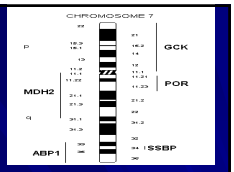
CYSTIC FIBROSIS

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



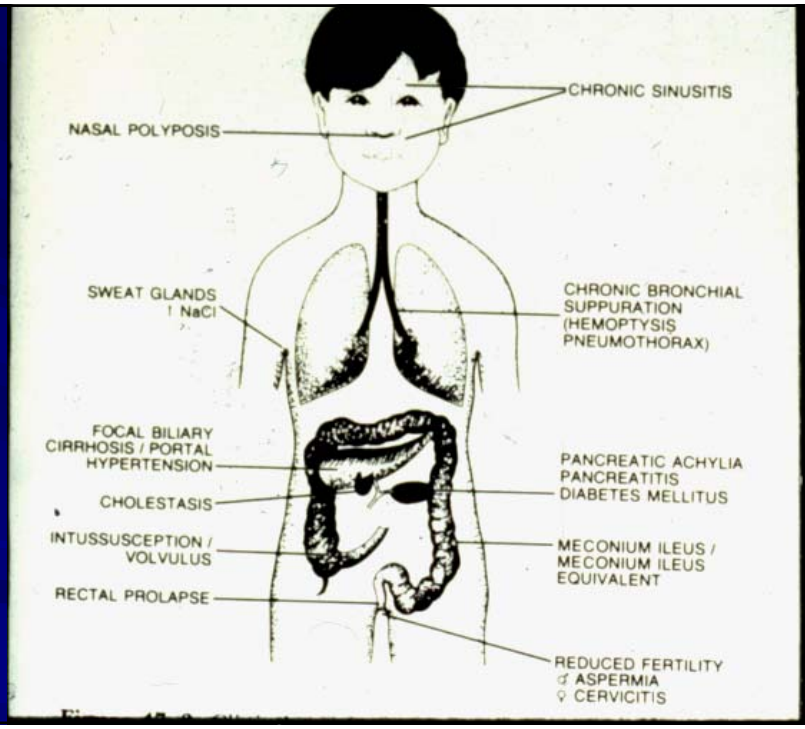
- Most common lethal genetic disease in Causasians
  - 30,000 affected individuals in US
  - 27,000 in Europe
- CFTR - cAMP regulated chloride channel located in apical membrane of glandular epithelium
  - Long arm of chromosome #7
    - D508 most common mutation
    - 1000 identified mutations
  - Encodes 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)

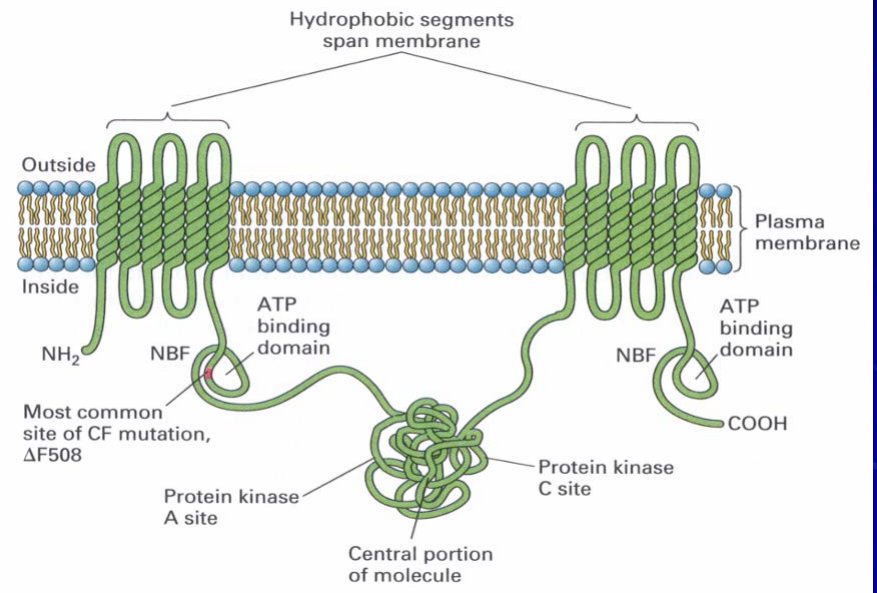
- **C** Chronic respiratory disease
- **F** Failure to thrive
- **P** Polyps
- **A** Alkalosis, metabolic
- **N** Neonatal intestinal obstruction
- **C** Clubbing of fingers
- **R** Rectal prolapse
- **E** Electrolyte ↑ in sweat
- **A** Aspermia / absent vas deferens
- **S** Sputum – S.aureus/P.aeruginosa



