

Pathology of the Respiratory System

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Disclaimer: While this material provides an over view of the field, it does not attempt to cover all diseases and the most recent scientific findings in the field.

General Pathology of the Respiratory System: Structure and Cell Biology

Respiratory System

- Conducting System
 - Nasal passages
 - Paranasal sinuses
 - Larynx, pharynx, trachea
 - Bronchi
- Transitional System
 - Bronchioles
- Gas exchange
 - Alveoli
- Respiratory system has many other functions
- Lymphoid system

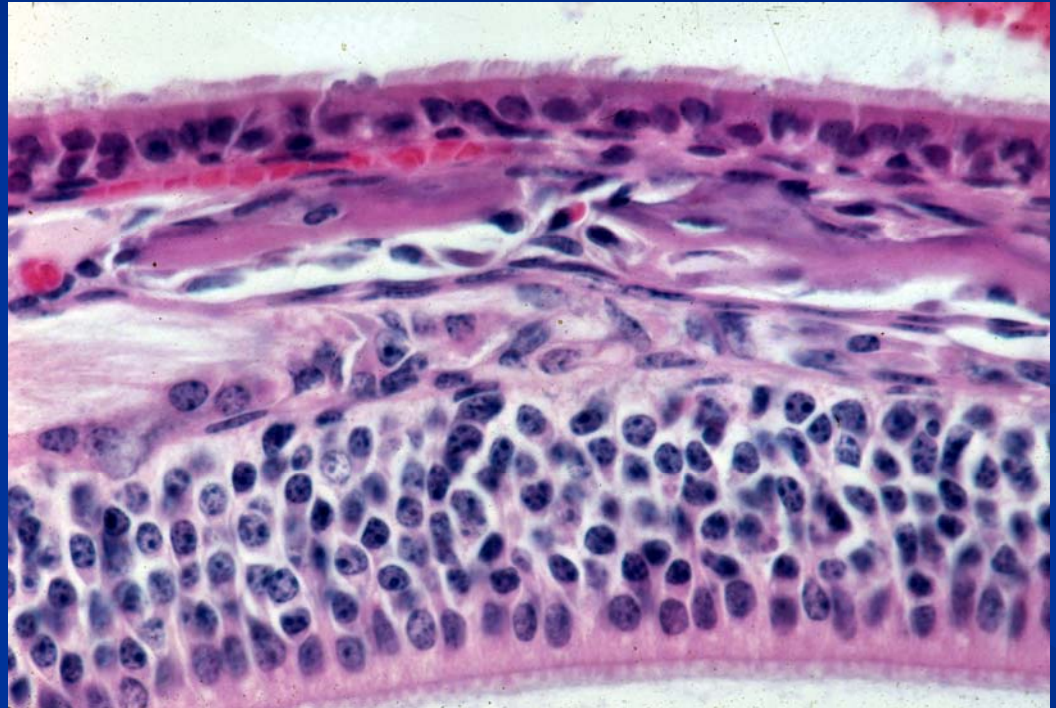
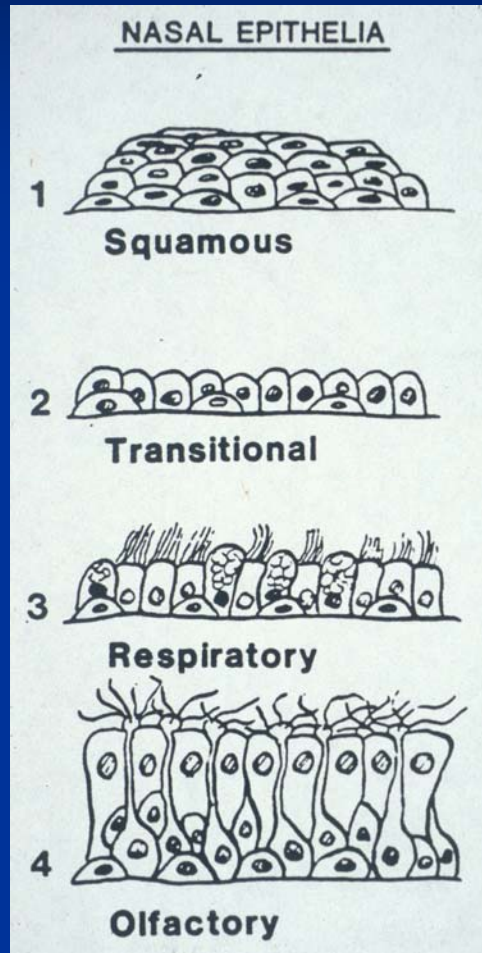
Conducting Airway Function

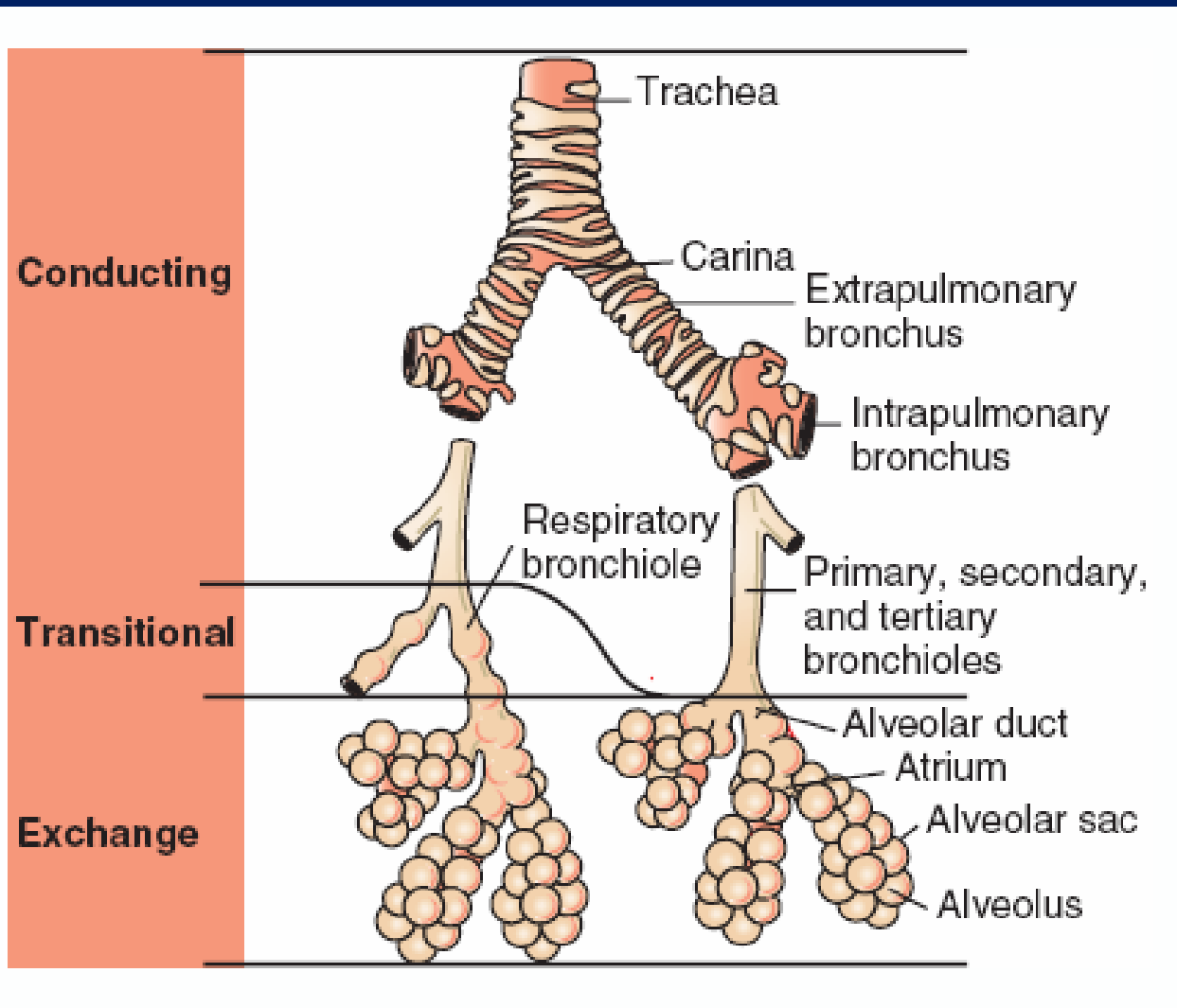
- Conduct, humidify and warm air
- Smell-find food, protection, pheromones
- Absorption of water soluble gases (SO_2 , O_3)
- "Filter" out all particles $\geq 10 \mu\text{m}$ in nasal cavity, particles $\geq 3 \mu\text{m}$ \nless lung
- Mucociliary clearance of particles including viruses and bacteria

Conducting Airway Function (cont)

- Protective reflexes: sneeze, cough reflex, broncho-constriction
- Xenobiotic metabolism – detoxification e.g. olfactory epithelium, Clara cells
- Immune function
- Nonspecific defenses - interferon, lysozyme, lactoferrin
- Normal flora - prevents colonization by pathogens

