Pathology of the Respiratory System: General Responses to Injury

"It may not be a perfect wheel, but it's a state-of-the-art wheel."

Respiratory Pathology

- Respiratory disease important in all species
  - Economic importance
  - Clinical importance
- Diagnosis is a challenge, both clinical and morphologic

Pathology of Respiratory System

- **Respiratory injury and response - Outline**
  - General
  - Upper respiratory tract
  - Lower respiratory tract
  - Pleura and thoracic cavity

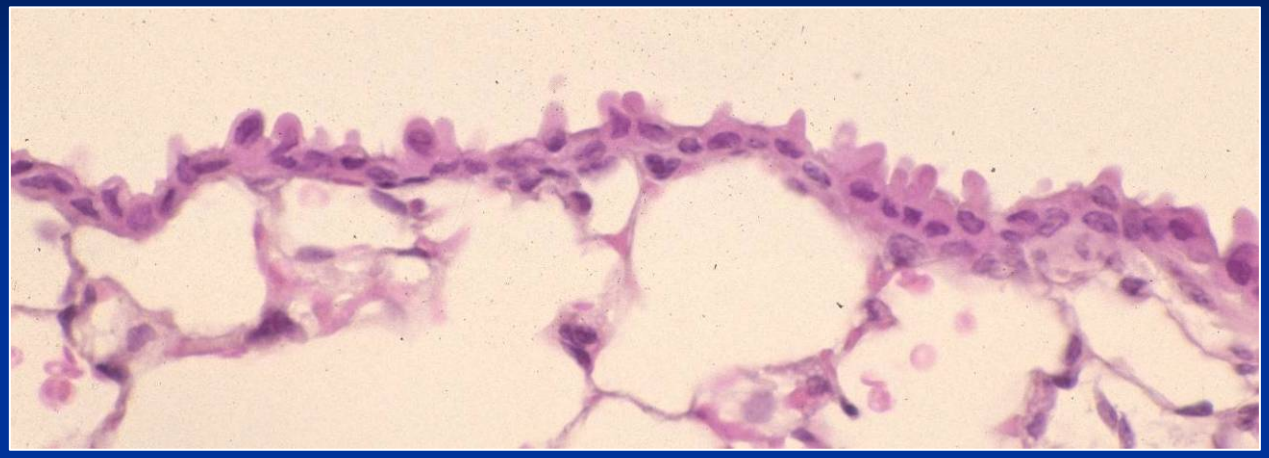
Injury

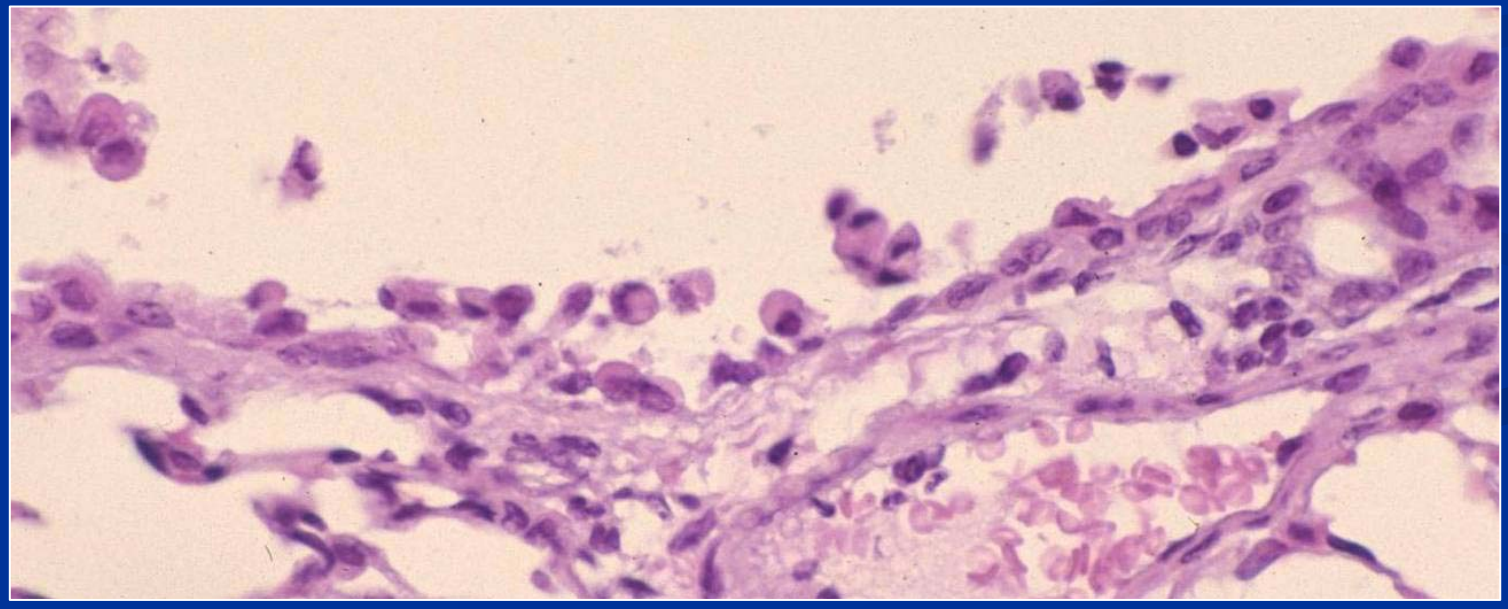
- Types of injury
  - Primary or secondary
  - Cell specific or non-specific
- Importance in repair process
  - Are stem cells injured?

Causes of Injury: Cell Specific

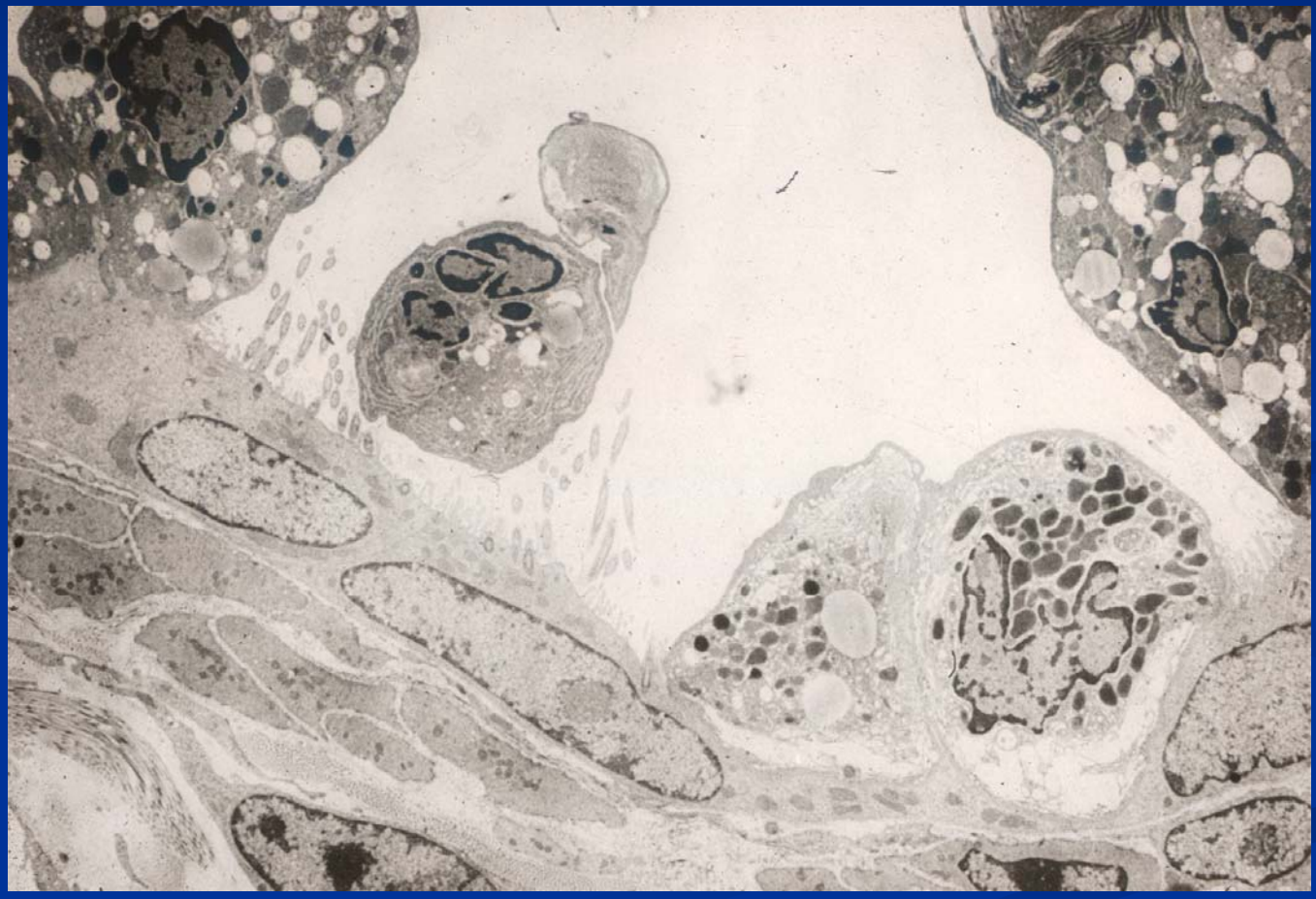
- Ciliated cell injury
  - Bacteria e.g. *Bordetella, Mycoplasma* spp
  - Viruses e.g. influenza, paramyxovirus
  - Air pollutants (NO_2 , SO_2 , O_3 , O_2)
- Clara cell injury
  - Metabolically activated xenobiotics (3 methylindole)

Clara Cell Necrosis



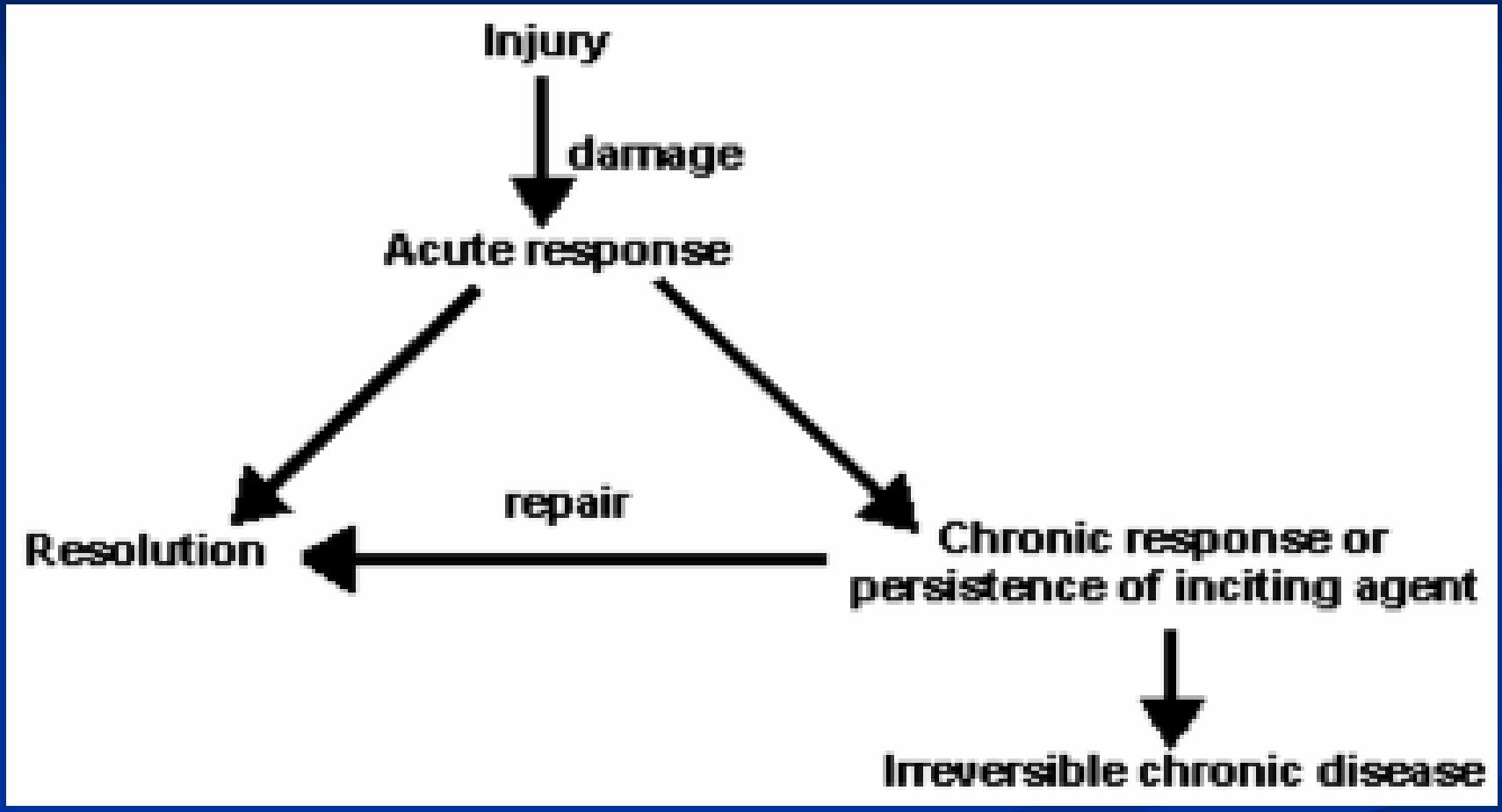


Clara Cell Necrosis



Causes of Injury: Non-specific

- Some viruses
- Chemicals (caustic agents)
- Foreign bodies


Injury
damage
Acute response
repair
Resolution
Chronic response or
persistence of inciting agent
Irreversible chronic disease

Response to Injury is Limited

- But can vary somewhat depending on
  - Causative agent
  - Route of exposure
  - Severity of exposure
  - Host defense

Diagnostic Aids

- Type of inflammatory response
- Presence of causative agent
- Presence of a specific agent-induced change e.g inclusion bodies
- Special stains
- Immunohistochemistry (IHC)
- Electron microscopy

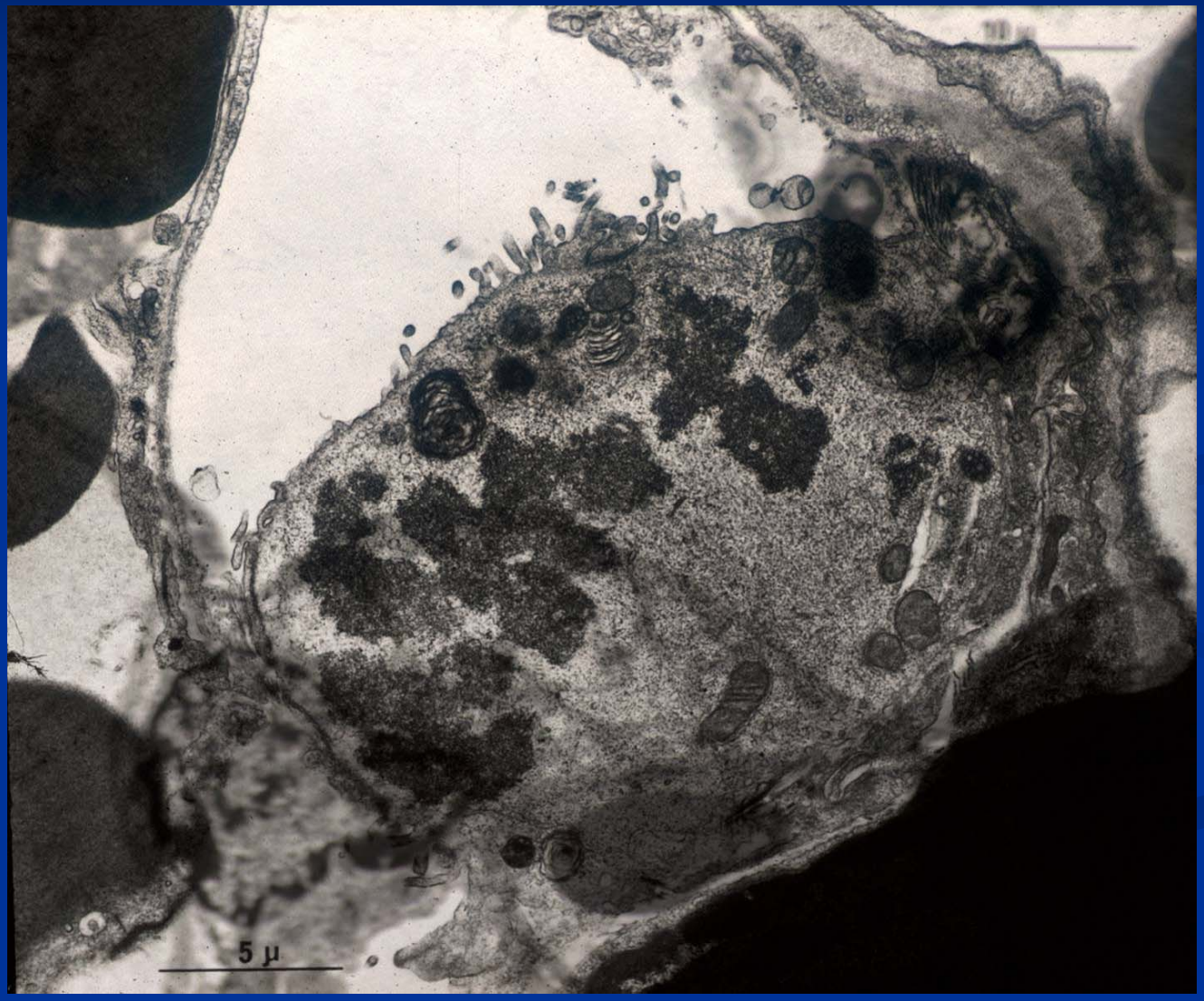
Response to Injury

- Edema
- Necrosis
- Inflammation
- Cell proliferation
- Fibrosis
- Granuloma formation

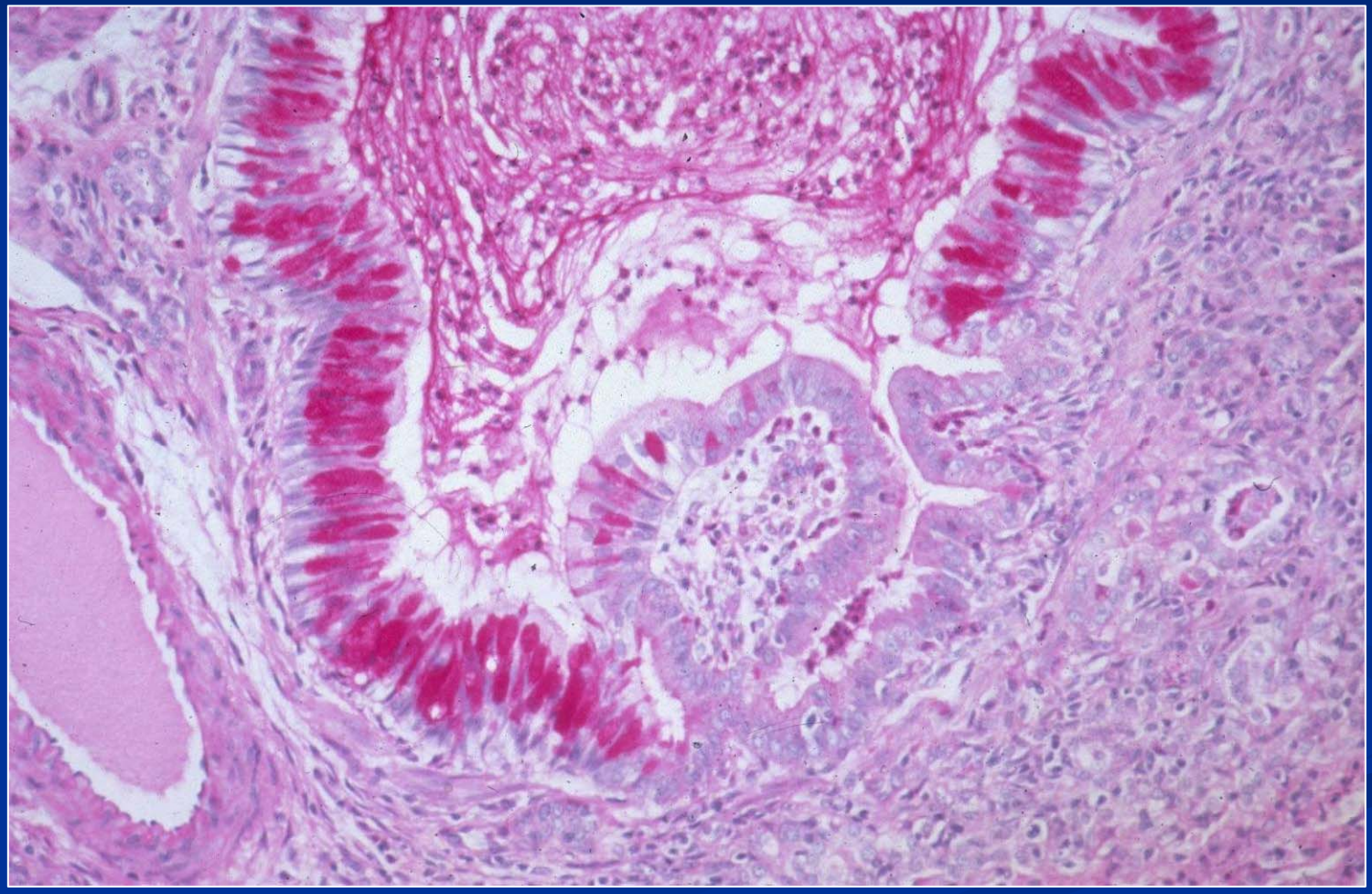
Consequences of Airway Injury

- Early Morphologic Changes
  - Inflammation
  - Epithelial hyperplasia – regenerative or due to irritant effects e.g. mucous cells
  - Epithelium metaplasia – effect on mucociliary escalator e.g.
    - Mucous
    - Squamous

