ASTHMA AND COPD
ARE THEY A SPECTRUM OF SAME DISEASE?

PATHOPHYSIOLOGY

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The Overlap Between Asthma and COPD

COPD=chronic obstructive pulmonary disease.

Adapted from American Thoracic Society. *Am J Respir Crit Care Med.* 1995;152(5 pt 2):S77-S121.
Soriano JB, et al. *Chest.* 2003;124:474-481.
Jeffery PK. *Am J Respir Crit Care Med.* 2001;152:S28-S38.

The Dutch Hypothesis

- **Various forms of airway obstruction are different expressions of a single disease**
  - Chronic nonspecific lung disease (CNSLD)
- **Host and environmental factors play a role in pathogenesis**
  - Host factors: atopy and AHR
    - Other endogenous factors: sex and age
  - Exogenous factors: allergens, viral infections, smoking (pollutants)
- **Diffuse airway obstruction = common pathophysiologic characteristic**

Orie et al. Bronchitis II Second International Symposium. Assen, Netherlands: Royal Van Gorcum; 1964:398-99

The British Hypothesis

- **Asthma and COPD are distinct entities caused by different mechanisms**
  - Differences in inflammation
  - Airway remodeling vs alveolar remodeling
  - Epidemiology

What Is Asthma? What Is COPD?

Asthma[1]

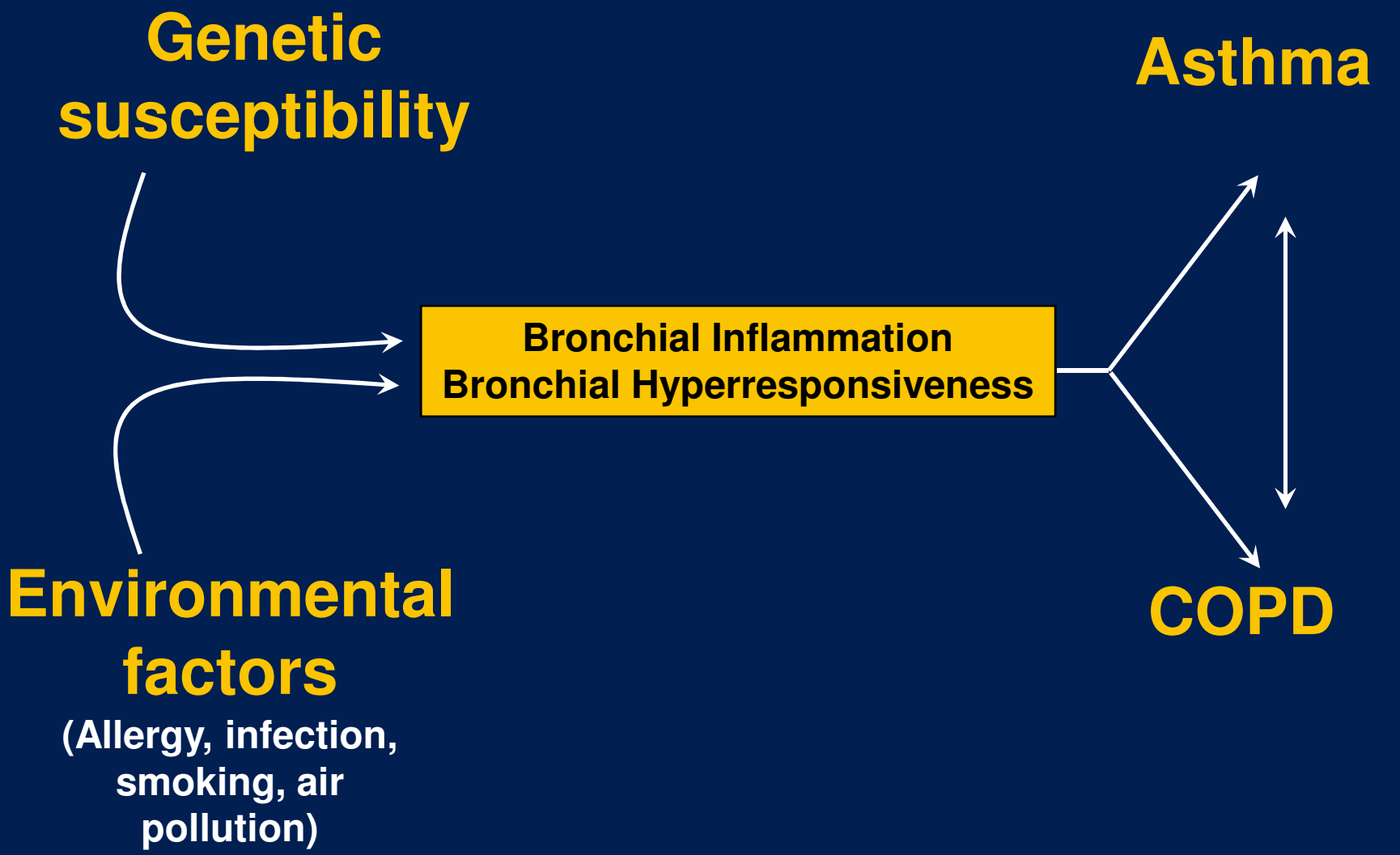
- A **chronic inflammatory disorder** of the airways in which many cells and factors play a role
- Inflammation results in
  - **Recurrent symptoms**
  - Variable **airflow obstruction** that is mostly **reversible**
  - Increase in existing **bronchial hyperresponsiveness**

COPD[2]

- A **preventable and treatable** disease
- Associated with significant **extrapulmonary effects** and important **comorbid conditions**
- Characterized by airflow limitation that is
  - **Not fully reversible**
  - **Usually progressive**
  - Associated with an **abnormal inflammatory response** to noxious particles or gases

1. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 29, 2007.
2. Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989. Accessed November 21, 2008.