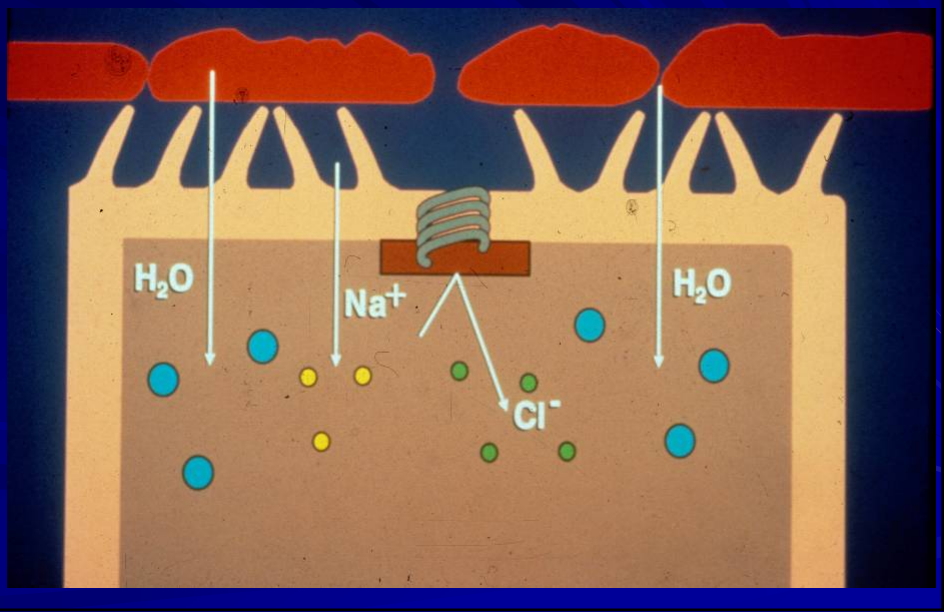
CFTR

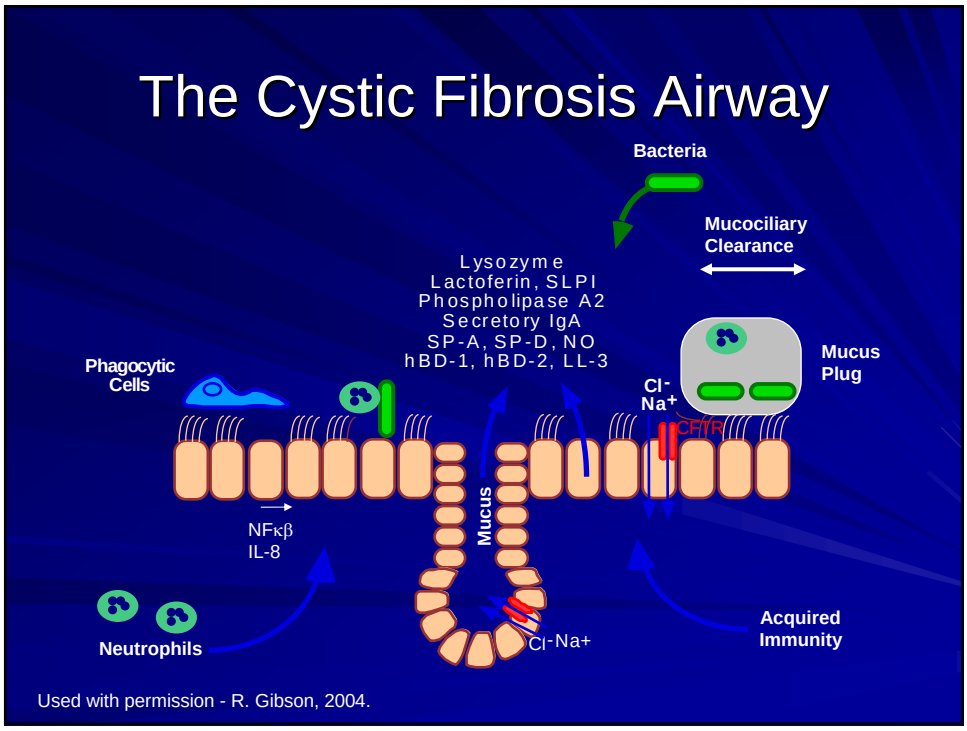
- Abnormalities in the CFTR protein change the constituents of mucous and result in abnormal reabsorption of water, creating thickened mucus and inadequate mucociliary function.
- The CF airway has many changes leading to mucous plugging, chronic infection, and inflammation.