Nasal Epithelium



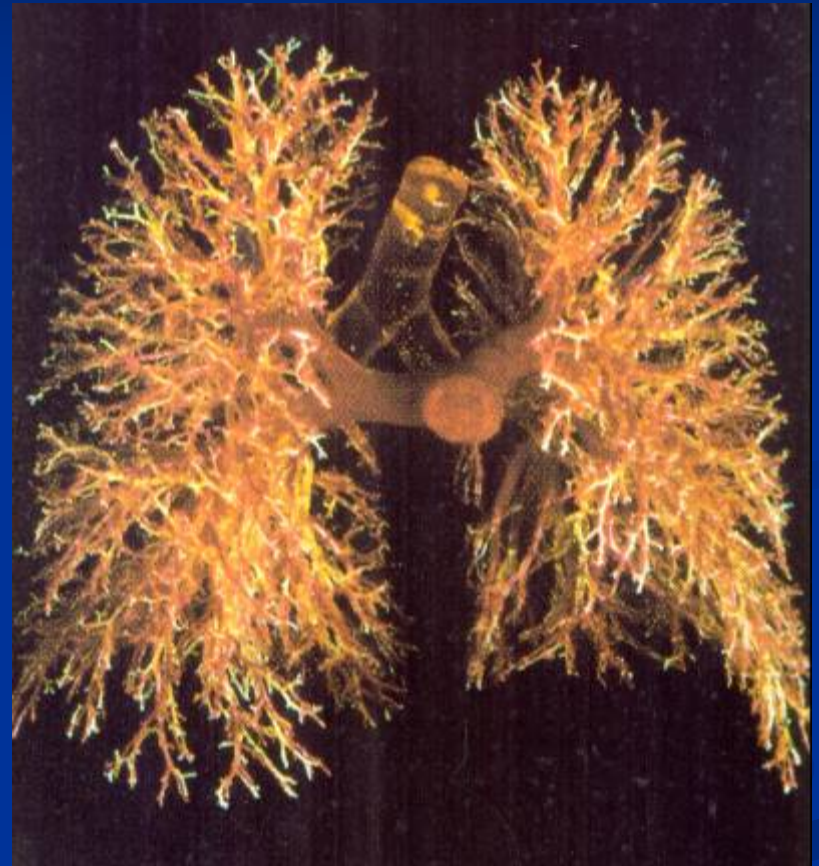


Comparative Respiratory Anatomy/Physiology

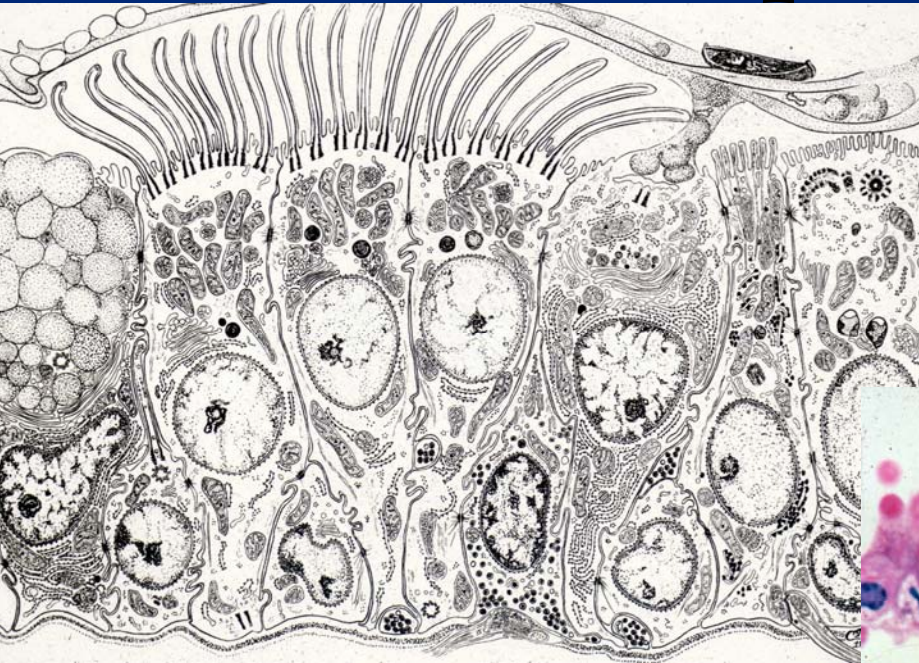
Airway Features	Mouse	Rat	Human
Branching Pattern of Airways	Monopodial	Monopodial	Dichotomous Symmetrical
Airway Generations	13-17	12-20	17-21
Respiratory Bronchioles	Absent	Absent	Extensive
Cartilage and Submucosal Glands in Intrapulmonary Bronchi	Absent	Absent	Present
Clara Cells (bronchi/bronchioles)	Abundant	Abundant	Less Abundant
Serous Cells in the Respiratory Epithelium	Absent	Present	Absent

Bronchi

- Epithelium
 - Pseudostratified ciliated columnar cells
 - Basal cells
 - Ciliated cells
 - Secretory cells
- Lamina propria mucosa
 - Elastic fibers
- Lamina muscularis mucosa
 - Smooth muscle fibers
- Propria - submucosa
- Hyaline cartilage
- Smooth muscle



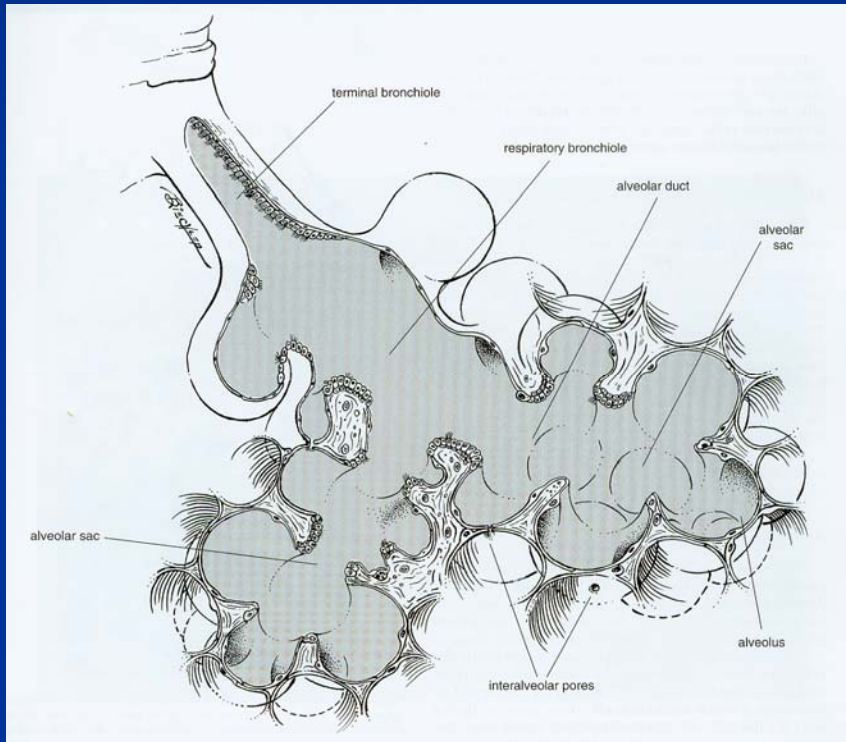
Bronchial/Bronchiolar Epithelium



- Ciliated cells
- Secretory cells
 - Serous and mucous cells decrease distally and Clara cells increase distally



Bronchioles



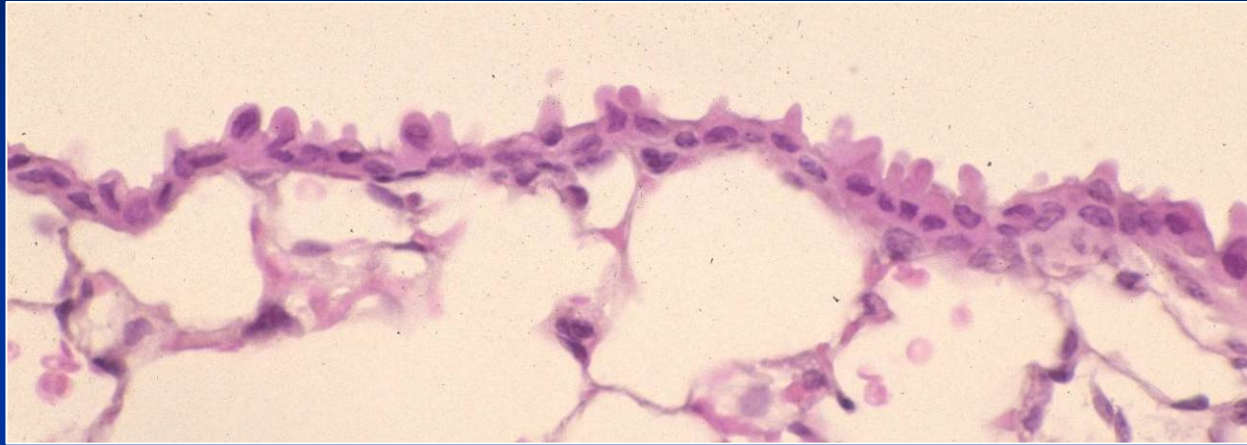
■ Epithelium

- Simple columnar or cuboidal
- Ciliated cells
- Clara cells
- NO mucous cells

■ Respiratory bronchioles

- In some species

Bronchioles – Clara Cells



- Non ciliated, columnar
- Secretory
- Cytochrome P450 enzyme rich
 - Similar to hepatocytes in liver
 - Species dependent
 - Also present in some alveolar cells

