0	1	2.5
	Primary bronchi	1	2	↓
	Smaller bronchi ↓	2	4 ↓	
		3		
		4		
		5		
		6-11	1×10^4	
	Bronchioles	12-23	2×10^4 ↓ 8×10^7	100 ↓ 5×10^3
Exchange surface	Alveoli	24	$3\text{-}6 \times 10^8$	$>1 \times 10^6$

Upper Airways

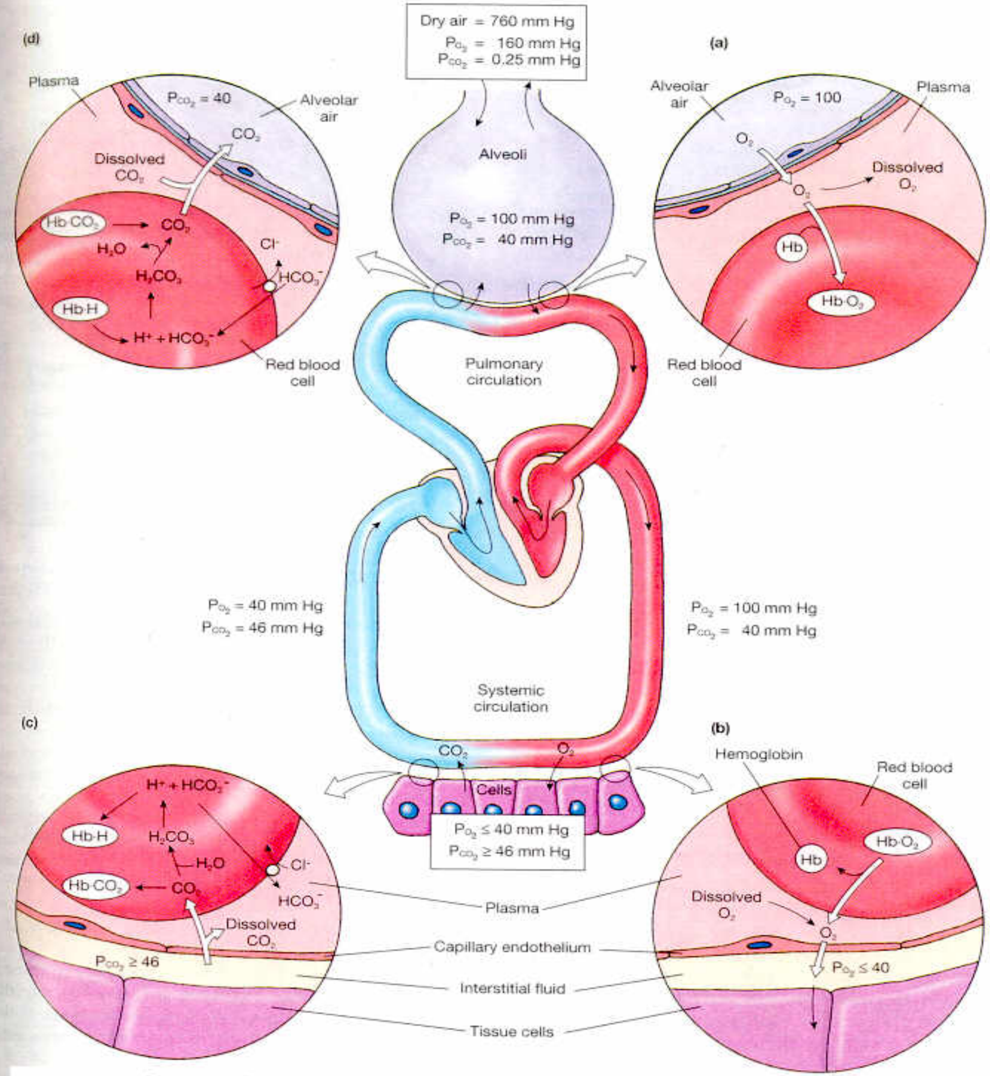


Deep Lung

- Bulk of lung tissue consist of exchange sacs known as alveoli
- Alveoli type I (exchange) Alveoli II cells (synthesis of surfactant)
- no SMC, but BM elastin
- Alveoli: blood air interface and mechanism of pressure, transport, diffusion etc become important
- Pulmonary circulation (pc) is a high-flow, low pressure system

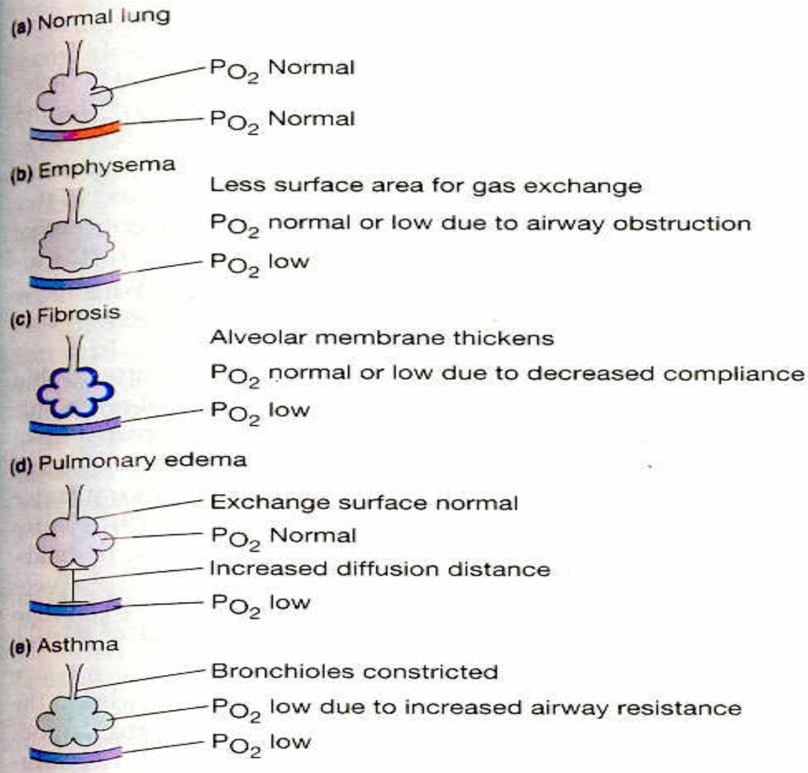


Summary



Summary of gas transport (a) Oxygen exchange between alveoli and blood. (b) Oxygen exchange from blood to cells. (c) Carbon dioxide exchange from cells to blood. (d) Carbon dioxide exchange from blood to alveoli.

Pathology



Pulmonary pathologies that affect alveolar ventilation and gas exchange (a) Normal lung. (b) In emphysema, destruction of alveoli results in less surface area for gas exchange. (c) In fibrotic lung diseases, thickening of the alveolar membrane from scar tissue will slow gas exchange. In addition, the loss of lung compliance may decrease alveolar ventilation, causing lower alveolar P_{O_2}. (d) In pulmonary edema, excess fluid in the interstitial space will increase the diffusion distance between the alveoli and the blood. P_{CO_2} in the arterial blood may be normal because of the higher solubility of carbon dioxide, but P_{O_2} is likely to be decreased. In addition, edema may cause a loss of compliance. (e) In asthma, narrowing of the bronchioles will cause a decrease in alveolar ventilation.

