GENERAL PATHOLOGY OF THE MAMMALIAN RESPIRATORY SYSTEM

THE UNIVERSITY of ADELAIDE

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The principals of the general pathology of the respiratory system have considerable commonality between humans and domestic animal species

This outline will, however, have a bias towards domestic animals as it is primarily intended for use by postgraduate students using experimental animal models of human diseases

Vulnerability of the respiratory system

The respiratory system is uniquely vulnerable to injury because of exposure by 2 routes:

Airborne (aerogenous): the involuntary nature of ventilation requires large volumes of air to be drawn into the lungs, which contain a variety of potentially injurious materials (airborne microorganisms, particles, and toxic gases)

Vascular (haematogenous): entire cardiac output flows through the extensive and delicate vascular bed of the gas exchange region of the lungs and can contain a wide variety of infectious agents and intrinsic/extrinsic toxins

Vulnerability of the respiratory system

In addition to injurious agents, inflammation and the reparative response to these insults compromises gas exchange

The route of entry determines the distinct pattern of resulting lesions

Respiratory system anatomy

The lungs are organised into lobes, bronchopulmonary segments, and terminal acini

Each lung is supplied by a single principal (primary) bronchus arising at the tracheal bifurcation, which is further subdivided into lobes, the gas exchange region ventilated through a lobar (secondary) bronchus

Lobes are further divided into individual lobules, separated by connective tissue septa, which are continuous with the pleura

Respiratory system anatomy

In domestic animals, the left lung is divided into cranial and caudal lobes, while the right lung, depending on species, is divided into cranial, middle (absent in horses), caudal and accessory lobes

The connective tissue subdividing lobes into lobules is prominent in cattle and pigs and, due to these thick interlobular septa, movement of air between lobules is almost absent in these species

Movement of air between lobules and adjacent alveoli (through the pores of Kohn) constitutes the collateral ventilation

Special features of laboratory rodent lungs

In mouse and rat lungs, there is a single left lobe and 4 right lobes

Cardiac muscle surrounds the major branches of pulmonary veins in most rodents and should not be misdiagnosed as medial smooth muscle hypertrophy

Intraalveolar haemorrhage is a consistent agonal finding in murine lungs, regardless of the mode of euthanasia

Rats have serous glands in the respiratory epithelium, which is unique to this species

Lung anatomy

Bronchopulmonary segment is an area supplied by a tertiary bronchus and is again divided by connective tissue septa, which tend to sequester inflammation

Terminal acinus is composed of one **terminal bronchiole**, which leads to **alveolar ducts** communicating with **alveoli**

Pulmonary vascular supply

Vascular arterial supply to the lung is dual:

Pulmonary circulation receives the entire right ventricular output and is high flow, low pressure and supplies alveolar parenchyma

Bronchial circulation is low flow, high pressure and supplies bronchi/bronchioles

Pulmonary vascular supply

Pulmonary veins drain the entire lung

Lymphatics are present in pleura and around airways and blood vessels, but do not extend into the alveolar septa

Lymphatics become greatly distended with fluid from oedema or pneumonia and sometimes contain metastatic emboli

Lung anatomy

Trachea and bronchi (but not bronchioles) are surrounded by rings of hyaline cartilage to resist physical deformation and maintain airway patency

Alveolar septa are tethered to the bronchiolar wall and, during inspiration, pull on the wall to maximise the luminal diameter

Airway histology

Trachea, bronchi and bronchioles are lined by pseudostratified epithelium

Composed of a mix of ciliated, mucous, club (Clara), serous and chemosensory (brush) cells

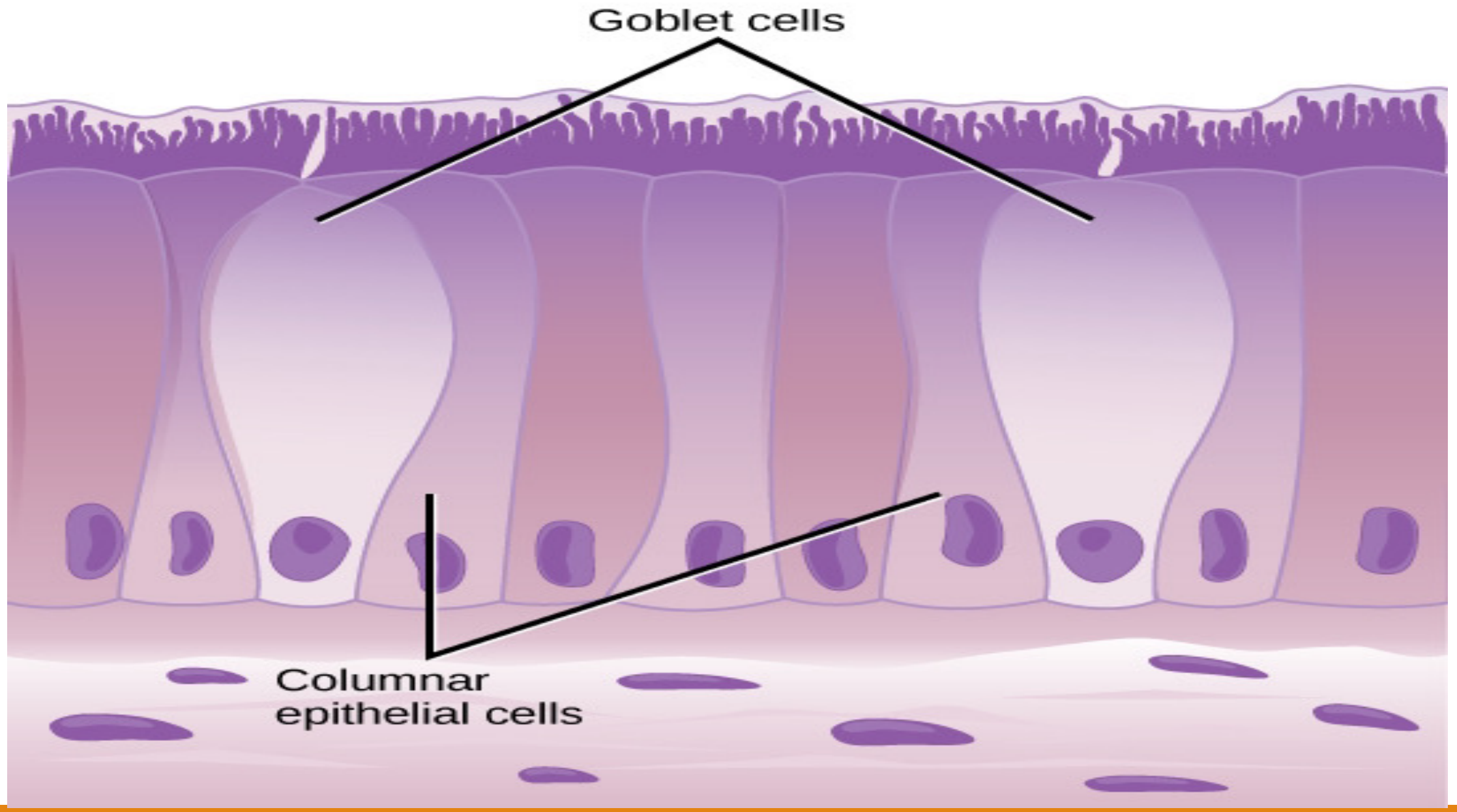
Airway histology

In general, the number of ciliated and mucous cells decreases in the distal airways

Ciliated cells clear airway-lining fluid and have a secretory function

Secretory cells include mucous, serous, and club cells and different microenvironments can induce metaplasia from one cell type to another

Mucous (goblet) cells form the mucous layer of the epithelial lining fluid

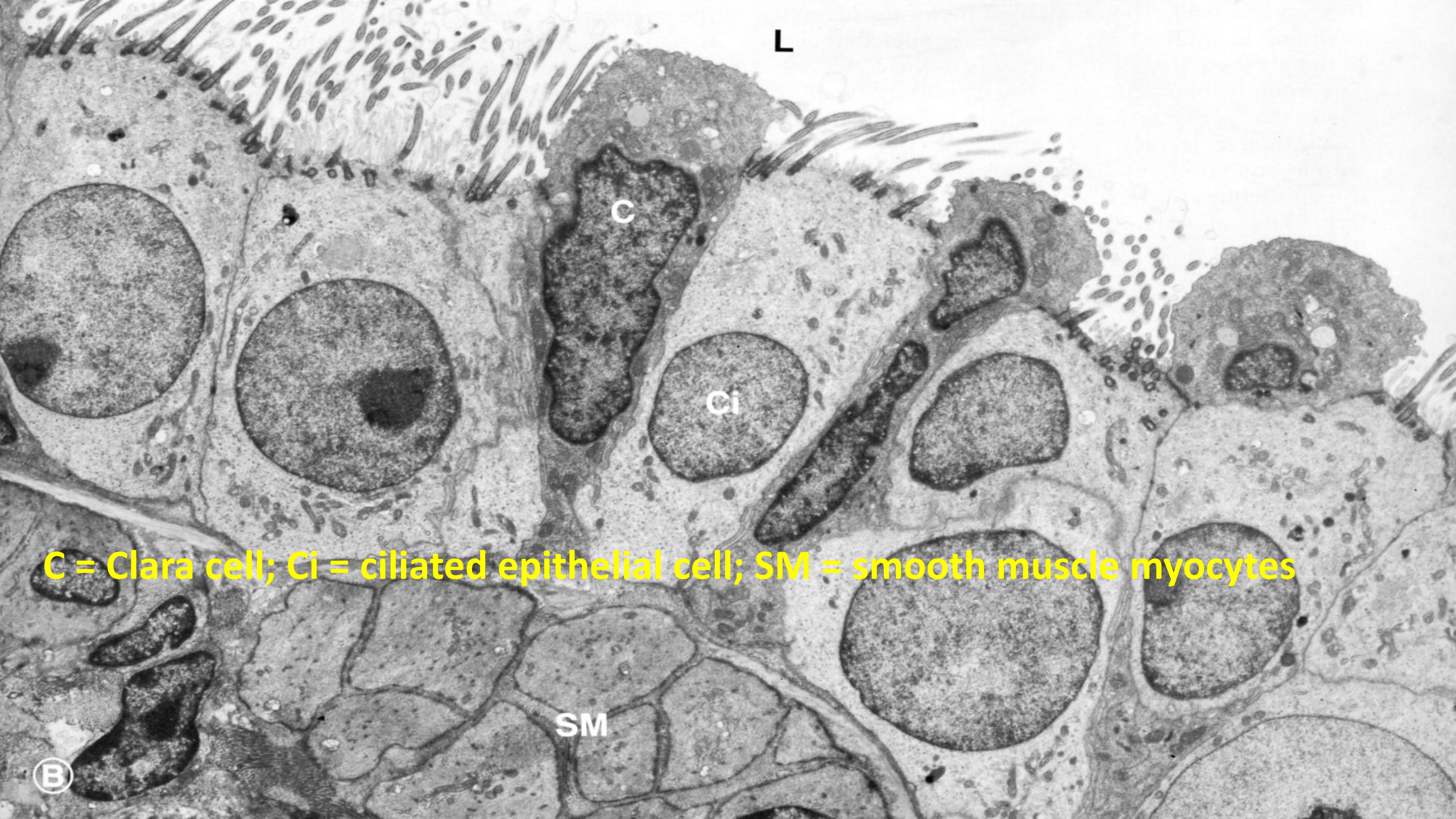

Goblet cells
Columnar
epithelial cells

Airway histology

Club (Clara) cells are progenitor cells for epithelial repair and may differentiate into other secretory or ciliated cells. They are very sensitive to a variety of xenobiotics and metabolism of these toxins can generate injurious intermediate metabolites. Club cell secretory protein can reduce the inflammatory response

