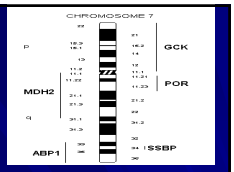
# CYSTIC FIBROSIS

Lynne M. Quittell, M.D.
Director, CF Center
Columbia University

## What is Cystic Fibrosis?

Chronic, progressive and life limiting autosomal recessive genetic disease characterized by chronic respiratory disease, pancreatic insufficiency, elevation of sweat electrolytes and male infertility

# Genetics of CF



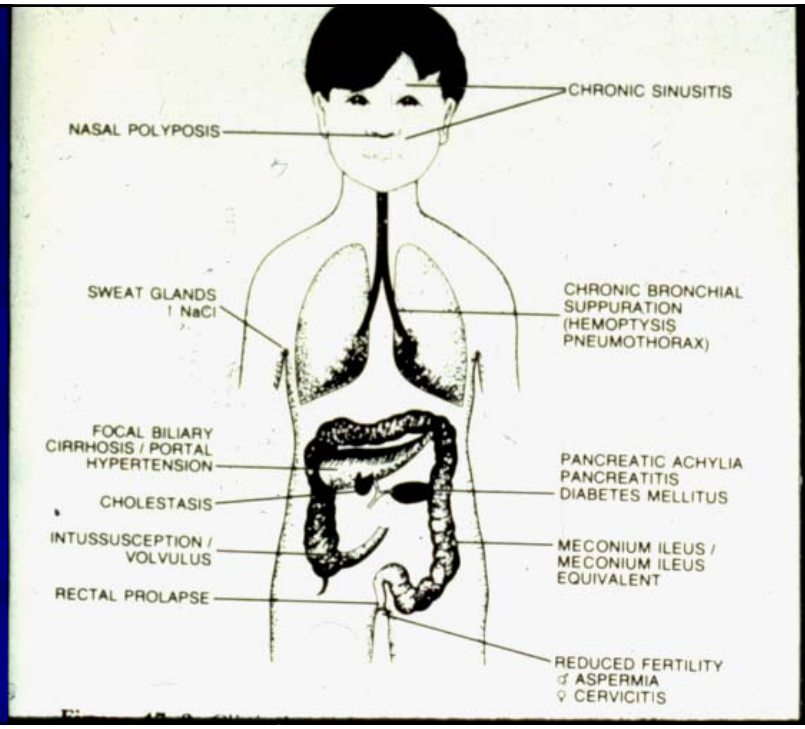

- Most common lethal genetic disease in Causasians
  - 30,000 affected individuals in US
  - 27,000 in Europe
- CFTR - cAMP regulated chloride channel located in apical membrane of glandular epithelium
  - Long arm of chromosome #7
    - D508 most common mutation
    - 1000 identified mutations
  - Encodes for a protein of 1480 amino acids
  - Defective ion transport

***"Wehe dem Kind, das beim Kuss auf die Stirn salzig schmekt, er ist verhext und muss bald sterben"***

*"Woe is the child who tastes salty from a kiss on the brow, for he is cursed , and soon must die"*

# Presentation (CF PANCREAS)

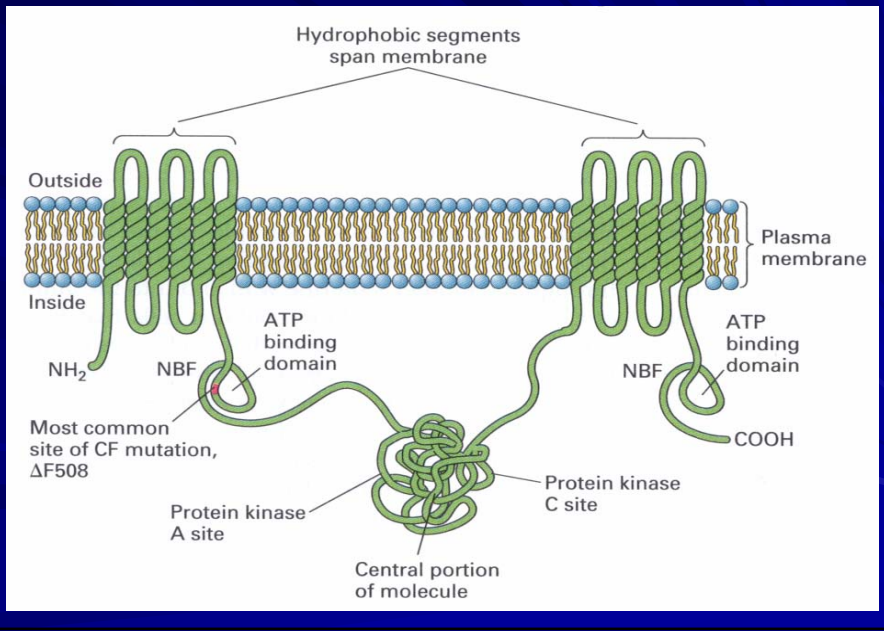
- **C** Chronic respiratory disease
- **F** Failure to thrive
- **P** Polyps
- **A** Alkalosis, metabolic
- **N** Neonatal intestinal obstruction
- **C** Clubbing of fingers
- **R** Rectal prolapse
- **E** Electrolyte ↑ in sweat
- **A** Aspermia / absent vas deferens
- **S** Sputum – S.aureus/P.aeruginosa