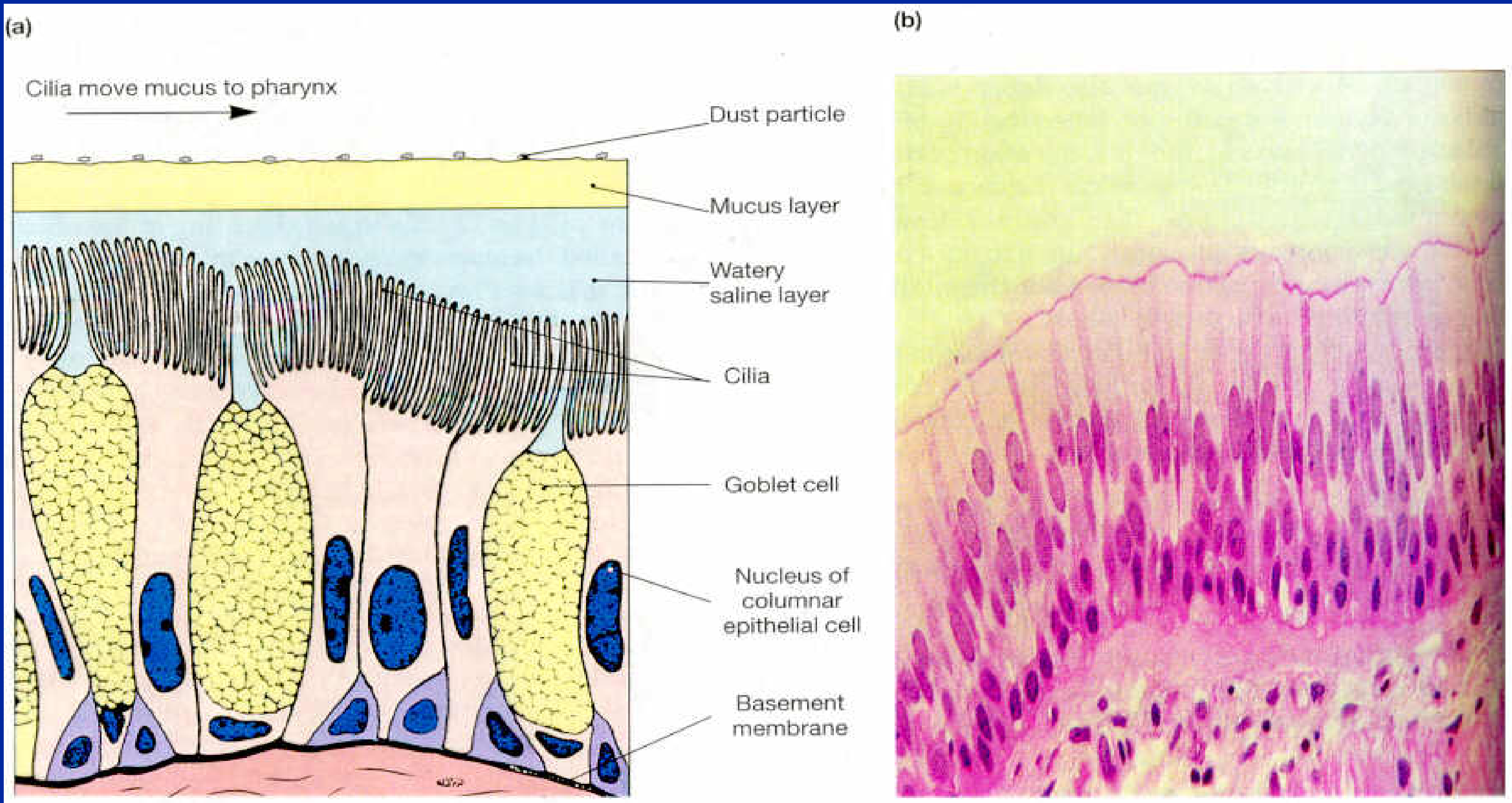
Epidemiological Trends in Asthma

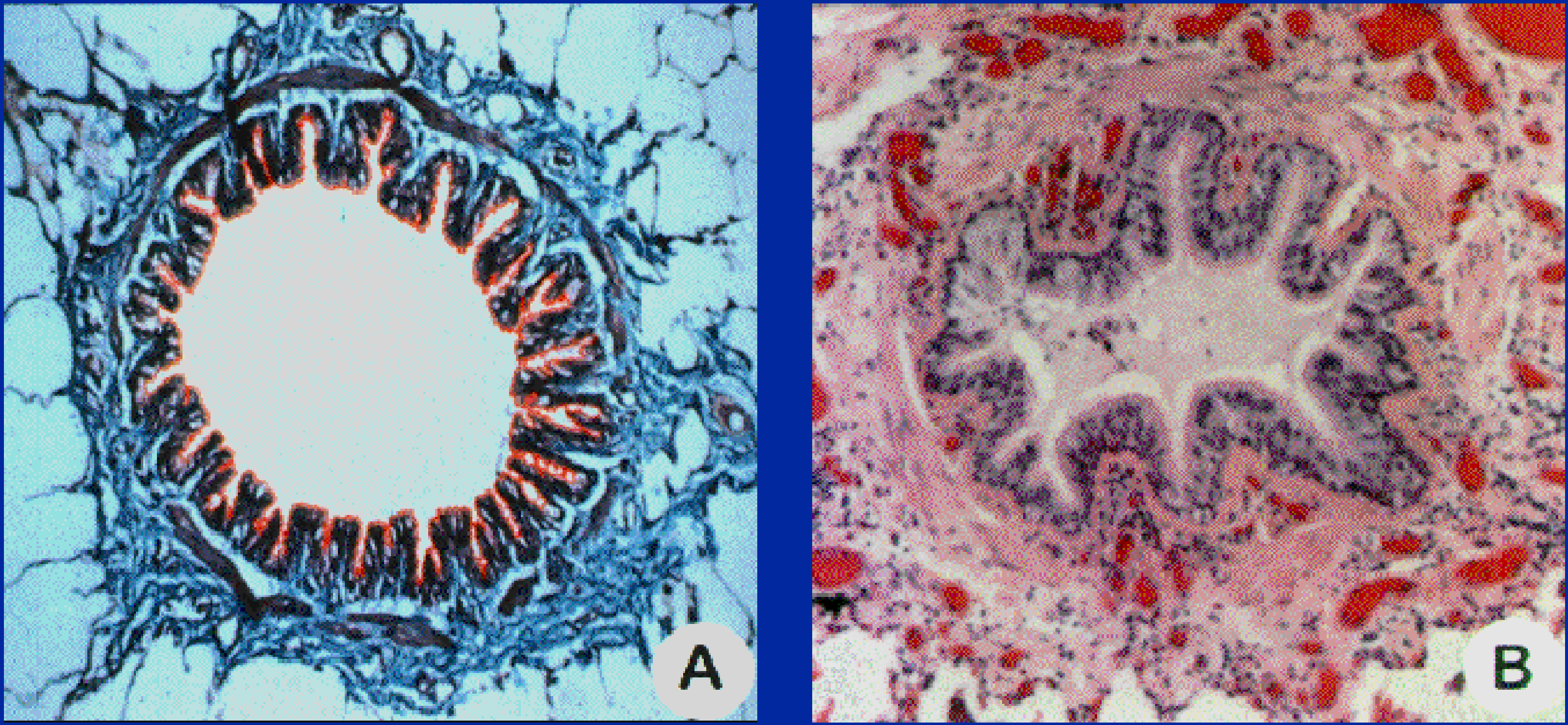
- Asthma affects 3% to 5% of the US population
- In the 90s, illness related costs were in excess of $6 billion/year in the US
- The death rate for asthma increased 40% 80s to 90s
- Asthma is particularly prevalent among children
- WTC syndrome - asthma-like disease due to ‘chemical’ dust

What and how?

- How does asthma affect airway narrowing?
- What is the role of the immune system in the disease process?
- What are the stimulus for remodeling?
- What are the structural changes that occur?
- What are the biochemical pathways that lead to wall remodeling?