Response to Injury - Proliferation



Mucous Hyperplasia



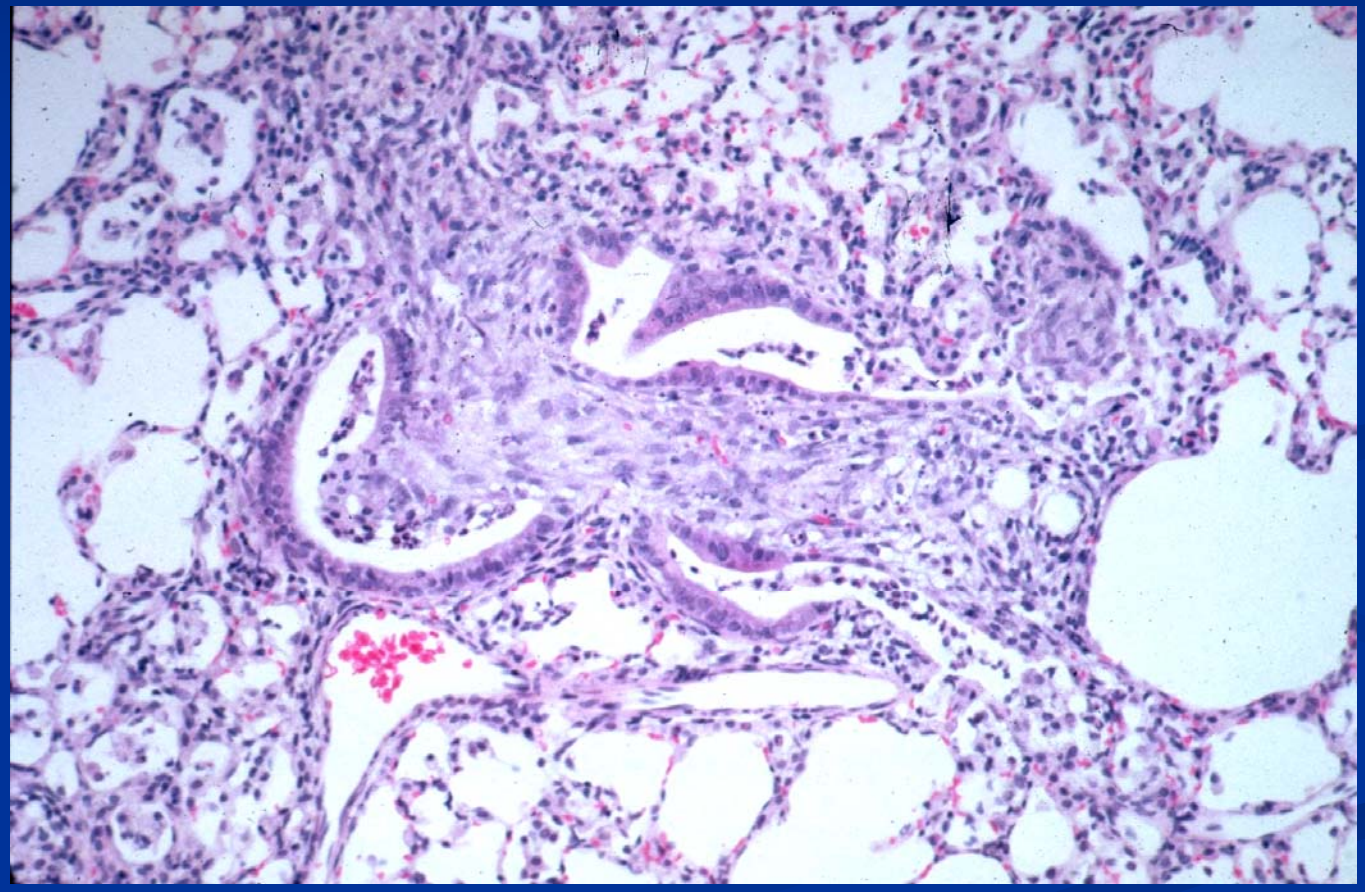
Consequences of Airway Injury

- Adverse Effects
  - Airway hyper-reactivity and bronchoconstriction
  - Modified mucus production
  - Decreased mucociliary clearance
  - Inflammation
  - Epithelial proliferation
  - Obstruction – complete or incomplete
  - Predisposition to infection
  - Fibrosis

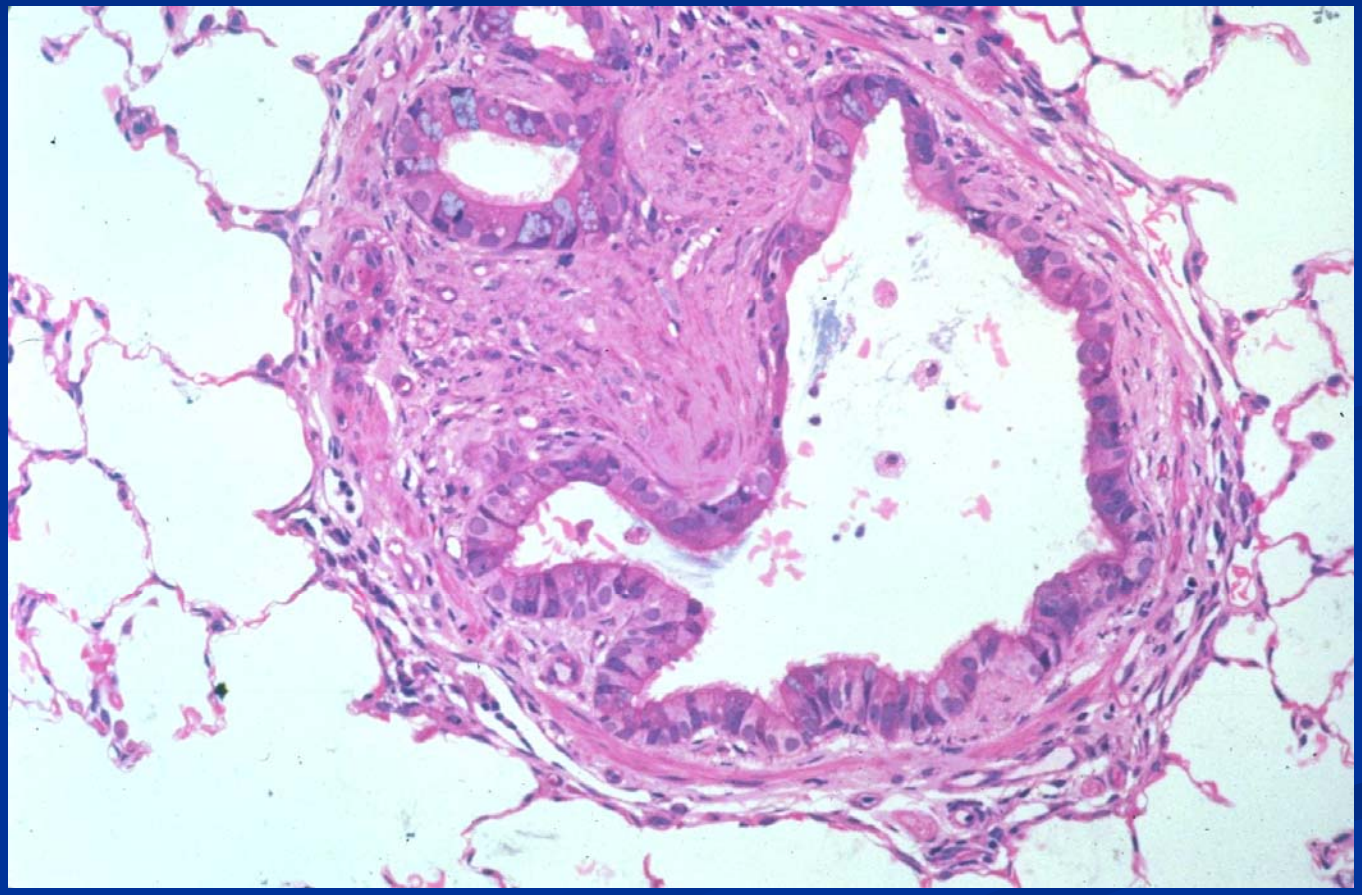
Chronic Effects of Airway Injury

- Fibrosis
  - Mural - fibrosing bronchiolitis
  - Intralumenal – bronchiolitis obliterans
  - Can lead to atelectasis (complete obstruction) or emphysema
- Destruction of surrounding tissue
  - Bronchiectasis
  - Abscess formation/empyema if infected
- Extension of infection e.g. pneumonia
- Neoplasia

Chronic Effects of Airway Injury



Chronic Effects of Airway Injury



Consequences of Lung Parenchymal Injury

- Edema
- Decreased surfactant ($\rightarrow$ atelectasis)
- Decreased defense mechanisms
- Epithelial proliferation/neoplasia
- Inflammation
- Fibrosis
- Predisposition to infection
- Immune mediated disease

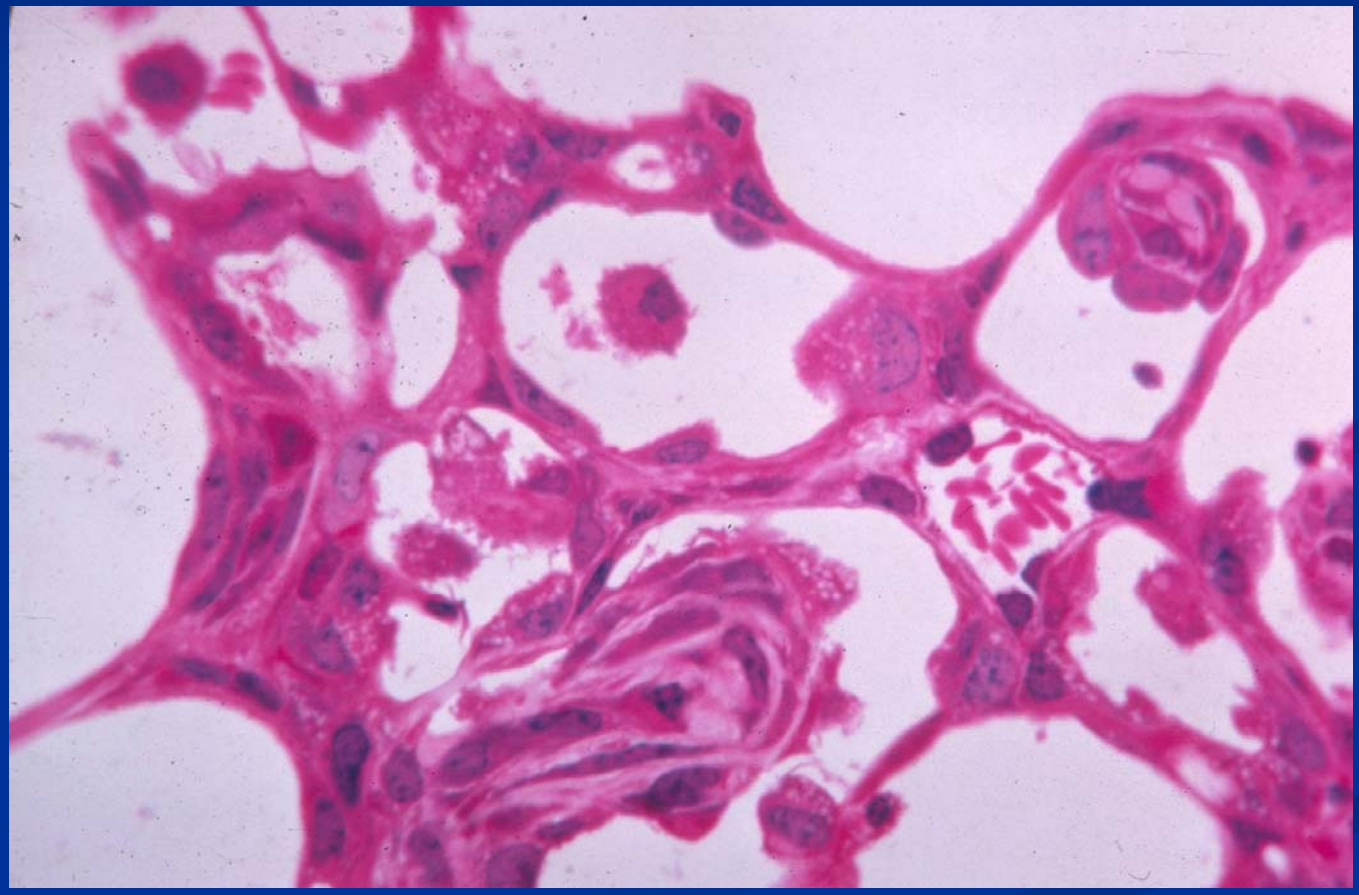
Repair of Injury to the Lung

- Repair can occur if
  - Stem cells are available
  - Basement membrane is intact
  - Inflammation is not too severe
  - Inciting agent is removed

Consequences of Basement Membrane Damage

- Chronic disease: fibrosis
- Severe destruction of tissue
  - Emphysema
  - Abscess
  - Sequestration

Consequences of Basement Membrane Damage - Lung



Diagnosis of Respiratory Disease

- Clinical disease, individual and group/herd
- Pulmonary function
- Clinical pathology
- Anatomic pathology – gross, microscopic, electron microscopy, IHC
- Bacteriology - culture, PCR, serology
- Virology – as bacteriology, virus isolation
- Parasitology
- Toxicology – analytical, feed microscopy

Pathology of Respiratory System

- Respiratory injury and response
- Upper Respiratory Tract
  - Developmental Abnormalities
  - Non infectious Disease
  - Infectious Disease
- Lower Respiratory Tract
- Pleura and thoracic cavity

Upper Respiratory System Developmental Abnormalities

- Examples
  - Maxillary sinus cysts - horse
  - Ciliary dyskinesis - dog
  - Tracheal hypoplasia - dog
  - Epiglottal hypoplasia - horse

Upper Respiratory System: Noninfectious Disease

- Tracheal collapse (dogs, horses)
- Laryngeal paralysis (dogs, horses)
  - Idiopathic laryngeal hemiplasia (roarer)
- Laryngeal edema
- Smoke inhalation

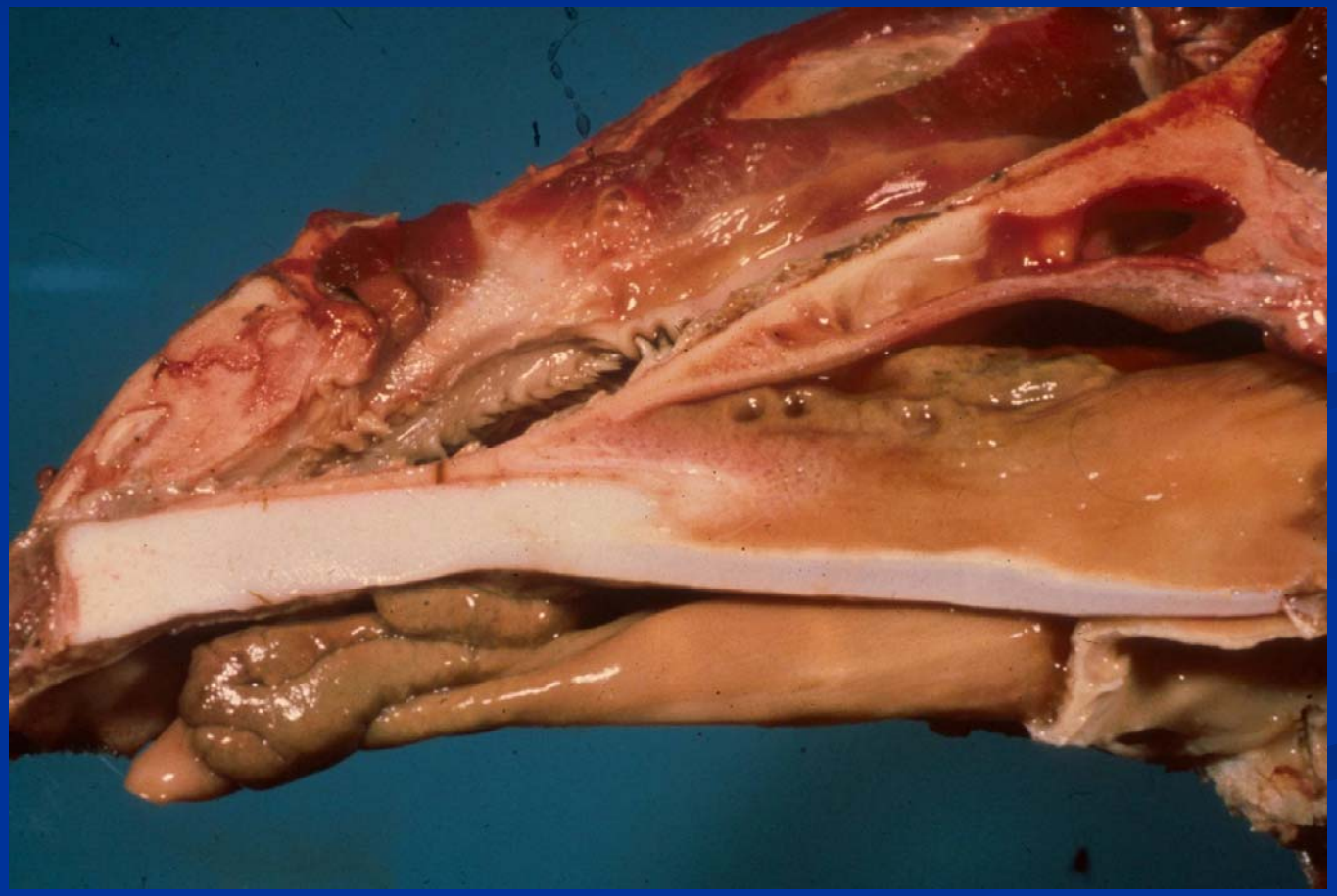
Noninfectious Disease: Differentials for Epistaxis

- Trauma
- Invasive intranasal lesion
  - Fungal infection
  - Neoplasia
- Bleeding disorder – genetic, infectious, or toxic origin
- Exercise induced pulmonary hemorrhage (EIPH) - horses

Proliferative Lesions of Nasal Cavity

- Nasal polyps (cats, horses)
  - Ethmoid hematoma
  - Nasopharyngeal polyps - cats
  - Granulomatous rhinitis
- Neoplasia
  - Carcinoma
  - Sarcoma

Proliferative Lesions of Nasal Cavity



Neoplasia of the Nasal Cavity:

- Mainly dogs, also cats and horses
- 80% malignant
- Clinical Signs
  - Unilateral or bilateral mucoid or bloody discharge
  - Intermittent sneezing
  - Obstruction of nasolacrimal duct
  - Facial swelling
  - Bony erosion
  - Neurologic signs occasionally

Neoplasia of the Nasal Cavity

Noninfectious Diseases of Upper Respiratory System

- Smoke inhalation
  - Thermal injury
    - Laryngeal/tracheal necrosis with fibrin
  - Also chemical induced pulmonary edema

Infectious Upper Respiratory Disease

- Balance of microbial flora upset
- Often viral, especially herpes viruses
- Bacterial disease secondary
- Possible sequella – osteomyelitis, meningitis, otitis

Infectious Upper Respiratory Disease

- Cattle
  - *Infectious bovine rhinotracheitis (IBR)
- Horses
  - *Equine rhinopneumonitis
  - Strangles (*Strep equi*)
- Pigs
  - *Pseudorabies
  - Atrophic rhinitis (*Past multocida*)

*Herpes viruses

Infectious Upper Respiratory Disease

- Dogs
  - Canine distemper virus
  - Infectious tracheobronchitis
  - Aspergillosis
- Cats
  - *Feline viral rhinotracheitis
  - Calicivirus
  - Cryptococcosis

*Herpes viruses

Pathology of Respiratory System

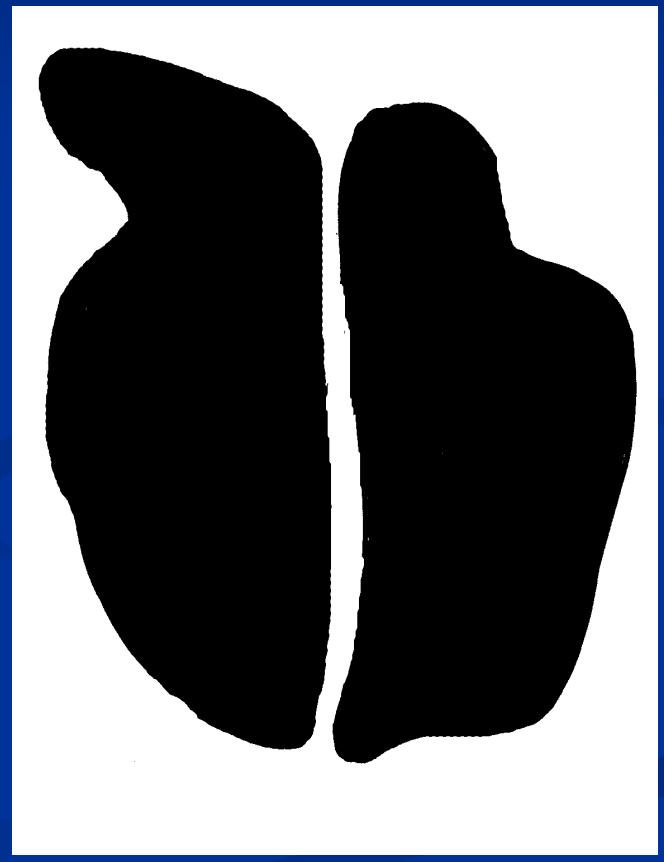
- Upper Respiratory Tract
- **Lower Respiratory Tract**
  - **Lung lesion distribution**
  - **Developmental Abnormalities**
  - **Non Infectious Disease**
  - **Pneumonias**
  - **Neoplasia**
- Pleura and thoracic cavity

