PULMONARY DISEASES OF VASCULAR ORIGIN

Pulmonary Edema

- ***Definition:***
- ***Pulmonary edema*** *is fluid accumulation in the tissue and air spaces of the lungs.*
- It leads to impaired gas exchange and may cause respiratory failure.
- It is due to either failure of the left ventricle to remove blood adequately from the pulmonary circulation *(cardiogenic pulmonary edema),* or injury to lung parenchyma or lung vasculature *(non-cardiogenic pulmonary edema).*
- It is a cardinal feature of congestive heart failure.

- **Signs and symptoms**
- The most common symptom of pulmonary edema is dyspnea, but other symptoms such as coughing up blood (pink, frothy sputum), excessive sweating, anxiety, and pale skin may be present.
- Shortness of breath manifest as orthopnea (inability to lie down flat due to breathlessness) and/or paroxysmal nocturnal dyspnea (episodes of severe sudden breathlessness at night).
- *These are common presenting symptoms of chronic pulmonary edema due to left ventricular failure.*

- The development of pulmonary edema may be associated with symptoms and signs of ***"fluid overload"***; peripheral edema of the ***"pitting"*** variety, raised jugular venous pressure and hepatomegaly, where the liver is enlarged and may be tender or even pulsatile.
- Other signs include *end-inspiratory crackles* (sounds heard at the end of a deep breath) on auscultation and the presence of a third heart sound.

Types of Pulmonary Edema

- *Classically it is cardiogenic (due to left ventricular causes),* but fluid may also accumulate due to *damage to the lung.*
- This damage may be due to ***direct injury or injury mediated by high pressures within the pulmonary circulation.***
- Pulmonary edema may form when mean pulmonary pressure rises from the normal of 15 mmHg to above 25 mmHg.

A. **Cardiogenic pulmonary edema:**

1. This may be due to left ventricular failure, resulting in elevation in pulmonary wedge pressure and pulmonary edema, arrhythmias, or fluid overload, e.g., from kidney failure or intravenous therapy.
2. Hypertensive crisis can cause pulmonary edema as the elevation in blood pressure and increased after load on the left ventricle hinders forward flow and causes the elevation in wedge pressure and subsequent pulmonary edema.

B. **Non-cardiogenic pulmonary edema:**

1. Negative pressure pulmonary edema in which a significant negative pressure in the chest (such as from inhalation against an upper airway obstruction) ruptures capillaries and floods the alveoli.
2. Neurogenic causes (seizures, head trauma, strangulation, electrocution).
3. Acute respiratory distress syndrome.

C. **Other causes of pulmonary edema:**

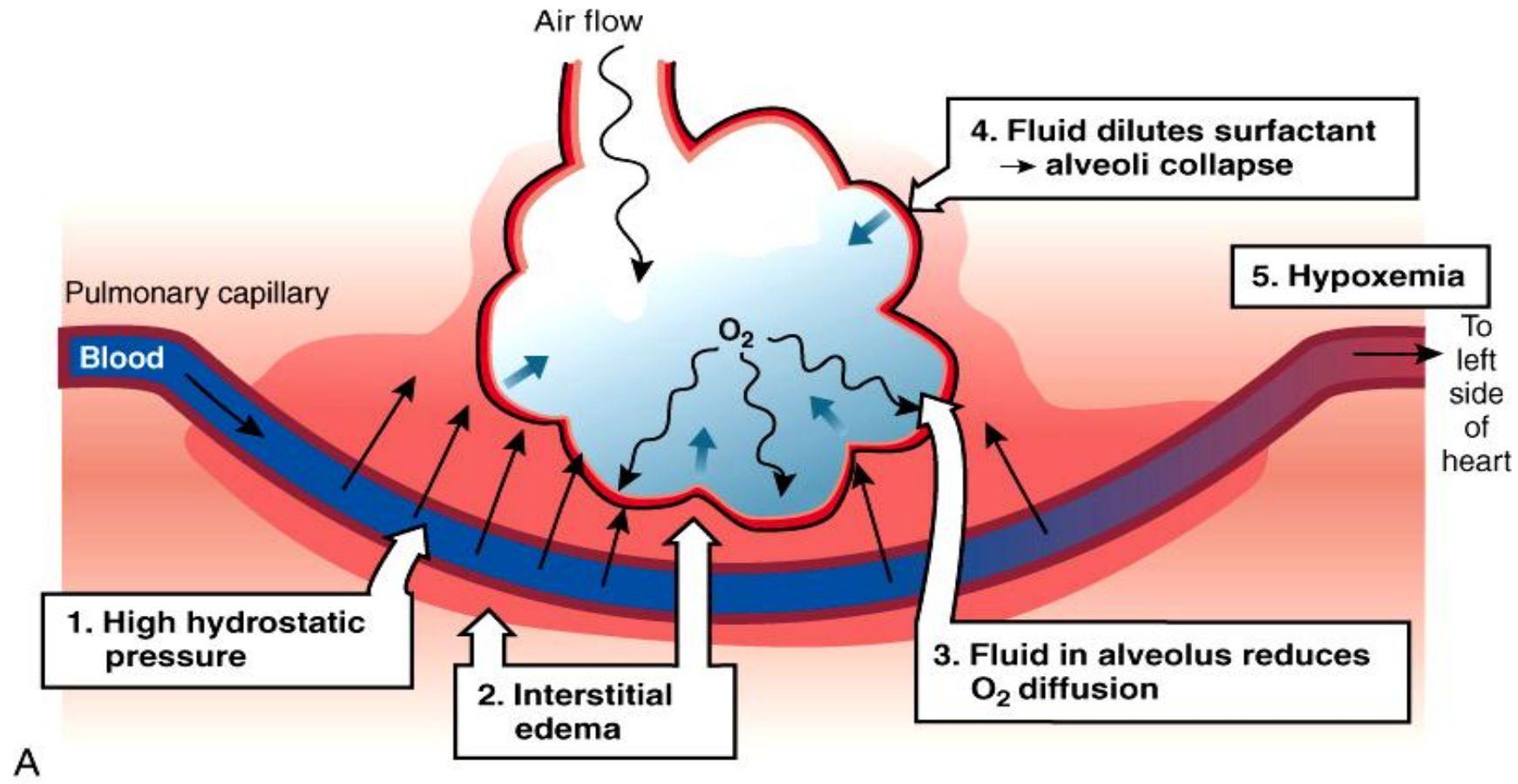
1. Injury to the lung vasculature and/or lung parenchyma.
2. Acute respiratory distress syndrome (ARDS).
3. Inhalation of hot or toxic gases.
4. Pulmonary contusion, i.e., vehicle accidents.
5. Aspiration, e.g., gastric fluid.
6. Re-expansion, i.e. post large volume thoracocentesis, resolution of pneumothorax, post-decortication, removal of endobronchial obstruction.
7. Re-perfusion injury, i.e. postpulmonary thromboendartectomy or lung transplantation.

