COPD--Changing Concepts of Pathogenesis and New Ideas for Old Treatments

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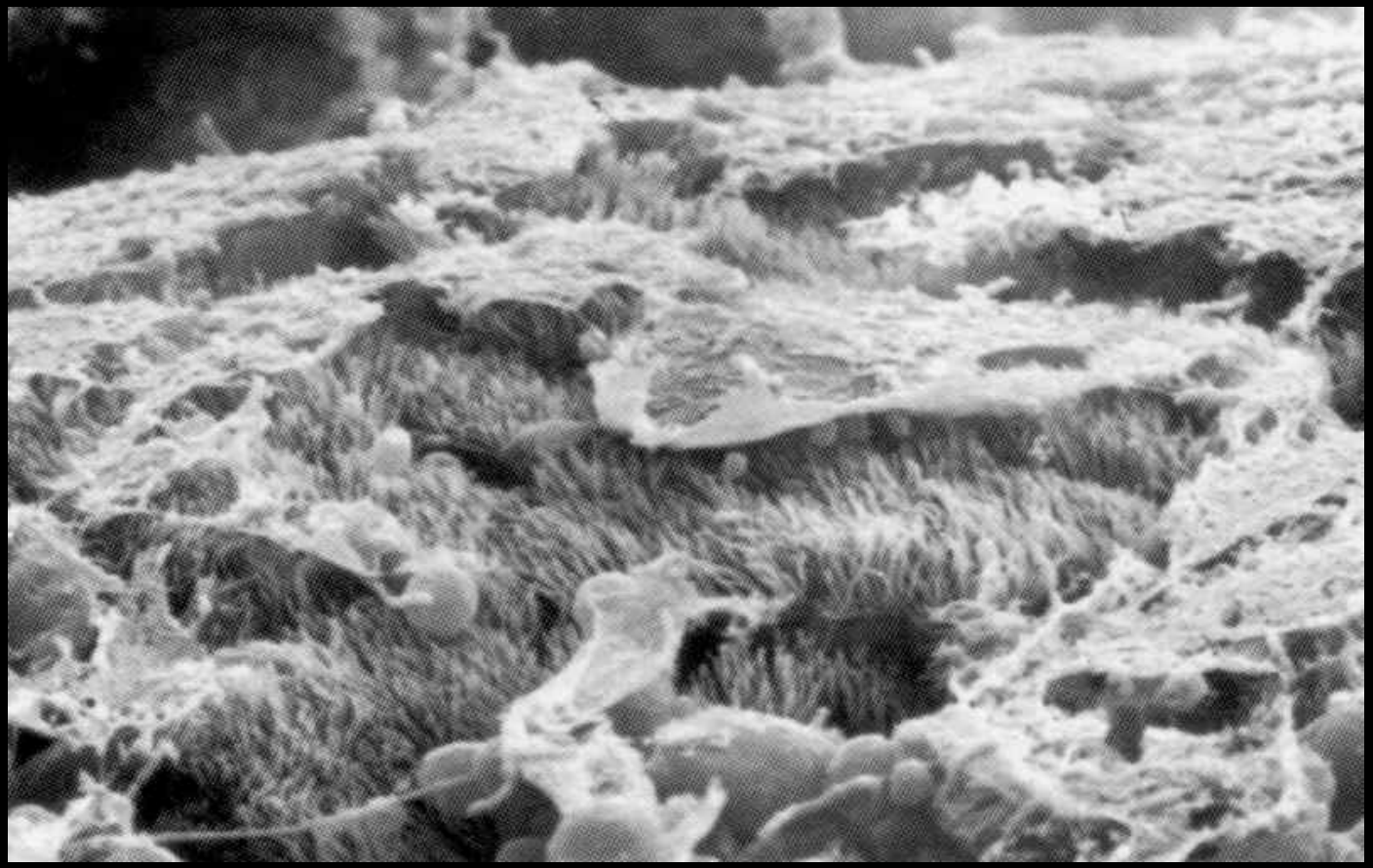
Chronic obstructive pulmonary disease (COPD)

"…a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible."

Scope of the Problem

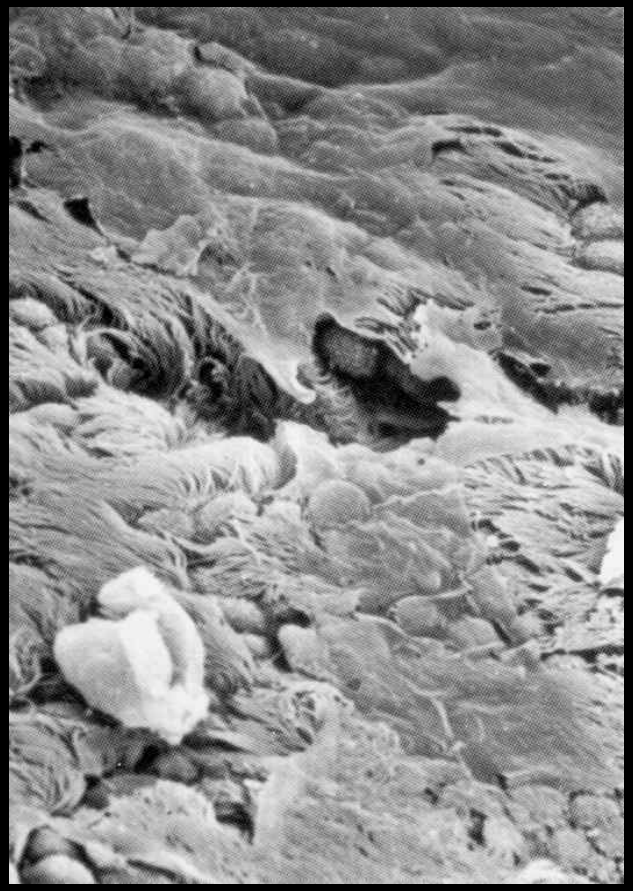
- COPD is incredibly common; estimates vary but likely > 6% population
- COPD is the fourth leading cause of death (since 1994). Estimated to be the third leading cause of death by 2020.
- In the US, direct costs of COPD are ~$29 billion and indirect costs are ~ $20 billion.