Interactions Between Asthma and COPD



Genetic Associations that Suggest a Common Origin in COPD & Asthma

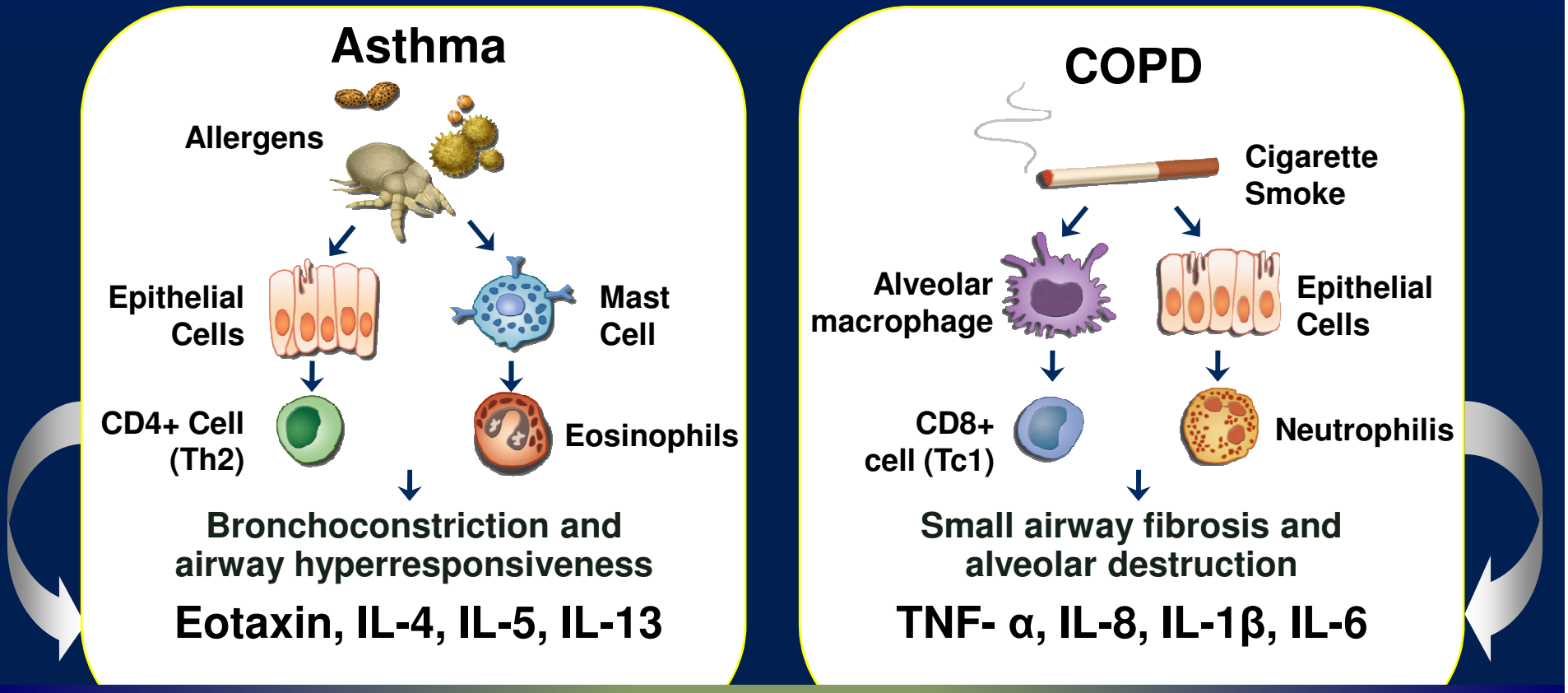
- IgE
- BHR
- Rate of FEV1 decline
- Airway thickness

IL-13

ADAM33

van der Pouw Kraan TC. Genes Immun 1999;61–65 Howard TD. Am J Respir Cell Mol Biol 2001;377–384 van der Pouw Kraan TC. Genes Immun 2002;436–439 Ohar JA [abstract]. Eur Respir J 2001;P3588 Simpson A. Am J Resp Crit Care Med 2005;55-60 Holgate ST. Thorax 2005;466-69 van Diemen CC. Am J Resp Crit Care Med 2005;329-33 Jongepier H. Clin Exp Allergy 2004;757-60

Inflammatory Cascade Differs Between Asthma and COPD

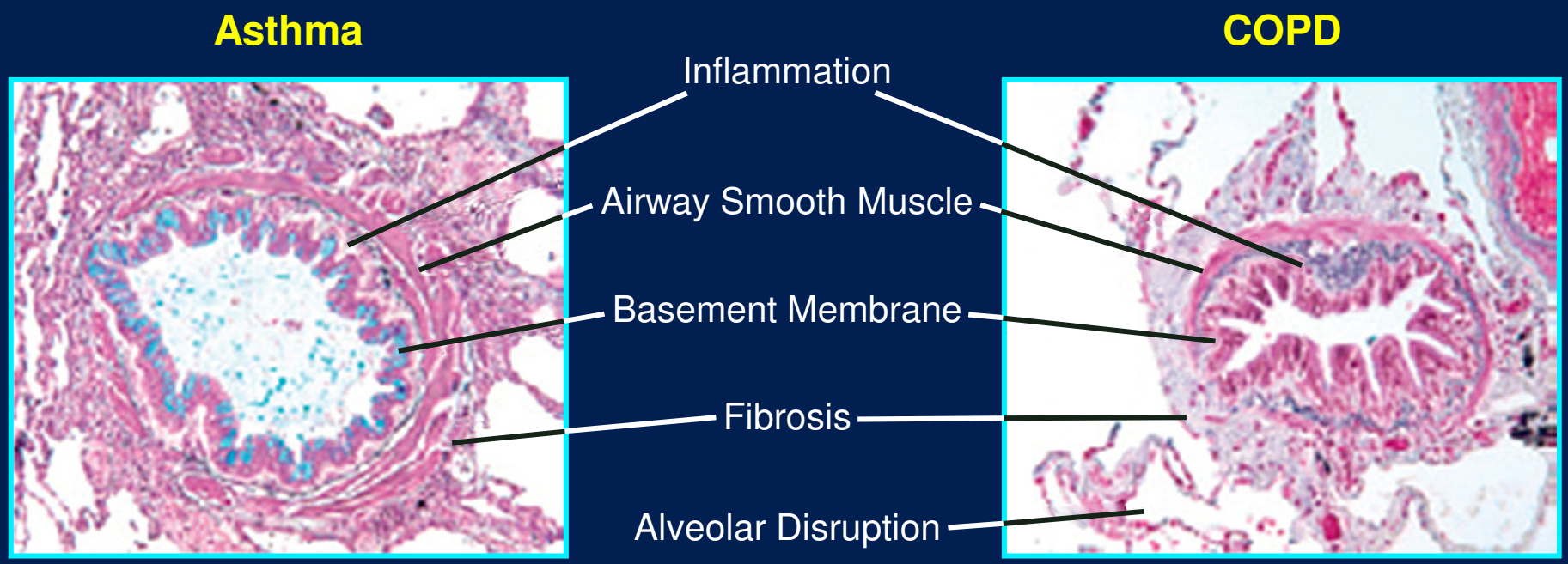


IL = interleukin; TNF = tumor necrosis factor.

Adapted from Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989. Accessed November 21, 2008.