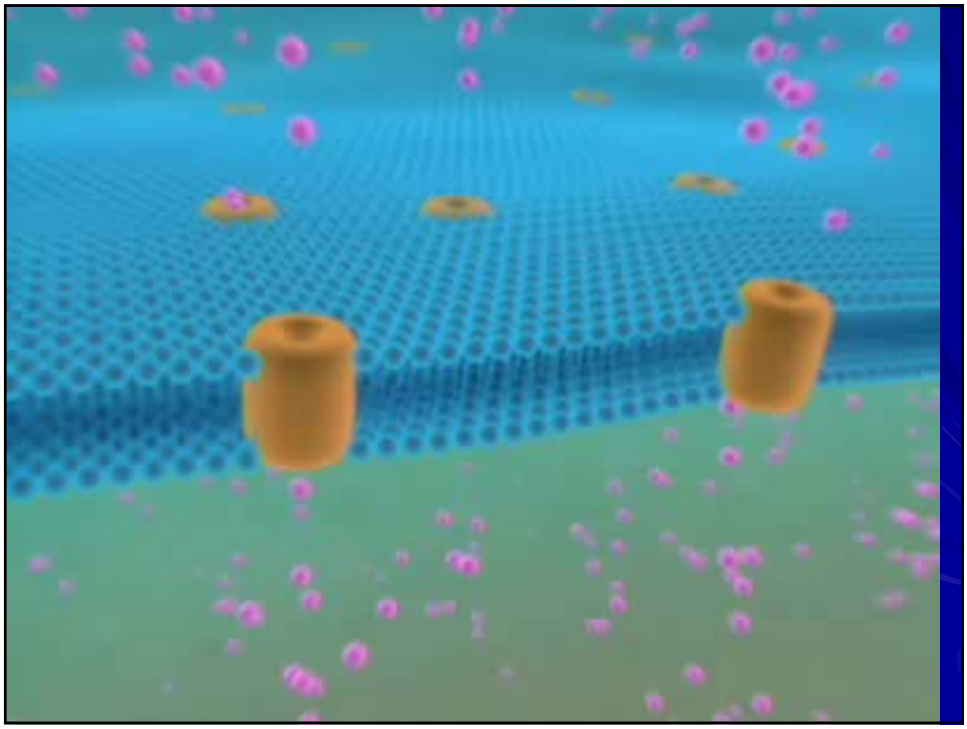
CFTR

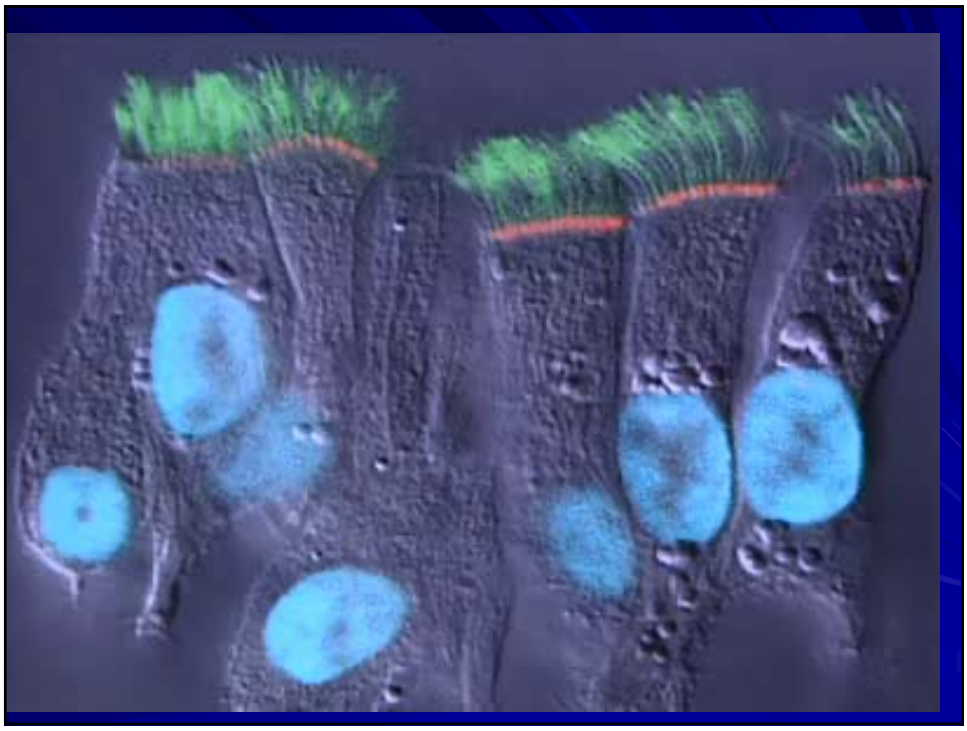


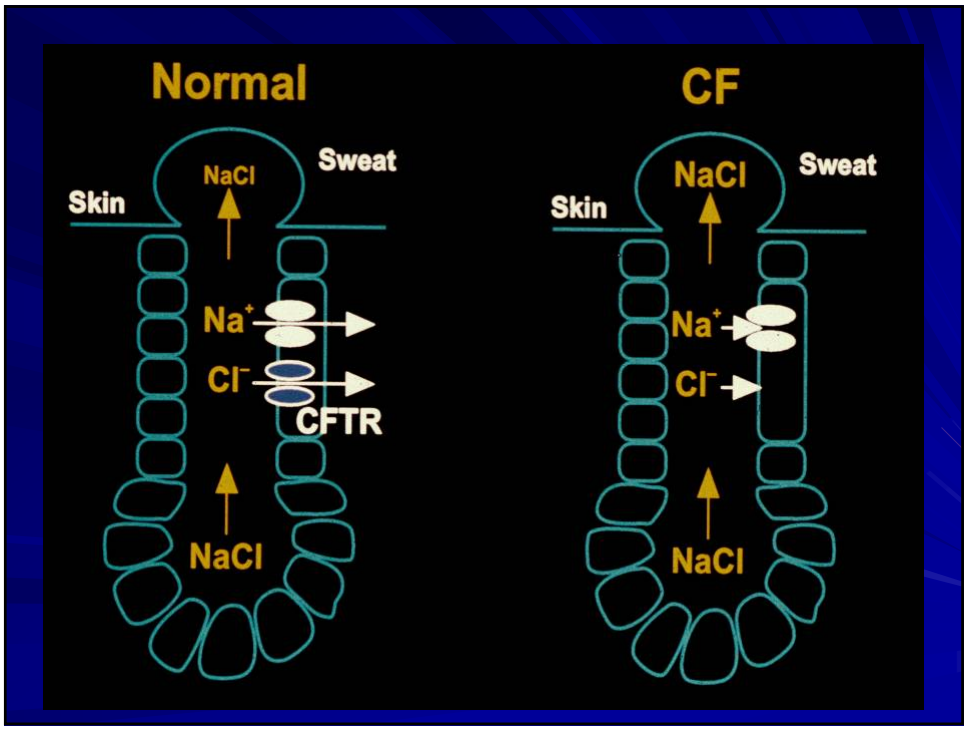
Hypothesis



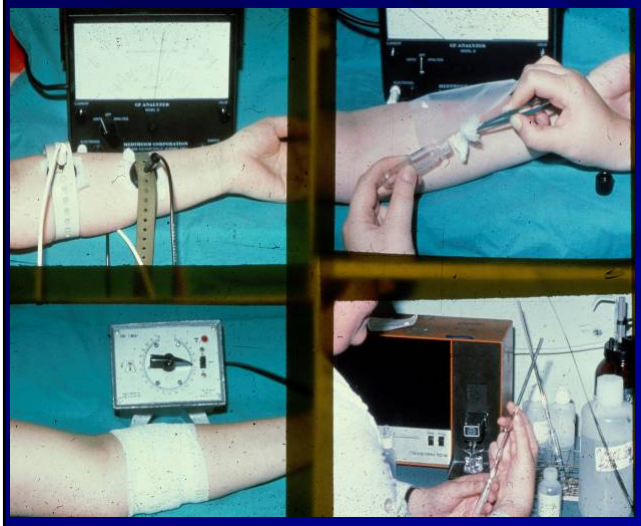

The Cystic Fibrosis Airway
Bacteria
Mucociliary Clearance
Lysozyme
Lactoferin, SLPI
Phospholipase A2
Secretory IgA
SP-A, SP-D, NO
hBD-1, hBD-2, LL-3
Phagocytic Cells
Mucus Plug
Cl-
Na+
CFTR
NFκβ
IL-8
Mucus
Neutrophils
Cl-Na+
Acquired Immunity
Used with permission - R. Gibson, 2004.






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

The sweat test (Chloride)