Chemosensory (brush) cell is infrequent and believed to detect irritants in inhaled air

Smooth muscle cells hypertrophy in chronic respiratory diseases and produce a wide array of cytokines, chemokines, growth factors, and extracellular matrix metalloproteases, permitting them to modify their surrounding interstitial matrix. Also secrete matrix proteins (fibronectin, elastin, laminins, and collagen) which modulate proliferation, migration and apoptosis of smooth muscle cells



C = Clara cell; Ci = ciliated epithelial cell; SM = smooth muscle myocytes

Airway histology

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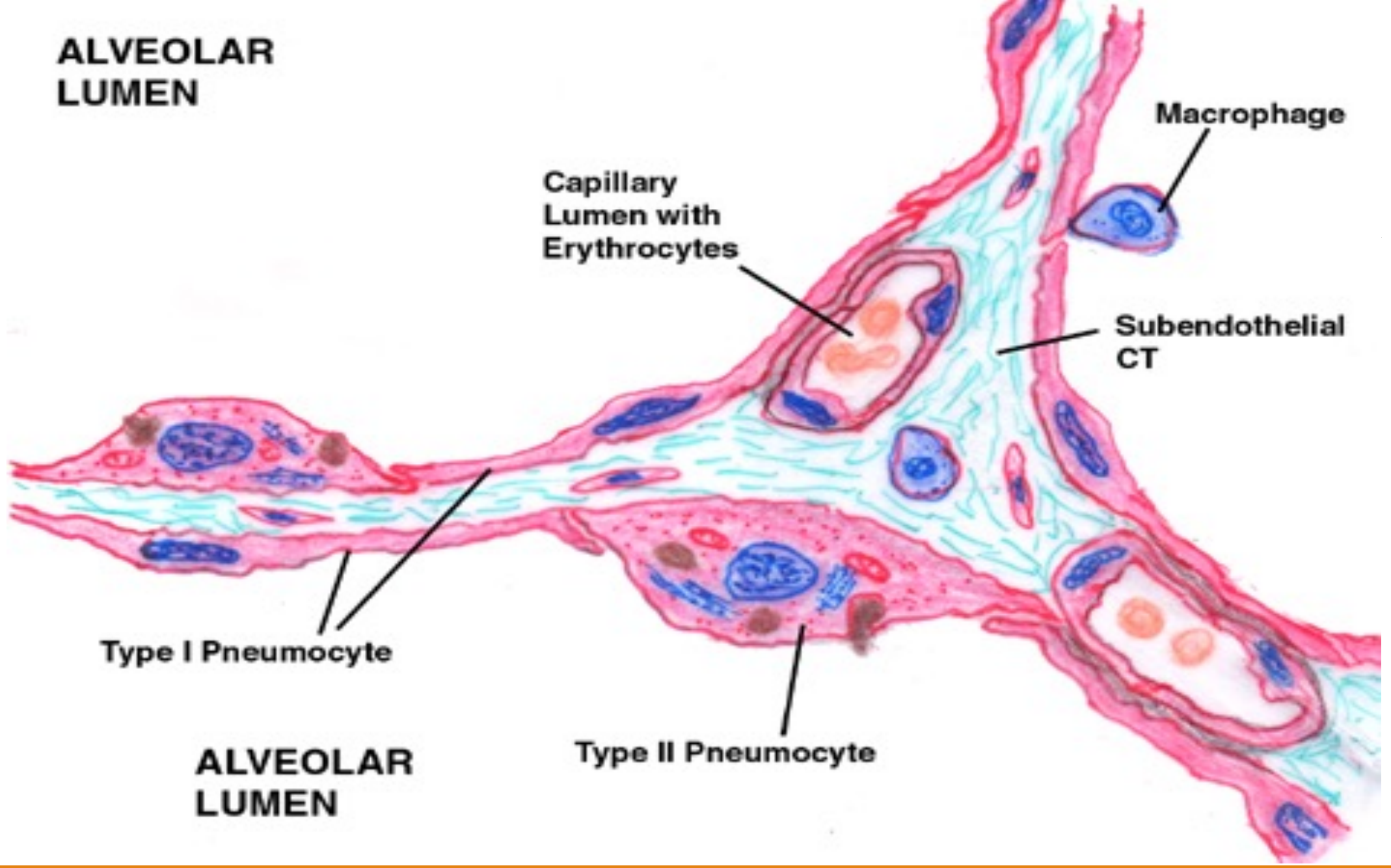
Lung Histology

Alveolar parenchyma is the site of gas exchange and epithelial layer is closely apposed to blood-filled capillaries

There are 5 major types of alveolar cell – type I and II pneumocytes, capillary endothelial cells, interstitial fibroblasts, and alveolar macrophages


ALVEOLAR
LUMEN
Macrophage
Capillary
Lumen with
Erythrocytes
Subendothelial
CT
Type I Pneumocyte
Type II Pneumocyte
ALVEOLAR
LUMEN

Type 1 pneumocytes

Large, flat, membranous epithelial cells that line ~90% of the alveolar surface

Terminally differentiated and non-mitotic cells, which are vulnerable to injury because of their large surface area

Irreversible injury causes sloughing from the basement membrane, which triggers a rapid regenerative response by Type II pneumocytes

Type I cells prevent movement of fluid into the alveolus and clear fluid and proteins from the alveolus during pulmonary oedema

Type II pneumocytes

Main cuboidal cell lining the alveolus, which

(1) synthesises pulmonary surfactant;

(2) serves as progenitor cells for replacement and turnover of alveolar epithelium;

(3) metabolises xenobiotics

Type II cells can rapidly proliferate to repopulate denuded basement membrane following injury to type I pneumocytes

Pulmonary surfactant

Forms a film at the air-liquid interface of terminal bronchioles and alveoli

The secretion is arranged in a functional surface-active form (tubular myelin), which adsorbs to the alveolar air-liquid interface

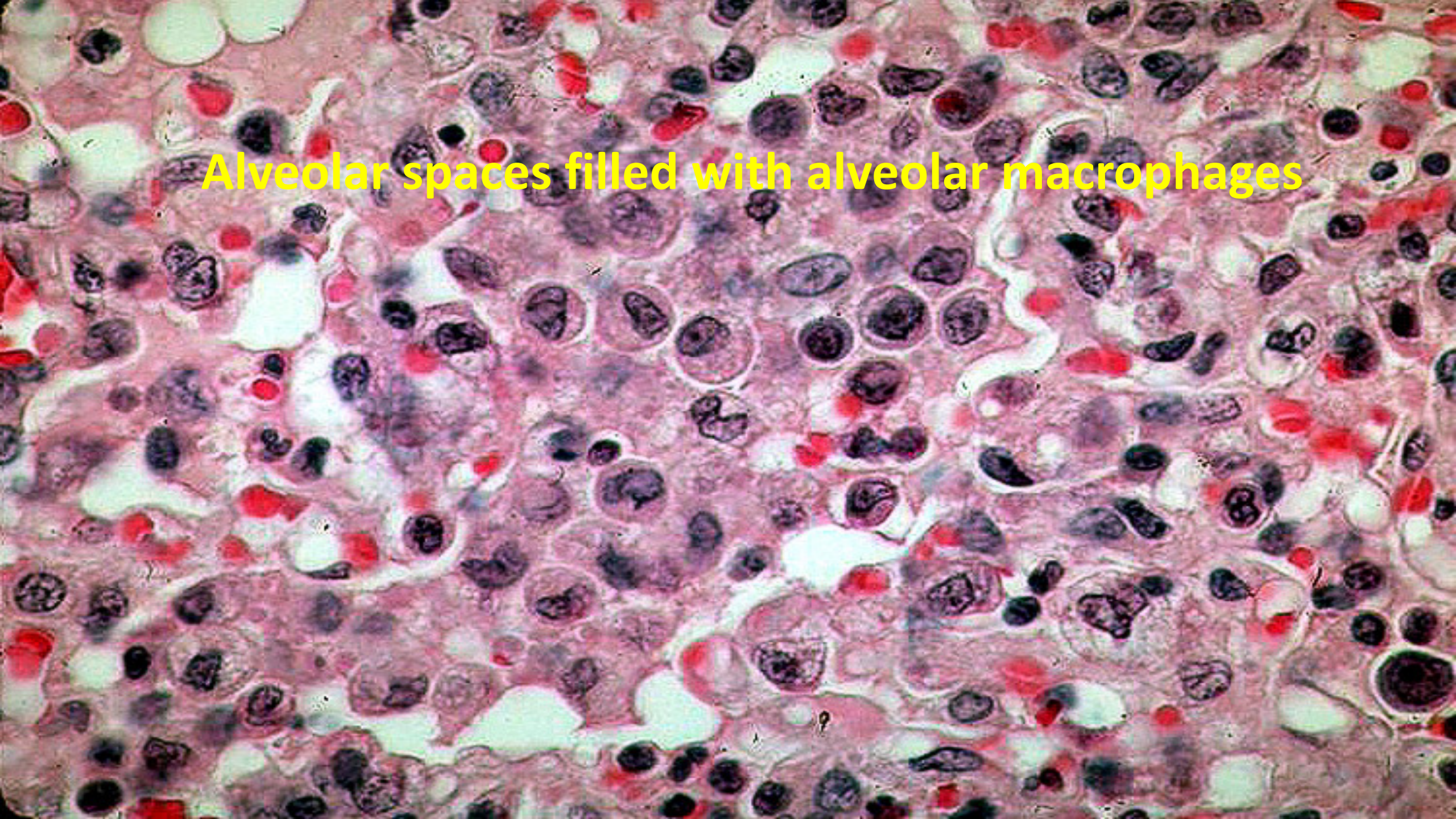
Its main function is to lower surface tension in alveolar space to prevent alveolar collapse during expiration