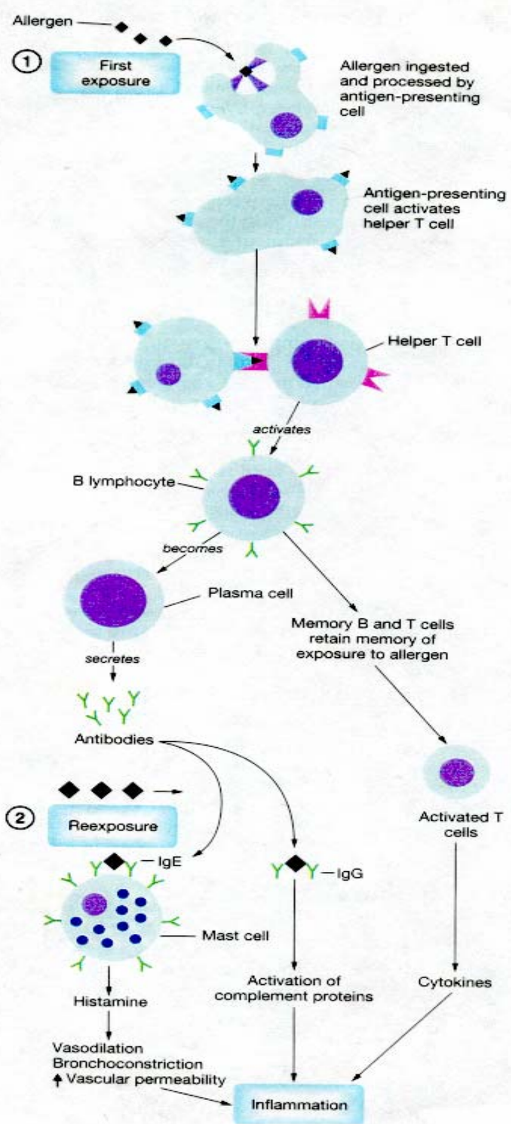
Airway Structure

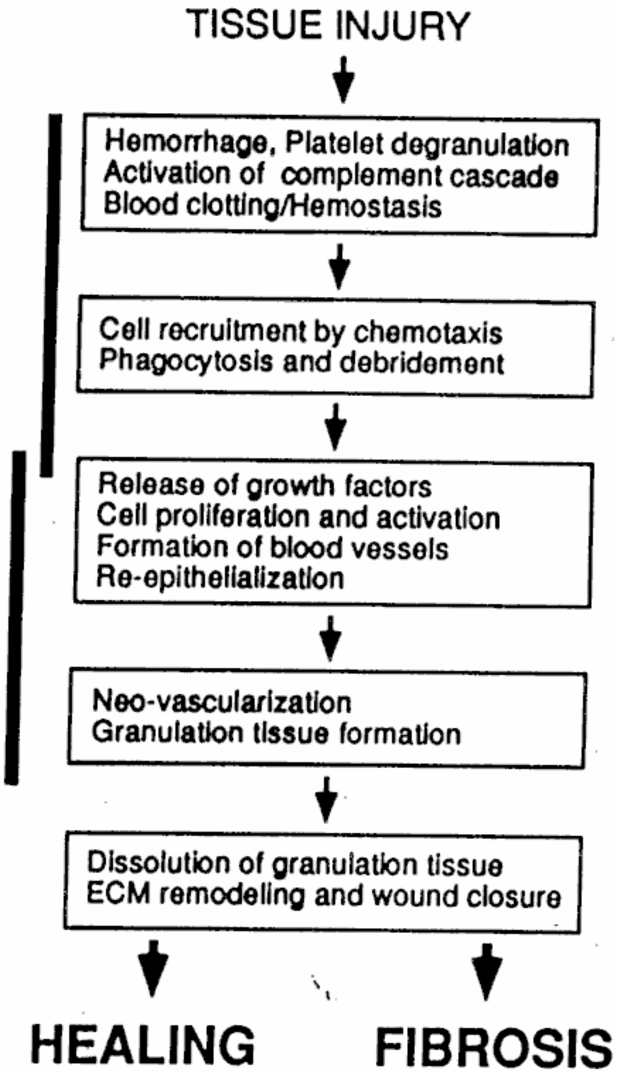




Constricted airways of normals (A) and asthmatics (B).
The asthmatic airway has a **thicker wall and fewer folds**,
leading to greater lumenal obstruction than in the normal airway.

Signaling Hierarchy





Induction & regulation of T_H cells.

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Please see:
Figure 3 in Liew, Foo Y. "TH1 and TH2 cells: a historical perspective." *Nature Reviews Immunology* 2, 55 - 60 (01 Jan 2002).

Transcriptional regulation of T_H cells

Please see:
Figure 4 in Liew, Foo Y. "TH1 and TH2 cells: a historical perspective." *Nature Reviews Immunology* 2, 55 - 60 (01 Jan 2002).

TCR Complex

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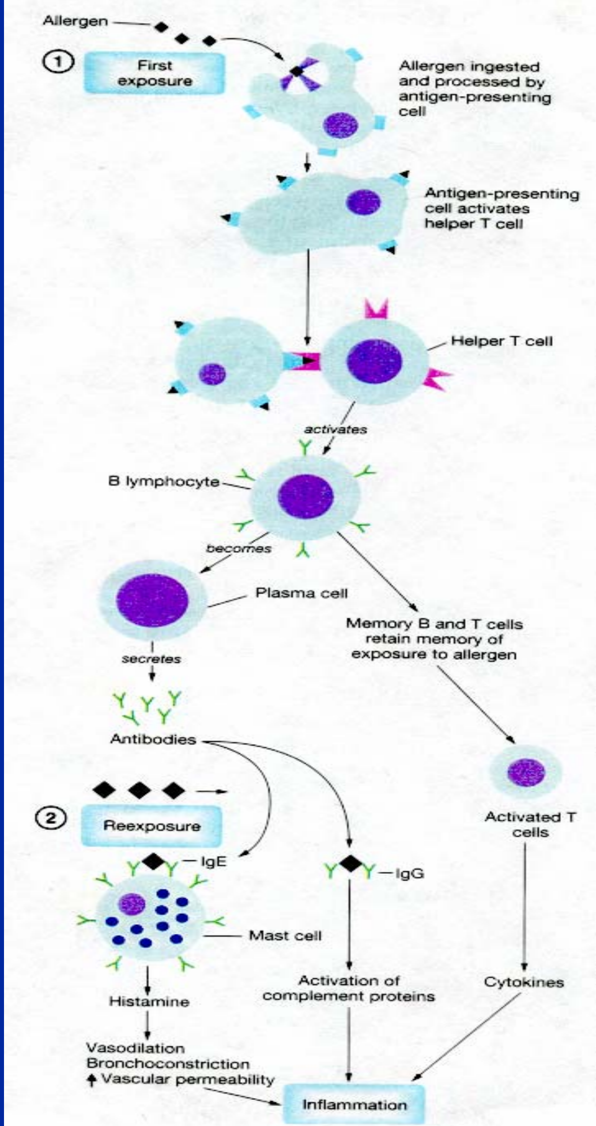
Please see:
Figure 1 in Koretzky, Gary A. and Myung, Peggy S. "Positive and negative regulation of T-cell activation by adaptor proteins." *Nature Reviews (Immunology)*, vol. 1, November 2001, pp. 95-97.

Asthma Immune System Overview



B Cell Regulation

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Please see:
Figure 2 in Hiroaki Niiro, Edward A. Clark. "Decision making in the Immune System: Regulation of B-cell fate by antigen-receptor signals." *Nature Reviews Immunology* 2, 945 - 956 (01 Dec 2002).

B Cell
Signal Transduction

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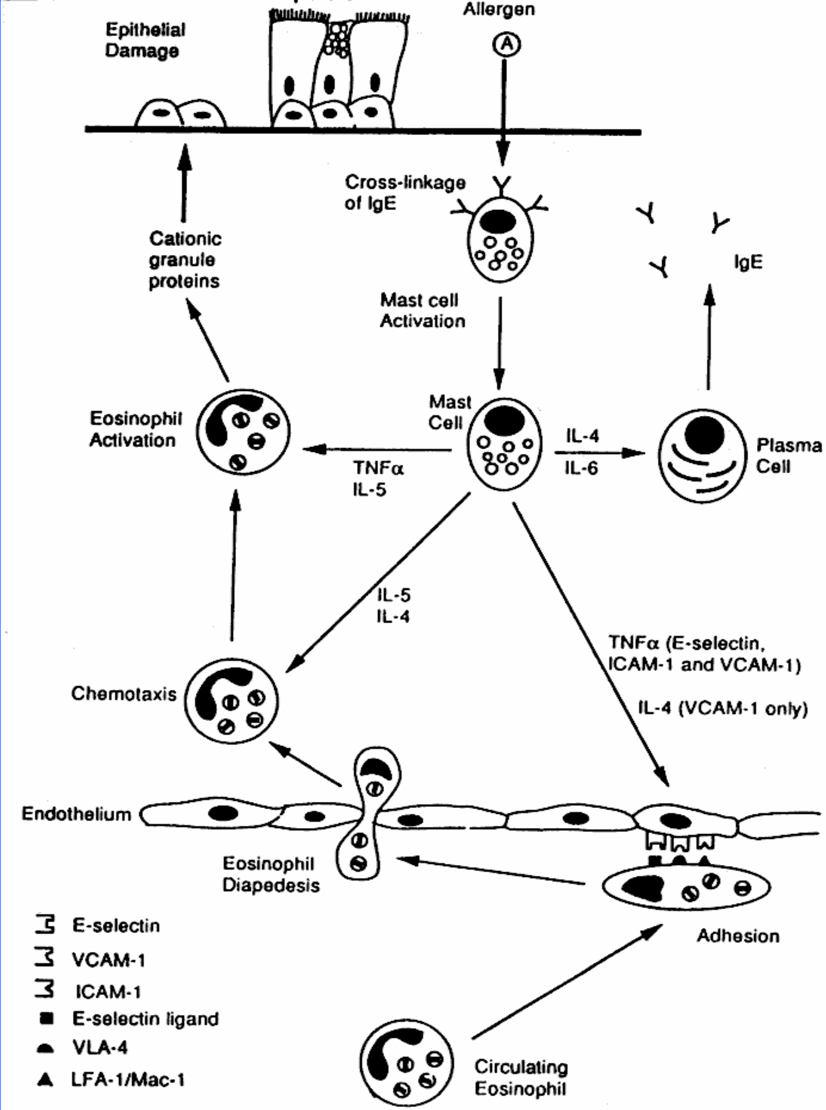
Please see:
Figure 1 in Hiroaki Niiro, Edward A. Clark. "Decision making in the Immune System: Regulation of B-cell fate by antigen-receptor signals." *Nature Reviews Immunology* 2, 945 - 956 (01 Dec 2002).

