

Chronic Obstructive Pulmonary Disease

Airway, alveolar, and small-airway pathology

Mechanisms • morphology • clinicopathologic correlation

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Learning outcomes

- Distinguish airflow obstruction from a restrictive ventilatory defect.
- Explain the structural patterns and mechanisms of emphysema.
- Relate mucus hypersecretion and bronchiolar remodeling to chronic bronchitis.
- Interpret the major morphologic findings and clinical complications of COPD.

COPD: Persistent symptoms and airflow limitation

- A common, preventable and treatable respiratory disease.
- Characterized by persistent respiratory symptoms and airflow limitation.
- Airway and/or alveolar abnormalities arise after exposure to noxious particles or gases.
- A single patient may exhibit multiple overlapping pathologic components.

Obstructive and restrictive physiology are distinct

Characteristic	Obstructive pattern	Restrictive pattern
Primary defect	Increased resistance to expiratory airflow	Reduced lung expansion and total lung capacity
Forced expiration	Maximal expiratory flow is reduced	FEV ₁ and FVC tend to decline proportionately
FEV ₁ /FVC	Typically decreased	Often preserved

Spirometry detects the obstructive defect

Typical spirometric finding in COPD

$$\mathbf{FEV_1 / FVC < 0.7}$$

- FEV₁: Forced expiratory volume in 1 second.
- FVC: Forced vital capacity.
- Airflow limitation is established by spirometry, not by cough alone.

COPD reflects disease at several anatomic levels

Bronchi

Mucus gland
enlargement and
excess secretions

Bronchioles

Inflammation, mucus
plugging and fibrotic
narrowing

Acini

Alveolar-wall
destruction and
reduced recoil

Three anatomic sites — schematic

The two major components commonly coexist

Emphysema

- Enlargement of distal airspaces
- Destruction of alveolar walls
- Reduced parenchymal elastic recoil

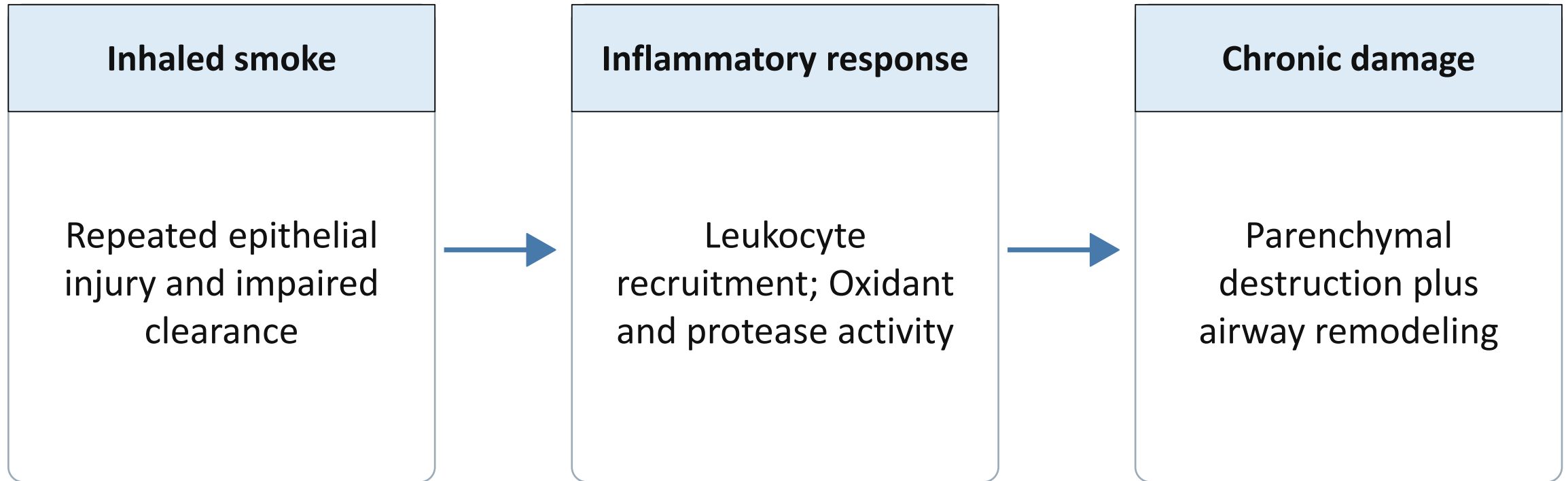
Chronic bronchitis

- Persistent productive cough
- Mucus hypersecretion and inflammation
- Airway narrowing / bronchiolar fibrosis

Small-airway disease contributes independently

- Bronchiolitis affects bronchioles rather than the large conducting airways.
- Chronic inflammation and fibrosis constrict narrow-caliber lumina.
- It adds airflow resistance even when emphysematous tissue destruction dominates.
- Obstructive pathology is therefore more than mucus in large bronchi.

Cigarette smoke is the principal shared exposure



Causal sequence — schematic

Susceptibility extends beyond smoking

- Poor early-life lung development may limit attained respiratory reserve.
- Environmental and occupational pollutants add chronic inhalational exposure.
- Airway hyperresponsiveness contributes in susceptible individuals.
- Genetic variation affects risk, including antiprotease pathways.

Shared exposure does not produce identical pathology

Predominant alveolar injury

- Loss of interalveolar septa
- Reduced elastic recoil
- Expiratory airway collapse

Predominant airway injury

- Gland and goblet-cell responses
- Inflammatory thickening
- Mucus plugging and fixed narrowing

Why emphysema and bronchitis are taught separately

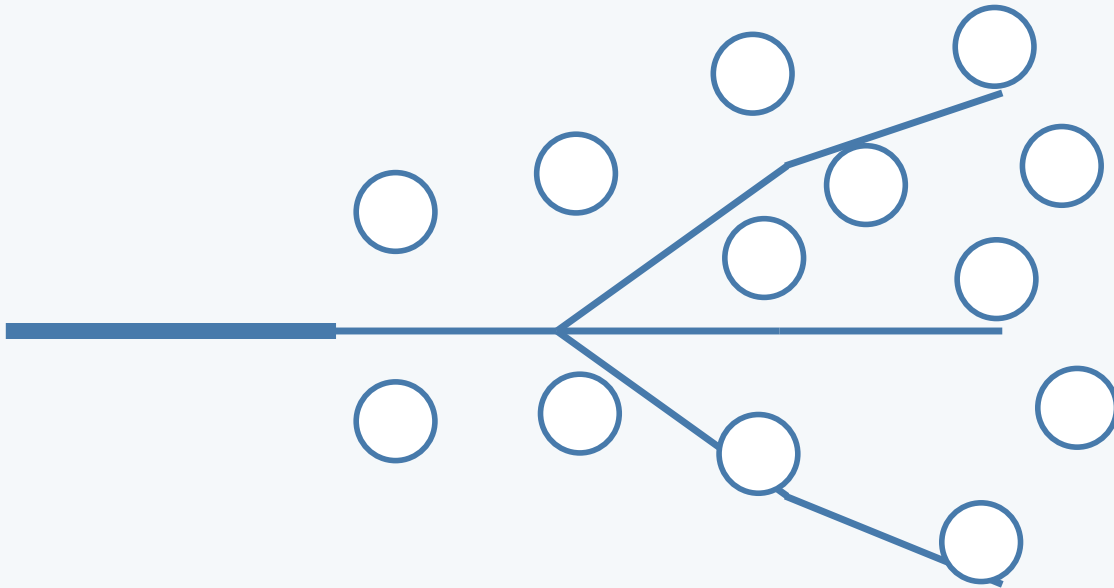
- They frequently occur together in the same person with COPD.
- Their central structural lesions differ: Alveolar wall versus airway wall.
- Each has a distinct mechanism of airflow limitation.
- Understanding both mechanisms explains heterogeneous clinical presentations.

Emphysema: A structural definition

- Irreversible enlargement of airspaces distal to terminal bronchioles.
- Accompanied by destruction of alveolar walls.
- The definition is morphologic: Dilatation alone is insufficient.
- Anatomic location within the acinus determines the emphysema pattern.

The respiratory acinus is the unit of injury

Acinar distribution — schematic (not histology)

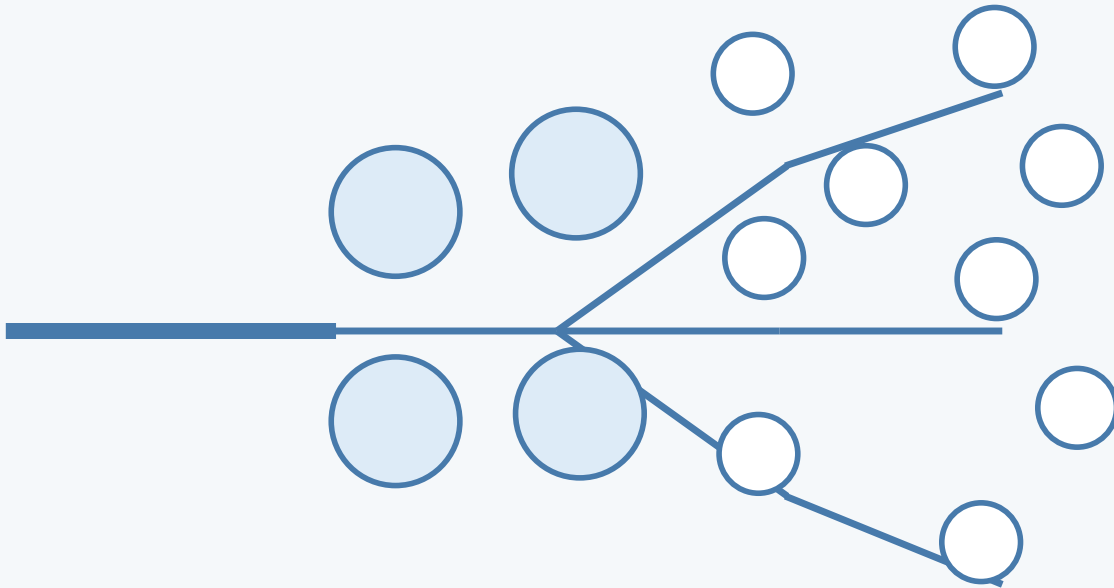


Characteristic distribution

- Terminal bronchiole leads to respiratory bronchioles.
- Alveolar ducts and alveoli form distal gas-exchanging units.
- The pulmonary lobule contains clusters of acini.