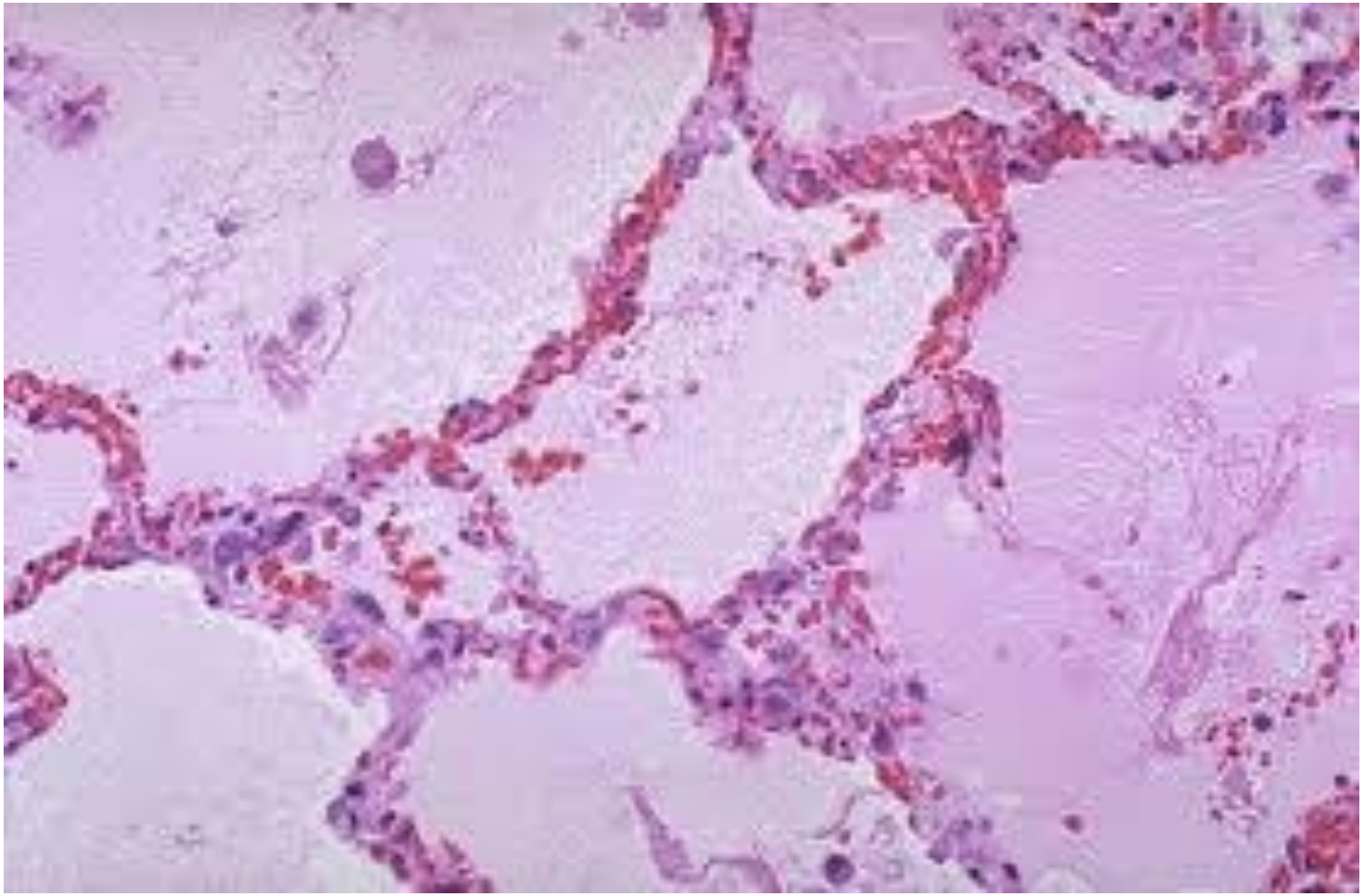
8. Swimming induced pulmonary edema, known as immersion pulmonary edema.
9. Transfusion Associated Circulatory Overload (TACO) occurs when multiple blood transfusions or blood-products (plasma, platelets, etc.) are transfused over a short period of time.

- Transfusion associated Acute Lung Injury (TRALI) is a specific type of blood-product transfusion injury that occurs when the donors plasma contained antibodies against the donor, such as anti-HLA or anti-neutrophil antibodies.
- Severe infection or inflammation which may be local or systemic.
- This is the classical form of ALI-ARDS.
- Arteriovenous malformation.
- High altitude pulmonary edema (HAPE).

- **The pulmonary wedge pressure** or **PWP**, or cross-sectional pressure (also called the pulmonary arterial wedge pressure or PAWP, pulmonary capillary wedge pressure or PCWP, or pulmonary artery occlusion pressure or PAOP), is the pressure measured by wedging a pulmonary catheter with an inflated balloon into a small pulmonary arterial branch.
- It estimates the left atrial pressure.
- Pulmonary venous wedge pressure (PVWP) is not synonymous with the above.