Normal Airway



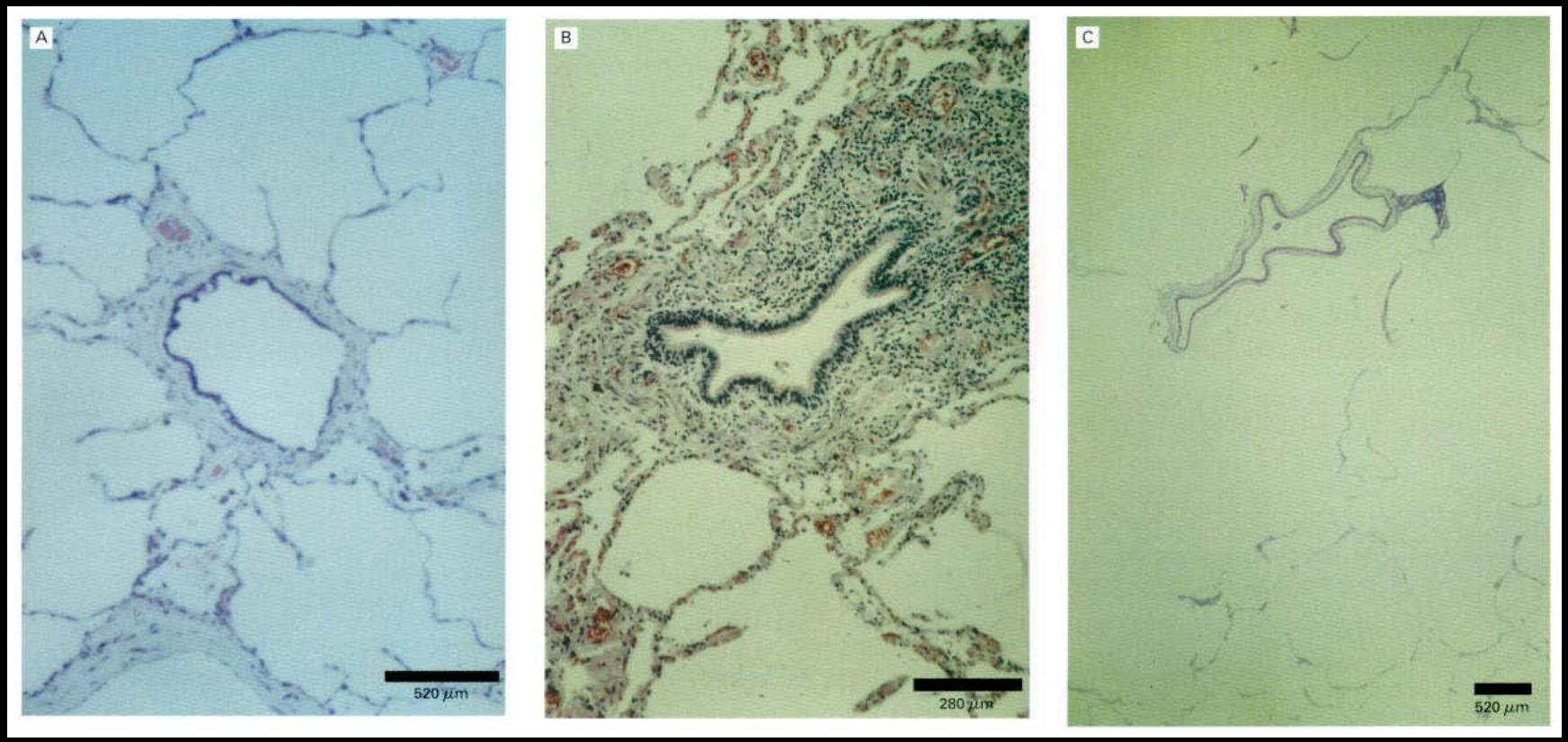
Jeffery PK. Thorax 53:129; 1998

Bronchial Surface after Subacute Exposure to Cigarette Smoke



Jeffery PK. Thorax 53:129; 1998

Histopathological Features of COPD



Barnes P. *NEJM*. 343(4):269-280, 2000

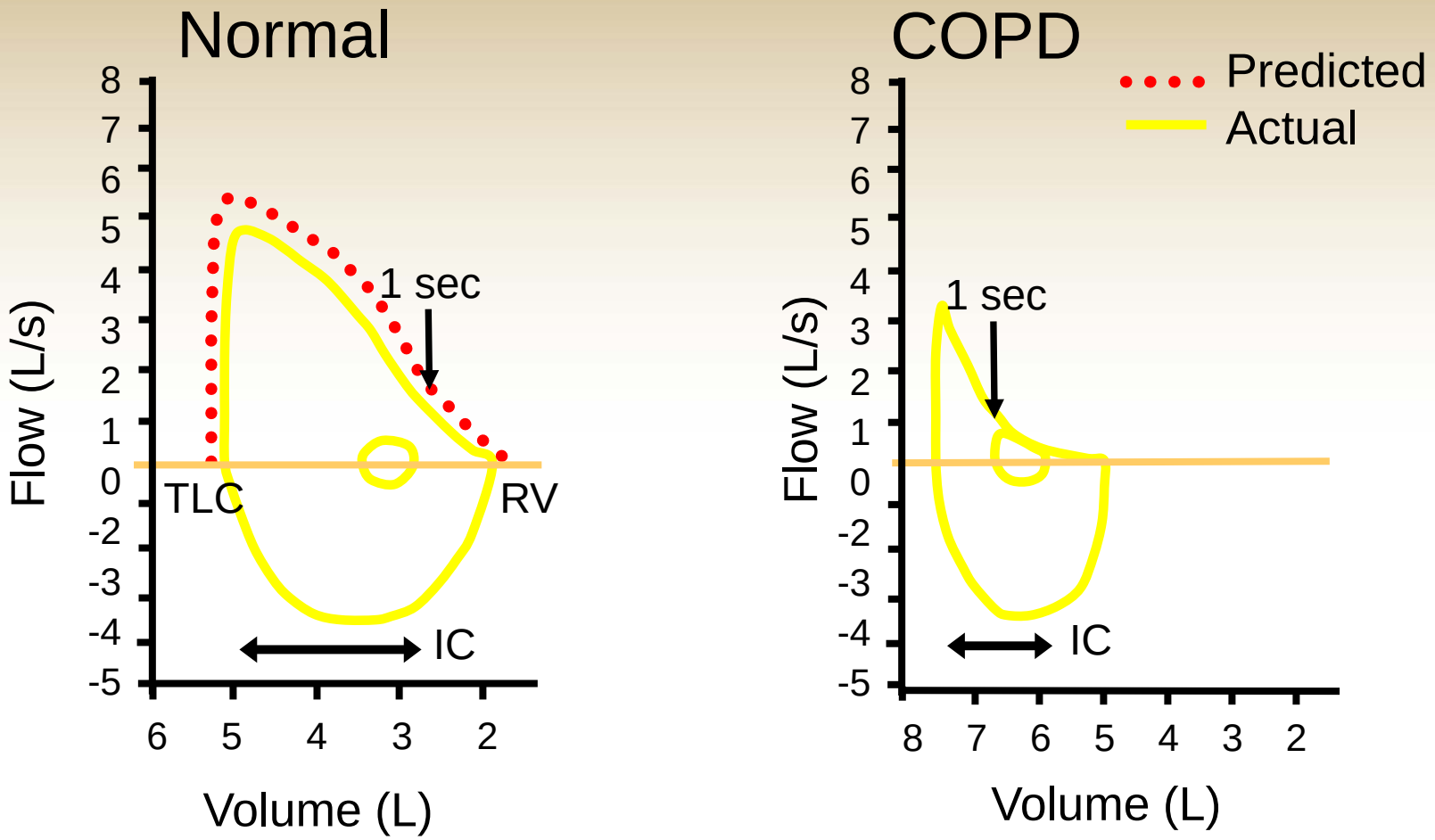
Clinical Features of COPD

- Smoker (usually > 1 pack/day for 20 years)
- Symptoms (begin in the fifth or sixth decade)
  - Cough
    - worse in am
    - sputum
      - generally mucoid and < 60 ml/day
      - purulent during exacerbation
  - Dyspnea
    - insidious in onset
    - worse with exertion
  - Wheezing

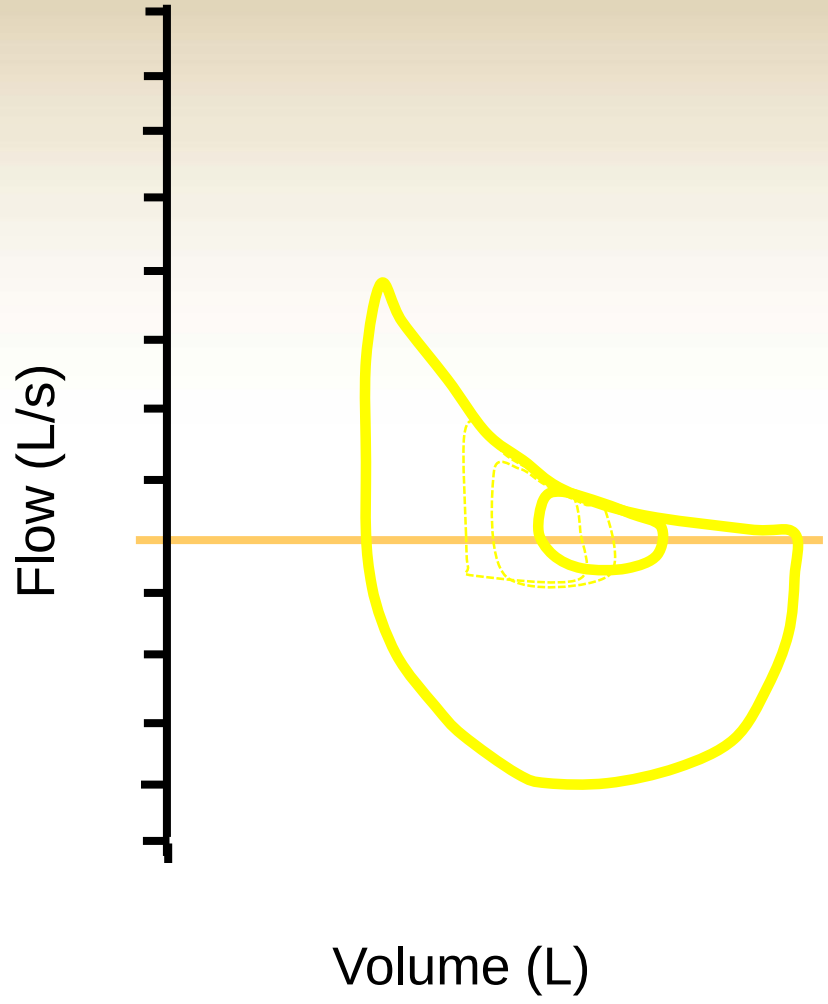
Pulmonary Function Tests

- COPD is diagnosed and staged primarily by pulmonary function testing (PFTs).
- Spirometry
  - decreased FEV1
  - decreased FEV1/FVC ratio (<0.7)
  - “coved” appearance to the expiratory limb of a flow-volume loop

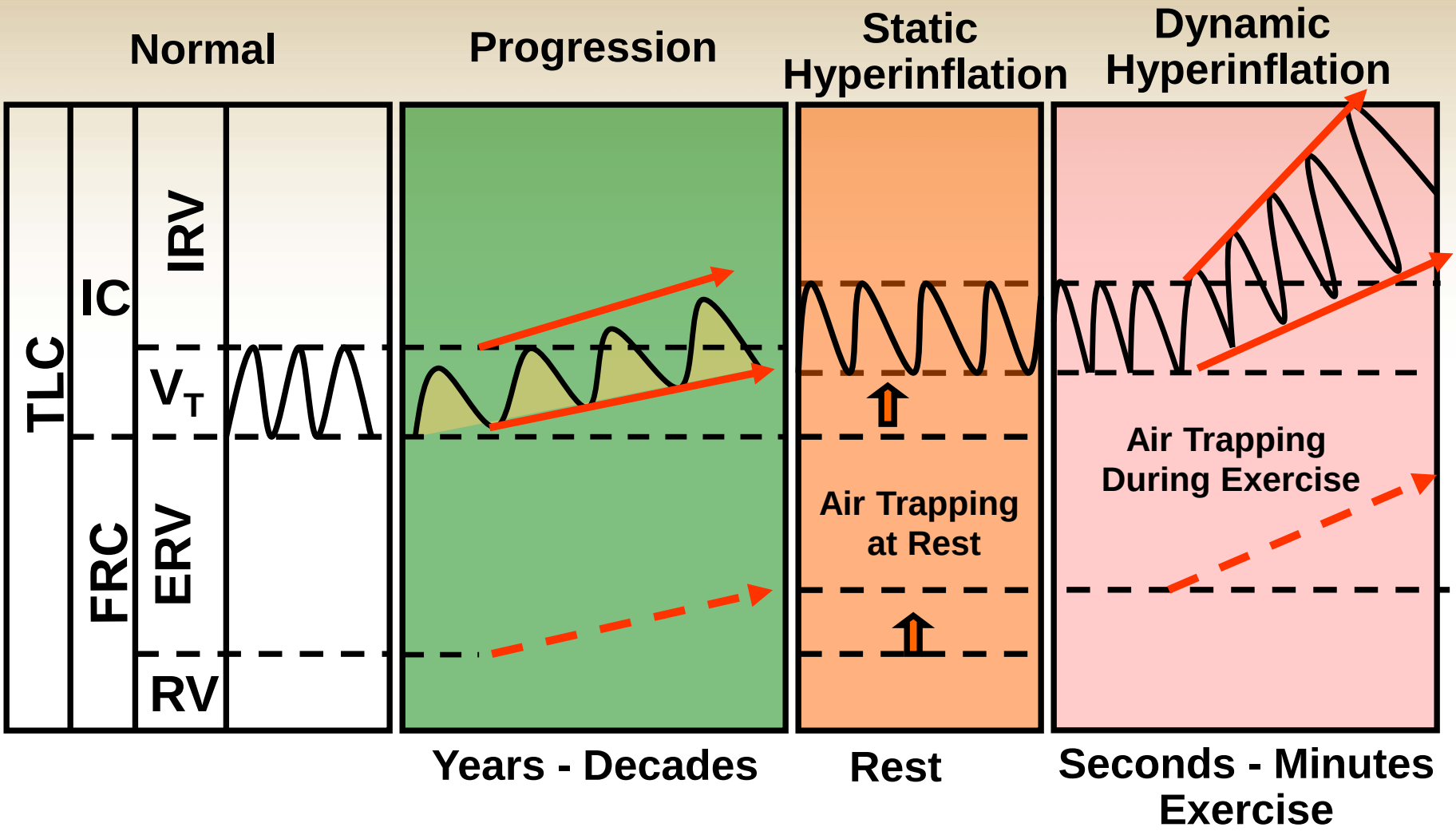
Flow Volume Loops



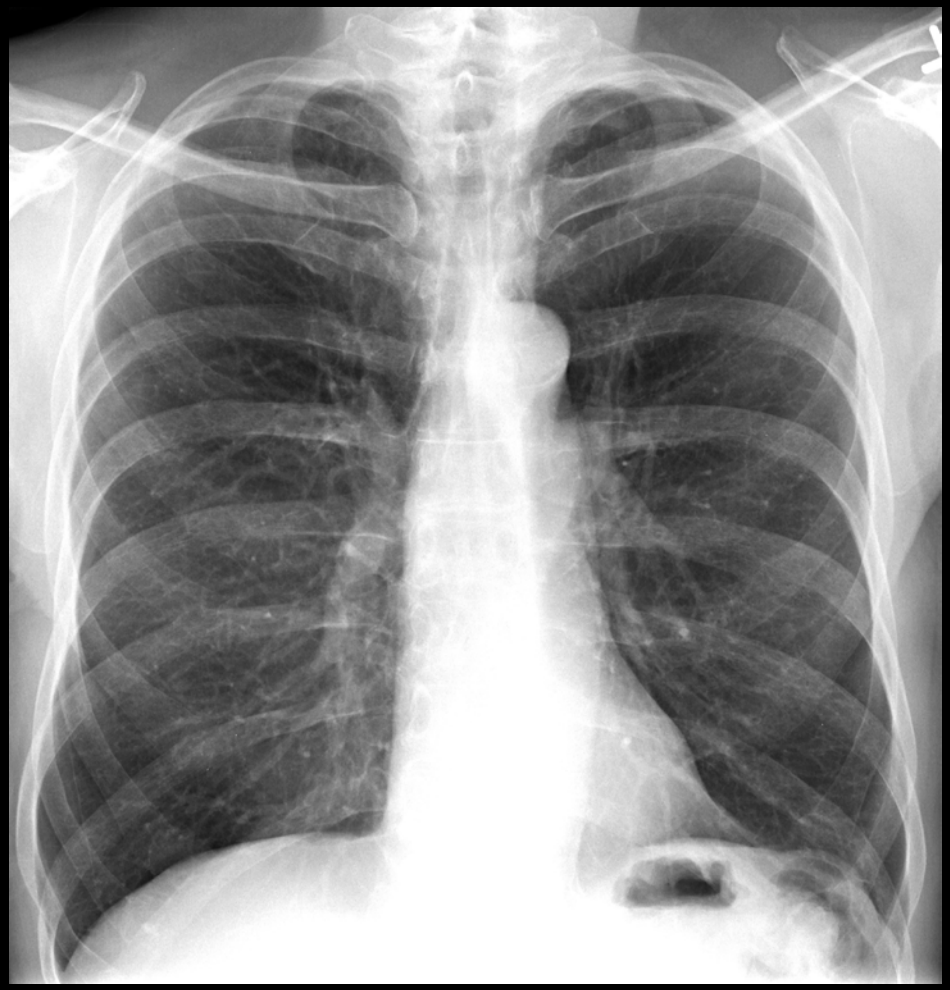
Flow Volume Loop During Exercise: obstructive lung disease