Centriacinar emphysema begins proximally

Acinar distribution — schematic (not histology)



Characteristic distribution

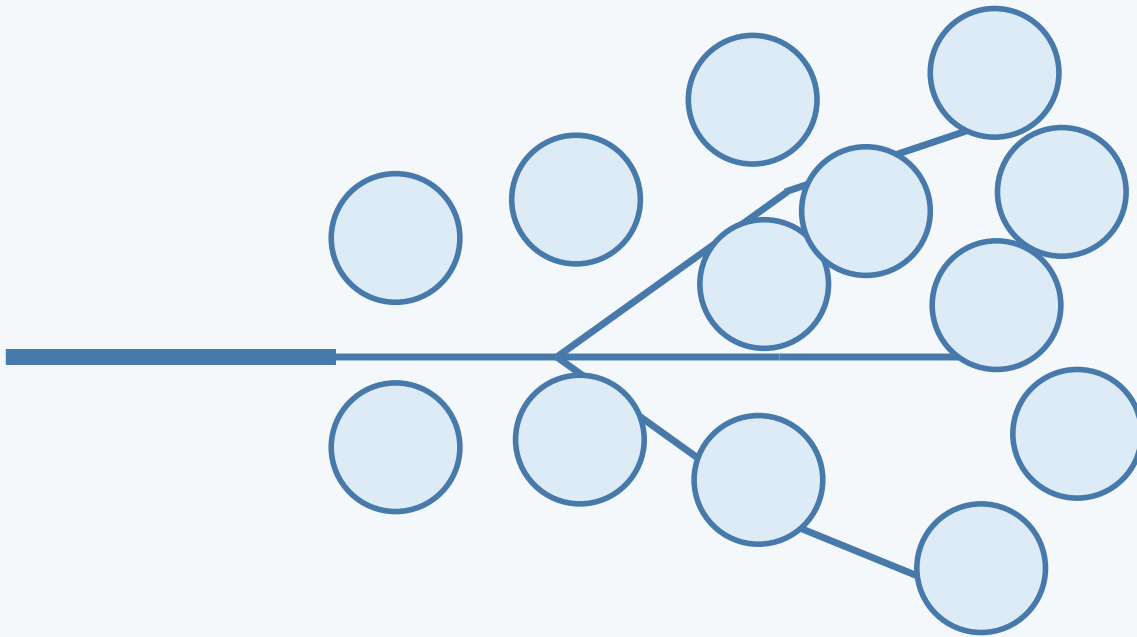
- Respiratory bronchioles within the acinus dilate and lose walls.
- Relatively spared distal alveoli may coexist in the same acinus.
- Severe disease may eventually extend into distal airspaces.

Centriacinar emphysema predominates in smokers

- The most common emphysematous pattern in clinically significant COPD.
- Strongly associated with heavy cigarette smoking.
- Lesions are usually more marked in upper lobes and apical segments.
- Central damage may become confluent with advanced disease.

Panacinar emphysema involves the entire acinus

Acinar distribution — schematic (not histology)



Characteristic distribution

- Enlargement extends from respiratory bronchiole to terminal alveoli.
- Relatively uniform acinar involvement contrasts with centriacinar sparing.
- Typically more severe in lower lung zones and bases.

Panacinar emphysema points toward antiprotease deficiency

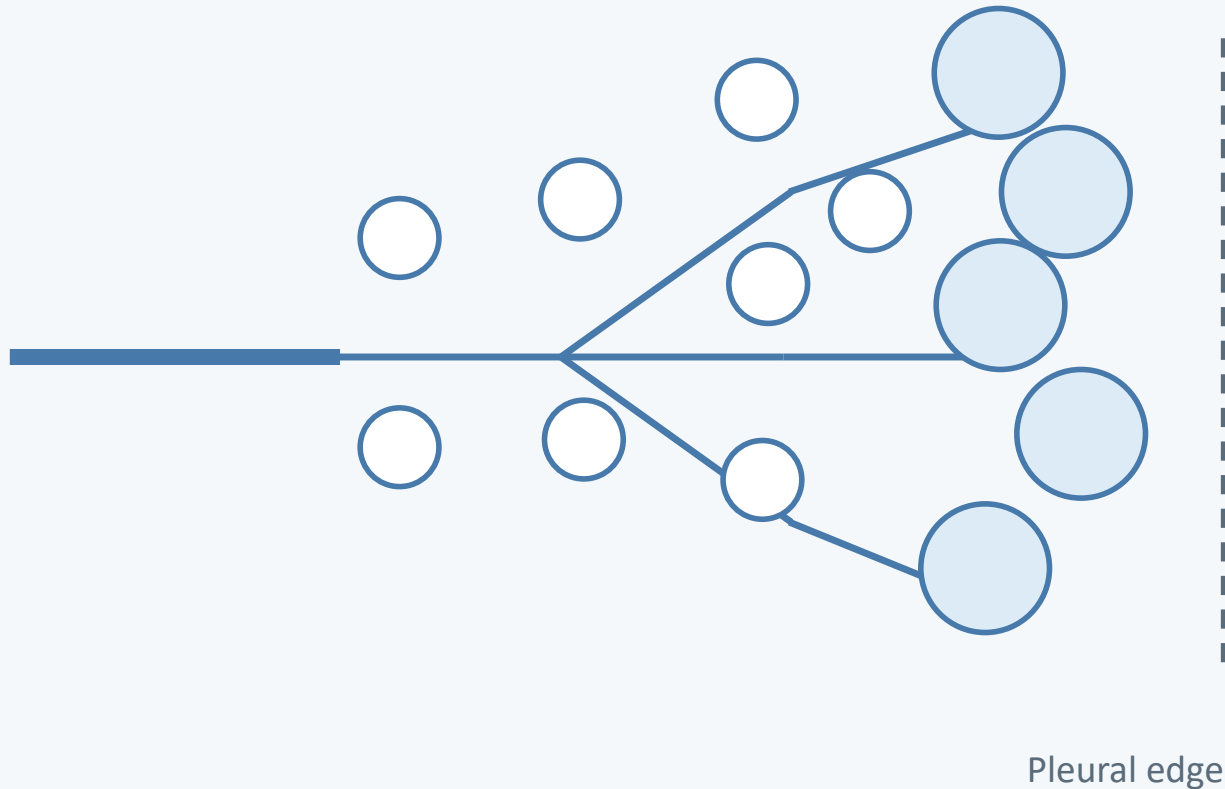
- Classically associated with α_1 -antitrypsin deficiency.
- Smoking amplifies risk and accelerates structural injury.
- The acinus is involved more uniformly than in smoking-related centriacinar disease.
- The distribution is often basilar rather than apical.

Centriacinar versus panacinar emphysema

Feature	Centriacinar	Panacinar
Acinar region	Proximal / respiratory bronchiolar	Entire acinus
Usual association	Cigarette smoking	α_1 -antitrypsin deficiency
Lung predominance	Upper lobes / apices	Lower zones / bases
Distal alveoli initially	Relatively preserved	Involved

Paraseptal emphysema preferentially affects distal acini

Acinar distribution — schematic (not histology)



Characteristic distribution

- Proximal acinus is relatively preserved.
- Distal airspaces near pleura or lobular septa are enlarged.
- Subpleural blebs can predispose to spontaneous pneumothorax.

Paraseptal emphysema has a characteristic location

- Pronounced adjacent to pleura and interlobular connective tissue septa.
- May occur near fibrosis, scar, or atelectatic lung.
- Often more conspicuous in the upper half of the lung.
- Can create cyst-like enlarged airspaces and subpleural blebs.