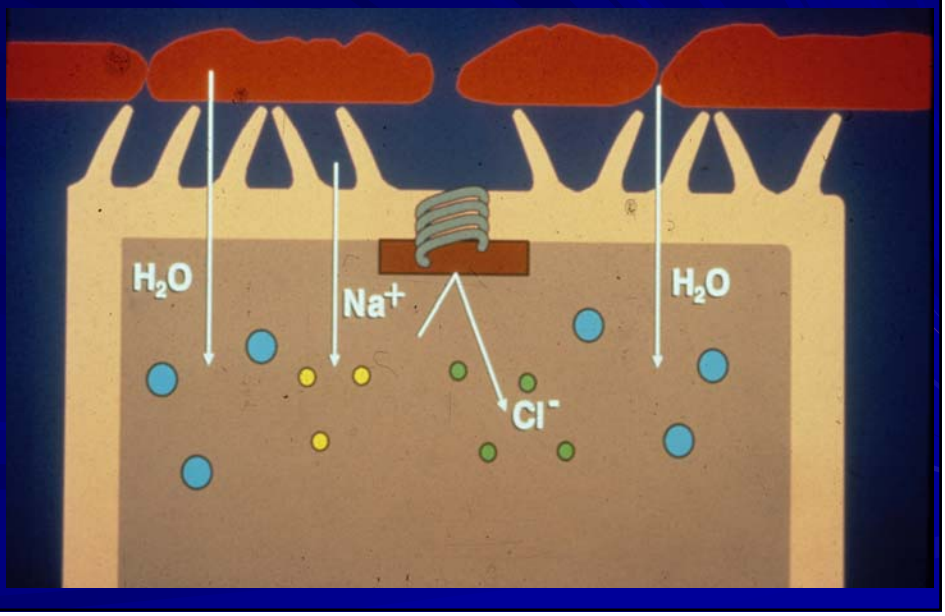
## CFTR

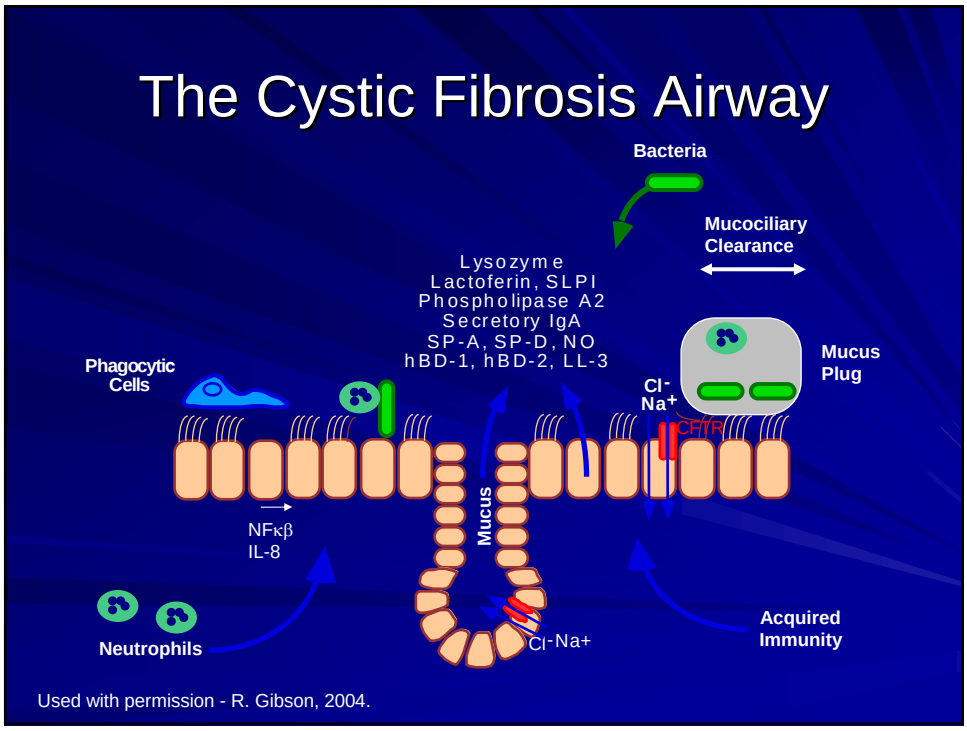
- Abnormalities in the CFTR protein change the constituents of mucous and result in abnormal reabsorption of water, creating thickened mucus and inadequate mucociliary function.
- The CF airway has many changes leading to mucous plugging, chronic infection, and inflammation.

