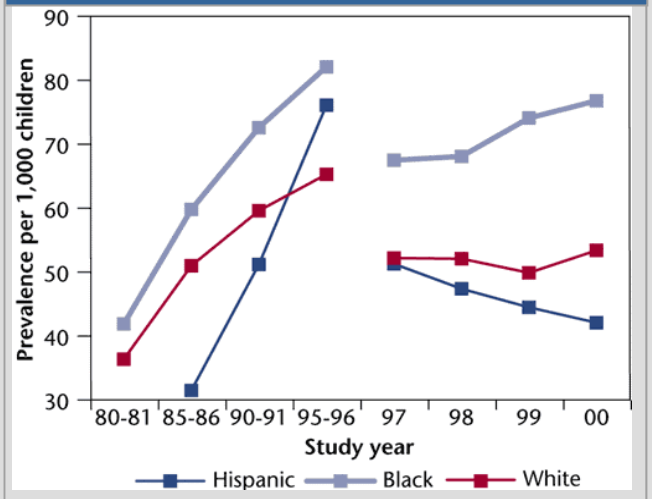
# Emily DiMango, MD
# Asthma II

Director

John Edsall/John Wood Asthma Center

Columbia University Medical Center

**Figure 1**
**Asthma Prevalence, 1980-2000**

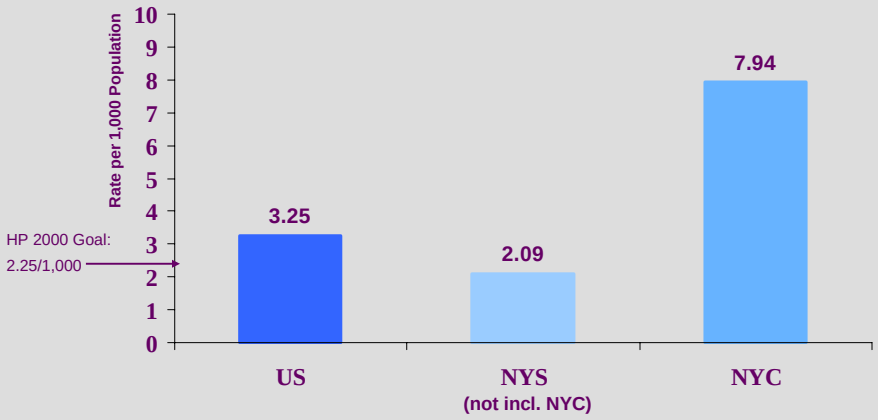


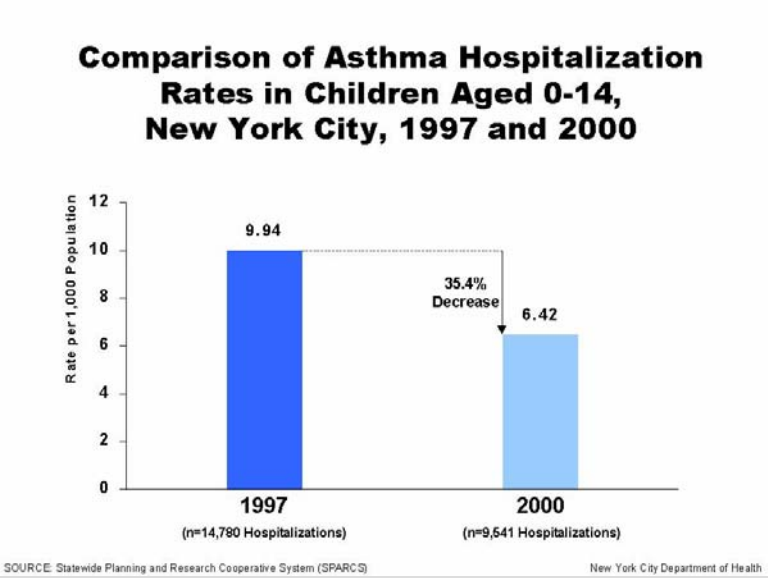

* Gap between 1995-1996 and 1997 indicates a break in trend due to the redesign of the 1997 NHIS.
Source: Data extracted from Akinbami and Schoendorf. *Pediatrics.* 2002.

# Asthma in the US

- 6% of the population (17 million)
- Most common cause of hospitalization among children
- Higher prevalence in some areas
- 5,000 deaths per year.
- Undertreated

## Comparison of Asthma Hospitalization Rates in Children Aged 0-14 in the U.S., NYS and NYC, 1999






# Risk factors for development of asthma

- Family history
- Sensitization to common allergens
- Maternal smoking
- Obesity
- Western lifestyle

- ?? Diet, pollution

# Protective associations

- Cat and dog exposure in early life (protects against all allergen sensitization)
- Exposure to farm animals in early life (endotoxin)
- Day care in first 6 months of life
- Multiple siblings

Ownby, etal. JAMA 2002
Braun-Fahrlander, et al. NEJM 2002

**Percentage of Children with Asthma According to the Number of Older Siblings and the Age at Entry into Day Care**

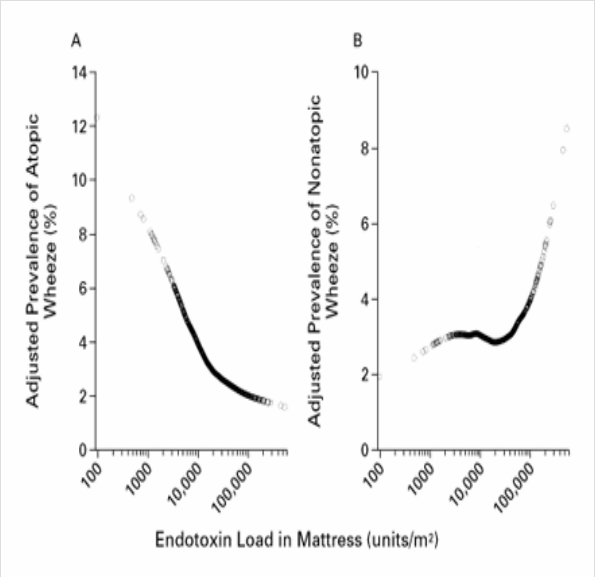
**TABLE 1.** PERCENTAGE OF CHILDREN WITH ASTHMA ACCORDING TO THE NUMBER OF OLDER SIBLINGS AND THE AGE AT ENTRY INTO DAY CARE.