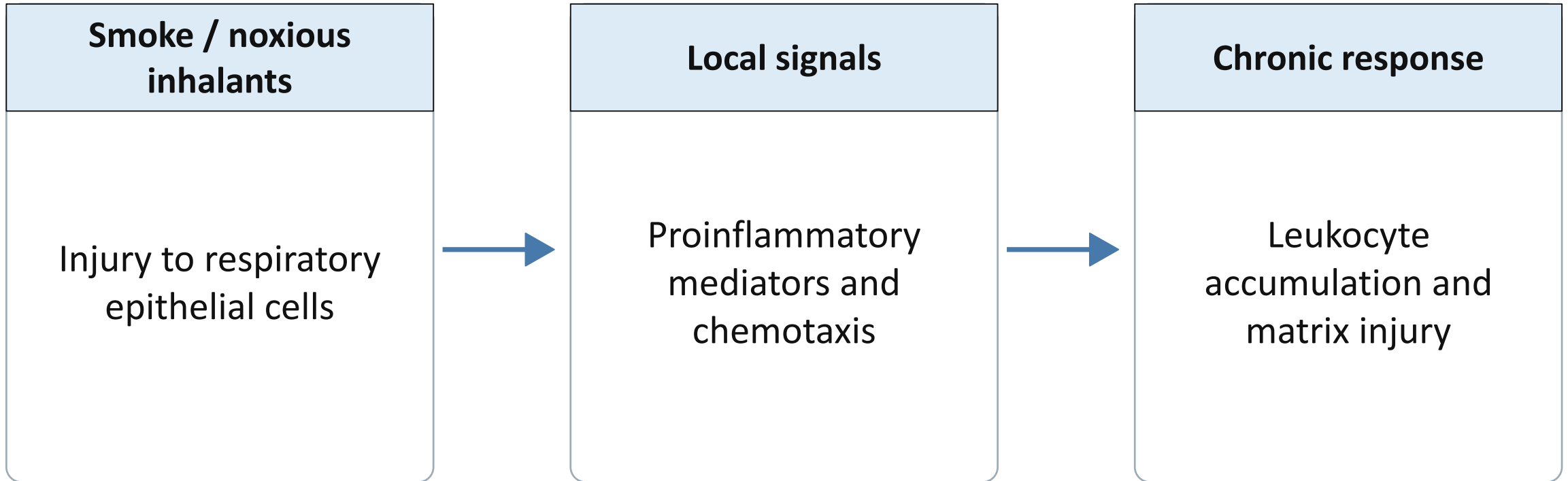
Irregular emphysema accompanies scars

- The acinus is affected unevenly rather than in a reproducible uniform pattern.
- Almost invariably accompanies areas of pulmonary scarring.
- Often limited to small foci.
- Usually of less clinical importance than centriacinar and panacinar disease.

Pattern recognition begins with acinar localization

Pattern	Principal site	Typical association
Centriacinar	Proximal acinus	Smoking; upper-lobe disease
Panacinar	Whole acinus	α_1 -antitrypsin deficiency; bases
Paraseptal	Distal subpleural acinus	Subpleural blebs / pneumothorax
Irregular	Scattered, scar-adjacent	Pulmonary fibrosis and scars

Emphysema begins with toxic epithelial injury

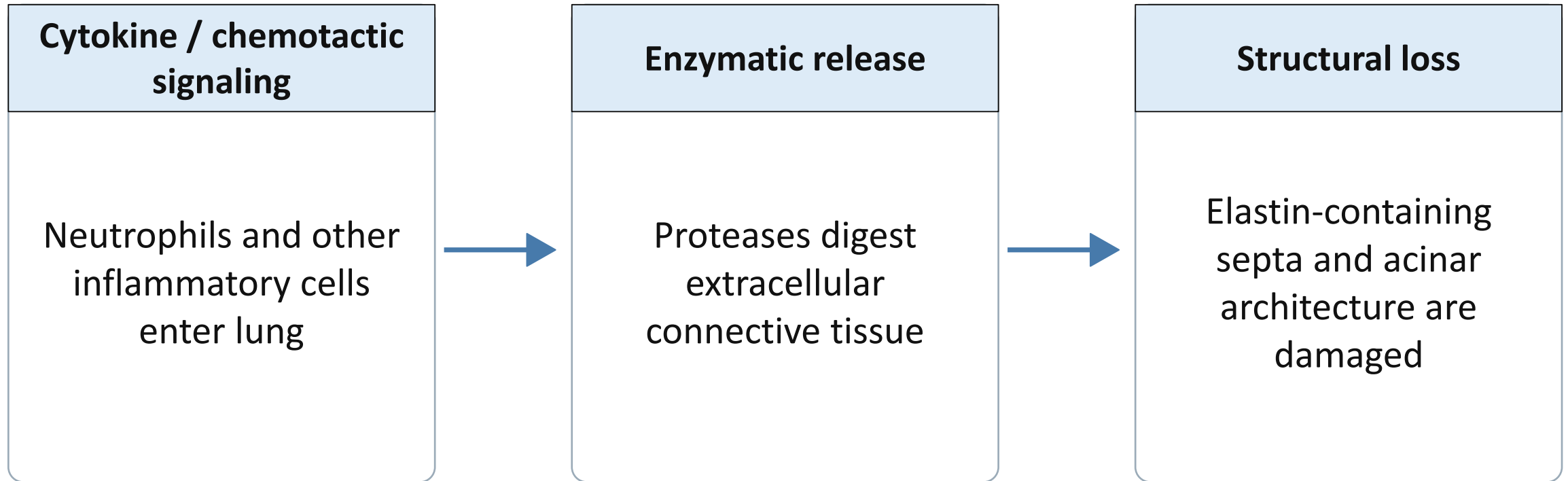


Causal sequence — schematic

Inflammatory mediators amplify alveolar damage

- Injured epithelium and resident macrophages release inflammatory mediators.
- Leukotriene B₄ and IL-8 are among mediators associated with recruitment.
- TNF and other cytokines amplify inflammatory reactions.
- Growth-factor signals contribute to tissue remodeling.

Innate inflammatory cells drive proteolytic injury

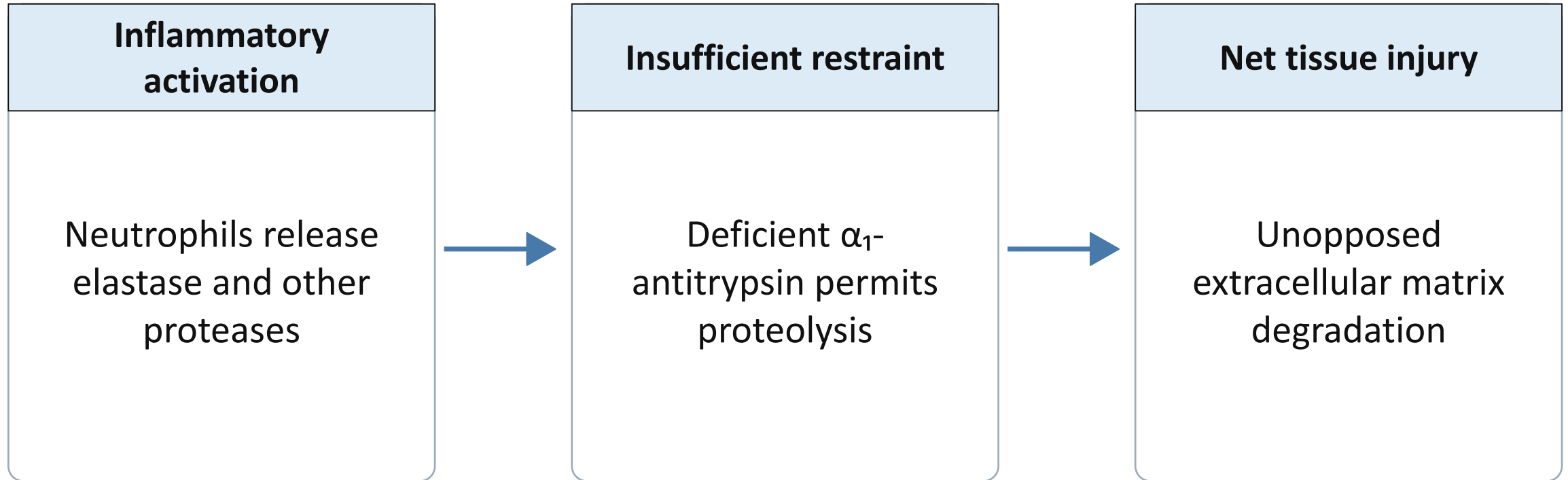


Causal sequence — schematic

Adaptive lymphocytes accumulate, but their role is uncertain

- T and B lymphocytes are found in chronically inflamed lung regions.
- Their accumulation accompanies sustained smoking-associated injury.
- The specific contribution of adaptive immunity to emphysema remains uncertain.
- Morphologic association does not by itself establish causal primacy.