Gross Lung Exam

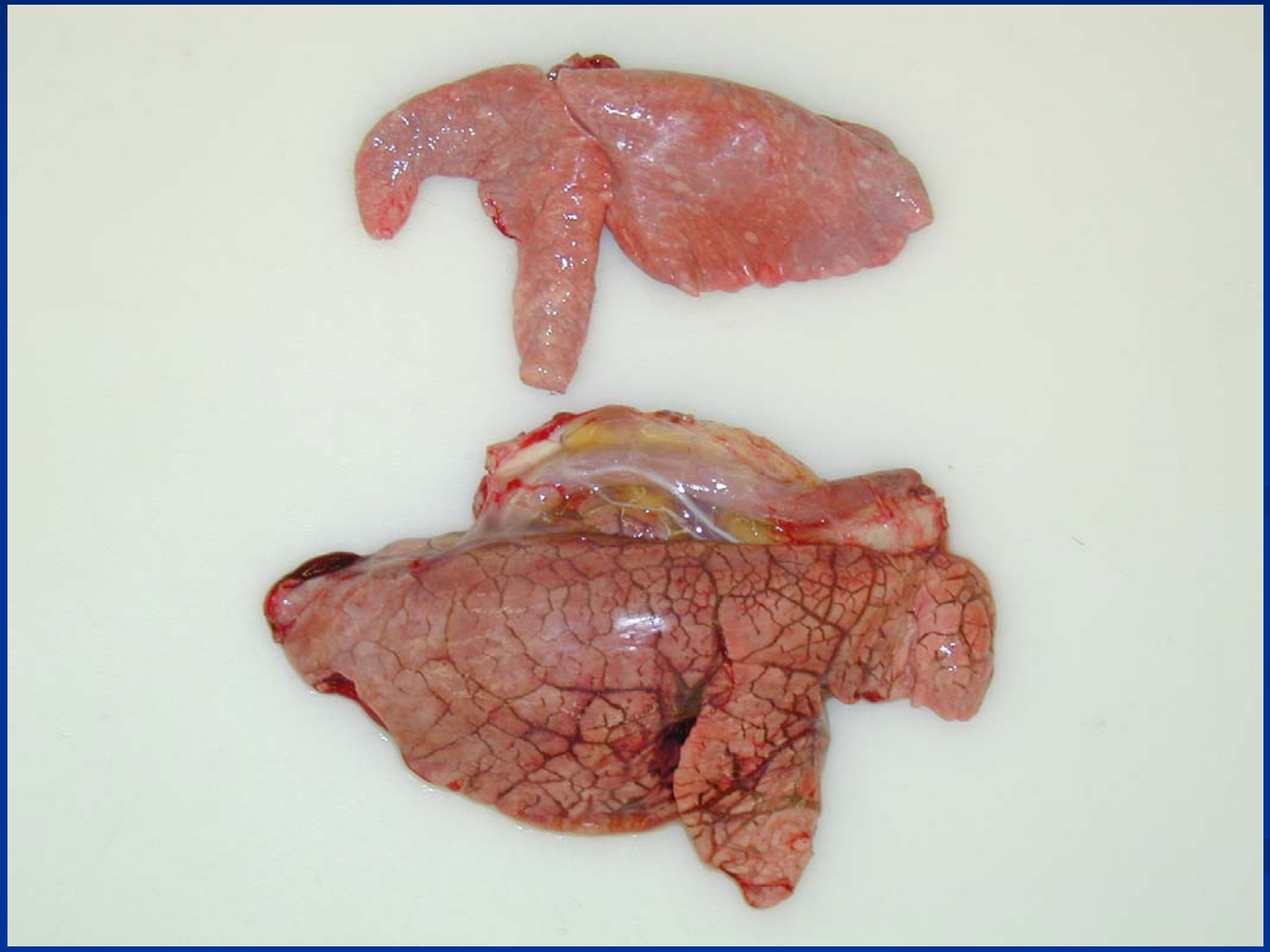
- Lesion distribution
  - Diffuse
  - Locally extensive
  - Focal/multifocal

Diffuse Pulmonary Disease

- Edema
- Atelectasis
- Interstitial pneumonia
- Mineralization
- Emphysema

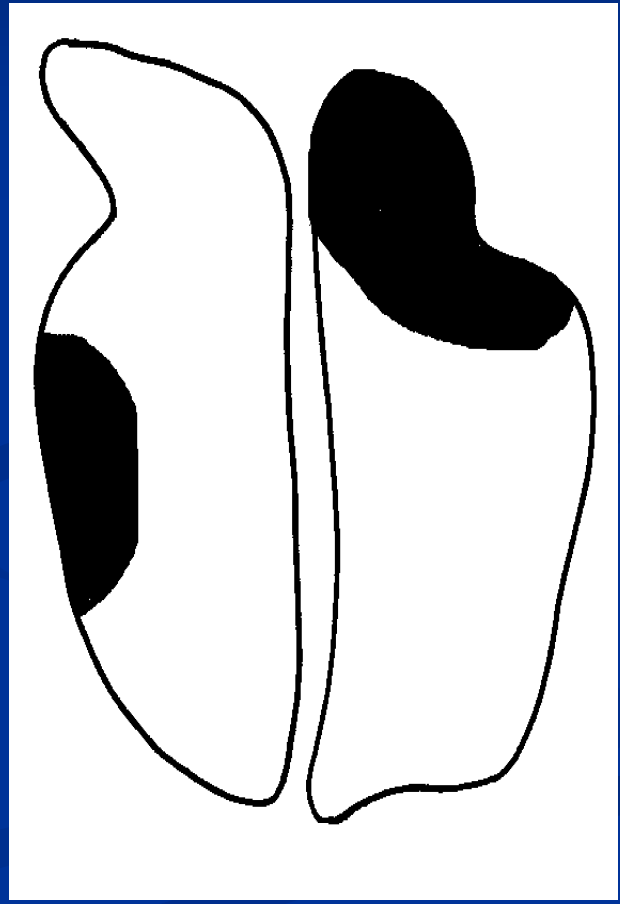


Normal and Pulmonary Edema

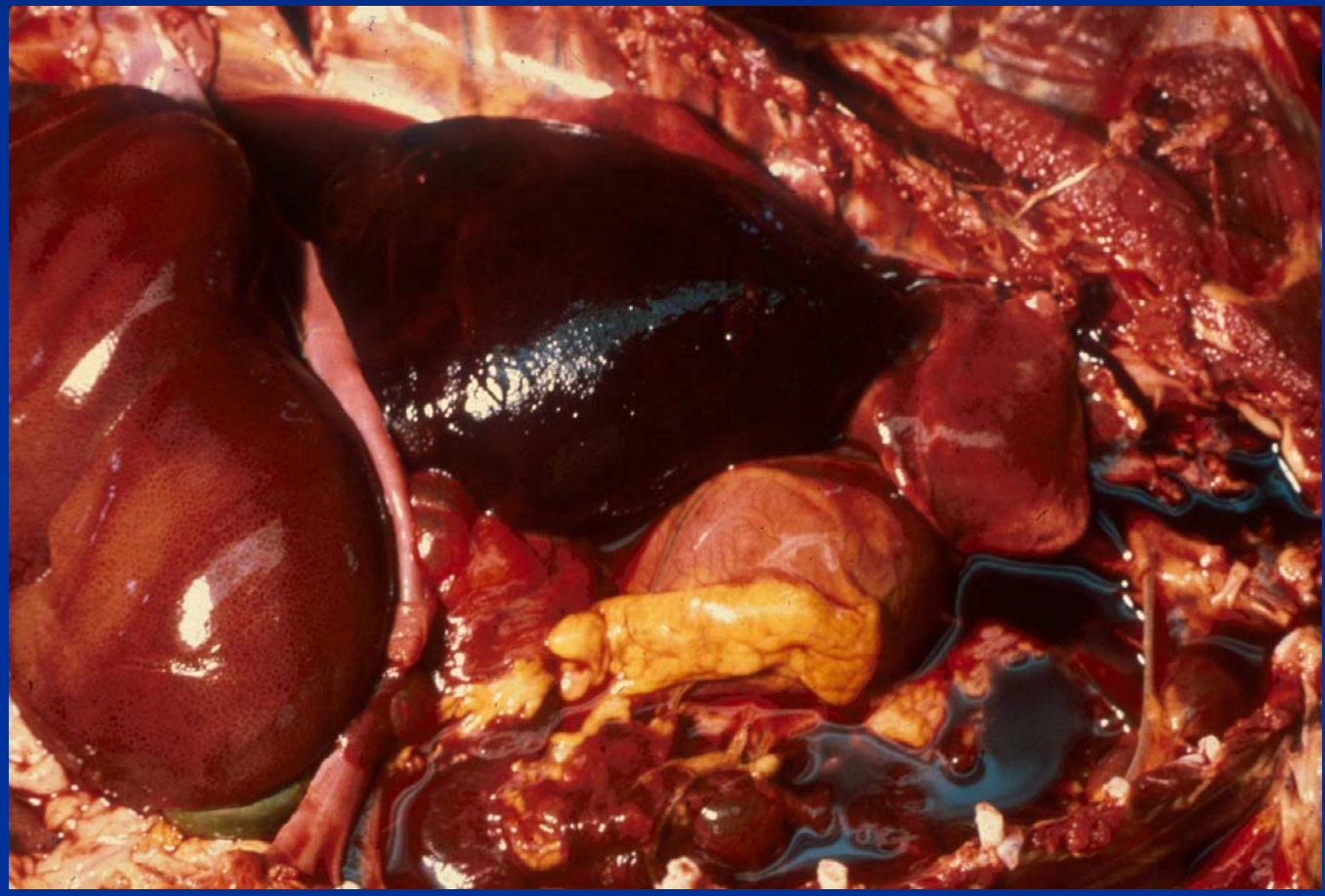


Locally Extensive Pulmonary Disease

- Cranioventral bronchopneumonia
  - Bacterial
  - Aspiration
- Granulomatous pneumonia
- Other: lobe torsion

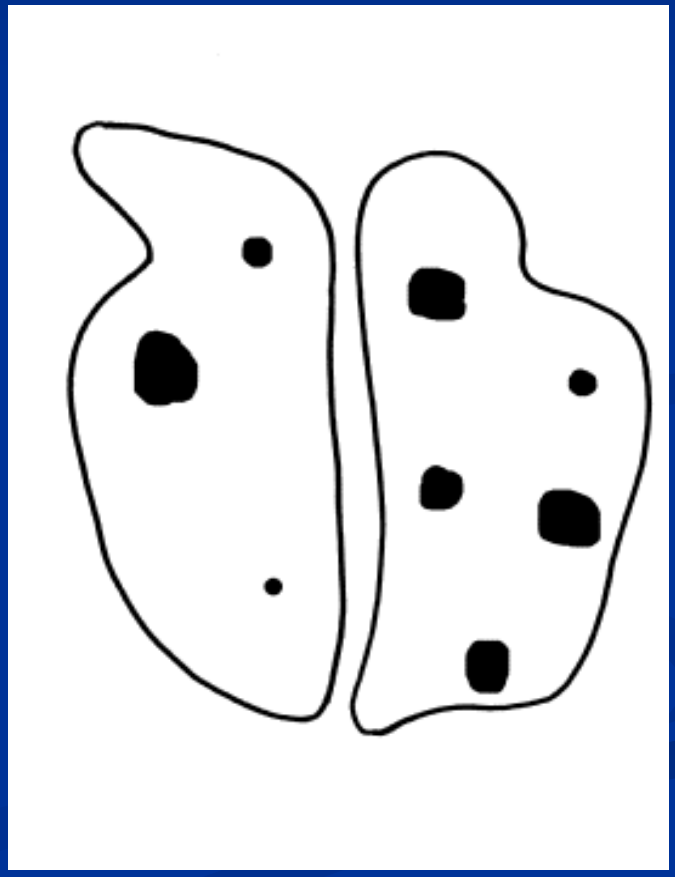


Locally Extensive Pulmonary Disease – Lobe Torsion - Dog



Focal/Multifocal Pulmonary Disease

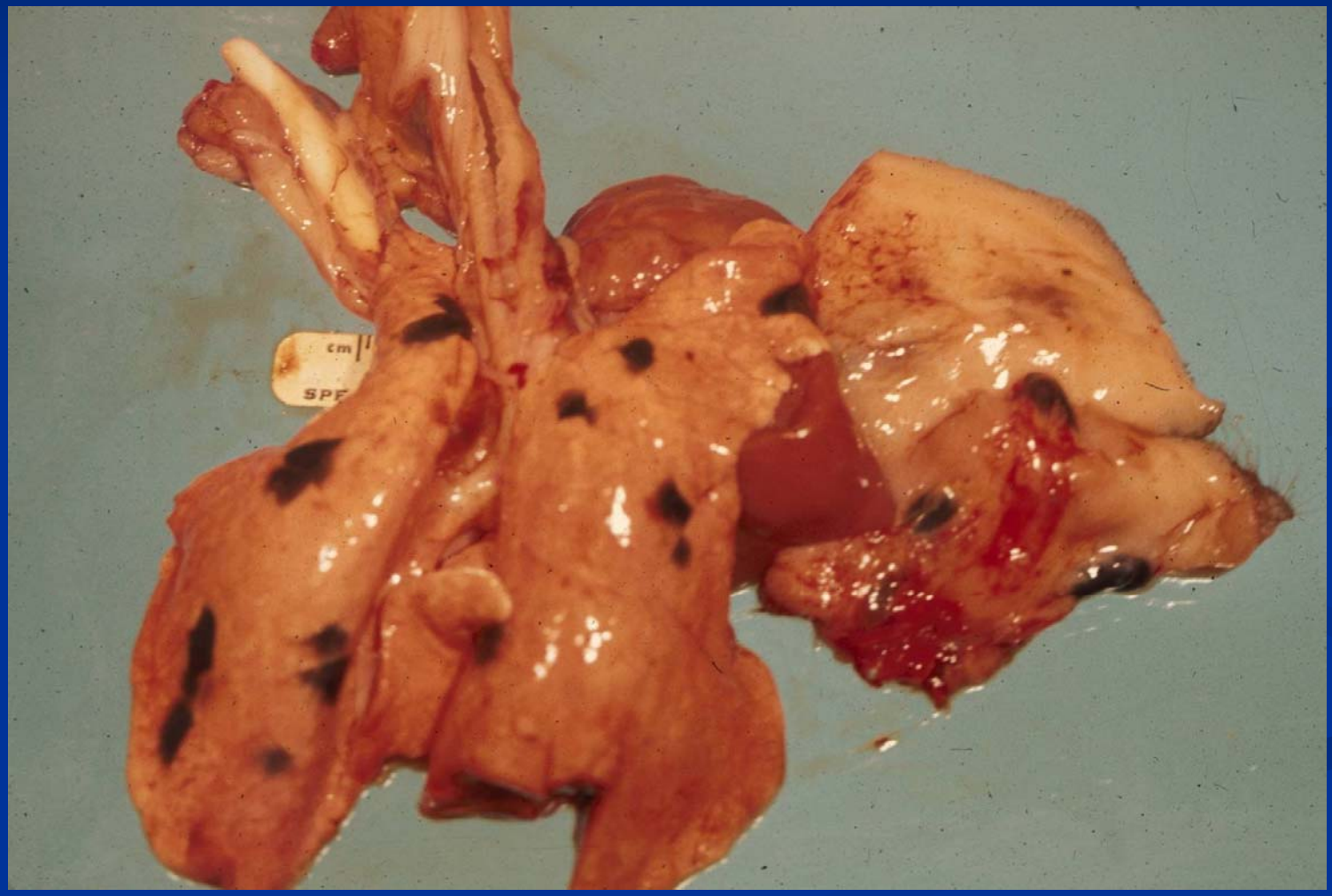
- Abscess
- Granuloma
  - Bacterial
  - Mycotic
  - Parasitic
  - Particulates
- Infarct
- Neoplasia



Developmental Lung Anomalies

- RARE
- Accessory lungs
- Pulmonary hypoplasia – cattle
- Pulmonary cyst
- Surfactant deficiency – horses
- Melanosis – pigs, cattle, sheep
- Bronchial hypoplasia with lobar emphysema– dogs

Developmental Lung Anomalies



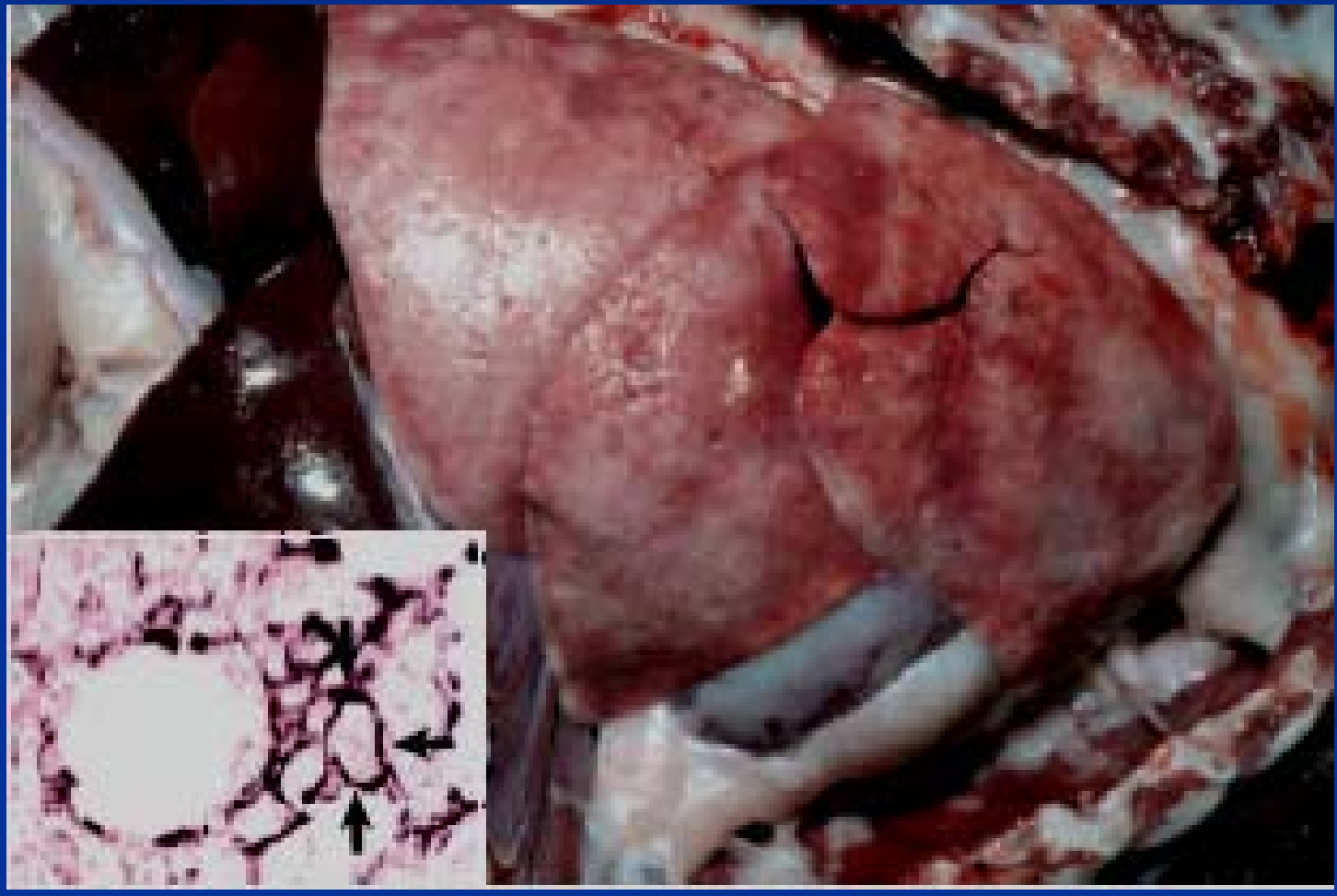
Developmental Abnormalities

- Pulmonary hypoplasia
  - Genetic
  - Primary, e.g., viral: border disease, swine influenza, Menangle virus.
  - Secondary, e.g., to diaphragmatic hernia.
- Surfactant deficiency - diffuse atelectasis.
  - Prematurity, e.g., lambs.
  - Hyaline membrane disease ("barkers") in foals, pigs

Pulmonary Mineralization

- Diffuse lesion (pumice lung)
  - Etiology
    - Uremia
    - Primary hyperparathyroidism
    - Hypercalcemia of malignancy
    - Vitamin D toxicosis
    - Gross and microscopic – interstitial pneumonia
    - Other organs affected
- Focal microlithiasis – old dogs