Gross Anatomy of the Lung

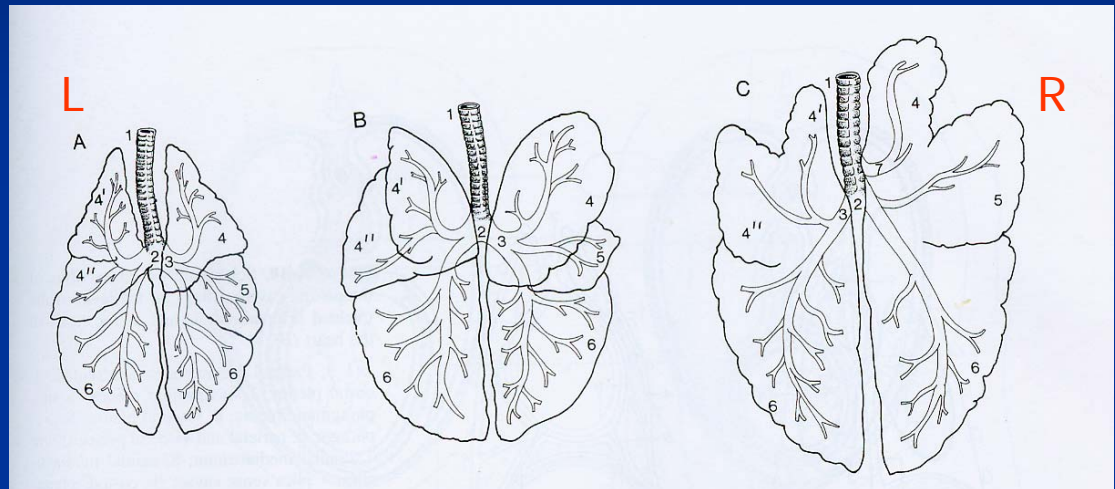
■ Basic anatomy:

■ Right side

- Cranial
- Middle
- Caudal
- Accessory

■ Left side

- Cranial (divided in most species)
- Caudal



Cat

Dog

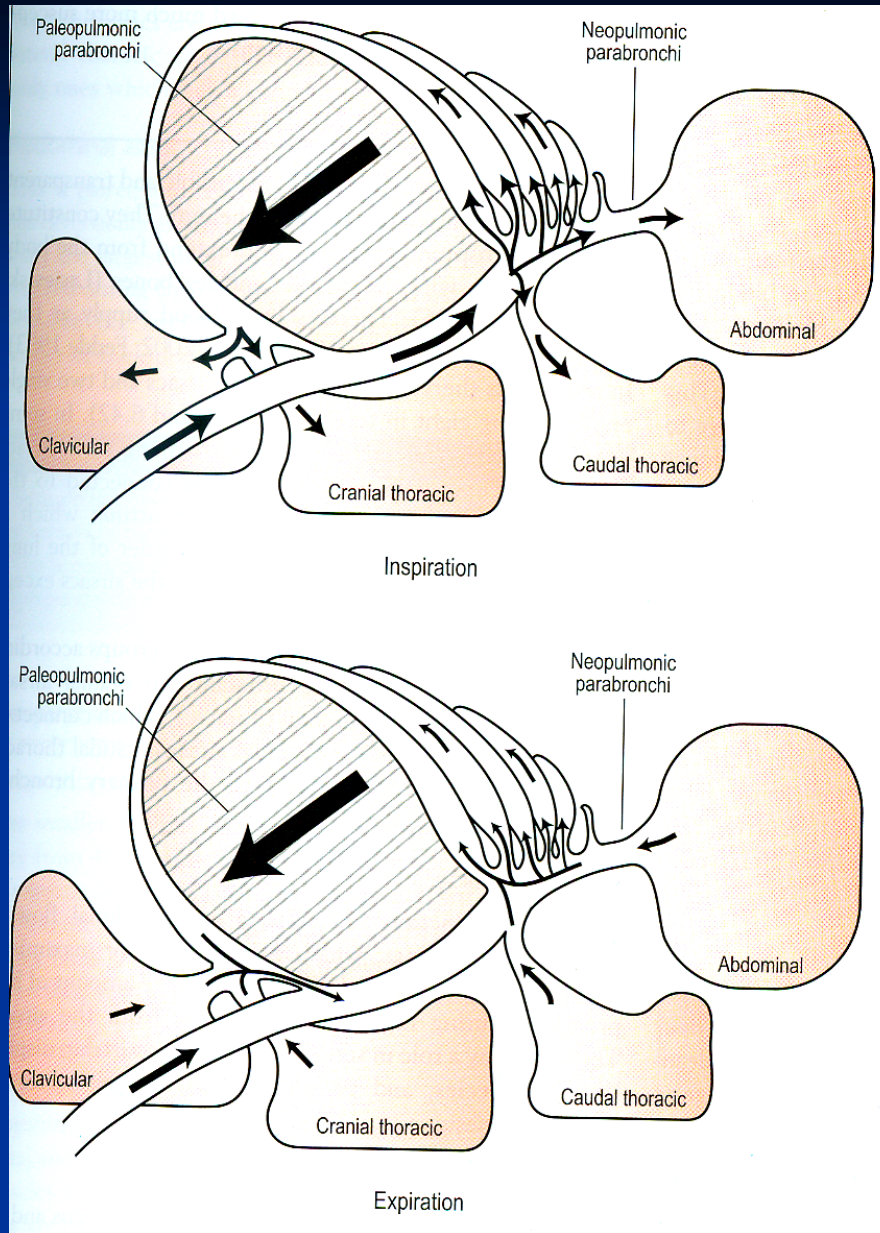
Pig

Comparative Respiratory Anatomy/Physiology

Lung Features	Cattle, Pigs	Sheep, Goats	Horses, Humans
Lobation	Good	Good	Poor
Secondary Lobulation	Good	Poor	Incomplete
Collateral Ventilation	Poor		Good
Pleura	Thick	Thick	Thick
Muscular layer of pulmonary blood vessels	Thick	Thick	Thick

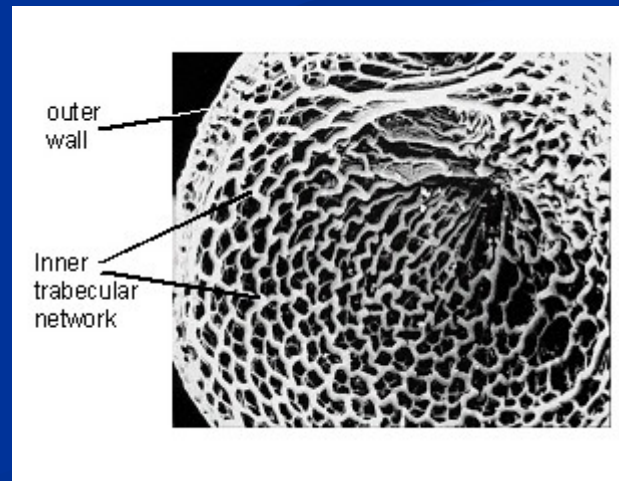
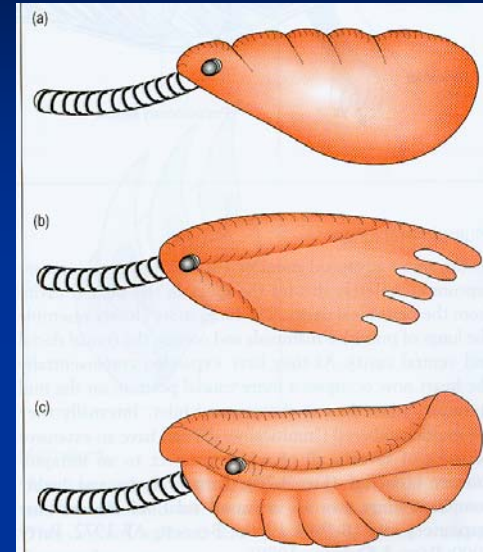
Birds