It is highly dynamic and also involved in immunoregulation and pulmonary defence functions

Fibroblasts and macrophages

Fibroblasts in the alveolar wall are heterogeneous in terms of morphology and functionality

Pulmonary macrophages are comprised of different types: alveolar, interstitial, pulmonary intravascular, dendritic cells, and pleural


Alveolar spaces filled with alveolar macrophages

Other pulmonary macrophages

Dendritic cells are ubiquitous immunoregulatory cells found in all tissues. They are motile cells involved in surveillance for antigens, with numerous, long processes, and function as antigen-presenting cells to T lymphocytes

Pulmonary intravascular macrophages form membrane-adhesive complexes with capillary endothelial cells which keep them localised to the vascular bed. Highly phagocytic and play a vital role in clearance of bacteria and particles from the pulmonary circulation. They release pro-inflammatory mediators and may contribute to lung injury

Pulmonary defences

Gas exchange means lungs are being constantly exposed to the environment and continuously challenged by large quantities of microorganisms and foreign material in inhaled air + opportunistic pathogens from upper respiratory tract

Lungs must maintain a normal balance of resident microbiota and prevent increased numbers in alveoli which induce inflammation and impede gas exchange

Because of the large blood flow through lungs, contamination by bacteria from bacteraemia is a constant threat

Defences against infectious agents

(1) **Mucus** lining the airways that entraps particles and microbes and is propelled by coughing/ciliary beating to the pharynx, where it is swallowed

(2) **Antibody and innate defence proteins** kill microbes directly to prevent colonisation of the mucosal surfaces + opsonise microbes to render them more easily ingested by phagocytes

(3) **Alveolar macrophages** recognise foreign invaders, especially in presence of opsonins, and engulf and kill these microbes without inducing inflammation

Failure of defence mechanisms

If these defence mechanisms cannot prevent infection, inflammation is triggered

Macrophages and an array of epithelial cells produce cytokines and mediators that recruit neutrophils and monocytes-macrophages

However, inflammatory exudates can cause harm by impairing gas exchange, injuring lung tissue, and fibrotic repair can decrease lung compliance and thicken the blood-gas barrier

Pulmonary defences

Localised areas of pneumonia may produce little disease as the lung has a great reserve capacity, but mild, diffuse changes can seriously compromise pulmonary function

Particle deposit in the respiratory tract depends upon size, density and charge

Particles >10µm are removed in nasal cavity; 3-10µm are trapped in tracheal/bronchial mucosa, where they are cleared by the mucociliary apparatus; and <5µm have the potential to reach terminal bronchioles and alveoli, but especially if 1-2µm

Pulmonary defences

In the deeper airways, airflow velocity decreases markedly and particle deposition results from sedimentation, diffusion, and electrostatic charge

Coughing and mucociliary clearance are the main mechanisms for clearing particles entrapped in airways. Airways are covered by a periciliary fluid layer (permitting cilia to beat effectively in a coordinated, unidirectional manner) and superficial mucous layer that contains sticky glycoproteins which trap particles

Mucociliary clearance can be impaired by infection, exposure to cold air/ammonia, squamous metaplasia from chronic infection or toxin exposure, inherited anomalies of ciliary structure or function (e.g. primary ciliary dyskinesia with immotile cilia), or abnormal mucous production (e.g. cystic fibrosis)

Pulmonary defences

Mucus contains antimicrobial factors that cause direct injury to pathogens, block attachment of bacteria to mucosal surfaces, or cause opsonisation of infectious agents

Alveolar macrophages are critical in the defence against deposited particles in alveoli and recycling and removing surfactant. Also provoke inflammation by releasing cytokines that attract leucocytes, but generally sequester and clear antigens and particles from alveoli without inciting an inflammatory response. In contrast to the mucociliary blanket, removal of particles from alveoli is inefficient

Pulmonary immune responses are initiated when inhaled antigens are engulfed by dendritic cells in airway lining and migrate to regional lymph nodes, where antigen is presented to lymphocytes

Pulmonary defences

Bronchial-associated lymphoid tissue (BALT) is not present in germ-free animals and may be a consequence of inflammation and antigenic stimulation

In summary, lung is protected from inhaled bacteria by filtering in nasal cavity, innate and acquired humoral defences, mucociliary clearance in airways, resident alveolar macrophages, and recruitment of neutrophils, macrophages, T-lymphocytes and natural killer cells

Atelectasis

Atelectasis = incomplete expansion of the lungs

Which are dark red and sunken relative to aerated lung

Microscopically, there are congested alveolar walls lying in close apposition, with small, residual lumina

May be congenital, obstructive (complete airway obstruction), or compressive (pleural or intrapulmonary space-occupying lesions)

ATELECTASIS

Alveolar spaces are collapsed and septa closely apposed

Emphysema

Occurs in 2 forms:

Alveolar (vesicular) with enlargement of alveoli due to destruction of alveolar septa

Interstitial with air in connective tissues and lymphatics (in interlobular septa, subpleura and around blood vessels and airways)

Coalescence of vesicles can produce large, air-filled bullae

Circulatory disturbances

Lung is a vascular organ with abundant capillaries organised into numerous alveoli with a large surface area

The entire output of right ventricle is delivered to the lung with each contraction, supplying venous blood for oxygenation

Hyperaemia/congestion

Hyperaemia is an *active process* that is part of acute inflammatory responses and is a feature of acute pulmonary injury

Pulmonary congestion is a *passive process* and may be caused by left heart failure or inflammation

However, pulmonary congestion is a common incidental finding at autopsy

The *colour* of the lung is often deceptive and changes in lung *texture* are a more valuable indicator of underlying disease


Passive pulmonary congestion
stion
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Veterinary Medicine

Pulmonary oedema

One of the most common abnormalities found in many diseases

If severe, it has a dramatic effect on lung function by:

decreasing compliance

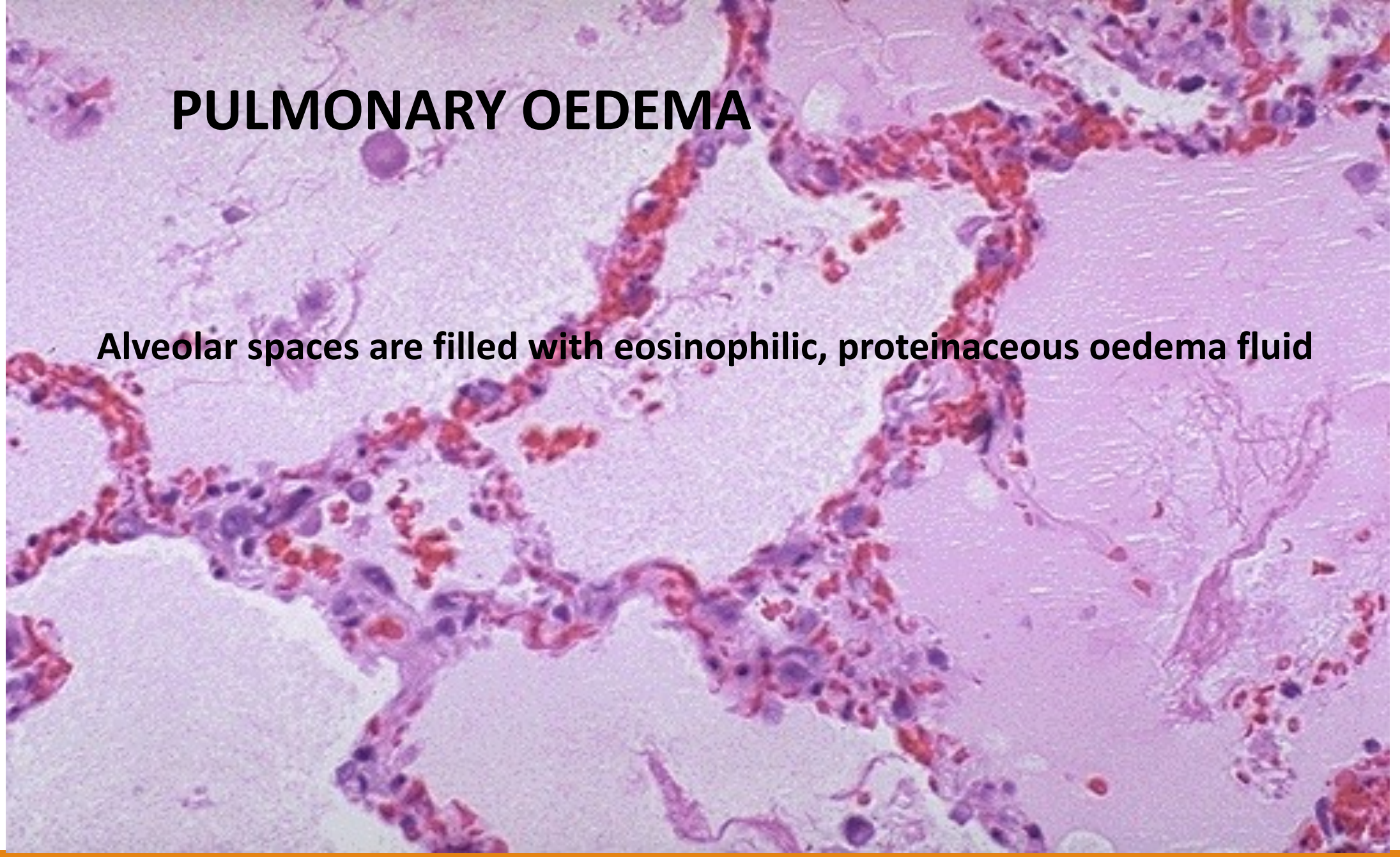
blocking alveolar ventilation

obstructing gas exchange across alveolar septa

decreasing the surface area of the alveolar air-liquid interface

proteins in oedema fluid interfere with surfactant function

PULMONARY OEDEMA



Alveolar spaces are filled with eosinophilic, proteinaceous oedema fluid

Pulmonary oedema

There is a derangement of the balance of hydrostatic and osmotic pressures between intravascular and interstitial compartments