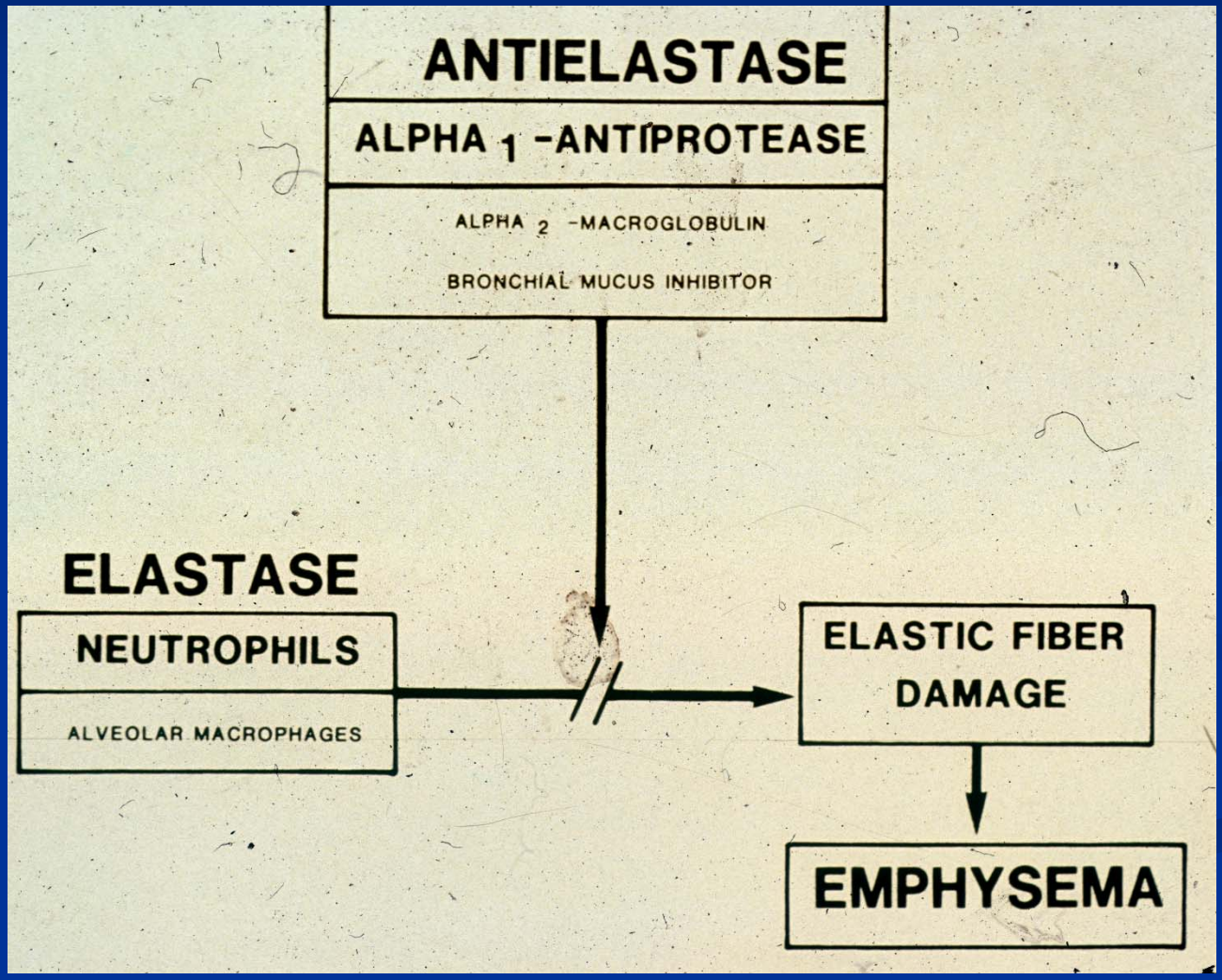
Pulmonary Mineralization -Dog



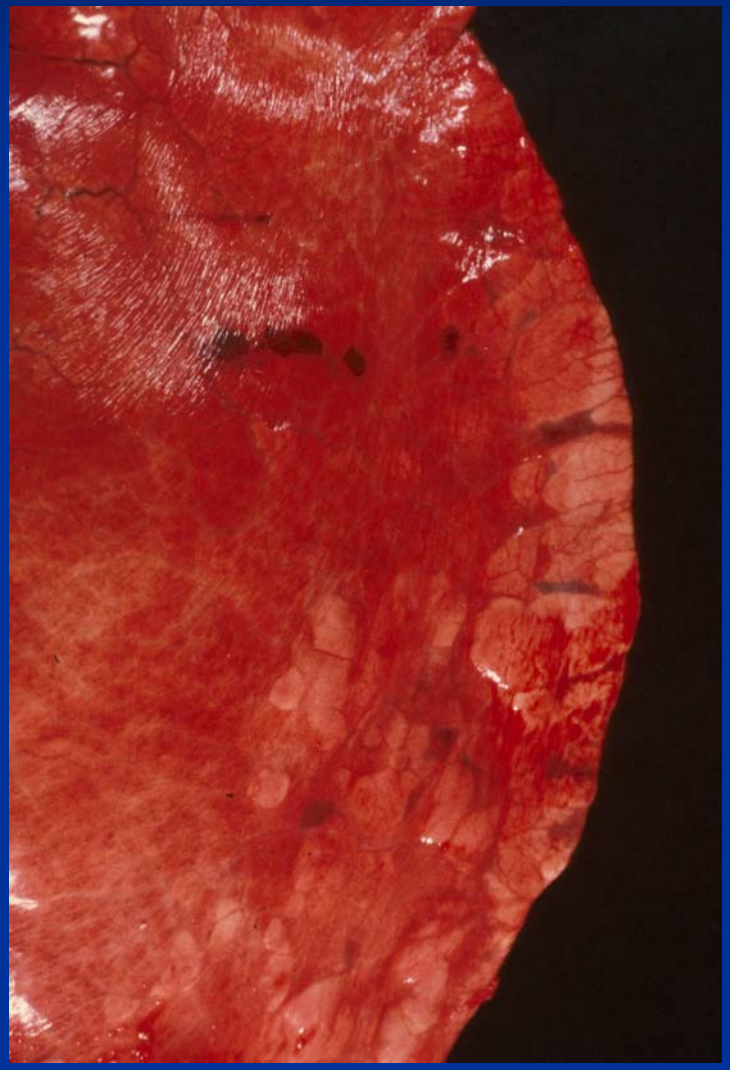
Abnormalities of Inflation – Emphysema

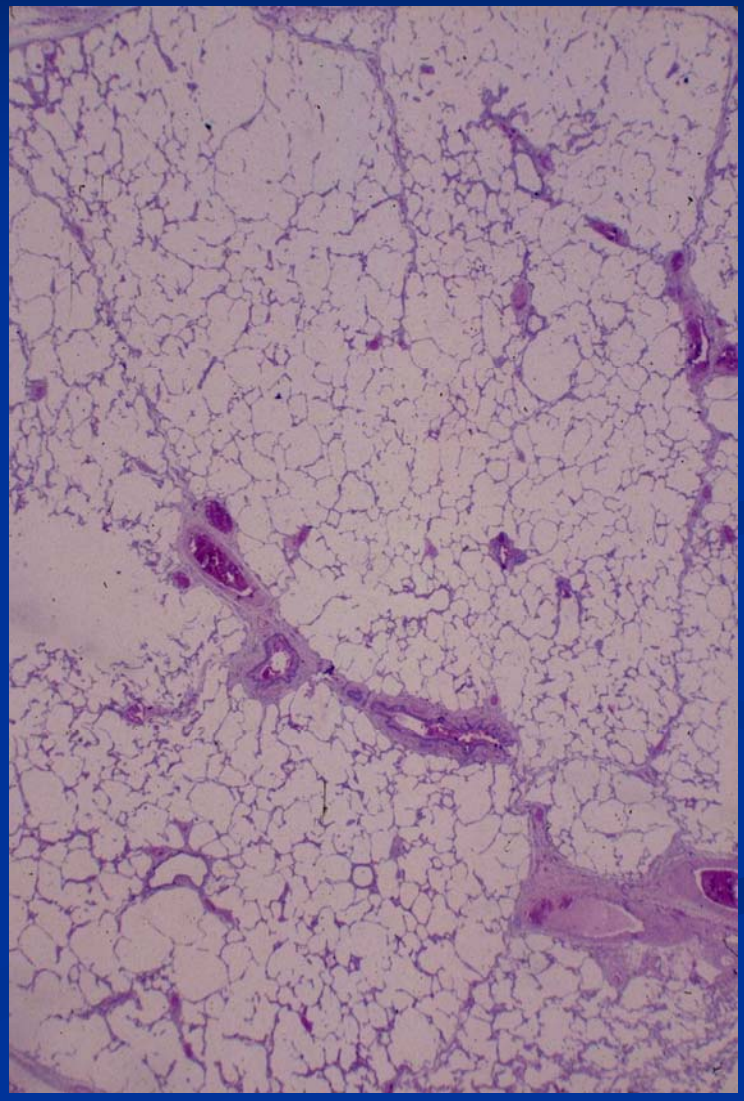
- Air in tissues
- Alveolar emphysema
  - Rupture of alveolar septa - human
  - Equine pulmonary emphysema (COPD, heaves)
- Interstitial emphysema (cattle)
  - Air in the interlobular septae and subpleurally
- Focal: secondary to atelectasis, scarring, incomplete obstruction of airways, or pneumonia.
- Senile "emphysema"- aged dogs, cats, horses

Alveolar Emphysema

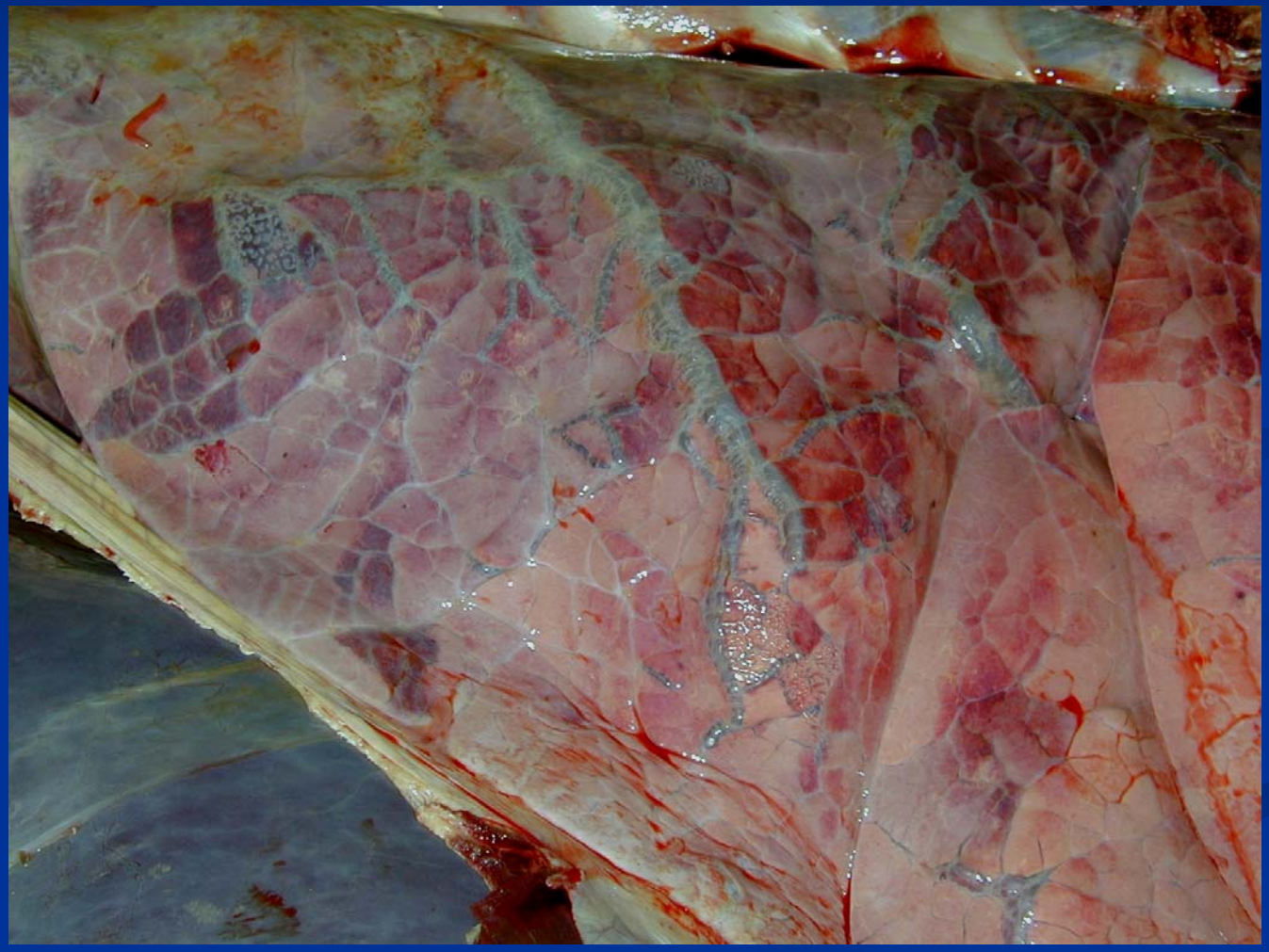


Abnormalities of Inflation – Alveolar Emphysema - Horse





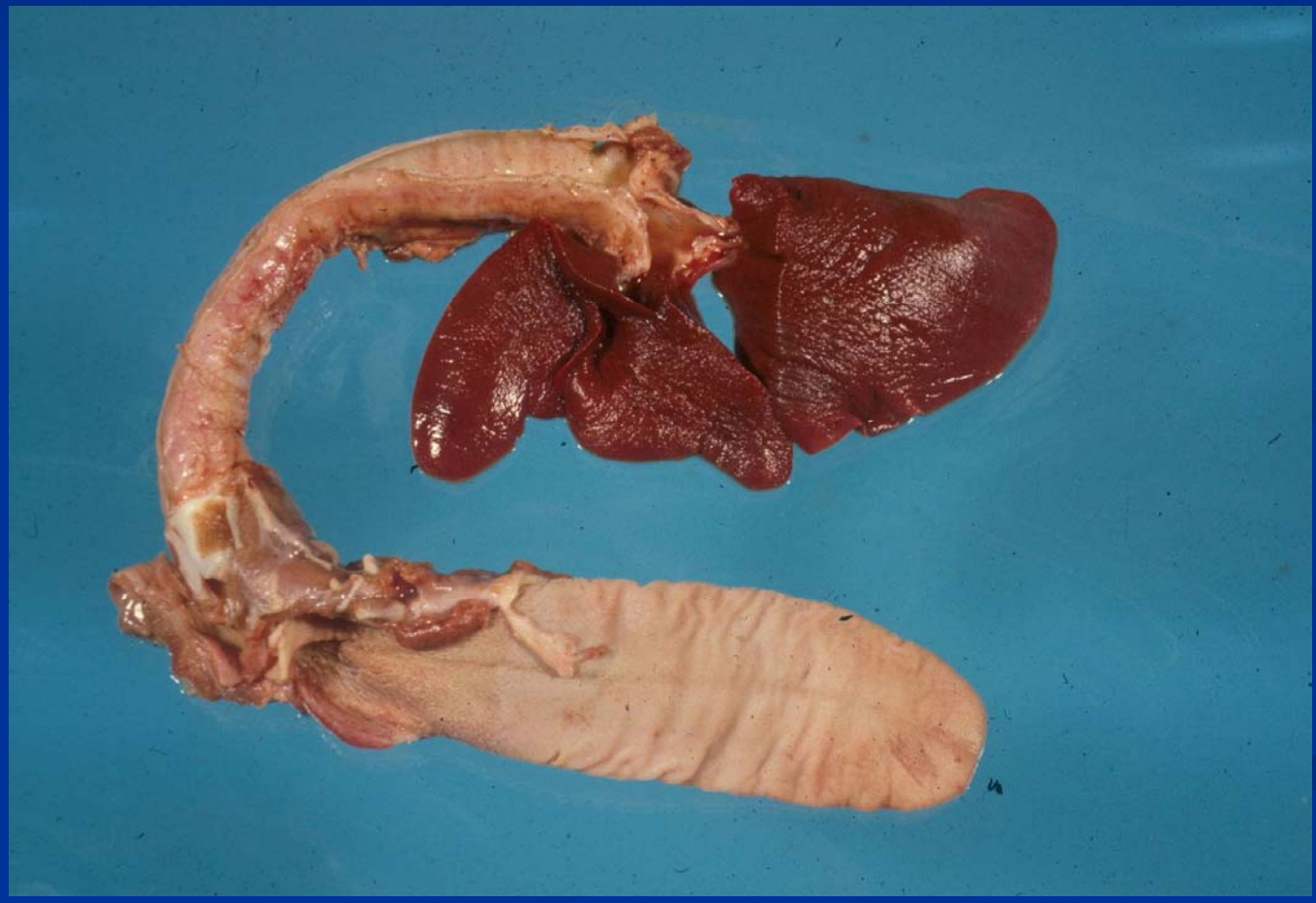
Abnormalities of Inflation – Interstitial Emphysema - Cow



Atelectasis

- Diffuse or multifocal
- Congenital atelectasis
- Acquired atelectasis
  - Compression collapse
  - Obstructive (focal)
  - Congestive or hypostatic atelectasis