- Air sacs
- Parabronchi and air capillaries

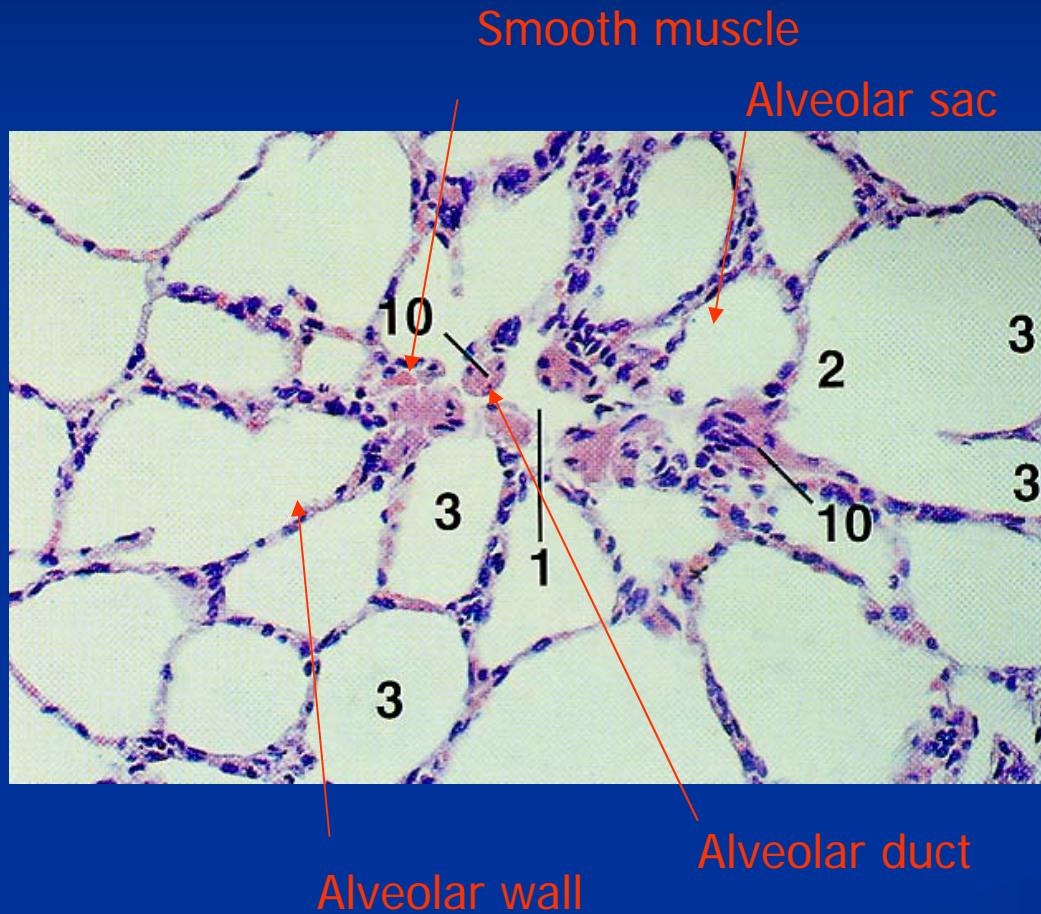


Reptiles

- Reptiles
 - Faveoli
 - Smooth muscle in the lung walls
 - Classified according to chambers
 - Unicameral
 - Paucicameral
 - Multicameral



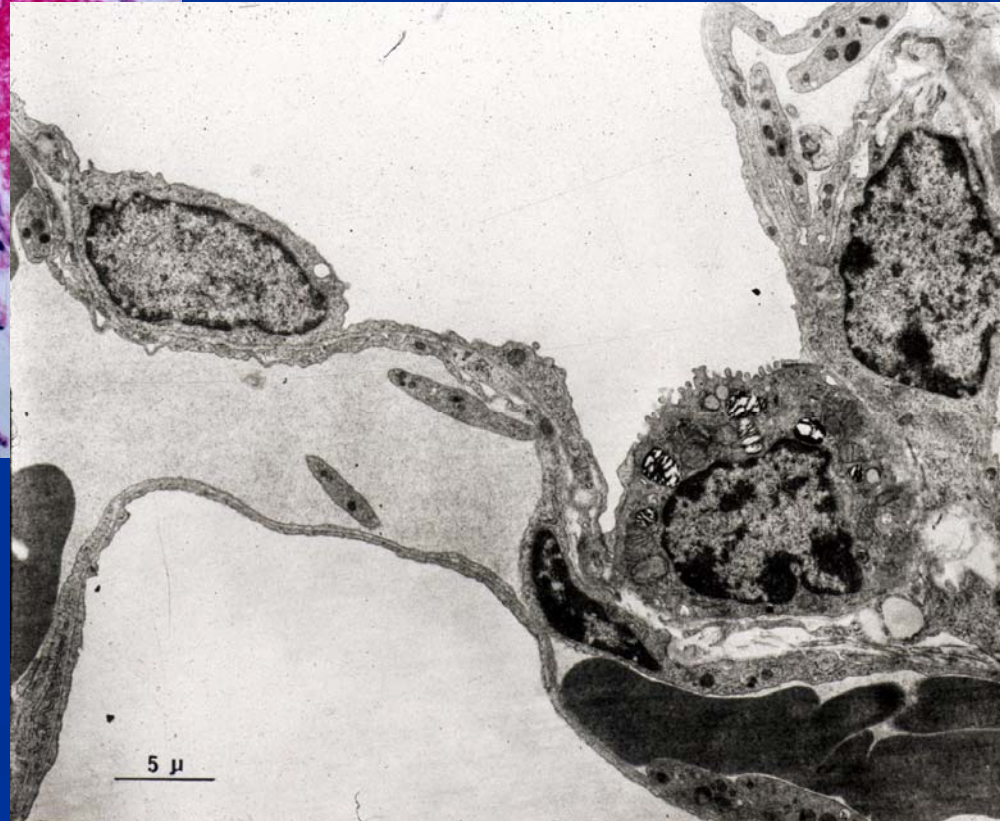
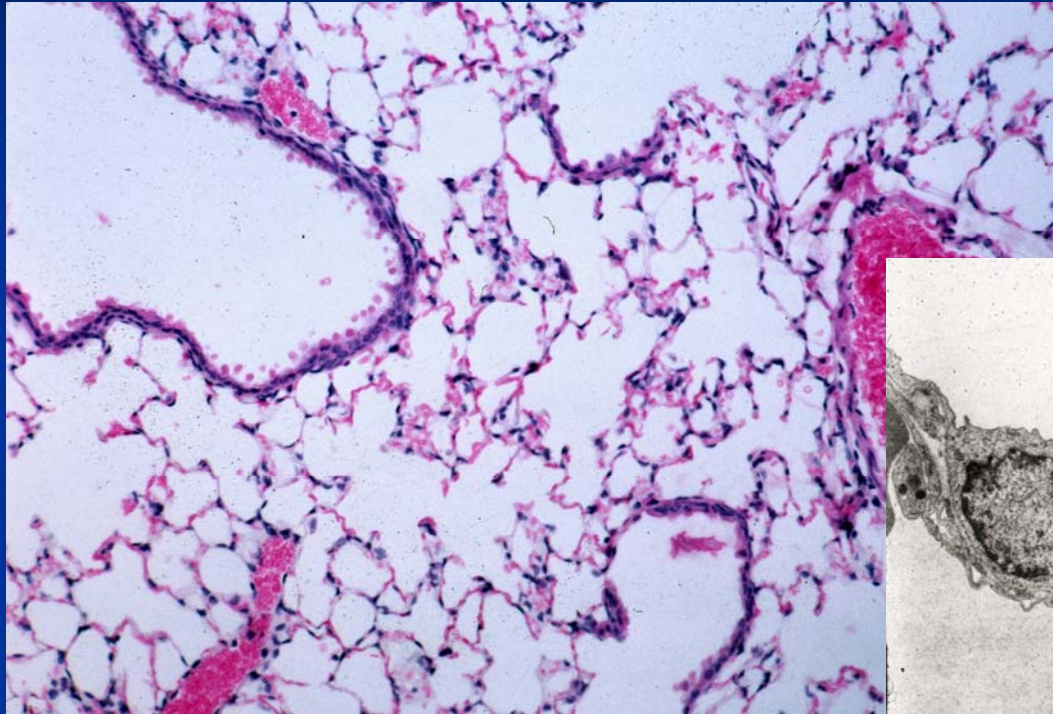
Pulmonary Region - Mammalian