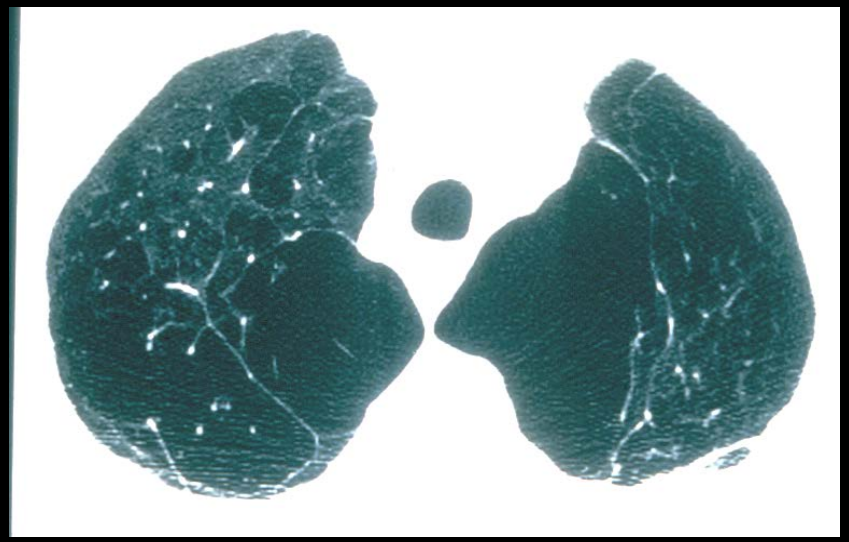
Effects of Exercise on Hyperinflation



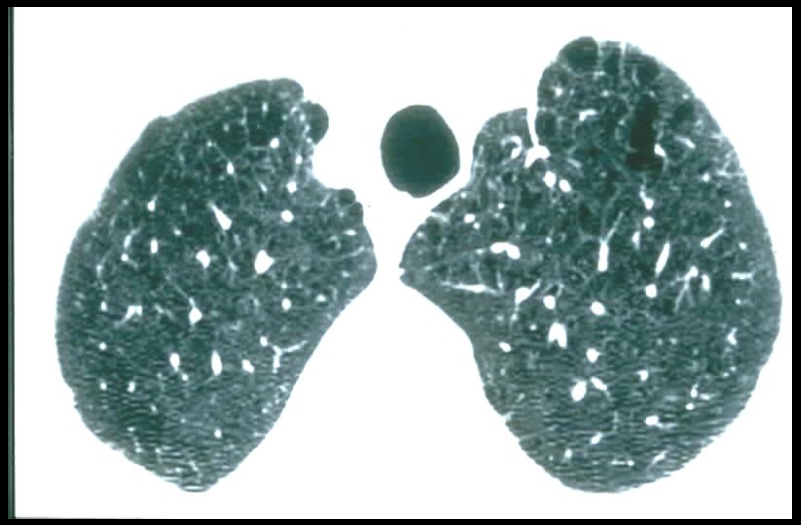
COPD CXR



Severe emphysema



Mild emphysema

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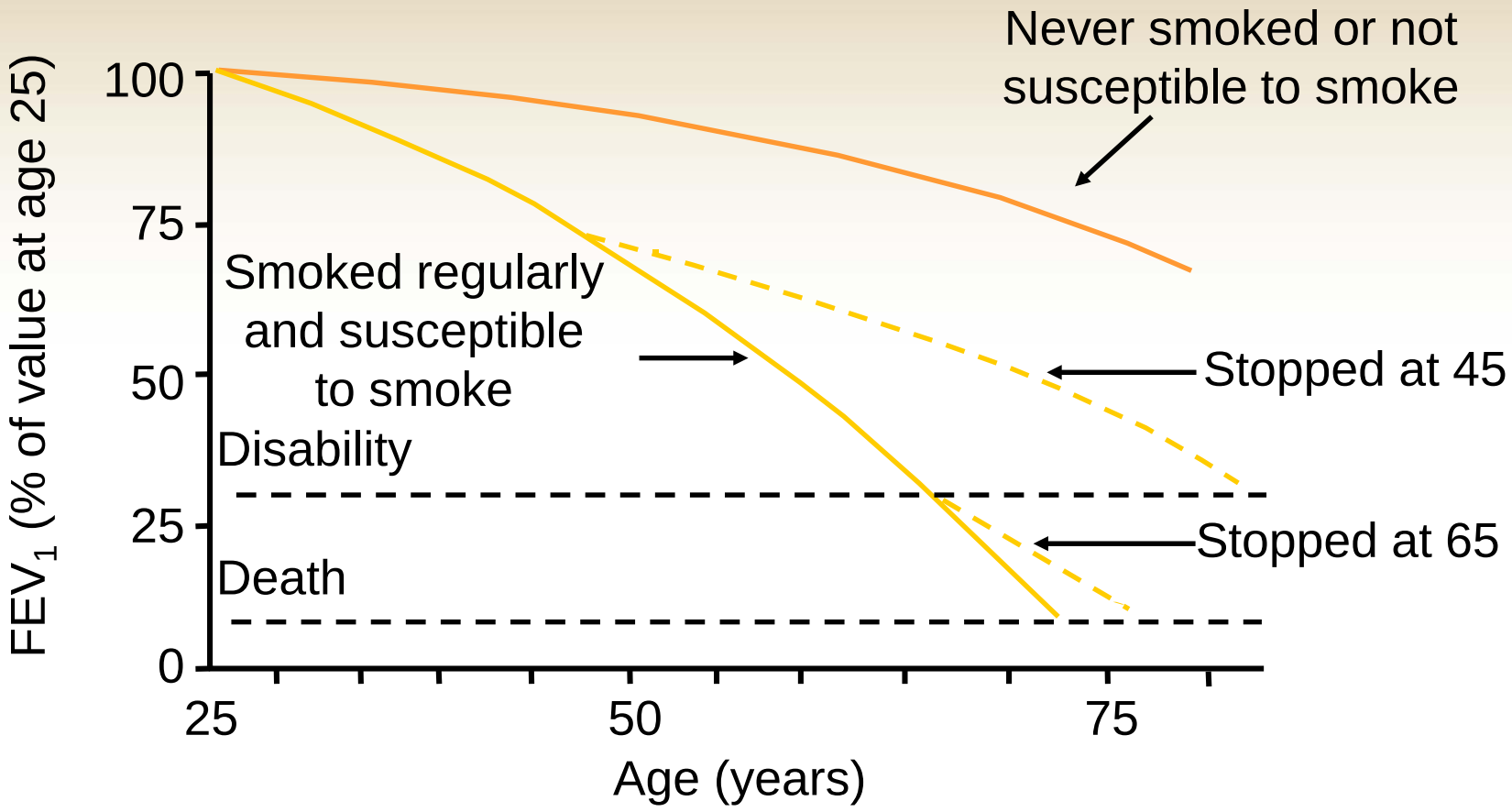
V 36.0cm
E
120

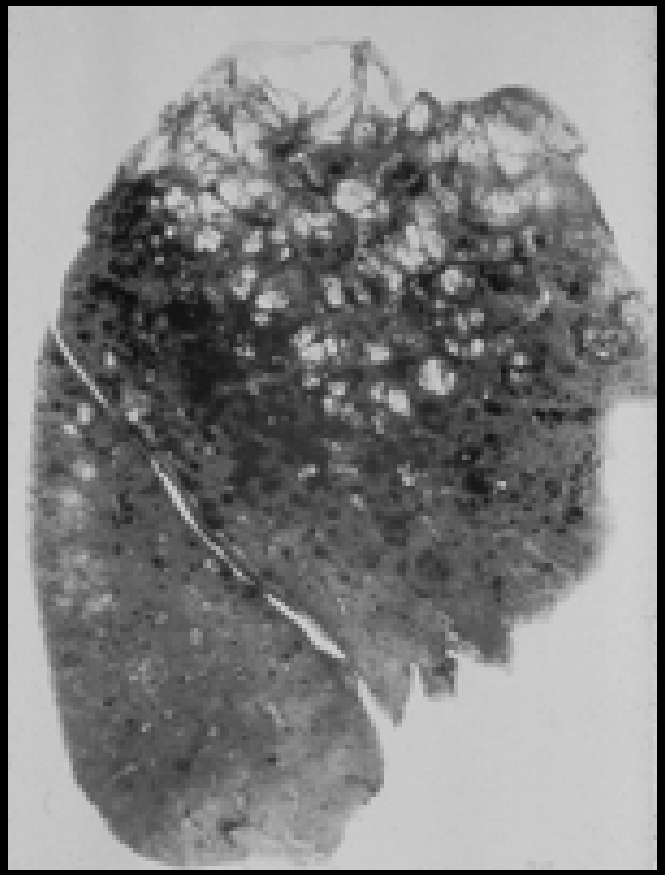

21
0
P

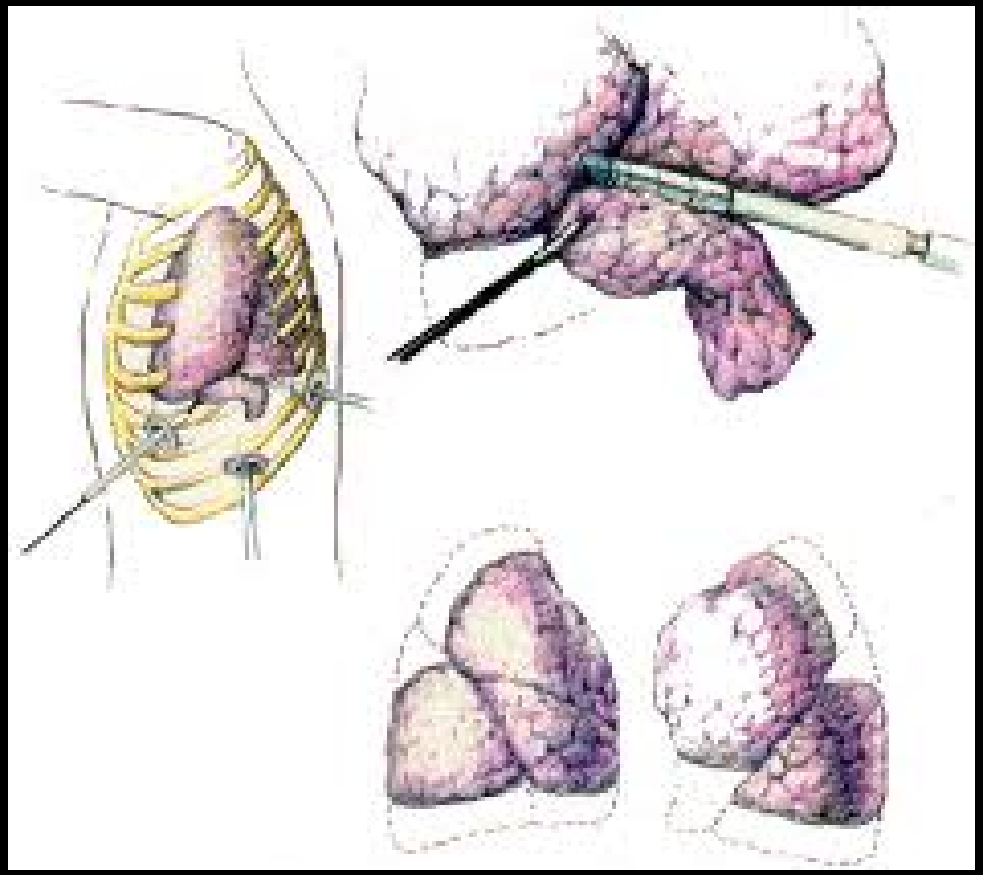
Decline of FEV_1 with Age and Smoking History



Fletcher C and Peto R. Br Med J. 1977;1:1645-1648.