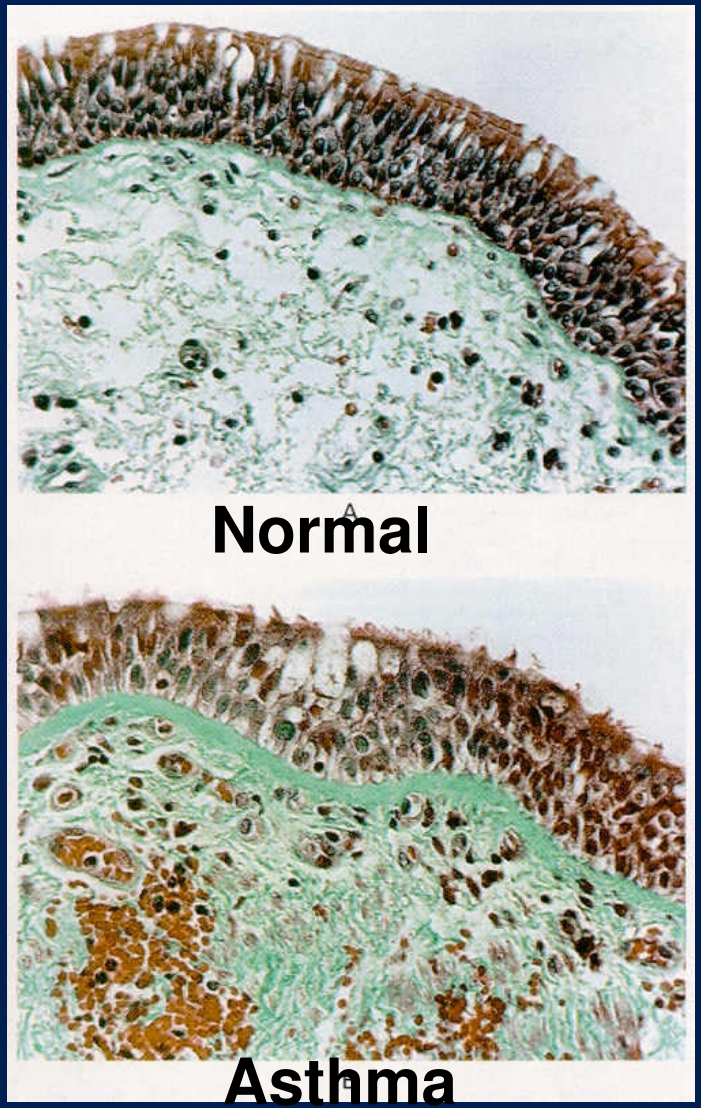
Pathophysiological Changes in Asthma and COPD

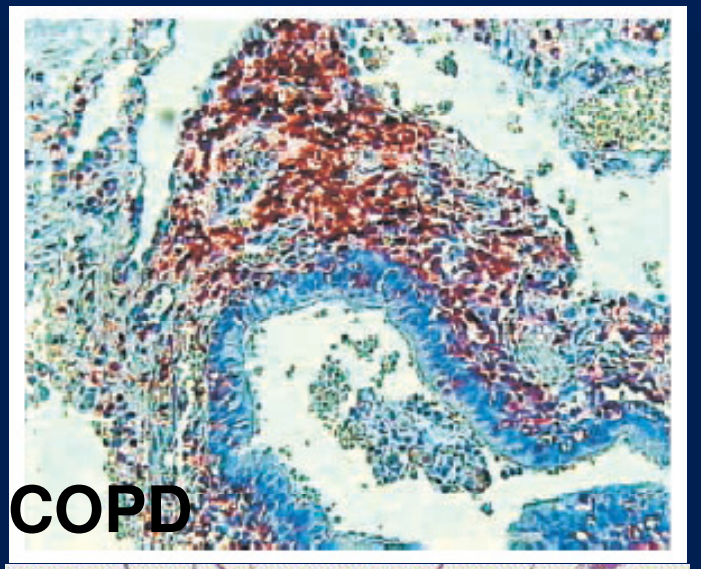
Contrasting Histopathology of Asthma and COPD

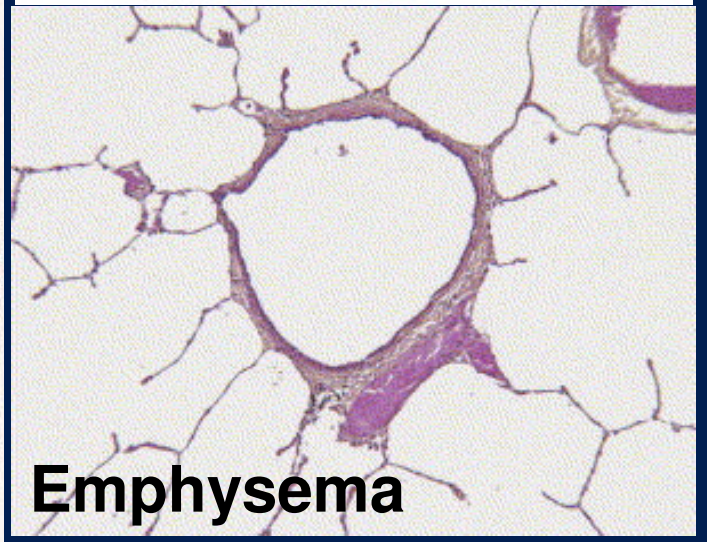


Adapted with permission from Barnes PJ. *Nature Rev Immunol.* 2008;8:183-192.

Structural Changes in Asthma and COPD







Inflammatory Phenotypes in Asthma vs. COPD

Asthma

- Eosinophils and mast cells
- Neutrophils (severe)
- CD 4+ T_H2 cells
- LTC4, D4, E4
- Cytokines
  - IL 4, IL 5, IL 13
  - RANTES, eotaxins, MCP-1

COPD

- Macrophages and neutrophils
- Eosinophils (exacerbations)
- CD 8+ T cells,
- LTB4, Interferon γ
- Cytokines
  - IL 8, IL-1
  - TNF-α

Fabbri, et al. Am J Respir Crit Care Med 2005; Vol 171: 686-698,

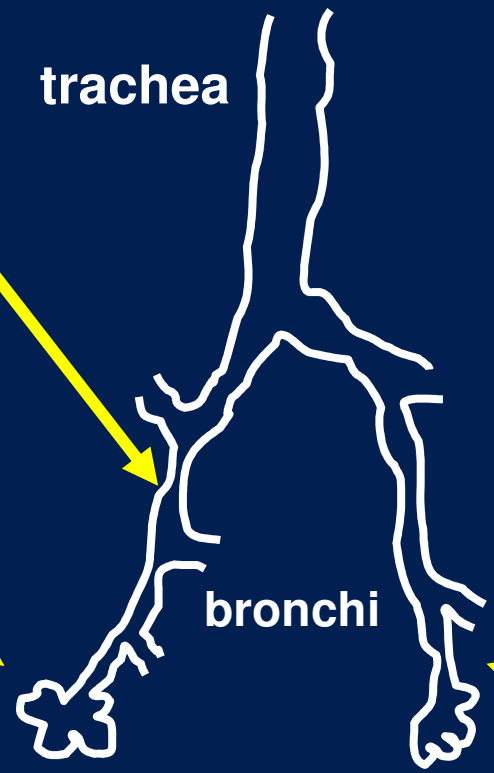
Sutherland. J Allergy Clin Immunol 2004; Vol 114 (4): 715-724