■ Acinus

- Branching respiratory bronchiole
- Alveolar duct
- Alveolar sac
- Alveoli

Lung Structure



Lung Cell Types – about 36

■ Alveolar cell types

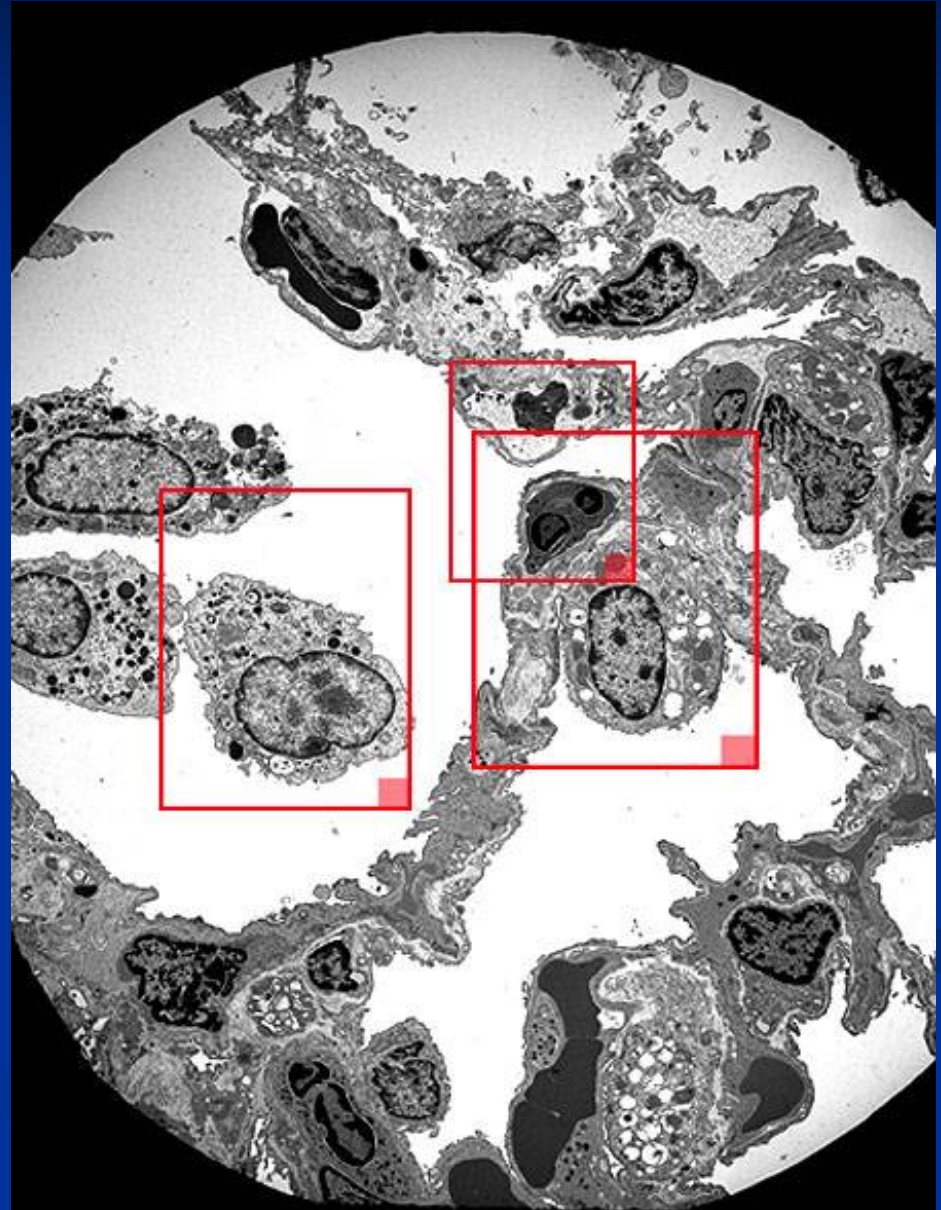
- Epithelium-Type I and Type II pneumocytes
- Capillary endothelium (nonfenestrated)
- Macrophages

■ Interstitial cells

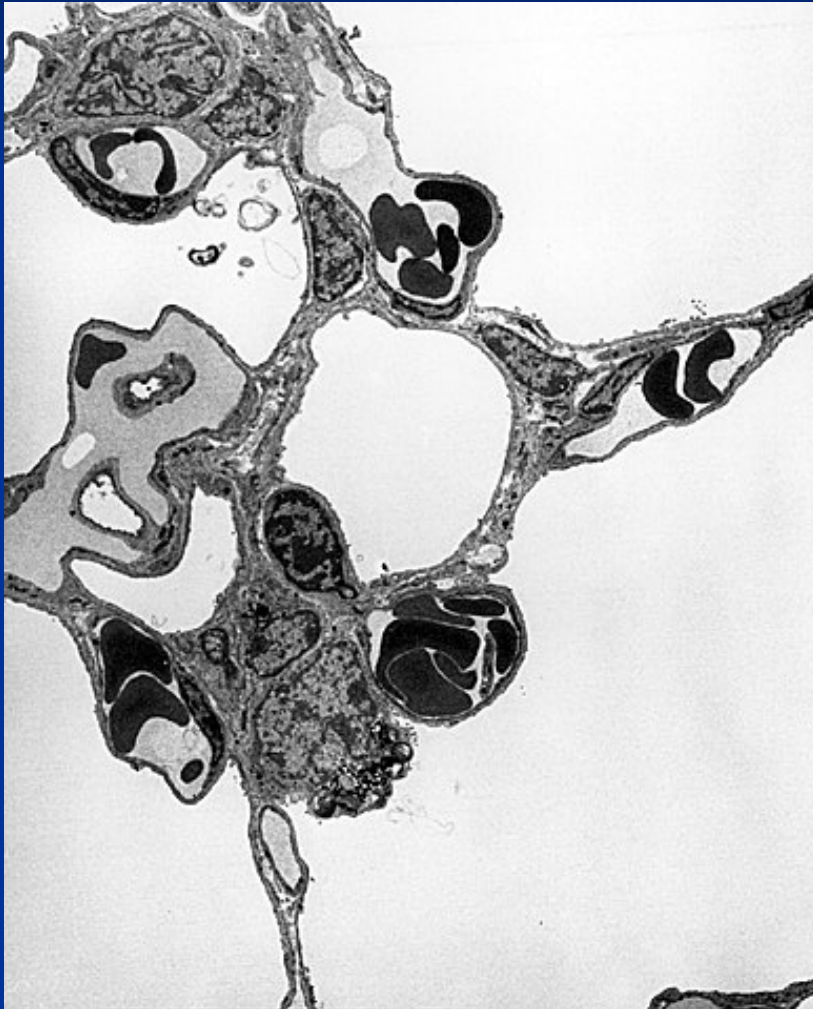
- Fibroblasts
- Contractile cells (myofibroblasts)
- Interstitial macrophages
- Dendritic cells (antigen presenting)

Alveoli

- Pulmonary alveolar macrophages
- Blood-air barrier
 - At minimal
 - Surfactant
 - Type 1 pneumocyte
 - Fused basal lamina
 - Capillary endothelial cell
- NO lymphatics

