



CYSTIC FIBROSIS

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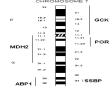


What is Cystic Fibrosis?

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



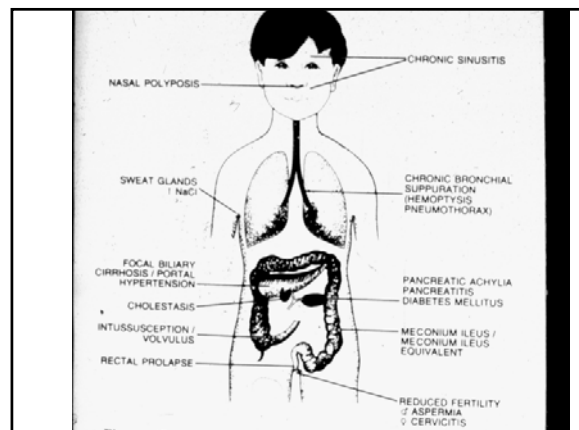
- Most common lethal genetic disease in Caucasians
 - 30,000 affected individuals in US
 - 27,000 in Europe
- CFTR - cAMP regulated chloride channel located in apical membrane of glandular epithelium
 - Long arm of chromosome #7
 - D508 most common mutation
 - 1000 identified mutations
 - Encodes for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

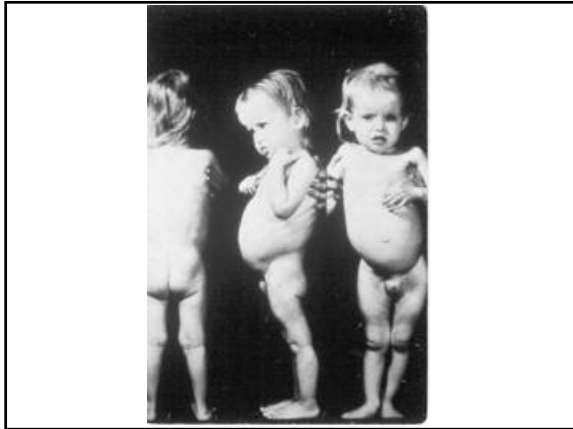
“Wehe dem Kind, das beim Kuss auf die Stirn salzig schmeckt, er ist verhext und muss bald sterben”

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

Presentation (CF PANCREAS)

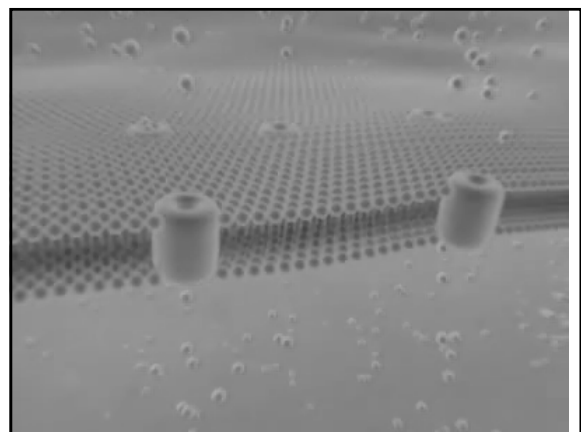
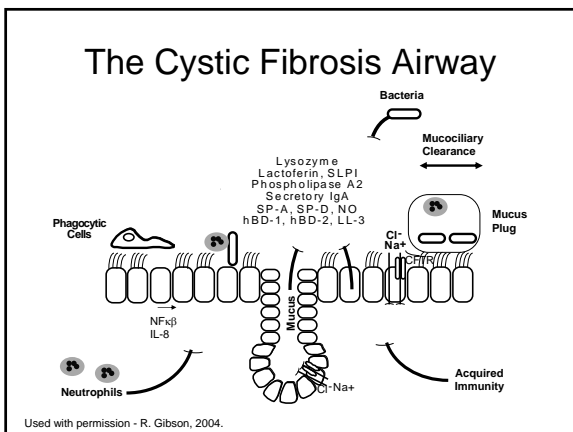
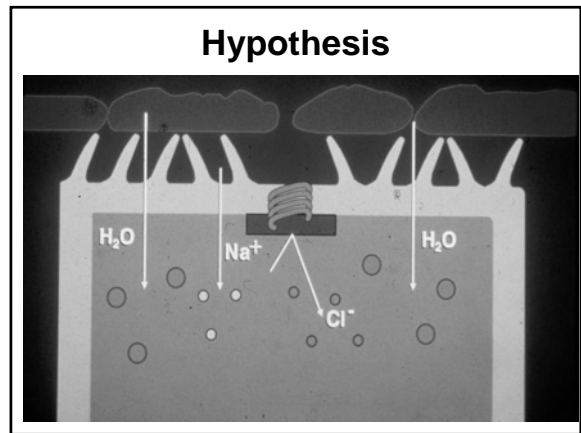
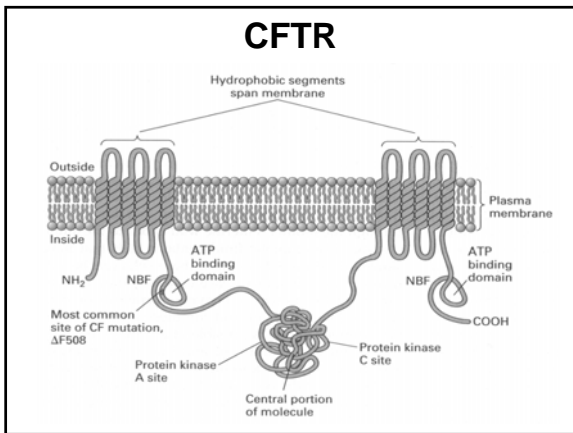
- C** Chronic respiratory disease
- F** Failure to thrive
- P** Polyps
- A** Alkalosis, metabolic
- N** Neonatal intestinal obstruction
- C** Clubbing of fingers
- R** Rectal prolapse
- E** Electrolyte ↑ in sweat
- A** Aspermia / absent vas deferens
- S** Sputum – S.aureus/P.aeruginosa

