The fate of inhaled drugs

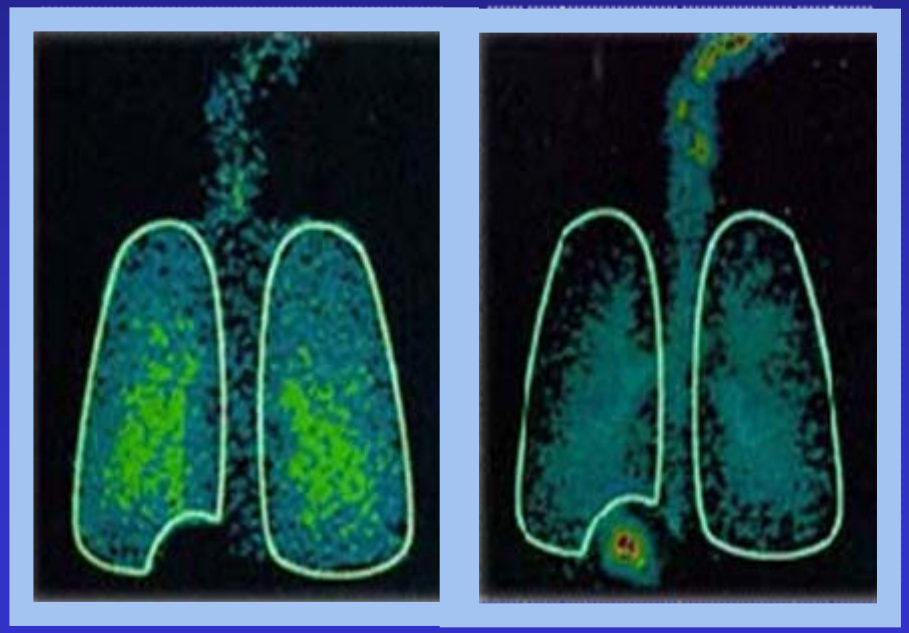
Mark Everard

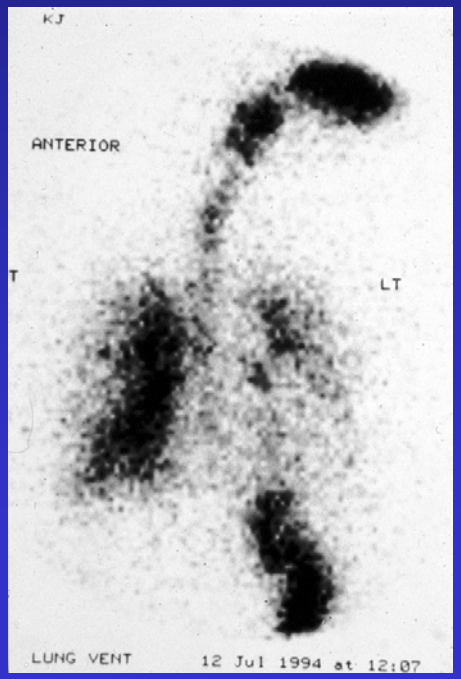
Sheffield Children's Hospital

Why Used Inhaled Therapy?

Drug is delivered directly to site of action

Spahan JD, Szefler SJ Pediatric Respiratory Medicine 2008





Oral vs Inhaled therapy

Fundamental differences

- *Lungs have evolved to exclude foreign material*

- *Even if you take the medication you may not derive any benefit*

Compliance x 2

regimen compliance

device compliance

[competence + contrivance]