Ball M *NEJM* 2000

| VARIABLE | NO. OF CHILDREN* | ASTHMA | RELATIVE RISK (95% CI)† | P VALUE |
|---|---|---|---|---|
| | | % | | |
| No. of older siblings‡ | | | | |
| 0 | 405 | 21 | 1.0 | |
| 1 | 385 | 19 | 0.9 (0.7–1.0) | 0.04 |
| 2 | 176 | 14 | 0.7 (0.5–1.0) | 0.04 |
| ⩾3 | 69 | 13 | 0.6 (0.4–1.0) | 0.04 |
| Age at entry into day care | | | | |
| >12 mo | 899 | 19 | 1.0 | |
| 7–12 mo | 28 | 18 | 0.9 (0.4–2.1) | 0.88 |
| Birth to 6 mo | 69 | 9 | 0.4 (0.2–1.0) | 0.03 |

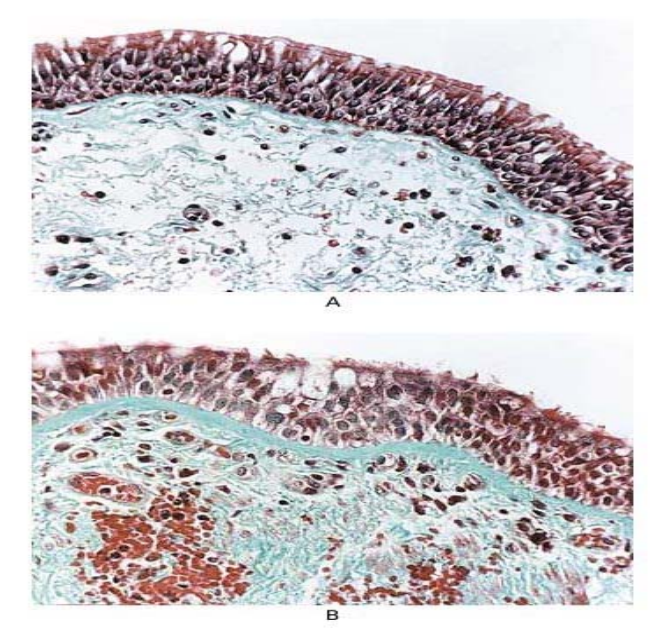
Effect of Endotoxin exposure on wheeze

**Braun-Fahrlander, C. et al. N Engl J Med 2002;347:869-87**




## *Asthma Definition*

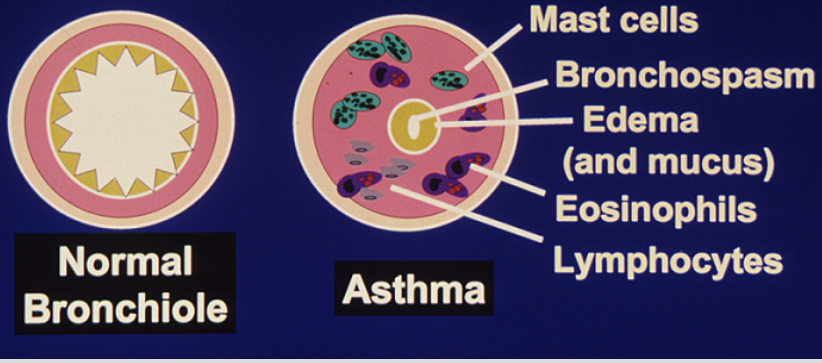
- Chronic inflammatory disorder of the airways
- Usually associated with atopy (extrinsic, intrinsic)
- Obstruction to airflow which is reversible (either spontaneously or with use of medications)
- Airway hyperresponsiveness and narrowing in response to a variety of stimuli



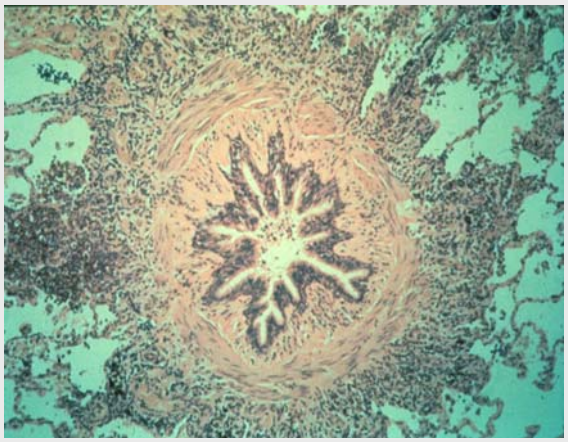

Busse, W, NEJM 2001; 344: 5

## Asthma: A Lung Disease with Airway

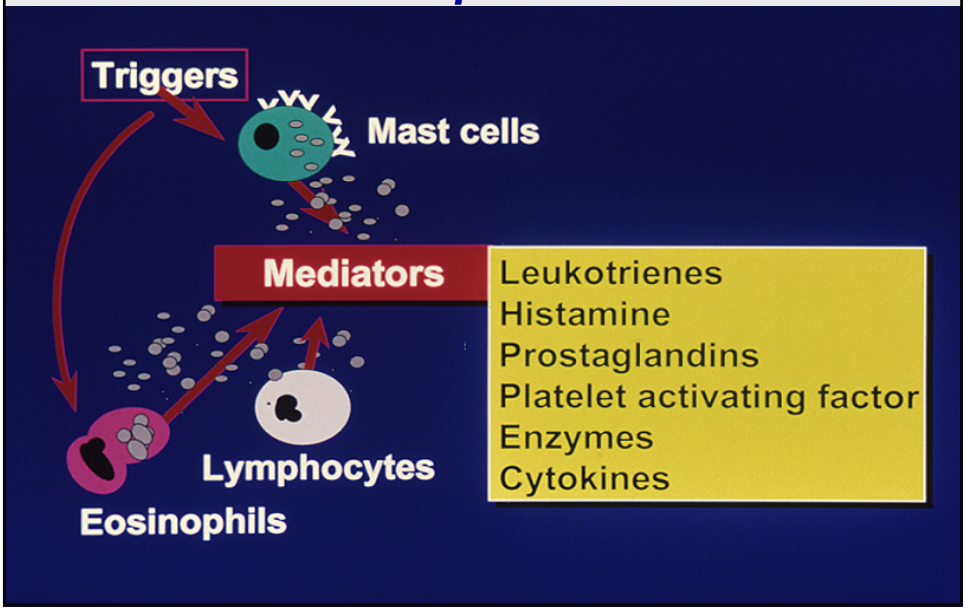
- Obstruction (at least partially reversible)
- Hyperreactivity
- Inflammation