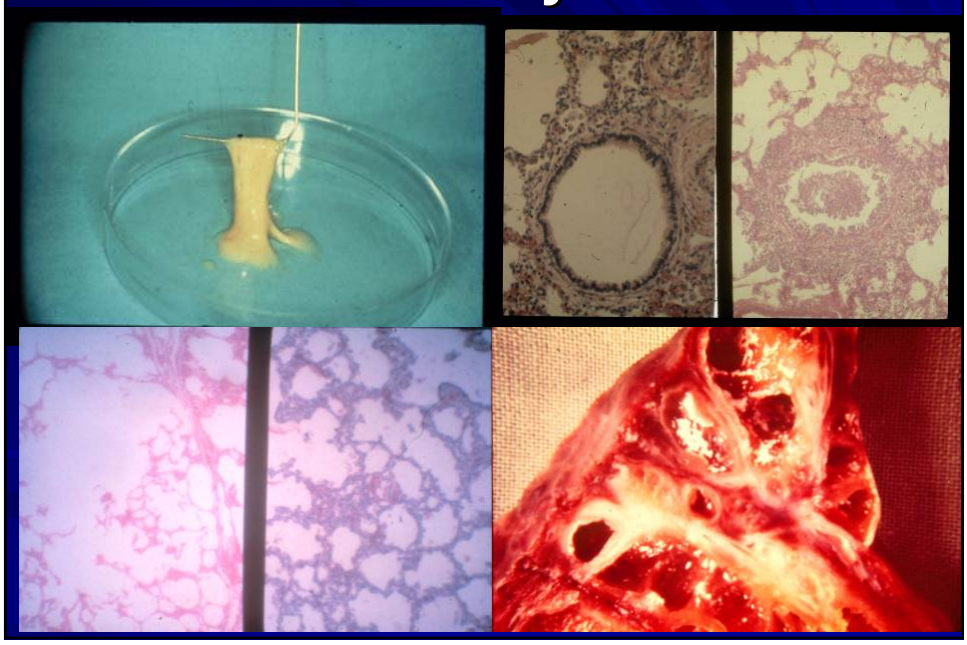


Normal
Under 40 mEq/L

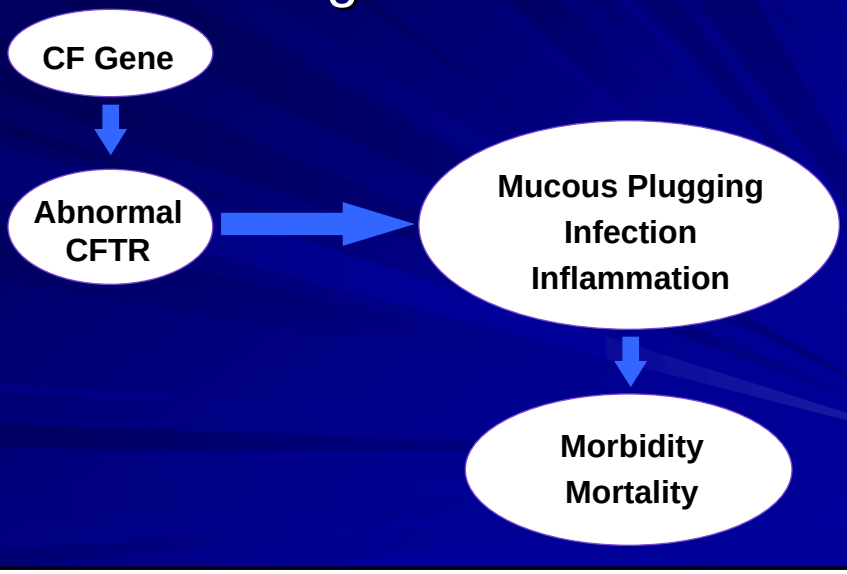
Borderline
40-60 mEq/L

Positive
Over 60 mEq/L

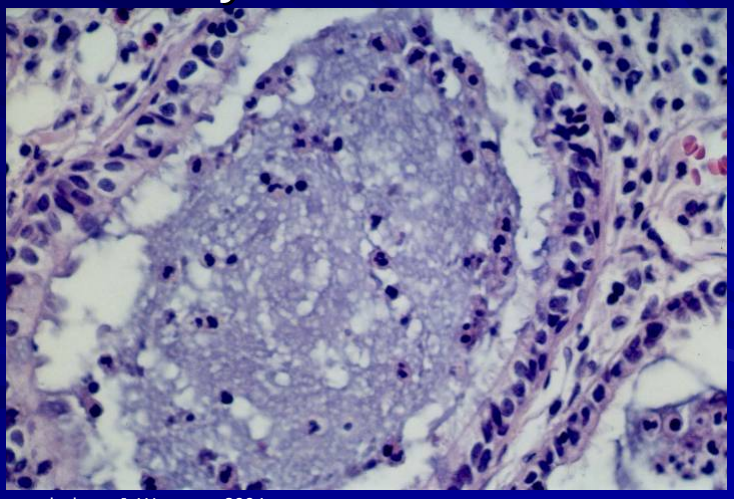
CF: Pulmonary Disease



Pathogenesis of Cystic Fibrosis Lung Disease

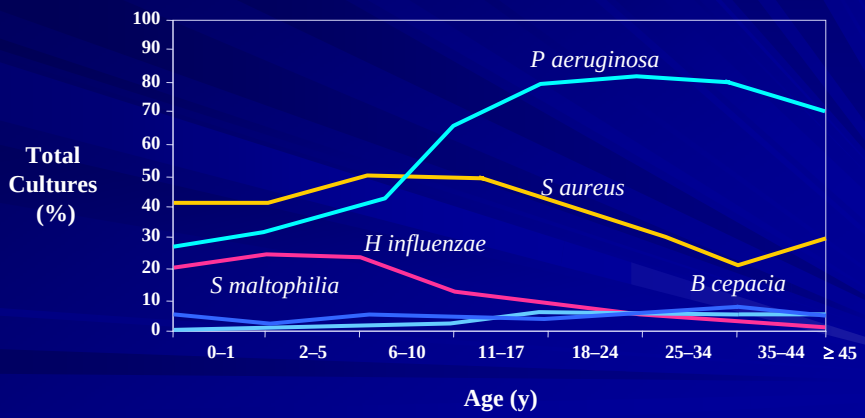


Airway Mucous Plugging, Infection, and Inflammation in Cystic Fibrosis



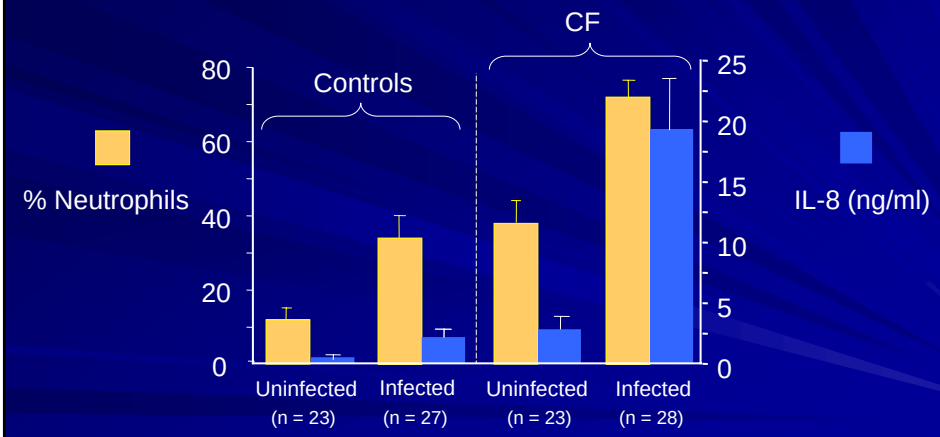
Used with permission – J. Wagener, 2004.

Major Airway Pathogens by Patient Age, 1999



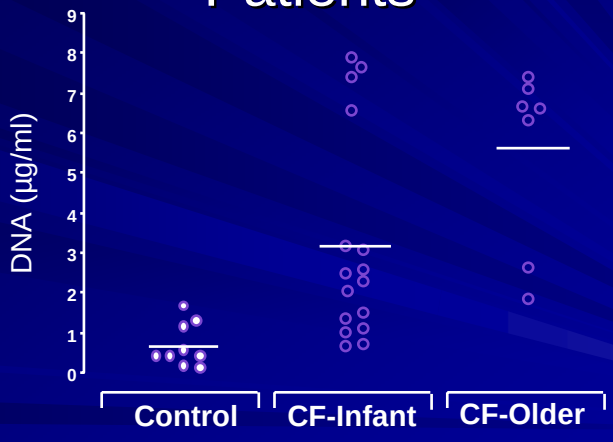
Patient Registry 1999 Annual Data Report. Bethesda, Md: Cystic Fibrosis Foundation; 2000.