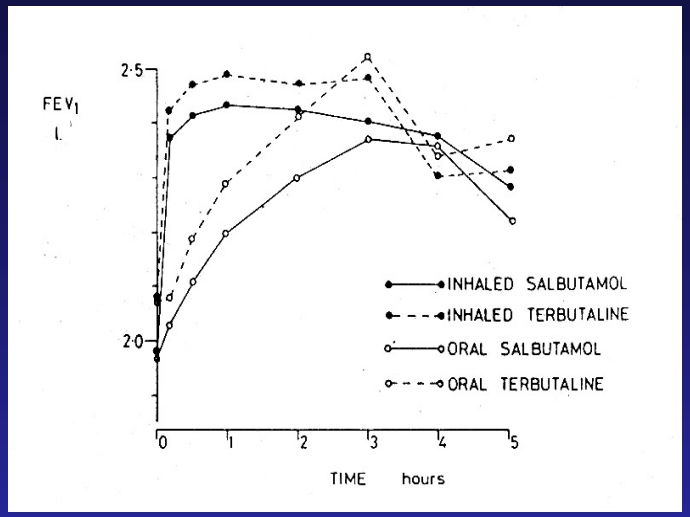
Inhaled Therapy for Pulmonary Disease

Speed of Onset

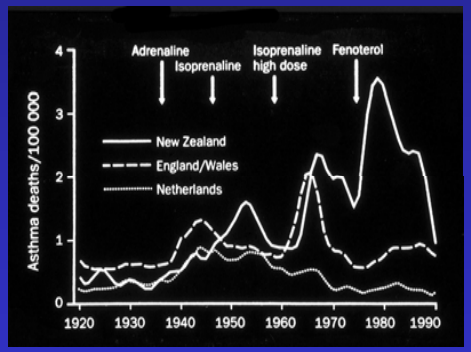
Therapeutic Index

Large luminal dose

Poorly absorbed drugs



Webb J et al Br J Dis Chest 1982



Inhaled Therapy for Systemic Therapy

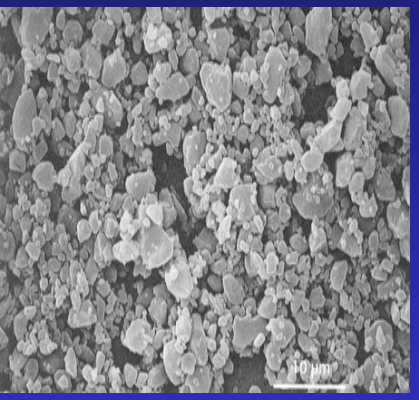
Very Large surface area

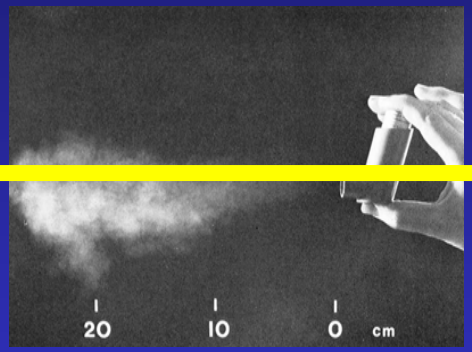
Inhaled Therapy

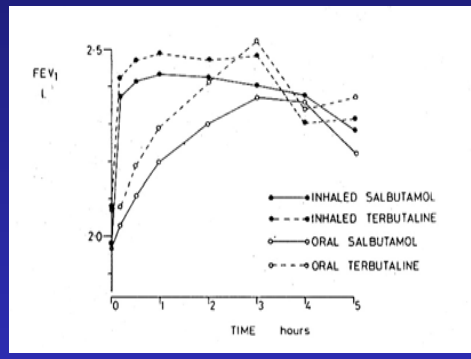
Device / Formulation

Drug

Therapeutic effect

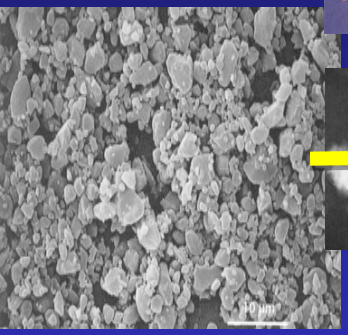




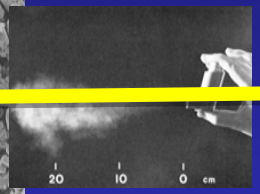


Inhaled Therapy -ISAM

Drug

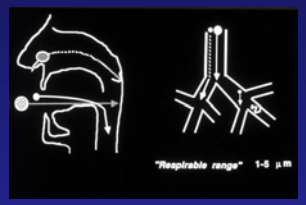


Device



Formulation issues
Availability
Cost
Target

Anatomy Physiology



Inter-subject variation

Age dependent

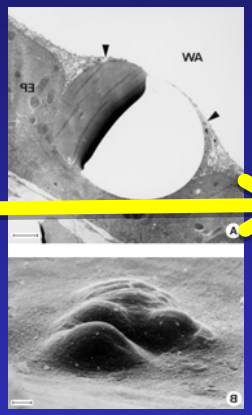
Disease

Generalised

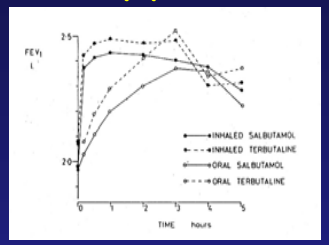
Variable

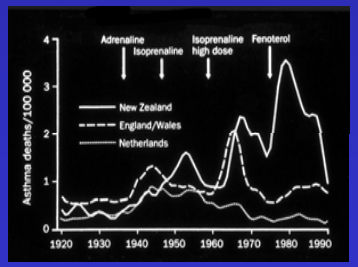
Progressive

Fate of drug



Therapeutic effect



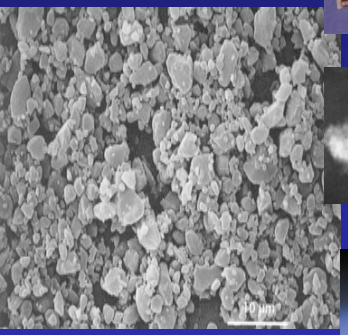


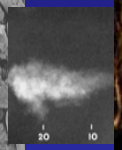
Adverse Effects

Sources of Variability in Lung Dose

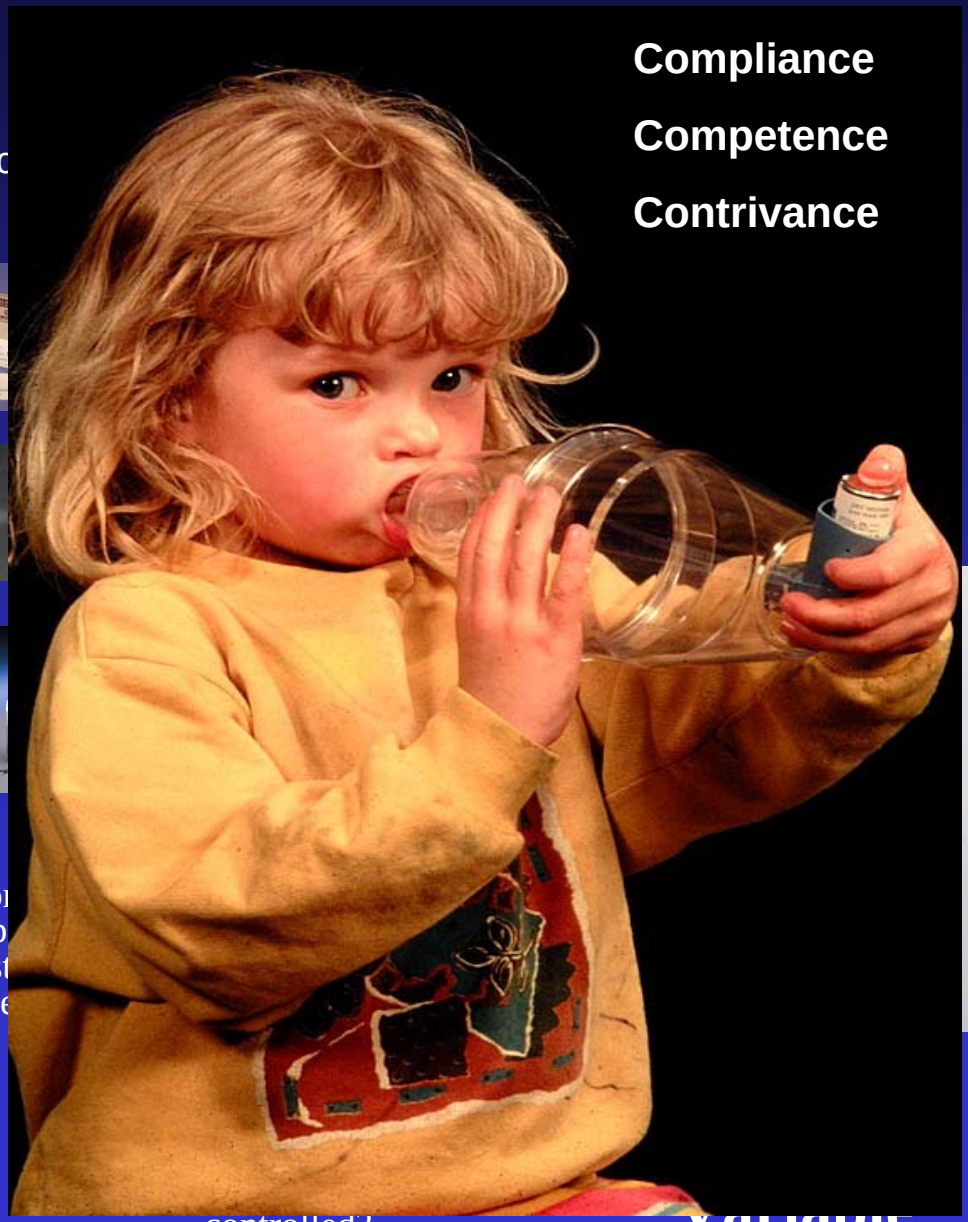
Drug

Devic





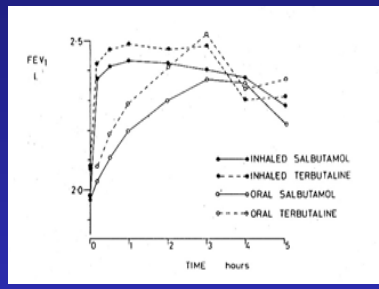
Formulatio
Availab
Cost
Targe



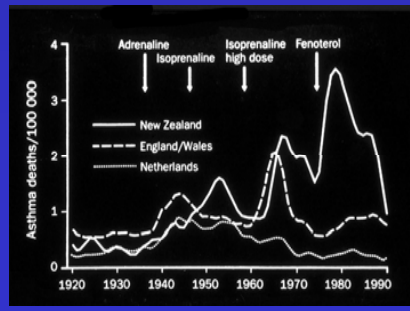
controlled?

Variable

Therapeutic effect



Adverse Effects



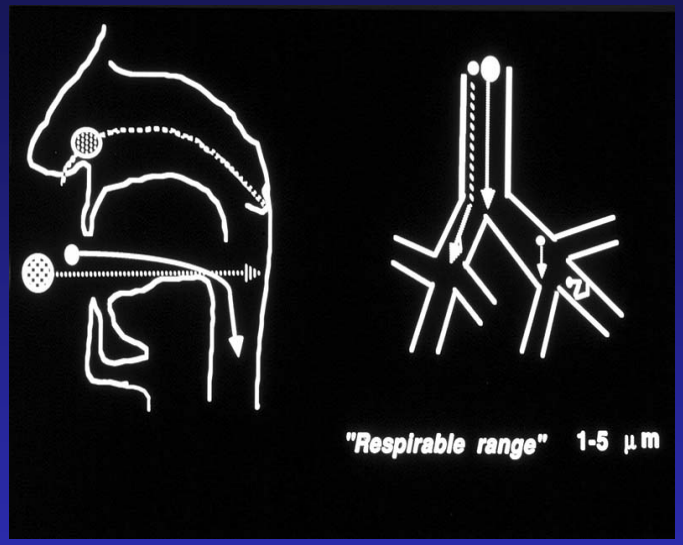
Basic Principles

Lungs have evolved to exclude foreign material

Defences

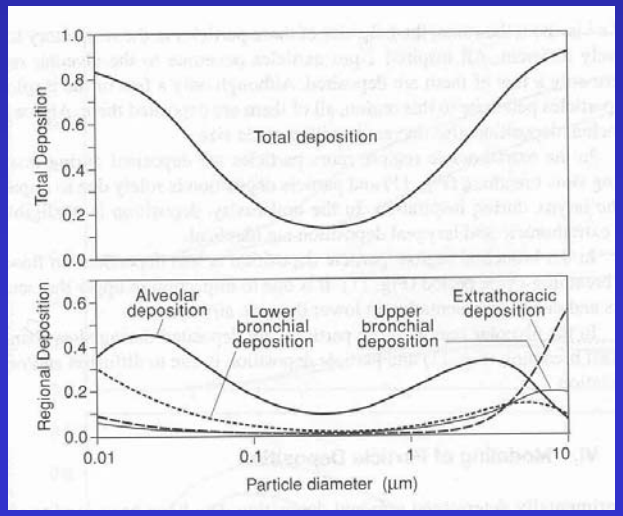
Airways anatomy

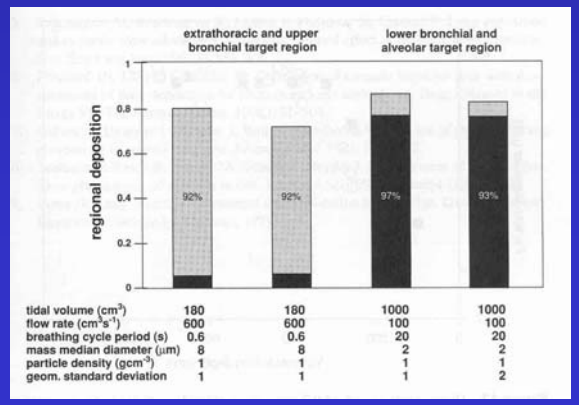
Cough
Mucocillary clearance



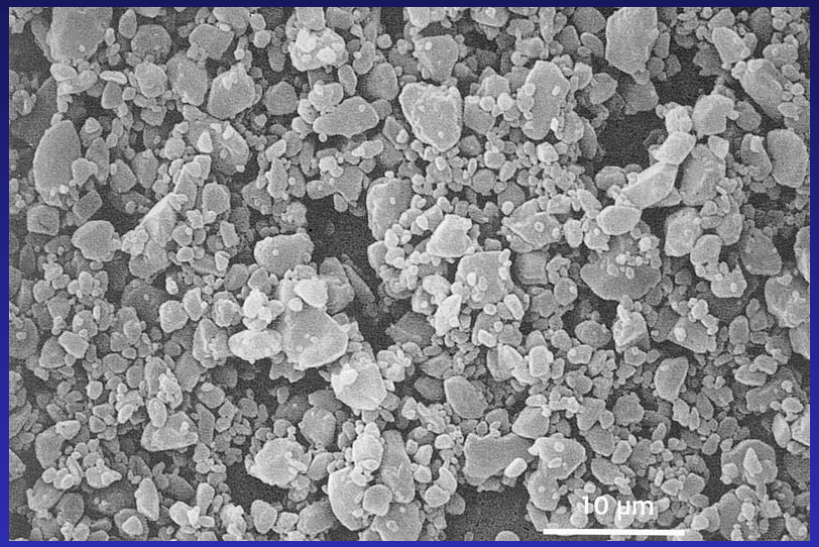
Deposition

Impaction
Sedimentation
Brownian motion

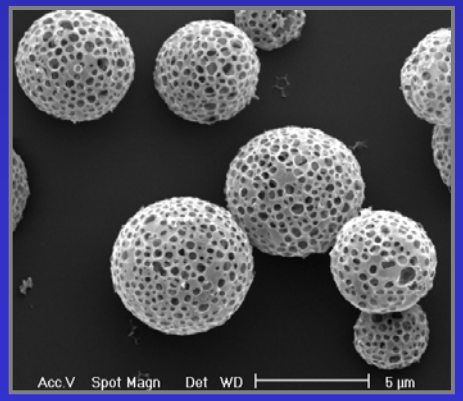




Energy Is Required for Aerosolisation



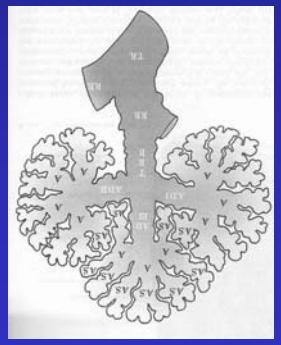
Jet nebuliser	compressed air
pMDI	CFC / HFA
Dry powder	patient