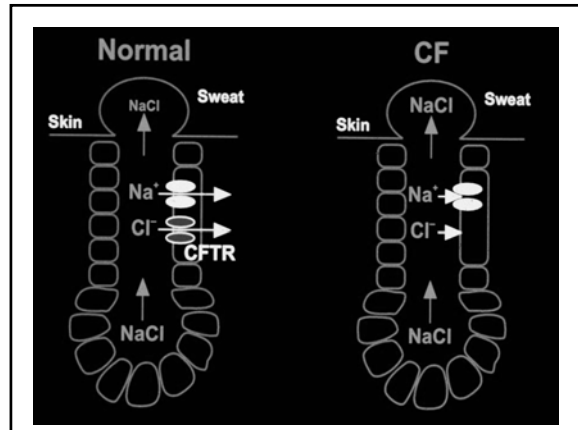
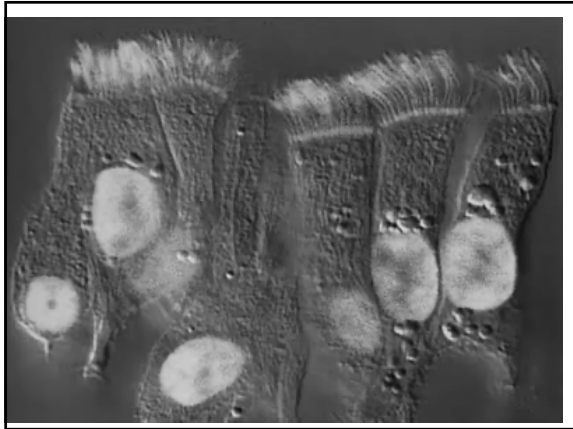




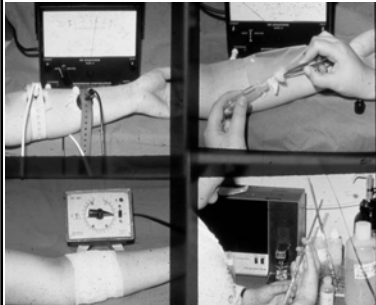
CFTR

- 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.





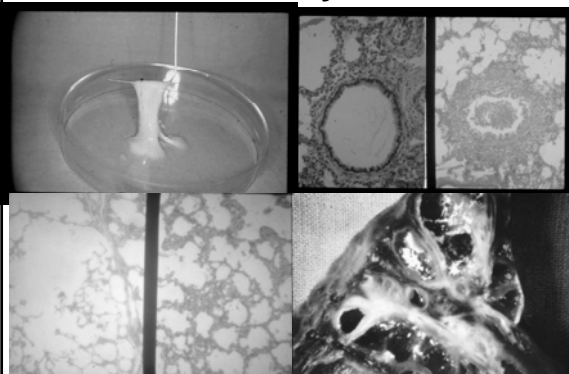
The sweat test (Chloride)



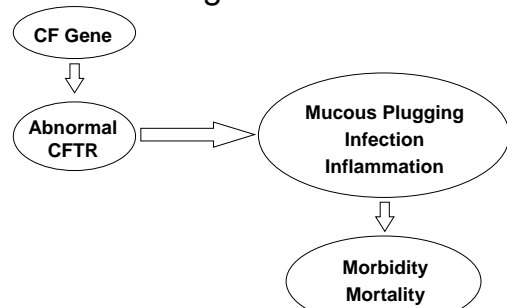
- Normal**
Under 40 mEq/L
- Borderline**
40-60 mEq/L
- Positive**
Over 60 mEq/L