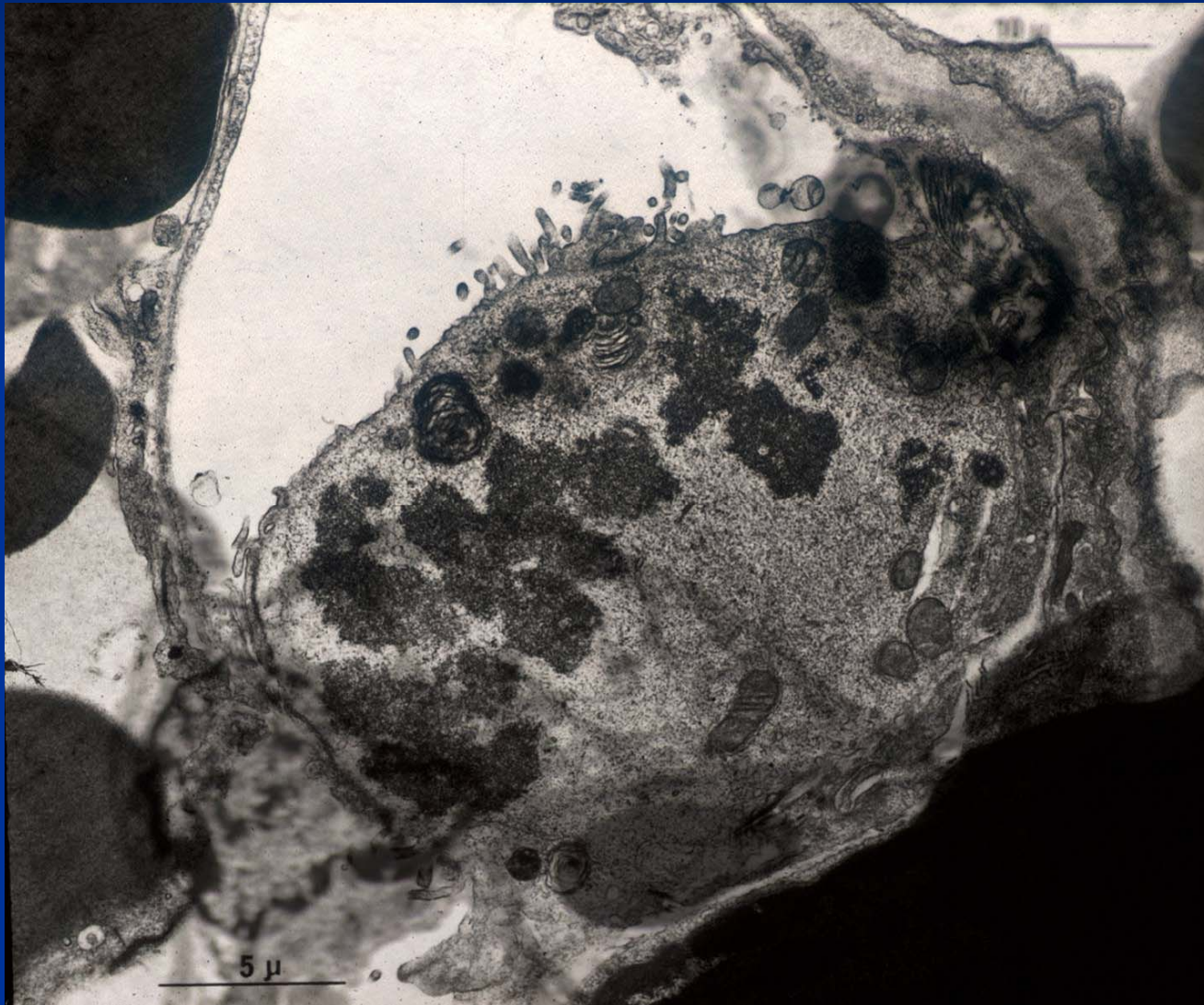


Alveolar Epithelial Cells



- Type 1 pneumocytes (membranous)
 - Flat/squamous
 - Nucleus protrudes into the alveolar lumen
 - 97% of the alveolar surface
 - Do not divide
- Type 2 pneumocytes (granular)
 - Cuboidal
 - Microvilli
 - Secrete surfactant – lamellar bodies -
 - Progenitor cell
- Are phagocytic

Proliferating Type II Cell



Endothelial Cells

- Gas exchange function
- Attenuated, large surface area
 - Highly susceptible to injury, e.g. oxygen, radiation, endotoxin
- Metabolism of endogenous and exogenous compounds
- Progenitor cells

Macrophages

- Alveolar
- Interstitial
- Intravascular – pigs, ruminants, cats, horses, marine mammals – similar to Kupffer cells in liver

Macrophages

- Play important roles in
 - Host defense – phagocytosis – can eliminate bacteria without inflammation
 - Inflammation – cytokines release, etc
- Specific receptors
 - Fc for antibody
 - Complement
 - TNF
 - CD40
 - Toll-like - recognition of microbial components
 - FAS – for apoptotic cells
 - “Scavenger”

Macrophages

■ Alveolar

- Live for a few days
- Can increase in a few hours by cell division and recruitment from interstitium
- Removed by mucociliary escalator

■ Interstitial

- From bone marrow/blood monocytes
- Live for weeks/months
- Enter alveolus or removed via lymphatics

Immune System

- T-lymphocytes in respiratory epithelium
- T and B cells in mucosal lamina propria
- Plasma cells in mucosa produce IgA
- Dendritic and other APC cells
- Organized lymphoid tissue (MALT: BALT and NALT) – covered by M-cells (modified epithelial cells)
- Draining lymph nodes

Immune System

- Airways - IgA – prevents attachment and absorption of antigens (immune exclusion)
- Lung - IgG (also IgE and IgM) – promotes uptake and destruction of inhaled pathogens by phagocytic cells (immune elimination)
 - IgG – acts as opsonizing antibody for alveolar macrophages and neutrophils

Additional Components of the Lung

- Other cell types
 - Mast cells
 - Neuroendocrine cells (airway epithelium)
- Collagen
 - Type IV – basement membrane
 - Type III – increases early after injury
 - Type I – increased late after injury
- Elastic fibers

Portals of Entry into the Respiratory System

Aerogenous (air)	Virus, bacteria, <i>Chlamydophila</i> , fungi, toxic gases, and pneumotoxics
Hematogenous (blood)	Virus, bacteria, fungi, parasites, toxins, and pneumotoxics
Direct extension	Penetrating wounds, migrating awns, bites, and ruptured esophagus or perforated diaphragm (hardware)

Vulnerability of Respiratory Tract

■ Aerogenous exposure

- Extensive surface area exposed (human - 200 m²)
- Large volume of air (human – 9,000 l/day)
- High concentration of noxious agents in air

■ Bloodborne exposure

- Entire cardiac output of right ventricle
- Extensive surface area of capillary bed (human – 70 m²)

Particle Deposition and Clearance

- Deposition – particle trapping
 - Impaction
 - $> 10\text{ }\mu\text{m}$ - nasal mucosa
 - $2\text{-}10\text{ }\mu\text{m}$ - tracheal and bronchial bifurcation
 - Sedimentation/diffusion – $< 2\text{ }\mu\text{m}$ – broncho-alveolar region
- Clearance – sneezing, coughing, mucociliary clearance and phagocytosis most important
- Retention = deposition - clearance

Factors Important in Particle Deposition/Clearance

■ Particle characteristics

■ Size

- Infective aerosols – particles $< 2\mu\text{m}$

■ Shape

- Some long slender particles, e.g. asbestos, bypass normal clearance mechanisms

■ Chemical nature e.g. inert vs reactive

■ Host characteristics

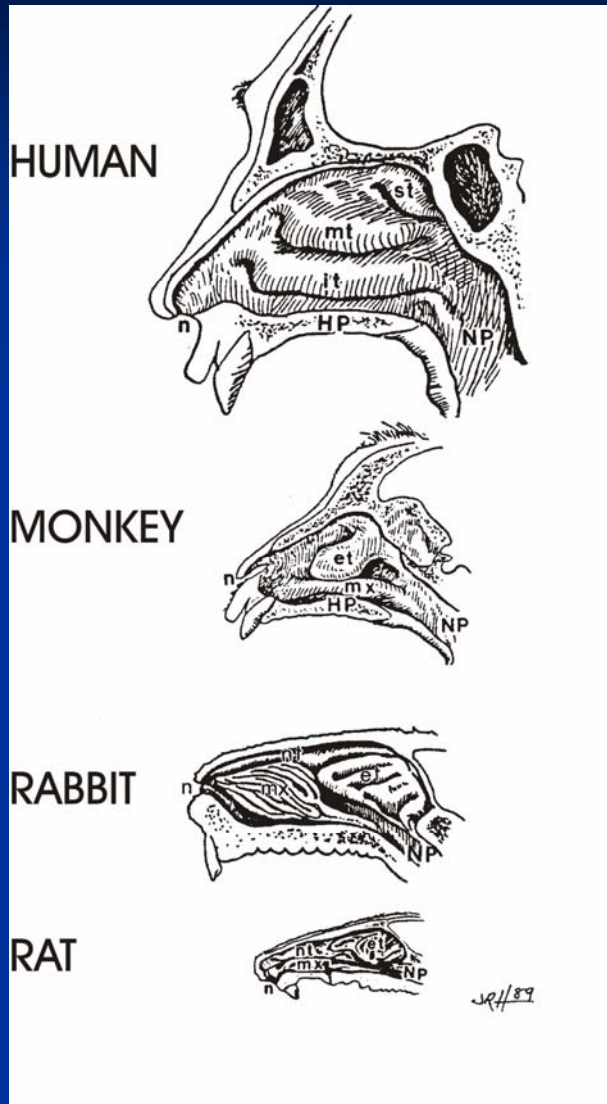
■ Species differences

- Nasal cavity complexity
- Bronchial branching and cells distribution

■ Individual status

- Prior damage
- Immune system

Comparative Nasal Airway Structure and Function



	Human	Monkey	Rat
Volume (cm ³)	16-19	8	0.4
Turbinate Anatomy	Simple	Simple	Complex
Olfactory Epithelial Surface Area	Small <10%	Moderate 20-30%	Large 50%
Breathing	Oronasal	Oronasal	Nasal

Normal Flora

- Normal bacterial flora present in extrathoracic respiratory tract
- Varies by species
- Includes those that are considered pathogens e.g. *P. multocida*, *M. haemolytica*, *B. bronchiseptica*
- Pili of normal flora adhere to receptors - prevent colonization by pathogens (competitive inhibition)
- Cleared from intrathoracic respiratory system by defense mechanisms