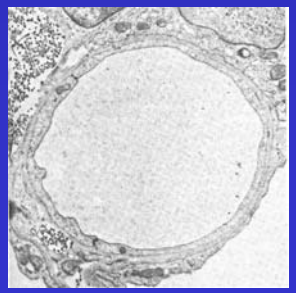


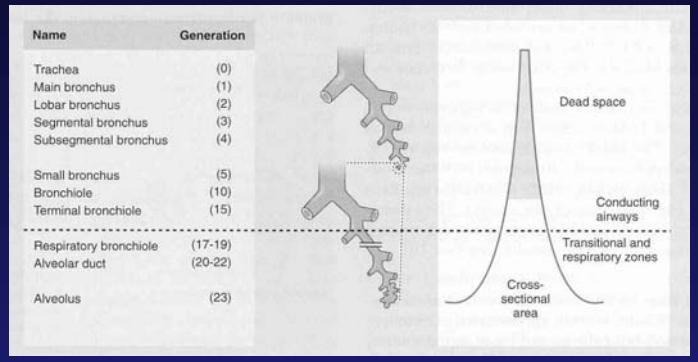
Lung Dose Variability - Healthy Adults

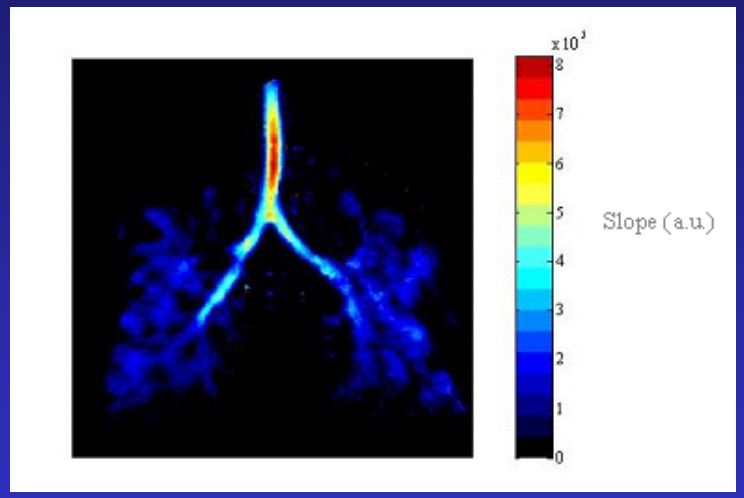
	Intra-subject CV%	Urinary Salbutamol (μg)	'Most efficient'
pMDI	**50.1** % [27-146.8]	**5.4** [0.69-17.6]	
pMDI+HC	**31.7** % [20.1-87]	**11.6** [2.2-35.9]	**7**
Breath Actuated	**33.4** % [10.5-61.9]	**8.8** [2.2-13.2]	**2**
Accuhaler/ Discus	**39.6** % [12.4-75.2]	**9.6** [4.1-14.7]	**3**
Turbohaler	**42.4** % [21.0-73.8]	**7.5** [2.6-17.6]	**1**

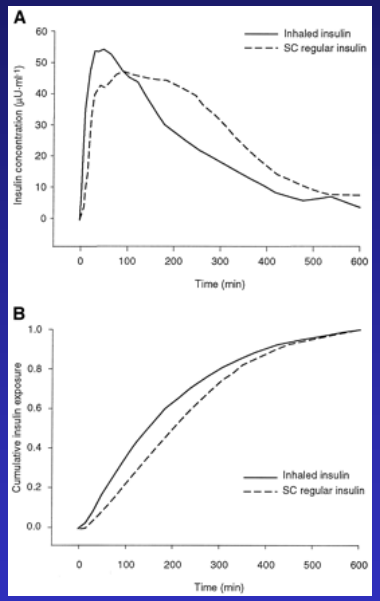
Everard et al J Aerosols Med



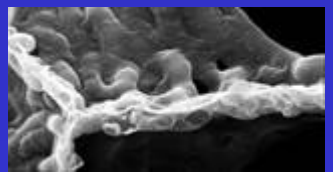




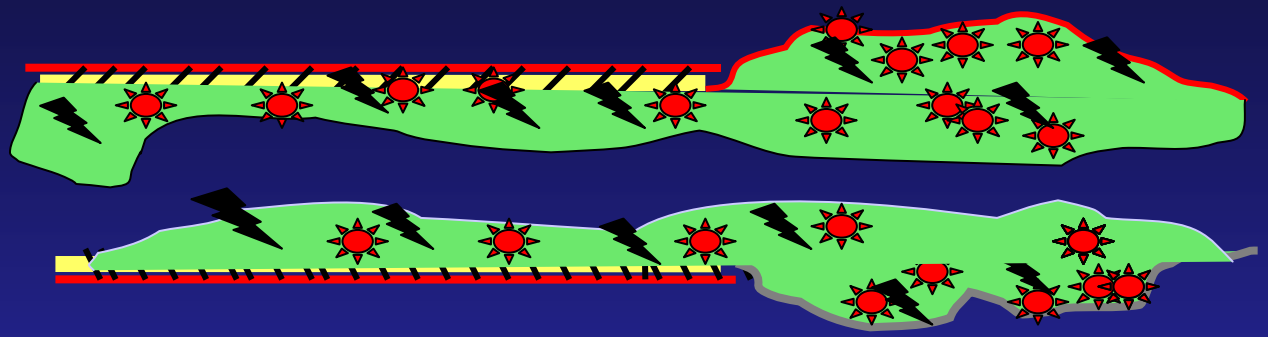


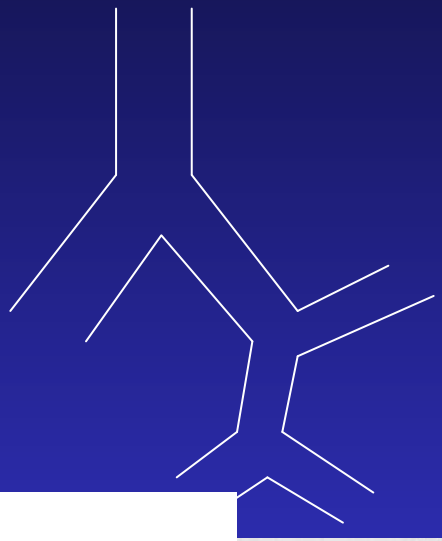


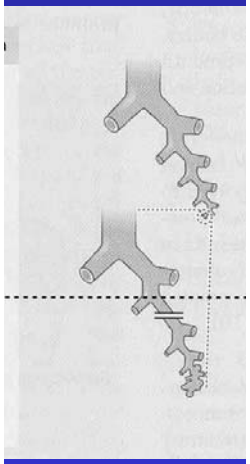
450 Mill. Alveoli
Surface Area of **150 m2**
Diameter ¼ mm
Gasex-change Area 80-90%

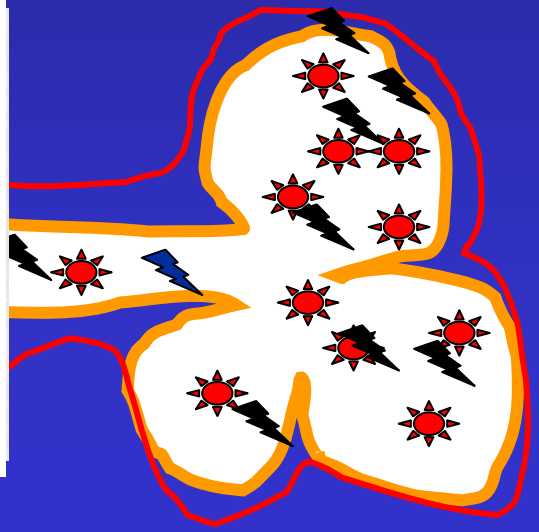


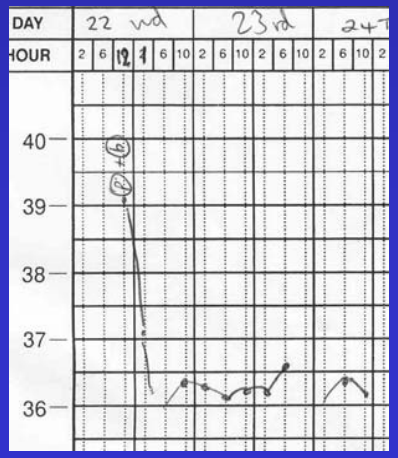
‘Bacterial Chest Infections’