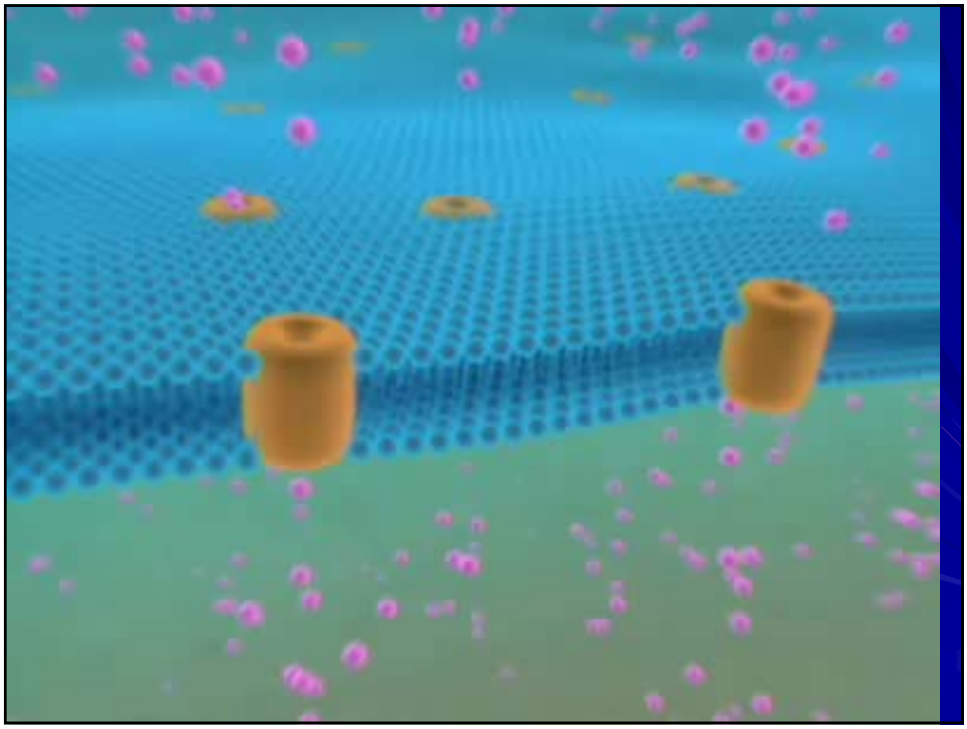
# CFTR

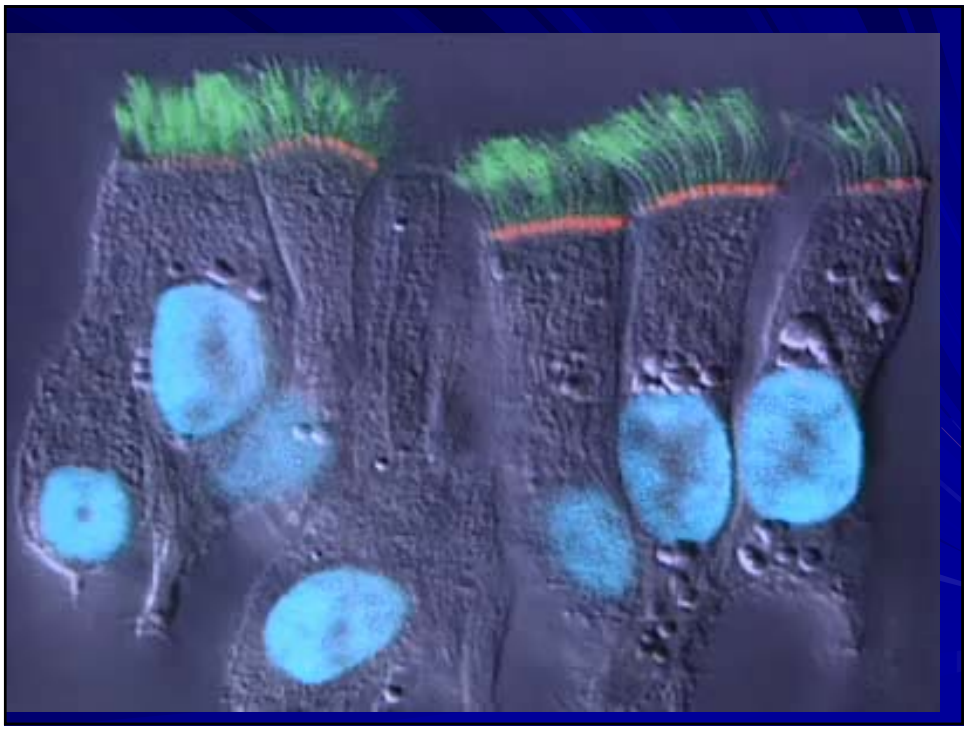


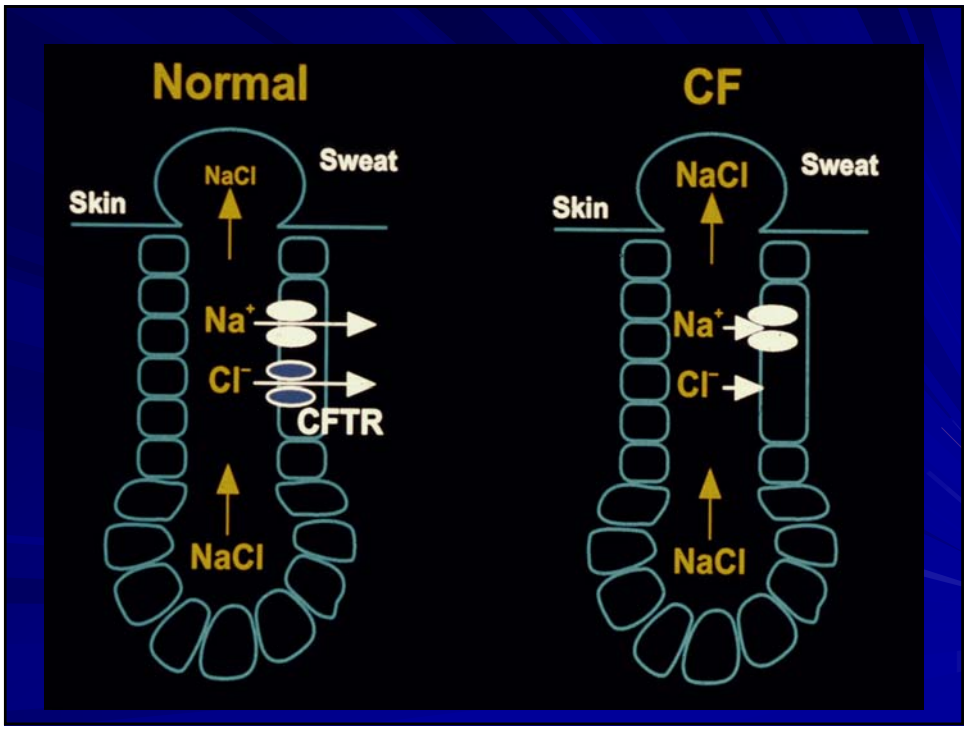

# Hypothesis



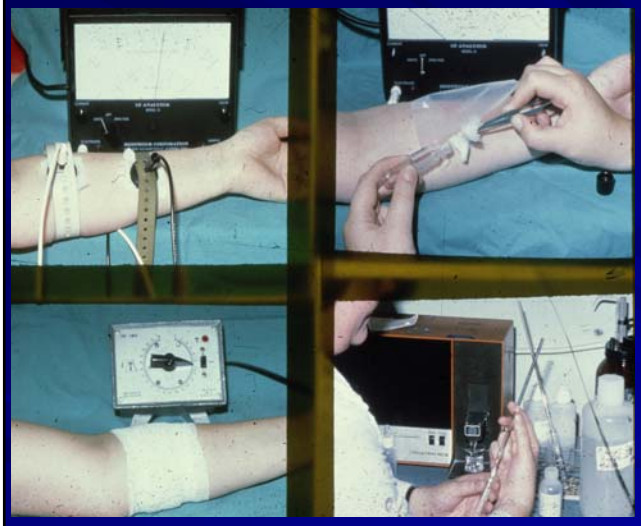

The Cystic Fibrosis Airway
Bacteria
Mucociliary Clearance
Lysozyme
Lactoferin, SLPI
Phospholipase A2
Secretory IgA
SP-A, SP-D, NO
hBD-1, hBD-2, LL-3
Phagocytic Cells
Mucus Plug
Cl-
Na+
CFTR
NFκβ
IL-8
Mucus
Neutrophils
Cl-Na+
Acquired Immunity
Used with permission - R. Gibson, 2004.