Protease–antiprotease balance protects alveolar walls



Causal sequence — schematic

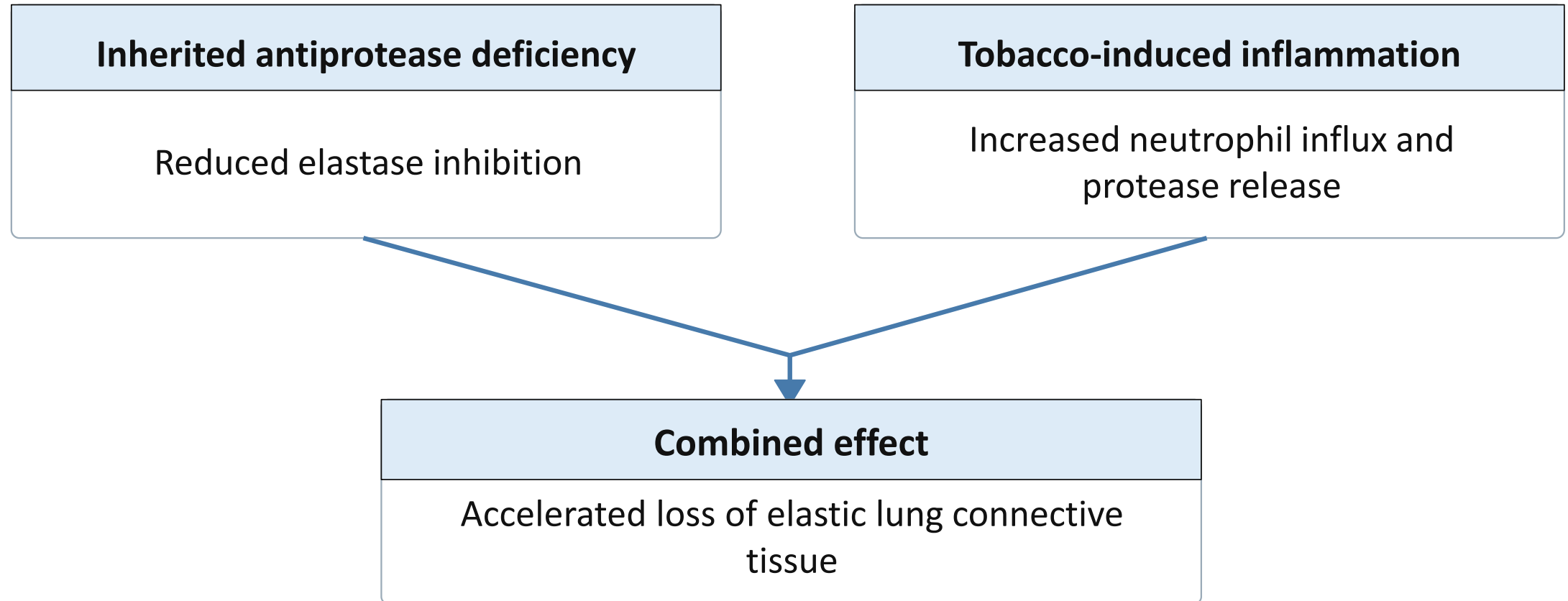
α_1 -Antitrypsin inhibits neutrophil elastase

- An antiprotease present in serum, tissue fluids, and macrophages.
- Restrains proteases released by activated neutrophils.
- Deficiency weakens protection against destruction of elastic tissue.
- Provides a mechanistic link between inherited susceptibility and emphysema.

The Pi locus provides the genetic context

- The proteinase inhibitor (Pi) locus is located on chromosome 14.
- The locus is polymorphic; The Z allele is linked to deficient circulating α_1 -antitrypsin.
- Severe deficiency predisposes to an earlier, often basilar panacinar pattern.
- Genetic susceptibility interacts strongly with smoking exposure.

Smoking and α_1 -antitrypsin deficiency act together

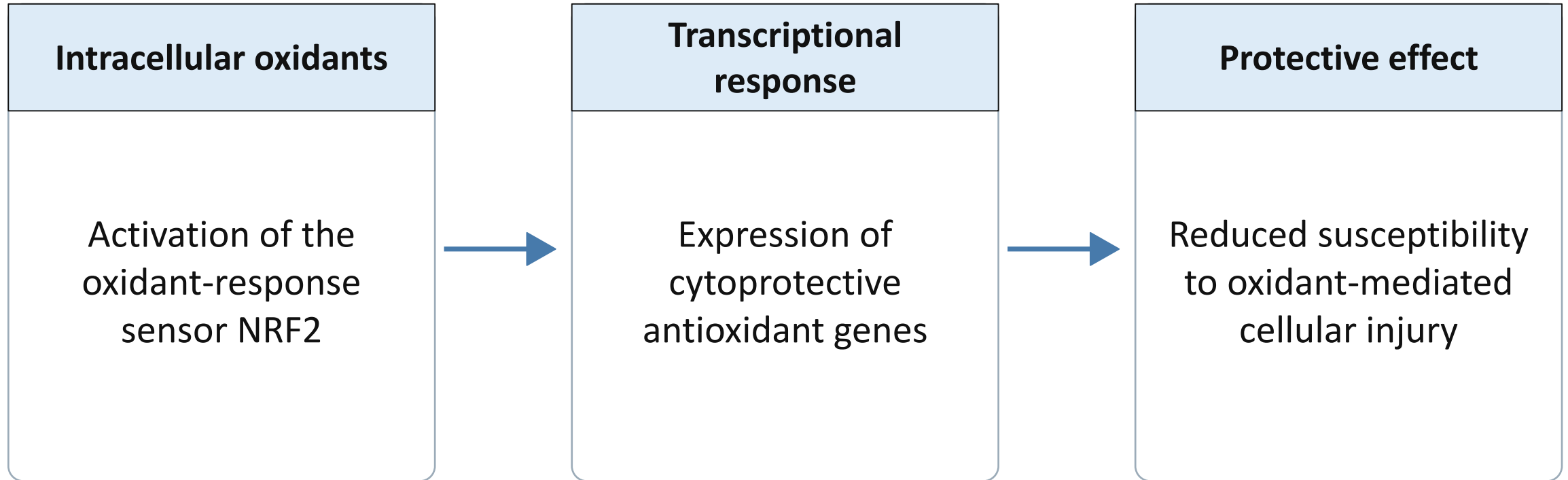


Convergent mechanisms — schematic

Oxidative stress adds a second major injury mechanism

- Oxidants are generated by tobacco smoke, inflammatory cells, and tissue injury.
- Excess oxidant exposure causes direct tissue injury and promotes inflammation.
- Endothelial dysfunction may accompany oxidant-mediated damage.
- Oxidative stress acts alongside protease imbalance rather than replacing it.

NRF2 coordinates cellular antioxidant defenses



Causal sequence — schematic

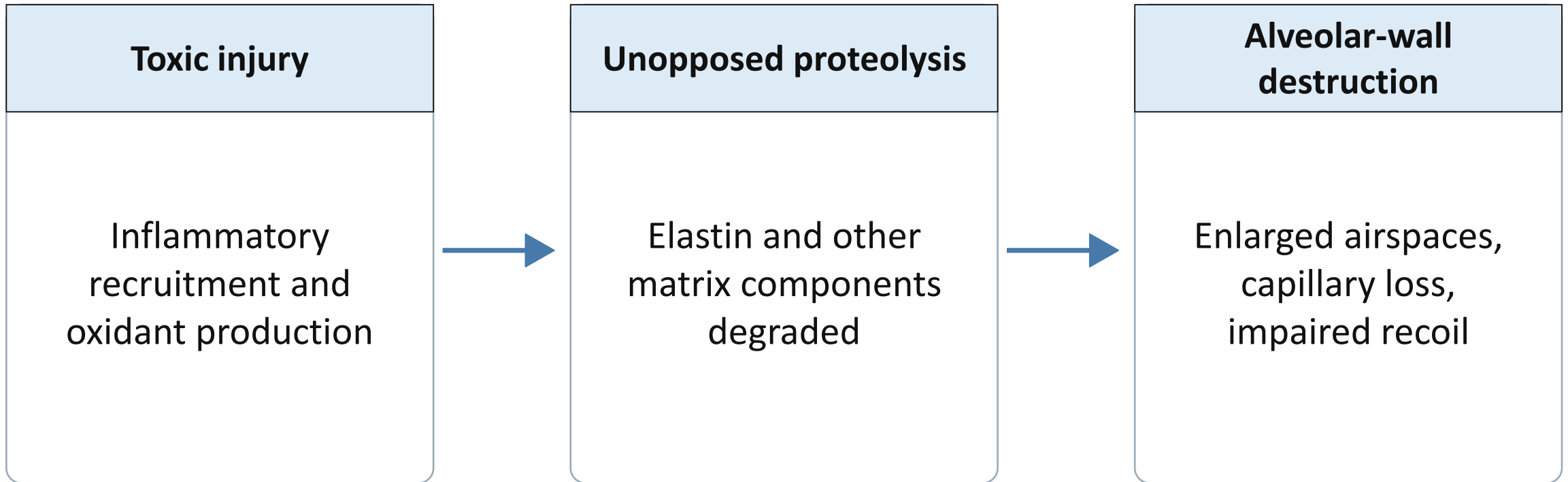
Why NFE2L2 matters in emphysema

- NFE2L2 encodes the transcription factor NRF2.
- Experimental inactivation makes mice more vulnerable to tobacco smoke injury.
- Human variants in the NRF2 response pathway are associated with smoking-related lung disease.
- The experimental and genetic observations support an oxidant-stress mechanism.

Infection typically exacerbates pre-existing emphysema

- Bacterial and viral infections are not considered primary initiators of emphysematous destruction.
- Superimposed infection can trigger marked clinical deterioration.
- Exacerbations occur against a background of damaged parenchyma and compromised airways.
- Distinguish cause of chronic injury from trigger of an acute episode.