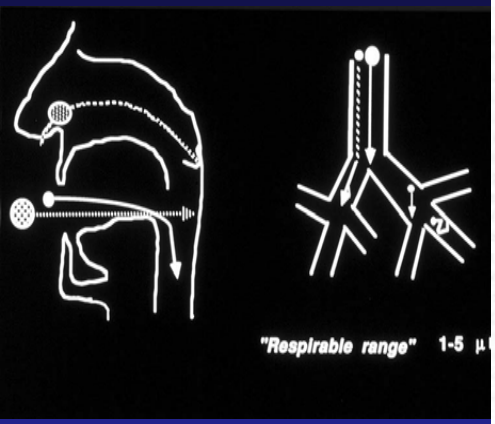


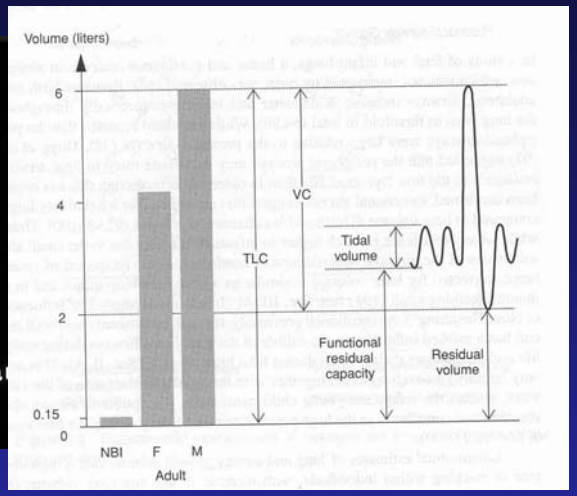


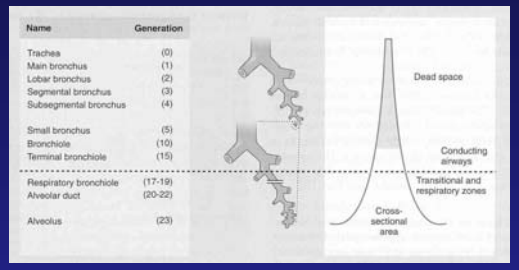


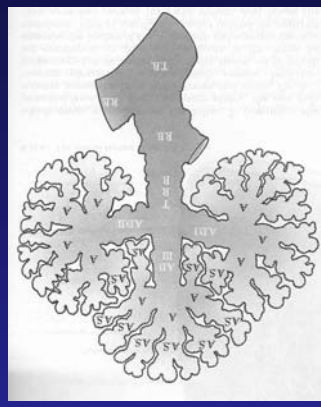


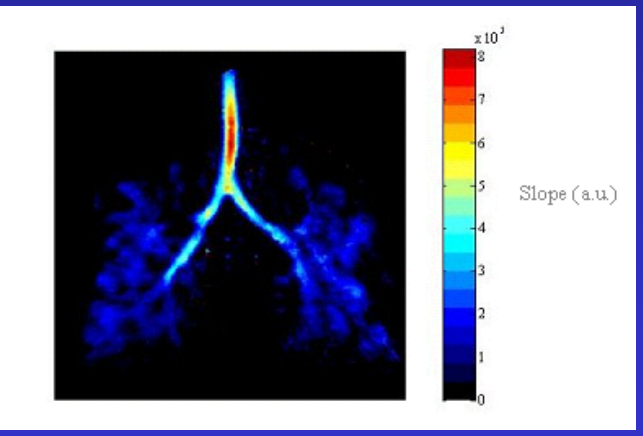
Drug Delivery is Non-Uniform

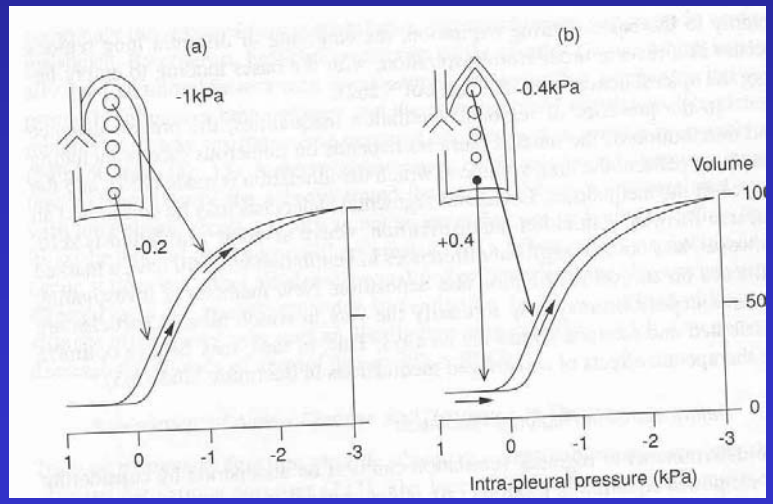


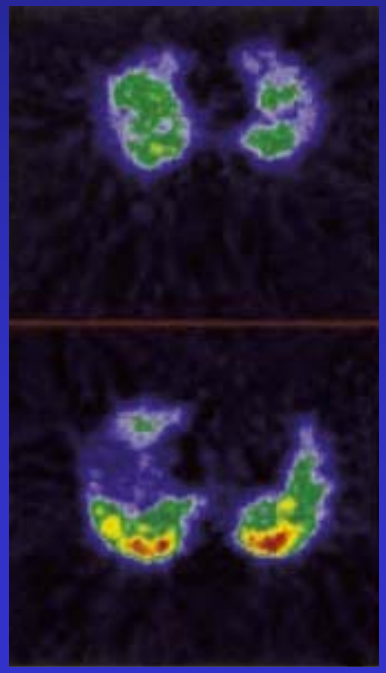




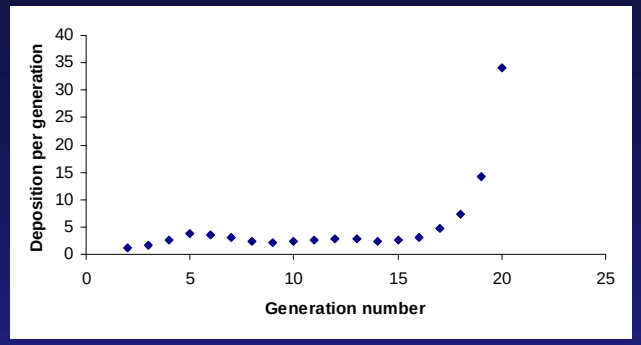


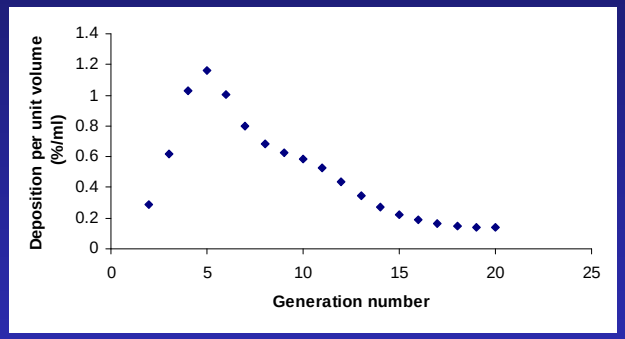


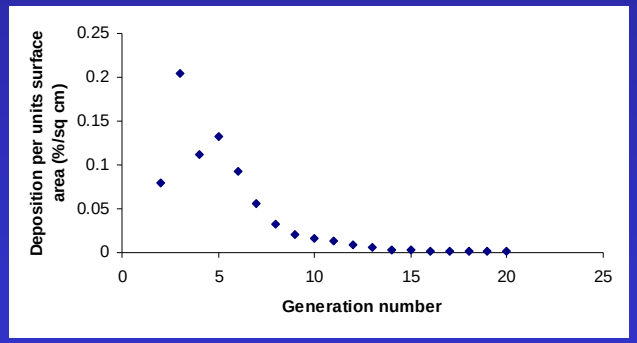




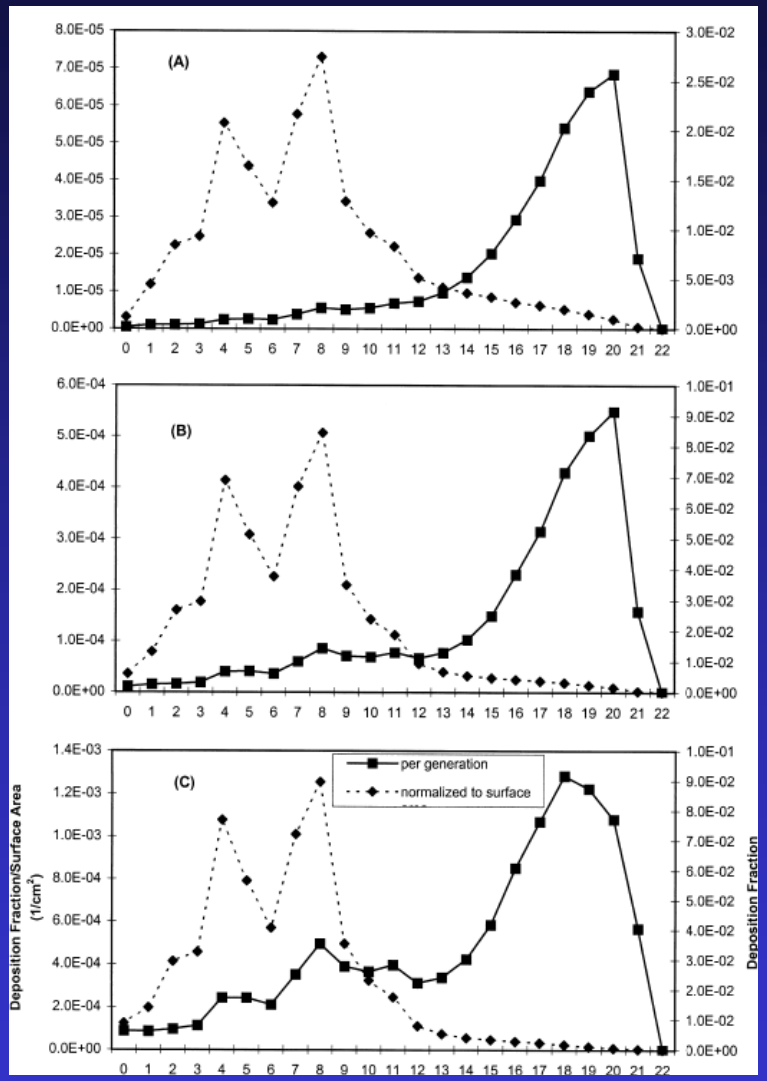
Distribution of Aerosol Deposition



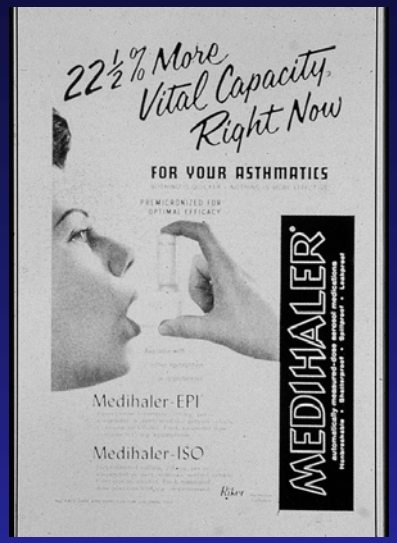


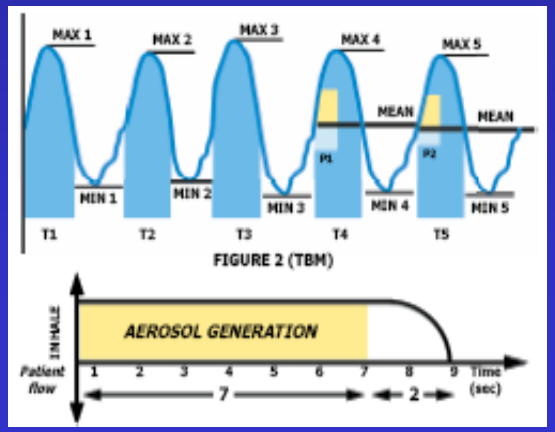


John Fleming, Southampton

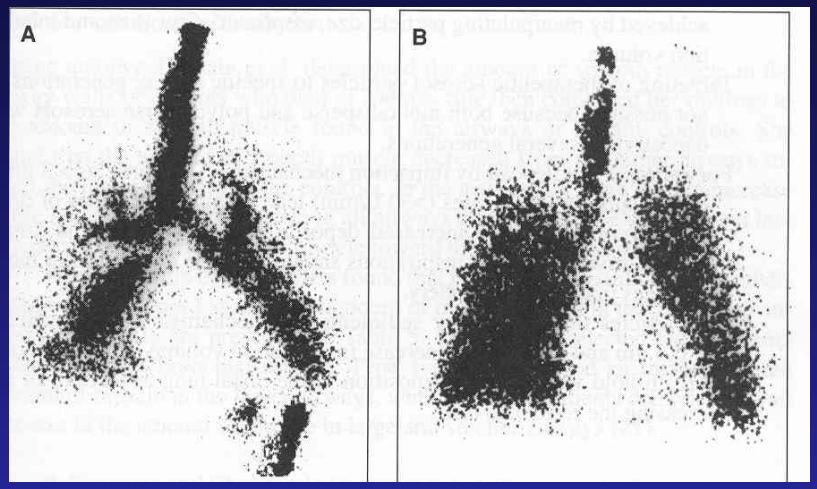


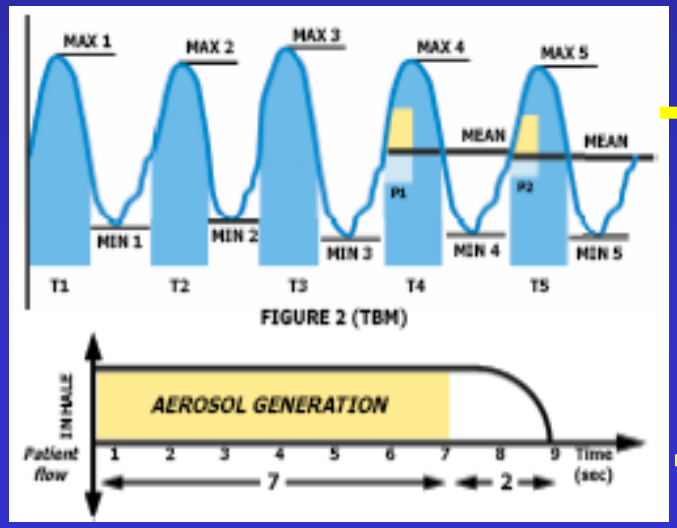
Martonen 2003


22½% More Vital Capacity Right Now
FOR YOUR ASTHMATICS
Medihaler-EPI
Medihaler-ISO
MEDIHALER