Normal
CF
Skin
NaCl
Sweat
Na+
Cl−
CFTR
NaCl
Skin
NaCl
Sweat
Na+
Cl−
NaCl

# The sweat test ( Chloride)

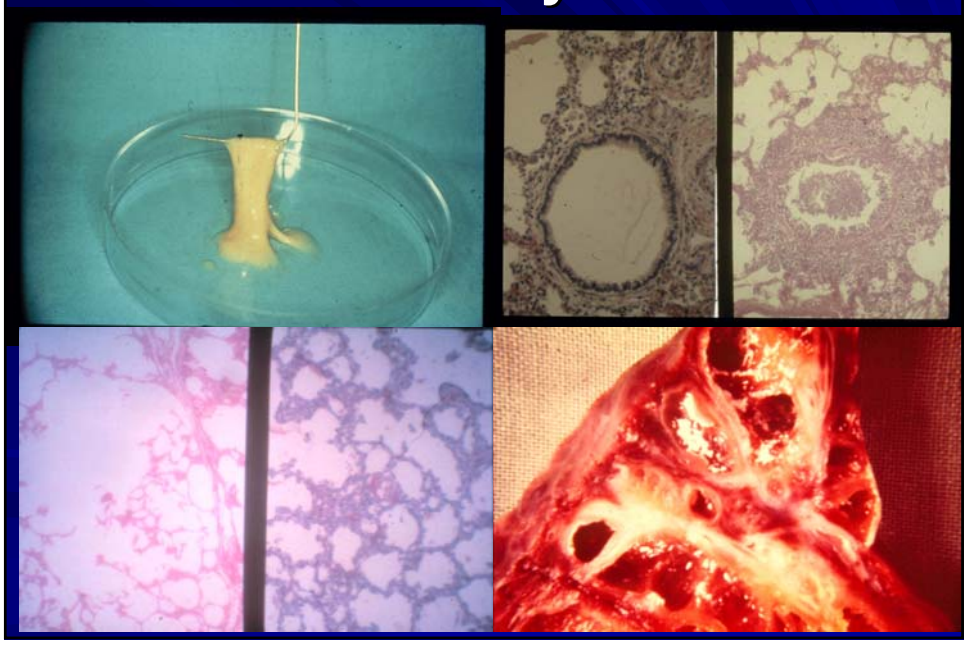


***Normal***
Under 40 mEq/L

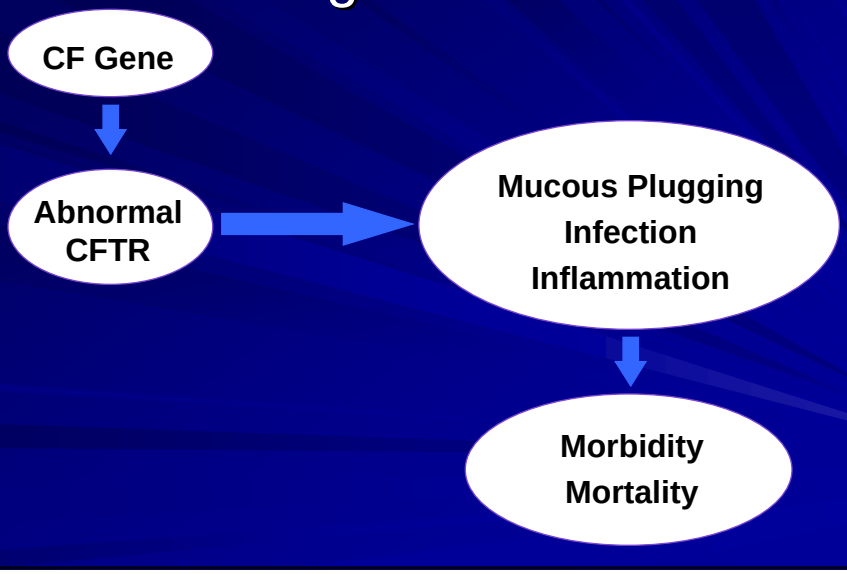
***Borderline***
40-60 mEq/L

***Positive***
Over 60 mEq/L

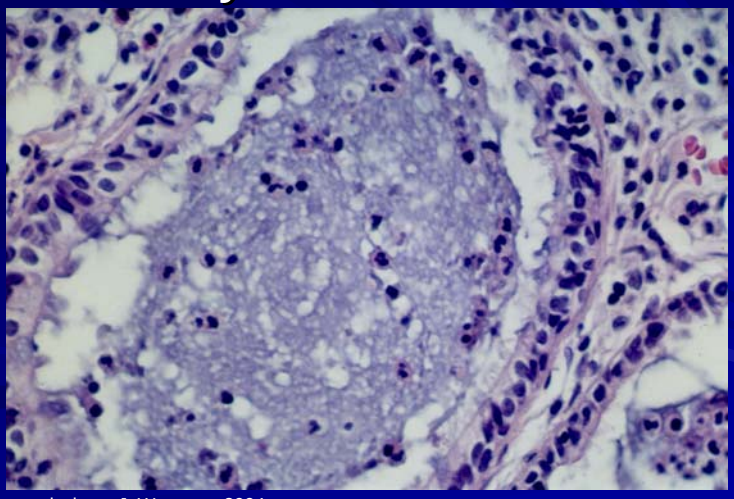
## CF: Pulmonary Disease



## Pathogenesis of Cystic Fibrosis Lung Disease

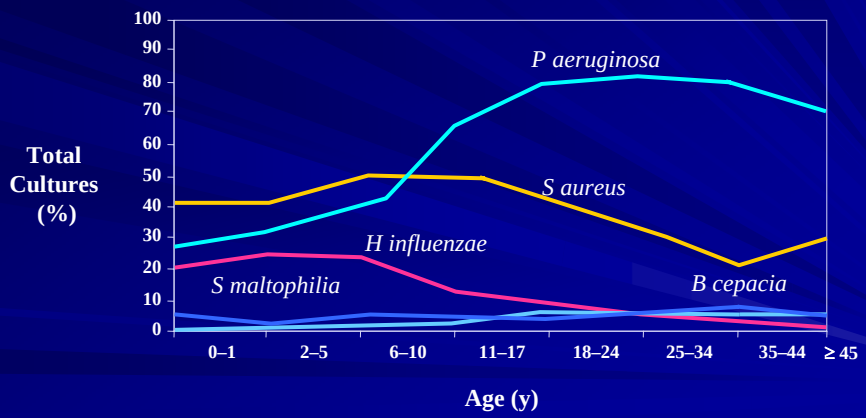


# Airway Mucous Plugging, Infection, and Inflammation in Cystic Fibrosis



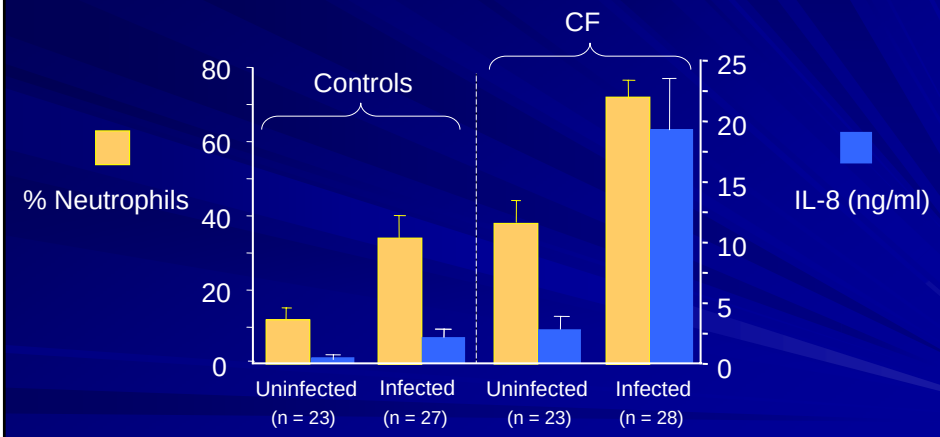
Used with permission – J. Wagener, 2004.

# Major Airway Pathogens by Patient Age, 1999



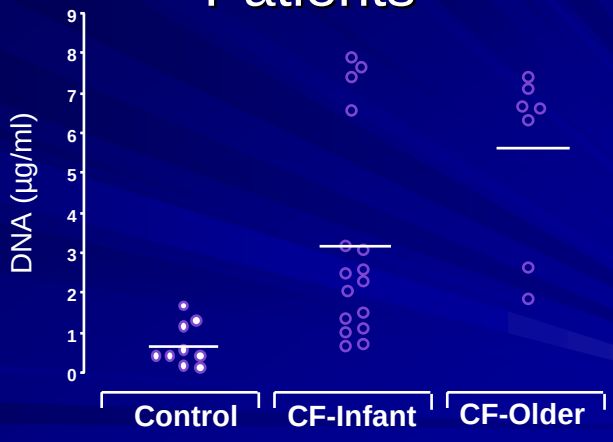

*Patient Registry 1999 Annual Data Report*. Bethesda, Md: Cystic Fibrosis Foundation; 2000.