## *Airway Inflammatory Changes*

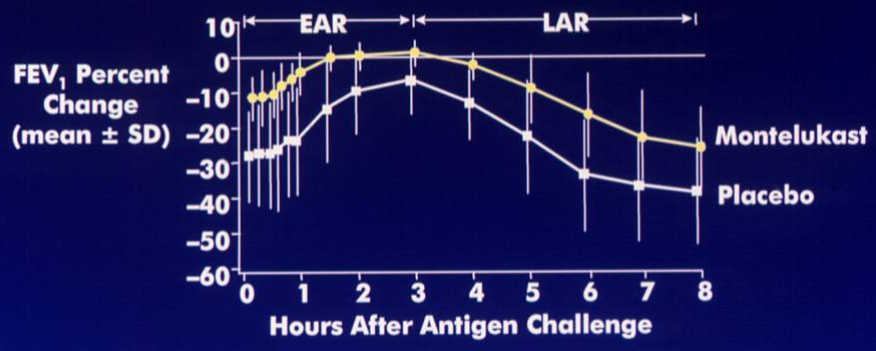


## *Airway inflammation - Early and late Response*



## Early and Late Asthmatic Response Following Antigen Challenge[24]

**12-patient, 2-period crossover study**




EAR = early asthmatic response; LAR = late asthmatic response

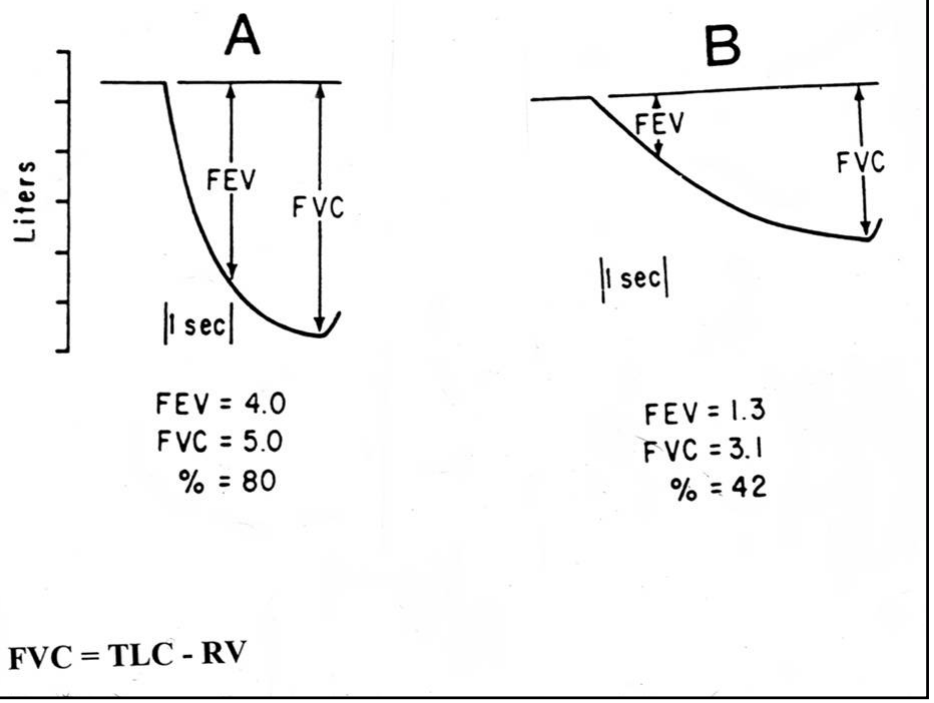
[24]Data on file at Merck & Co., Inc.: DA-SNG14.