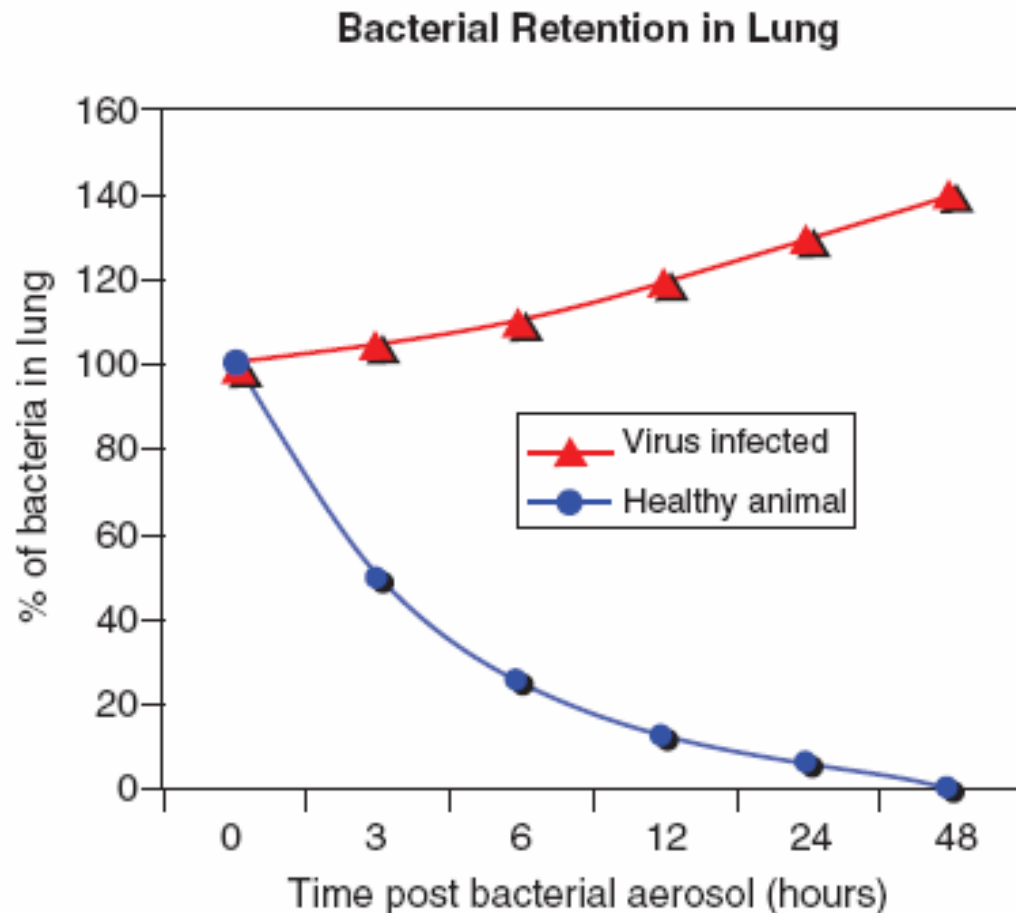


Fig. 9-7 Pulmonary clearance and retention of bacteria following inhalation of an experimental aerosol of bacteria.

Acknowledgment: this and subsequent tables from
A. Lopez (2006) Respiratory system. In: *Special Pathology*.
2nd Edn. McGavin and Zachary, Eds, In press.

Main Defense Mechanisms of the Respiratory System

Conducting system (nose, trachea and bronchi)	Mucociliary clearance, antibodies, lysozyme, mucus
Transitional system (bronchioles)	Clara cells, antioxidants, lysozyme, antibodies
Exchange system (alveoli)	Alveolar macrophages (inhaled pathogens), intravascular macrophages (circulating pathogens), opsonizing anti- bodies, surfactant, antioxidants

Defense Mechanisms – Mucociliary Clearance

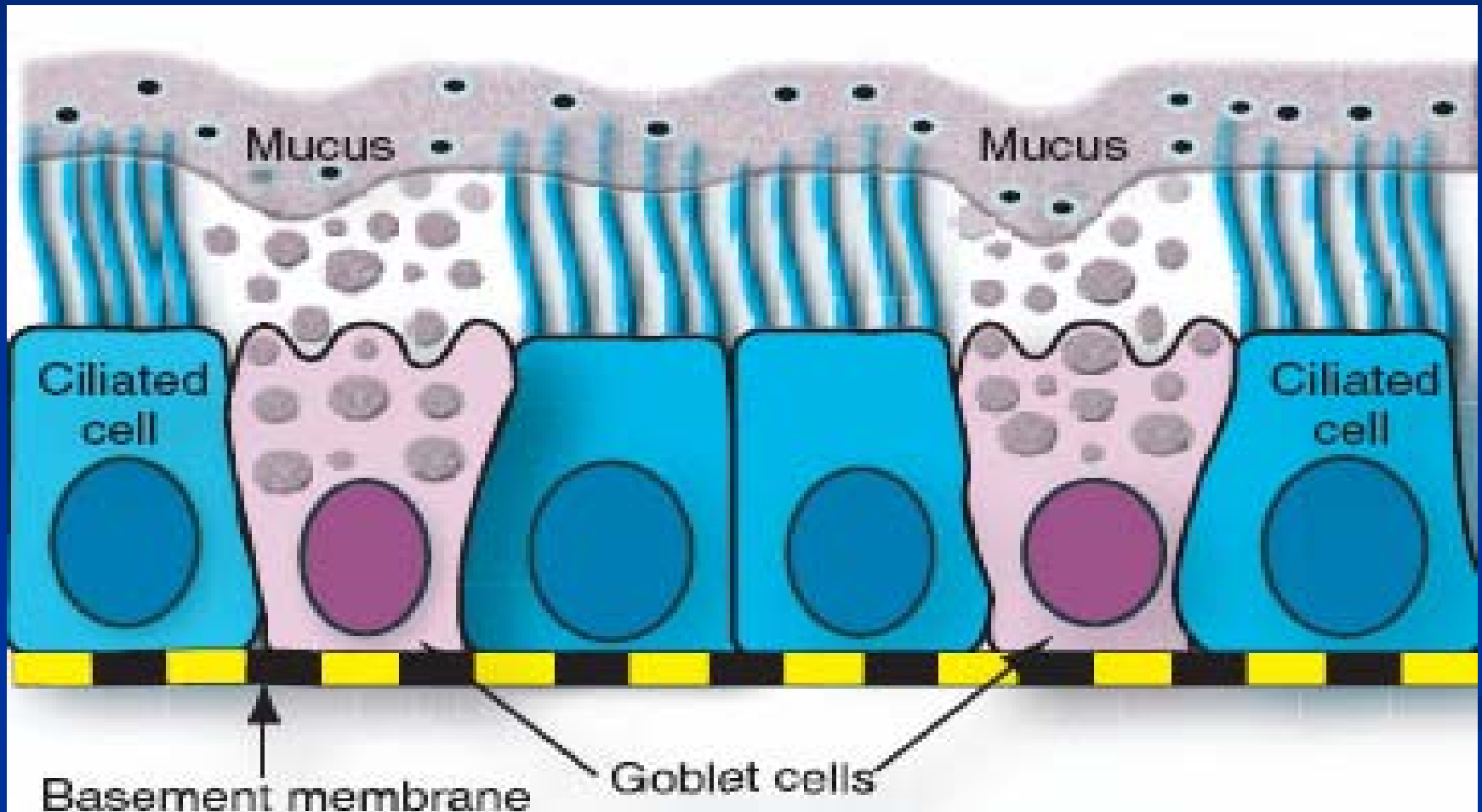


Table 9-2 Defense Mechanisms Provided by Some Cells and Secretory Products Present in the Respiratory System

Cell/Secretory Product	Action
Alveolar macrophage	Phagocytosis, main line of defense against inhaled particles and microbial pathogens in the alveoli
Intravascular macrophage	Phagocytosis, removal of particles, endotoxin, and microbial pathogens in the circulation
Ciliated cells	Expel mucus and inhaled particles and microbial pathogens by ciliary action
Clara cells	Detoxification of xenobiotics (mixed function oxidases) and protective secretions against oxidative stress and inflammation

Table 9-2 Defense Mechanisms Provided by Some Cells and Secretory Products Present in the Respiratory System

Cell/Secretory Product	Action
Mucus	Traps inhaled particles and microbial pathogens and neutralizes soluble gases
Surfactant	Protects alveolar walls and enhances phagocytosis
Lysozyme	Antimicrobial enzyme
Transferrin and lactoferrin	Inhibition and suppression of bacterial growth
α_1 -Antitrypsin	Protects against the noxious effects of proteolytic enzymes release by phagocytic cells; also inhibits inflammation
Interferon	Antiviral agent and modulator of the immune and inflammatory responses

Table 9-2 Defense Mechanisms Provided by Some Cells and Secretory Products Present in the Respiratory System

Cell/Secretory Product	Action
Interleukins	Chemotaxis, up-regulation of adhesion molecules
Antibodies	Prevent microbe attachment to cell membranes, opsonization
Complement	Chemotaxis; enhances phagocytosis
Antioxidants*	Prevent injury caused by superoxide anion, hydrogen peroxide, and free radicals generated during phagocytosis, inflammation, or by inhalation of oxidant gases (ozone, NO ₂ , SO ₂)

*Superoxide dismutase, catalase, glutathione peroxidase, oxidant free radical scavengers (tocopherol, ascorbic acid).