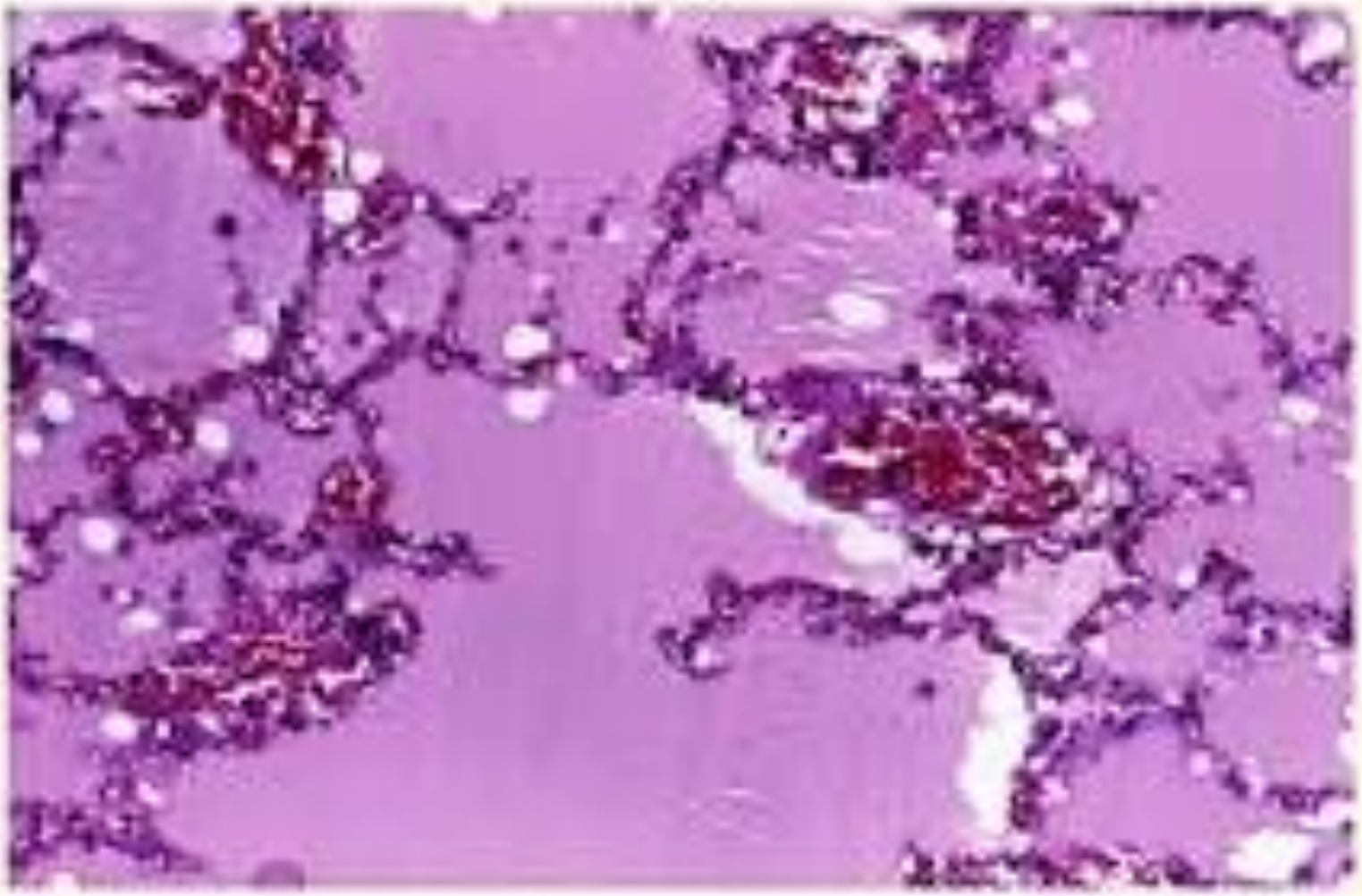
Pulmonary Edema





The alveoli in this lung are filled with a smooth pink material characteristic for pulmonary edema.

Pulmonary Edema



Hypostatic Pneumonia

- Hypostatic pneumonia is the term used for ***collection of edema fluid and secretions in the dependent parts of the lungs in severely debilitated, bed-ridden patients.***
- The accumulated fluid in the basal zone and posterior part of lungs gets infected by bacteria from the URT and sets in bacterial pneumonia.
- Hypostatic pneumonia is a ***common terminal event in the old, feeble, comatose d patients.***

Pulmonary Hypertension

- Normally, the pulmonary arterial circulation is one of low resistance; high flow and low pressure system with much lower blood pressure than the systemic blood pressure (***one eighth*** of systemic pressures).
- It does not exceed 30/15 mmHg even during exercise.
- Normally, blood pressure in the pulmonary veins is between 3 and 8 mmHg.

- **Definition:**
- **Pulmonary hypertension** is defined as a systolic blood pressure in the pulmonary arterial circulation above 30 mmHg; (when mean pulmonary pressures reach ***one fourth or more of systemic levels***).
- It is most often ***secondary to a decrease*** *in the cross-sectional area of the pulmonary vascular bed*, or to *increased pulmonary vascular blood flow*.
- ***Pulmonary hypertension is broadly classified into 2 groups:*** primary (idiopathic) and secondary; the latter being more common.

Primary (Idiopathic) Pulmonary Hypertension

- Primary or idiopathic pulmonary hypertension is an uncommon condition of ***unknown cause***.
- **The diagnosis** can be established only after a thorough search for the usual causes of secondary pulmonary hypertension.
- The patients are usually young *females between the age of 20 and 40 years*, or *children around 5 years* of age.

- **Etio-Pathogenesis:**
- Though the etiology of primary pulmonary hypertension is unknown, ***a number of etiological factors have been suggested to explain its pathogenesis:***

1. ***Neurohumoral vasoconstrictor mechanism*** may be involved leading to chronic vasoconstriction that induces pulmonary hypertension.
2. The occurrence of disease in young females has prompted a suggestion that ***unrecognized thrombo-emboli or amniotic fluid emboli*** during pregnancy may play a role.

3. There is a suggestion that primary pulmonary hypertension may be ***a form of collagen vascular disease.***
- This is supported by occurrence of Raynaud's phenomenon preceding the onset of this disease by a number of years in many patients, and disease association with SLE, scleroderma and rheumatoid arthritis.
4. ***Pulmonary veno-occlusive disease*** characterized by fibrous obliteration of small pulmonary veins is believed to be responsible for some cases of primary pulmonary hypertension, especially in children.
- This is generally considered a consequence of thrombosis or vasculitis.

5. ***Ingestion of*** substances like ***'bush tea', oral contraceptives*** and ***appetite depressant agents*** like aminorex are believed to be related to primary pulmonary hypertension.
6. ***Familial occurrence :*** The vast majority of cases of pulnonary hypertension are sporadic, and only 6% are familial with an autosomal dominant mode of inheritance.

Secondary Pulmonary Hypertension

- When pulmonary hypertension occurs secondary to a recognized lesion in the heart or lungs, it is termed as secondary pulmonary hypertension.
- It is the most common type and may be encountered at any age, but more frequently over the age of 50 years.

- **Causes:**
- *Based on the underlying mechanism, causes of secondary pulmonary hypertension are divided into the following 3 groups:*

A. ***Antecedent heart disease (Passive pulmonary hypertension):***

- This is the commonest and is produced by diseases raising pressure in the pulmonary veins and ultimately pulmonary arterial hypertension e.g.

1. Mitral stenosis.
2. Chronic left ventricular failure (e.g. in severe systemic hypertension, aortic stenosis, myocardial fibrosis).