Alveoli are normally kept free of fluid (“dry’) by: (1) tight junctions between type I pneumocytes, which are a barrier to albumin flux across blood-air barrier; (2) active Na pumps on basolateral, and passive Na channels on apical, surfaces of type II pneumocytes, which have a net effect of transporting Na out of airspaces into the interstitium, with a resultant flow of water by osmosis; (3) drainage of fluid from interstitium to lymphatics is facilitated by negative pressure in lymphatic vessels; and (4) fluid resorption by bronchiolar club cells

Causes of pulmonary oedema

Major causes of pulmonary oedema are (1) increased hydrostatic pressure (increased venous pressure from left-sided heart failure (*cardiogenic oedema*) and (2) increased permeability of blood-alveolar barrier (*non-cardiogenic oedema*), which is a rapid onset, high protein oedema

Other causes include diffuse alveolar damage, sepsis or endotoxaemia, anaphylaxis or drug-induced histamine release

Causes of pulmonary oedema

Less commonly, hypoproteinaemia from renal glomerular, liver or intestinal disease; obstruction of lymphatics by neoplasms; increased intracranial pressure from CNS trauma (neurogenic pulmonary oedema), probably related to catecholamine-induced pulmonary hypertension/increased vascular permeability; post-anaesthetic pulmonary oedema; and acute upper airway obstruction from asphyxiation leading to increased intraalveolar pressure

Pulmonary oedema

Gross (macroscopic) findings

Wet, heavy lungs which do not completely collapse when the thorax is opened

Fluid seeps from the cut surface

Chronic oedema causes an increased number of alveolar macrophages and, in left-sided heart failure, may contain phagocytosed erythrocytes or haemosiderin (“heart failure cells”)

Note: pink fluid often fills alveoli in autolysed carcasses or those euthanased with barbiturates

Pulmonary oedema

Histologically, if fluid accumulation exceeds clearance by lymphatics, it will accumulate in alveoli, leading to decreased surfactant function, reduced surface tension, and alveolar collapse and impaired lung function

Oedema fluid can be microscopically colourless and manifest only as expansion and separation of the extracellular matrix, especially surrounding blood vessels.

With increased protein content, oedema appears eosinophilic and homogeneous or finely granular

Pulmonary thromboembolism

Thrombus formation in vessels involves Virchow's triad of underlying mechanisms:

Increased blood coagulability (major cause)

Damage to endothelial cells or the vessel wall

Stasis of blood flow

May be embolism to pulmonary vessels of thrombi, bacteria or foreign material

Pulmonary thromboembolism

Thrombi that develop *in situ* in lungs are usually microscopic, whereas grossly visible thrombi are usually emboli from a distant site

Microvascular thrombi dissolve rapidly after death if the fibrinolytic system has been activated (as in disseminated intravascular coagulation or DIC), the absence of thrombi thus not excluding this condition

Pulmonary thromboembolism

Lungs are strategically situated to catch emboli carried in venous blood (e.g. from valvular endocarditis, jugular thrombosis associated with catheterisation, and deep vein thrombosis)

Signs and sequelae of pulmonary thromboembolism depend on:

(1) extent of vascular obstruction

(2) rapidity of its development

(3) presence of sepsis

Pulmonary thromboembolism

Since lung is supplied by pulmonary and bronchial arteries and has extensive collateral vessels, infarction does not normally follow thromboembolism

More likely to occur at periphery of the lung or if the bronchial or systemic circulation is also impaired (e.g. concurrent heart failure)

However, emboli that obstruct larger branches of pulmonary artery may cause sudden death

Pulmonary embolism

Septic embolism with massive numbers of bacteria cause acute pulmonary oedema or interstitial lung disease. When it is less fulminant, can lead to multifocal infarcts, abscesses or suppurative embolic pneumonia

Fat emboli can occur from bone marrow at fracture sites, severe hepatic lipidosis when hepatocytes rupture, or subcutaneous fat necrosis associated with pancreatitis, diabetes mellitus or vitamin E deficiency

Small numbers of megakaryocytes can be found in pulmonary capillaries and this is usually an incidental finding

Pulmonary haemorrhage

Varies from small petechiae to extensive filling of large areas by blood

Haemorrhages can be distinguished from congestion as former are usually multifocal or patchy splashes of blood, while the latter is diffuse in affected areas

Occur frequently with haemorrhagic diatheses, including thrombocytopaenia, rodenticide toxicity (e.g. warfarin), sepsis, DIC, and severe congestion

Pulmonary haemorrhage

Can also be caused by vasculitis, pulmonary hypertension, infarction, ruptured aneurysms, trauma, haemangiosarcoma, and drug reactions

Abscesses that erode large blood vessels cause massive haemorrhage

Exercise-induced pulmonary haemorrhage is common in strenuously exercising horses and massive such haemorrhage is most common cause of sudden death in racing horses

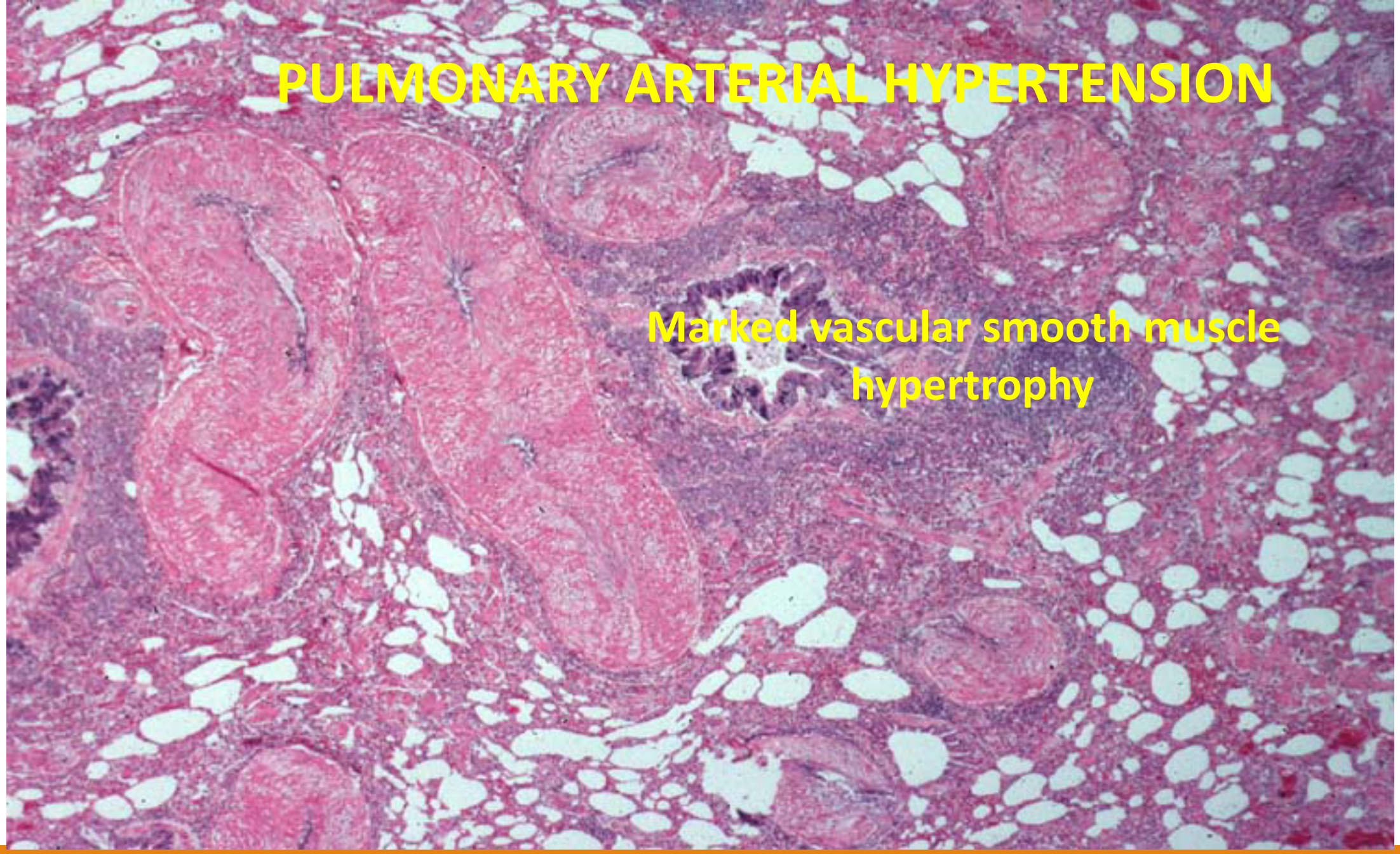
Pulmonary arterial hypertension (PAH)

Excessive vasoconstriction and thrombosis leads to vascular remodelling with dysregulation of vascular tone, abnormal cell growth (thickening of tunica intima by endothelial proliferation and later fibrosis, hypertrophy of tunica media smooth muscle, and adventitial oedema/fibrosis), with apoptosis and inflammation

Pulmonary arterial hypertension

Severe, acute PAH results in endothelial degeneration, vasoconstriction, fibrinoid necrosis of vessel wall, vasculitis. “onion skin”, concentric fibrosis, and proliferation of smooth muscle cells

PULMONARY ARTERIAL HYPERTENSION



Other vascular pathologies

Pulmonary venous hypertension is commonly caused by left-sided heart failure and, when chronic, results in pulmonary oedema, increased number of lung macrophages (sometimes containing haemosiderin – but "heart failure cells" are not pathognomonic of heart failure as also seen with pulmonary haemorrhage), and remodelling of pulmonary veins

Pulmonary vasculitis occurs as septic vasculitis with numerus neutrophils infiltrating vessel walls

Pulmonary mineralisation occurs with uraemia in smooth muscle/CT

Anatomical patterns of lung injury

Damage to the lungs varies according to:

(1) the nature of the causative agent

(2) its distribution (especially the route by which it reaches the lung)

(3) its persistence

Pulmonary diseases can be classified in several ways

Morphological pattern – according to the initial site of involvement and pattern of spread (e.g. bronchopneumonia, interstitial lung disease, airway disease, bronchointerstitial lung disease, and embolic pneumonia)