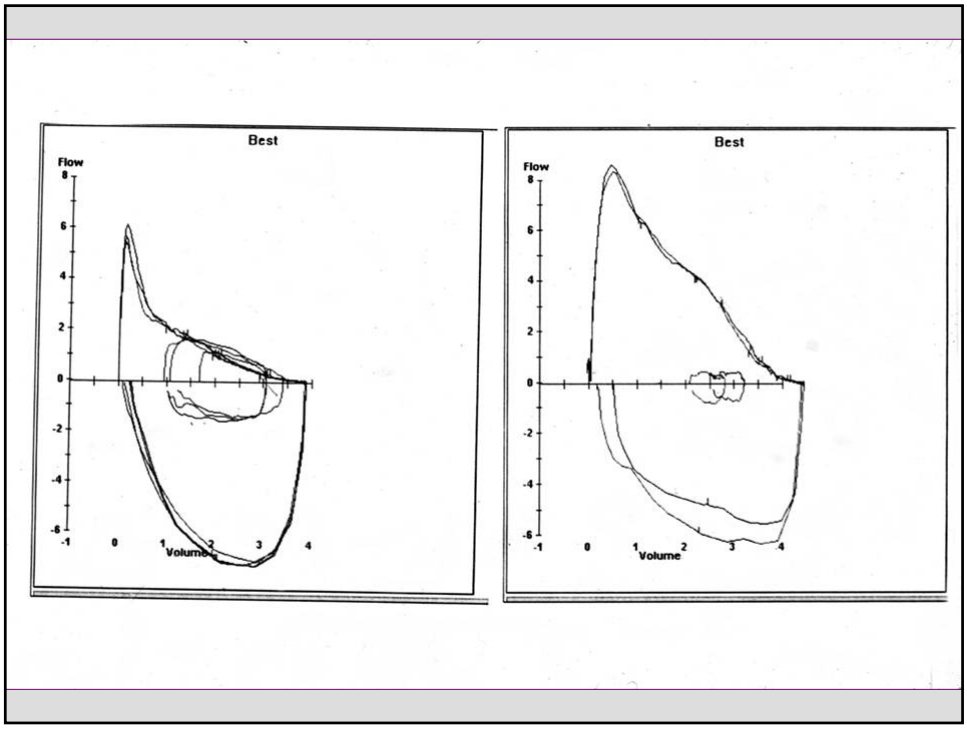
## *Diagnostic Criteria For Asthma*

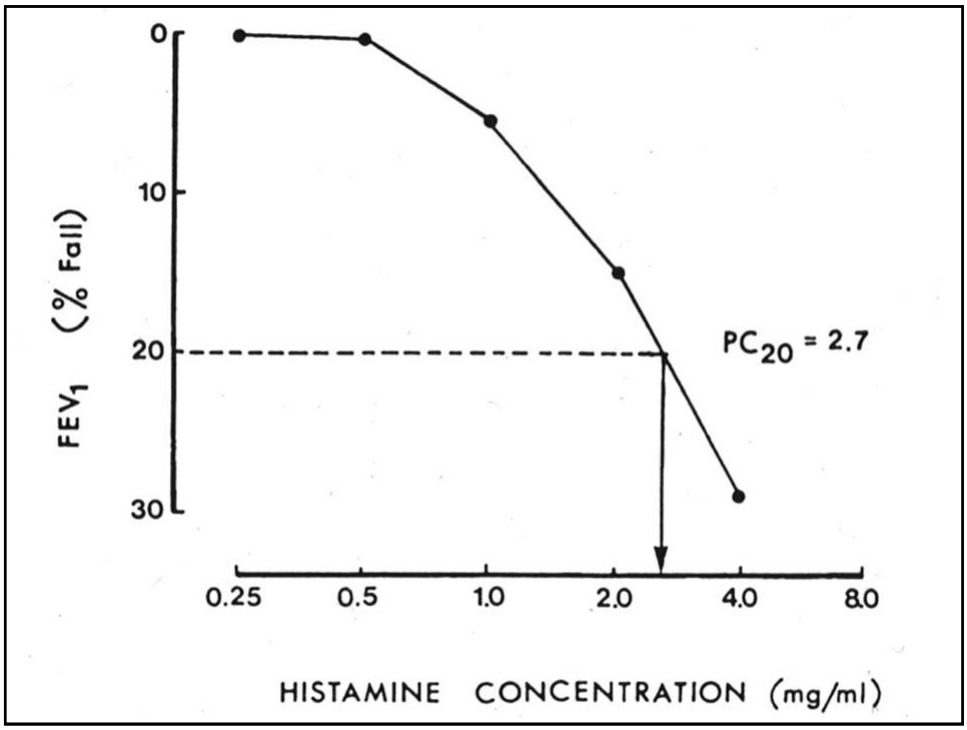
- Cough, dyspnea, wheeze, chest tightness
- Waxing and waning symptoms
- Heightened airway reactivity – exacerbations upon exposure to stimuli
- Episodic airflow limitation in response to antigenic triggers.

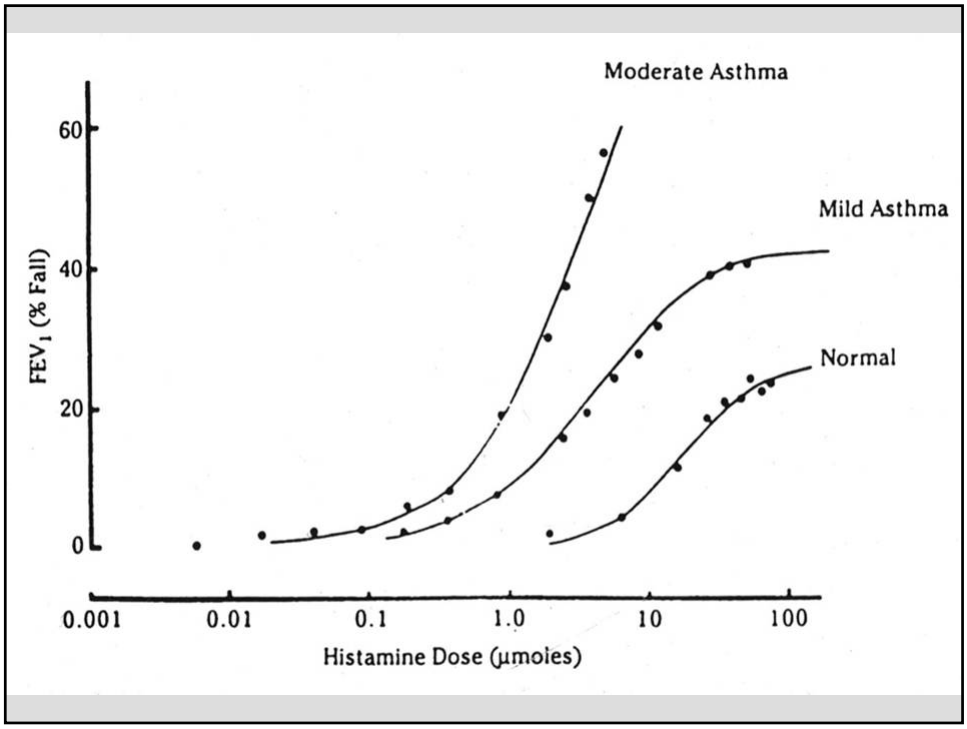
# Physiologic features of asthma

- Reversible airflow limitation (obstructive defect) with a significant (>12%) change in FEV1 in response to inhaled bronchodilator.
- response to bronchoprovocation testing - challenge with agent (histamine, cold air) which provokes bronchial narrowing (decrease of 20%in FEV1) in sensitive individuals. (Clinical trials, professional athletes)

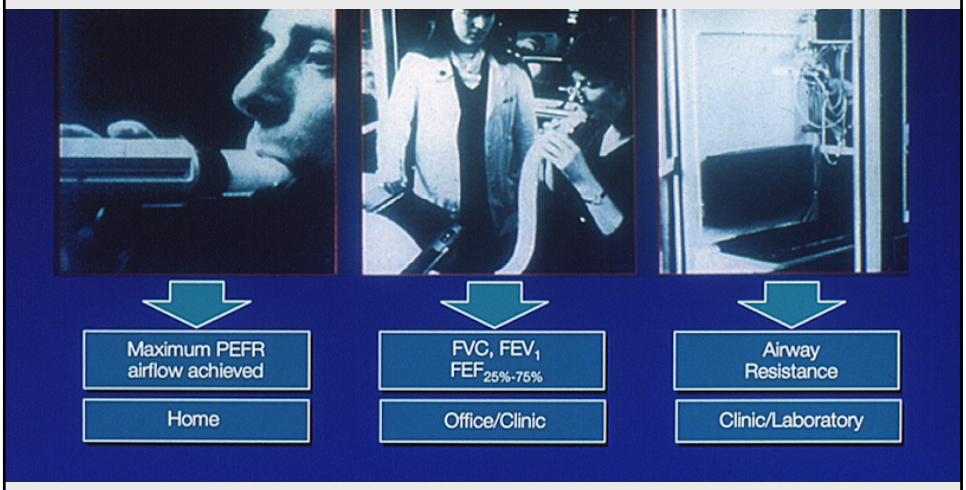



Best
Flow
Volume
Best
Flow
Volume


0
10
20
30
FEV1 (% Fall)
PC20 = 2.7
0.25
0.5
1.0
2.0
4.0
8.0
HISTAMINE CONCENTRATION (mg/ml)




## *Methods For Measuring Airway Caliber*



## Asthma exacerbation

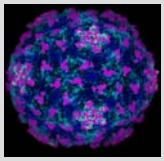
- Asthma trigger leads to bronchoconstriction and increase in airway inflammation– narrowing of airway lumen
- Increased resistance to airflow
- Reduction in FEV1, PEFR
- Will reverse either spontaneously (eventually) or with use of medication

## ***Contributing Factors to Asthma Exacerbation***

- Poorly controlled airway inflammation
- Cold air
- Exercise
- Upper respiratory tract infection
- sinusitis, rhinitis, GERD
- First or second hand tobacco smoke
- environmental allergens – indoor and outdoor