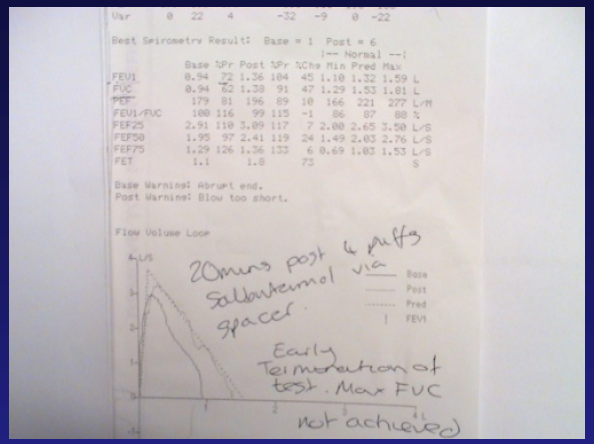

MAX 1
MAX 2
MAX 3
MAX 4
MAX 5
MEAN
MEAN
P1
P2
MIN 1
MIN 2
MIN 3
MIN 4
MIN 5
T1
T2
T3
T4
T5
FIGURE 2 (TBM)
INHALE
AEROSOL GENERATION
Patient flow
1 2 3 4 5 6 7 8 9
Time (sec)
7
2

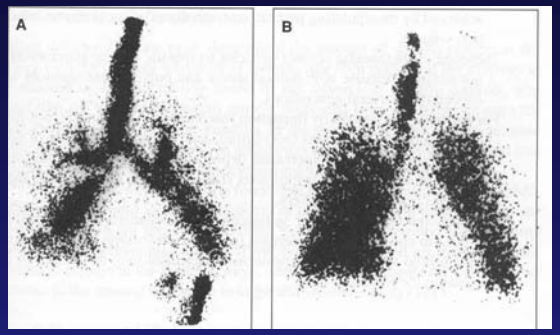
Does Breathing Pattern Matter?