B. ***Hyperkinetic (Reactive) pulmonary hypertension (Congenital left to right shunts):***

- In this group are included causes in which the blood enters the pulmonary arteries in greater volume or at a higher pressure. For example:

1. Patent ductus arteriosus.
2. Atrial or ventricular septal defects.

C. ***Vaso-occlusive pulmonary hypertension:***

- All conditions which produce progressive diminution of the vascular bed in the lungs are included in this group.
- **Vaso-occlusive causes may be further sub-divided into 3 types:**

1. ***Recurrent pulmonary emboli or blocking in the pulmonary circulation:***

- Presence of these emboli leads to a reduction in the functional cross-sectional area of the pulmonary vascular bed, leading in turn to increased vascular resistance. e.g.

I. Multiple emboli or thrombi
II. Sickle cell disease
III. Schistosomiasis

2. ***Chronic obstructive or interstitial lung disease:*** which is accompanied by destruction of lung parenchyma and consequent reduction in alveolar capillaries.

- This causes increased pulmonary arterial resistance and secondarily, elevated arterial pressure. e.g.

I. Chronic emphysema
II. Chronic bronchitis
III. Bronchiectasis
IV. Pulmonary tuberculosis
V. Pneumoconiosis

3. ***Vaso-constrictive type:***

- There is widespread and sustained hypoxic vasoconstriction and alveolar hyperventilation leading to pulmonary hypertension e.g.

I. In residents at high altitude.
II. Pathologic obesity (Pickwickian disease).
III. Upper airway disease such as tonsillar hypertrophy.
IV. Neuromuscular diseases such as poliomyelitis
V. Severe kyphoscoliosis.

Pathogenesis of Pulmonary Hypertension

- ***Pulmonary endothelial cell and/or vascular smooth muscle dysfunction*** is the probable underlying basis for most forms of pulmonary hypertension.
- In cases of **secondary pulmonary hypertension,** endothelial cell dysfunction arises as a result of shear and mechanical injury to increased blood flow in left to right shunts, or biochemical injury produced by fibrin in recurrent thrombo-embolism).

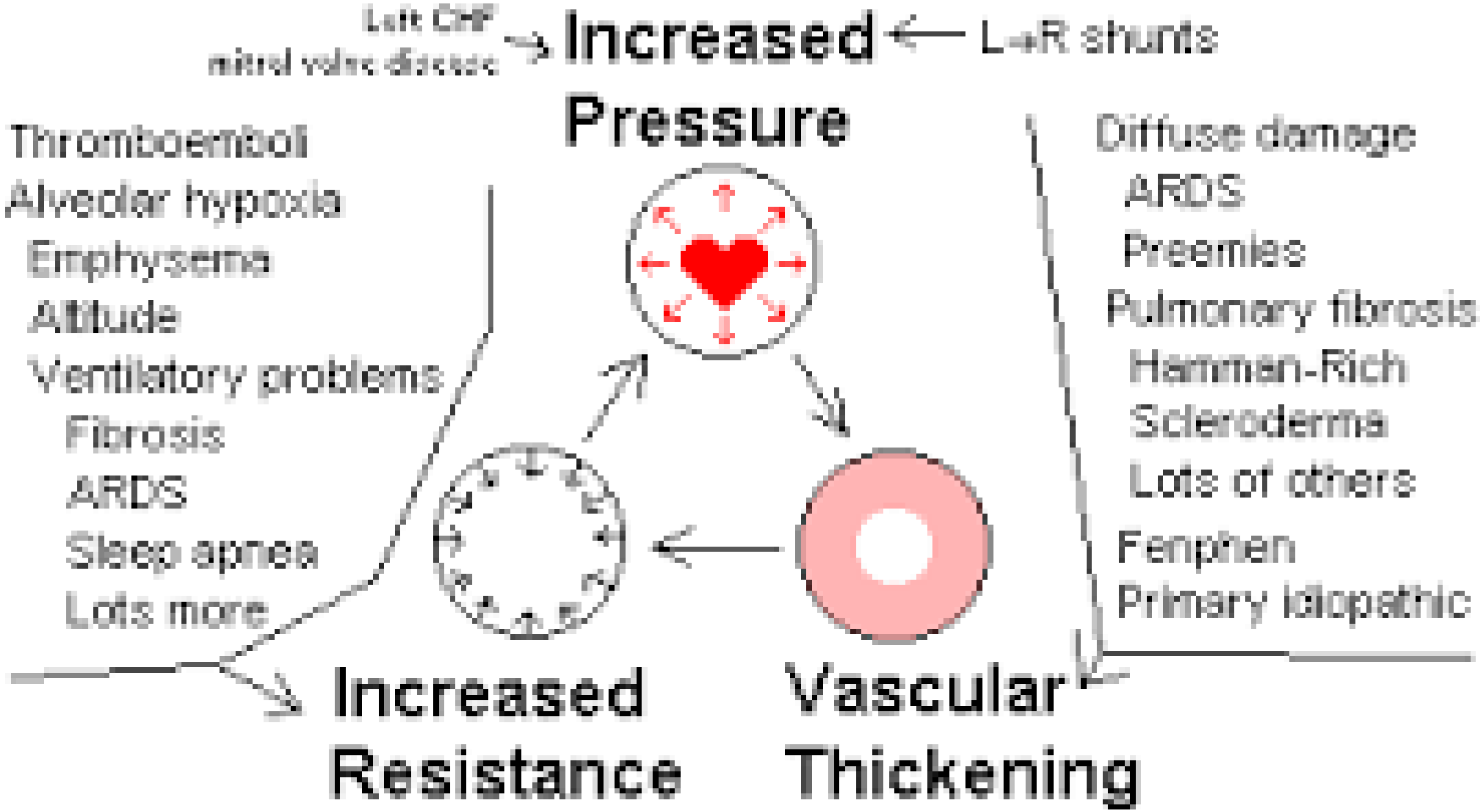
- Endothelial cell dysfunction ***reduces production*** of vasodilatory agents e.g., nitric oxide, and prostacyclin, while ***increasing synthesis*** of vasoconstrictive mediators like endothelin.
- In addition, there is production of growth factors and cytokines that induce the migration and replication of vascular smooth muscle and elaboration of extracellular matrix.
- In **primary pulmonary hypertension,** especially in the uncommon **familial form, the TGF-β signaling pathway** has emerged as a key mediator of endothelial and smooth muscle dysfunction.