## Evidence of increased inflammation in BALF of infants with CF

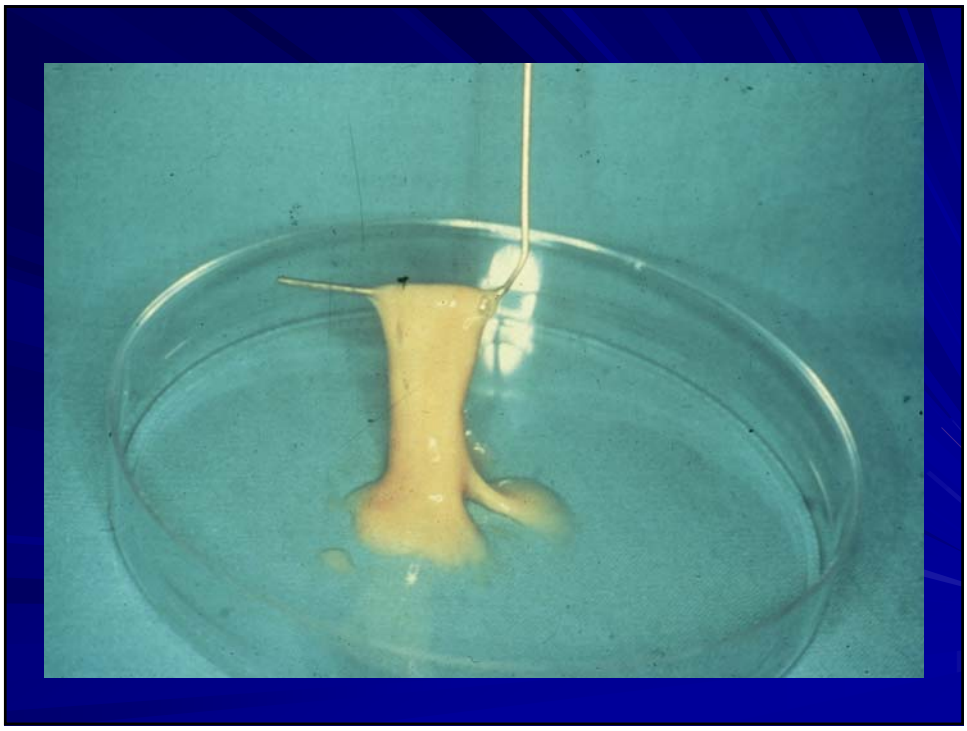


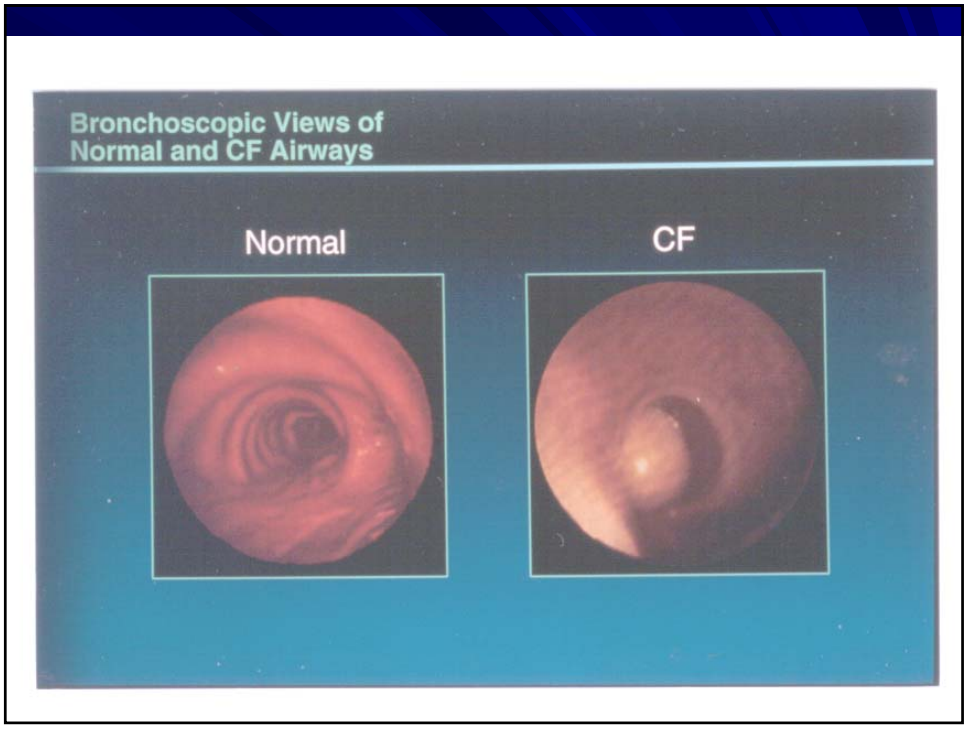

Adapted from Muhlebach et al. *Am J Respir Crit Care Med* 1999; 160: 186-191.

## DNA in Bronchoalveolar Lavage Fluid from Cystic Fibrosis Patients

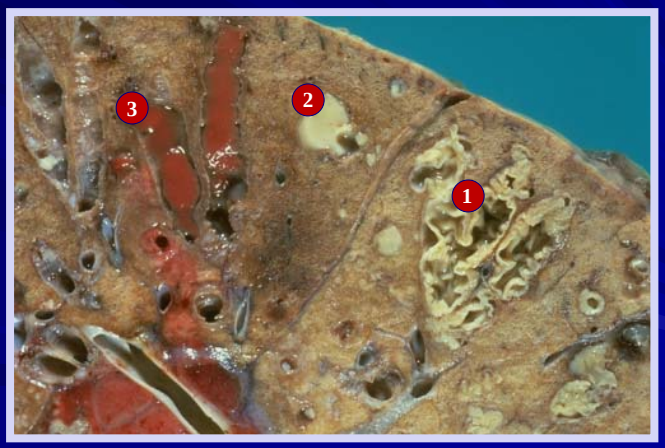



Kirchner et al. *Am J Respir Crit Care Med* 1996; 154: 1426-1429.




Bronchoscopic Views of
Normal and CF Airways
Normal
CF

# CF Lung: End-Stage Bronchiectasis




# CF Lung Function

PULMONARY FUNCTION TESTS:

| | NORMAL | MILD | MODERATE | SEVERE |
|---|---|---|---|---|
| $FEV_1$ | NL | NL | ↓ (70%) | ↓↓ (40%) |
| $FEF_{25-75}$ | NL | ↓(70%) | ↓↓ (40%) | ↓↓↓ (20%) |
| MEFV |  |  |  |  |
| VC | NL | NL | ↓ | ↓↓ |
| TLC | NL | NL or ↑ | NL or ↑ | ↓ |
| RV/TLC | 25% | ↑ (35%) | ↑↑ (50%) | ↑↑↑ (70%) |
| $PaO_2$ | NL | ↓ (94) | ↓↓ (85) | ↓↓↓ (60) |
| $PaCO_2$ | NL | NL | NL | ↑↑ |

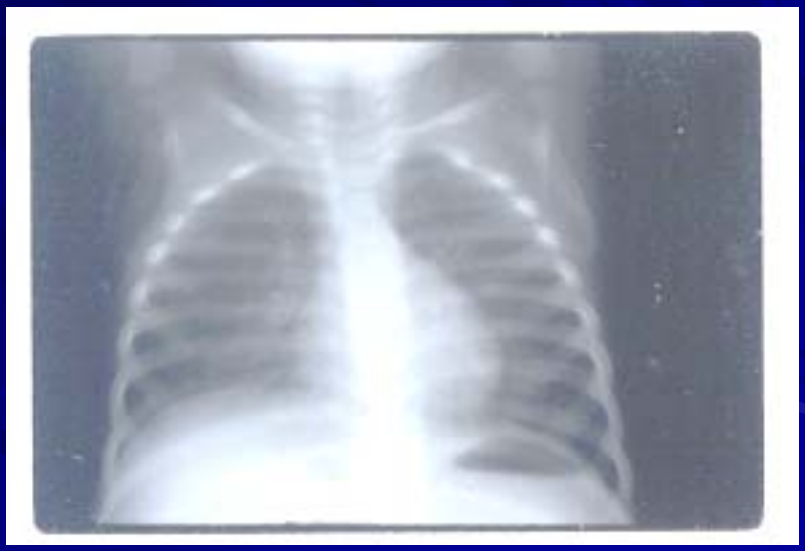
## Lung function in CF

- ↑ A-a gradient
- ↓ compliance
- ↓ flow rates at low lung volumes
- ↑ slope of phase III nitrogen washout
- ↑ physiologic dead space
- ↓ exercise tolerance