Asthma
Immune System
Overview
Early Response



Mast Cells

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Please see:
Box 1 in Toshiaki Kawakami, Stephen J. Galli. "Regulation of mast-cell and basophil function and survival by IgE." *Nature Reviews Immunology* 2, 773 - 786 (01 Oct 2002).

Mast Cell Activation

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Figure 1 in Toshiaki Kawakami, Stephen J. Galli. "Regulation of mast-cell and basophil function and survival by IgE." *Nature Reviews Immunology* 2, 773 - 786 (01 Oct 2002).

Mast Cell Activation

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Please see:
Figure 3 in Toshiaki Kawakami, Stephen J. Galli. "Regulation of mast-cell and basophil function and survival by IgE." *Nature Reviews Immunology* 2, 773 - 786 (01 Oct 2002).

Asthma pathogenesis

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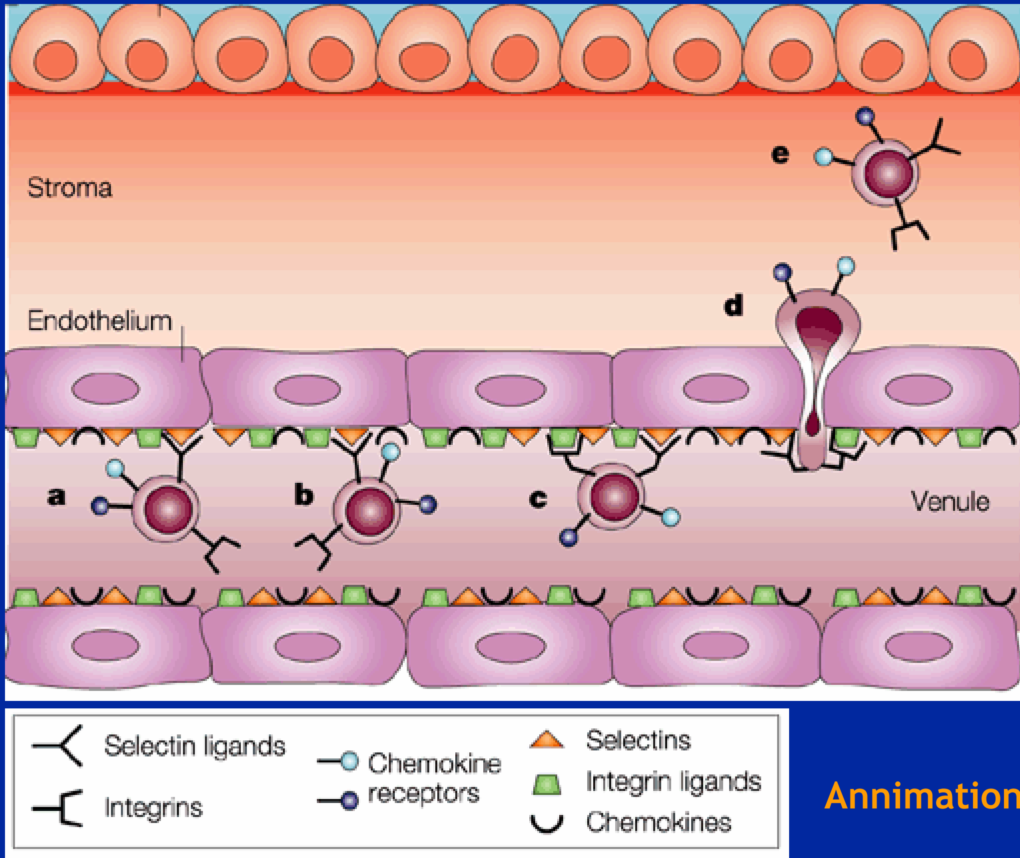
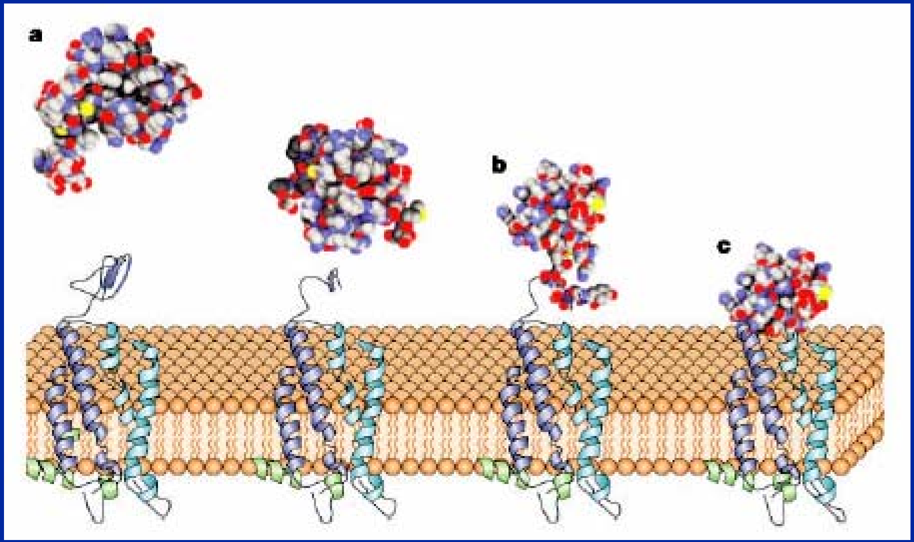
Please see:
Figure 1 in Nicholas W. Lukacs. "Role of chemokines in the pathogenesis of asthma." *Nature Reviews Immunology* 1, 108 - 116 (01 Nov 2001).