- Specifically, germline mutations of **bone morphogenetic protein receptor type 2** (BMPR-2), a cell surface molecule that binds to a variety of TGF-β pathway ligands, have been demonstrated in 50% of familial cases.
- The *BMPR2 gene product is* inhibitory in its effects on proliferation; hence, loss of function mutations of this gene result in abnormal vascular endothelial and pulmonary smooth muscle proliferation.
- The endothelial proliferations in these instances usually are **monoclonal, reiterating the genetic basis of their origin.**

- However, not all persons with germline mutations of *BMPR2 develop primary pulmonary hypertension, suggesting* the existence of **modifier genes that probably** affect penetrance of this particular phenotype.
- Studies on sporadic forms of primary pulmonary hypertension point to a possible role for the **serotonin transporter gene (5*HTT*).**
- *Pulmonary smooth muscle cells* from some patients with primary pulmonary hypertension demonstrate ***increased proliferation on exposure to serotonin or serum.***

- Genetic polymorphisms of *5HTT that lead to enhanced expression of the transporter* protein on vascular smooth muscle are postulated to cause their proliferation.

Pulmonary Hypertension



Morphology of Pulmonary Hypertension

- Irrespective of the type of pulmonary hypertension chronic cases lead to cor-pulmonale.
- The pathological changes are confined to the right side of the heart and pulmonary arterial tree in the lungs.
- There is hypertrophy of the right ventricle and dilatation of the right atrium.
- The vascular changes are similar in primary and secondary types and involve the entire arterial tree from the main pulmonary arteries down to the arterioles.

- *Vascular alterations in all forms of pulmonary hypertension (primary and secondary) involve the entire arterial tree and include:*

1. **Arterioles and small pulmonary arteries:**

- These branches show the following changes:

I. Medial thickening, and hypertrophy.
II. Thickening and reduplication of internal and external elastic laminae.
III. Persons with idiopathic pulmonary arterial hypertension have characteristic plexiform lesions, in which endothelial proliferation forms multiple lumina within small arteries where they branch from a medium sized artery.

IV. In these vessels, the wall thickness may exceed the diameter of the lumen, which is sometimes narrowed to the point of near-obliteration.

- These lesions are not so marked in secondary pulmonary hypertension.

2. **Medium-sized muscular pulmonary arteries:**

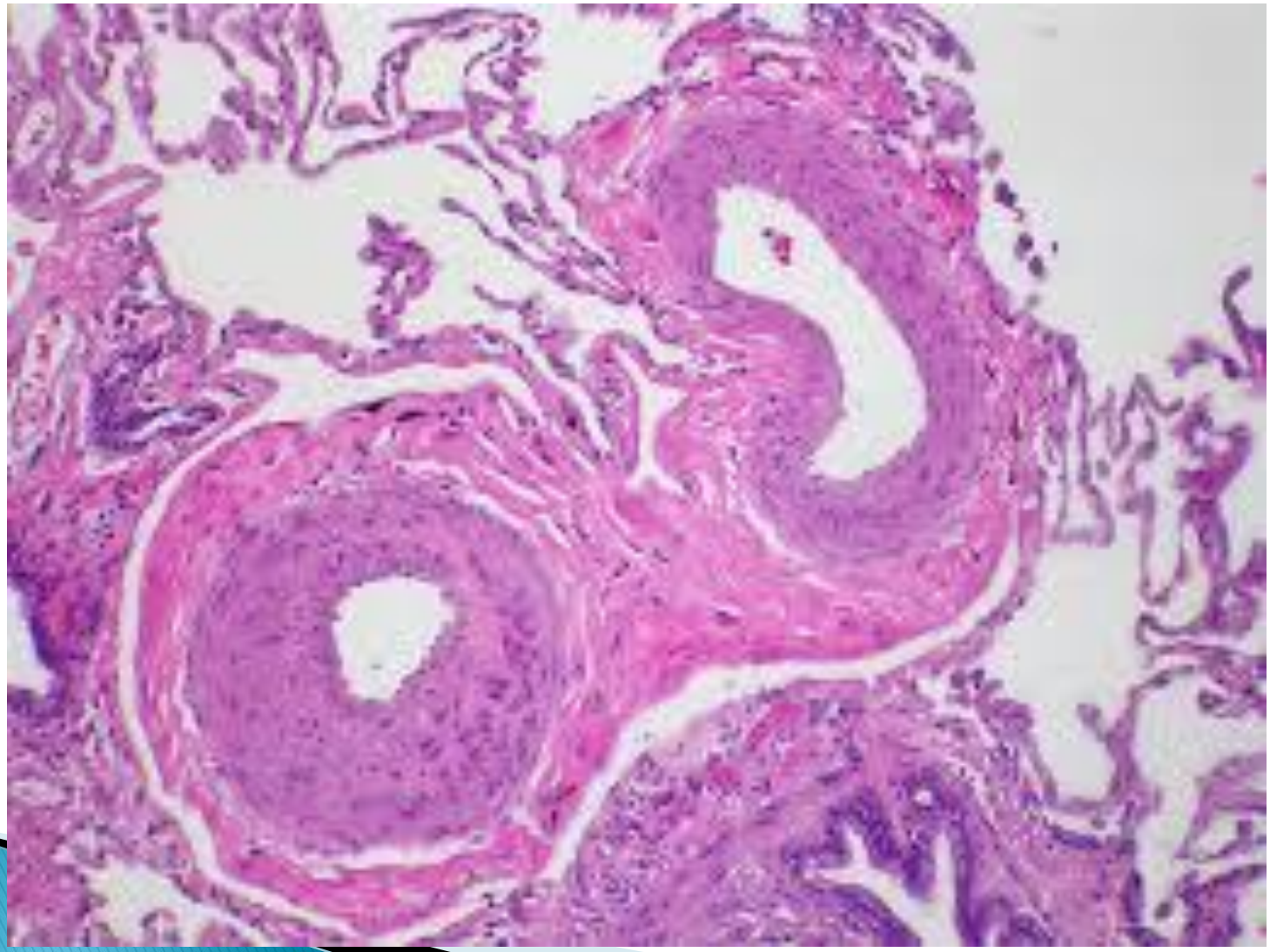
- There is proliferation of myointimal cells and smooth muscle cells causing:

I. Concentric thickening of the intima.
II. Medial hypertrophy is not so marked in secondary pulmonary hypertension.
III. Narrowing of the lumina
IV. Adventitial fibrosis.
V. Thickening and reduplication of elastic laminae.