Mauad T, Dolhnikoff M. Curr Opin Pulm Med 2008; 14: 31 - 38

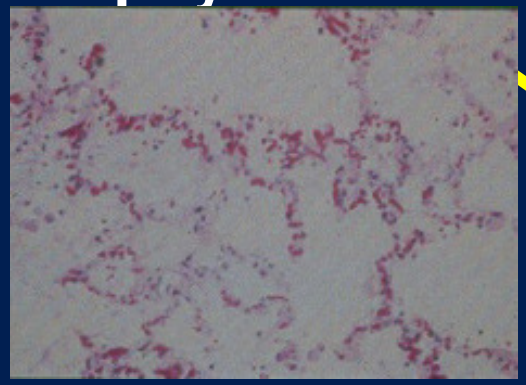
Site of Airway Obstruction in Asthma and COPD:

Asthma in Medium Sized Airways, COPD in the Small Airways

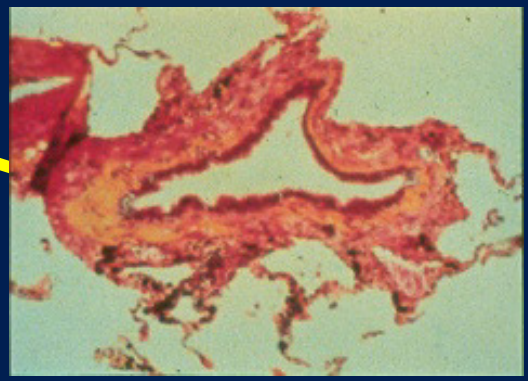
Asthma



Emphysema



Chronic Bronchitis



However,

- **Asthma is often progressive process with partially reversible component that can involve small peripheral airways**
- **CT scans demonstrating increased airway wall thickness like COPD**
  - Volume of lung in density range c/w emphysema: 5% in mild and 23% severe asthmatics

Sciurba FC Chest 2004:126:17S

Inflammation- Similarities

1. **Alveolar inflammation demonstrated in asthma ***
2. **Severe asthma- BAL with neutrophils ****
3. **COPD: tissues eosinophils during exacerbations**
   - Pts with eosinophils have better response to steroids ***

* Kraft M.Am J Respir Crit Care.Med 1996:154:1505

**Wenzel S Am J Respir Crit Care Med:1999:160:1001

***Chanez P Am J Respir Crit Care Med 1997:155:1529

Pathophysiology of Asthma

- **Inflammation in asthma is characterized by eosinophils, CD4+ T-lymphocytes, macrophages and mast cells**
- **Prominent pathological features of asthma include:**
  - airway hyperresponsiveness
  - episodic bronchospasm in the large airways
  - vasodilation and angiogenesis
- **Severe asthma can be classified into two subtypes: eosinophil (+) and eosinophil (-)**
- **Neutrophils are found in severe, corticosteroid-dependent asthma**

Pathophysiology of COPD

- **COPD is a disease characterized by inflammation in:**
  - airways
  - systemic circulation
- **COPD is a systemic disease that can cause weight loss and muscle weakness**
- **Prominent pathological features of COPD include:**
  - mucus hypersecretion
  - small airway fibrosis
  - alveolar destruction
  - extrapulmonary effects

Pulmonary Function

- **Classically**
  - Asthma reversible airway obstruction
  - COPD partially reversible

Boulet L Can Respir J 1998:5:270
Fabbri LM Am J Respir Crit Care Med 2003:167:418
Magnussen H. Clin Exp Allergy 1998 28:187

Spirometry Is Essential in Both Asthma and COPD

Asthma

- **Necessary to establish a diagnosis[1]**
- **Low FEV_1 is strongly predictive of risk for exacerbations[1,2]**
- **Important in assessing control[1]**

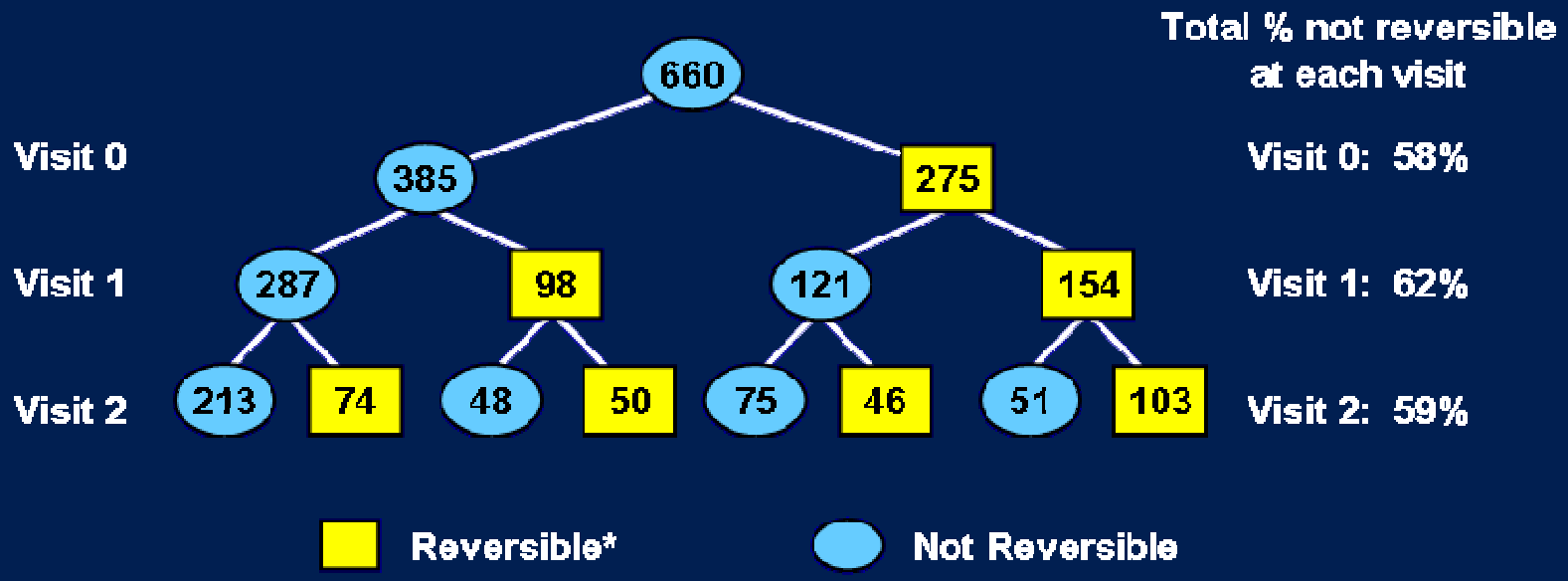
COPD

- **Essential for diagnosis[3]**
- **Used to determine severity, which is linked to**
  - Treatment decisions
  - Prognosis

1. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
2. Fuhlbrigge AL et al. *J Allergy Clin Immunol*. 2001;107:61-67.
3. Global Initiative for Chronic Obstructive Lung Disease. http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989.