Impairment of Defense Mechanisms

- Viral-bacterial synergism
 - Impair phagocytic function 5-7 days post-infection
 - Mucociliary effects
- Toxic gases – ammonia, hydrogen sulfide
- Immunodeficiency/suppression – genetic, infectious, toxic
- Effect on cilia – anesthesia, ciliary dyskinesia
- Effect on mucous – dehydration – increase viscosity
- Hypoxia and pulmonary edema –
 - Impair phagocytosis
 - Alter surfactant production

Respiratory Evaluation Methods

- Functional evaluation
 - Respiratory rate, compliance, diffusion capacity, etc
- Imaging
 - Radiography, MRI, etc
- Endoscopy
- Tracheal aspirates and broncho-alveolar lavage (BAL)
- Whole lung biochemistry
- Morphology
 - Biopsy
 - Necropsy – gross and microscopic evaluation

Aspirate/Lavage Evaluation

- Microbiology
- Cytology
 - Cell number and differential
 - Microorganisms
 - Particulates
- Biochemistry
 - Enzymes e.g. LDH, β glucouronidase, sialic acid
 - Protein content

Gross Examination of the Respiratory System

- External evaluation of the head, nares
- Cut diaphragm
- Remove rib cage
- Visually evaluate lung (color, size, etc) and thoracic contents
- Sample for bacteriology if needed
- Remove pluck and examine
- Evaluate lung

Gross Examination of Respiratory Tract

- Lung
 - Size - collapse? – in situ evaluation
 - Color
 - Texture on palpation
 - Lesion distribution
 - Cut surface
 - Airways
- Surface of lung and rib cage
- Contents of thoracic cavity
- Evaluate air sacs in birds
- Head – evaluate nasal passages, sinuses as needed
 - Longitudinal vs transverse sections

Lung Palpation - Texture

- Consistency of whole lung and of lesions
- Spongy - normal
- Firm - pneumonia
- Nodular - abscesses, granulomas, neoplasia
- Rubbery - interstitial pneumonia, edema
- Crepitant - emphysema, overinflation

Gross Lung Exam

- Lesion distribution
 - Diffuse
 - Locally extensive
 - Focal/multifocal
- Estimate of lesion extent e.g. % lung affected
- Artifacts
 - Autolysis
 - Edema
 - Atelectasis
 - Rumenal fluid/food in lungs

Tissue Preparation for Microscopic Examination

- Selection of tissues (affected vs normal)
- Fixation
 - Immersion
 - Intratracheal/intranasal – always in rats, mice
 - Whole body vascular perfusion
 - Artifact induction
- Fixatives
 - Neutral buffered 10% formalin (light microscopy)
 - Tellyesniczky/Feke's (light microscopy, tumor counts)
 - Glutaraldehyde \pm paraformaldehyde (electron microscopy)
 - 4% paraformaldehyde (electron and confocal microscopy, *in situ* hybridization)
- Decalcification – for examination of nasal passages

Morphologic Evaluation

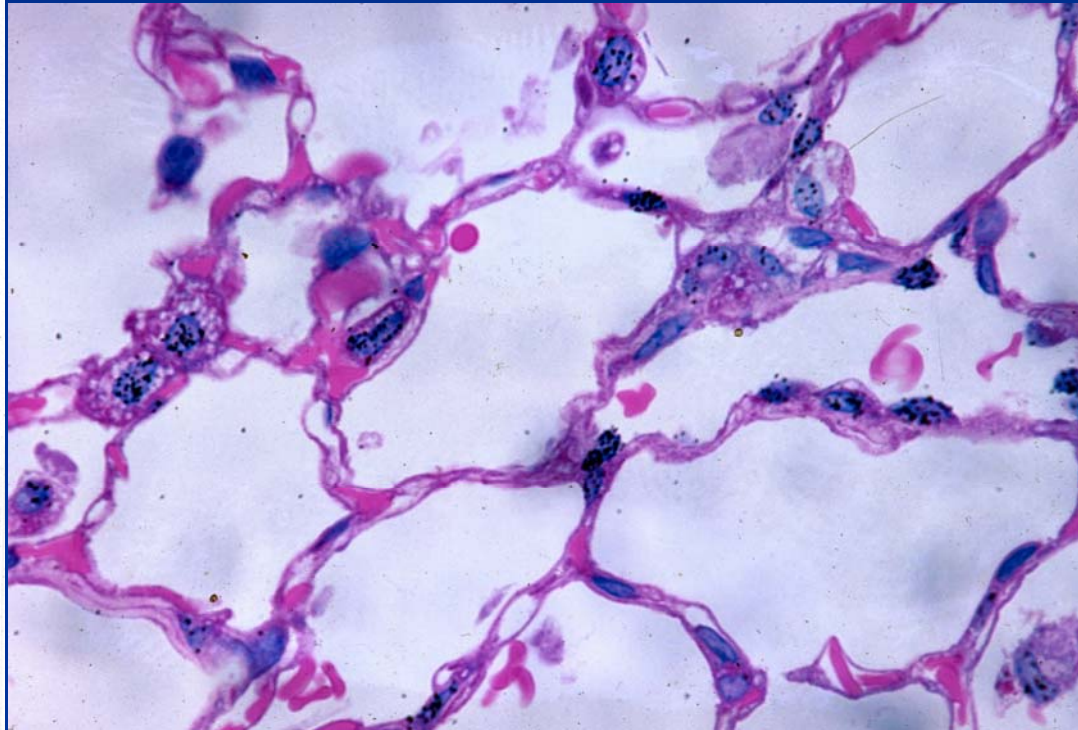
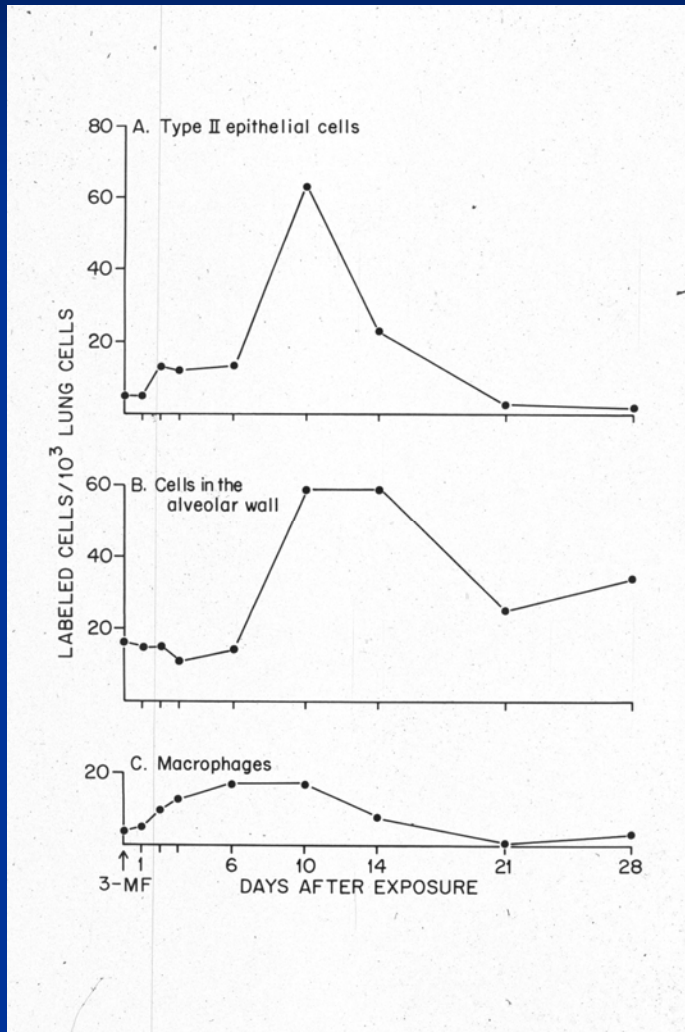
■ Qualitative

- Structural or cellular changes
- Light, electron, and confocal microscopy
- Special stains and immunohistochemistry
- *In situ* hybridization

■ Quantitative

- Morphometry/stereology
 - Number or volume of cells/organelles/matrix
- Cell kinetics - cell proliferation
 - Immunohistochemistry- BrDU, PCNA, etc.

Cell Kinetics



Useful Histochemical Stains

- Elastin
 - Weigert, Verhoeff-hematoxylin, Gomori methods
- Connective tissue
 - Masson's trichrome, Van Gieson's, Sirius Red
 - Snook's reticulin (type III collagen)
- Mucopolysaccharides (goblet cells) and glycosaminoglycans
 - Periodic-acid-Schiff (PAS), Alcian blue, toluidine blue, and ruthenium red (for EM)
- Basement membrane
 - Gomori's methenamine silver (GMS) and PAS

References

- Lopez A. Respiratory system. In: *Special Pathology*. 2nd Edn. McGavin and Zachary, Eds, (2006) In press.
- Haschek W.M., H. P. Witschi, and K. Nikula. Respiratory system. In: *Handbook of Toxicologic Pathology*. Haschek, W. M., Rousseaux, C.G., and Wallig, M.A. 2nd Ed., 2002. Academic Press, San Diego, California. pp. 3-83.
- FOR IMAGES: [Necropsy Show and Tell: Veterinary Pathology Images](#) Dr. John M. King, Professor of Veterinary Pathology College of Veterinary Medicine, Cornell University Ithaca, NY 14853 jmk31@cornell.edu ...
w3.vet.cornell.edu/nst/