Evidence of increased inflammation in BALF of infants with CF

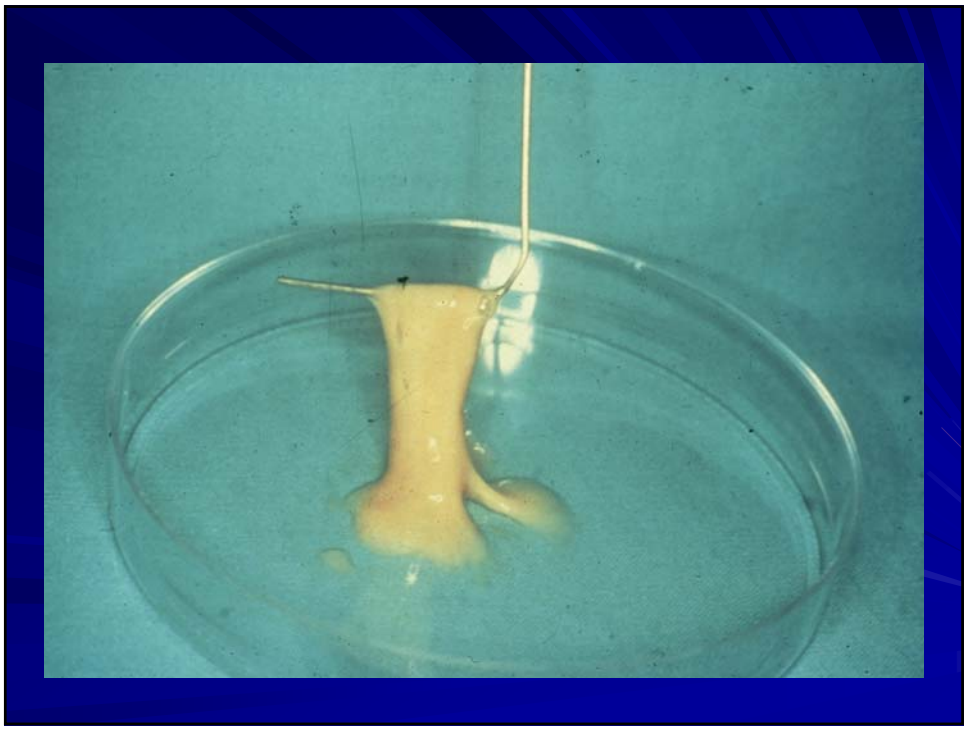


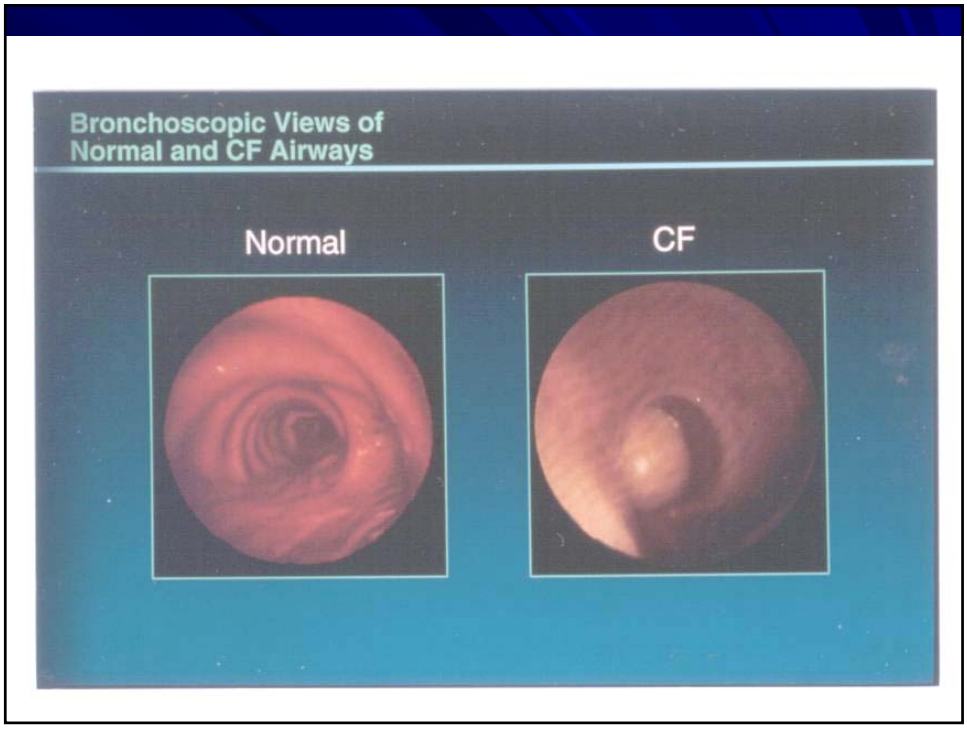
Adapted from Muhlebach et al. *Am J Respir Crit Care Med* 1999; 160: 186-191.

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	↑↑

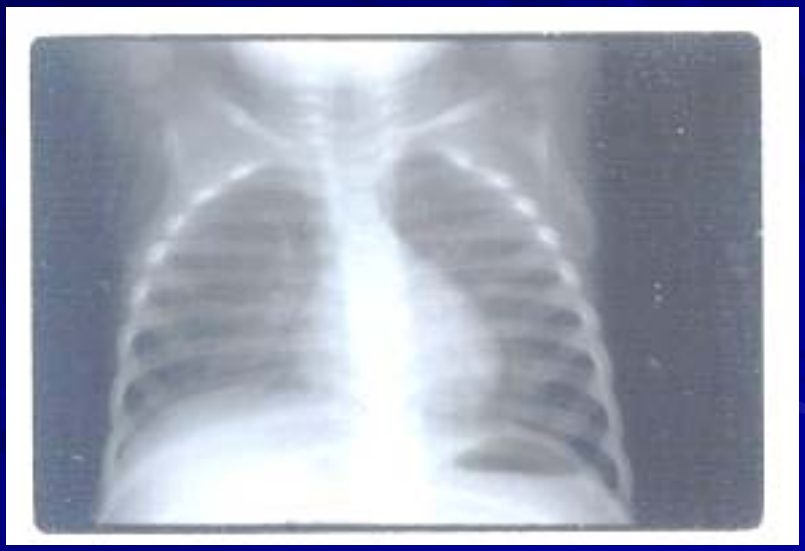
Lung function in CF

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

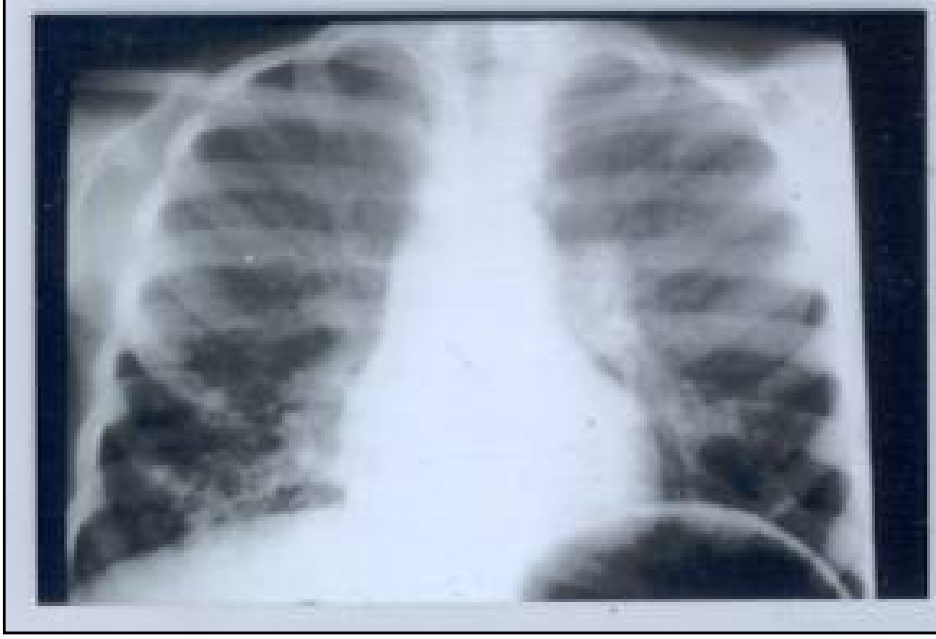
Signs and Symptoms of Pulmonary Exacerbation