Acute Bronchodilator Response Does not Differentiate Between Asthma and COPD:

Changes in Responder Classification After Albuterol and Ipatroprium Bromide



Numbers in circles refer to the total classified as positive responders at that visit and those in squares are the nonresponders on the same occasion.

* Reversible defined as ≥ 12% and 200-mL increase in FEV_1 following 4 puffs (360 mcg) of albuterol.

Calverley et al. *Thorax*. 2003;58:659-664.

Physiologic Differences Between Asthma and COPD

	Asthma	COPD
Elastic recoil	Normal	Decreased
Diffusion capacity (DL_{CO})	Normal or Increased	Decreased
Lung volume	Normal	Hyperinflation
Bronchodilator response	Flow-dominant	Volume-dominant

Sciurba FC. *Chest*. 2004;126:117S-124S.

Lung Volumes

- **Nonreversible COPD pts 83% had improvement in lung volumes**
  - Those with most severe disease > improvement
- **Asthma study 15% reversibility in lung volumes not FEV-1**

O'Donnel C Eur Respir J 2001:18:914

Smith HR Chest 1992:101:1577

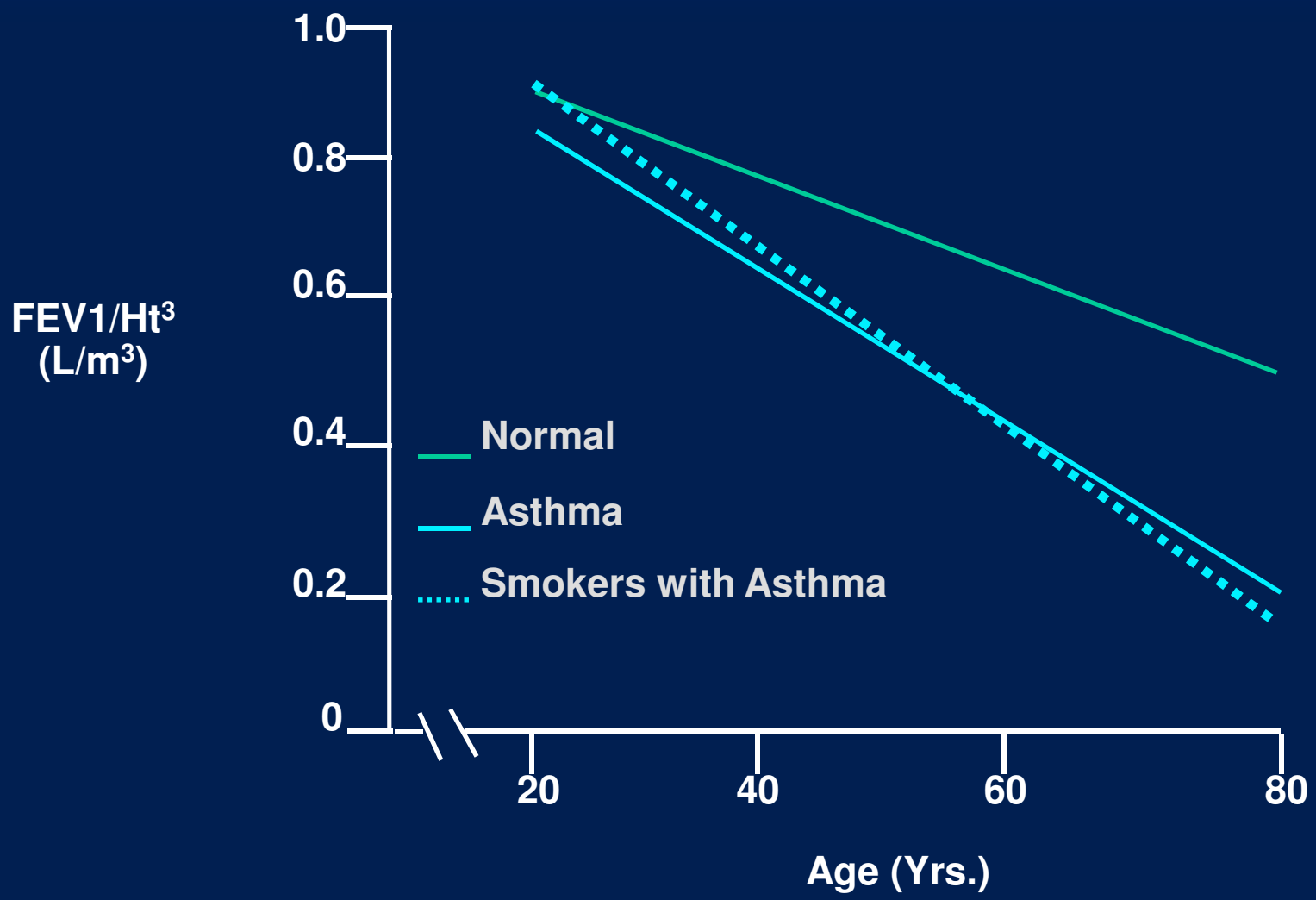
Airway Hyperresponsiveness

- **Positive Methacholine occurs in nearly all asthmatics, < 5% normals**
- **63% of men and 87% of women with COPD show AHR with < 25 mg/ml of metacholine**
  - Lower PFT'S associated with >AHR, decline in lung function and mortality
  - Smoking cessation has positive effect on AHR and improves FEV1 greater in those with AHR