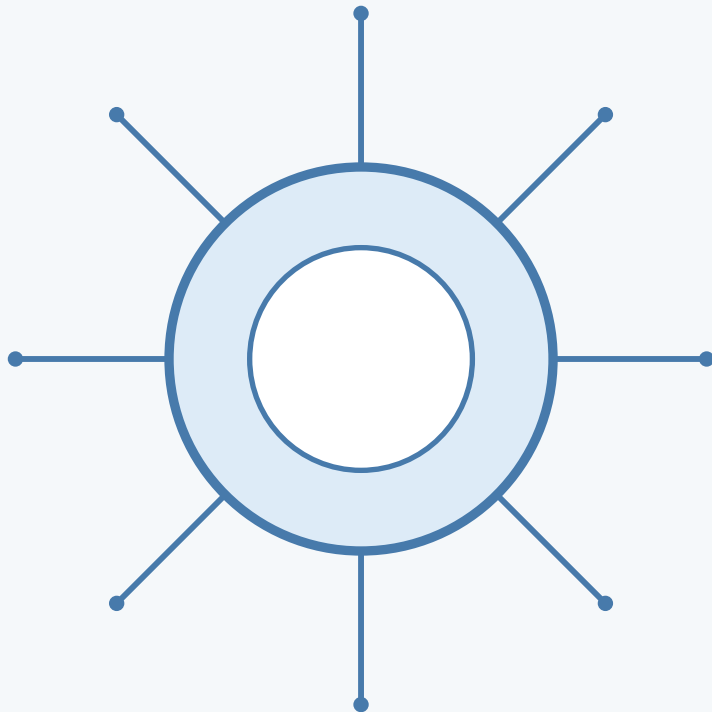
The mechanisms converge on irreversible wall loss



Causal sequence — schematic

Elastic recoil normally holds small airways open

Small-airway cross-section — schematic

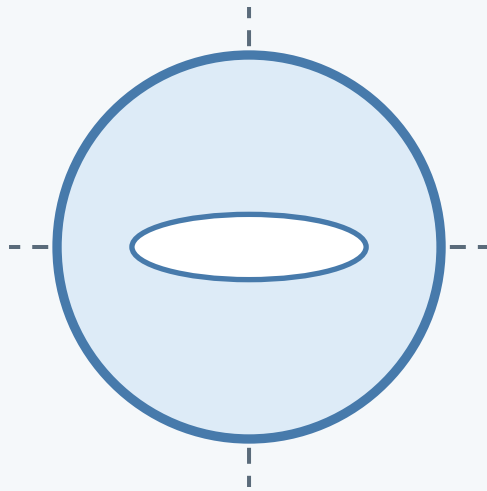


Why airflow changes

- Alveolar septa apply radial traction to nearby bronchioles.
- Intact elastic tissue helps prevent expiratory narrowing.
- Patent small airways support expiratory airflow.

Lost radial traction promotes expiratory collapse

Small-airway cross-section — schematic



Why airflow changes

- Emphysema destroys elastic septa and airway attachments.
- Reduced outward traction permits bronchiolar collapse on expiration.
- Obstruction may be functional without a solid luminal blockage.

Two processes narrow airflow in emphysema

Loss of elastic support

- Reduced radial traction
- Early airway collapse during exhalation
- Reduced elastic recoil

Small-airway inflammation

- Bronchiolar wall thickening
- Peribronchiolar fibrosis
- Additional narrowing of the airway lumen

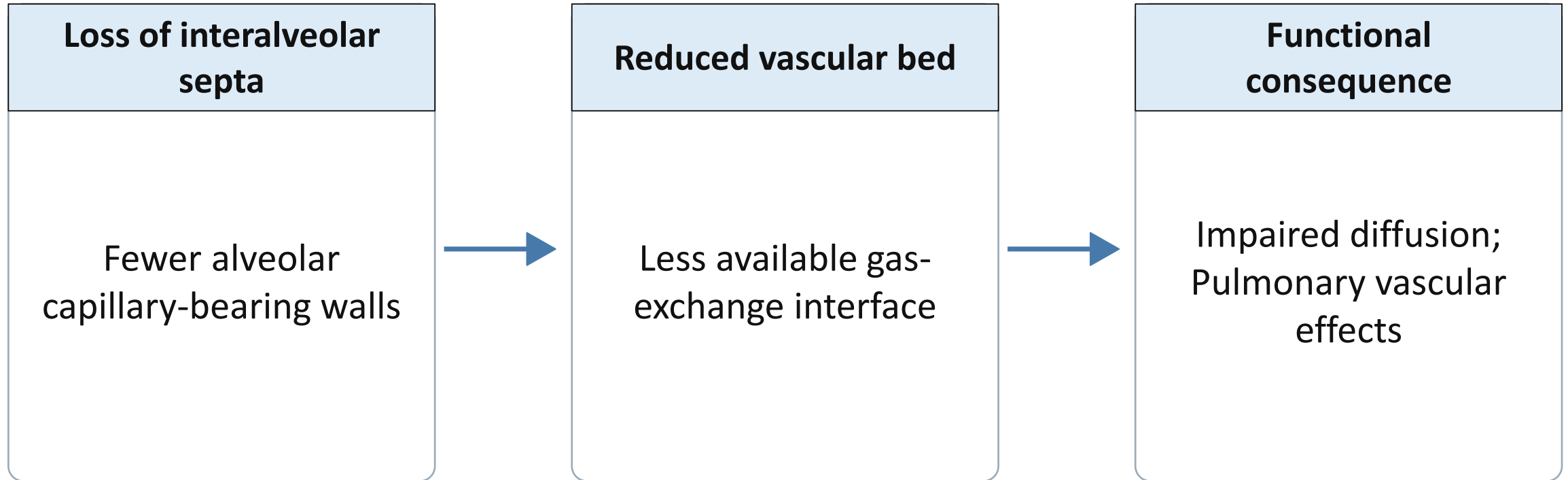
Gross emphysema produces voluminous lungs

- Lungs become overinflated and may overlap the heart anteriorly.
- The diaphragm is flattened by persistent hyperinflation.
- Smoking-associated damage is usually greater in upper lung regions.
- Large enlarged airspaces may be evident on lung cut surfaces.

The microscopic signature is alveolar-wall destruction

- Enlarged airspaces are separated by attenuated septa.
- Focal centriacinar fibrosis may be present.
- Destroyed septa can terminate as blind, club-shaped remnants.
- Airspace enlargement reflects actual loss of tissue architecture.

Capillary loss follows septal destruction



Causal sequence — schematic

Advanced emphysema can create blebs and bullae

- Confluent wall destruction creates abnormally large airspaces.
- Blebs and bullae may distort adjacent bronchioles and pulmonary vessels.
- Subpleural blebs are clinically relevant because rupture can cause pneumothorax.
- These are consequences of structural injury, not a substitute for microscopic diagnosis.

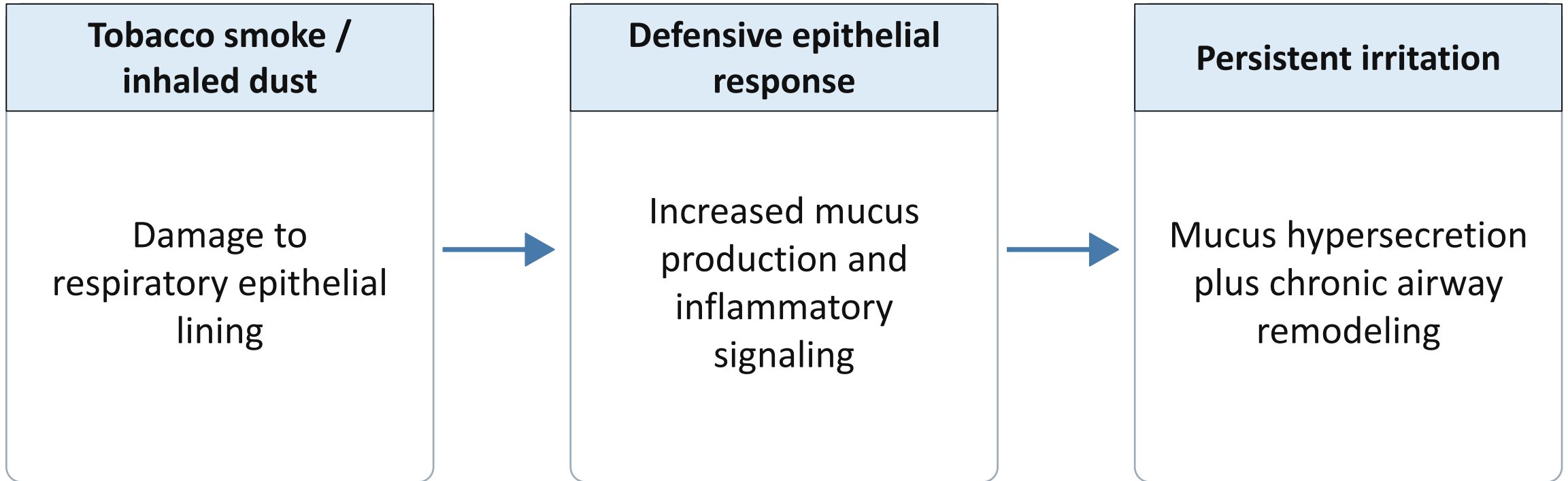
Chronic bronchitis is defined by cough and sputum

Clinical definition of chronic bronchitis

≥ 3 months / year $\times \geq 2$ years

- Persistent productive cough meets this duration pattern.
- The two years are consecutive.
- No other identifiable cause should account for the chronic productive cough.

Bronchitis begins with chronic inhalational irritation



Causal sequence — schematic

Large-airway mucous glands enlarge early

- Mucus hypersecretion initially becomes prominent in large airways.
- Enlarged submucosal glands are a characteristic tissue response.
- Accumulated secretions contribute to persistent productive cough.
- Gland enlargement is distinct from the bronchiolar fibrosis that fixes obstruction.