- 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

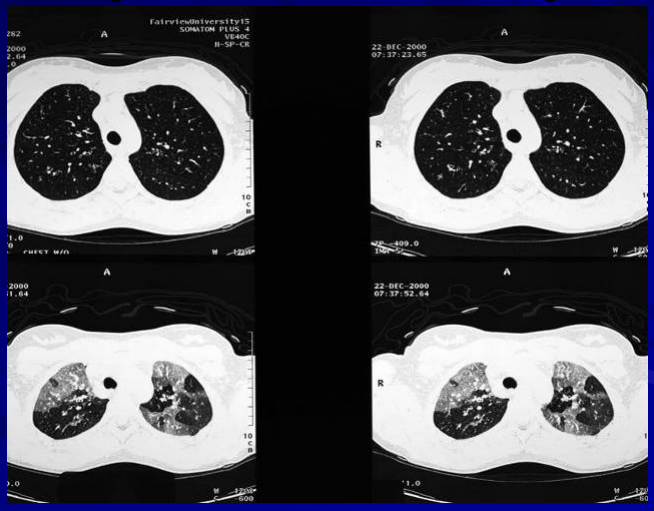
CF mild disease



Bronchiectasis

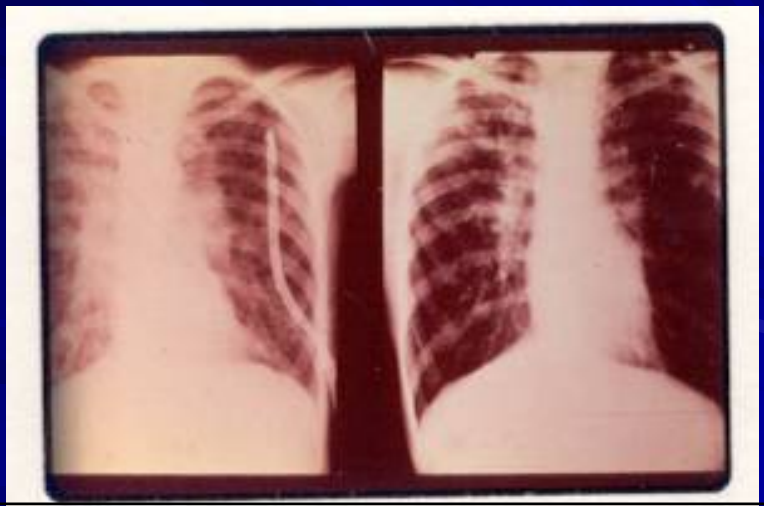


High-Resolution Inspiratory and Expiratory CT Scan in 12 year old

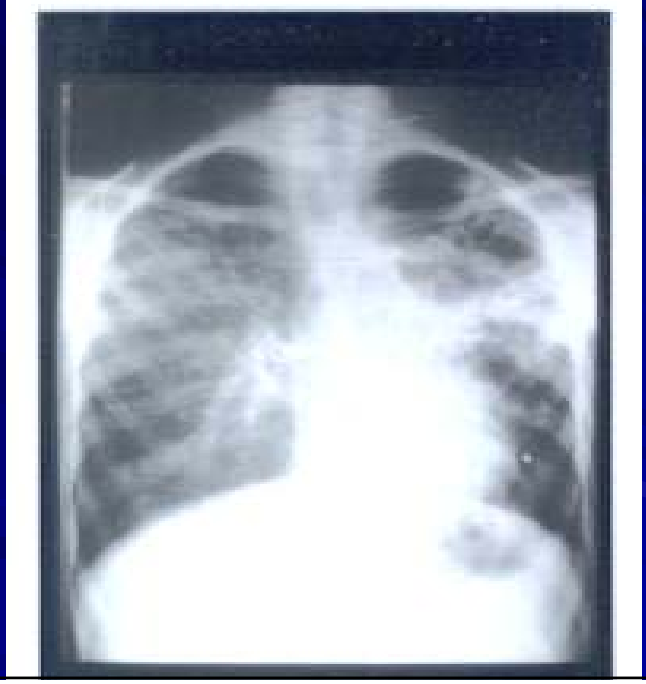


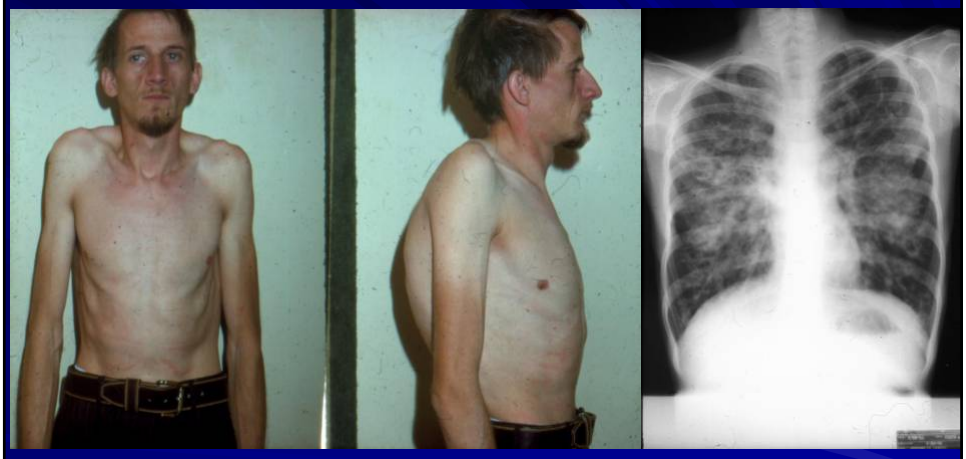
Used with permission - C. Milla, 2004.