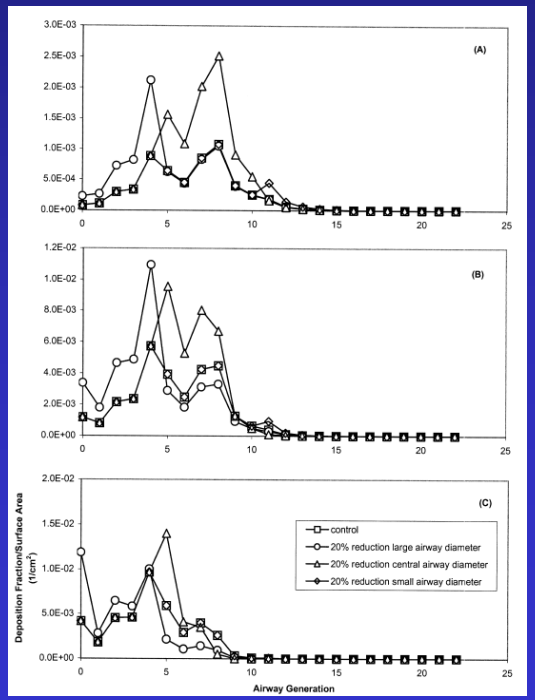


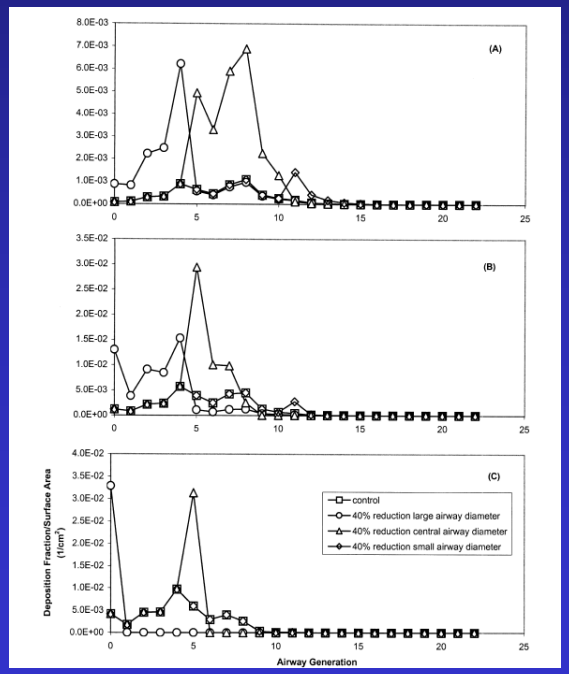
Impact of Disease - Asthma





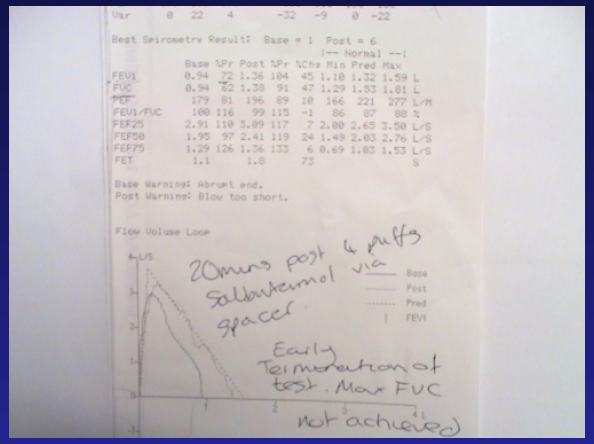
Laube B 1992

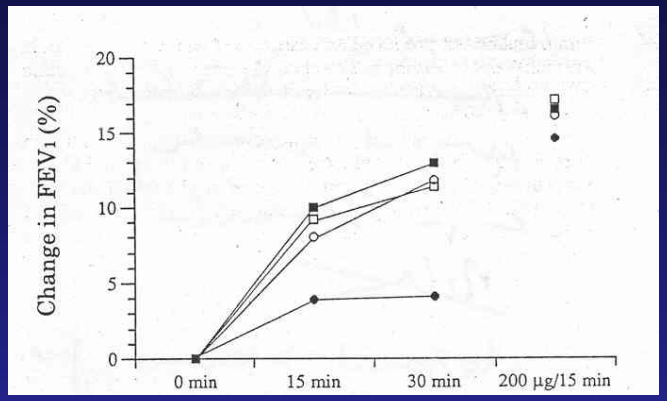


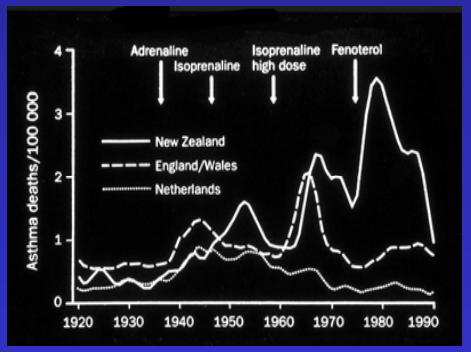


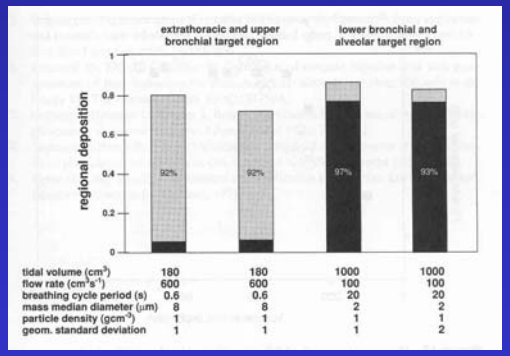
Martonen 2003

Impact of Disease - Asthma

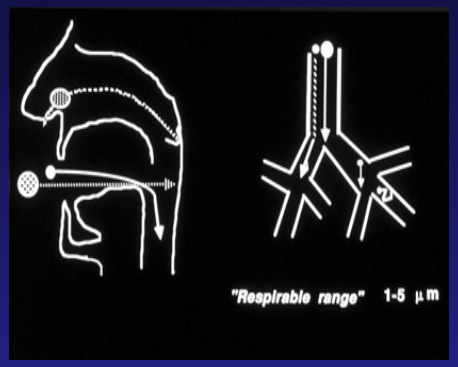


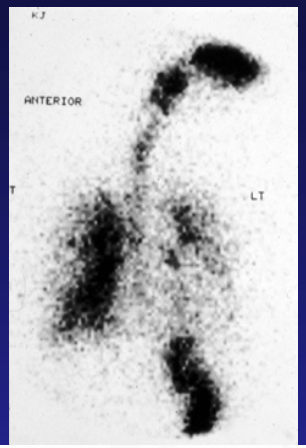


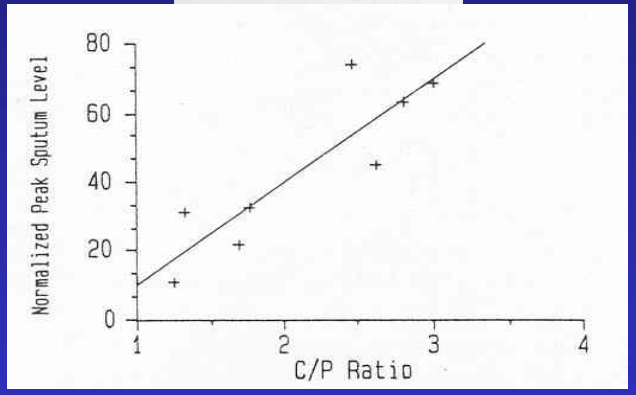


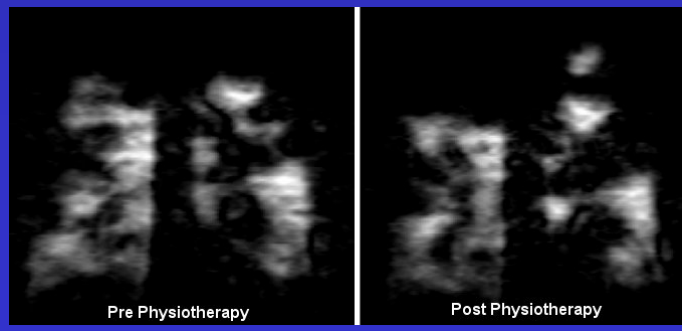


Impact of Disease

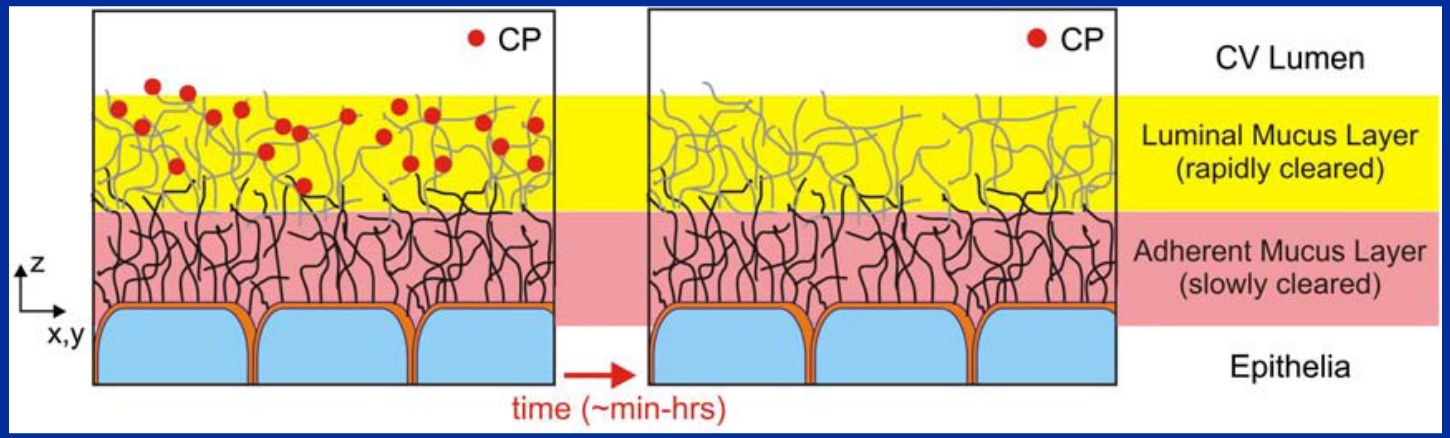


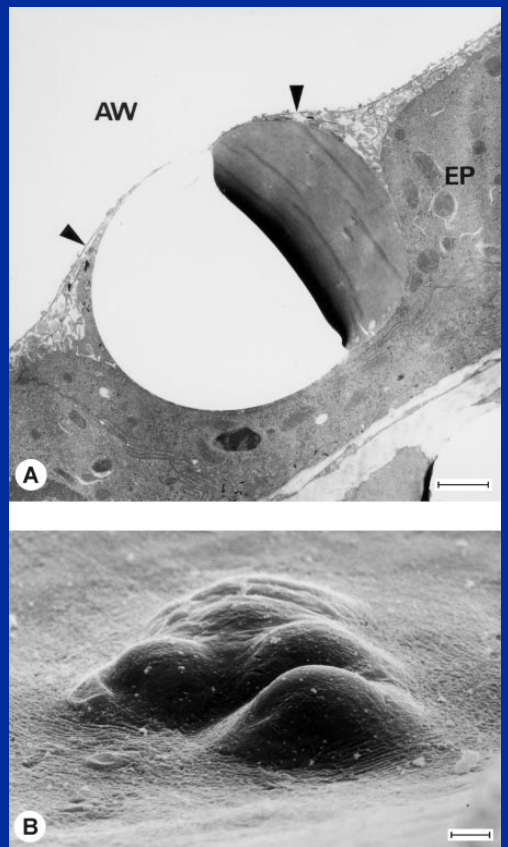


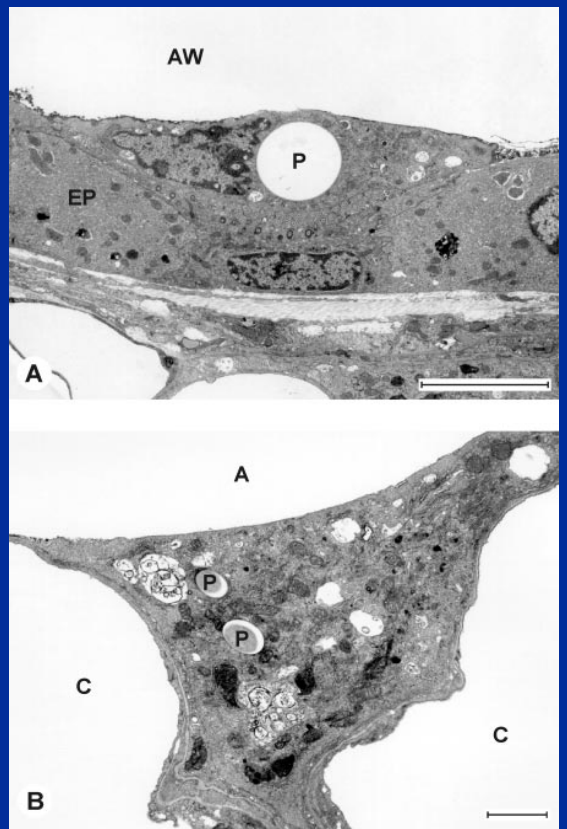


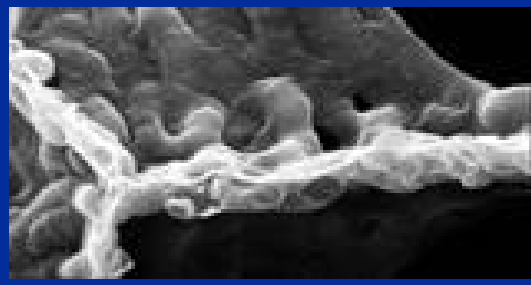


Fate of Deposited Particles

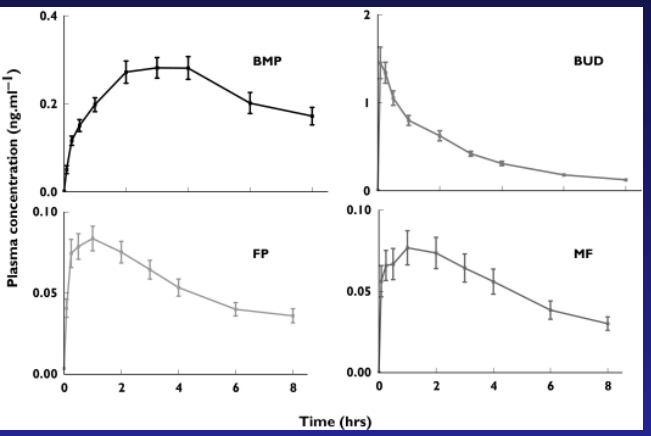


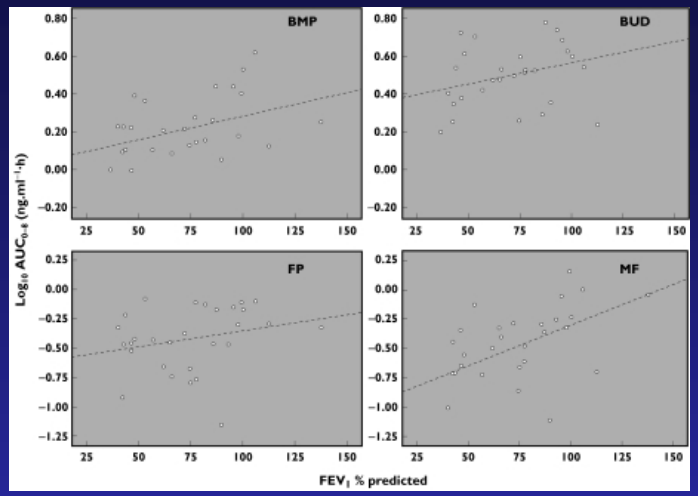