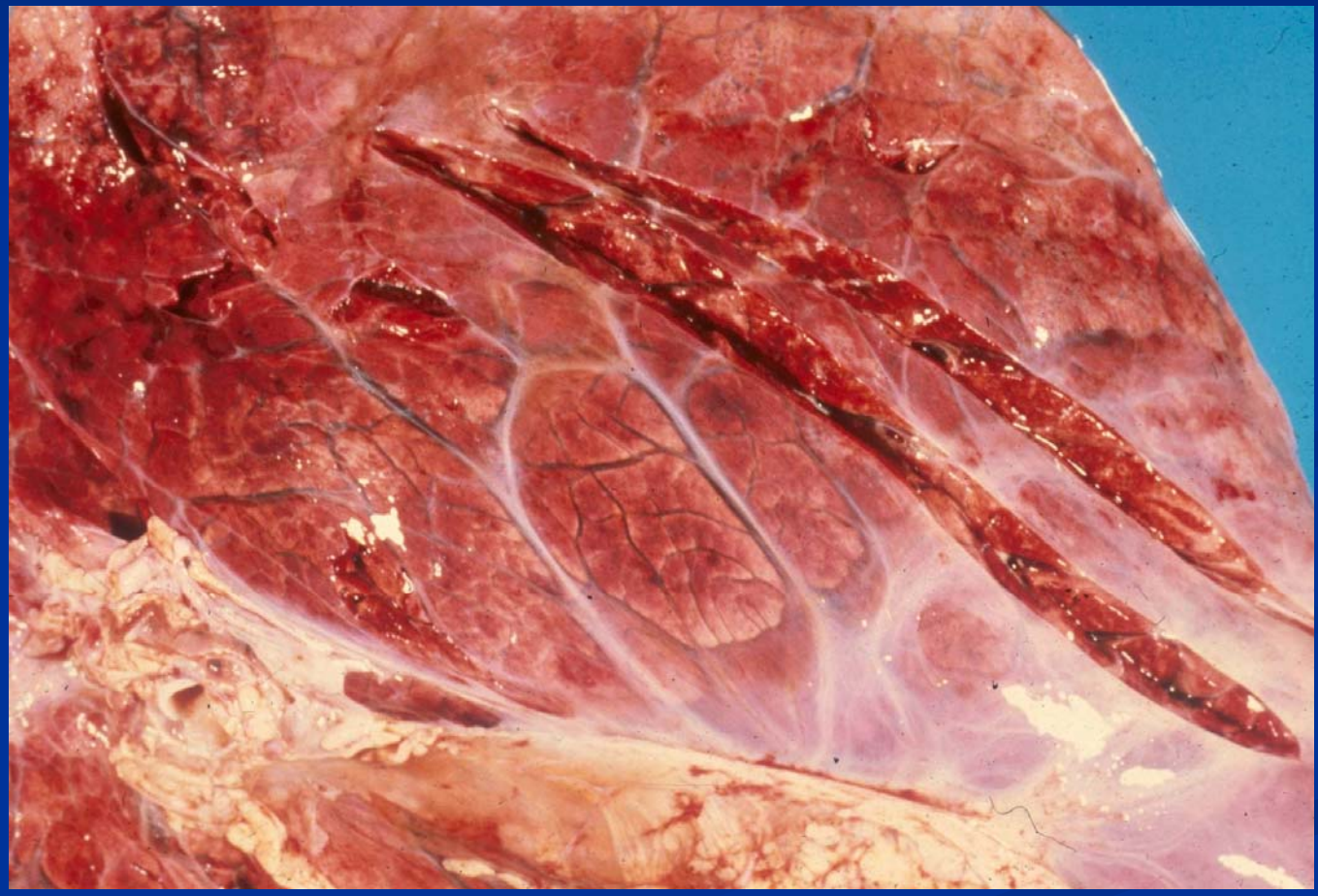
Aquired Atelectasis - Dog



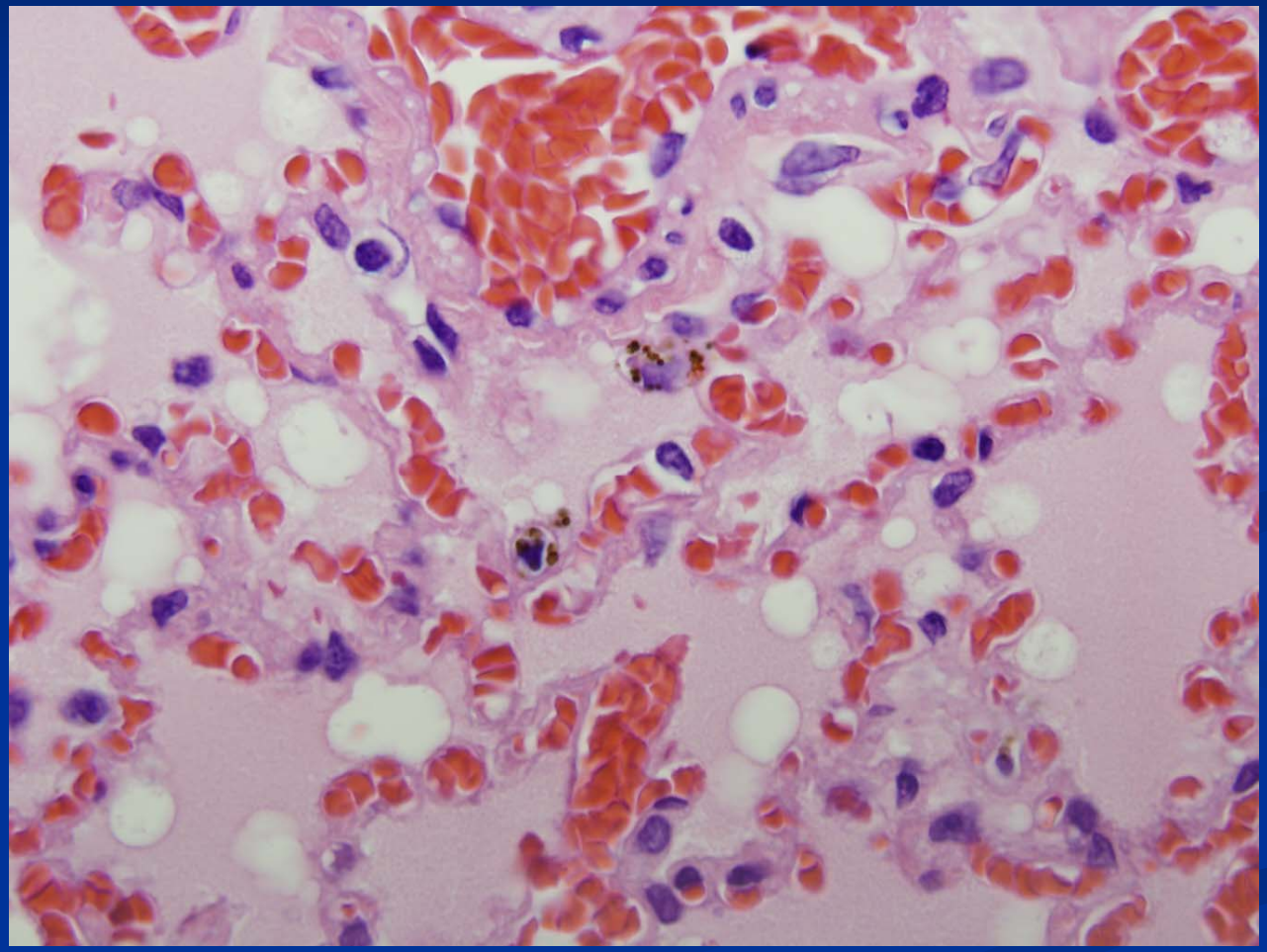
Circulatory Disturbances

- Diffuse pulmonary edema
- Hemorrhage
  - Petechia, ecchymosis
  - EIPH
- Embolism, thrombosis, infarction
- Pulmonary hypertension

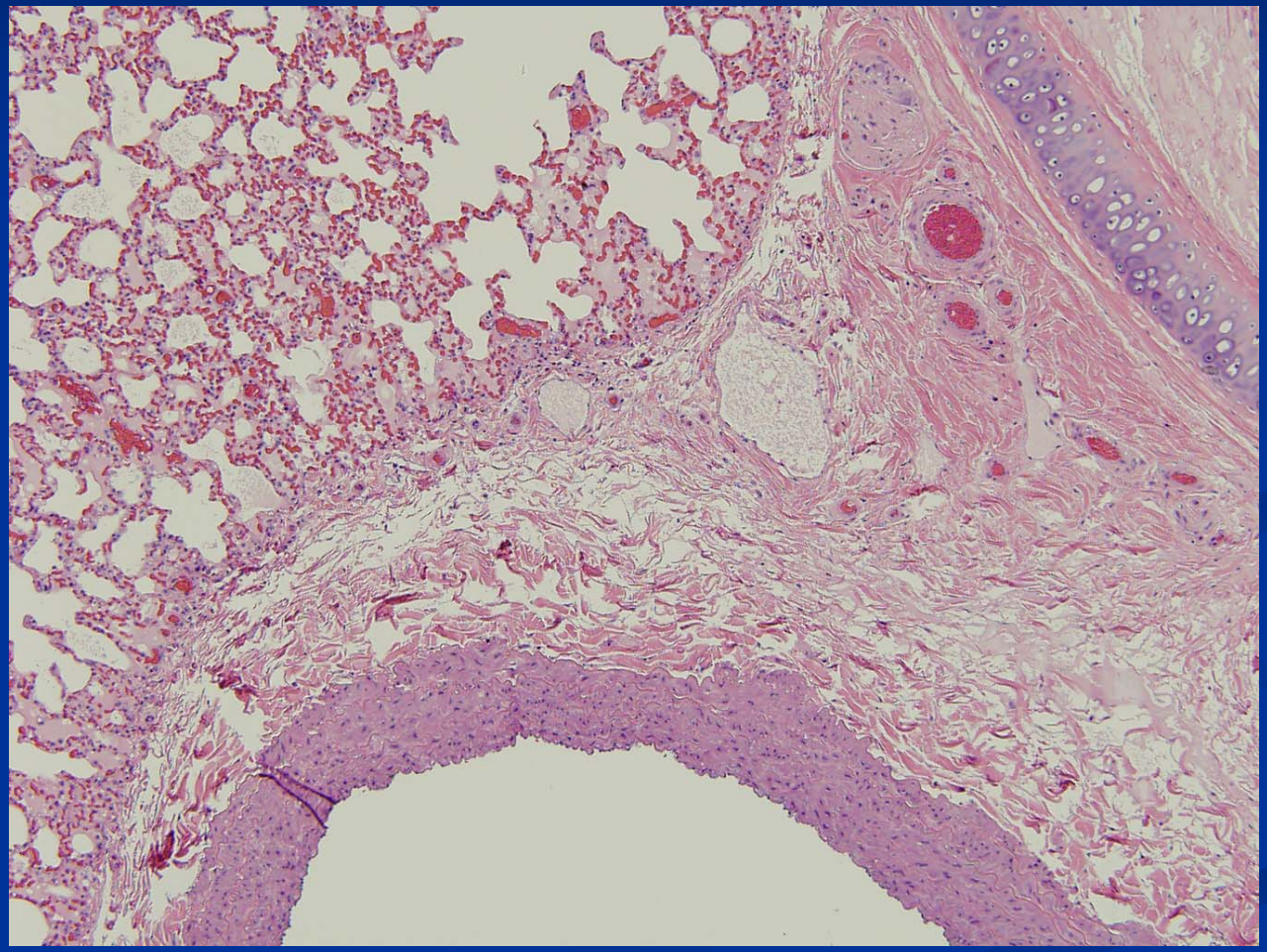
Pulmonary Edema – Cow



Cardiogenic Edema—Dog



Cardiogenic Edema—Dog



Mechanisms of Pulmonary Edema

- Altered hemodynamics
  - Increased capillary hydrostatic pressure
  - Decreased plasma oncotic pressure
- Increased permeability of air-blood barrier (noncardiogenic)
- Lymphatic obstruction
  - Note normal location of lymphatics
- Airway obstruction

Pulmonary Edema - Increased Capillary Hydrostatic Pressure

- Cardiogenic – most common
- Hypervolemic - iatrogenic
- Acute CNS injury

  - epinephrine release

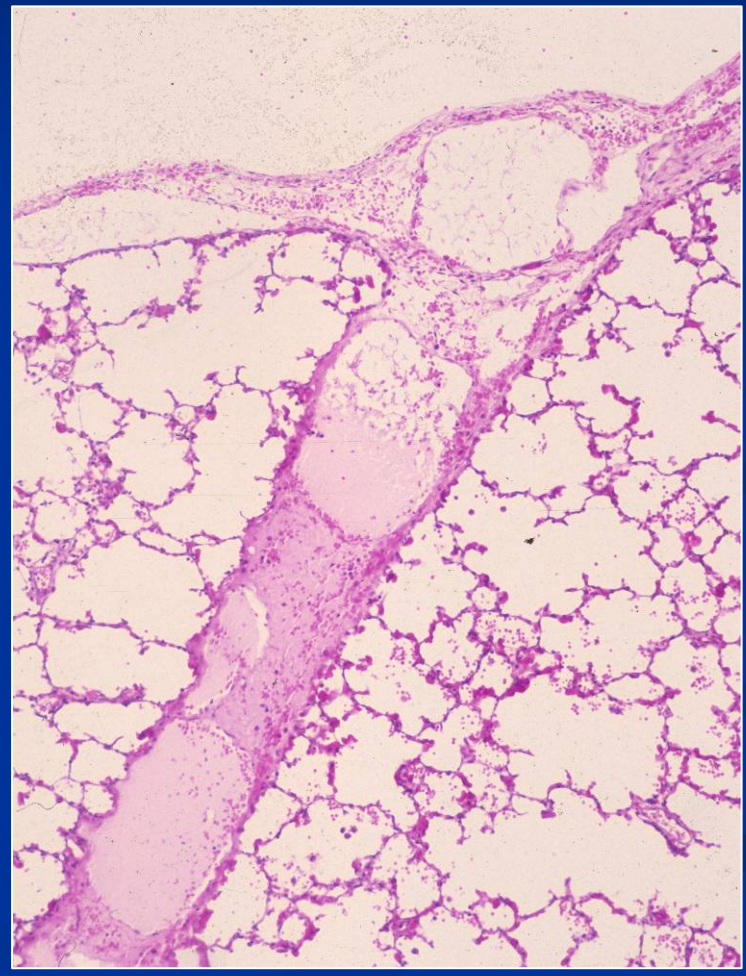
  - direct or via cardiac injury (brain-heart syndrome)

Pulmonary Edema - Increased Capillary Hydrostatic Pressure

Cardiogenic

- Toxic – e.g. fumonisins, gossypol
- Nutritional – e.g. vitamin E/selenium deficiency
- Degenerative
- Cardiomyopathy
- Congenital heart defects

Pulmonary Edema – Pig



Increased Permeability of Air-Blood Barrier

- Endothelial/epithelial injury – inhalation/boodborne exposure
  - Toxic e.g. smoke, paraquat, oxygen
  - Viral
  - Bacterial
- Inflammation
- Anaphylaxis
- Hypoxemia

Embolism, Thrombosis, Infarction

- Embolism/Thromboembolism
  - Infectious
  - Neoplastic
  - Aseptic
- Thrombosis
- Infarction rare due to dual blood supply

Embolism, Thrombosis - Cow

Hemorrhage

- Petechial hemorrhage
  - Septicemia
- Ecchymotic hemorrhage
  - Coagulation defects
- Other
  - Trauma
  - Method of euthanasia

Inflammation of the Lung: Pneumonia

- Limited types of response
- Diagnosis/Etiology
  - Palpation
  - Distribution of lesions
  - Pathology
  - Ancillary information (clinical, laboratory)

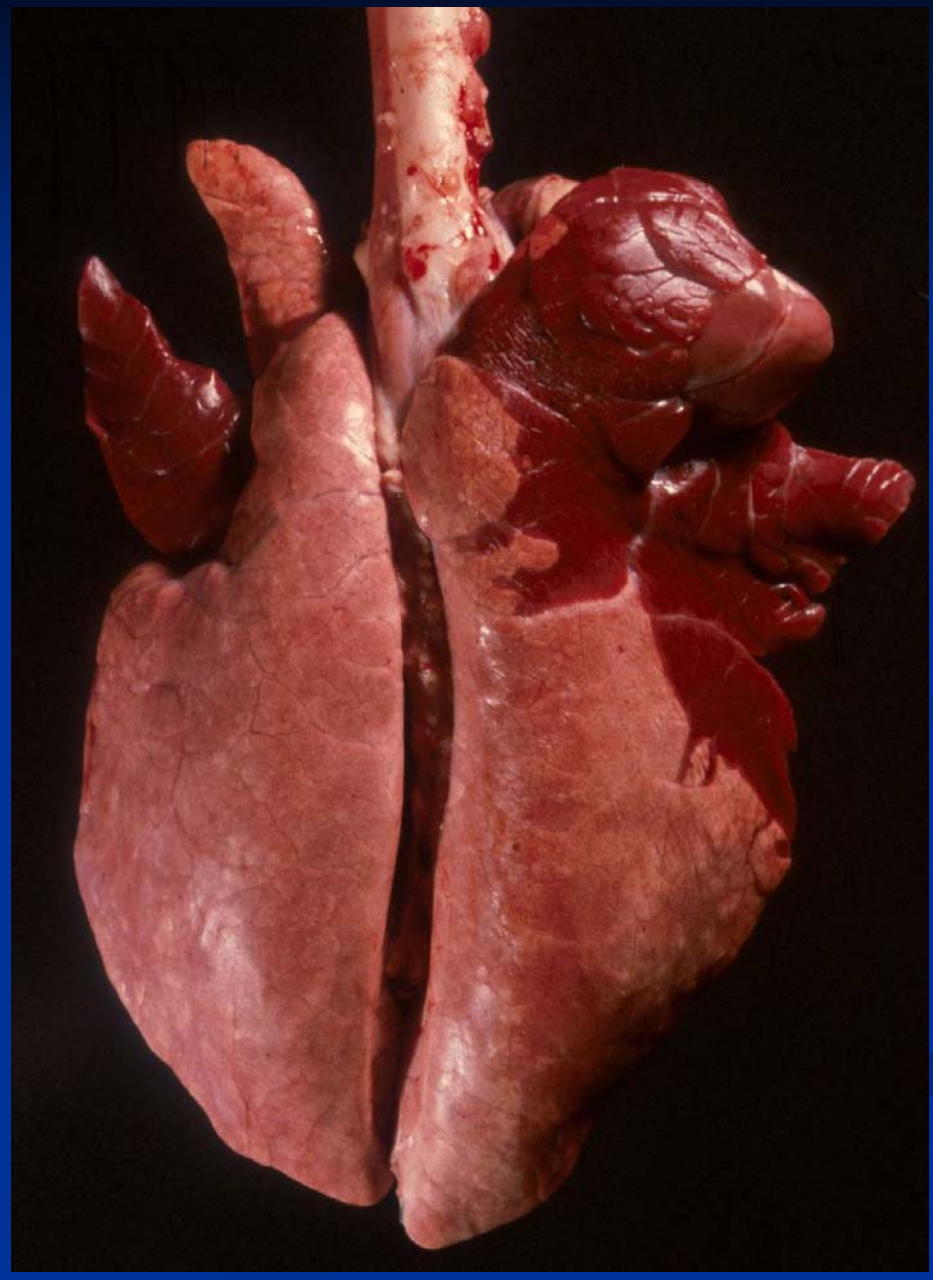
Types of Pneumonia

- Bronchopneumonia
- Interstitial pneumonia
- Embolic pneumonia
- Granulomatous pneumonia

Bronchopneumonia

- Inflammation of airways and adjacent parenchyma
- Inhaled agents
  - Bacteria
- Generally suppurative
- Anteroventral
- Aspiration

Broncho-pneumonia - Pig



Bronchopneumonia: Bacterial

- Generally young, stressed animals
- Predisposition
  - Stress
  - Viral infection
  - Immune deficiency/suppression

Bronchopneumonia

- Classical stages
  - Hyperemia plus edema (mins-hrs)
  - Red hepatization (2-3 days)
  - Gray hepatization (5-7 days)
  - Resolution (7 days to 4 weeks)

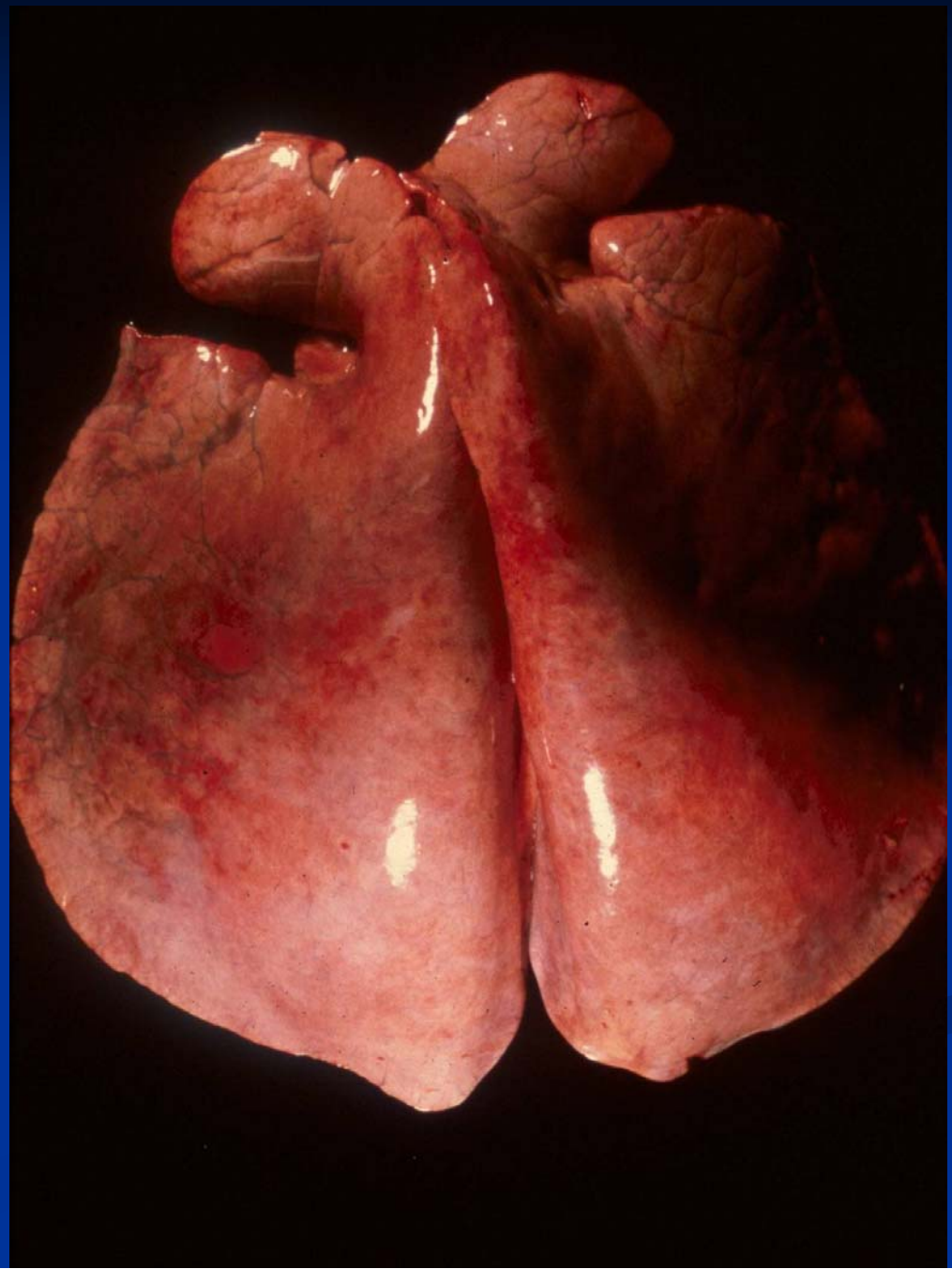
Bronchopneumonia

- Common sequelae
  - Death (hypoxemia, toxemia)
  - Septicemia
  - Pleuritis
  - Chronic bronchopneumonia
  - Abscesses
  - Bronchiectasis
  - Atelectasis