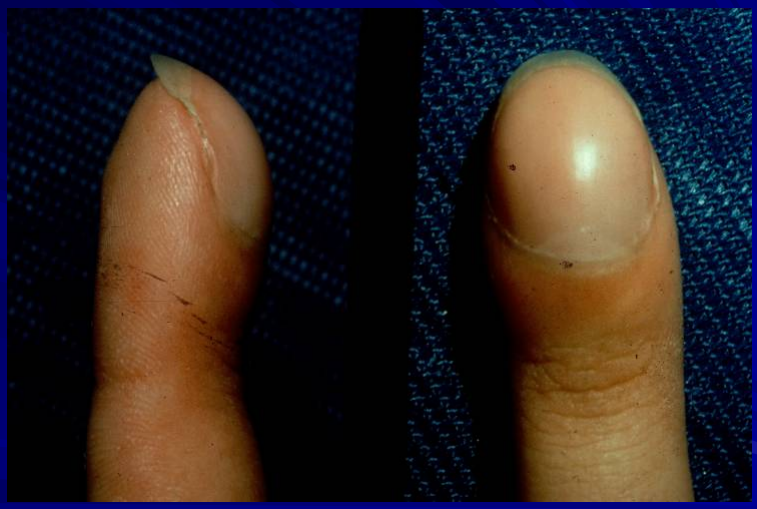
CF Pneumothorax



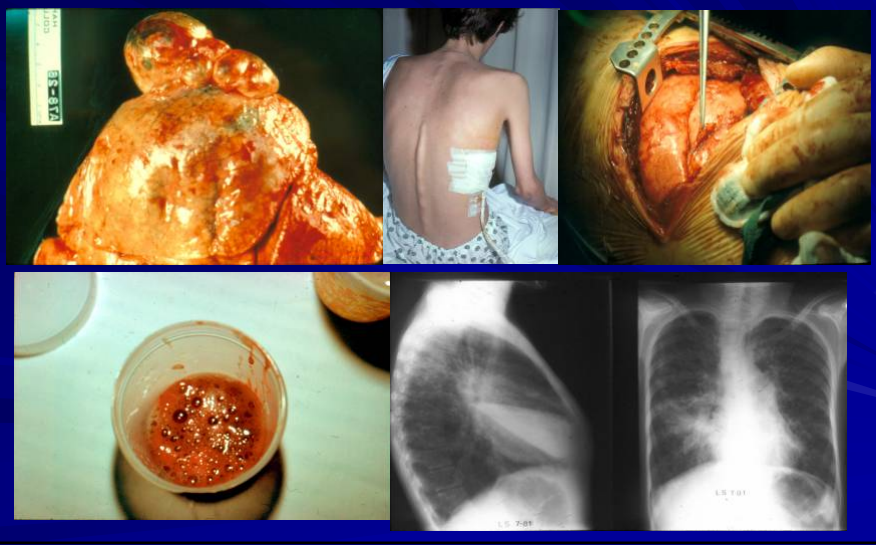
BLEBS



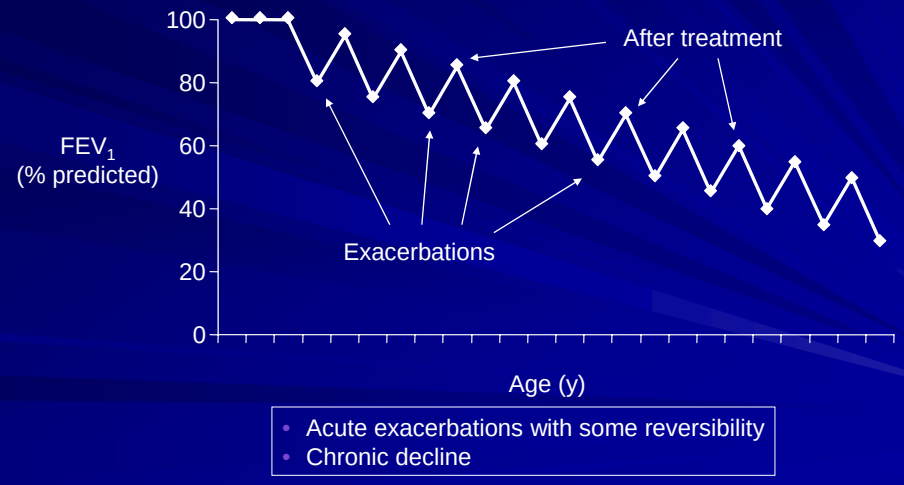




CF: Pulmonary Complications



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

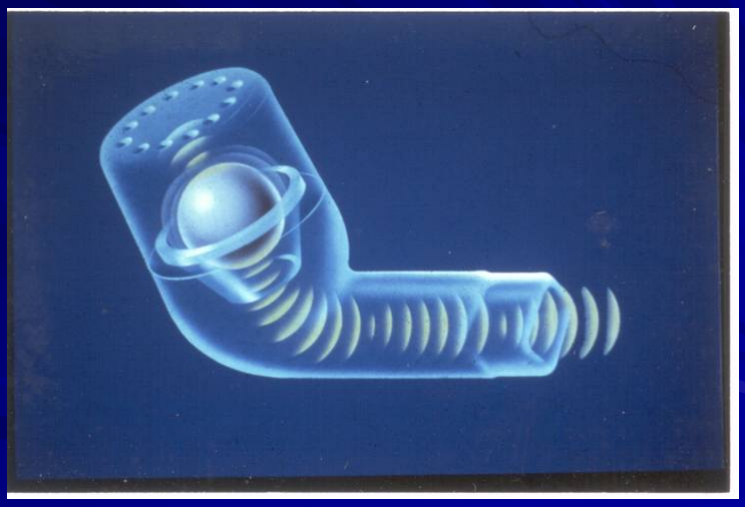
Airway Clearance

- CPT
- Vest
- Flutter
- ACB

ISSUES

- Reflux
- Risk factor for *Pa*
- Adherence

CF Flutter



Anti-inflammatory Rx

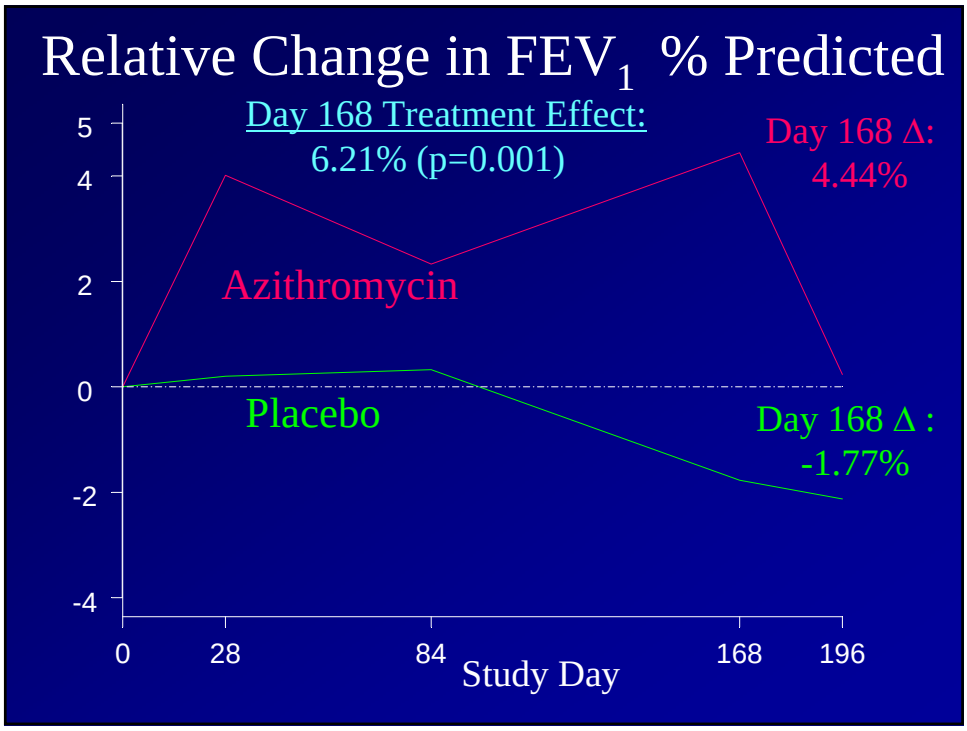
- **Steroids**
  - **inhaled v oral**
- **Ibuprofen**
- **Macrolides**

ISSUES

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

Diffuse Pan-bronchiolitis (DPB)

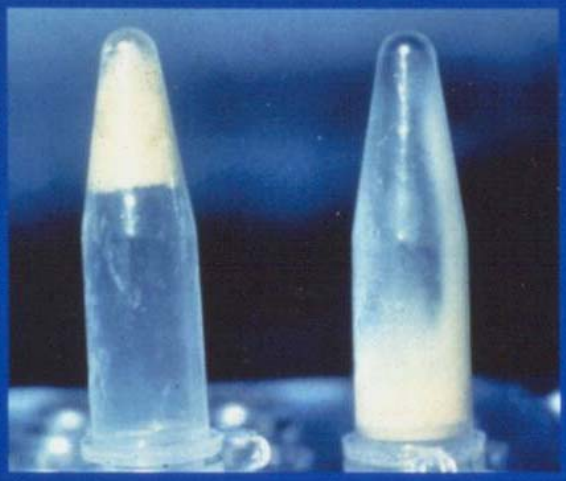
- DPB clinically resembles CF
  - More common in Japan than in Western countries
  - Age of onset between 30 and 60 years of age
- Chronic lower respiratory tract infection
  - Neutrophils predominant inflammatory cell
  - *H. influenzae* and *S. pneumonia* early in disease
  - *P. aeruginosa* major 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



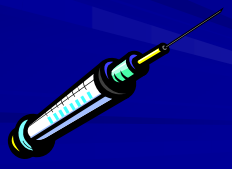
Shak S, et al. Proc Natl Acad Sci USA 1990;87:9188-92