Tashkin D An J Crit Care Med 1996:153:1802

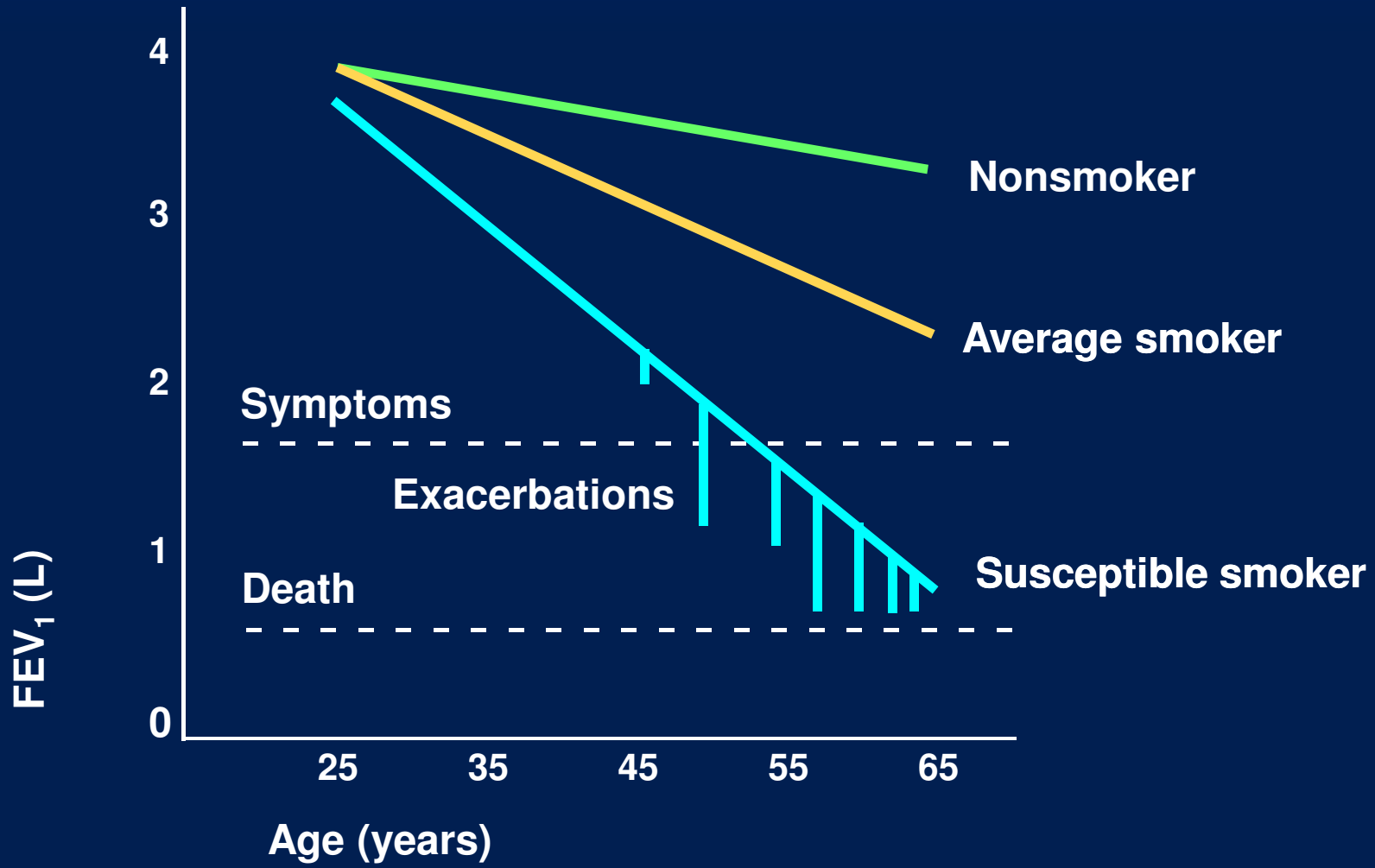
Wise RA et al. Chest 2003; 12: 4:449- 458

Natural History of Asthma



Peat JK. Eur J Respir Dis. 1987

Natural History of COPD



Mannino DM. *Chest.* 2002;121:121S-126S.

Fletcher and Peto, 1977

Physiologic Differences

Asthma

- Normal DLCO
- Normal lung volume
- Normal elastic recoil
- Flow dominant BD response

COPD

- Abnormal DLCO
- Hyperinflation
- Decreased elastic recoil
- Volume dominant BD response

Sciurba FC, CHEST 2004;117S-124S

Asthma Imitates Mild/Moderate COPD With Increasing Age

Asthma in young age

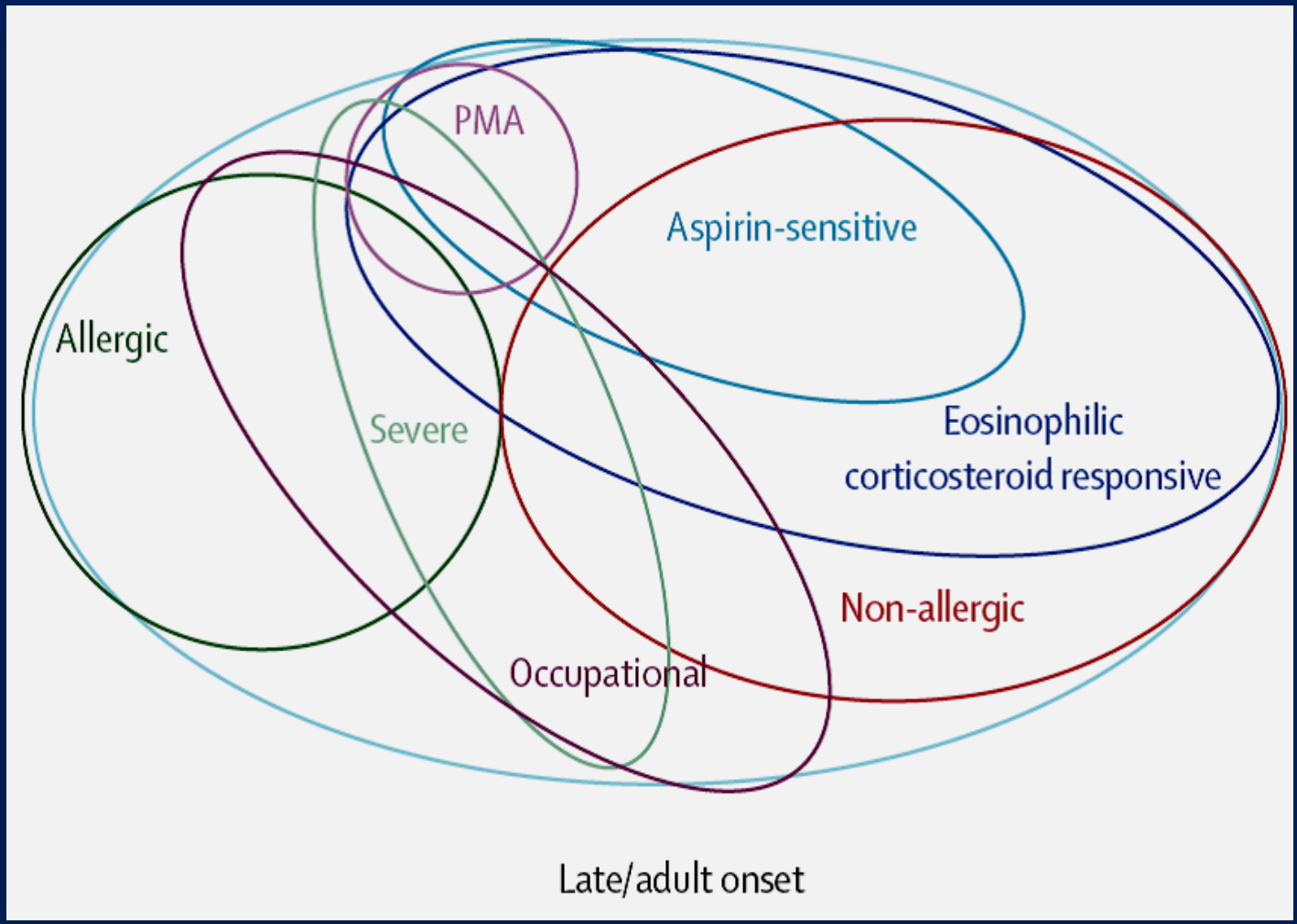
- ±80% extrinsic
- Often normal FEV_1
- Often reversible obstruction
- Remission likely (60%–70% patients)