# Asthma Triggers

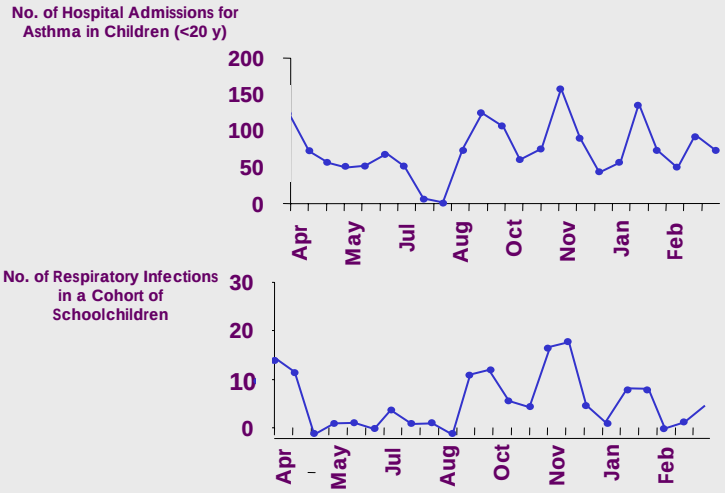




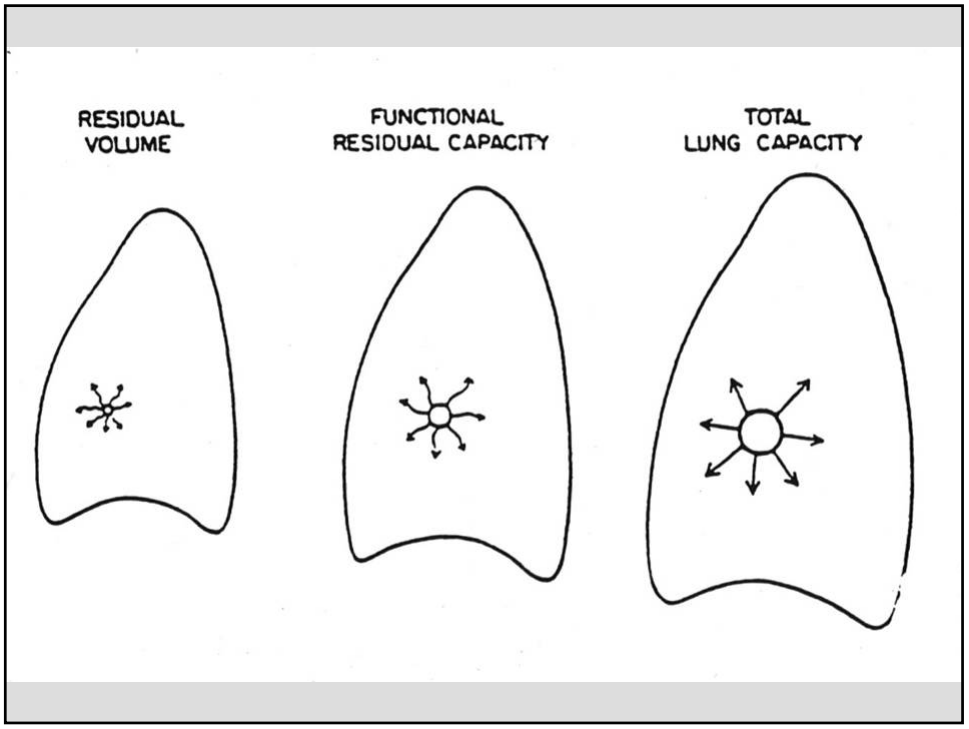


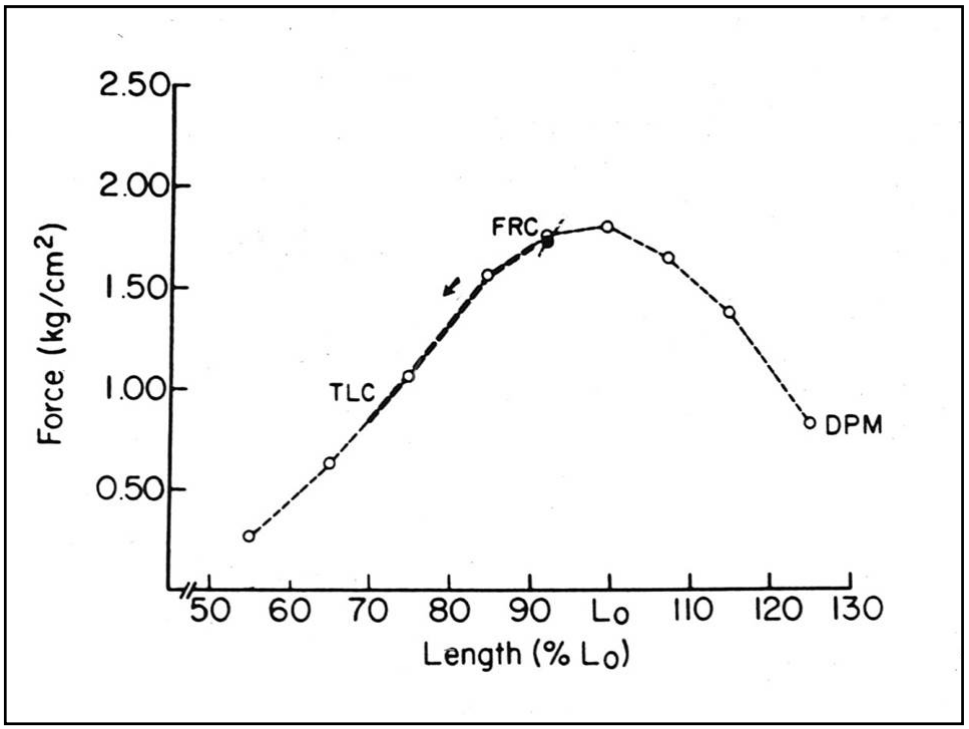
# *Seasonal Patterns in Viral Infection and Asthma Exacerbation*

***Hospital Admissions 1989-1990***




*In Wessex Regional Health Authority.
Johnston SL, et al. *Am J Respir Crit Care Med*. 1996;154:654-660.


RESIDUAL VOLUME
FUNCTIONAL RESIDUAL CAPACITY
TOTAL LUNG CAPACITY


2.50
2.00
1.50
1.00
0.50
Force (kg/cm²)
FRC
TLC
DPM
50
60
70
80
90
Lo
110
120
130
Length (% Lo)

## Gas exchange abnormalities in acute asthma exacerbation

- Low V/Q leads to hypoxemia
- Increased ventilatory drive leads to reduction in pCO2.
- As severity of airflow obstruction increases, respiratory muscle fatigue develops and $pCO_2$ "pseudo-normalizes" then becomes elevated.