Lungs too big? Make them smaller…





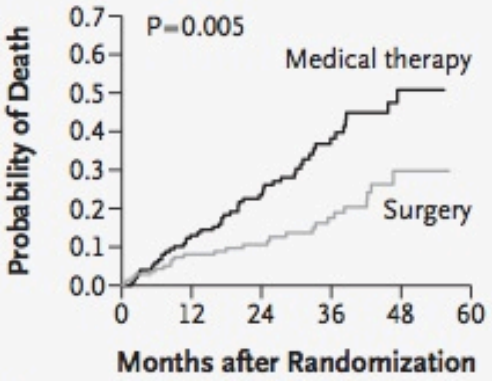
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 22, 2003 VOL. 348 NO. 21

A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

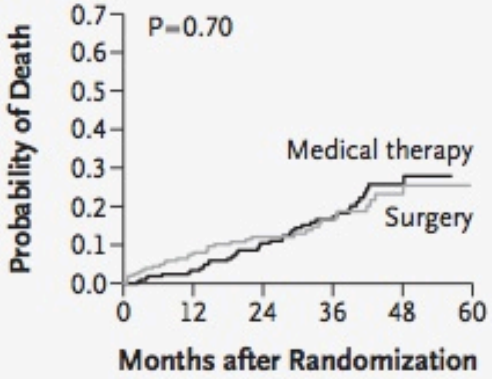
National Emphysema Treatment Trial Research Group*

D Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)



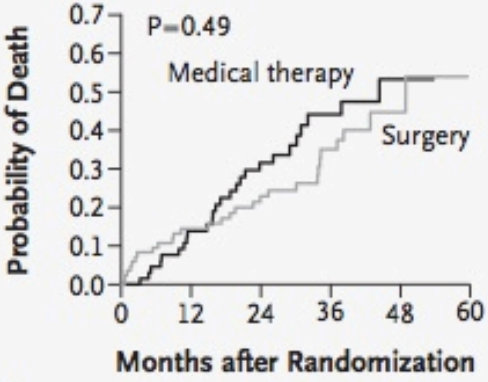
No. at Risk					
Surgery	139	121	93	61	17
Medical therapy	151	120	85	43	13

E Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=419)



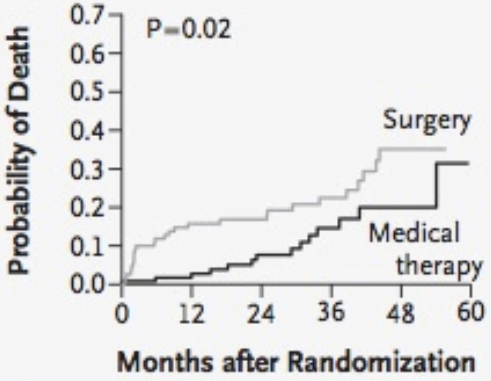
No. at Risk					
Surgery	206	176	124	82	35
Medical therapy	213	192	149	104	35

F Non–Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=149)



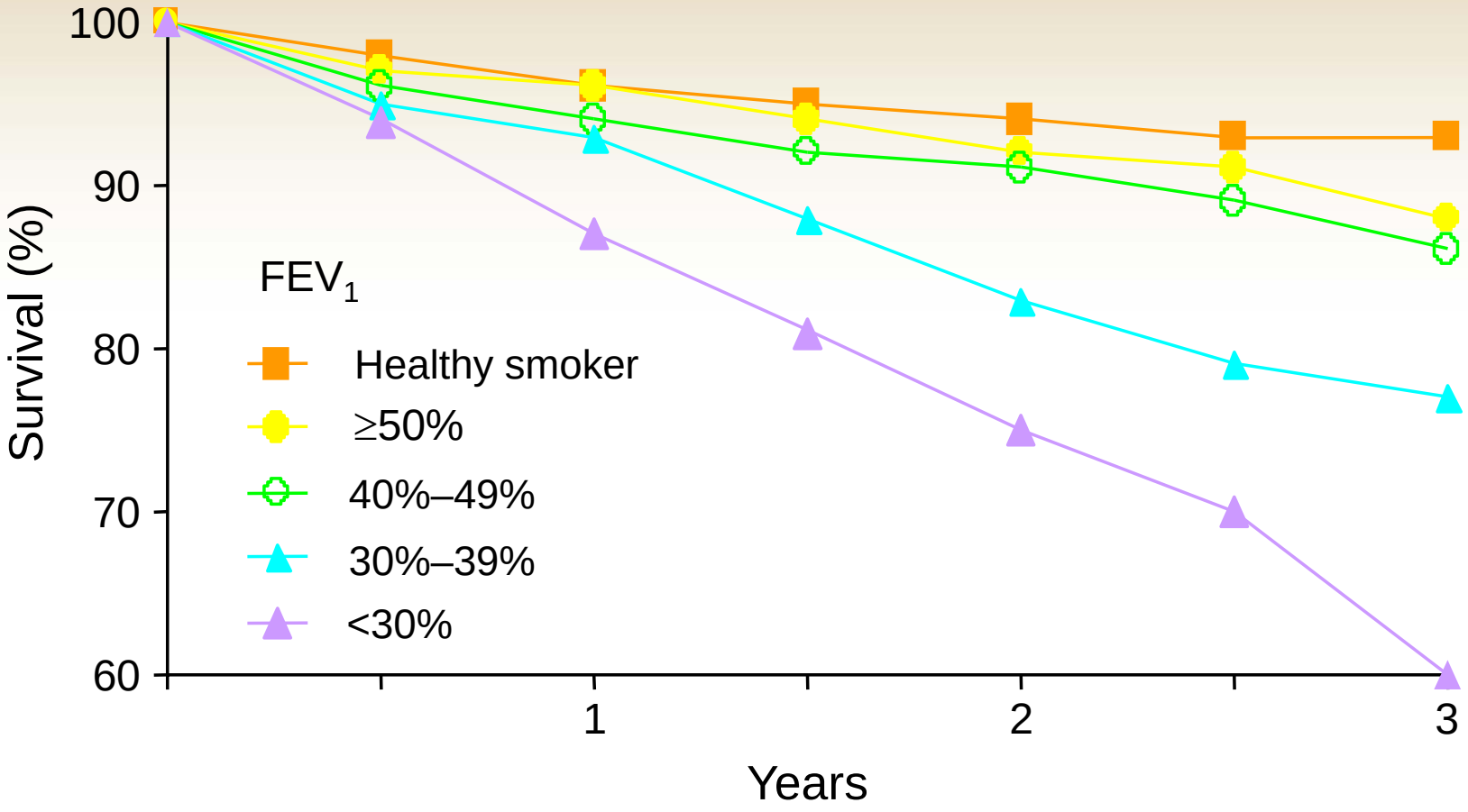
No. at Risk					
Surgery	84	67	52	28	6
Medical therapy	65	55	36	17	5

G Non–Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=220)



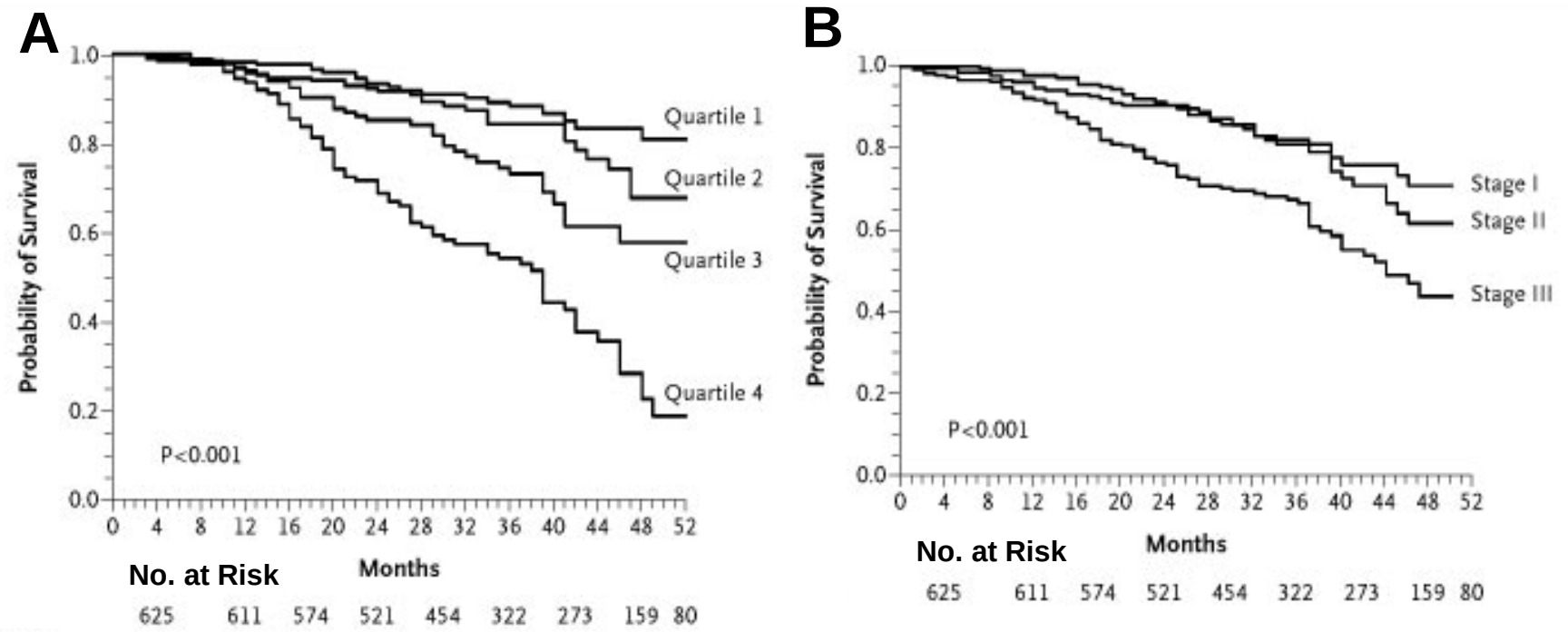
No. at Risk					
Surgery	109	83	71	43	12
Medical therapy	111	96	69	40	17

FEV_1: Prognostic Implications



Anthonisen NR, et al. *Am Rev Respir Dis*. 1986;133:14-20.