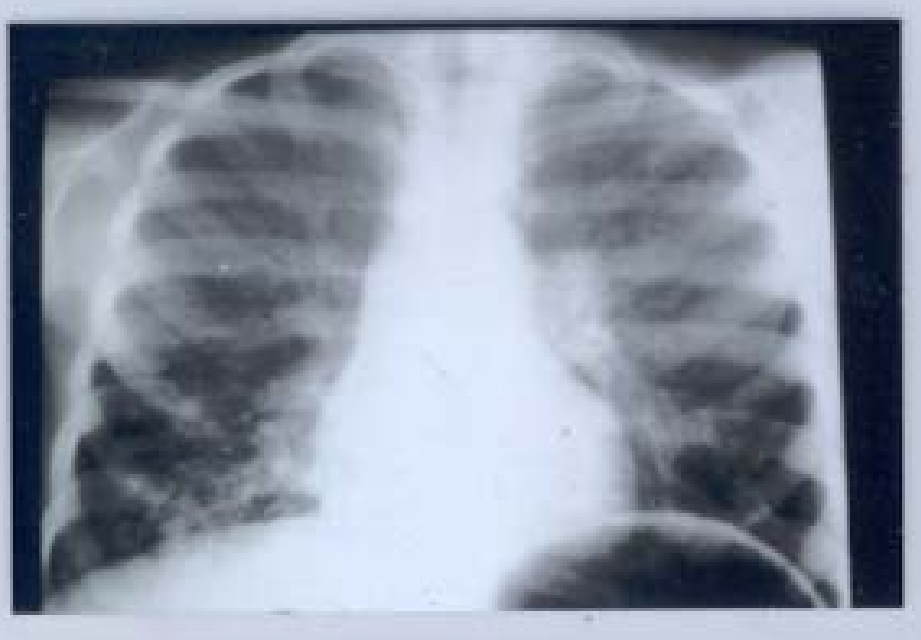
## Signs and Symptoms of Pulmonary Exacerbation

- Increased cough
- Increased sputum
- Weight loss
- School/work absenteeism
- Increased dyspnea
- New chest findings
  - rales, wheezes
- Decreased exercise tolerance
- Decreased FEV1
  - down 10%
- New radiographic findings

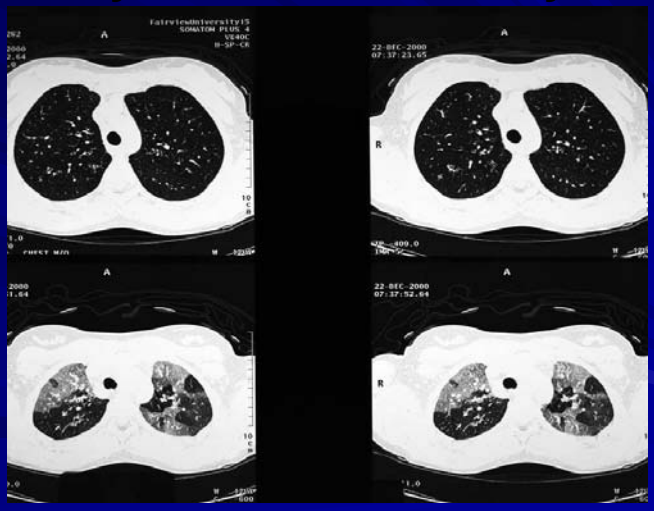
## CF mild disease



## Bronchiectasis



# High-Resolution Inspiratory and Expiratory CT Scan in 12 year old



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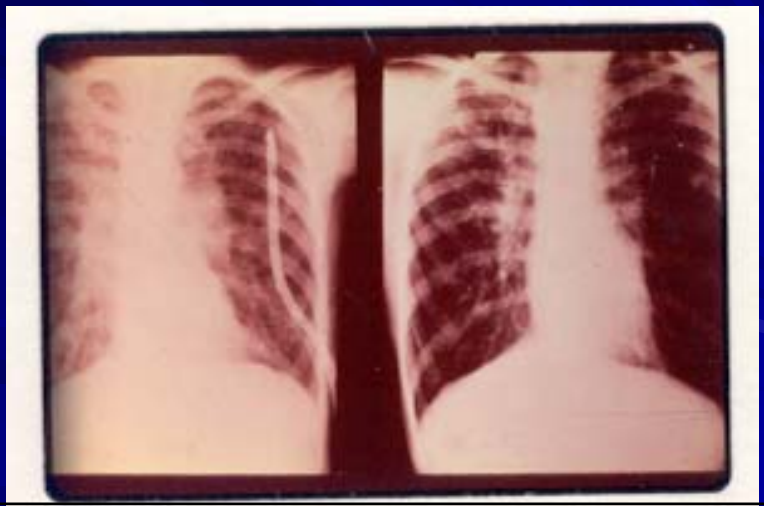
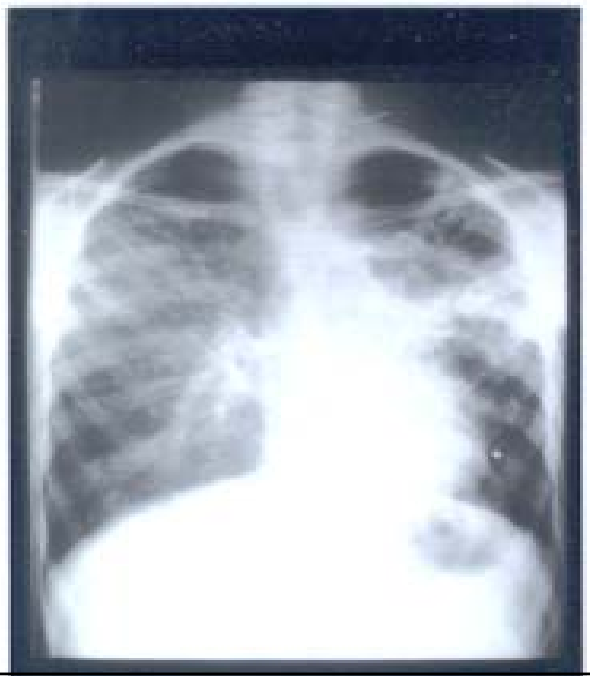
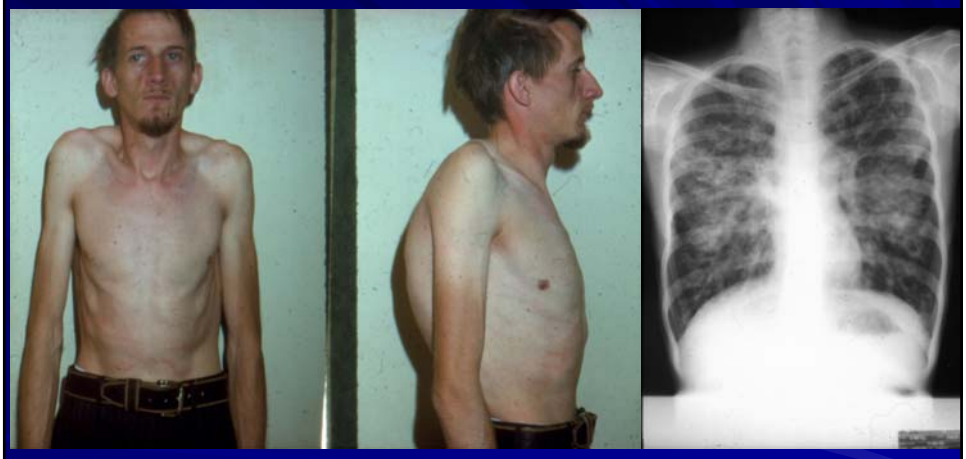
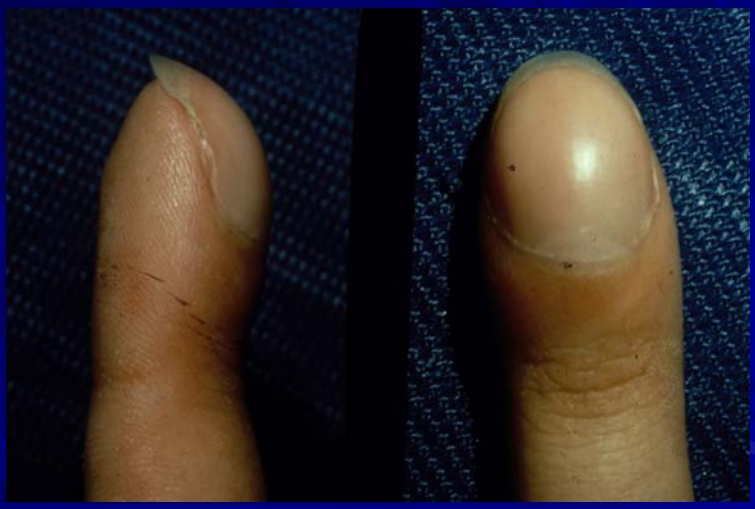
# CF Pneumothorax