## Physical Examination

***Physical examination of the chest may be normal.***

- **Wheezing or prolonged force expiration**
  - **may not correlate with obstruction**
- **Hyperinflation of the lungs**
- **Use of accessory muscles**

## Pathologic targets in asthma

- Bronchial smooth muscle
- Airway inflammatory cells
- Inflammatory cytokines
- Bronchial epithelium
- Bronchial blood vessels (anti-VLA-4)

## Reliever vs. controller medications

Reliever medications

- Short acting bronchodilators

Controller medications

- Inhaled corticosteroids
- Leukotriene modifiers
- Theophylline
- Cromolyn
- Long acting bronchodilators

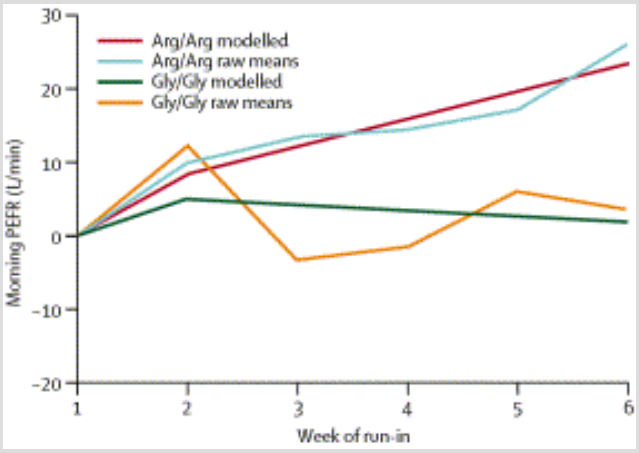
## $ß_2$-agonists (Albuterol)

- Bind to $ß_2$ receptors on airway smooth muscle cells, cause relaxation of muscle and bronchial dilatation
- Most effective bronchodilators available, short term relief of bronchoconstriction
- Rapid onset of activity; duration of action 3-6 hours.
- “rescue” therapy for symptom relief
- no effect on chronic inflammation

## Side effects of $b_2$ agonists

- Due to <u>non-airway</u> $b_2$ activity: skeletal muscle tremor
- Due to overlap $b_1$ activity: tachycardia, arrhythmia, hypokalemia
- Excessive use related to higher mortality and morbidity – may be marker for more severe disease/airway inflammation
- Possible tachyphylaxis – mild downregulation of cell surface receptor number and desensitization of the receptor to drug – not clinically significant.

Effect of polymorphisms at the amino acid residue 16 locus of the $B_2$ adrenergic receptor




## Glucocorticoids (Steroids)

- Most effective anti-inflammatory agent for treatment of persistent asthma
- Reduce influx of inflammatory cells into the airways (eosinophils, lymphs)
- Reduce production of pro-inflammatory cytokines by airway epithelial cells
- Reduce airway edema and mucus production
- May reduce airway remodeling

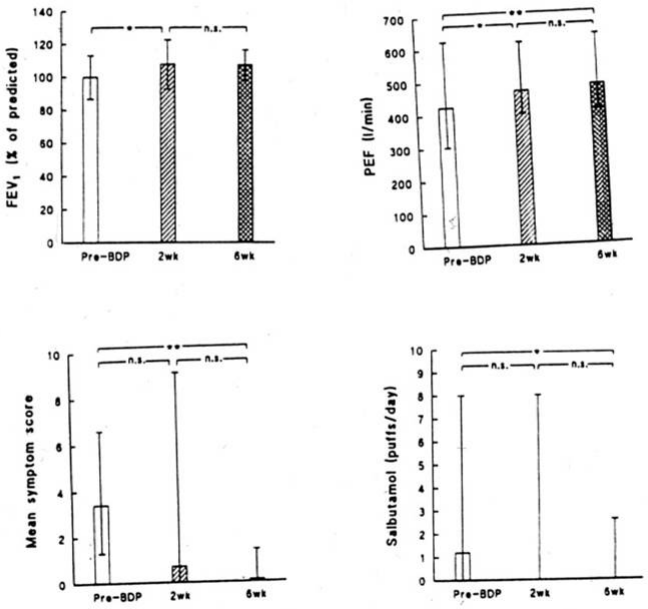
## Inhaled glucocorticoids

- First line therapy for all but very mild asthma
- Early initiation of therapy may preserve lung function over long term

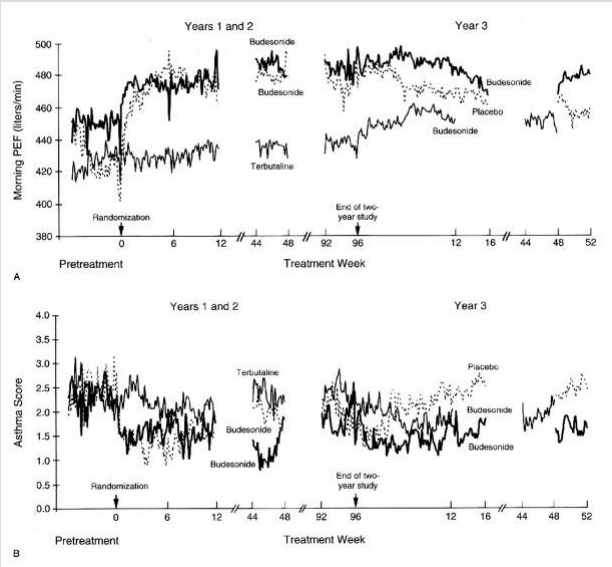
## Side effects of inhaled steroids

- Thrush and dysphonia are local effects
- Potential systemic effects: growth retardation, adrenal suppression, osteoporosis, cataracts, acne, skin fragility with high doses.