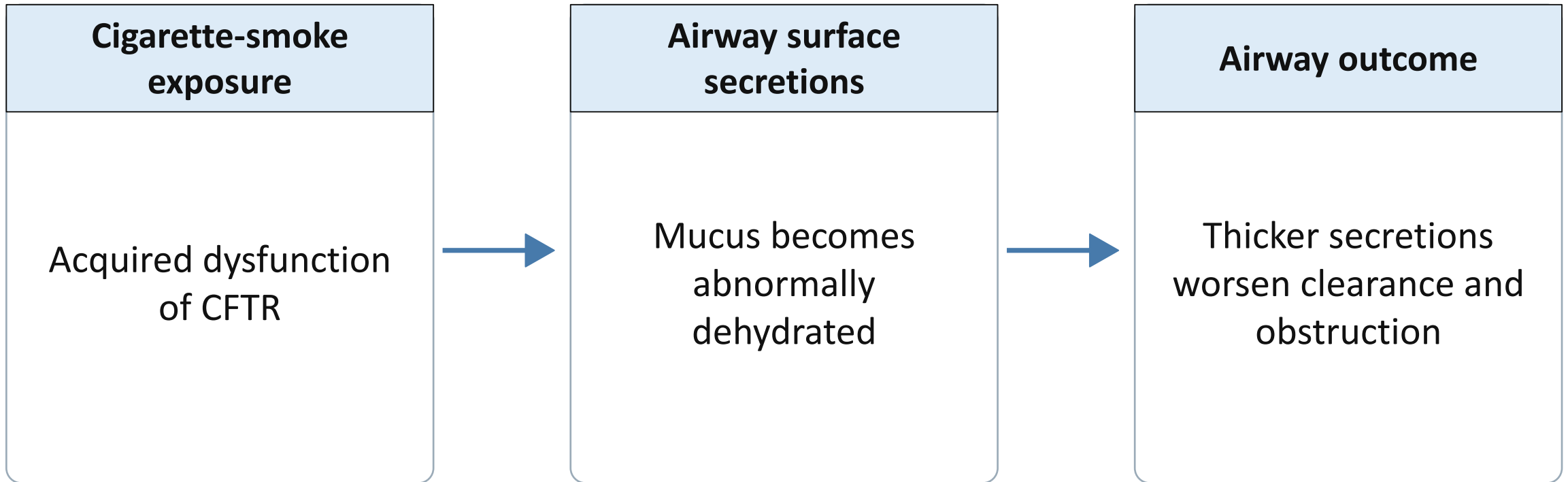
Goblet-cell expansion extends mucus production distally

- Goblet-cell numbers increase in smaller bronchi and bronchioles.
- Excess mucus can plug narrow bronchiolar lumina.
- Distal plugging adds a direct mechanical component to airflow obstruction.
- A response that may be protective becomes harmful when prolonged.

Histamine and IL-13 participate in mucus hypersecretion

- Inflammatory mediators contribute to enlargement and secretory responses.
- Histamine and interleukin-13 are implicated by the textbook.
- The full basis of mucus hypersecretion remains incompletely understood.
- Do not mistake mediator association for a complete single-pathway explanation.

Smoking can cause acquired CFTR dysfunction

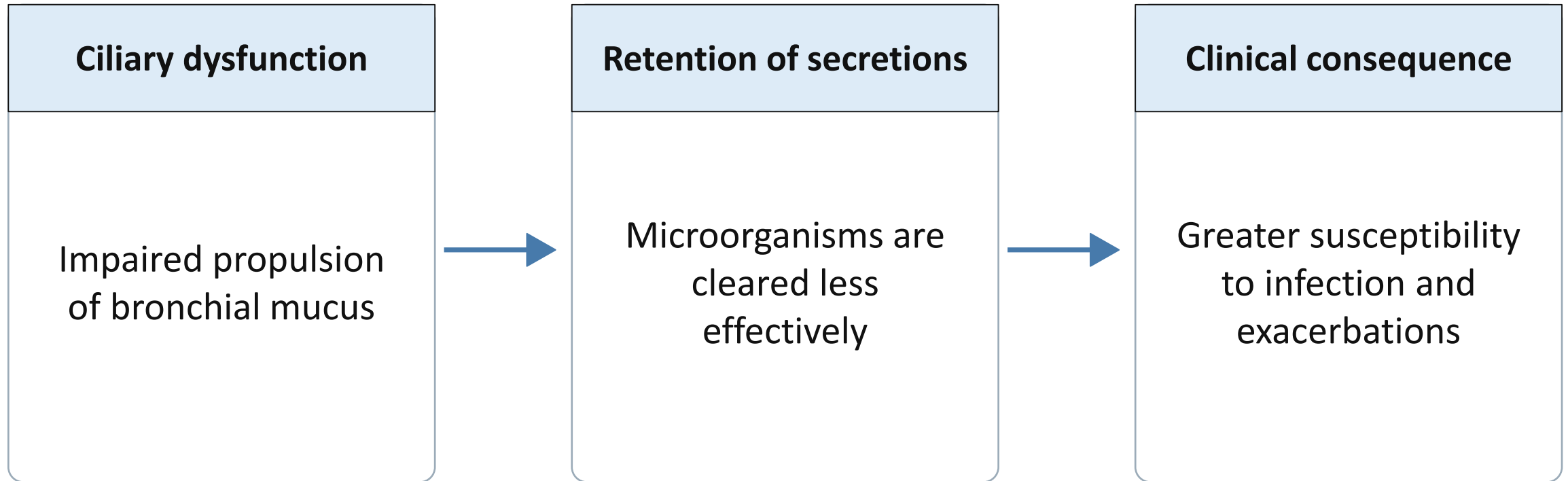


Causal sequence — schematic

Inflammation creates a self-sustaining airway injury

- Damaging inhalants induce acute and chronic inflammatory responses.
- Neutrophils, macrophages, and lymphocytes participate.
- Persistent inflammatory injury drives wall thickening and fibrosis.
- Exacerbation and baseline structural disease involve related but distinct processes.

Smoke compromises the mucociliary escalator

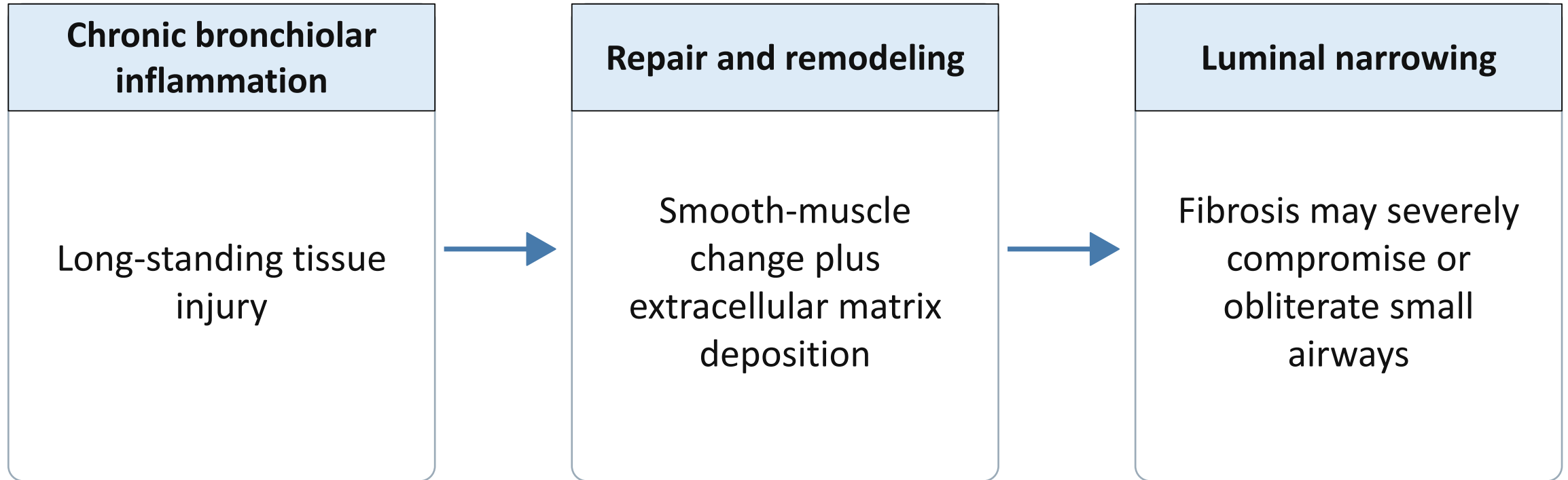


Causal sequence — schematic

Infection perpetuates bronchitis but rarely initiates it

- The initiating exposure is usually chronic inhalational irritation.
- Infection can help maintain airway inflammation once established.
- Acute infectious episodes are important triggers of exacerbations.
- Separate the longitudinal pathogenesis from episodic clinical worsening.