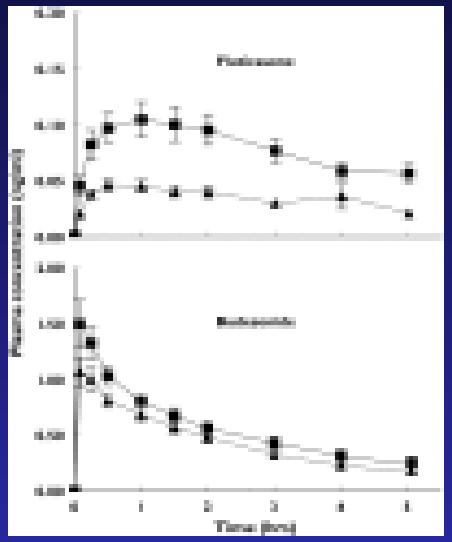


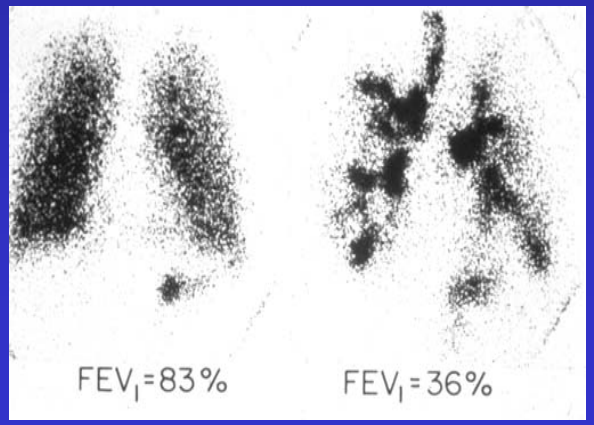


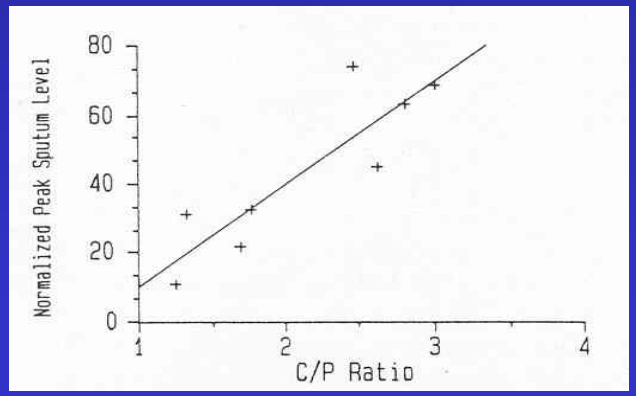
Mucocillary Clearance & Absorption

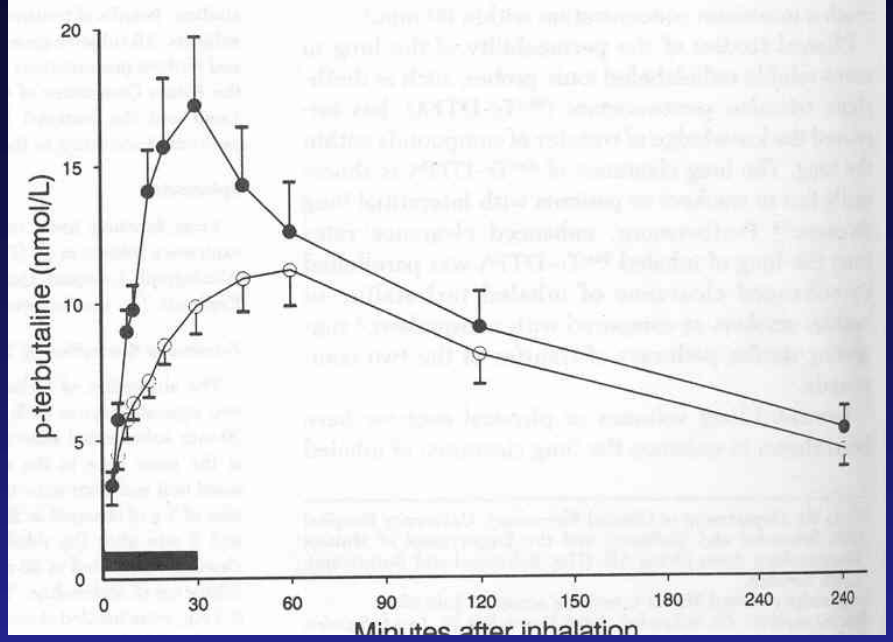


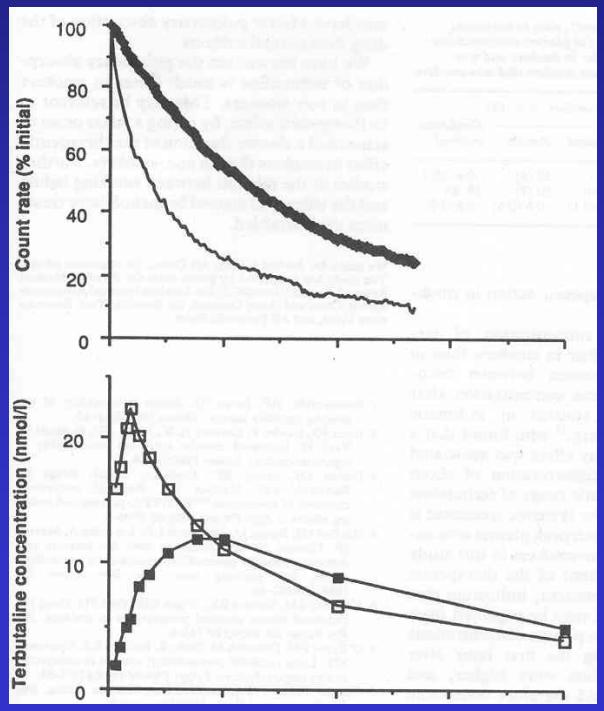




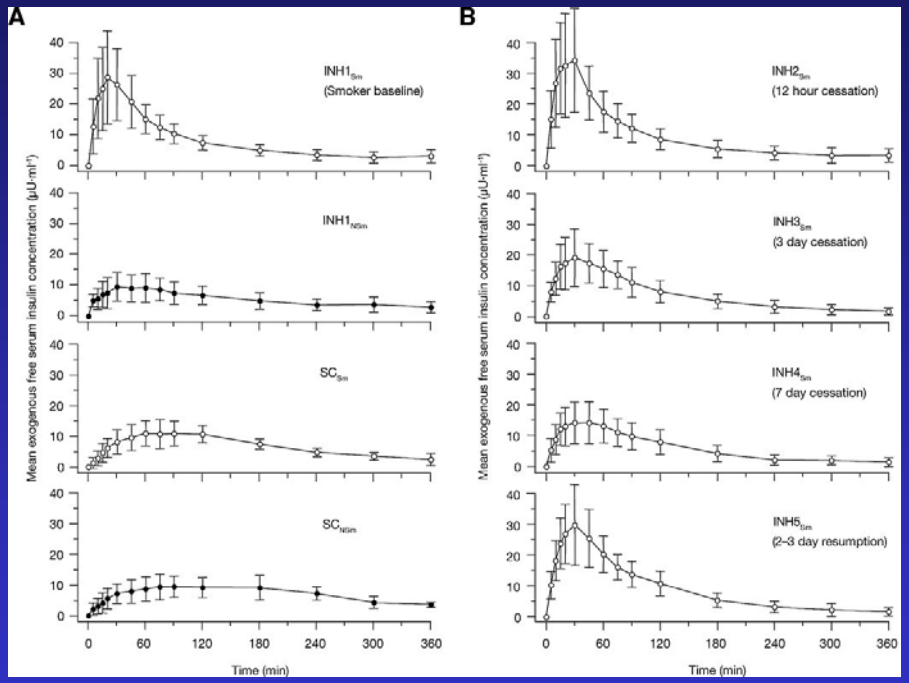






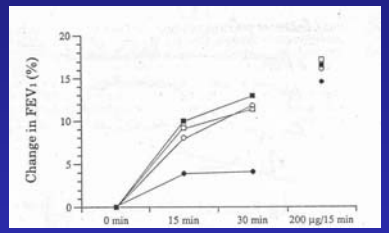


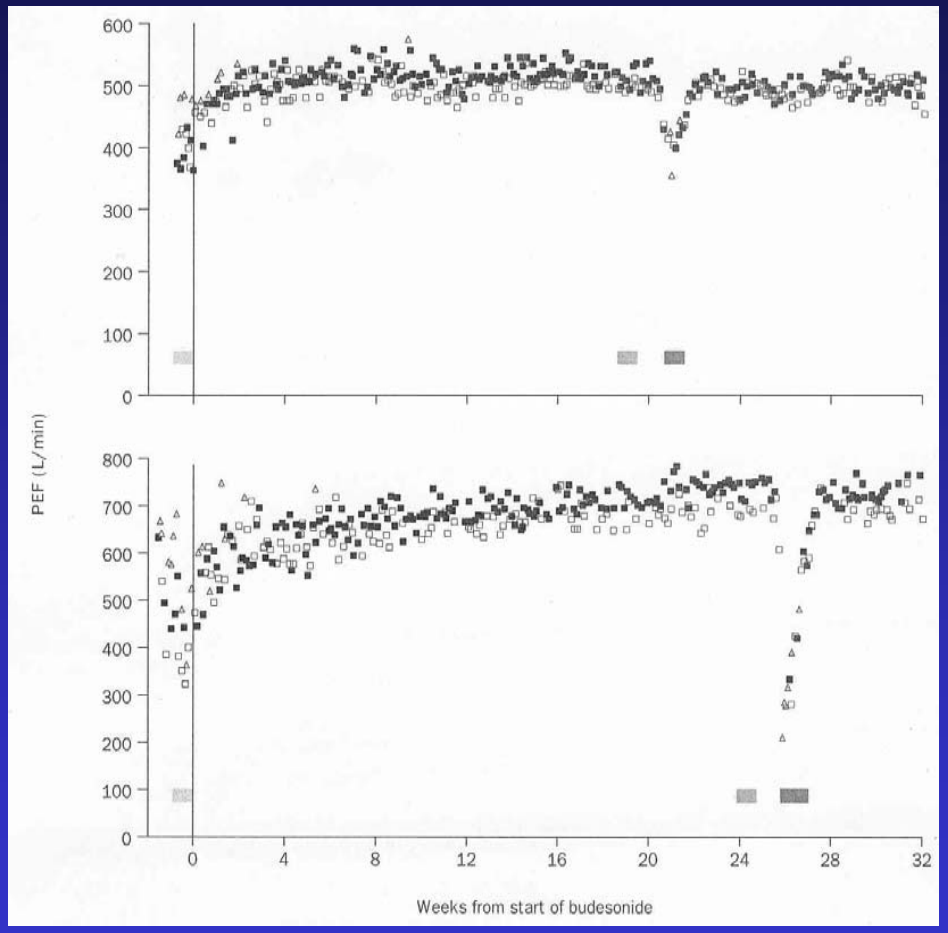
Borgstrom 1992



Becker RHA 2006

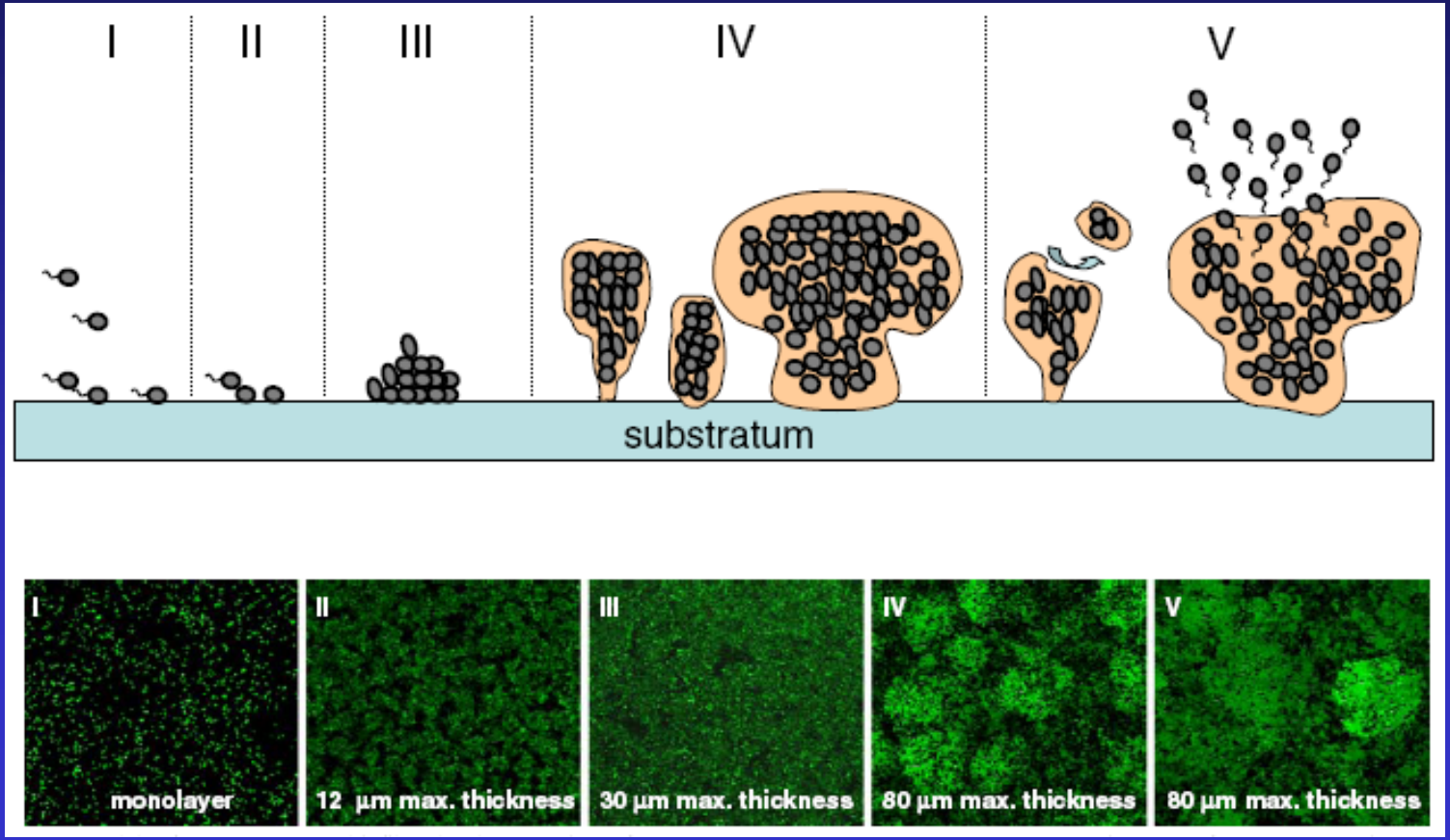
Poor control vs Exacerbation



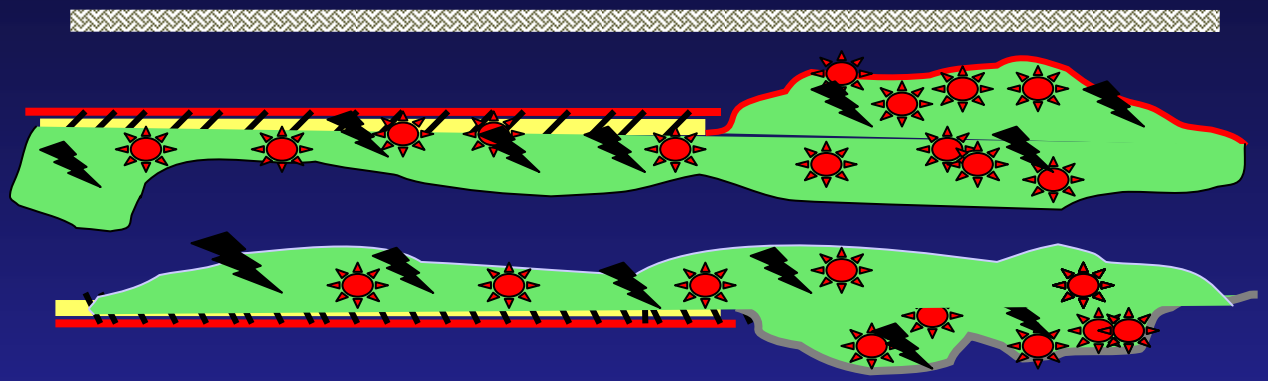


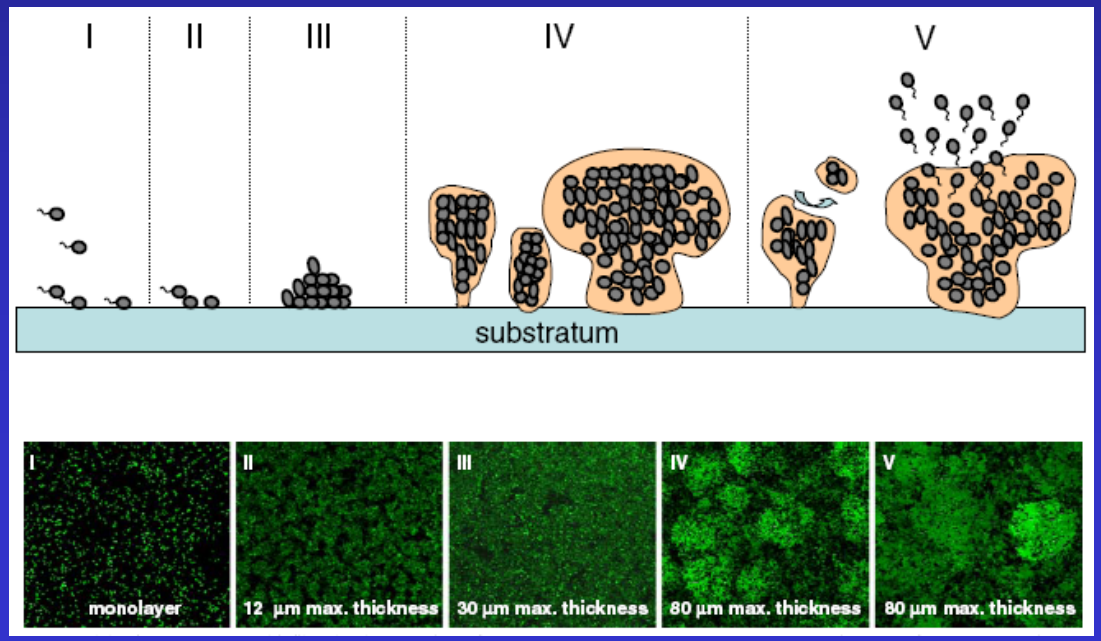
Reddel H Lancet 1999

Biofilms

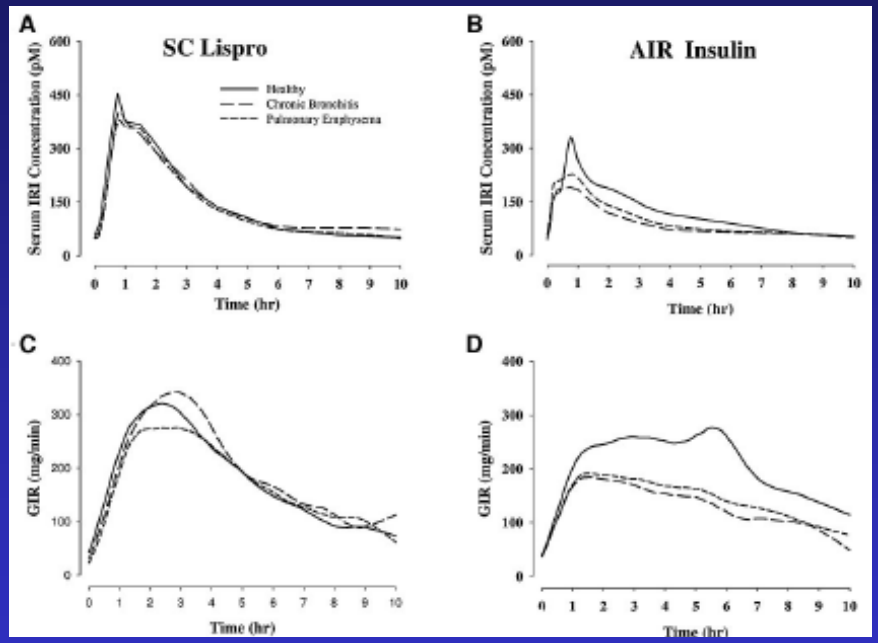

I
II
III
IV
V
substratum
I
monolayer
II
12 µm max. thickness
III
30 µm max. thickness
IV
80 µm max. thickness
V
80 µm max. thickness