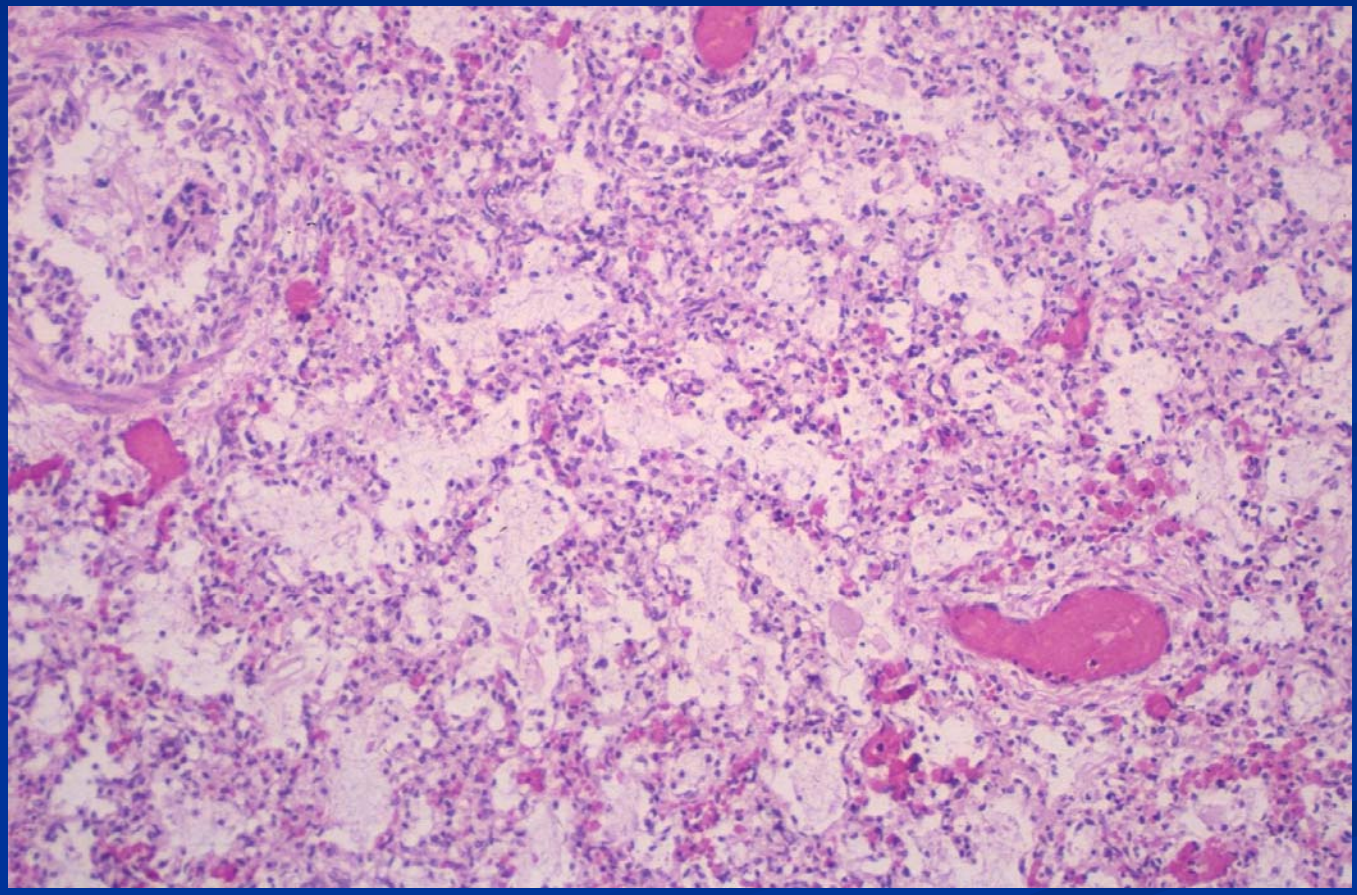
Interstitial Pneumonia

- Inflammation of interstitium-generally without airway involvement
- Diffuse distribution
- Non-suppurative
- Exposure via blood or inhalation

Interstitial Pneumonia - Horse



Interstitial Pneumonia - Foal



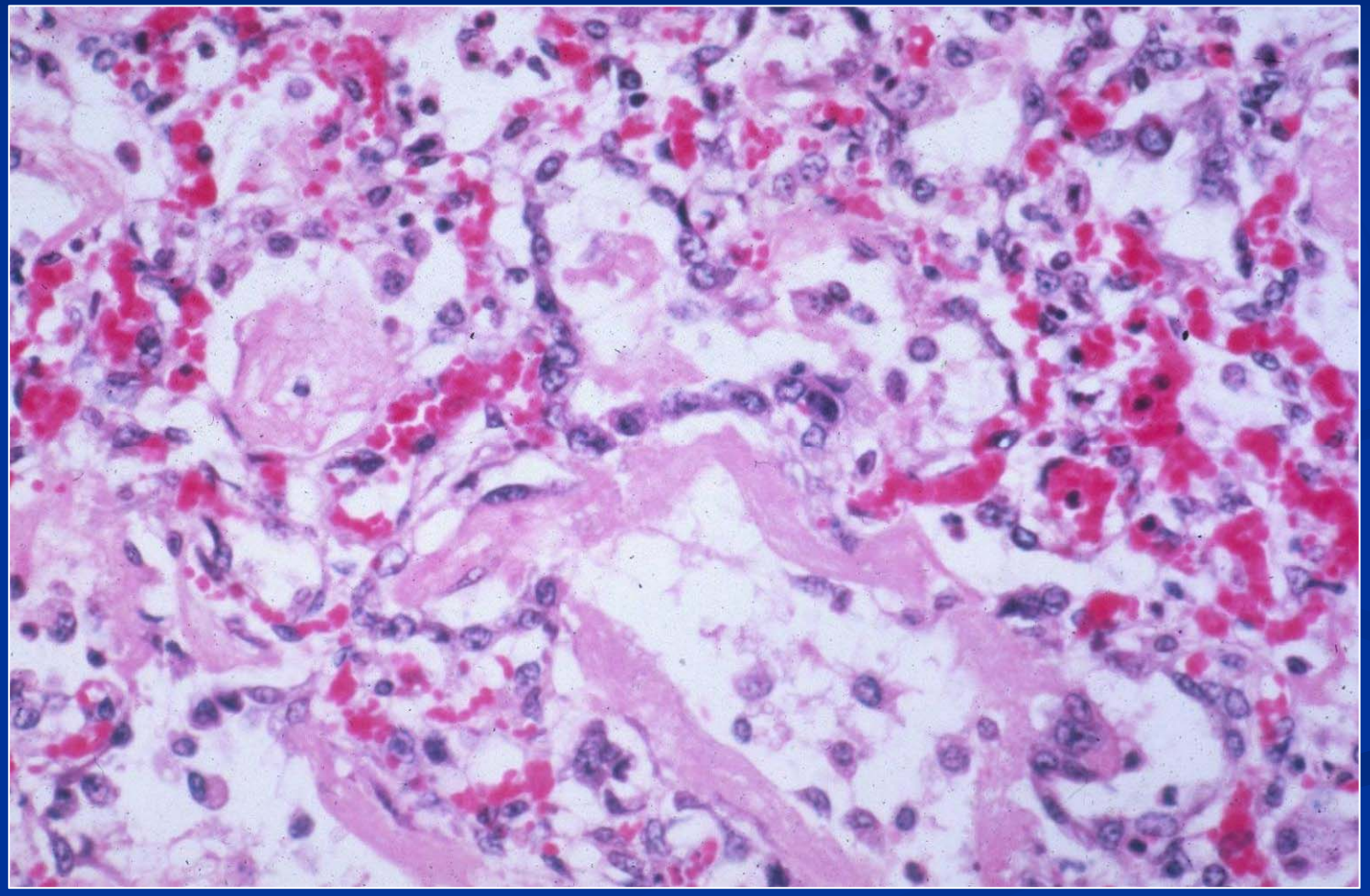
Etiology of Interstitial Pneumonias

- Viral
- Bacterial
- Mycotic
- Protozoal
- Other parasitic
- Toxic
- Hypersensitivity

Interstitial Pneumonia

- Lesion lacks etiologic specificity
- Acute exudative phase (ARDS)
- Subacute proliferative phase (3 days)
- Chronic phase (7-14 days)

Subacute Interstitial Pneumonia - Cow



Interstitial Pneumonia

- Possible sequela
  - Resolution
  - Fibrosis
  - Persistence
  - Bacterial bronchopneumonia

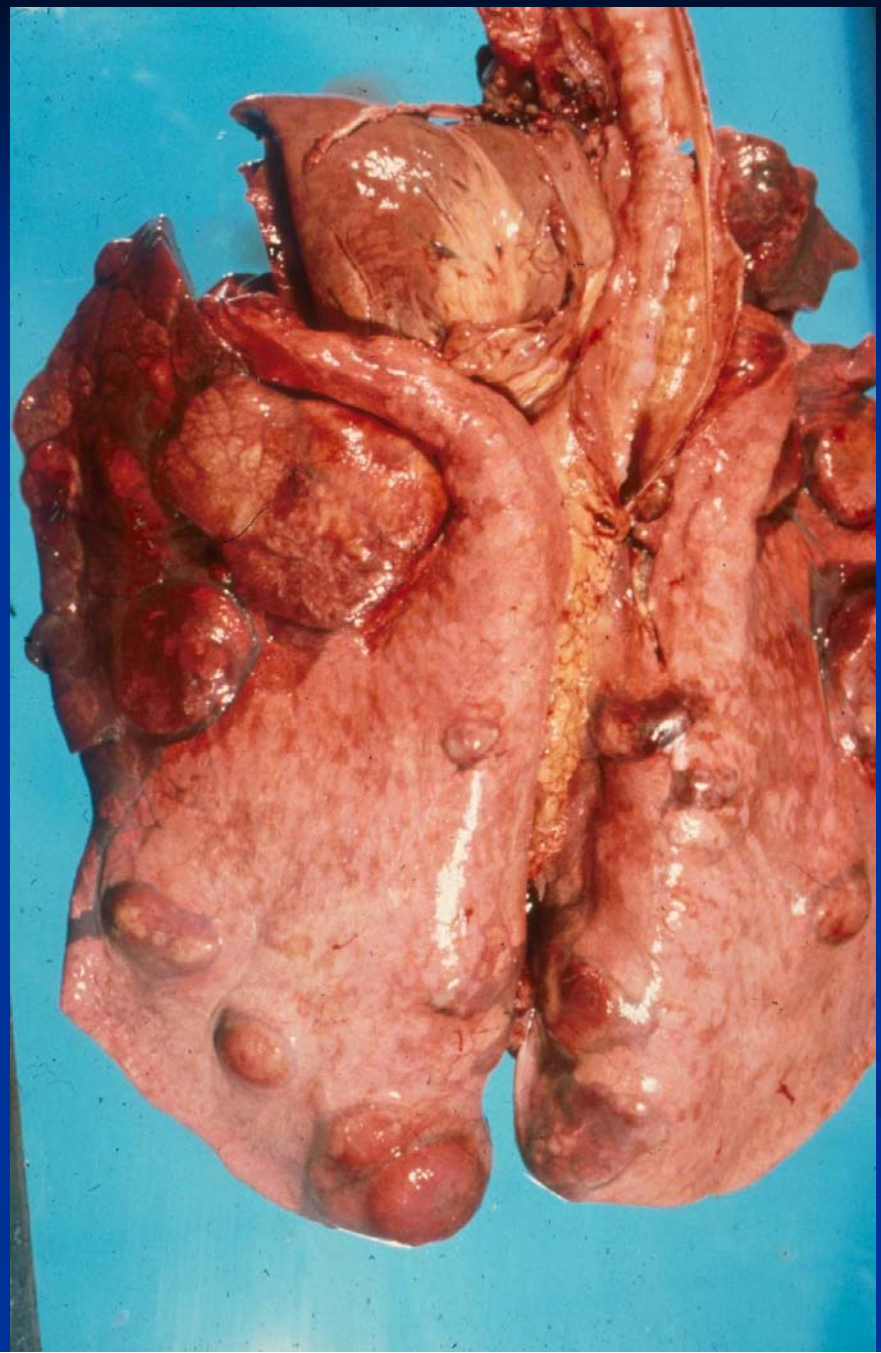
Bronchointerstitial Pneumonia

- **Microscopic diagnosis only**
  - Components
    - Interstitial pneumonia (non-suppurative)
    - Bronchiolitis
  - Etiology
    - Some viruses e.g. herpesvirus, BRSV
    - Mycoplasma

Multifocal Lesions

- Abscess
  - Bronchogenic
  - Septic emboli
  - Aspiration
- Foreign body
- Granuloma
- Neoplasia

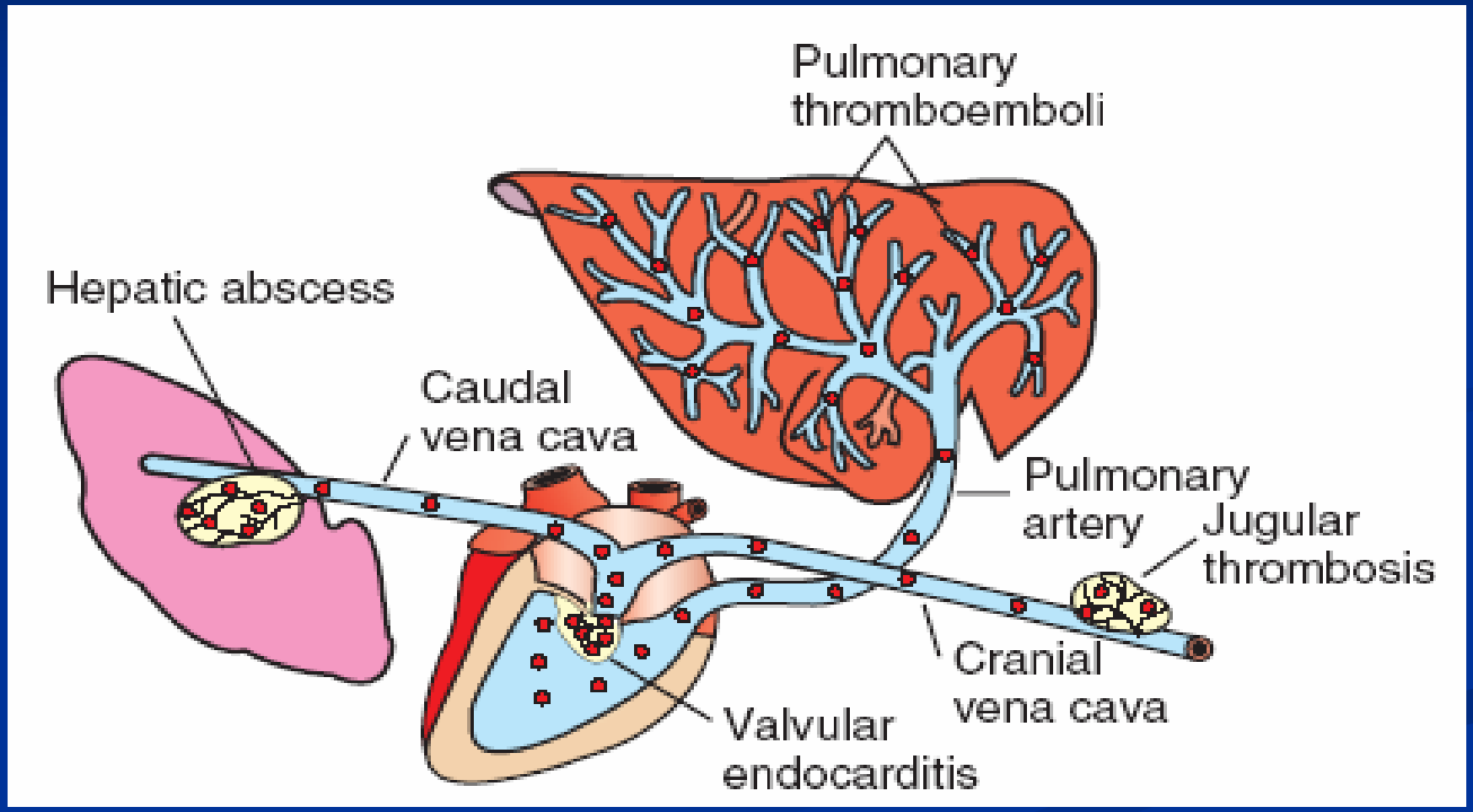
Multifocal Abscesses - Horse



Embolic Pneumonia

- Etiology
  - Bacterial (abscesses)
    - Vegetative endocarditis
    - Septicemia
    - Ruptured liver abscess
  - Mycotic (granulomas)
    - Rumen ulcers
    - GI ischemia
  - Foreign body (e.g. iv injection, hair)

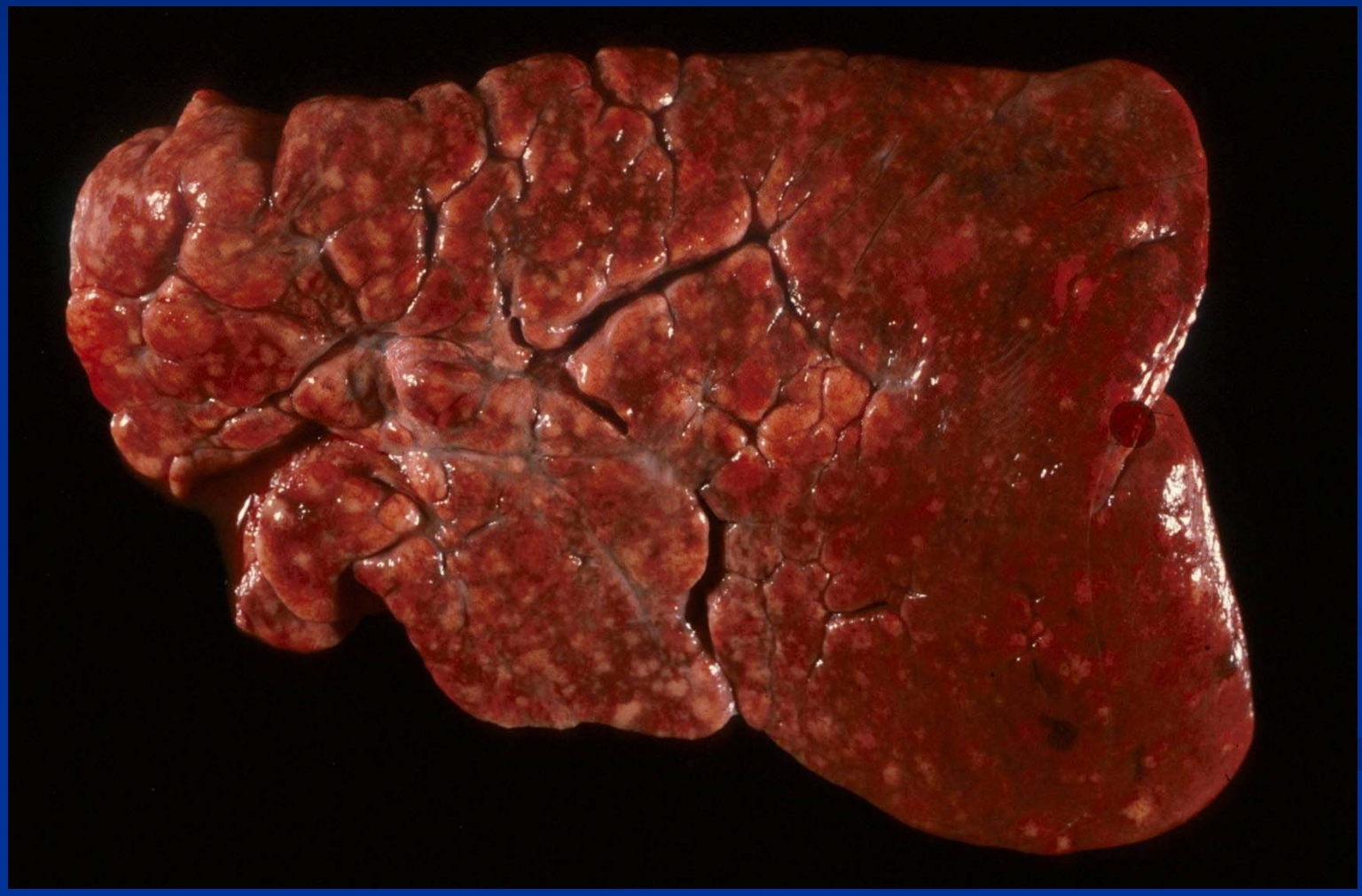
Pulmonary Emboli



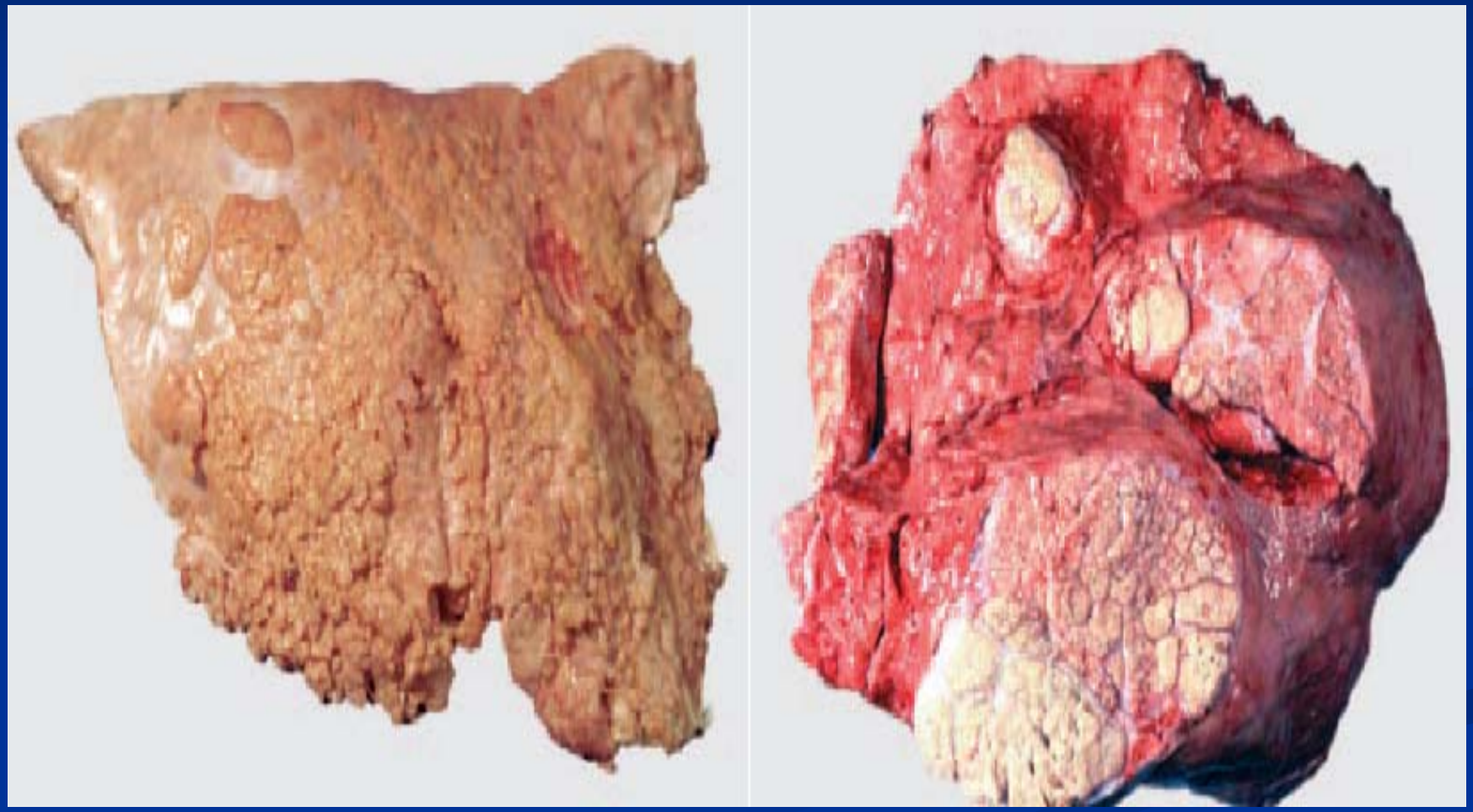
Granulomatous Pneumonia

- Inhaled or blood-borne agents
- Large areas are affected vs. pulmonary granulomas
- Multifocal to locally extensive distribution
- Agent persists and incites granulomatous response
- Etiology: mycotic, bacterial, particulates