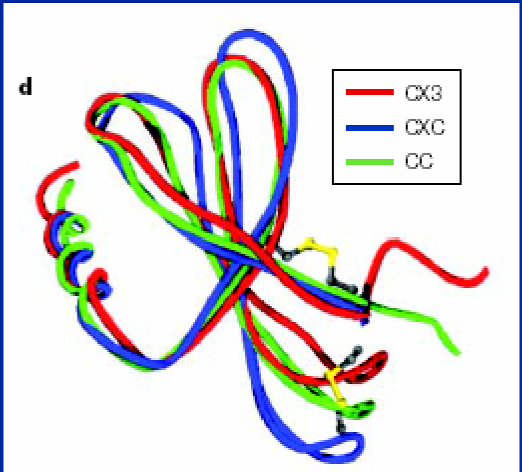
Leukocyte Rolling



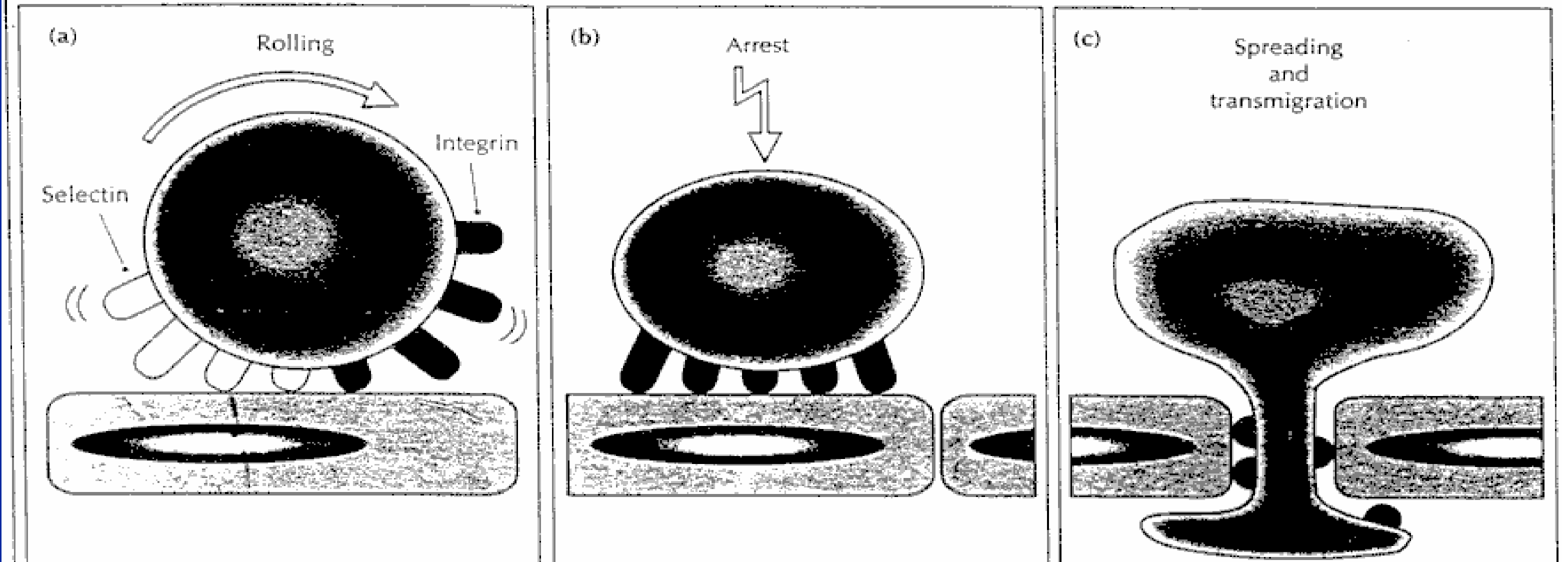
Annimation

Chemokine Signaling





Leukocyte rolling and transmigration

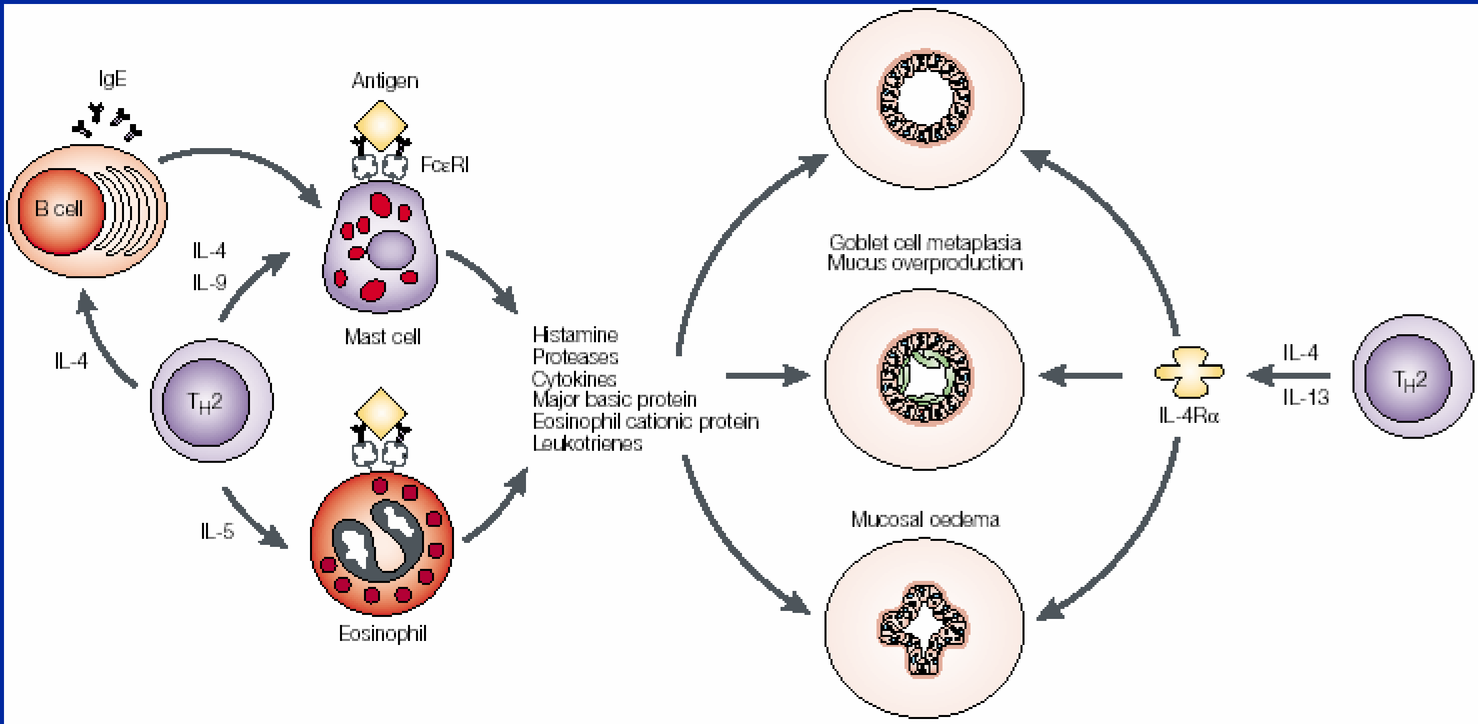


T lymphocytes, monocytes and eosinophils roll by means of the selectins (L-selectin on lymphocytes; E- and P-selectins on endothelium) and the integrins ($\alpha 4\beta 1$ and $\alpha 4\beta 7$). This activity does not appear to require integrin activation.

Cellular arrest occurs under conditions of flow when $\alpha 4$ integrin binds firmly to its ligand VCAM-1 after becoming activated. The molecular details of activation are not yet certain; candidates are inflammatory mediators such as platelet activating factor (PAF) or chemokines, possibly the selectins, and ligand itself may induce necessary changes for stable binding.

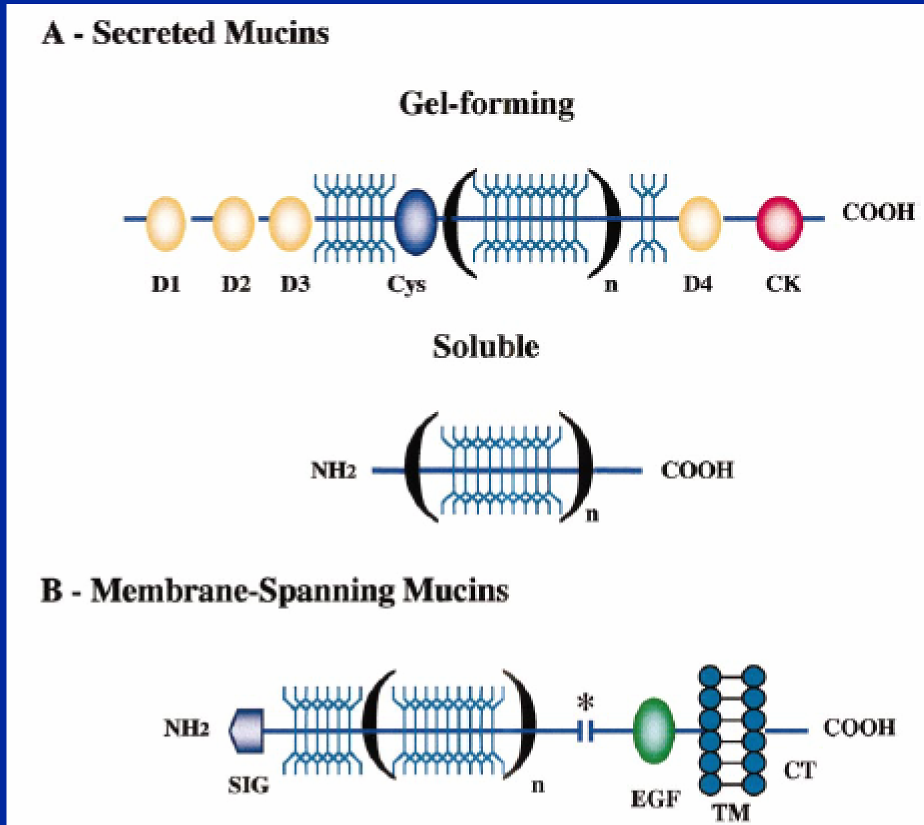
Leukocytes use the $\beta 2$ integrins LFA-1 and Mac-1 to firmly adhere to the endothelium, flatten and move into the tissue space via ligation with ICAM-1. In some circumstances, the $\alpha 4\beta 1$ integrin can accomplish this goal independently of the $\beta 2$ integrins.