# SHORT TERM EFFICACY OF INHALED STEROIDS

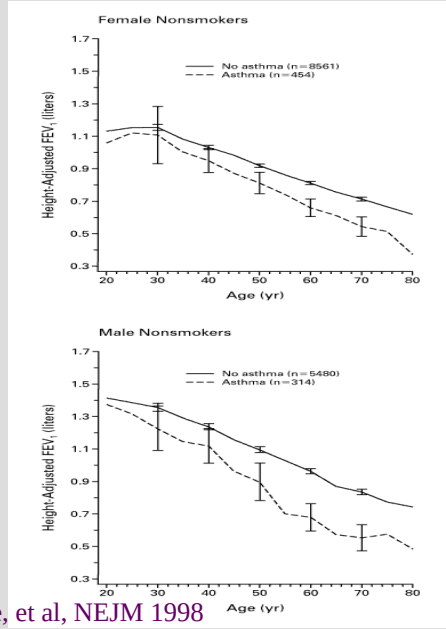



Early initiation of inhaled corticosteroids preserves lung function




Haahtela, T. et al. N Engl J Med 1994;331:700-705

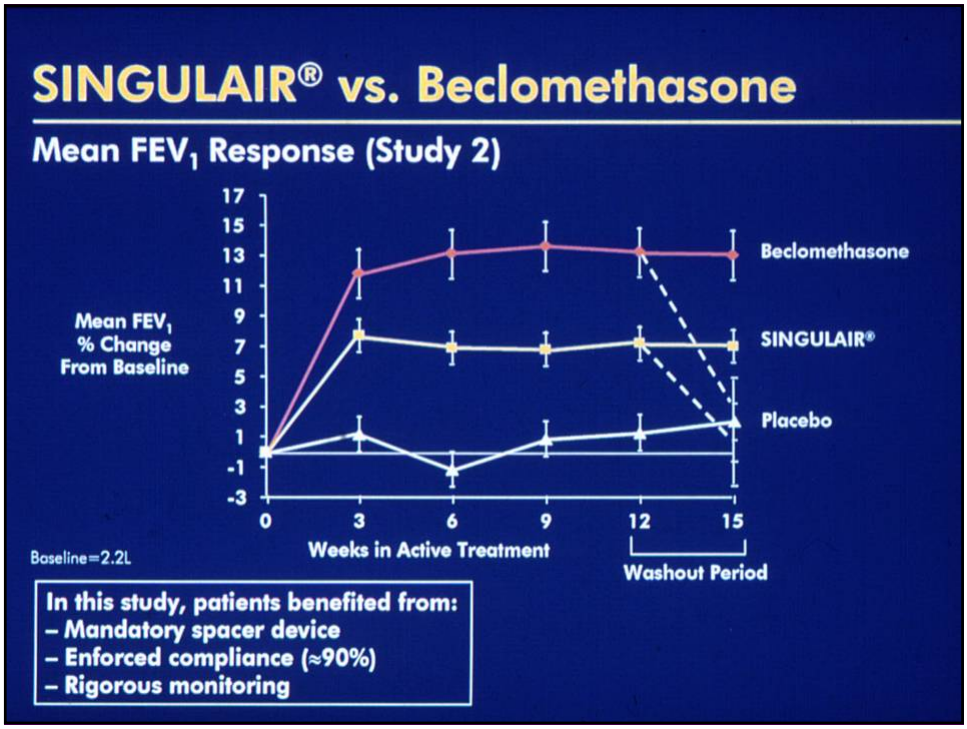
Accelerated decline in lung function among asthmatics




Lange, et al, NEJM 1998

# Leukotrienes in Asthma

- Chemoattractant for eosinophils
- Smooth muscle contraction
- Vascular permeability
- Enhanced mucus production
- Can block by leukotriene synthesis inhibitors or receptor antagonists (oral agents)

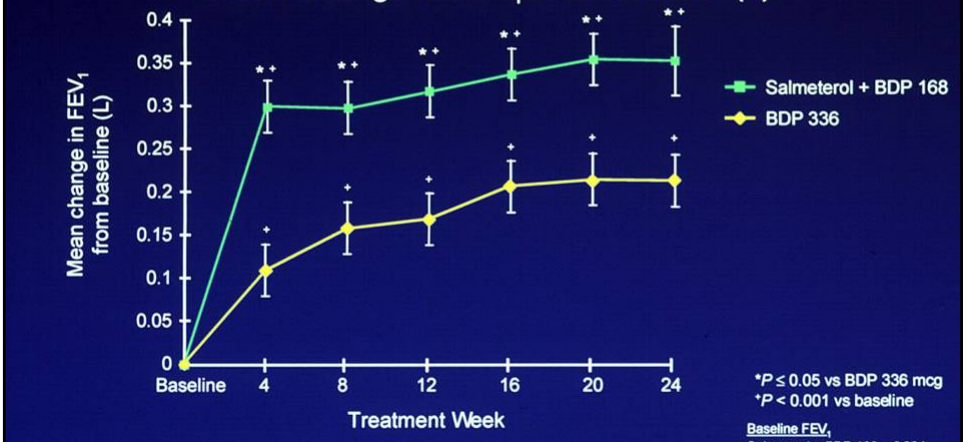



# Long acting beta agonists

- Inhaled salmeterol (component of Advair®)and formoterol
- Duration of action 12 hours, bid drug
- Delayed onset of action (30 minutes)
- Efficacious in moderate to severe asthma
- Allow reduction of inhaled steroid dose
- **Not monotherapy**; ie use only as add on therapy to anti inflammatory agents – avoid masking of inflammation

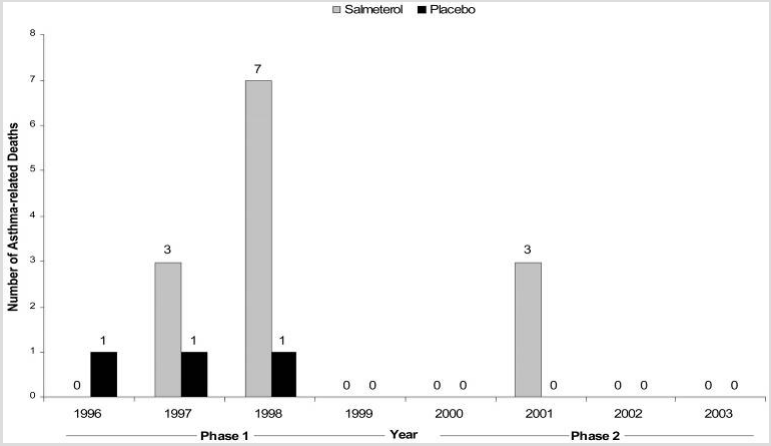
- **New black box warning: Increased mortality and serious events in some patients taking long acting beta agonists, particularly African Americans**

## Effect of Salmeterol added to low dose inhaled steroids




Adapted from J. Murray, *Allergy and Asthma Proc.* 1999;20:173-180.