Asthma in old age

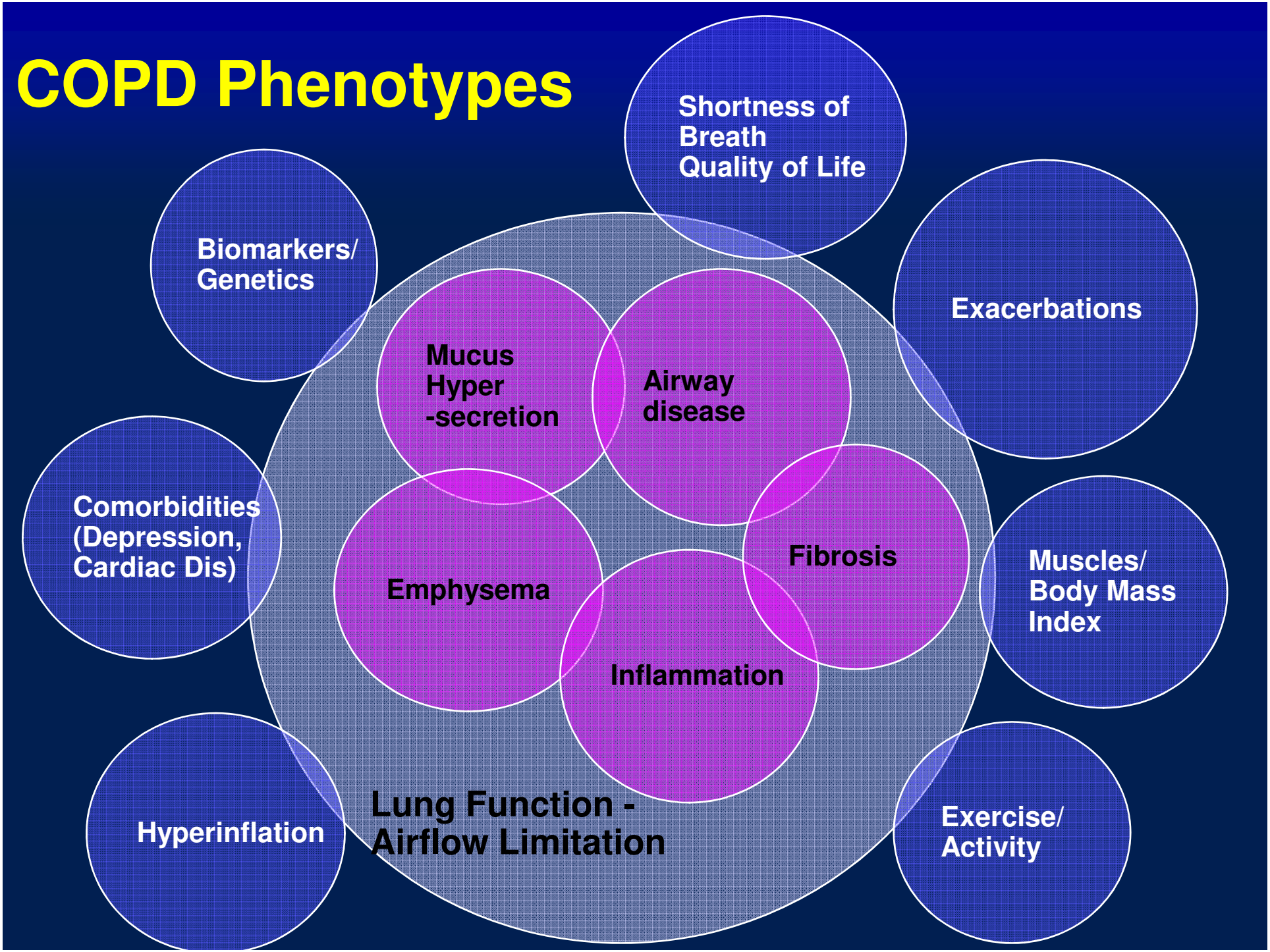
- Mainly intrinsic
- Often reduced FEV_1 (60% of patients)
- Often less reversible obstruction
- Remission unlikely (20% patients)

Braman SS. *Clin Geriatr Med.* 2003;19:57-75.