Small-airway fibrosis generates fixed resistance



Causal sequence — schematic

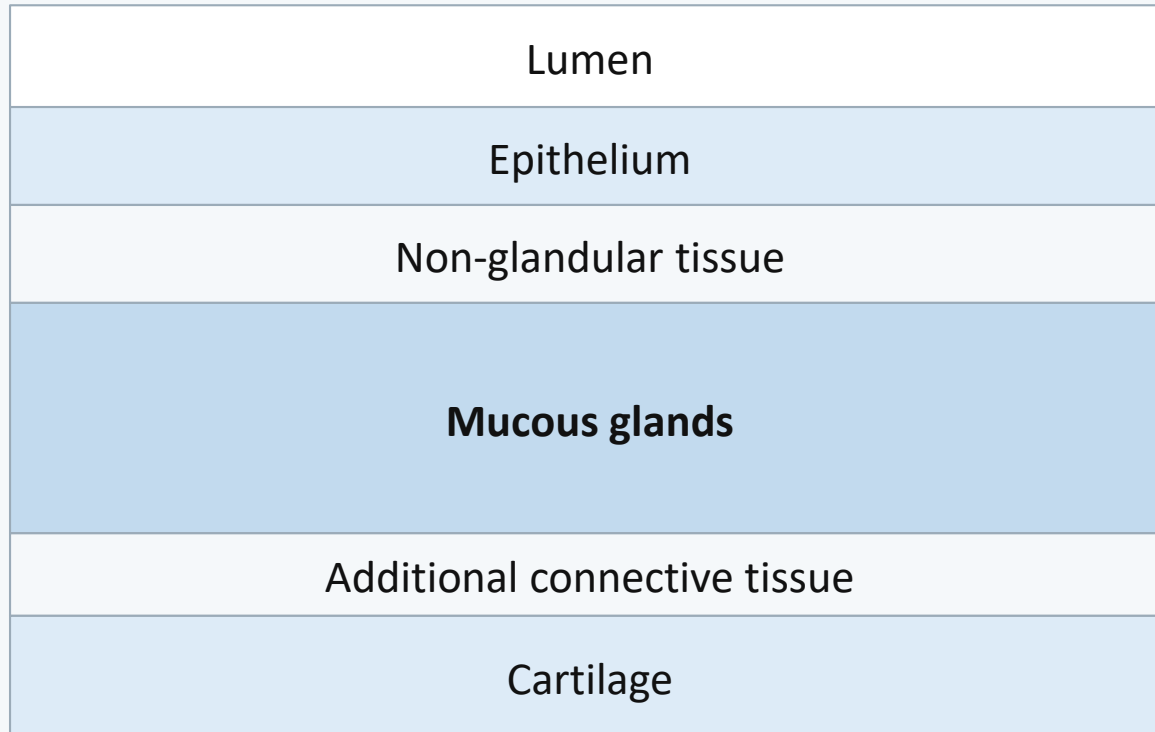
Gross bronchitis features congested, mucus-filled airways

- Airway mucosa can be hyperemic, swollen, and edematous.
- Mucinous or mucopurulent secretions are often excessive.
- Thick casts may fill bronchi and bronchioles.
- Gross appearances reflect mucosal inflammation and secretory excess.

Microscopy shows chronic bronchial wall remodeling

- Chronic inflammatory infiltrates are rich in lymphocytes and macrophages.
- Bronchiolar smooth muscle may be hypertrophied.
- Extracellular matrix deposition and peribronchiolar fibrosis thicken walls.
- Goblet cells and mucus-secreting glands are increased.

Reid index quantifies the mucous gland layer



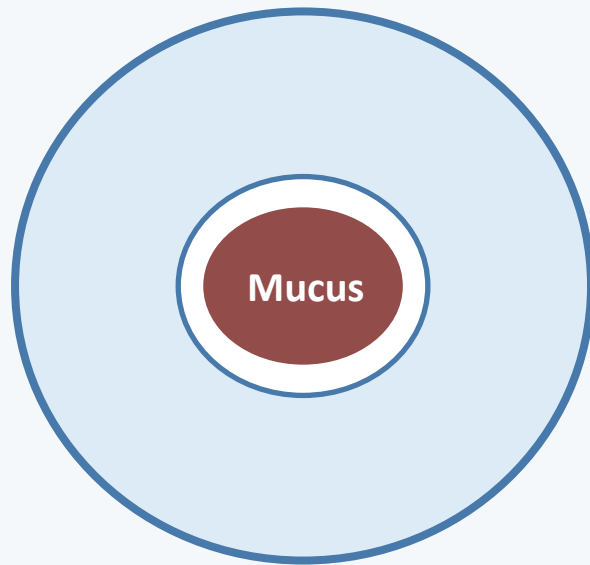
Gland thickness

**Reid index = gland-layer
thickness / wall thickness**

- Measured between bronchial epithelium and cartilage.
- A value around 0.4 is described as normal in the source.
- In chronic bronchitis the index tends to rise with severity and duration.

Mucus and fibrosis can close bronchiolar lumina

Small-airway cross-section — schematic



Why airflow changes

- Intraluminal mucus physically reduces available airway caliber.
- Peribronchial inflammation and fibrosis thicken the wall.
- Advanced remodeling can culminate in luminal obliteration.

Tobacco injury may produce epithelial atypia

- Bronchial epithelium may undergo squamous metaplasia.
- Dysplasia can accompany chronic exposure to mutagenic smoke constituents.
- Metaplasia and dysplasia are distinct from mucous gland hyperplasia.
- These epithelial changes reflect chronic irritation and mutagenic injury.

Emphysema and bronchitis obstruct by different routes

Mechanism	Emphysema	Chronic bronchitis
Principal structure	Alveolar septa / small-airway supports	Bronchi and bronchioles
Dominant change	Tissue destruction and recoil loss	Mucus, inflammation, fibrosis
Major flow effect	Dynamic expiratory collapse	Luminal narrowing and plugging
Diagnostic focus	Acinar destruction	Secretory and airway-wall changes

COPD usually begins insidiously

- Exercise-related dyspnea develops slowly and increases over time.
- Chronic cough may be mild initially but becomes more prominent.
- Sputum production varies with the bronchitic component.
- Infectious exacerbations may be the first striking clinical presentation.

Symptoms fluctuate within persistent structural disease

- COPD symptoms may wax and wane despite lasting structural abnormalities.
- Symptoms can be more pronounced in the morning.
- Superimposed infections can produce marked episodic deterioration.
- A wheeze during exacerbation does not by itself establish asthma.

Emphysema-dominant COPD has recognizable physiology

Characteristic findings

- Prominent exertional dyspnea
- Barrel-shaped, hyperinflated chest
- Prolonged expiration; Pursed-lip breathing

Functional correlations

- Marked overdistension of the lungs
- Reduced pulmonary diffusion capacity
- Resting blood gases may remain relatively preserved

Bronchitis-dominant COPD emphasizes secretions

Common presentation

- Persistent sputum-producing cough
- Frequent infective exacerbations
- Airway resistance increased

Advanced gas-exchange consequences

- Hypoxemia and hypercapnia
- Cyanosis in severe cases
- Pulmonary hypertension and cor pulmonale

The classic COPD phenotypes are extremes, not categories

- Historical descriptions contrast emphysema-dominant and bronchitis-dominant patients.
- Most patients have mixed emphysematous and bronchitic changes.
- The relative components influence symptoms, gas exchange, and imaging.
- Avoid treating classical labels as mutually exclusive modern diagnoses.

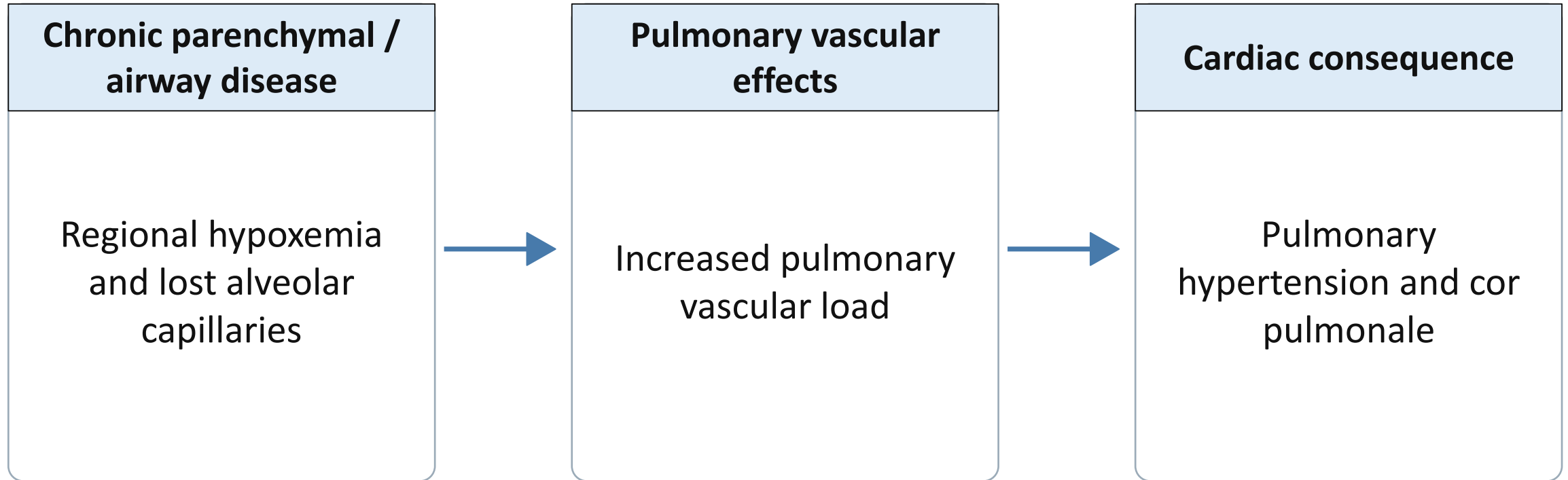
Airflow obstruction is not specific to COPD