3. **Large pulmonary arteries:** due to:

I. ***Atheromatous deposits (atheromas)*** in the main elastic arteries, similar to those in systemic atherosclerosis.

Pulmonary Hypertension



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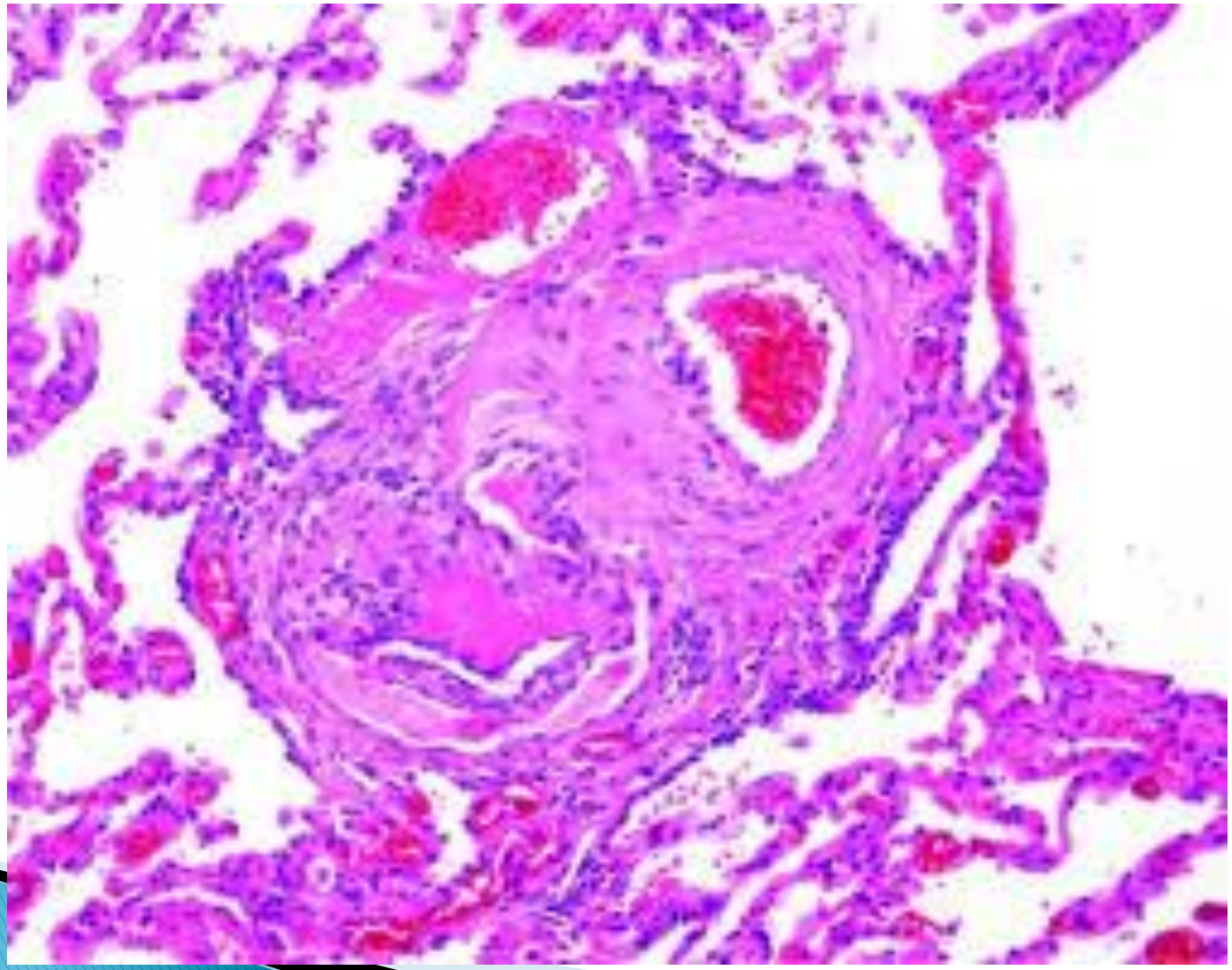

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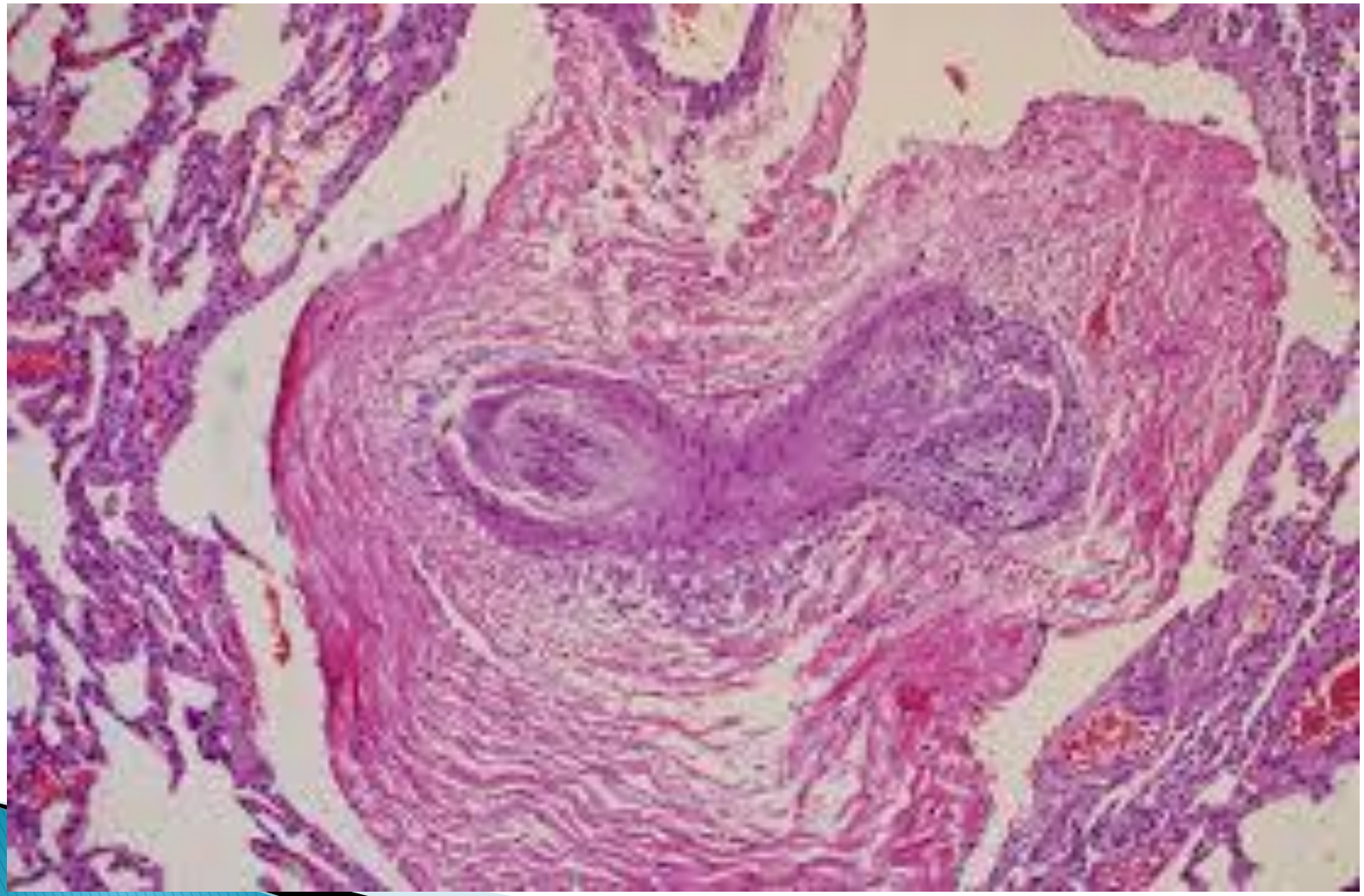