Histological character - fibrinous, suppurative, granulomatous, necrotising, proliferative or fibrosing

Pneumonia

Pneumonia generally refers to any lesion of the lungs, whether it is exudative or proliferative, alveolar or interstitial

Pneumonitis is sometimes used as a synonym for pneumonia

Distribution of inflammatory lung lesions can be

Cranioventral – most bronchopneumonias (in domestic animals)

Multifocal – embolic pneumonias

Diffuse – interstitial pneumonias

Locally extensive – granulomatous pneumonias

Gross morphology of pneumonia

The lung texture can be firmer or harder (indurated) as in bronchopneumonias, more elastic (rubbery) than normal lungs as in interstitial pneumonias, or nodular, characterising granulomatous pneumonia

The term consolidation is often used to denote a firm lung that is filled with exudate

Airway disease

Lesions that specifically target airways include (1) those causing epithelial necrosis; (2) those that induce airway inflammation; and (3) a combination of these two processes

Diseases may affect bronchi, bronchioles, or both

When both airways and alveolar epithelial cells are damaged = bronchointerstitial pneumonia

Clinical signs

Major consequences of these diseases are coughing/dyspnoea, airway obstruction (contraction of smooth muscle, leucocytes/mucous in airway lumen, and thickening of airway wall by oedema/leucocytes), and impairment of lung defences

Pulmonary compliance (measure of lung's ability to stretch and expand) decreases due to increased pressure required to ventilate alveoli

Bronchitis

Bronchitis is caused by viral or bacterial infection, allergic disease, or exposure to irritant and toxins

Bronchial exudates may be catarrhal (usually relatively mild and caused by irritation with secretion of mucous by goblet cells and bronchial glands), mucopurulent, fibrinous (loosely adherent fibrinous exudate to mucosa and, when there is epithelial necrosis = fibrinonecrotic), fibrinopurulent, or purulent (exudate is yellow or white and viscid)

Bronchitis

Bronchial necrosis can be resolved by epithelial regeneration if the offending stimulus is removed or neutralised. Severe/prolonged epithelial injury causes fibrosis and mononuclear cell (lymphocytes, macrophages, plasma cells) infiltration + epithelial hyperplasia, hyperplasia of mucous-producing cells, and/or squamous metaplasia

With chronic bronchial obstruction/infection, may be permanent dilatation of bronchi (bronchiectasis) due to bronchial wall destruction and luminal obstruction by exudate

Chronic bronchitis

Grossly, there is excessive mucous or mucopurulent exudate

Microscopically, hyperplasia/hypertrophy of bronchial glands, hyperplasia of goblet cells, and variable hyperplasia, ulceration, or squamous metaplasia of the surface epithelium

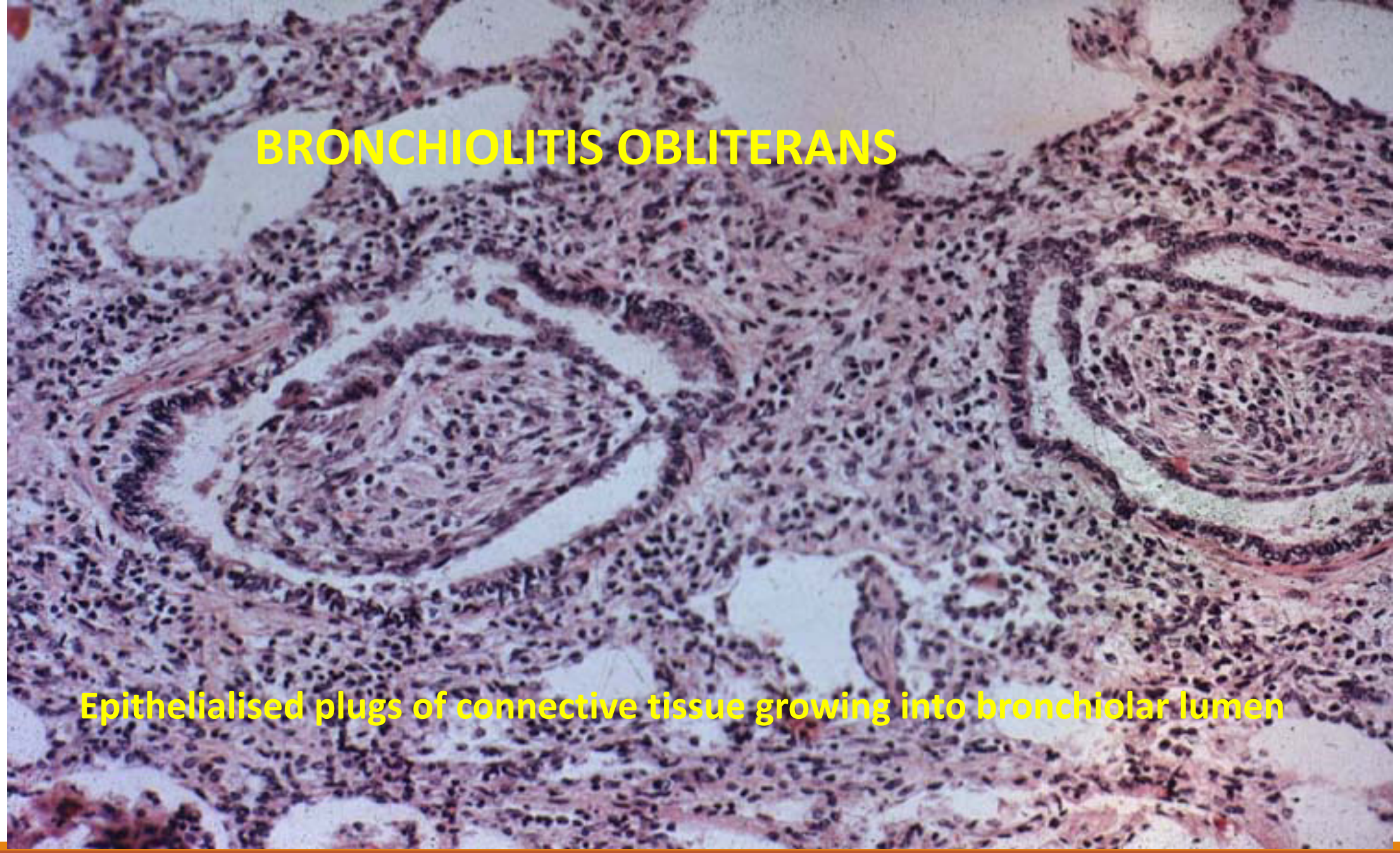
Intraluminal mucous is admixed with neutrophils

Primary ciliary dyskinesia – inherited immotile cilia syndrome, predisposing to infection

Bronchiolitis

Bronchiolar necrosis and inflammation – results in airway obstruction more readily due to lack of cartilage rings and small luminal size, permitting collapse and exudate occlusion. If airway obstruction is complete, leads to atelectasis; if partial, air trapping and over-distension of alveoli occurs

Bronchiolitis obliterans is a sequel to bronchiolar damage and denotes the presence of fibrous polyps occluding the lumen - represents wound healing gone awry with unresolved exudates organised by fibrovascular granulation tissue and reepithelialisation


BRONCHIOLITIS OBLITERANS
Epithelialised plugs of connective tissue growing into bronchiolar lumen

Bronchopneumonia

Most common form of pneumonia in domestic animals originating at the bronchiolar-alveolar junction

Caused by an airborne route of entry of mainly bacteria and mycoplasmas

Almost always restricted to cranioventral lobes (anterosuperior is human equivalent) in domestic animals due to gravitational influences and increased deposition of particles and pooling secretions, with neutrophils and sometimes fibrin and macrophages filling bronchiolar/alveolar airspaces

Affected lungs sink to bottom of container when placed in fixative

Bronchopneumonia

Terminal bronchioles are especially vulnerable to bacterial infection

Have limited protection from mucociliary clearance operative in larger airways and alveolar macrophages present in more distal airways + debris from alveoli is cleared across bronchiolar lumina so bronchiolar inflammation often obstructs this clearance of bacteria and exudates from alveoli

Bronchopneumonia is usually caused by opportunistic bacteria and requires increased exposure of the lung to bacteria and impaired defences (by stress, viral/mycoplasmal infection, exposure to cold and toxic gases)

Bronchopneumonia

Grossly, there is consolidation = increase in texture or induration

Lesions are dark red-purple, maroon, or pink-grey in colour, depending on the age and nature of the process, and oedematous – catarrhal/purulent material can be expressed from small airways