Airway Hyper-responsiveness



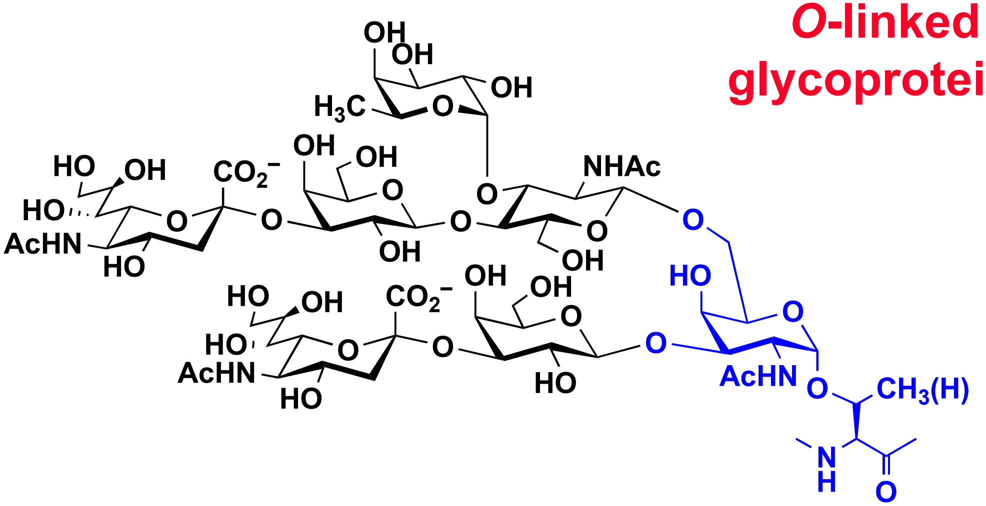
Mucins

Gel forming	MUC2	11p15·5
	MUC5AC	11p15·5
	MUC5B	11p15·5
	MUC6	11p15·5-p15·4
Soluble	MUC7	4q13-q21
	MUC9	1p13
Transmembrane	MUC1	1q21
	MUC3A	7q22
	MUC3B	7q22
	MUC4	3q29
	MUC12	7q22
	MUC13	3q13·3
Unknown	MUC8	12q24·3
	MUC11	7q22



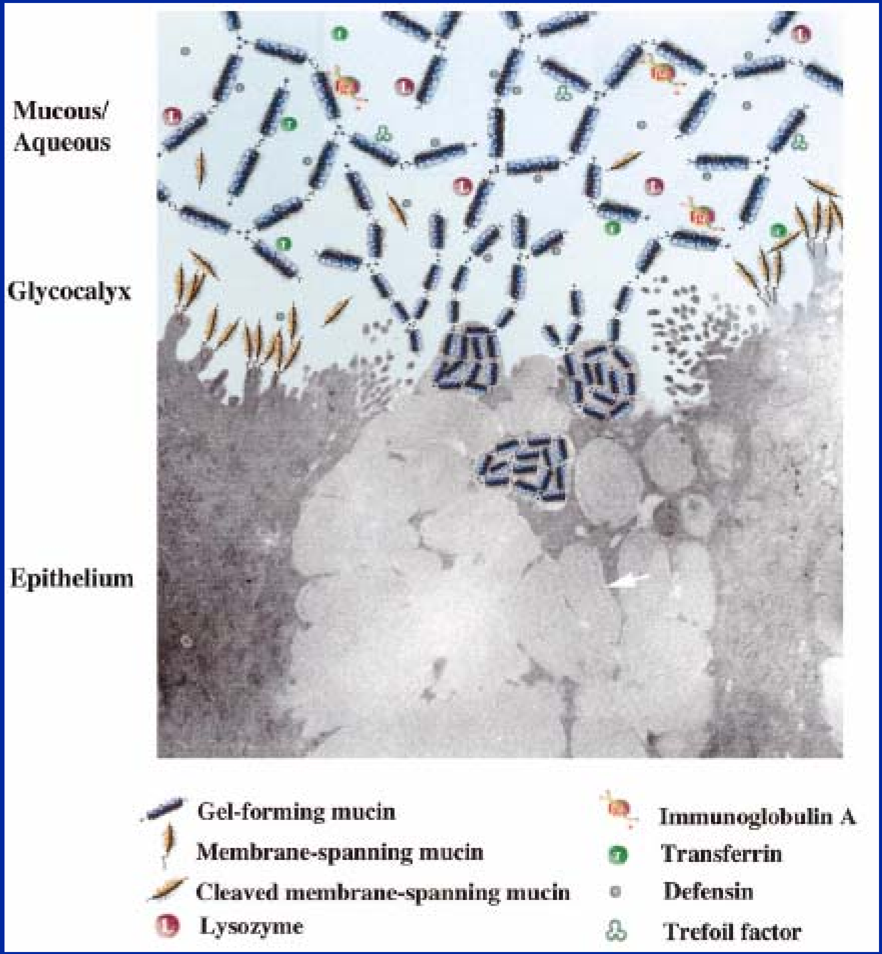
Sugar Chains in Mucins

Mucin-type *O*-linked glycoproteins



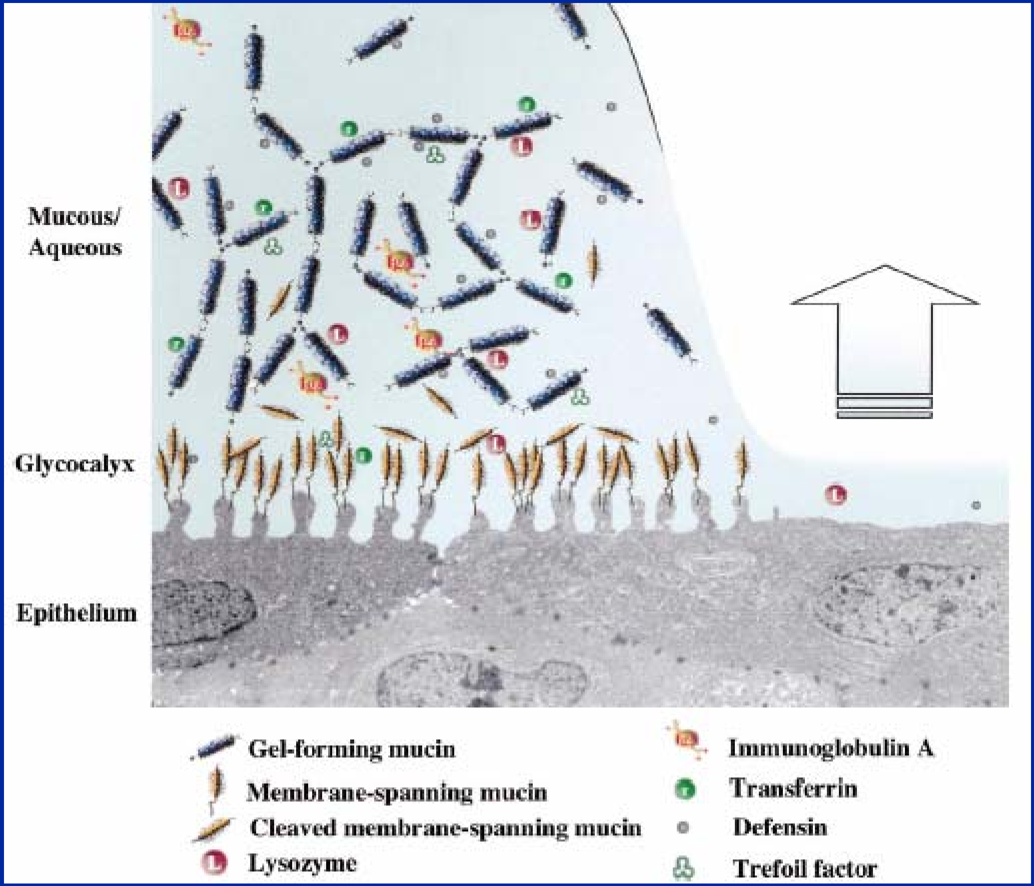
The one commonality of mucin-type *O*-linked glycans is their core GalNAc residue