The BODE Score

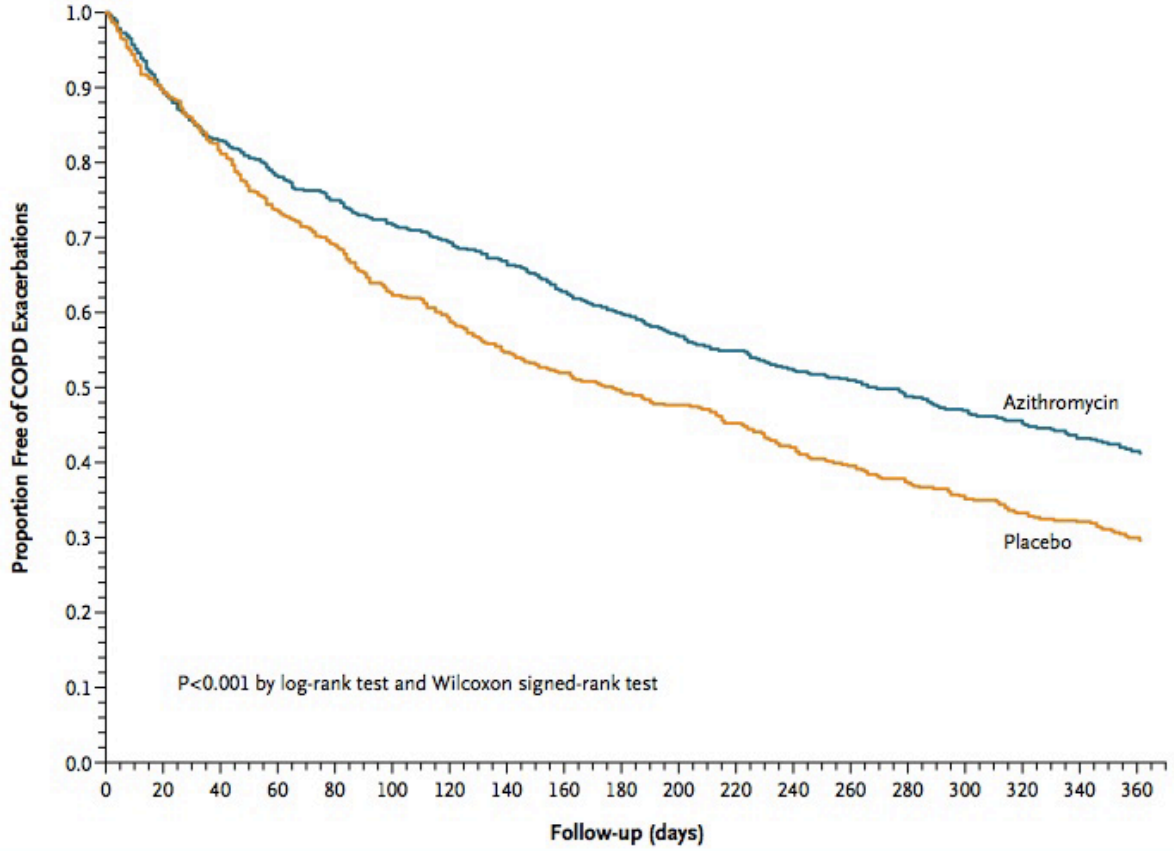


Celli BR, et. al. *N Engl J Med.* 2004;350:1005-12.

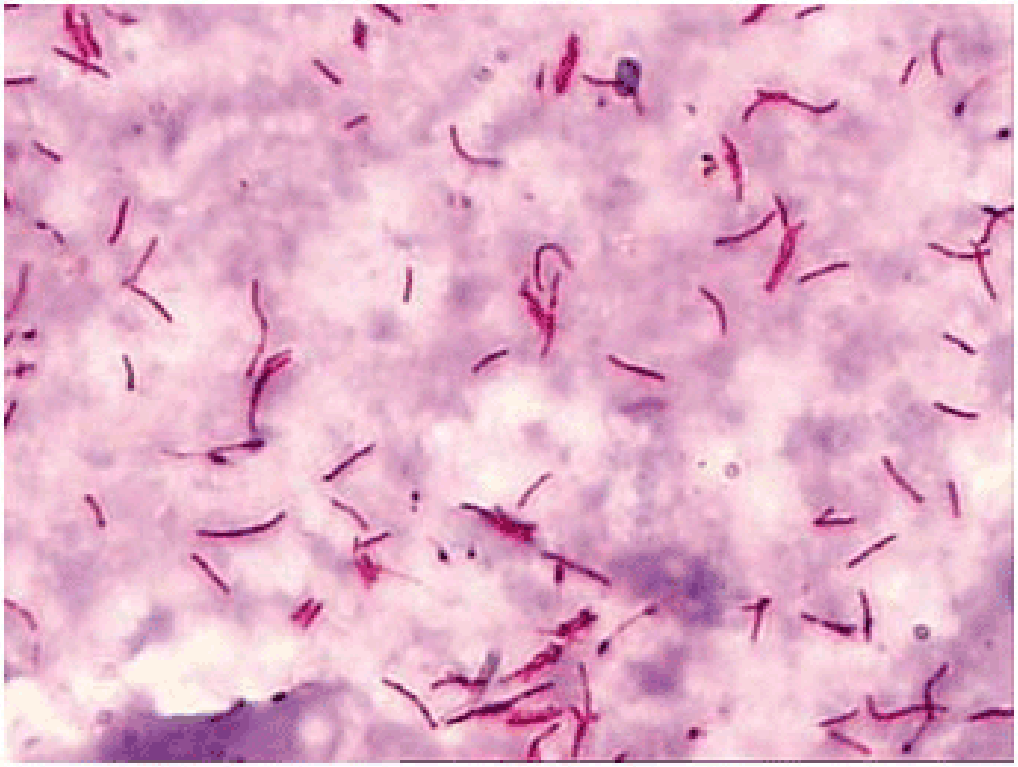
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD



Why I don’t like this study…

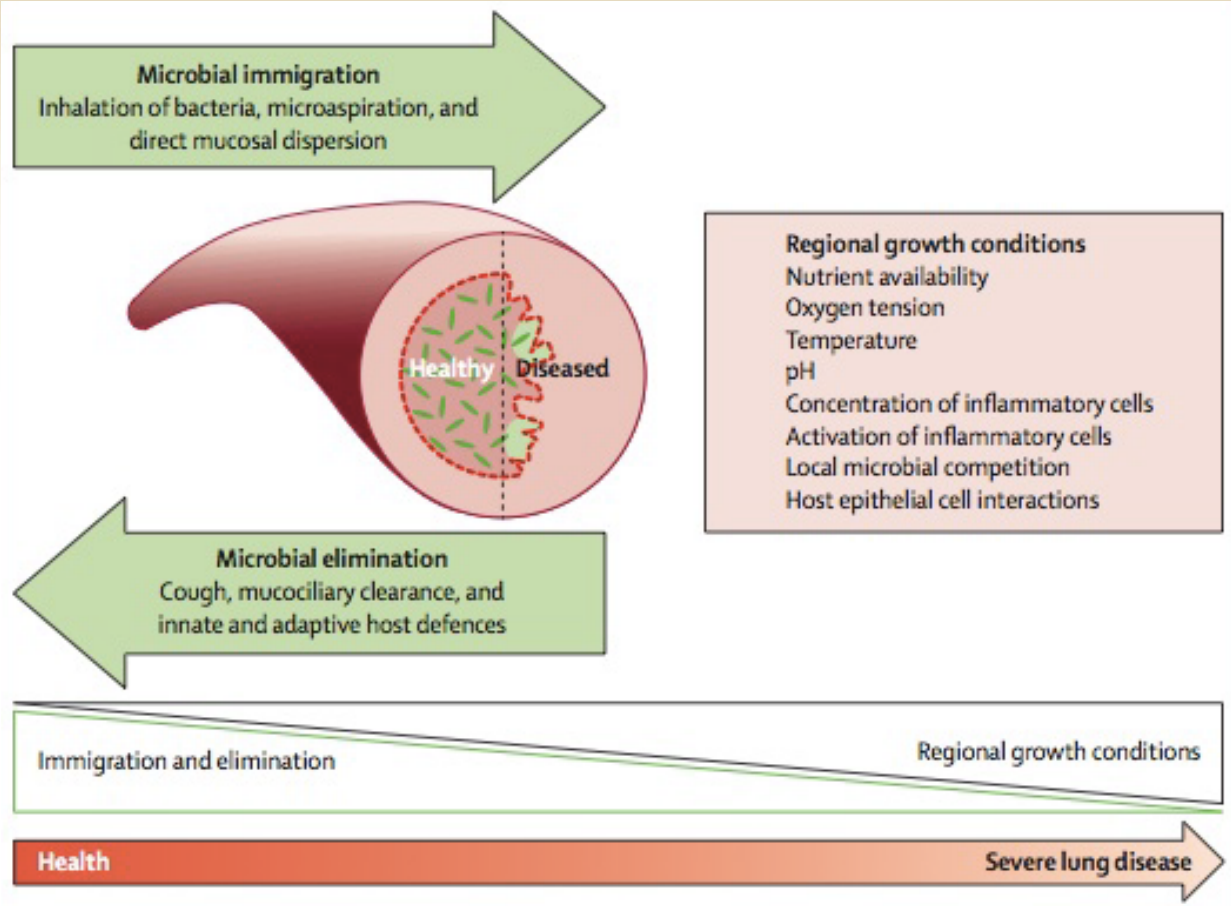


Lung Microbiome

- Conventional wisdom--healthy lungs are sterile
- Culture independent techniques demonstrate a complex bacterial microbiome in the lung.
  - post partum the lung is populated by microbes derived from the mother
  - the most common phyla observed in normal lung are *Bacteroides*, *Firmicutes,* and *Proteobacteria*
  - distinct lung microbiota and altered diversity are observed in lung disease