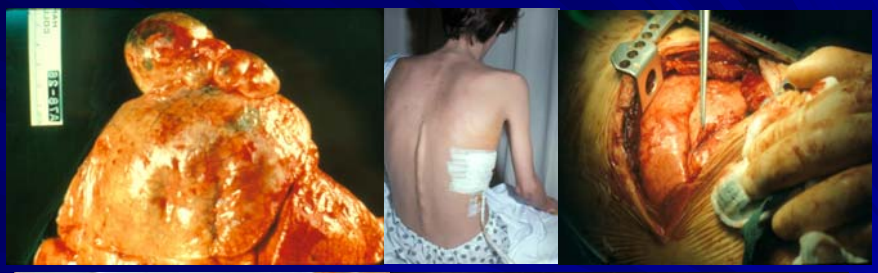
**BLEBS**

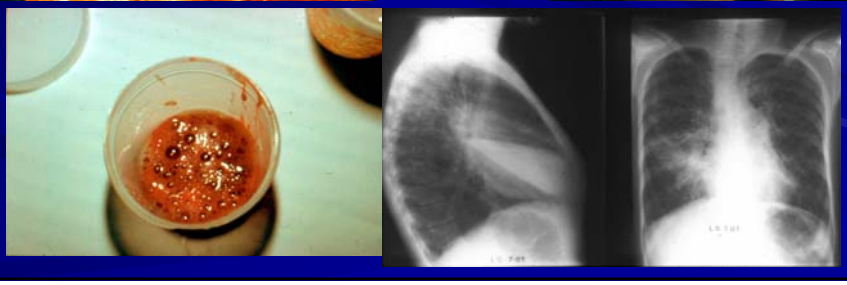




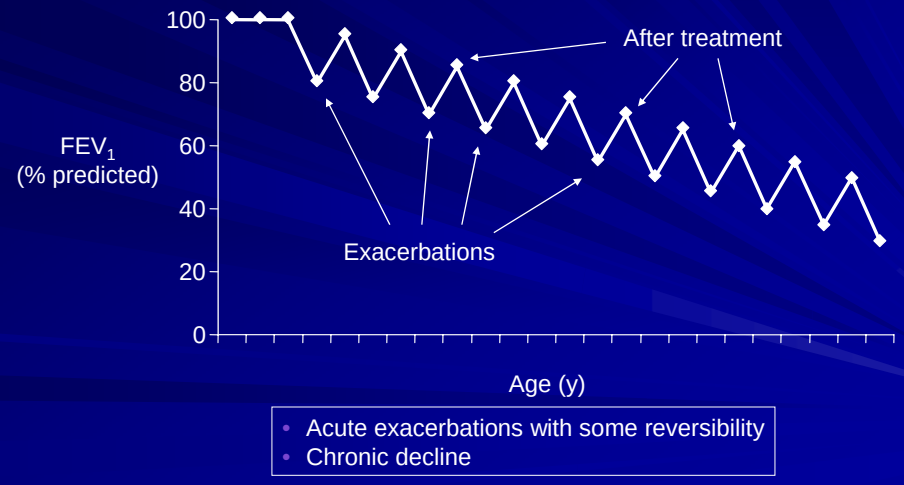


## CF: Pulmonary Complications





# Exacerbations Contribute to the Deterioration of Lung Function




- Acute exacerbations with some reversibility
- Chronic decline

Used with permission from P. Flume.

# CF: Respiratory management

- Regular visits to CF Center
- Airway clearance
- Mucus thinners (DNase, hypertonic saline)
- Antibiotics( PO-IV-Aerosol)
- Anti inflammatory drugs

## Airway Clearance

- CPT
- Vest
- Flutter
- ACB

**ISSUES**

- Reflux
- Risk factor for *Pa*
- Adherence

## CF Flutter

## Anti-inflammatory Rx

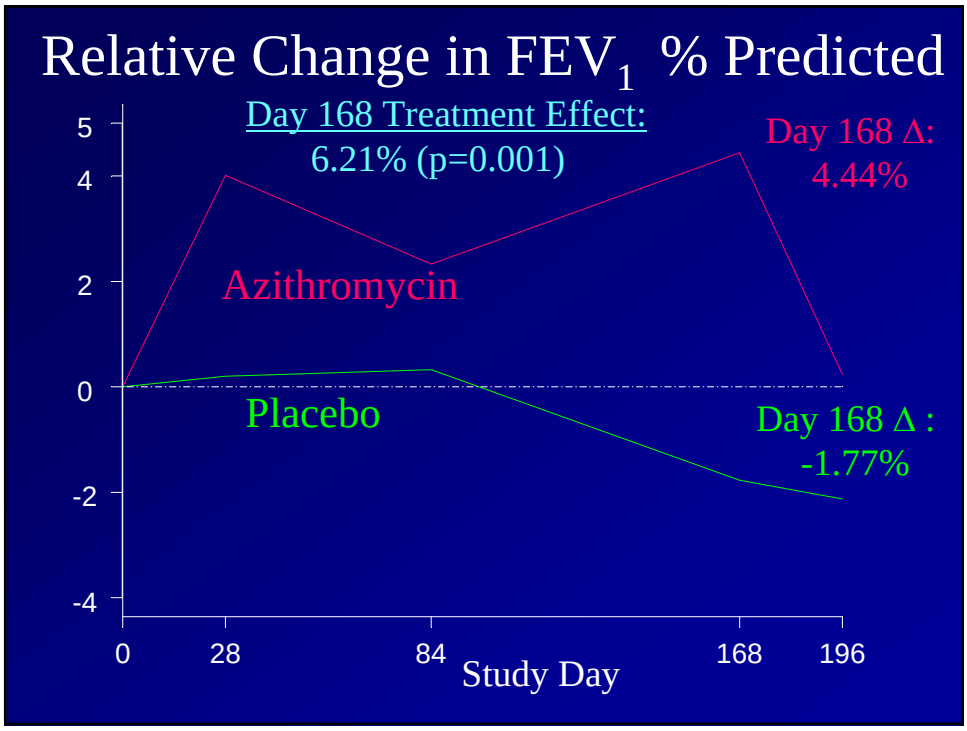
- **Steroids**
  - **inhaled v oral**
- **Ibuprofen**
- **Macrolides**