## Occurrence of asthma-related deaths by phase and study year




Nelson, H. S. et al. Chest 2006;129:15-26

## *Anticholinergic Drugs (Ipratropium Bromide)*

- Block muscarinic receptors on airway smooth muscle
- Inhibit bronchoconstriciton caused by cholingeric nerves, no action against the direct effects of mediators on airway smooth muscle
- slower onset of action; reduced efficacy compared with $b_2$ agonists
- Additive when used in combination with $b_2$ agonists

## theophylline

- Phosphodiesterase inhibitor – increases intracellullar cAMP in inflammatory cells
- Anti-inflammatory and bronchodilator properties
- Additive therapy when not adequately controlled with inhaled steroids
- Therapeutic ratio limits use; better agents available; more selective agents under study

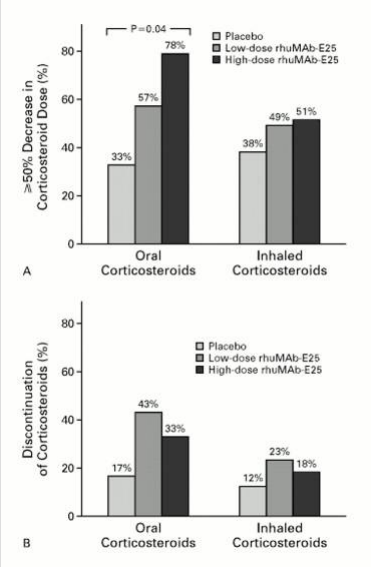
## Biologics in treatment of asthma

- Targeted toward specific mediators
- Anti-IL5 tested, not efficacious
- Monoclonal Ab-IgE is first compound commercially available.
- Expensive

## Monoclonal Ab – IgE (omalizumab, xolair®)

- Approved for treatment of moderate and severe asthma only in atopic asthma
- Effective in reducing asthma exacerbation rate and reducing required corticosteroid dose
- Subcutaneous injections 1-2x/month

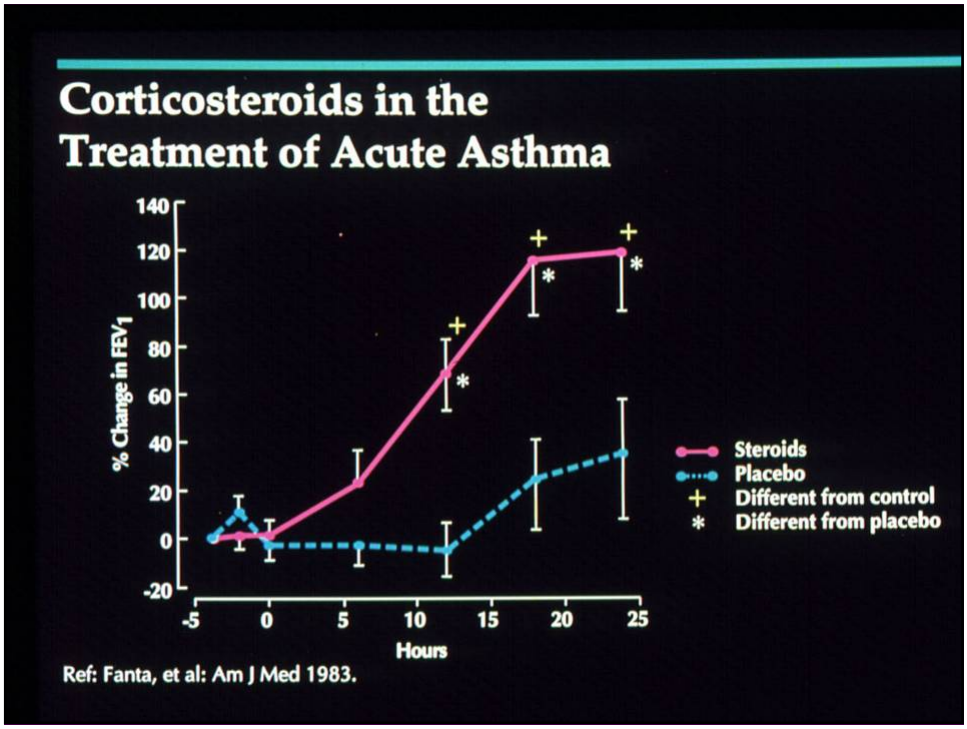
Effect of anti-IgE on corticosteroid dose in severe asthmatics




Milgrom, H. et al. N Engl J Med 1999;341:1966-1973

# Treatment of acute asthma exacerbation

- High dose $b_2$ agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation




## Assessment of asthma severity during office visits

- Nocturnal awakenings from asthma symptoms
- Days per week with symptoms
- Need for rescue bronchodilators
- Activity limitation because of asthma

## *NAEPP (2002) Guidelines for Asthma Severity classification*

- Mild intermittent: symptoms < 2x/week, nocturnal symptoms < 2x/month, normal FEV1
- Mild persistent: symptoms 3-6x/week, 3-4 awakenings/month, normal FEV1
- Moderate persistent: daily symptoms, >5 nocturnal awakenings/month, FEV1 60-80%
- Severe persistent: continual symptoms, FEV1 < 60%

## Long term control of asthma

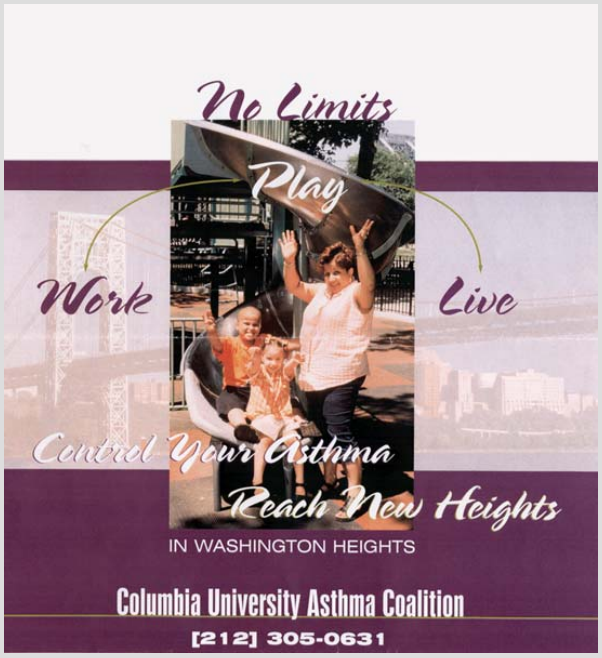
- **Symptoms occurring more than twice per week is an indication for *daily* anti-inflammatory therapy.**
- Step up anti-inflammatory therapy based on need for bronchodilators and frequency of symptoms
- Can use leukotriene modifiers and long acting b-agonist as steroid sparing agents.

## Asthma which is difficult to control

- Observe inhaler technique
- Other diagnoses
- Adherence to regimen
- Reflux or sinusitis present
- Senistivity to medication (NSAIDS, food additives)
- Abuse of OTC inhalers
- Environmental stimulus – mold, smoking

## Future Goals

- Pharmacogenetics
- Identification of genes responsible for disease
- Biologics (monoclonal blocking antibodies)
- Th2/Th1 balance - vaccines
- Reduce racial disparities in asthma morbidity and mortality


No Limits
Play
Work
Live
Control Your Asthma
Reach New Heights
IN WASHINGTON HEIGHTS
Columbia University Asthma Coalition
[212] 305-0631