Mucins

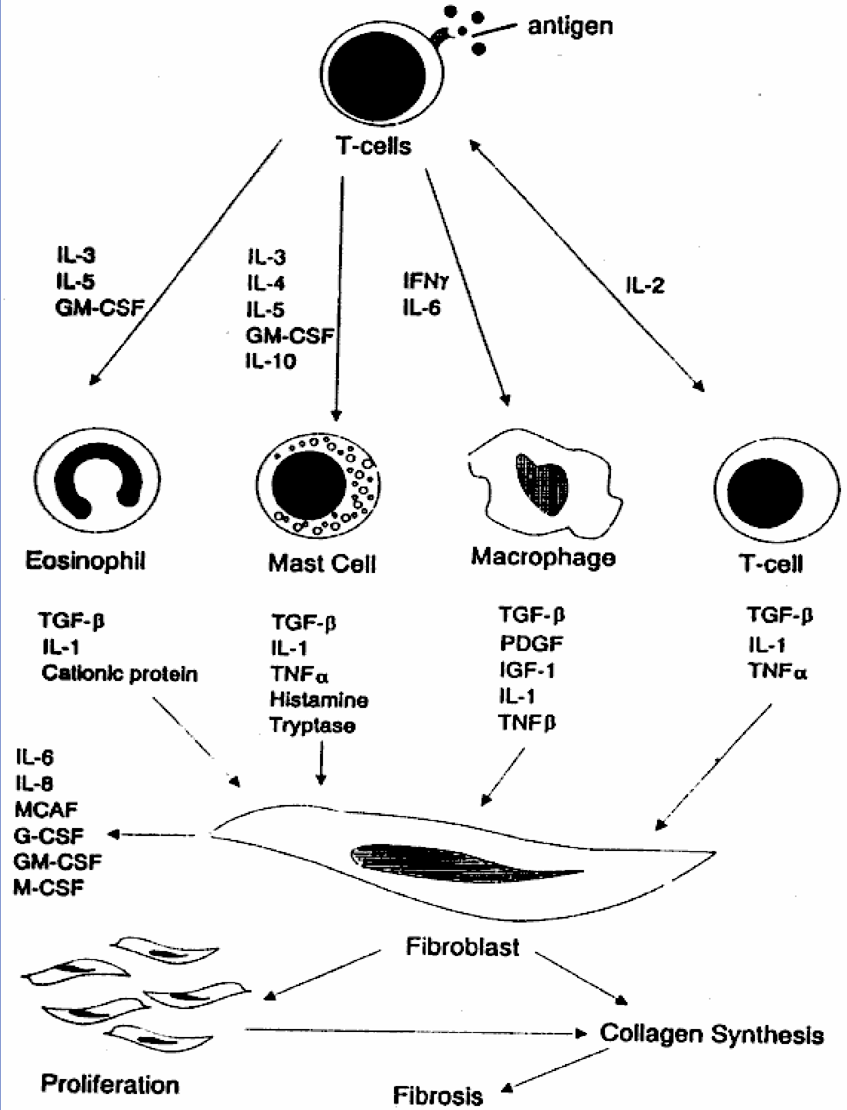


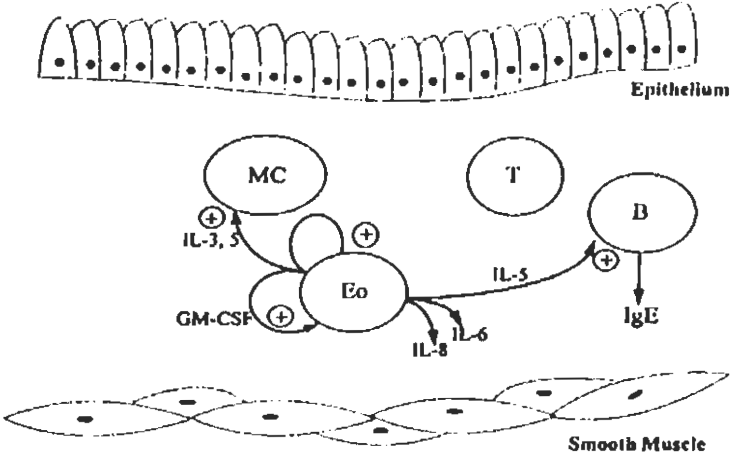
Mucous/
Aqueous
Glycocalyx
Epithelium
Gel-forming mucin
Membrane-spanning mucin
Cleaved membrane-spanning mucin
Lysozyme
Immunoglobulin A
Transferrin
Defensin
Trefoil factor

Mucin Changes

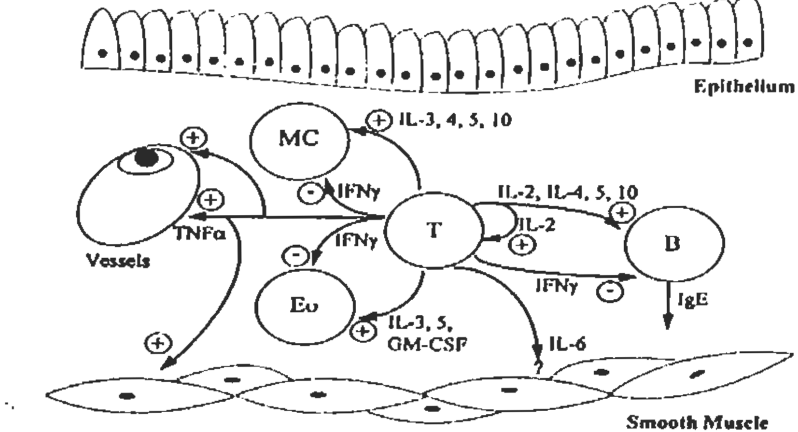


Acute to Chronic

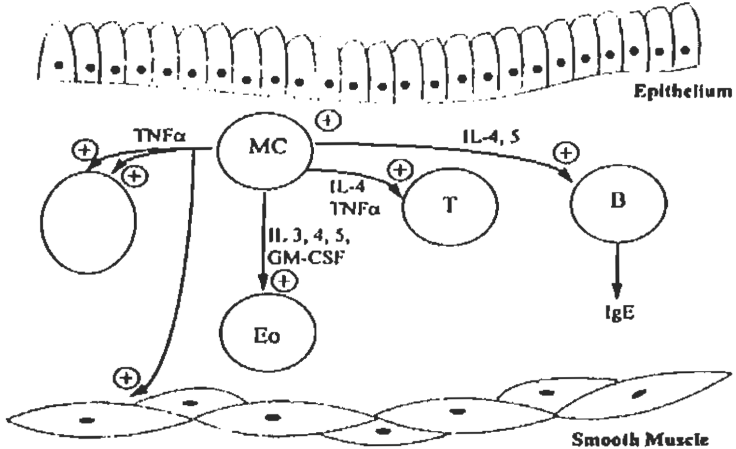




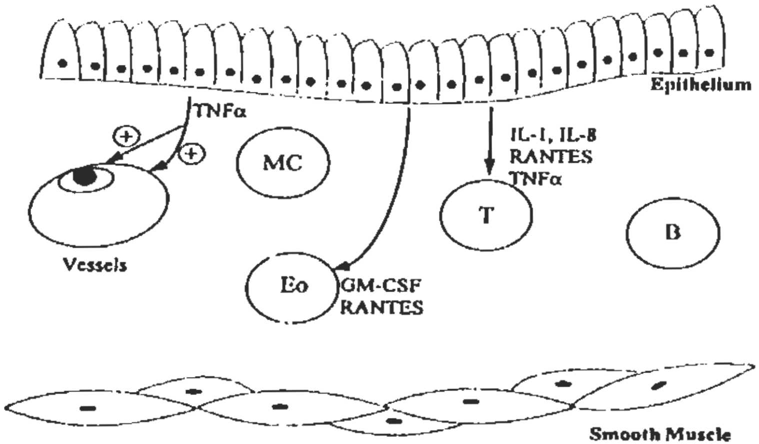
Eosinophils produce IL-1, IL-2, IL-3, IL-5, IL-6, IL-8, GM-CSF, and TGFβ.



T-lymphocytes. Th1 produces IL-2, IL-3, GM-CSF, IFNγ, TNFα, and TNFβ; Th2 produces IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and GM-CSF.