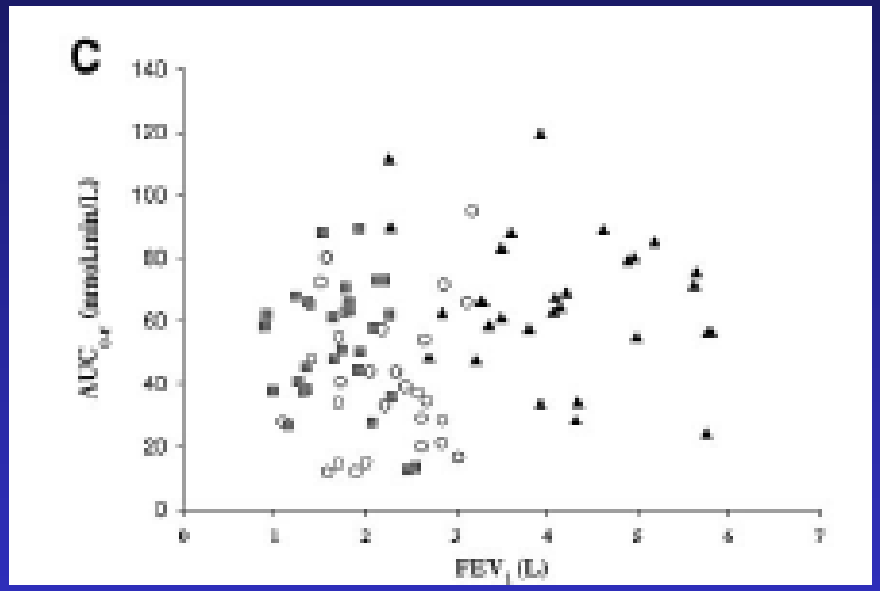
Bacterial Bronchitis
inc CF, bronchiectasis, COPD





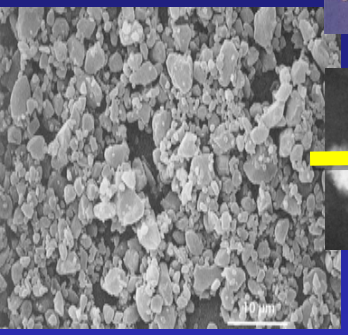
COPD and Insulin



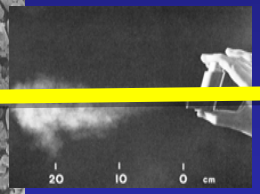


Inhaled Therapy

Drug

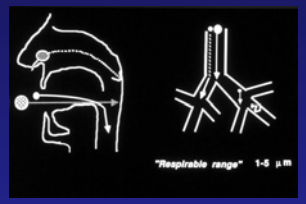


Device



Formulation issues
Availability
Cost
Target

Anatomy Physiology



Inter-subject variation

Age dependent

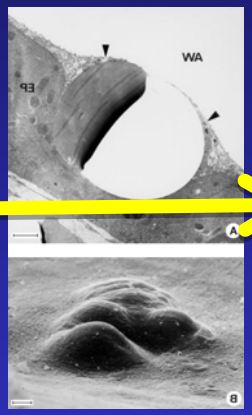
Disease

Generalised

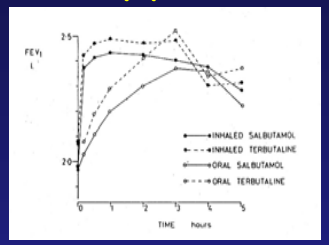
Variable

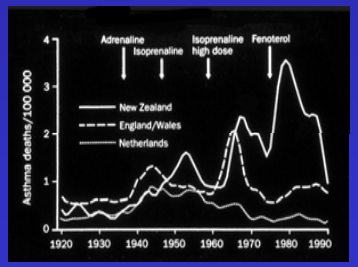
Progressive

Fate of drug



Therapeutic effect





Adverse Effects

Summary

- We are taking on the forces of evolution, pathogens and disease [& regulators!]
- Aerosol are best used in healthy individuals
- Intervene early while you can effectively
- Asthma is relatively easy