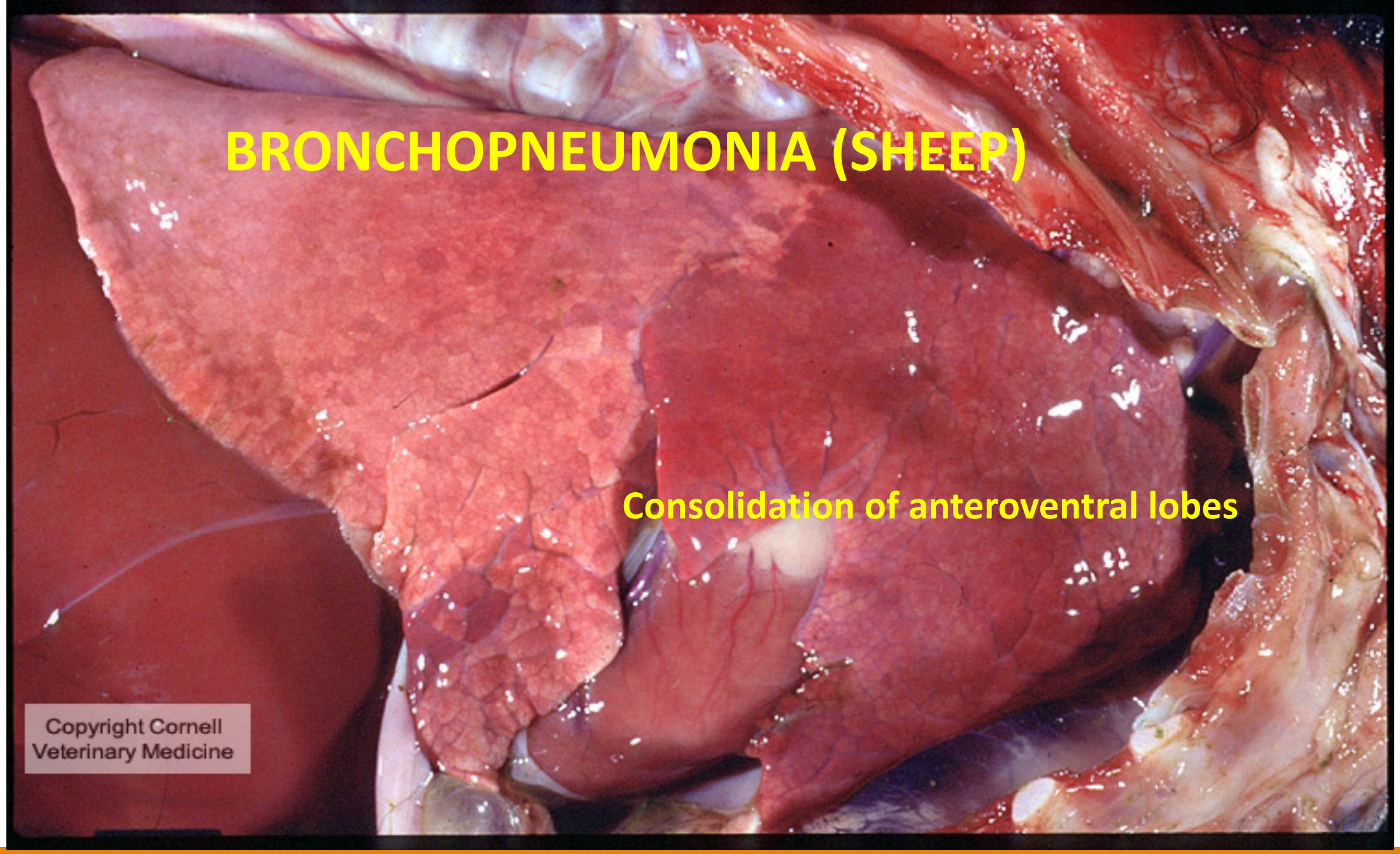
Bronchopneumonia

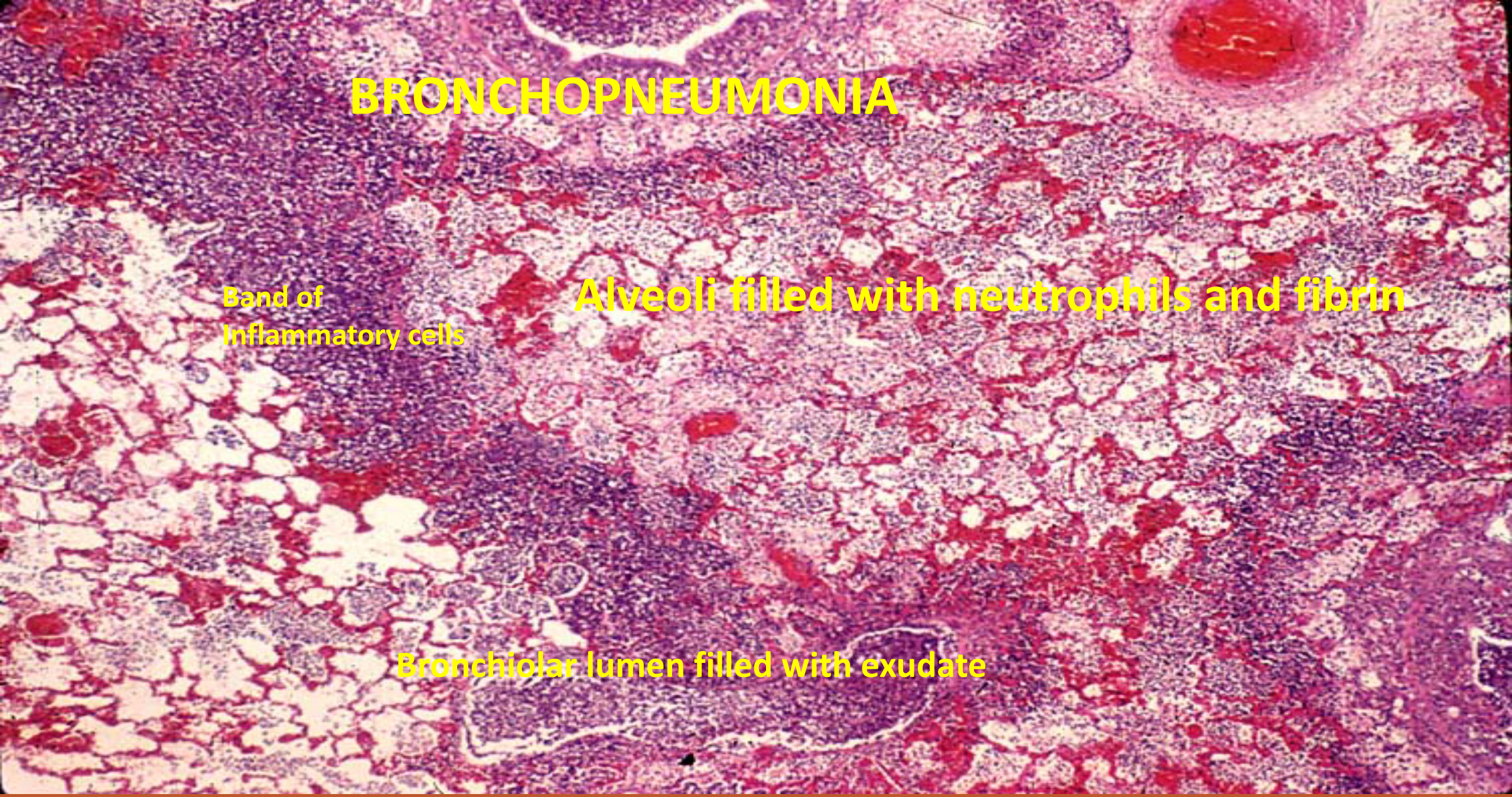
Lesions of bronchopneumonia have a lobular or lobar distribution

Bronchiolar/alveolar lumina are filled by neutrophils and cellular debris, mucous, fibrin, and macrophages and the walls are infiltrated by neutrophils

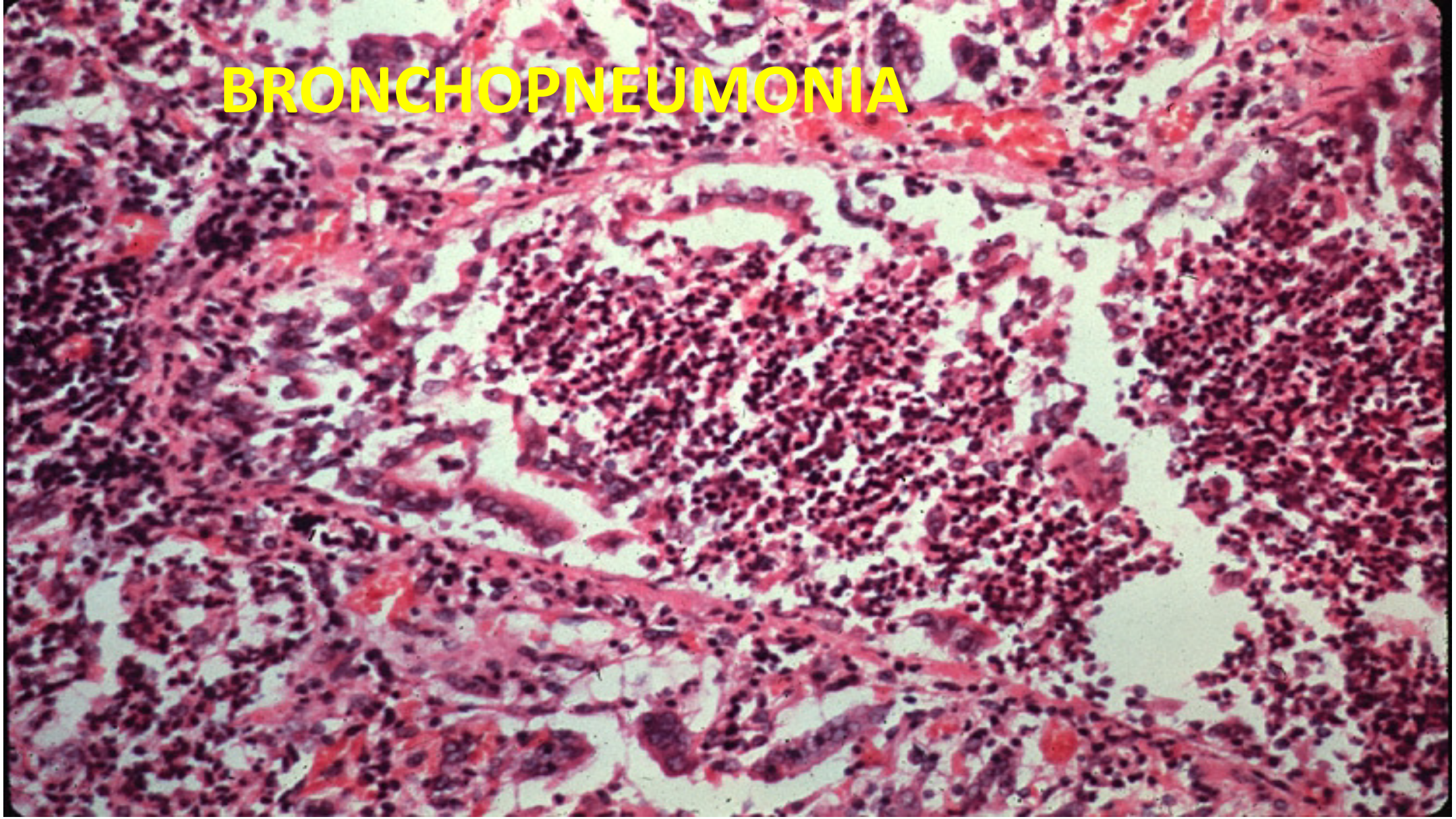

BRONCHOPNEUMONIA (SHEEP)
Lobar consolidation

BRONCHOPNEUMONIA (SHEEP)




BRONCHOPNEUMONIA
Band of
Inflammatory cells
Alveoli filled with neutrophils and fibrin
Bronchiolar lumen filled with exudate

BRONCHOPNEUMONIA



Accumulation of bronchiolar luminal exudate containing abundant neutrophils with sloughing of damaged lining epithelium

Bronchopneumonia

Resolution is possible if the infectious agent is removed by immune response/antimicrobial therapy. Neutrophils undergo apoptosis and fibrin is removed by plasmin and/or phagocytosed by macrophages