Asthma: Definition of Adult Phenotypes

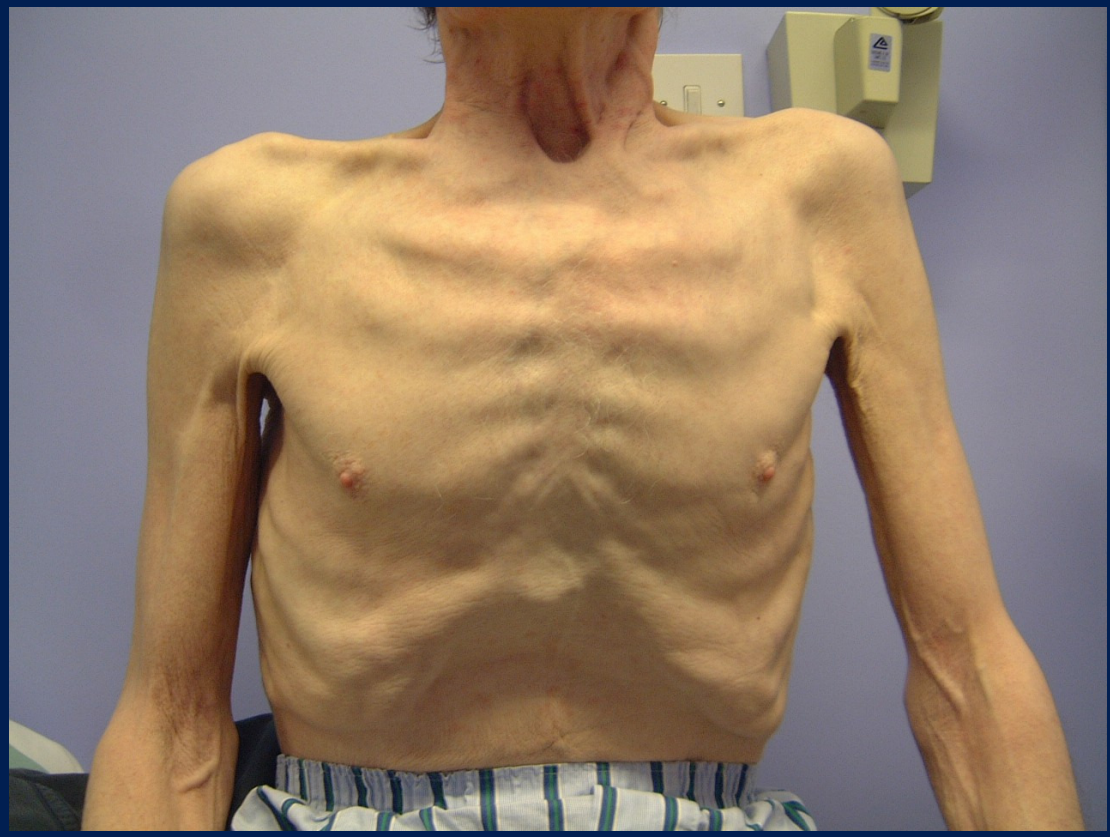


Wenzel SE. Lancet 2006;368:804-813

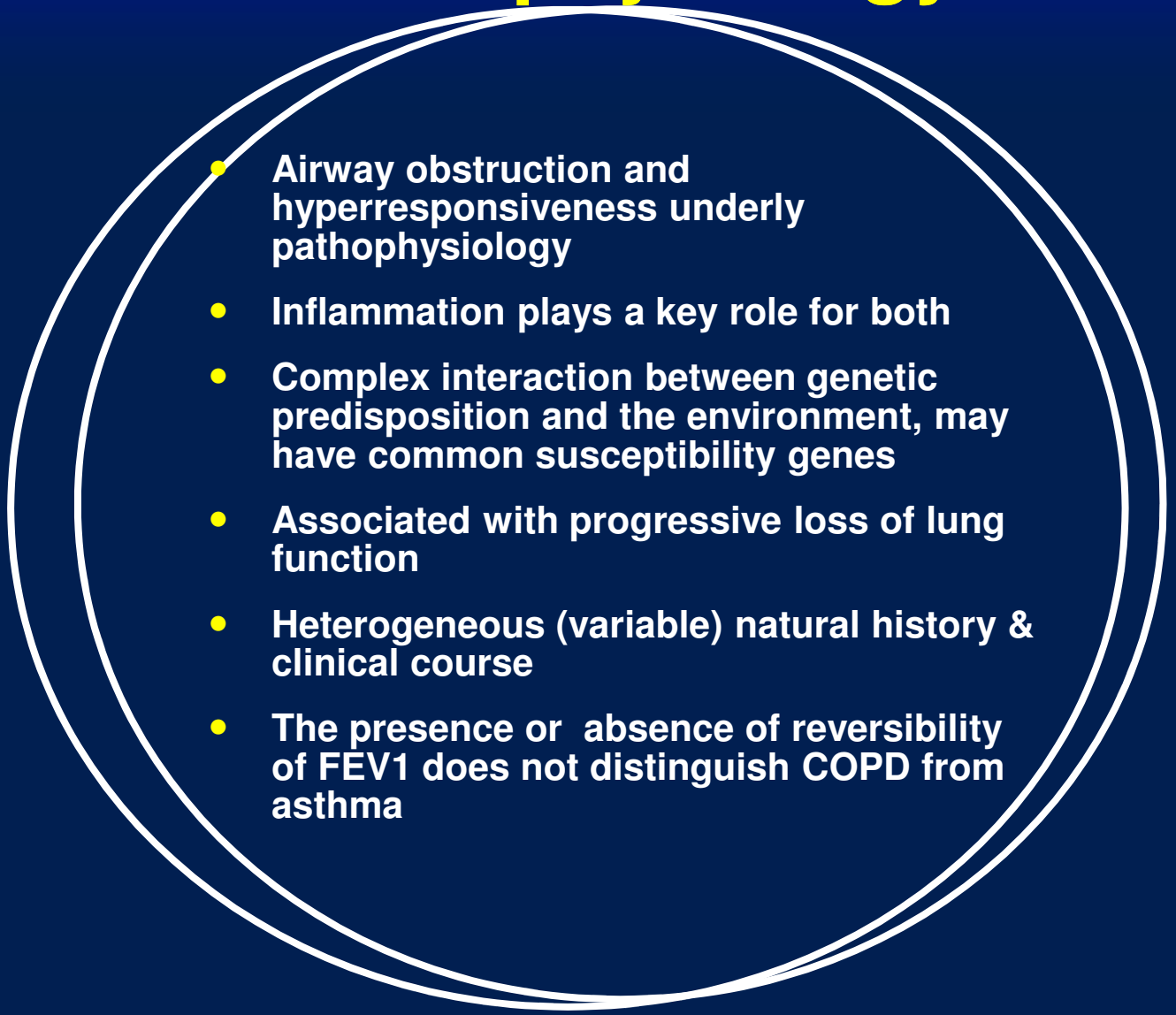

COPD Phenotypes
Shortness of Breath Quality of Life
Biomarkers/ Genetics
Exacerbations
Mucus Hyper -secretion
Airway disease
Comorbidities (Depression, Cardiac Dis)
Fibrosis
Muscles/ Body Mass Index
Emphysema
Inflammation
Hyperinflation
Lung Function - Airflow Limitation
Exercise/ Activity

Systemic Consequences of COPD

- Weight loss with decreased fat-free mass
- Muscle wasting and weakness
- Cardiac co-morbidity
- Other systemic effects:
  - osteoporosis
  - anemia
  - depression



Similarities Between Asthma and COPD Pathophysiology



Differences Between Asthma and COPD Pathophysiology

Asthma

- Usually intermittent airflow obstruction but sometimes has a less reversible obstruction
- High levels of bronchial responsiveness
- Cellular inflammation with eosinophils, mast cells, T lymphocytes, in severe disease neutrophils
- Broad inflammatory mediator responses
- Airway remodeling (epithelial injury and fibrosis)

COPD

- Progressive airflow obstruction
- Most patients have increased bronchial responsiveness
- Cellular inflammation including neutrophils, macrophages, eosinophils and mast cells may occur in exacerbations
- Cytokine, chemokine, protease responses
- Emphysema (lung destruction) frequent
- Systemic consequences