Treating Airway infections

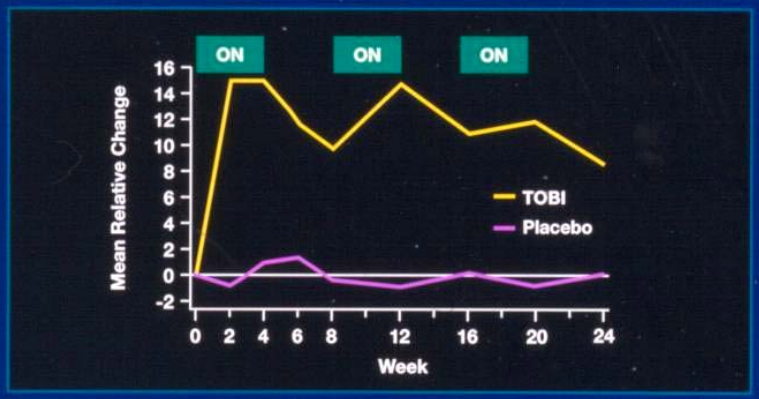
- Prophylactic treatment
  - prevent colonization
- Exacerbations
  - improves lung function
  - reduces inflammation
  - decreases bacterial density
- First isolates
  - may delay colonization

Antibiotics

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

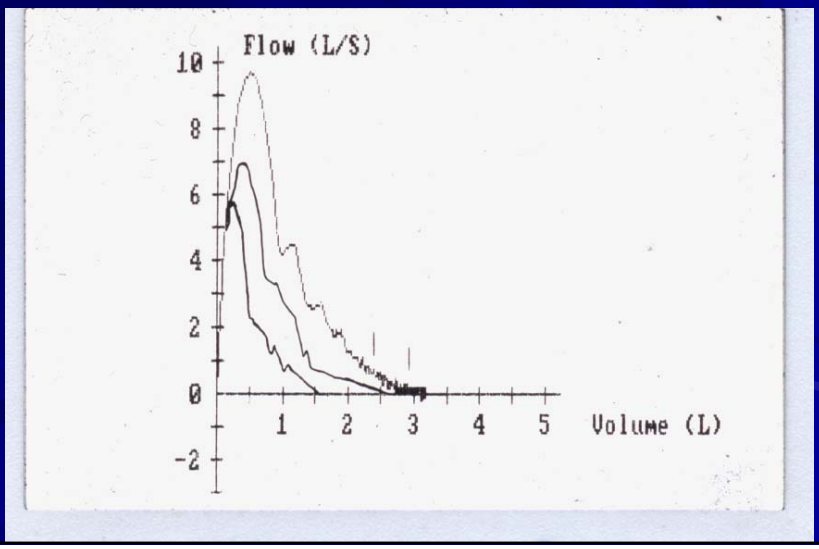


Mean Relative Change in FEV_1% Predicted (002 Study)



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

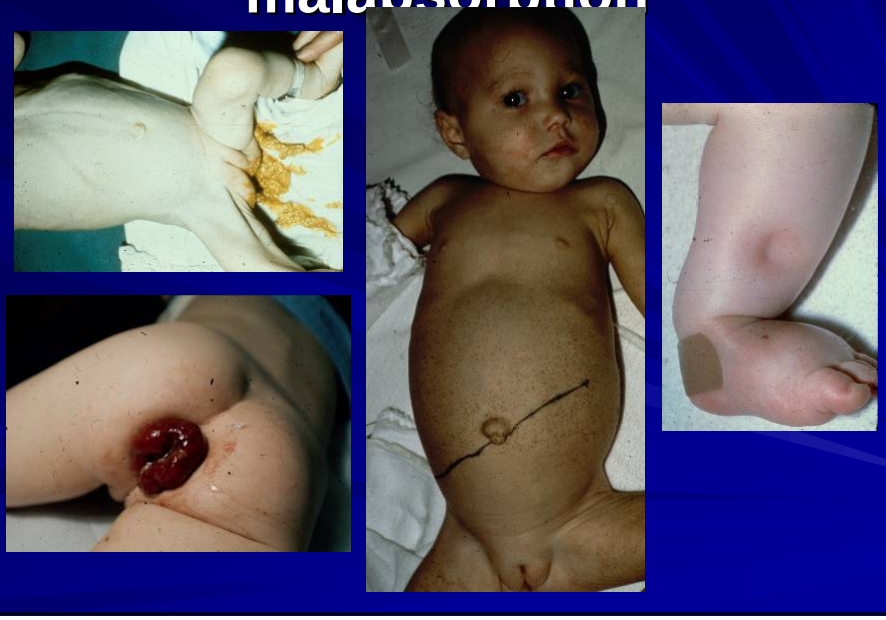
CF PFT's



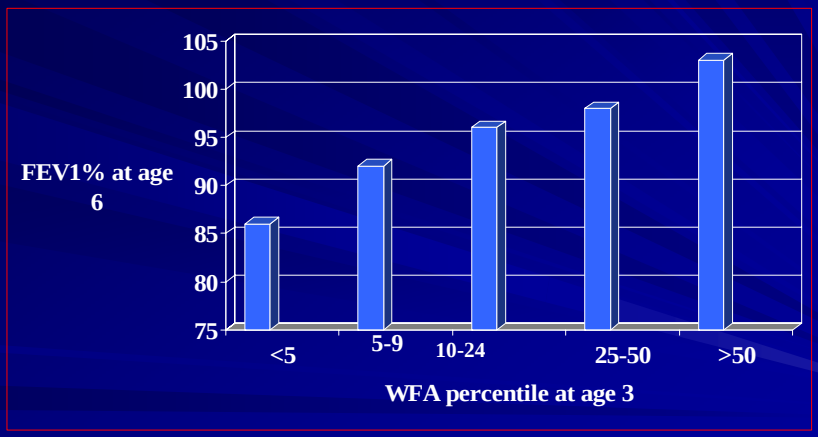
CF: Gastrointestinal Disease

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

CF: Pancreas-malabsorption

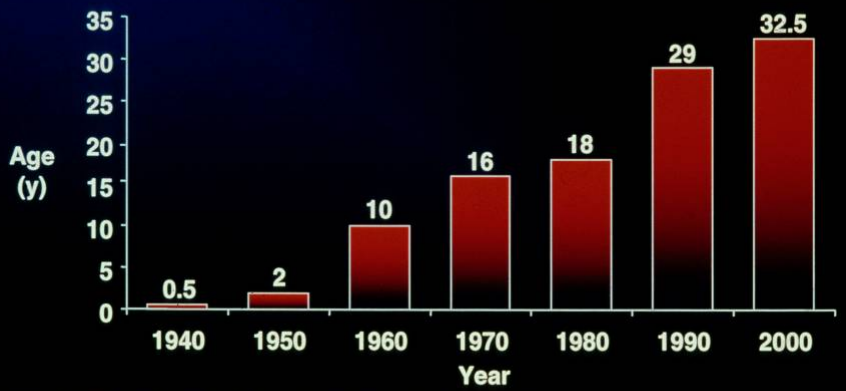


Nutrition and CF



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.