Disease	Leading lesion	Helpful clinical distinction
COPD	Chronic bronchiolar and/or acinar damage	Persistent limitation; exposure-related
Asthma	Bronchospasm, inflammatory response	Often reversible/episodic component
Bronchiectasis	Permanent bronchial dilation and scarring	Chronic purulent sputum; infection

Asthma and COPD can have overlapping reversibility

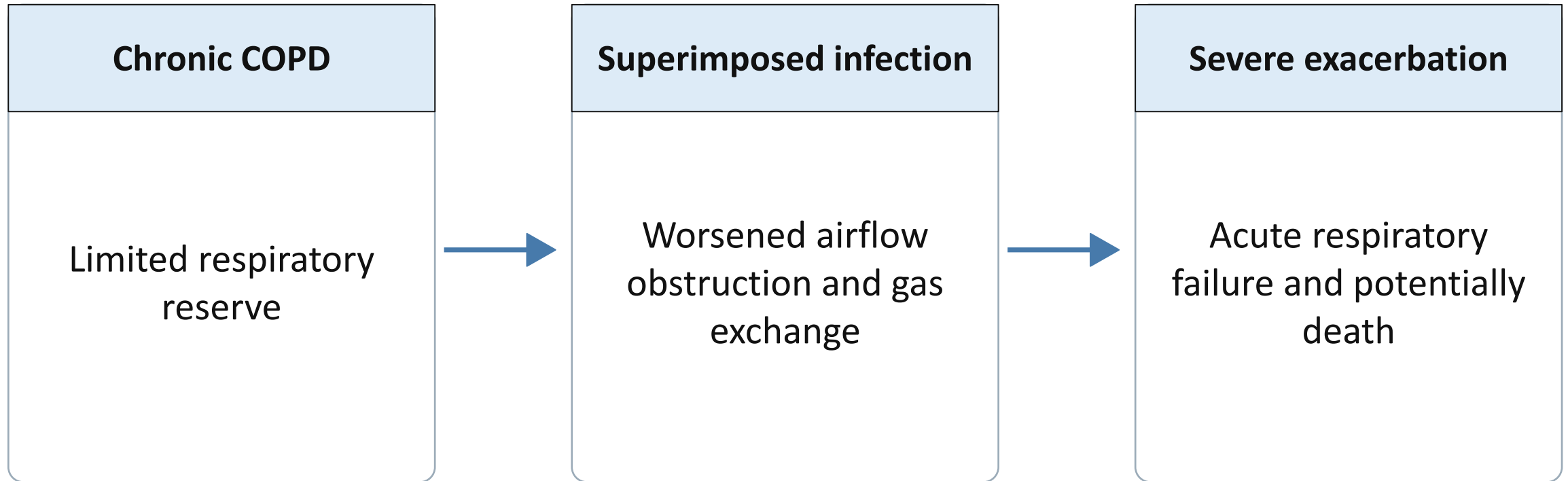
- Asthma is classically distinguished by reversible bronchospasm.
- Some patients with asthma develop a persistent, less reversible component.
- Some patients with typical COPD show a partially reversible component.
- Interpret airflow physiology alongside exposure history and structural disease.

Hypoxemia and vascular-bed loss promote pulmonary hypertension



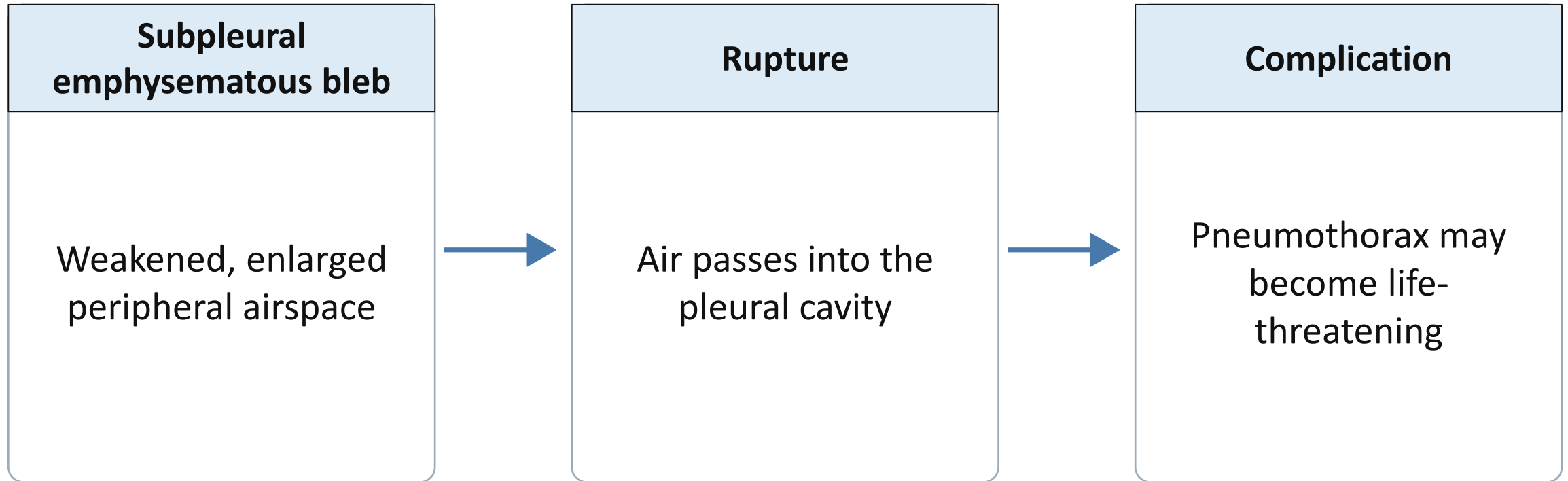
Causal sequence — schematic

Acute infection can precipitate respiratory failure



Causal sequence — schematic

Rupture of a subpleural bleb causes pneumothorax



Causal sequence — schematic

Mucus plugs have clinical as well as mechanical significance

- Mucus plugs may block bronchiolar lumina and worsen airflow limitation.
- Retention of secretions contributes to infection susceptibility.
- The source notes an association between mucus plugging and all-cause mortality.
- An association does not establish that a mucus plug independently causes death.

Intervention targets exposure, airflow and complications

- Smoking cessation and prevention of inhalational exposure address upstream injury.
- Bronchodilators, selected inhaled anti-inflammatory treatment, and oxygen therapy.
- Exacerbations may require antimicrobial and supportive treatment.
- Selected patients may undergo bullectomy, lung-volume reduction, or transplantation.

Prevention is central because structural destruction persists

- Emphysematous alveolar-wall loss is anatomically irreversible.
- Fixed bronchiolar fibrosis is not equivalent to transient bronchospasm.
- Avoiding smoke and other harmful particles may limit ongoing injury.
- Early intervention is therefore mechanistically important.

Case: Progressive dyspnea and apical injury

Clinical scenario

A long-standing smoker reports increasing exercise intolerance. Imaging describes hyperinflation. A lung specimen shows predominant injury around respiratory bronchioles in upper-lobe acini.

Question Which emphysema pattern best matches the localization, and what accounts for expiratory limitation?

Interpretation

Centriacinar emphysema. Septal elastin loss reduces radial traction, allowing small-airway collapse during expiration.

Case: Diffuse basilar acinar enlargement

Clinical scenario

A younger patient develops severe emphysema with lower-zone predominance. Histology shows diffuse enlargement from respiratory bronchioles through distal alveoli.

Question Which etiologic susceptibility is especially important, and why?

Interpretation

α_1 -Antitrypsin deficiency. Reduced elastase inhibition permits excessive proteolysis; Smoking further increases risk.

Case: Productive cough and thickened bronchi

Clinical scenario

A patient has productive cough for four months each year over three consecutive years. Large airways show enlarged submucosal glands; Bronchioles contain plugs and peribronchiolar fibrosis.

Question Does the clinical definition of chronic bronchitis apply, and which lesion causes fixed obstruction?

Interpretation

Yes, after excluding another cause. Fibrotic remodeling of small bronchioles causes a fixed component, supplemented by mucus plugging.

Case: Sudden deterioration in advanced COPD

Clinical scenario

A person with advanced emphysema develops acute pleuritic symptoms and abrupt breathlessness. Known peripheral airspaces include large subpleural blebs.

Question What mechanical complication should be considered?

Interpretation

Rupture of a subpleural bleb can produce pneumothorax.

Integrated pathology: Where each symptom originates

Finding	Dominant structural/pathophysiologic basis
Progressive dyspnea	Air trapping, expiratory collapse, reduced gas exchange
Chronic sputum	Large-airway gland hypertrophy and goblet-cell hyperplasia
Low diffusion capacity	Alveolar septal and capillary-bed loss
Cor pulmonale	Pulmonary hypertension with chronic gas-exchange disease

Final synthesis: COPD is two injuries plus small-airway disease

Alveoli

Emphysema destroys septa, capillaries and elastic support.

Bronchi

Chronic bronchitis increases mucus secretion and produces cough.

Bronchioles

Inflammation, mucus and fibrosis narrow distal airways.

Patient

These lesions combine to cause persistent airflow limitation and complications.

Primary reference and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 15, “The Lung,” printed pp. 617–622.
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