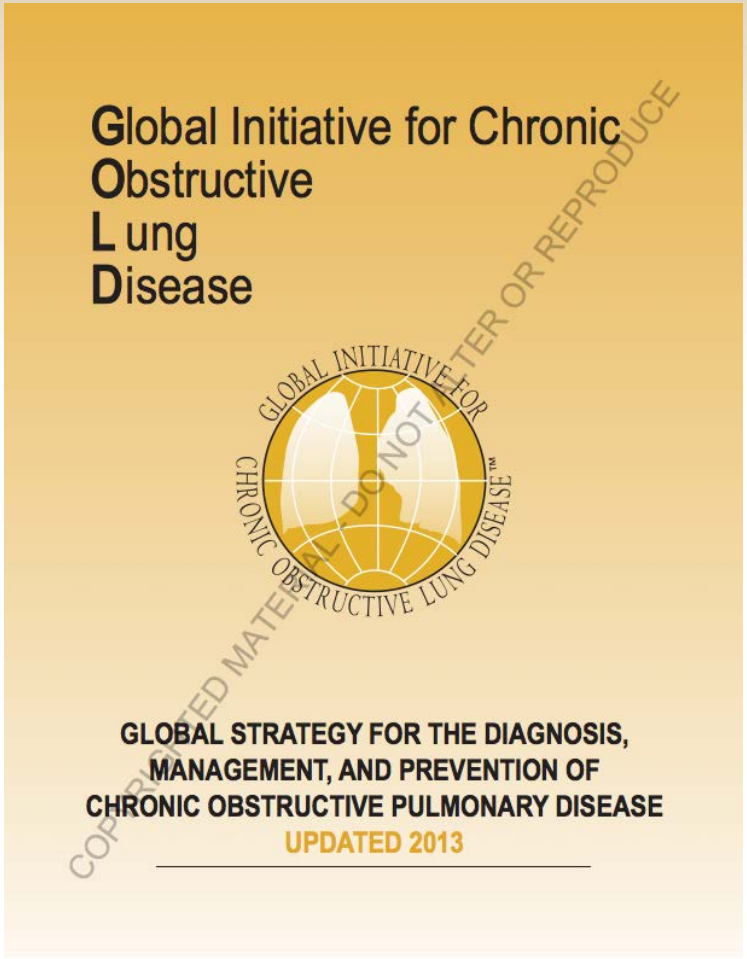
Expert Review Respir Med 2013; 7:245-57

Lung microbiome in COPD



Dixon RP, Martinez, FJ, Huffnagle GB. ***Lancet* 2014; 384: 691–702**

Guidelines for COPD

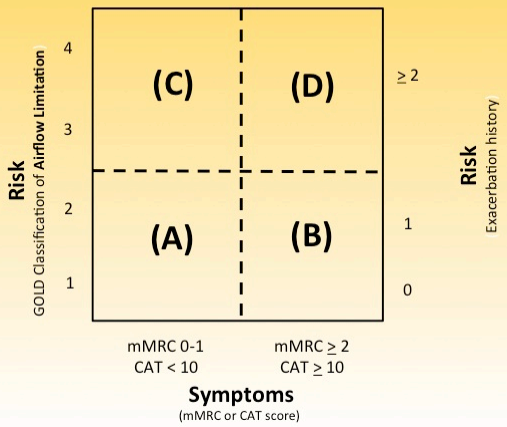


Classification by Severity:

GOLD Guidelines

Stage	Characteristics
0: At risk	Normal spirometry Chronic symptoms (cough, sputum)
I: Mild	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without chronic symptoms (cough, sputum)
II: Moderate	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted With or without chronic symptoms (cough, sputum)
III: Severe	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted With or without chronic symptoms (cough, sputum)
IV: Very Severe	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted; or $FEV_1 < 50\%$ predicted plus chronic respiratory failure ($PaO_2 < 60$ mm Hg) or clinical signs of right heart failure

Global Initiative for Chronic Obstructive Lung Disease
www.goldcopd.com/



Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk.)*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce symptoms

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce risk

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: COPD Medications

Beta$_2$-agonists
Short-acting beta$_2$-agonists (SABA)
Long-acting beta$_2$-agonists (LABA)
Anticholinergics
Short-acting anticholinergics (SAMA)
Long-acting anticholinergics (LAMA)
Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler
Methylxanthines
Inhaled corticosteroids (ICS)
Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler
Systemic corticosteroids
Phosphodiesterase-4 inhibitors

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		Theophylline
B	LAMA *or* LABA	LAMA and LABA		SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.		*C*arbocysteine *SABA and/or* SAMA Theophylline

Prevention of AECOPD

- Smoking cessation
- Pharmacotherapy
  - Bronchodilators: LAMA and LABA
  - Inhaled corticosteroids
  - Combination therapy: ICS + LABA
  - Azithromycin
  - PDE4 inhibition
- Immunizations
  - Influenza, pneumococcal
- Rehabilitation and education

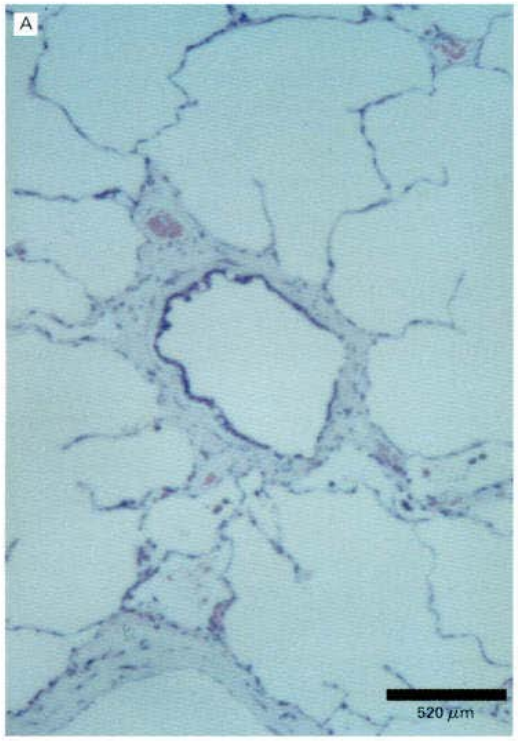
Using inhalers

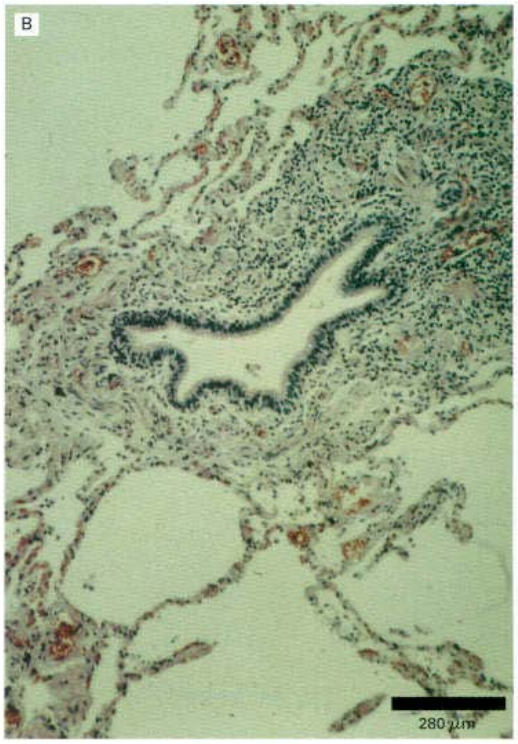
- Inhaled medications are the cornerstone of asthma and COPD therapy
- Poor technique is reported in up to 94% of patients
- Improper inhaler use leads to poor disease control
- Patient who never receive instruction and those who use more than one type of device make more mistakes

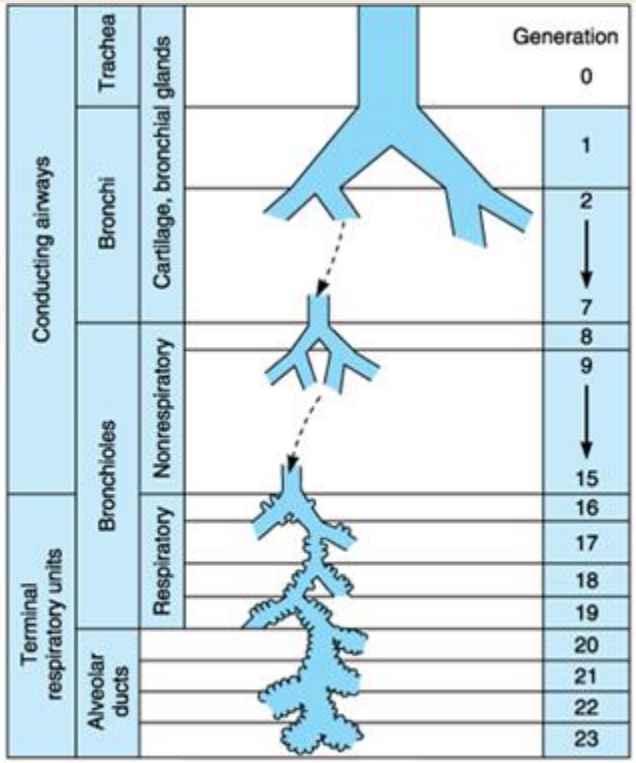
Inhaler instruction

- Helps improve technique and self-efficacy
- Can be effectively taught by anyone who is properly trained
- Is poorly taught by most physicians
- Is more effective as a demonstration than in written form
- Benefits are short lived. Techniques need to be reinforced to be effective long term.

The problem with inhaled therapy…







Source: McPhee SJ, Ganong WF: *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th Edition: http://www.accessmedicine.com

aer·o·sol

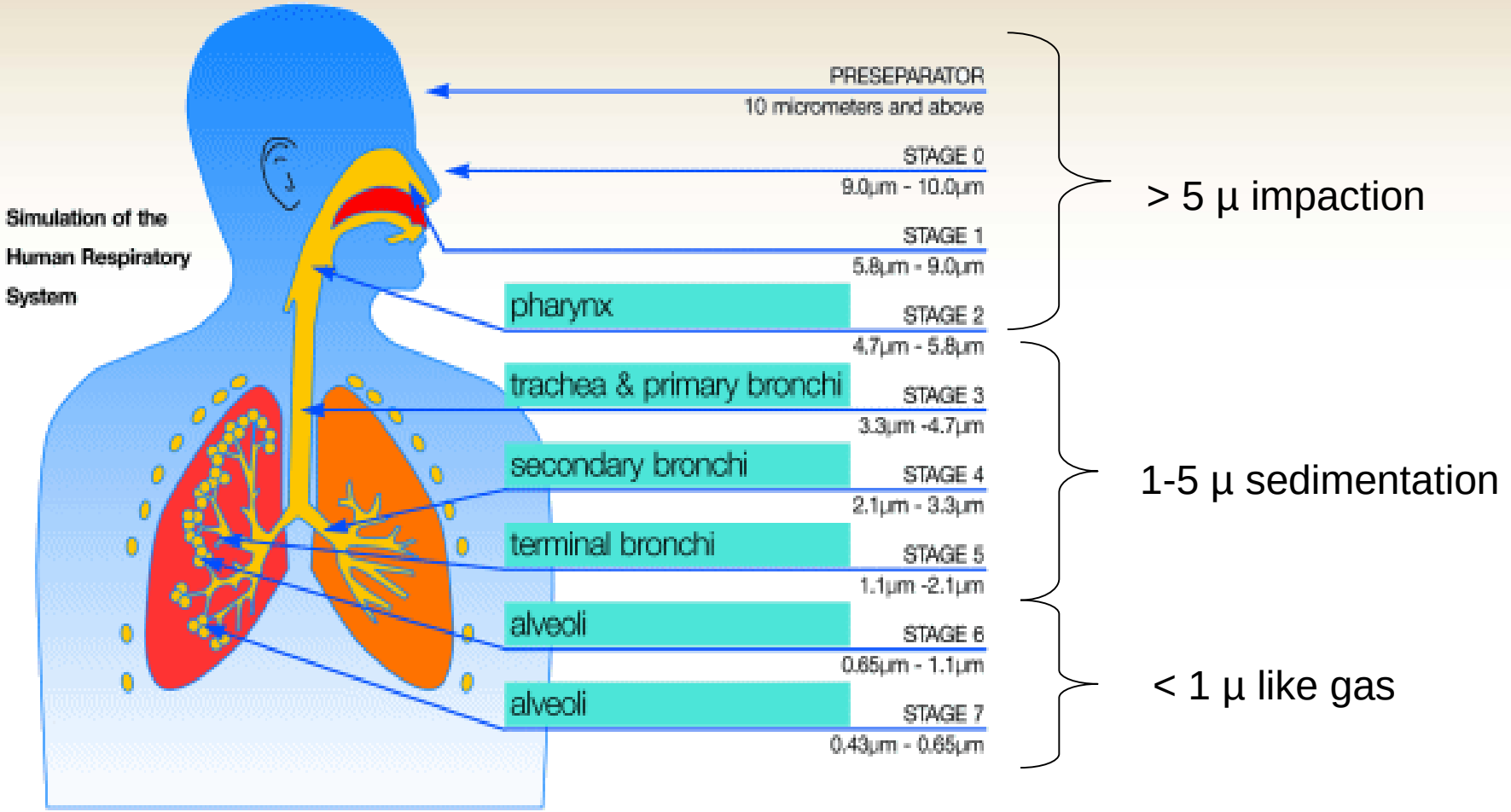
noun: **aerosol**; plural noun: **aerosols**

1. a substance enclosed under pressure and able to be released as a fine spray, typically by means of a propellant gas.