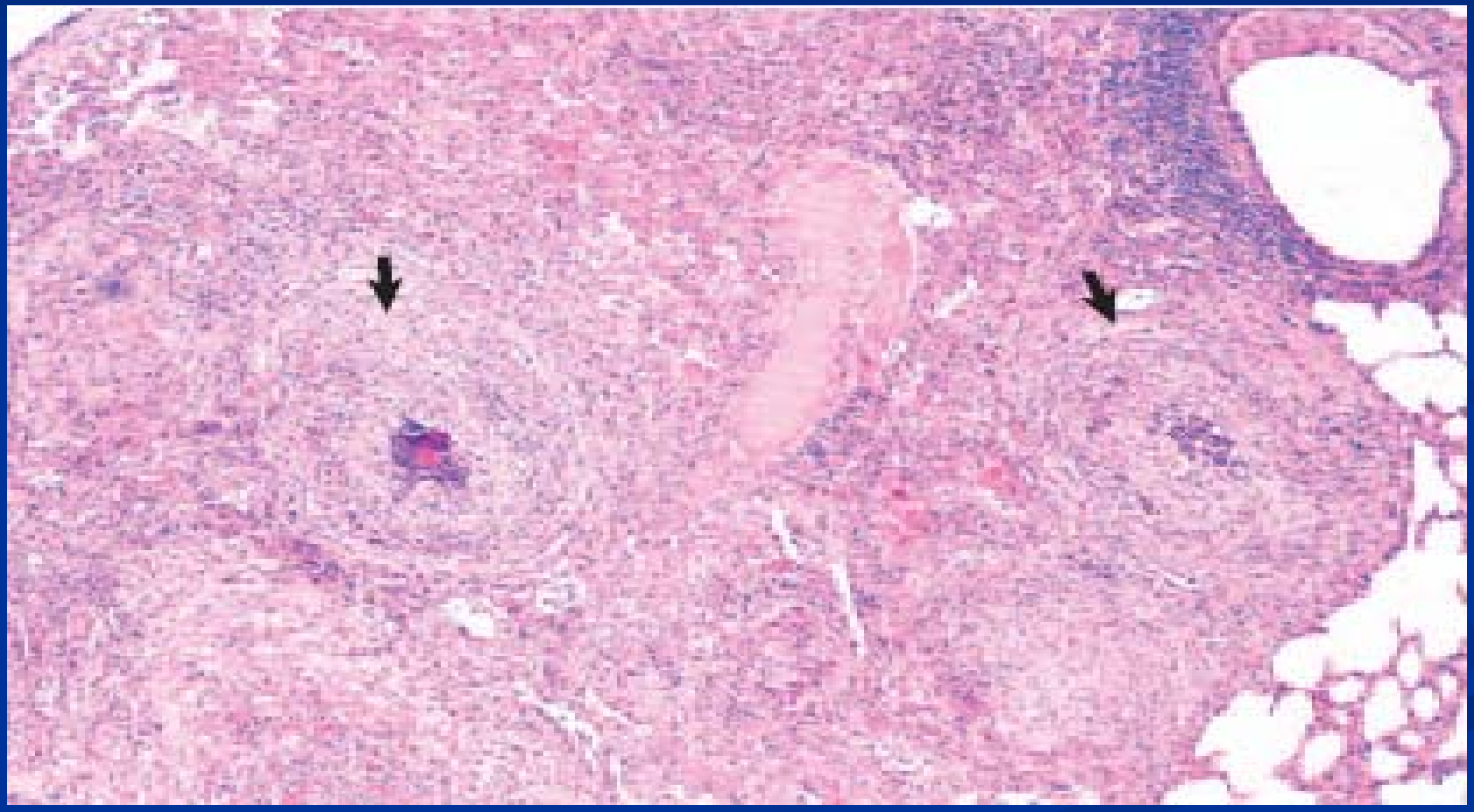
Granulomatous Pneumonia - Dog



Tuberculosis - Cow



Tuberculosis - Cow

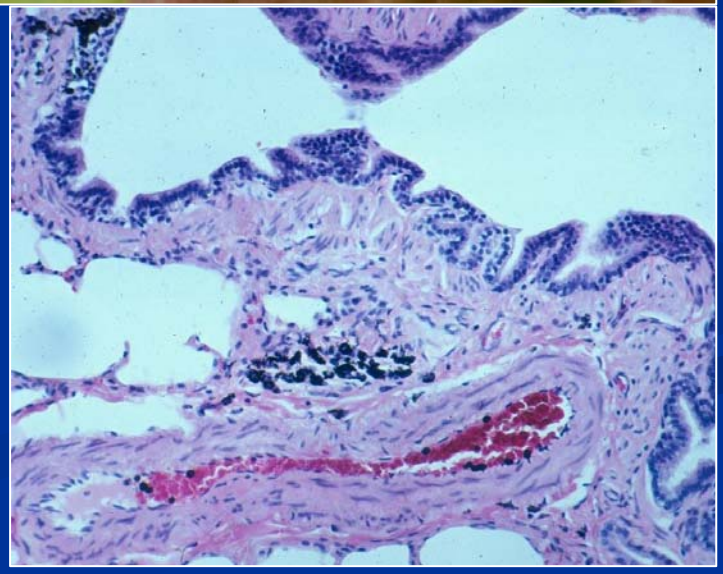


Pneumoconiosis

- Anthracosis
- Asbestosis
- Silicosis
- Clay - bentonite – cat litter ?????

Pneumoconiosis - Anthracosis

- Species: dogs, humans, etc, living in cities
- Disease: benign accumulation of carbon



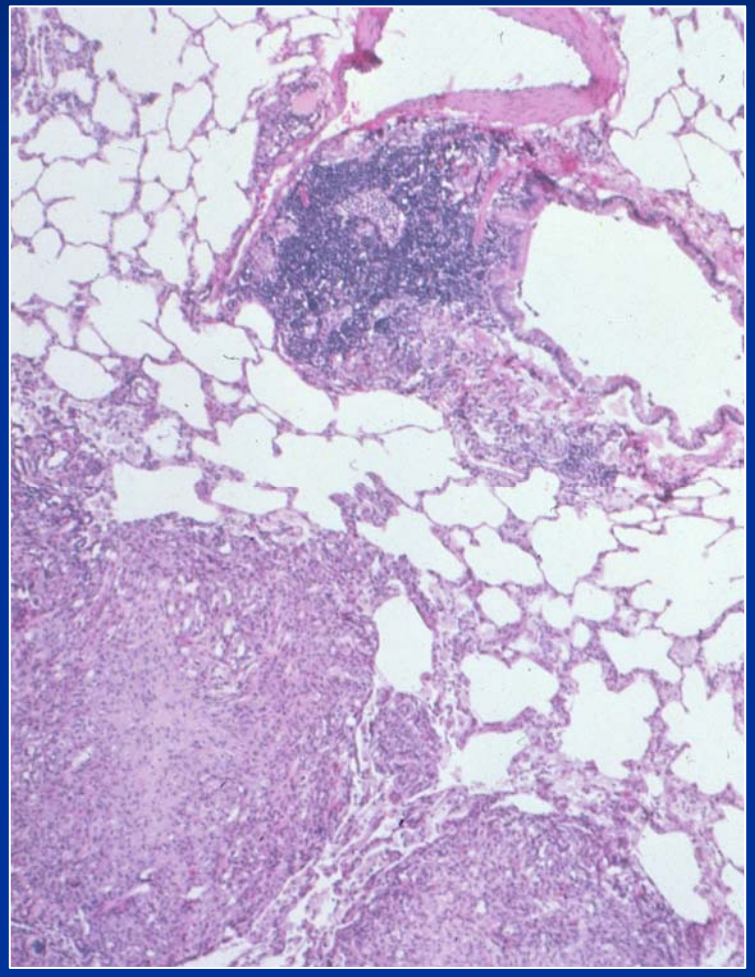
Pneumoconiosis - Asbestosis

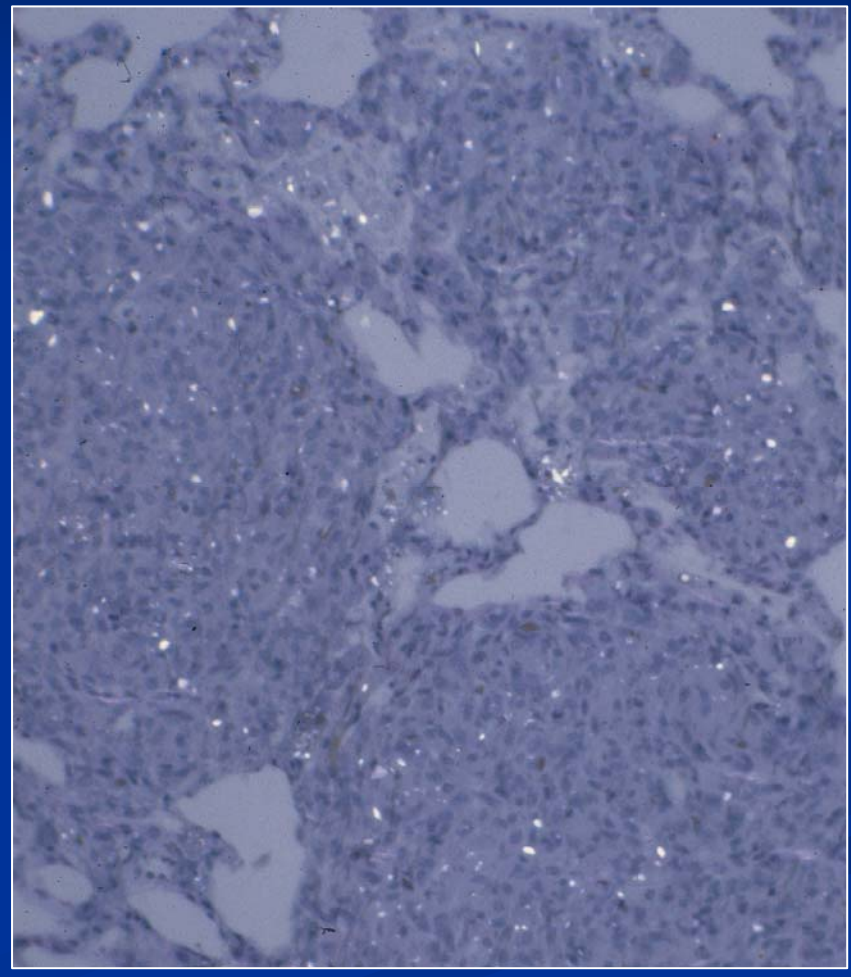
- Species: man, dog, cattle
- Lesions
  - Inflammation, fibrosis, asbestos bodies
  - Mesothelioma
- Pathogenesis: macrophage and epithelial injury

Pneumoconiosis - Silicosis

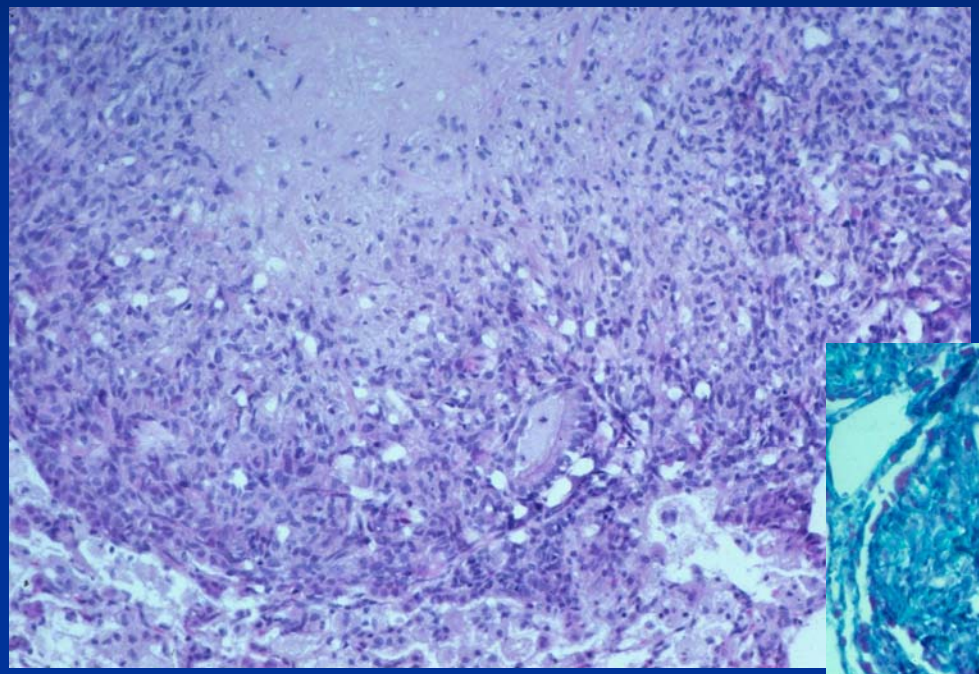
- Species: humans, horses, wildlife and zoo animals
- Origin: mines, sandblasting, sand flouncing
- Pathology: progressive granulomatous disease
- Pathogenesis: cytotoxicity to macrophages

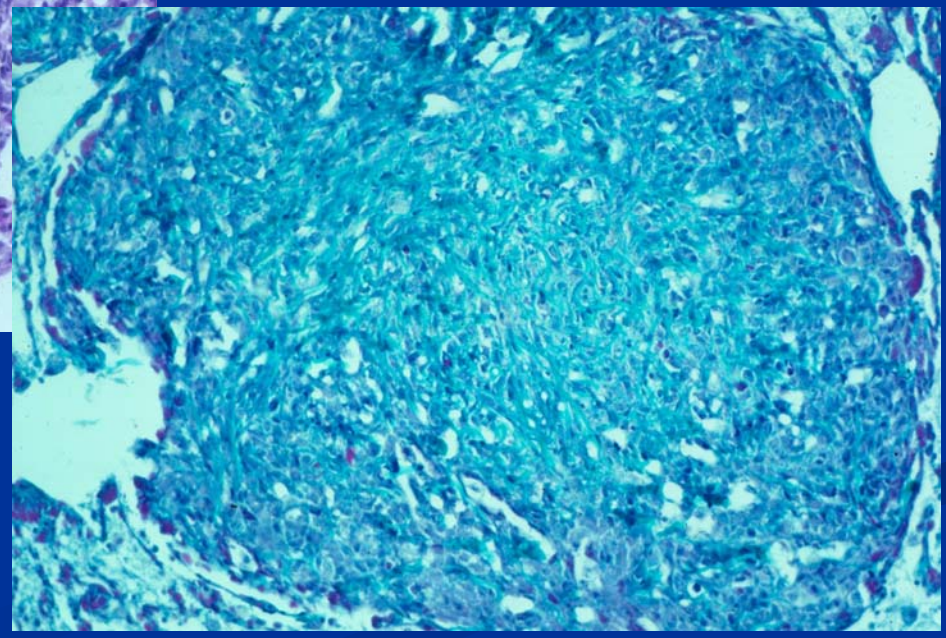
Silicosis – Rat (Exp)





Pneumoconiosis - Silicosis





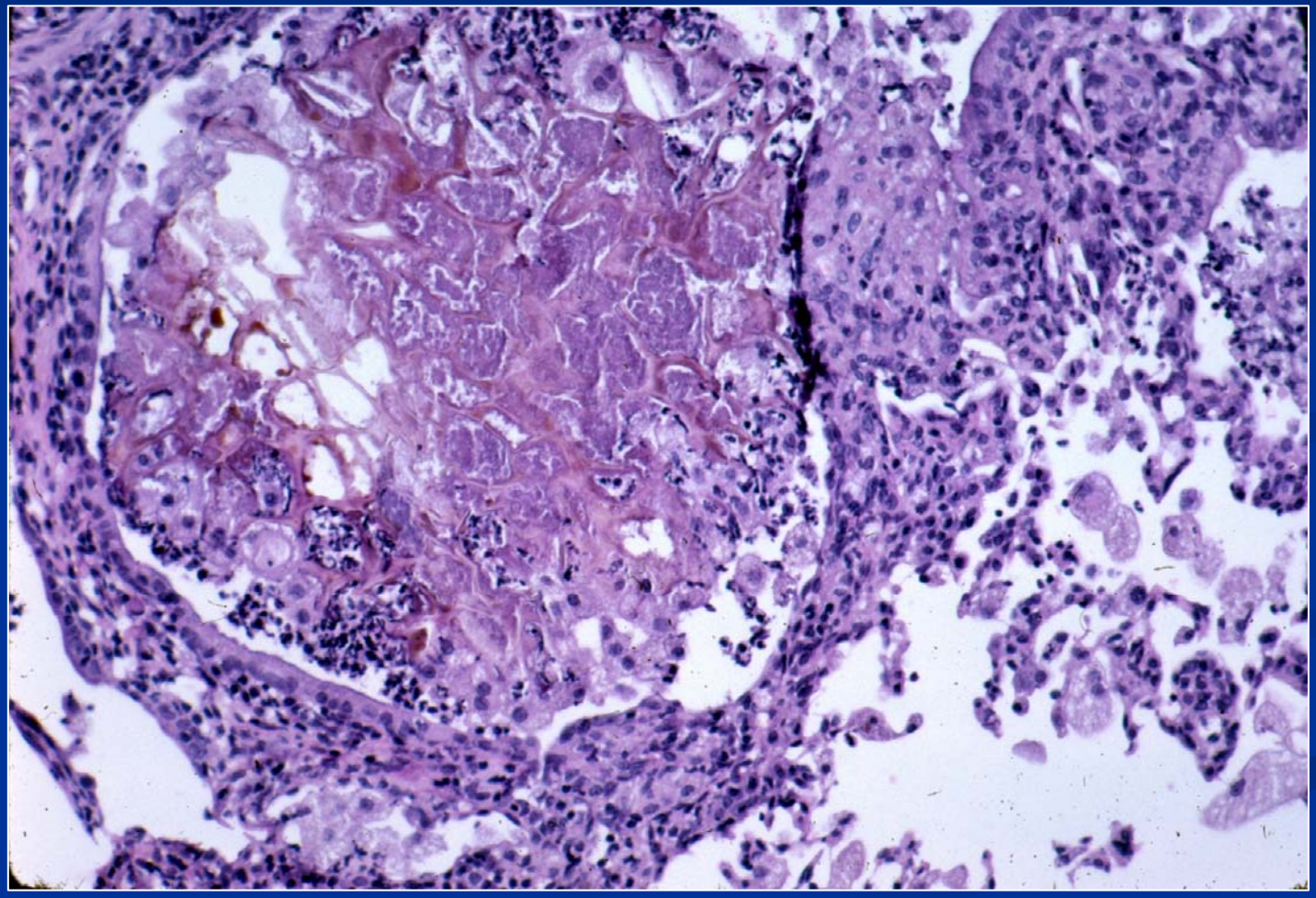
Aspiration Pneumonia

- Etiology/predisposing factors
  - Iatrogenic
  - Cleft palate
  - Anesthesia
  - CNS disorder
  - White muscle disease
  - Improper force feeding
  - Prenatal stress

Aspiration Pneumonia cont.