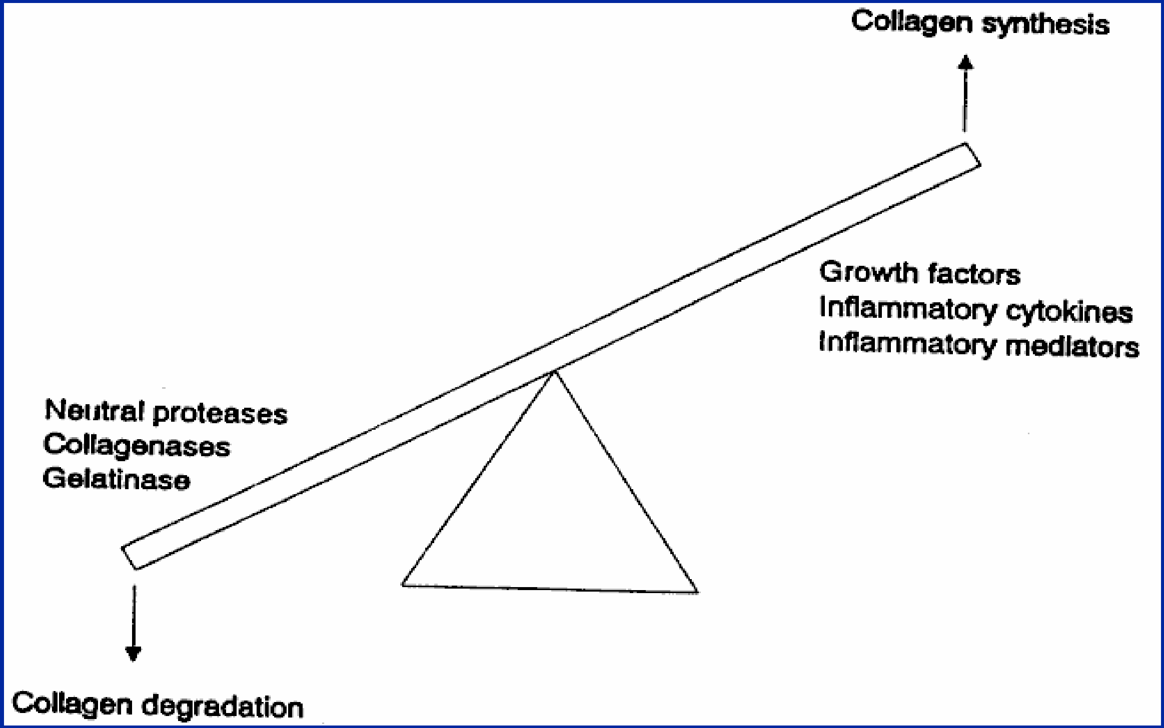


Mast cells produce IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, GM-CSF, TNFα, and TGFβ.

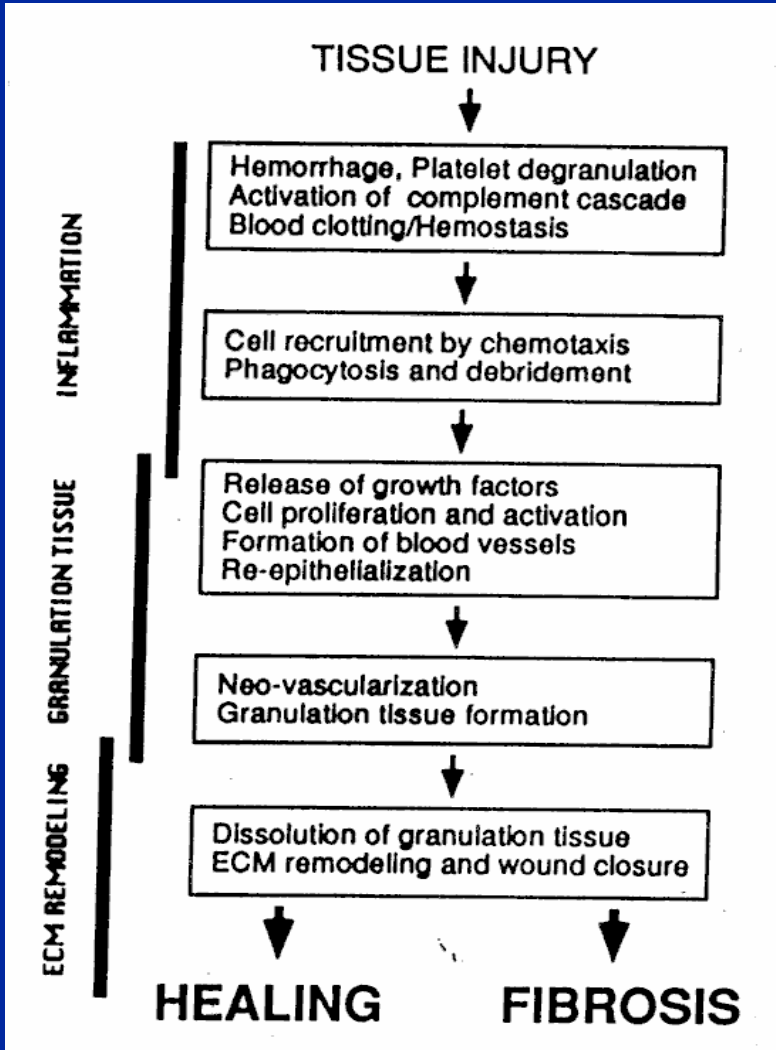


Epithelial cells produce IL-1, IL-6, IL-8, GM-CSF, TNFα, and RANTES.

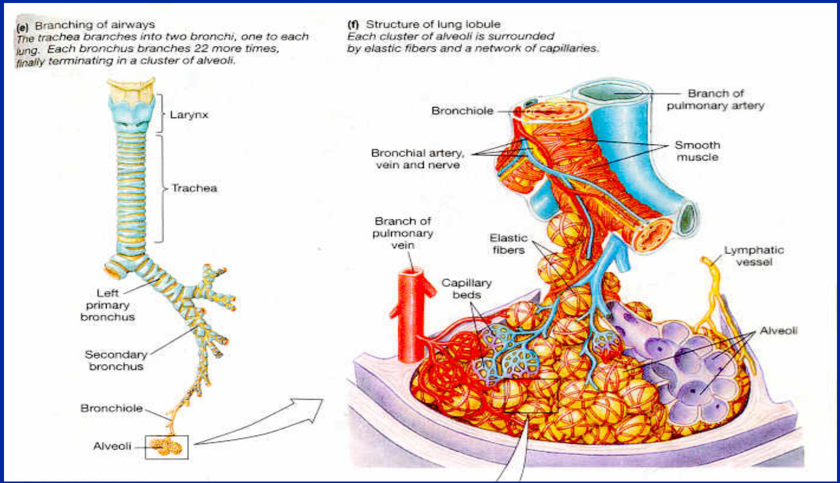
Balance


Collagen synthesis
Growth factors
Inflammatory cytokines
Inflammatory mediators
Neutral proteases
Collagenases
Gelatinase
Collagen degradation

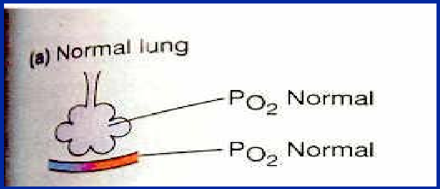
Signaling Hierarchy



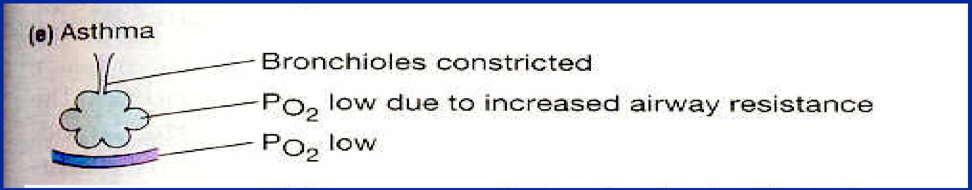
Pathology



(e) Branching of airways
The trachea branches into two bronchi, one to each lung. Each bronchus branches 22 more times, finally terminating in a cluster of alveoli.
Larynx
Trachea
Left primary bronchus
Secondary bronchus
Bronchiole
Alveoli
(f) Structure of lung lobule
Each cluster of alveoli is surrounded by elastic fibers and a network of capillaries.
Bronchiole
Branch of pulmonary artery
Bronchial artery, vein and nerve
Smooth muscle
Branch of pulmonary vein
Elastic fibers
Lymphatic vessel
Capillary beds
Alveoli



(a) Normal lung
PO2 Normal
PO2 Normal



(e) Asthma
Bronchioles constricted
PO2 low due to increased airway resistance
PO2 low