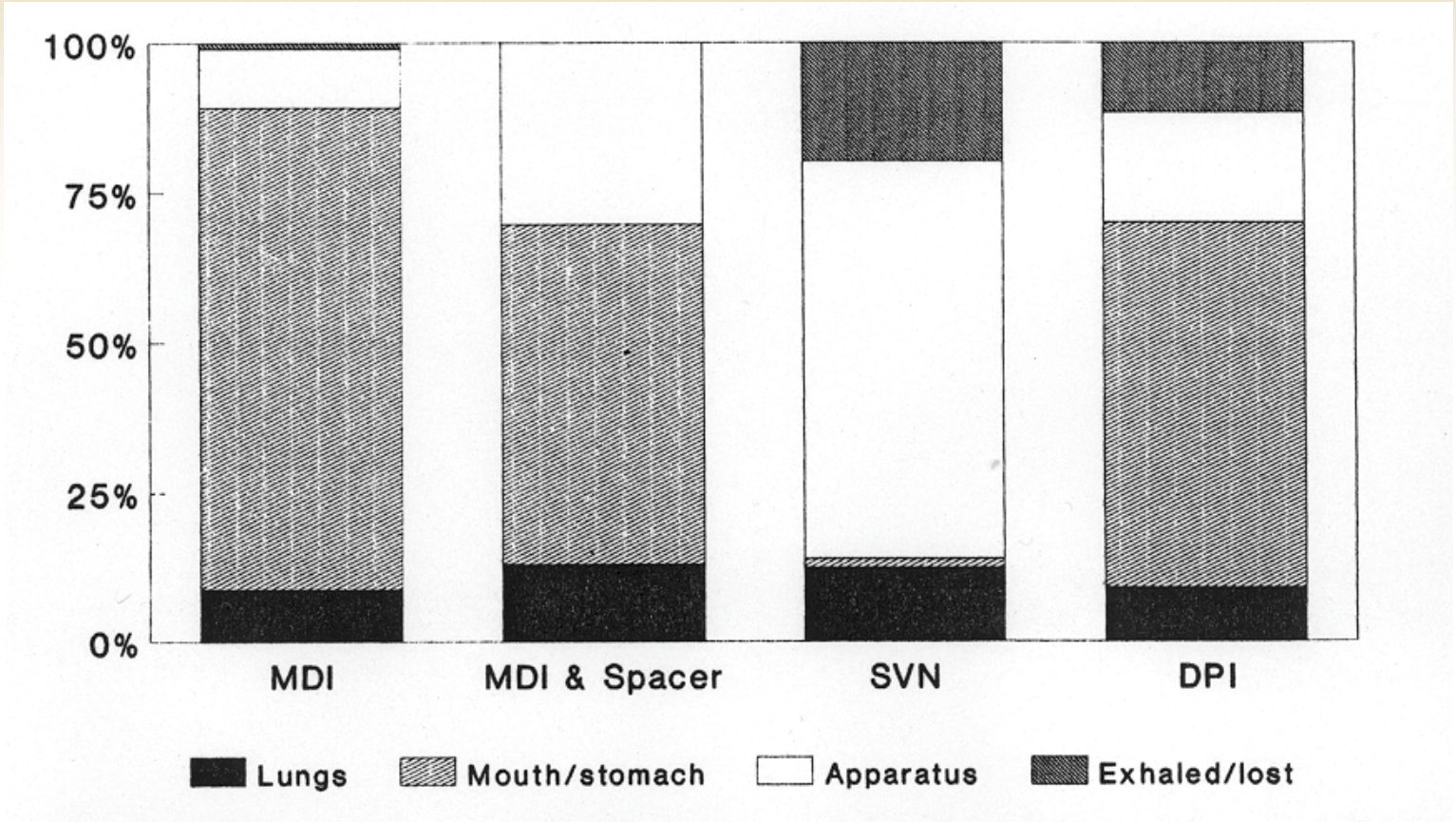
CHEMISTRY

a colloidal suspension of particles dispersed in air or gas.

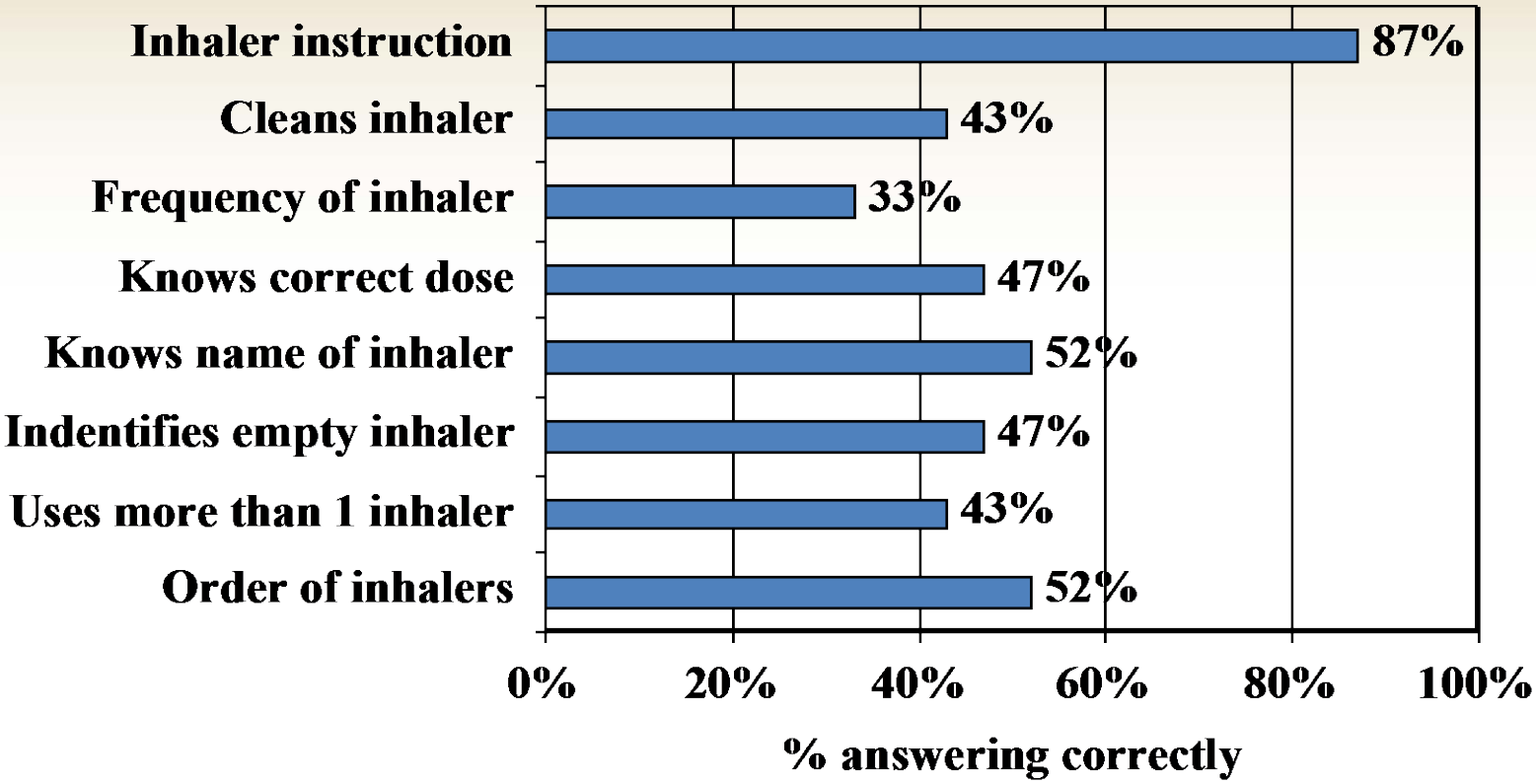
Where do the particles go?