**ISSUES**

- Safety
- Adherence
- ? Delay in progression of the disease

## Diffuse Pan-bronchiolitis (DPB)

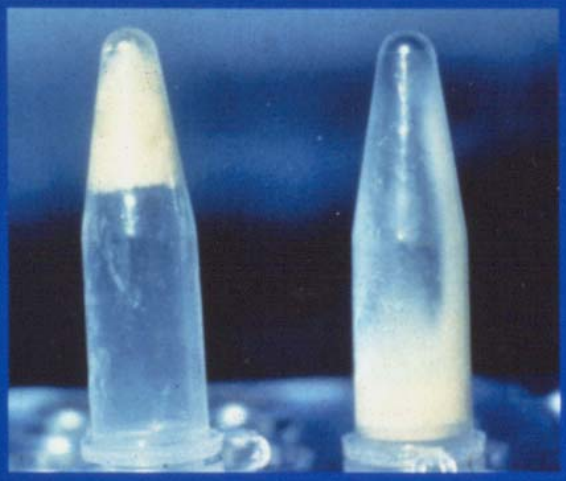
- DPB clinically resembles CF
  - More common in Japan than in Western countries
  - Age of onset between 30 and 60 years of age
- Chronic lower respiratory tract infection
  - Neutrophils predominant inflammatory cell
  - *H. influenzae* and *S. pneumonia* early in disease
  - *P. aeruginosa* major pathogen later
    - 70% of patients have mucoid strains
  - Progress to bronchiectasis and respiratory failure
- Pancreatic insufficiency *not* a clinical feature




## DNase

- Recombinant DNase
- Hydrolyzes DNA
- Aerosolized

## Pulmozyme Increases the Pourability of Cystic Fibrosis Sputum



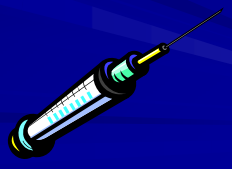
Shak S, et al. Proc Natl Acad Sci USA 1990;87:9188-92

## Treating Airway infections

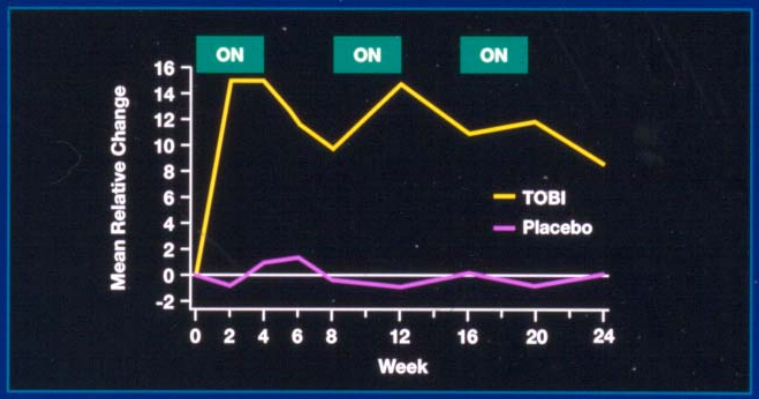
- Prophylactic treatment
  - prevent colonization
- Exacerbations
  - improves lung function
  - reduces inflammation
  - decreases bacterial density
- First isolates
  - may delay colonization

# Antibiotics

- Oral
- IV
- Aerosolized
- Special Considerations:
  - Volume of distribution
  - Sensitivities
  - Drug Interactions
  - Side effects

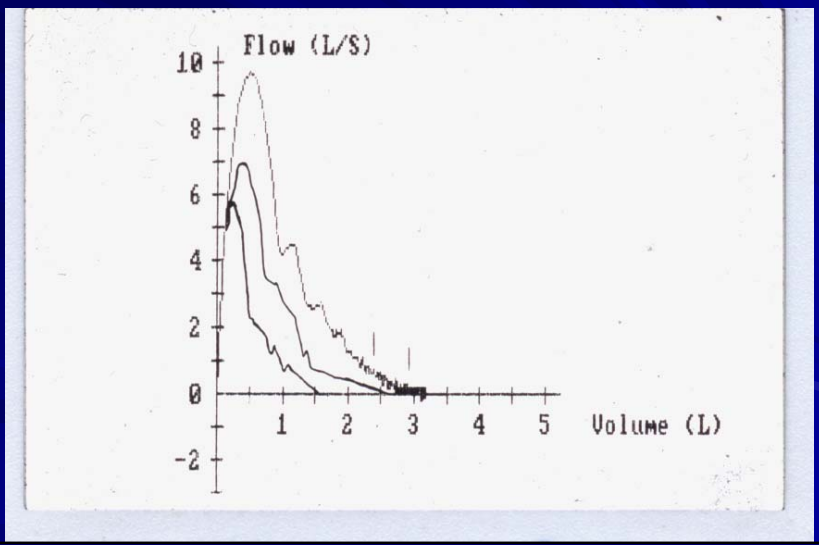


## Mean Relative Change in $FEV_1$% Predicted (002 Study)




Ramsey BW. Presented at the Eleventh Annual North American Cystic Fibrosis Conference; October 23-26, 1997; Nashville, Tennessee.

## CF PFT's

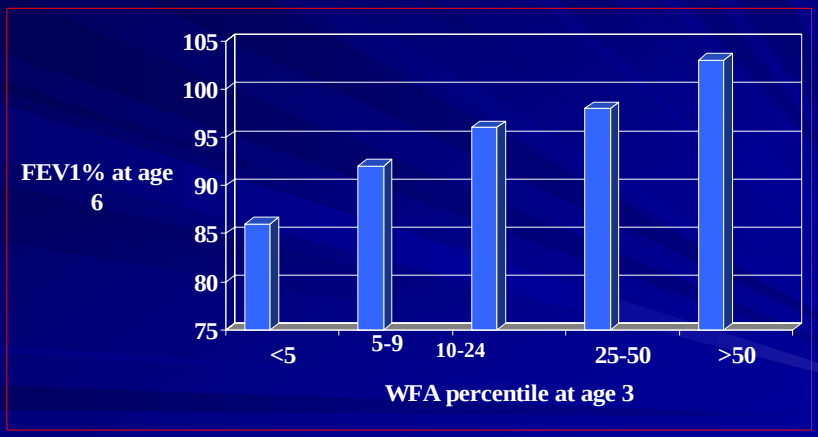



## CF: Gastrointestinal Disease

- Pancreatic insufficiency/malabsorption
- Lipo-soluble vitamin deficiency
- Failure to thrive
- Neonatal intestinal obstruction (15%)
- Recurrent distal intestinal obstruction
- Biliary stasis

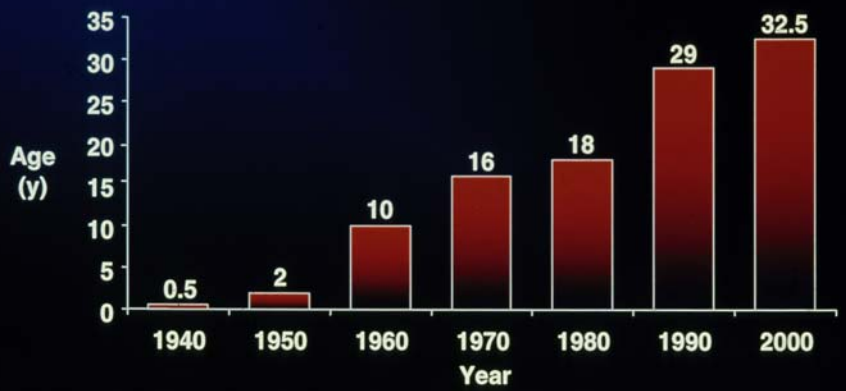
## CF: Pancreas-malabsorption

# Nutrition and CF




Konstan et. Al. Pediatr Pulmonol 2000

## Median CF Survival Age, 1940–2000




Data from Cystic Fibrosis Foundation, Bethesda, Md. Available at: http://www.cff.org/slidepresentation_files /frame. htm#slide0015.htm.