- Response to aspirated material
- Lesion
  - Bronchopneumonia
  - Distribution
    - Anteroventral/locally extensive
    - Multifocal
  - Severity
  - Identification of foreign material

Aspiration Pneumonia - Mouse



Fetal Aspiration Pneumonia

- Fetal hypoxia and acidosis (fetal distress)
- Relaxation of anal sphincter with release of meconium into amniotic fluid
- Loss of glossal reflex allows aspiration of amniotic fluid containing squames and meconium
- May also aspirate pathogens if placentitis present
- Inflammation results – easily missed

Viral Pneumonias

- Lesions
  - Interstitial pneumonia
  - Bronchointerstitial pneumonia
- Rarely kill without bacterial infection
- Diagnosis

Viral Infection

- Can lead to secondary infection
  - Depress macrophage function
  - Impair mucociliary clearance
  - Allow bacterial multiplication
- Can lead to airway hyperreactivity

Major Viral Diseases

- Especially important
  - Herpesviruses
    - Can remain latent till stress occurs
    - Can remain carrier
  - Influenza
    - Avian influenza – also felids, humans affected
    - Canine influenza – equine mutation
  - Paramyxoviruses

Bacterial Pneumonia

- Air-borne (aerogenous)
  - Bronchopneumonia (AV)
- Hematogenous: diffuse, multifocal (interstitial or embolic pneumonia)
- Secondary to
  - Infection: virus, mycoplasma, chlamydia
  - Stress e.g. shipping
  - Other e.g. environmental conditions

Bacterial Pneumonia (cont)

- Bacterial injury
  - Establishment by evasion of host defense system
  - Endotoxins
  - Exotoxins
  - etc
- Diagnosis

Mycobacterial Disease

- Zoonotic disease, reportable
- *Mycobacterium tuberculosis* (tuberculosis)
  - Man, cattle, dog, primate
- *M. bovis*
  - Man, cattle, swine, elephant, lion
- *M. avium*
  - Avian, swine, primate, dog
- Recent concerns in deer, elk

Mycobacteriosis

- Most systems can be affected
  - Ruminants: primary pulmonary
  - Pigs: ingestion, can disseminate to lung
- Pathology: granulomas
- Pathogenesis

Mycotic Pneumonia

- Etiologic agents
  - *Cryptococcus neoformans, C. gatti*
  - *Histoplasma capsulatum*
  - *Aspergillus spp.*
  - *Blastomycosis dermatiditis*
  - *Coccidiodes immitis*

Aspergillosis

- Canine
  - Nasal
  - Disseminated if immunosuppressed
- Avian – pulmonary, air sacs (invasive/noninvasive)
- Equine - gutteral pouch infection
  - Pulmonary granulomas (embolic)
- Bovine – secondary to rumenal ulcers
  - Pulmonary granulomas (embolic)
  - Placental leading to abortion

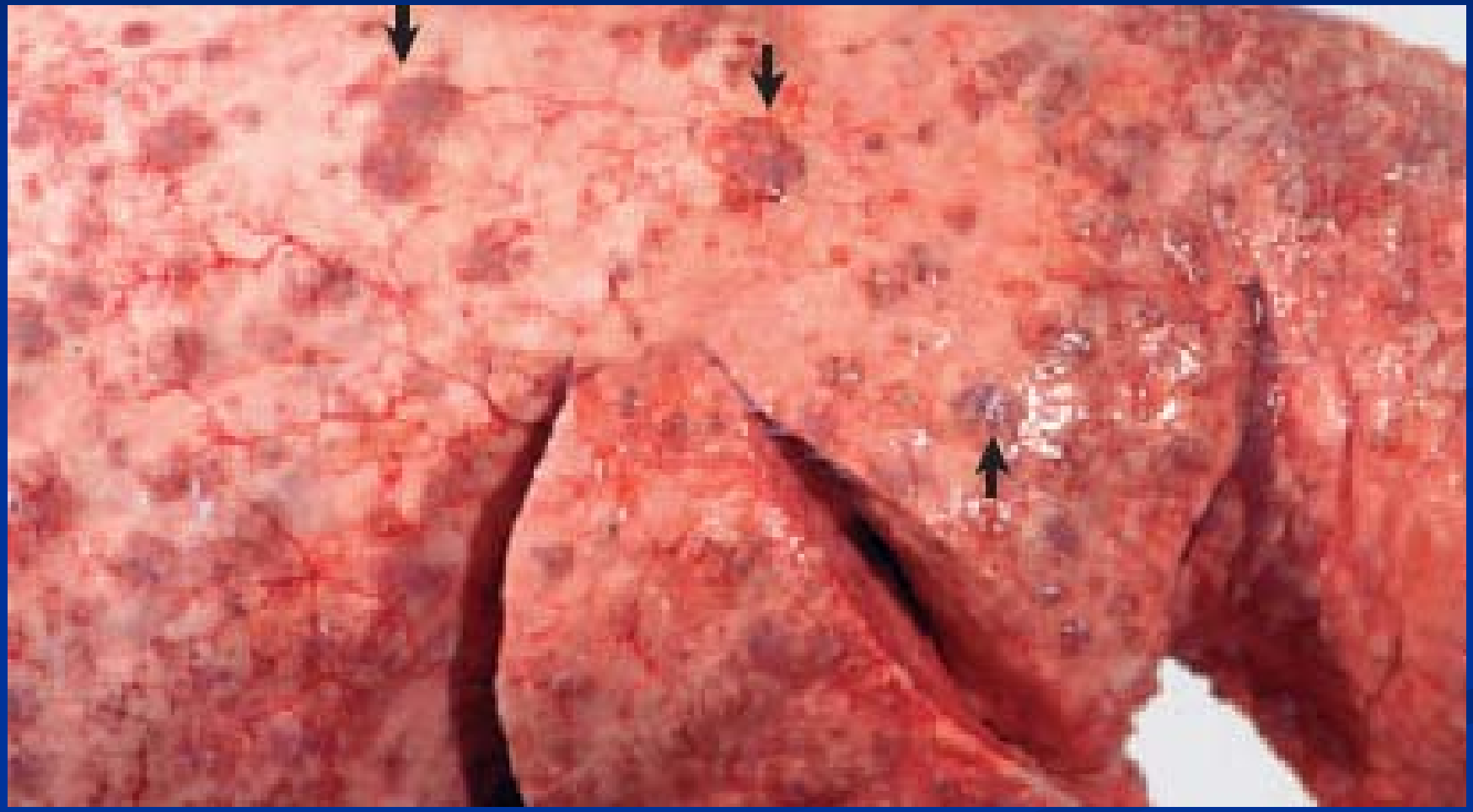
Mycotic/Protozoal Pneumonias Secondary to Immunosuppression

- *Toxoplasma gondii*
  - Cat, dog, man, etc. (zoonosis)
  - Frequently associated with distemper, AIDS
- *Pneumocystis spp*
  - Foals, pigs. man, laboratory animals

Parasitic (Verminous) Pneumonia

- Effect on host
  - Obstruct airways
  - Granulomas, multifocal, caudo-dorsal
  - Necrosis leading to loss of function
  - Secondary bacterial bronchopneumonia
  - Hypersensitivity reaction
  - Often see eosinophils

Muellerius spp - Sheep



Toxic Lung Injury

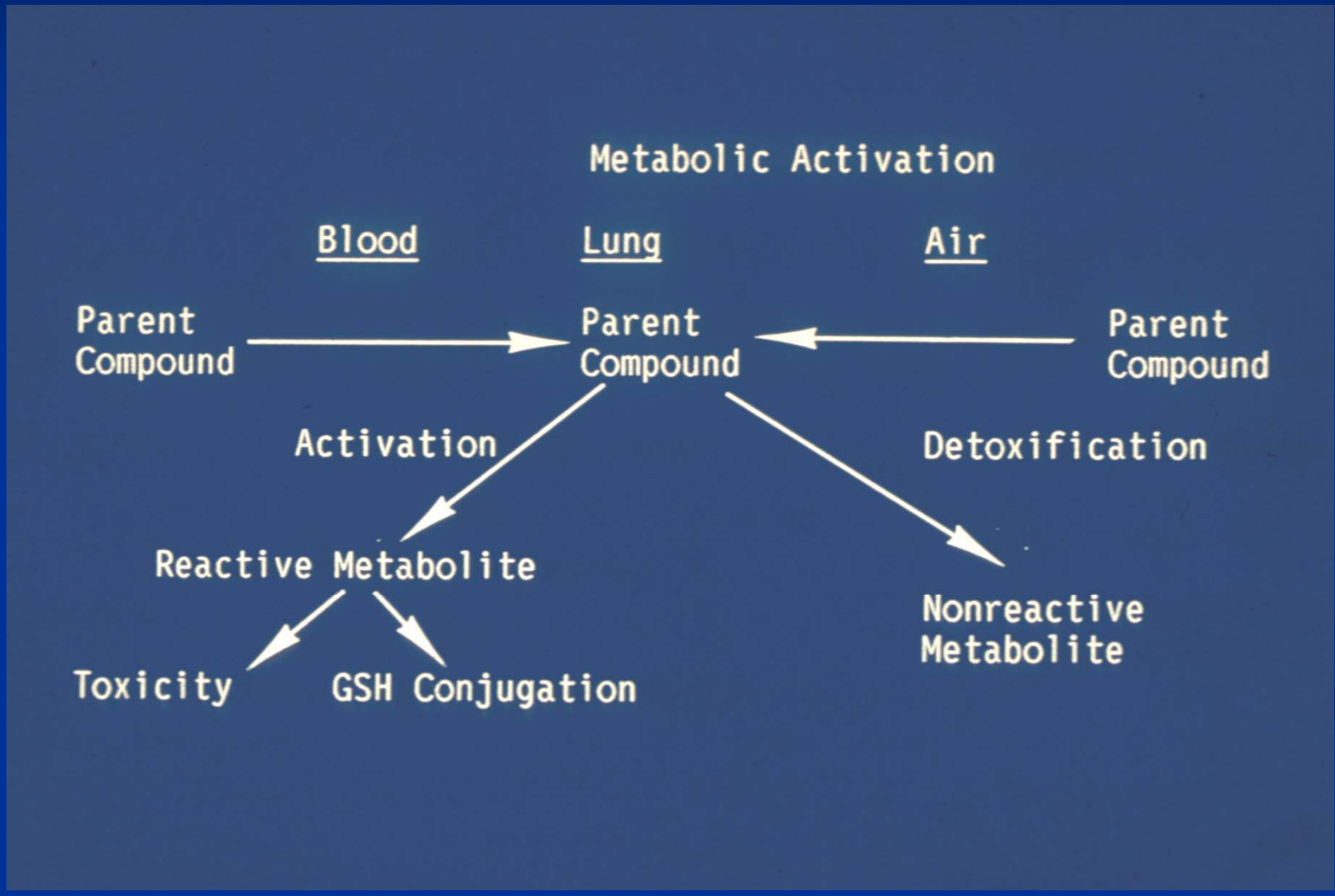
Cell Specific Toxic Injury

- Ciliated cells - NO_2 , SO_2 , O_3
- Mucous cells - smoking, SO_2
- Nonciliated (Clara) cells/olfactory epithelium - metabolically activated agents e.g. 3 methylindole
- Endothelial cells – pyrrolizidine alkaloids, oxygen, endotoxin
- Epithelial type I cells – paraquat
- Macrophages - silica

Mechanisms of Toxicity

- Direct acting e.g., oxygen (high conc)
- Indirect acting
  - Metabolic activation e.g., 3 methylindole
  - Cyclic oxidation of parent compound eg, paraquat
  - Immune mediated e.g., asthma
- Xenobiotic interaction e.g., with oxygen

Mechanisms of Toxicity



Chemically Induced (Toxic) Pulmonary Injury

- Etiology
  - 3-methylindole: cattle, sheep, goats
  - 4-ipomeanol: cattle
  - *Perilla frutescens* ketone: cattle, horses
  - Pyrrolizidine alkaloids: cattle, horses swine, sheep (mainly hepatic)
  - Paraquat: dogs, cats, man
  - Chemotherapeutic agents e.g. bleomycin
- Pathology: interstitial pneumonia

Smoke Inhalation

- Injury due to
  - Thermal injury (URT)
  - Chemical injury (LRT)
- Lesions
  - Laryngeal/tracheal necrosis with fibrin
  - Delayed pulmonary edema
  - Soot particles often seen

Immune-Mediated Diseases

- Type I hypersensitivity: IgE mediated
  - Asthma or anaphylaxis
- Type III hypersensitivity : IgE mediated
  - Hypersensitivity “pneumonitis”
- Type IV hypersensitivity : cell mediated
  - Granulomatous disease

Anaphylaxis

- Species: cattle, horses, cats
- Type I hypersensitivity
- Etiology
  - Iatrogenic: antibiotic injection, vaccination
  - Ruptured liver abscess, etc
- Pathology
  - Pulmonary edema with eosinophils
  - Airway constriction

Hypersensitivity Pneumonias

- Equine Allergic Pneumonitis/Chronic Obstructive Pulmonary Disease (COPD) – types I and III hypersensitivity
- Type III hypersensitivity to organic antigens e.g. humans, cattle
- Drug hypersensitivity

Parasitic Hypersensitivity

- Parasitic infection in cattle
  - *Dictyocaulus vivaparous*
- Parasitic infection in dogs
  - *Dirofilaria immitis* larvae

Primary Lung Neoplasia

- Rather rare in domestic animals
- Generally in old animals
- Most epithelial
- Generally solitary
- Clinical signs
- Diagnosis

Neoplasia

- Primary neoplasia
  - Epithelial - carcinomas
  - Mesenchymal tumors
  - Lymphomatoid granulomatosis

Table 9-5 Classification of Pulmonary Neoplasms

PRIMARY EPITHELIAL ORIGIN

Benign

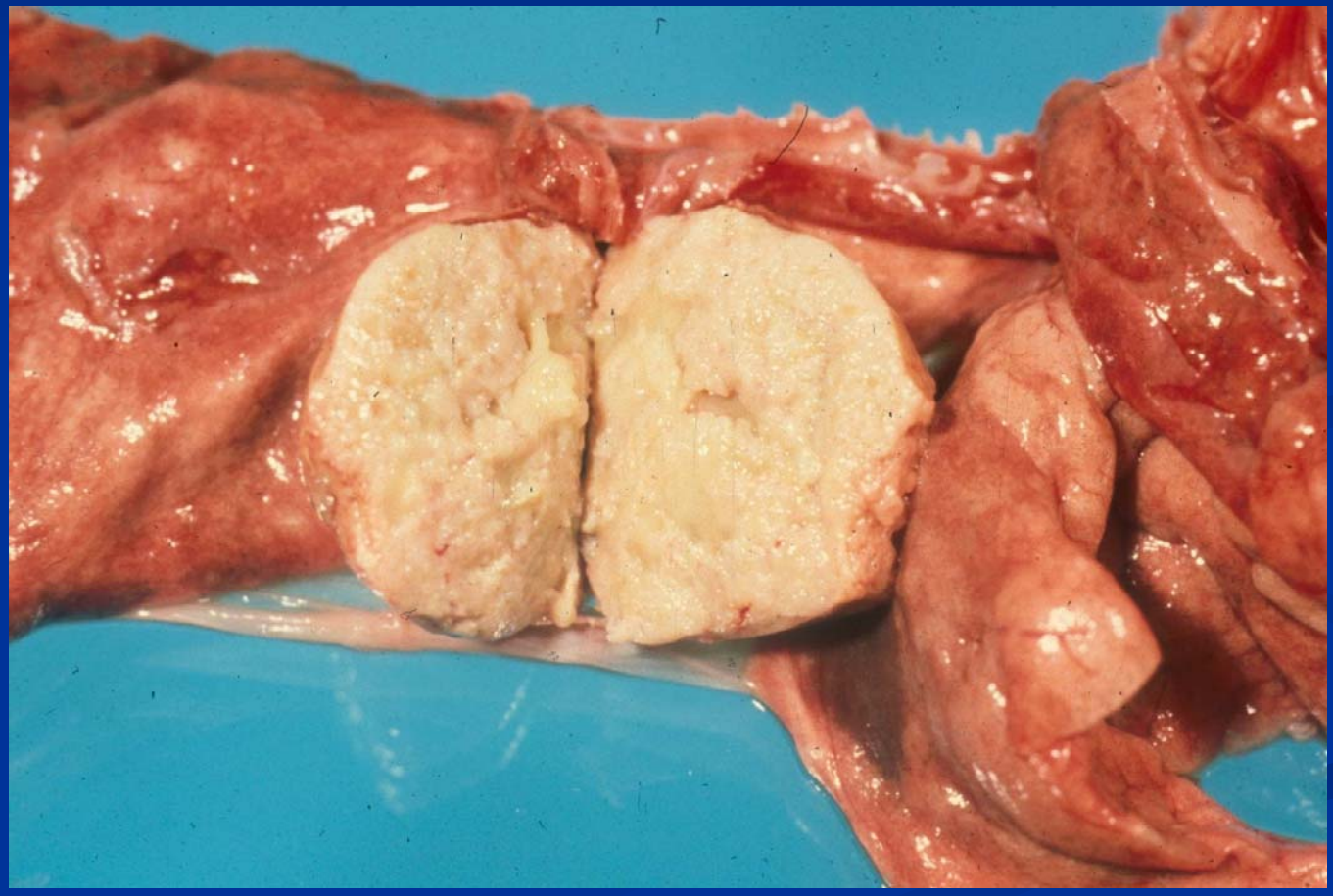
Papillary adenoma
Bronchiolar-alveolar adenoma

Malignant

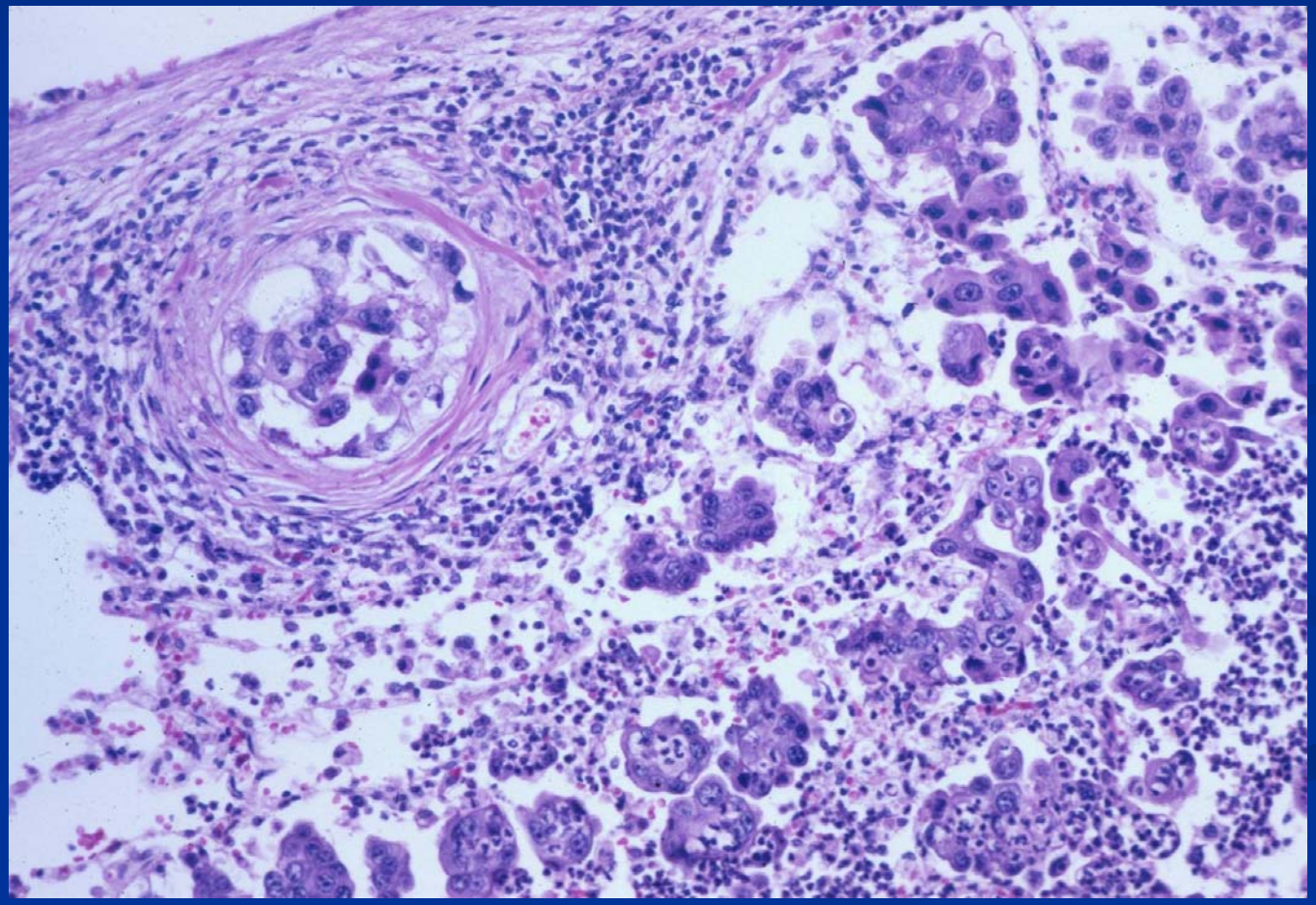
Adenocarcinoma (acinar or papillar)
Squamous cell carcinoma
Adenosquamous carcinoma
Bronchiolar-alveolar carcinoma
Small cell and large cell carcinomas
Anaplastic (undifferentiated) carcinoma
Carcinoid tumor (neuroendocrine)
Ovine (retroviral) pulmonary carcinoma

From Lopez (2006)

Neoplasia - Carcinoma



Neoplasia – Carcinoma - Dog



Neoplasia

- Secondary (metastatic) neoplasia
  - More common
  - Adenocarcinoma (mammary, thyroid)
  - Osteosarcoma /chondrosarcoma
  - Hemangiosarcoma
  - Lymphosarcoma
  - Histiocytic sarcoma

Pathology of Respiratory System

- Respiratory injury and response
- Upper respiratory tract
- Lower respiratory tract (lung)
- **Pleura and thoracic cavity**

Diseases of the Pleura and Thoracic Cavity

- Pleuritis/Pyothorax
- Hydro-, Chylo-, Hemo-thorax
- Pneumothorax
- Mineralization
- Neoplastic - mesothelioma

Uremic Mineralization

Pleuritis/Pyothorax

- Primary
- Secondary
  - Extension of pneumonia
  - Ruptured lung abscess
  - Traumatic penetration
    - Bite wound
    - Awn

Nocardiosis - Cat