Death occurs only if ~20-40% of lung is affected by acute, fulminant lobar bronchopneumonia, with mortality usually due to sepsis rather than respiratory failure

Bacteraemia is frequent with severe, peracute bronchopneumonia

Chronic bronchopneumonia

Up to 80% of the lung can be involved in chronic bronchopneumonia, highlighting the great functional reserve of lung that must be overcome before bronchopneumonia causes death by filling alveoli with exudate

In infection remains active, chronic bronchopneumonia develops, leading to pulmonary fibrosis, bronchiectasis, abscess formation, sequestration (when necrotic lung tissue with aggregated purulent exudate is separated from contiguous viable tissue by a fibrous capsule) and pleural adhesions

Sequestra are permanent and non-functional, acting as a nidus for persistent bacterial infection

Aspiration pneumonia

Caused by aspiration of foreign material and the response depends on the nature of this material, bacteria carried with it, and lung distribution

Aspiration of vomitus can be rapidly fatal due to bronchospasm or acute pulmonary oedema (before there is time for inflammation to develop)

Interstitial pneumonia

An inflammatory process occurring primarily in any of the 3 layers of alveolar walls – capillary endothelium, alveolar epithelium and basement membrane, and contiguous bronchiolar interstitium, representing the interstitium of the lung

Contrasts with bronchitis/bronchiolitis (involving airways) and bronchopneumonia (involving airspaces of alveoli and distal airways)

Interstitial pneumonia

Most common form of interstitial lung disease is diffuse alveolar damage (DAD) with diffuse damage to type I pneumocytes or endothelial cells of alveolar septa, leading to oedema, hyaline membrane formation, proliferation of type II pneumocytes, and interstitial fibrosis

Gross DAD lesions are widely distributed throughout the lungs, often with greater involvement of caudodorsal regions (versus cranioventral distribution of bronchopneumonia)

3 histological phases of interstitial pneumonia

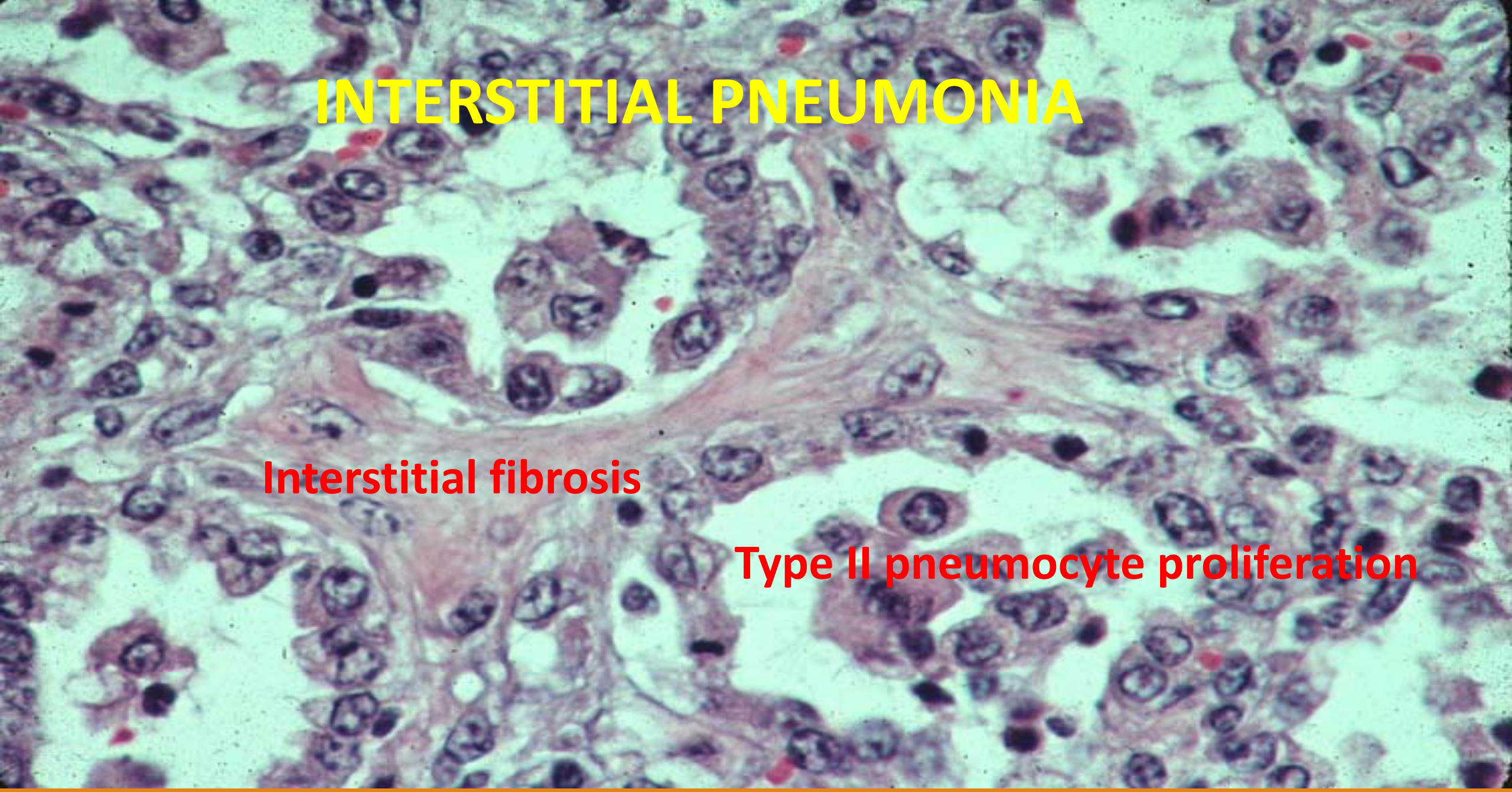
1. **exudative phase – alveolar septa are congested and alveoli contain protein-rich oedema fluid and fibrin strands with a variable number of neutrophils and macrophages. Characteristic finding is presence of hyaline membranes, which are linear masses of eosinophilic material in alveoli/alveolar ducts comprised of aggregates of fibrin, other serum proteins, and cellular debris**

2. **subacute proliferative phase – type II pneumocyte repair of alveolar epithelium by spreading along the alveolar surface, proliferating to replace damaged epithelium, secreting new basement membrane, and differentiating into type I pneumocytes**

3 histological phases of interstitial pneumonia

This is a dysfunctional stage of repair as these type II cuboidal cells block effective gas exchange. Surplus cells undergo apoptosis but, if the injurious stimulus persists, may remain for long periods of time and, when proliferation is particularly exuberant, can be mistaken for neoplasia

3. chronic fibrosing phase – either in alveolar septum or as part of organisation of alveolar exudates by fibrovascular granulation tissue (ingrowth of fibroblasts and neovascularisation by new capillaries). Normally, type II pneumocytes limit fibrosis, but when injured can stimulate fibroplasia. May not be permanent and fibrosis can be removed by matrix metalloproteinases. However, when the process is chronic, marked interstitial fibrosis confers a guarded prognosis


INTERSTITIAL PNEUMONIA
Interstitial fibrosis
Type II pneumocyte proliferation

INTERSTITIAL PNEUMONIA

Causes of diffuse alveolar damage

Pulmonary infections (viruses), thermal injury, acid injury from aspiration of sterile vomitus in monogastric animals, toxic gases (nitrous and sulphuric oxides, chlorine, 100% oxygen, ammonia, ozone), ingested toxins (paraquat, kerosine), septicaemia and endotoxaemia, massive trauma, strangulation, near drowning, ischaemic lung injury, chronic left-sided heart failure, uraemia, irradiation, surfactant dysfunction, adverse drug reactions, acute hypersensitivity pneumonitis, and ventilator-induced lung injury with over-distension of alveoli

Bronchointerstitial pneumonia

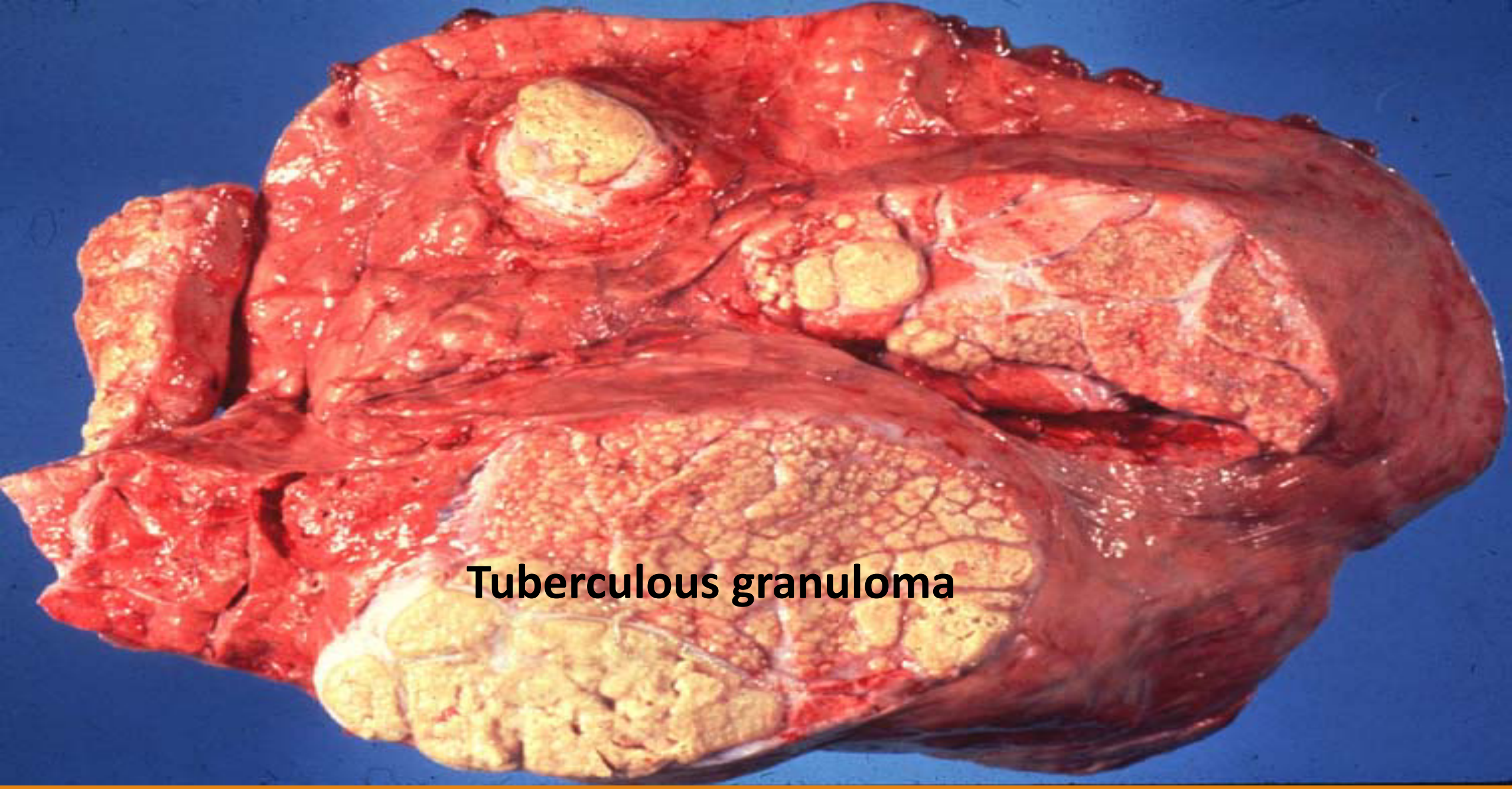
Denotes the presence of both bronchiolar necrosis and diffuse alveolar damage and is a manifestation of injury to both bronchiolar and alveolar epithelium