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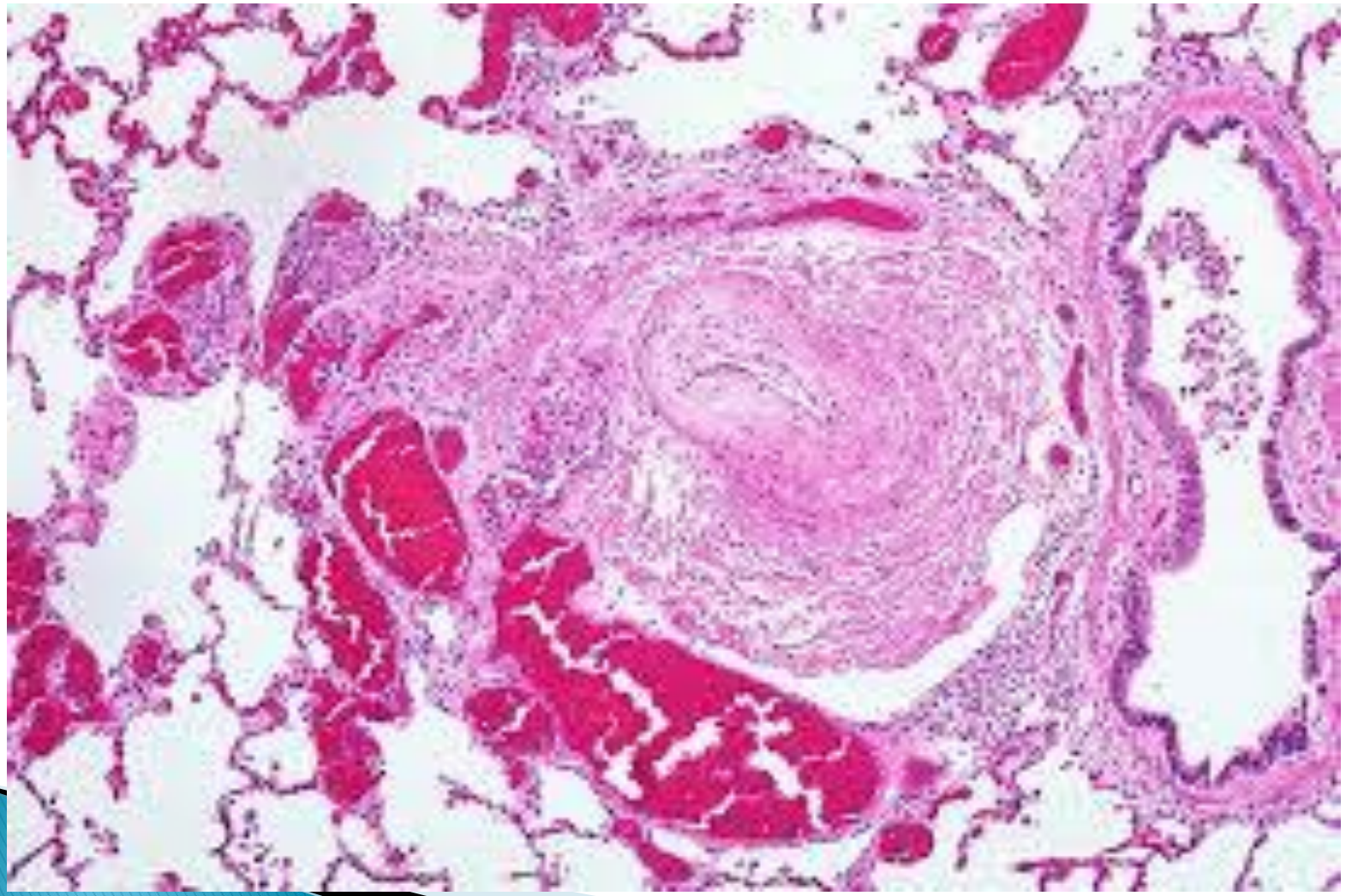