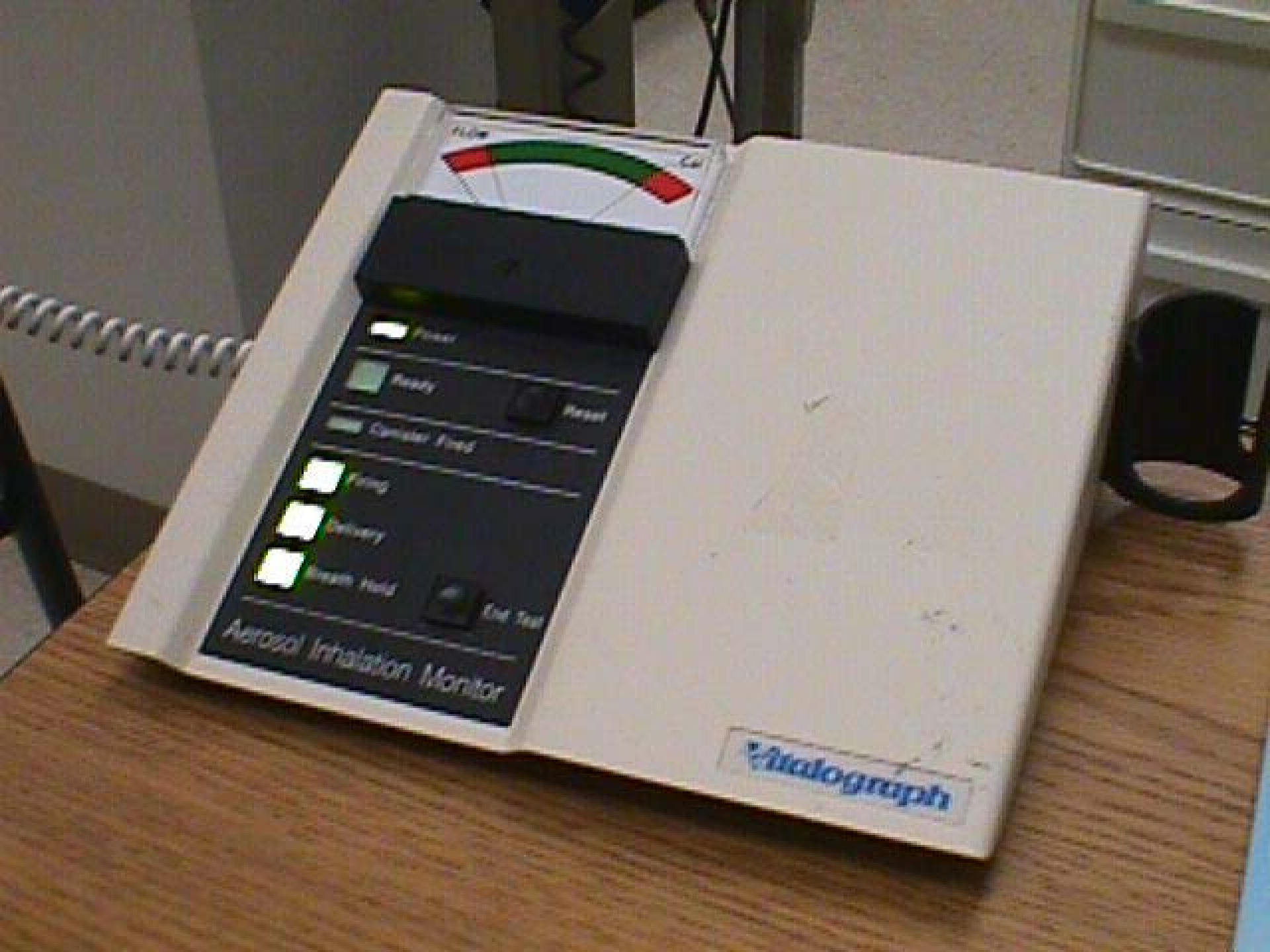


Pattern of Aerosol Deposition: comparison of delivery devices

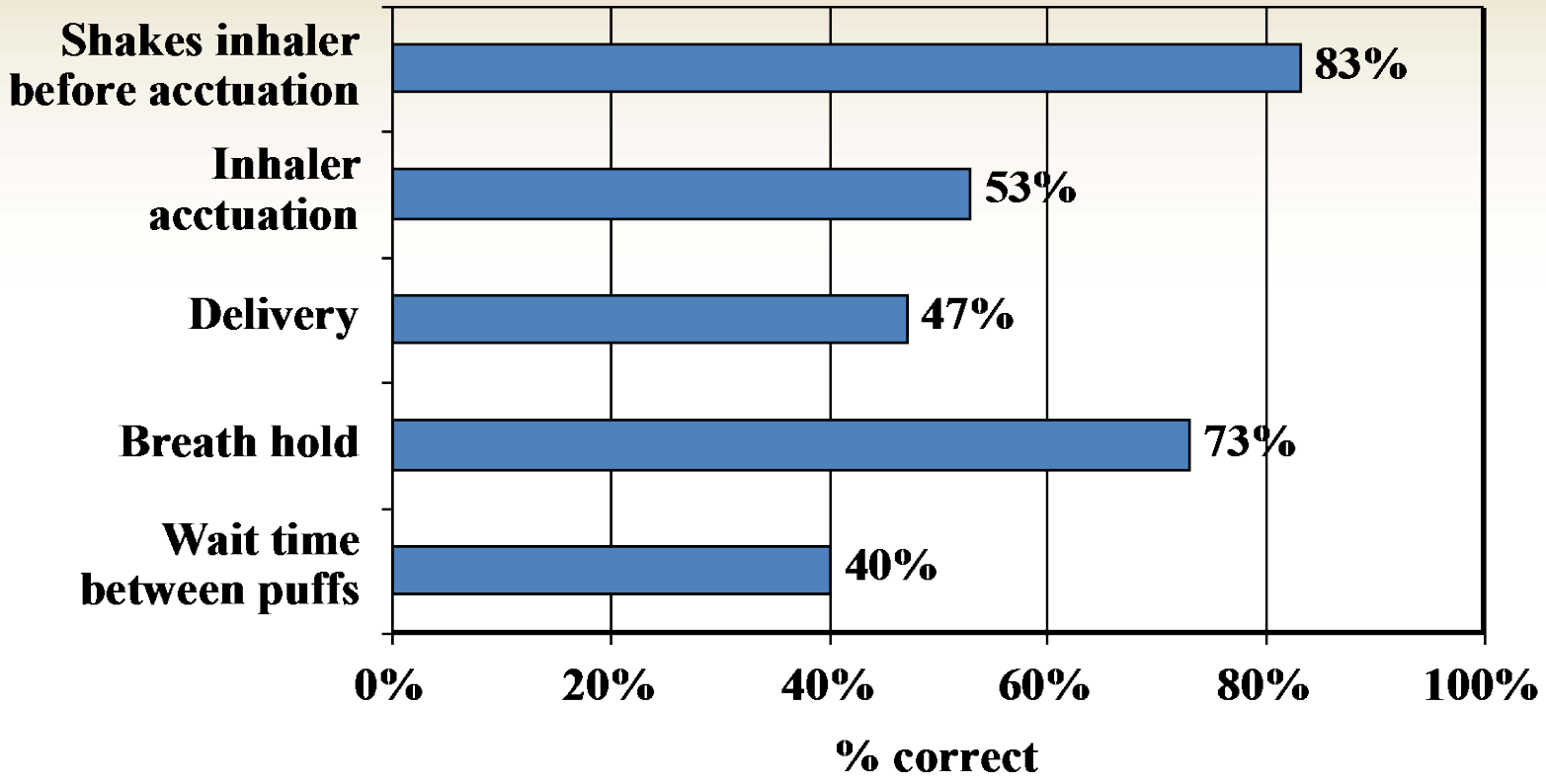


Evaluation of MDI teaching: questionnaire (n=30)




Power
Ready
Reset
Canister Empty
Firing
Delivery
Breath Hold
End Test
Aerosol Inhalation Monitor
Intalograph

Evaluation of MDI teaching: vitalograph demonstration (n=30)



VA Ann Arbor Healthcare System Pharmacy: (866) 316-9350 Patient:_____ Date:_____

INHALER INSTRUCTIONS **Ask your healthcare provider how to use these correctly**

Inhaler Type	**Metered dose**			**Dry Powder**	**Capsule**	
Inhaler Name **(Use the inhalers that are checked)**	☐  albuterol (Proventil HFA®)	☐  ipratropium (Atrovent HFA®)	☐  budesonide/ formorterol (Symbicort®)	☐  mometasone (Asmanex®)	☐  formoterol (Foradil®)	☐  tiotropium (Spiriva®)
# of Puffs						
Times Per Day	**As Needed**	**___ Times Per Day**	**___ Times Per Day**	**___ Times Per Day**	**2 Times Per Day**	**1 Time Per Day**
Primary Action	(Beta-2 agonist) Opens large airways Short acting	(Anticholinergic) Opens small airways Short acting	(Inhaled Steroid/ Beta-2 agonist) Decreases airway swelling and opens large airways. Long acting	(Inhaled Steroid) Decreases airway swelling Long acting	(Beta-2 agonist) Opens large airways Long acting	(Anticholinergic) Opens small airways Long acting
Important Points to Remember	Use as rescue for shortness of breath or wheezing. Works within minutes. May make you feel jittery*. **Prime inhaler with two sprays before very first use and if not used in over 3 days*	Use even if you don't think you need it. Works within 30 minutes*. Not a rescue for asthma attacks. **Prime inhaler with two sprays before very first use and if not used in over 3 days*	Use even if you don't think you need it. After removing from foil package, write the date on the inhaler and discard after 90 days. Rinse mouth after use. Not a rescue for asthma attacks.	Use even if you don't think you need it. After removing from foil package, write the date on the inhaler and discard after 45 days. Rinse mouth after use. Not a rescue for asthma attacks.	Use even if you think you don't need it. Refrigerate unopened capsule packages. Can store at room temperature for 4 months. Not a rescue for asthma attacks.	Use even if you think you don't need it. Not a rescue for asthma attacks.

Rev. 11/11

Refer to back for instructions on how to use each type of inhaler.

PHE Approved 2/2012

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

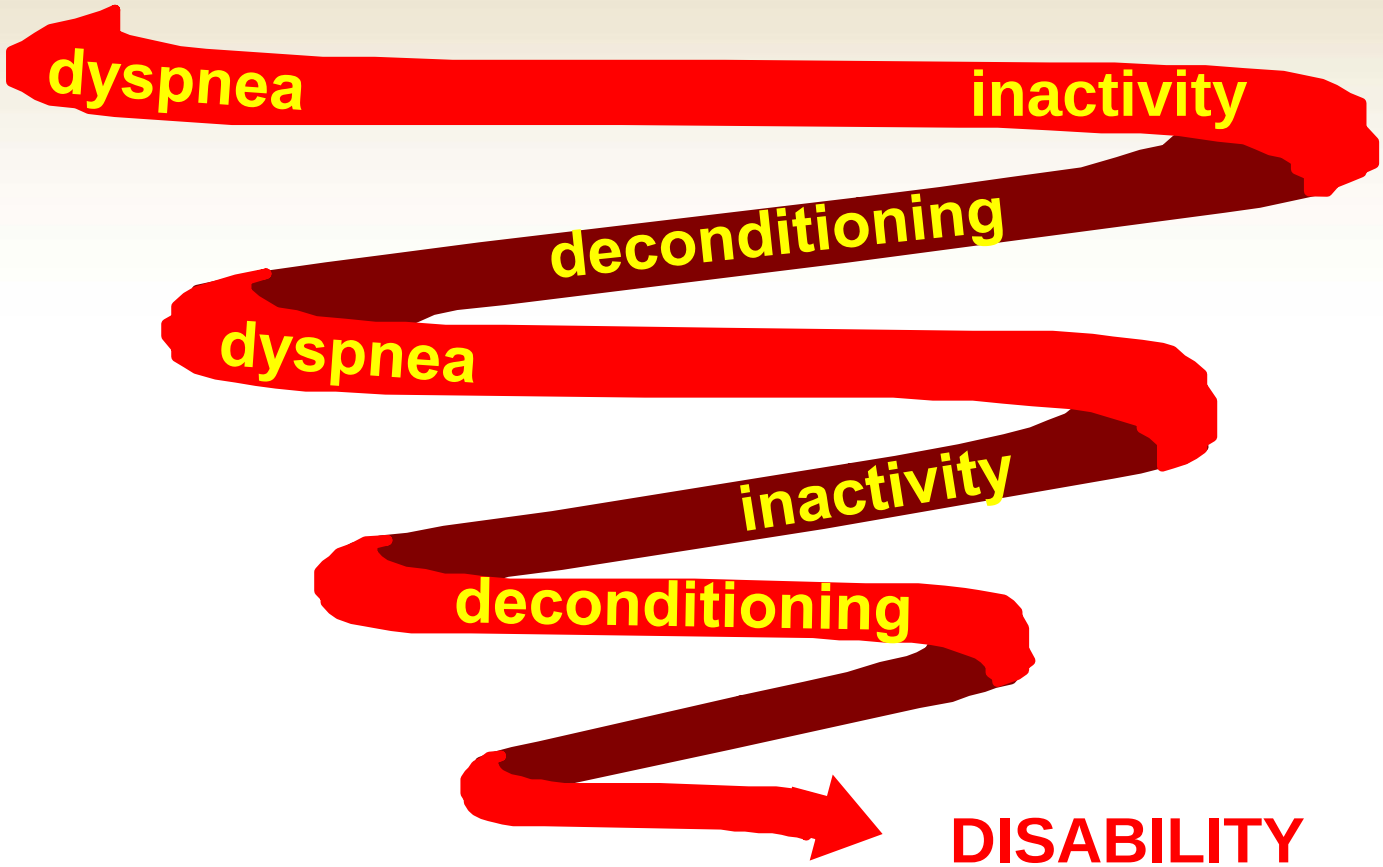
Hurdles to inhaler education

- Consistency
- Repetition
- Adaptibility
  - For each patient
  - As inhalers change
- Who will teach?

Possible Solution?

https://vimeo.com/140420509

The Dyspnea Spiral in COPD



Pulmonary Rehabilitation Program Components

- Education
- Respiratory care instruction
- Psychosocial support
- Exercise training

Long-term Effects of PR Plus Maintenance

- Improvement in
  - Dyspnea
  - Exercise capacity
  - Rate of decline of FEV_1
  - Severity of disease by BODE index
  - Success rate of smoking cessation
  - Survival, number of respiratory deaths
- Effects are sustained up to 3 years

Summary: COPD Management