Other pneumonias

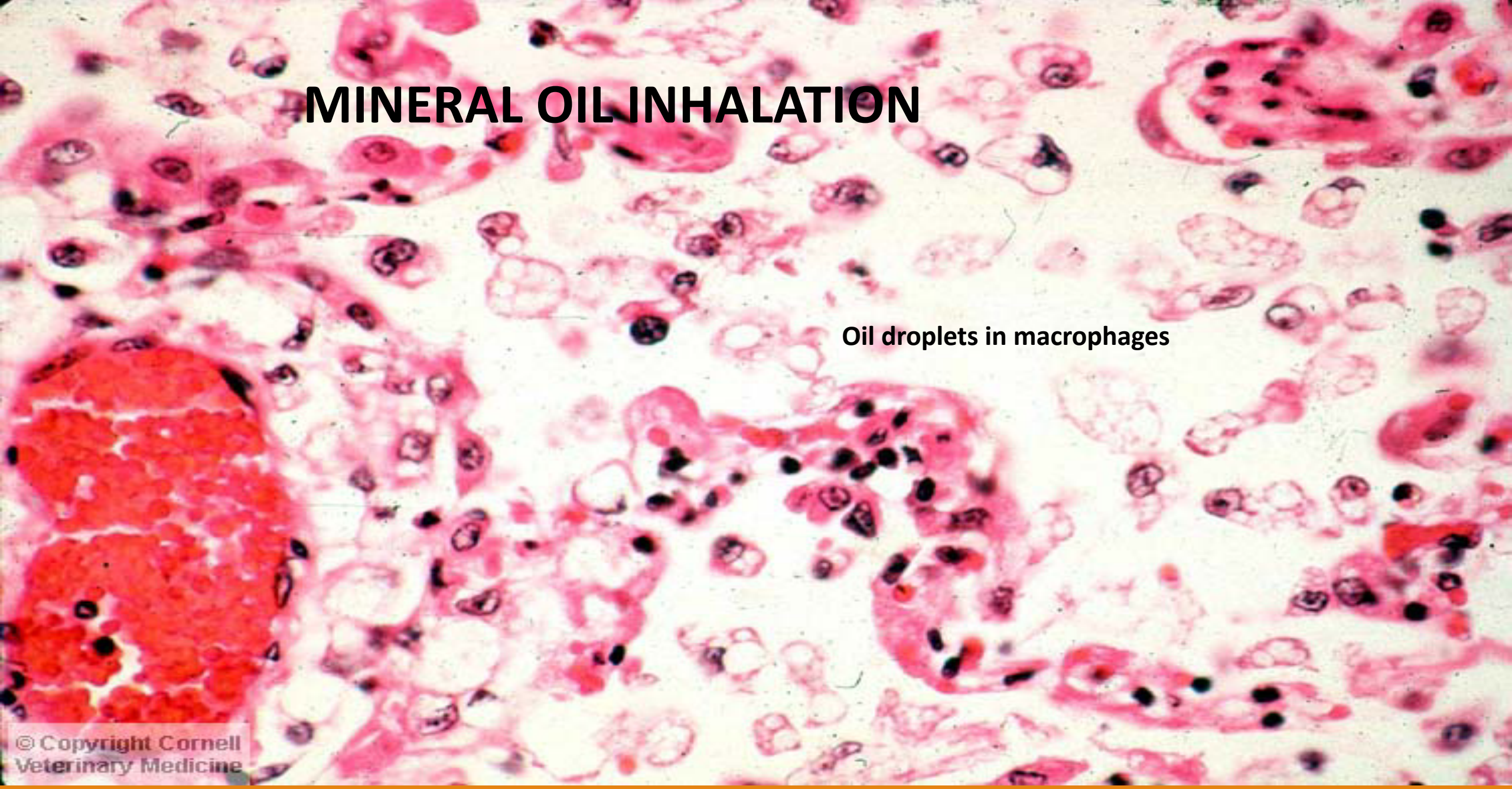
Granulomatous pneumonia (e.g. mycobacterial and fungal infections)

Neonatal hyaline membrane disease due to failure of immature type II pneumocytes to secrete surfactant

Lipid pneumonia – a form of aspiration pneumonia in which oil droplets (those of animal origin being particularly irritant) are aspirated into lungs


Tuberculous granuloma

MINERAL OIL INHALATION



Oil droplets in macrophages

Alveolar filling disorders

Characterised by accumulation of abnormal material within alveoli because clearance is impeded. Histologically, alveoli are filled with foamy macrophages

These disorders include alveolar proteinosis and phospholipidosis (with alveoli filled by acellular, granular material consisting of proteins/phospholipids), pulmonary hyalinosis (aggregates of macrophages and mutinucleated giant cells containing hyaline or laminated material), and pulmonary alveolar microlithiasis (with concentrically laminated, PAS-positive concretions)

Pneumoconioses – lung disease ensuing from inhalation and retention of inorganic dusts (e.g. asbestosis, anthracosis, silicosis)

Toxic lung disease

Several mechanisms can be involved:

(1) inhalation of gases or fumes directly toxic to epithelium or endothelium

(2) ingestion of toxins metabolised to reactive intermediates mainly by club cells or type II pneumocytes

(3) hypersensitivity reactions

(4) effects of inhaled, persistent material (e.g. asbestos, fibreglass)

(5) xenobiotic-induced carcinogenesis

Embolic pneumonia and lung abscesses

Embolic pneumonia results from haematogenous distribution of infections and/or inflammatory processes within the lung – multifocal distribution

Lung abscesses may reflect an embolic process, but can arise from chronic bronchopneumonia

Pulmonary neoplasia

Clinically, signs of neoplasia vary with the degree of invasiveness, amount of parenchyma involved, and location of metastases

Respiratory failure is rare, but may ensue if tumours occupy a large proportion of the lung parenchyma

Clinical signs of neoplasia

The effects of specific anatomical structures being compromised explains the clinical signs:

Coughing caused by compression of a bronchus

Pleural effusion and dyspnoea caused by invasion of pleural lymphatics and regional lymph nodes

Haemoptysis from blood vessel erosion

Cytokine production can lead to malaise, anorexia, and cachexia

Pulmonary neoplasia

It may sometimes be grossly difficult to differentiate primary lung cancer from pulmonary metastases resulting from malignant tumours in other tissues

Features supporting the diagnosis of primary lung neoplasms include absence of a primary tumour in a distant organ and the presence of a single, large lung mass, with or without smaller masses

Because pulmonary carcinomas often form intrapulmonary metastases, the presence of tumour emboli within vessels is not helpful in distinguishing primary from metastatic tumours

Pulmonary neoplasia

Most primary tumours are malignant and appear as solitary masses of variable size that, with time, can metastasise to other areas of lung and distant organs

Secondary neoplasms in lung are all malignant by definition because they result from metastases to lungs from malignant neoplasms elsewhere

Metastatic pulmonary neoplasms

Metastatic tumours commonly occur in lungs because of the organ's rich capillary and lymphatic network. Since pulmonary capillaries are the first filter net for tumour emboli released into the vena cava or pulmonary arteries, secondary neoplasms are relatively common in comparison to primary tumours

Metastatic lung tumours are usually multiple, scattered throughout all pulmonary lobes, of variable size and, according to growth pattern (may form acini, solid sheets, lepidic growth along pre-existing alveolar septa, and/or clusters in blood vessels), can be nodular, diffuse or radiating

Pleura

A continuous layer of mesothelial cells, subdivided into a parietal pleura (covering the thoracic wall, diaphragm, and mediastinum) and a visceral pleura (covering the lungs)

Flattened mesothelial cells have surface microvilli and tight junctions between cells and play a role in maintaining a proper thoracic fluid balance. Pleural fluid is normally present in very small amounts (1-2 ml) and acts as a lubricant during respiration

Mesothelial cells sample materials (including bacteria) in thoracic cavity using pinocytosis and phagocytosis and participate in inflammation by producing cytokines. Capable of synthesising large amounts of collagen and other extracellular matrix proteins

Pleura

In response to injury, mesothelial cells become cuboidal and the pleura has limited local defences

Pneumothorax – presence of air or gas in pleural cavity, resulting in atelectasis if severe because negative intrapleural pressure cannot be maintained – can be spontaneous or traumatic

Non-inflammatory pleural effusions

Hydrothorax – accumulation in pleural space of transudate, which is clear, watery and colourless or pale yellow, with low protein and cell content

Chylothorax – accumulation in pleural space of lymph, which appears milky and has high triglyceride and lymphocyte content (usually idiopathic – causes atelectasis and stimulated pleural effusions

Haemothorax – presence of blood in pleural cavity, usually due to traumtic rupture of blood vessels, but also with coagulopathies, rupture of vascular tumours, and erosion of blood vessels by inflammation or neoplasms

Pleura

Pleuritis (pleurisy) – pleural defences against microorganisms are much weaker than those of the lung and even a few bacteria reaching the pleural surface can have serious consequences

When suppurative exudates fill pleural cavity = **pyothorax** or **empyema**

Neoplasia arising from mesothelium = **mesothelioma**