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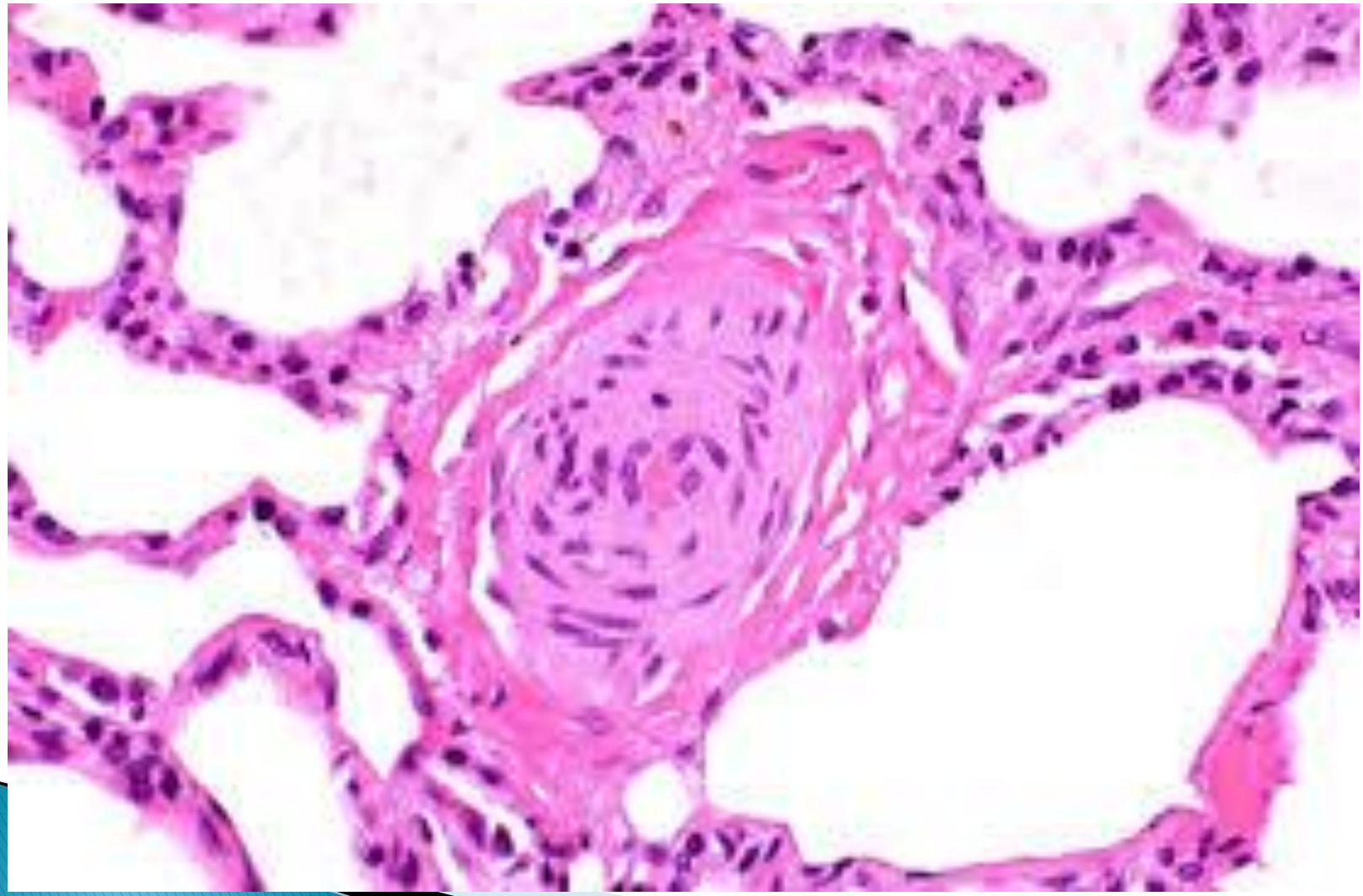

Clinical Features of Pulmonary Hypertension

- ***Secondary pulmonary hypertension*** may develop at any age.
- The clinical features reflect the underlying disease, usually pulmonary or cardiac, with accentuation of respiratory insufficiency and right sided heart failure.
- ***Primary pulmonary hypertension,*** on the other hand, is almost always encountered in young adults, more commonly women, and is marked by fatigue, syncope (particularly on exercise), dyspnea on exertion, and sometimes chest pain.

- Severe respiratory insufficiency and cyanosis develop, and death usually results from right sided heart failure (de-compensated cor-pulmonale) within 2 to 5 years of diagnosis.
- Some amelioration of the respiratory distress can be achieved by vasodilators and antithrombotic agents, and continuous prostacyclin infusions may prolong life (months to years), but without lung transplantation the prognosis is poor.

Diffuse Alveolar Hemorrhage Syndromes

- While there may be several ***"secondary"*** causes of pulmonary hemorrhage (necrotizing bacterial pneumonia, passive venous congestion, bleeding diathesis), the diffuse alveolar hemorrhage syndromes constitute a group of ***"primary"*** immune-mediated diseases that manifest as the ***triad of hemoptysis, anemia, and diffuse pulmonary infiltrates.***

Goodpasture's Syndrome

- **Definition:**
- Goodpasture's syndrome or pulmonary hemorrhage syndrome is the prototype disorder of this group.
- It is an uncommon but intriguing condition characterized by a combination of necrotizing hemorrhagic interstitial pneumonitis and rapidly progressive glomerulonephritis.

- **Etio-pathogenesis:**
- The condition results from immunological damage produced by anti-basement membrane antibodies formed against antigens common to the glomerular and pulmonary basement membranes.
- The trigger for initiation of this autoimmune response is not clear; it could be virus infection, exposure to hydrocarbons and smoking.

- Both the renal and the pulmonary lesions are caused by antibodies targeted against the non-collagenous domain of the α3 chain of collagen IV.
- These antibodies can be detected in the serum of more than 90% of persons with Goodpasture syndrome.

Morphology of Goodpasture Syndrome

- **Grossly:**
- The lungs are heavy, with areas of red-brown consolidation, due to **diffuse alveolar hemorrhage.**
- **Microscopically**:
- The features vary according to the stage of the disease.
- ***In acute stage,*** there are focal areas of hemorrhages in the alveoli and focal necrosis in the alveolar walls.

- ***In more chronic cases,*** there is organization of the hemorrhage leading to interstitial fibrosis and fibrous thickening of the septa, filling of alveoli with hemosiderin-laden macrophages, and hypertrophic type II pneumocytes.
- Presence of **hemosiderin, both within macrophages and extracellularly,** is characteristic, indicating earlier episode(s) of hemorrhage.
- The characteristic **linear pattern of immunoglobulin deposition (usually IgG, sometimes IgA** or **IgM**) that is the hallmark diagnostic finding in renal biopsy specimens also may be seen along the alveolar septa.

Clinical features of Goodpasture Syndrome

- The condition occurs commonly in the 2nd or 3rd decades of life with preponderance in males.
- The pulmonary manifestations generally precede the renal disease.
- Most cases present with hemoptysis accompanied with dyspnea, fatigue, weakness and anemia.
- Renal manifestations soon appear which include hematuria, proteinuria, uremia and progressive renal failure.

- Plasmapheresis and immunosuppressive therapy have markedly improved the once-dismal prognosis for this disease.
- Plasma exchange removes offending antibodies, and immunosuppressive drugs inhibit antibody production.
- With severe renal disease, renal transplantation is eventually required.

Idiopathic Pulmonary Hemosiderosis

- Idiopathic pulmonary hemosiderosis is a rare disease of uncertain etiology that has pulmonary manifestations and histological features similar to those of Goodpasture syndrome, but there is no associated renal disease or circulating anti-basement membrane antibody.
- Most cases occur in children, although the disease is reported in adults as well, who have a better prognosis.

- With steroid and immunosuppressive therapy, survival has markedly improved from the historical 2.5 years; thus, an immune-mediated etiology is postulated.


THANK YOU