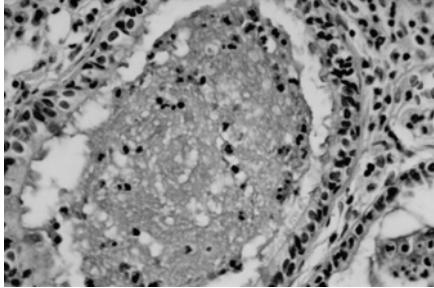
CF: Pulmonary Disease



Pathogenesis of Cystic Fibrosis Lung Disease

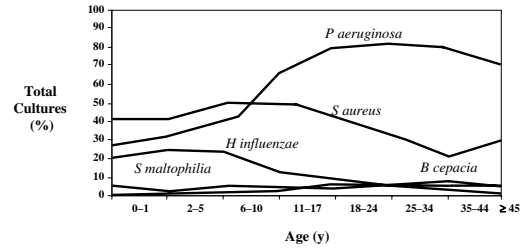


Airway Mucous Plugging, Infection, and Inflammation in Cystic Fibrosis



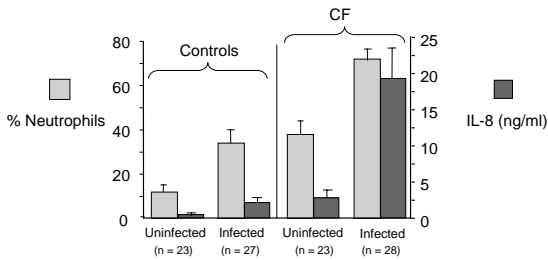
Used with permission – J. Wagener, 2004.

Major Airway Pathogens by Patient Age, 1999



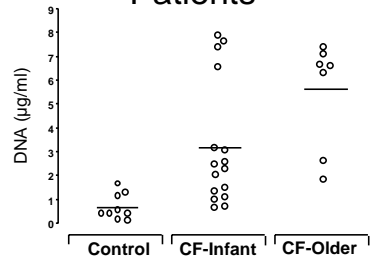
Patient Registry 1999 Annual Data Report. Bethesda, Md: Cystic Fibrosis Foundation; 2000.

Evidence of increased inflammation in BALF of infants with CF

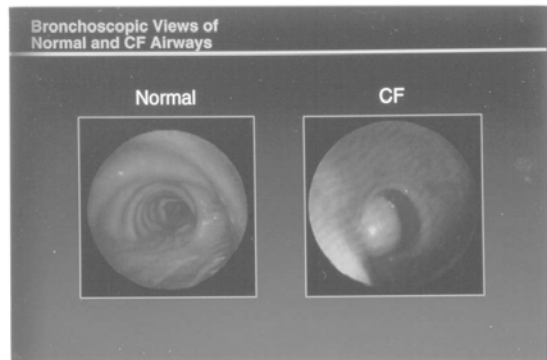
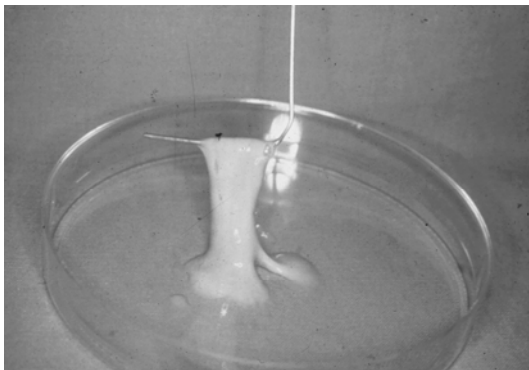


Adapted from Muhlebach et al. *Am J Respir Crit Care Med* 1999; 160: 186-191.

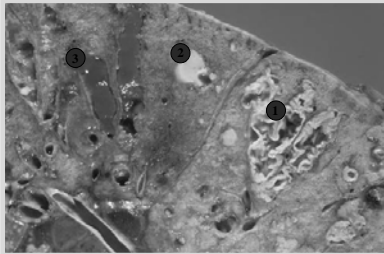
DNA in Bronchoalveolar Lavage Fluid from Cystic Fibrosis Patients



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



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

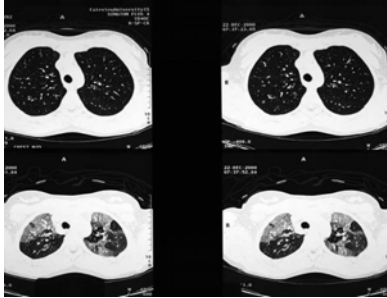
CF mild disease



Bronchiectasis

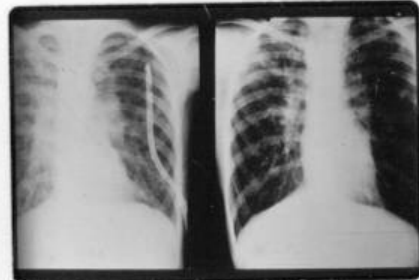


High-Resolution Inspiratory and Expiratory CT Scan in 12 year old



Used with permission - C. Milla, 2004.

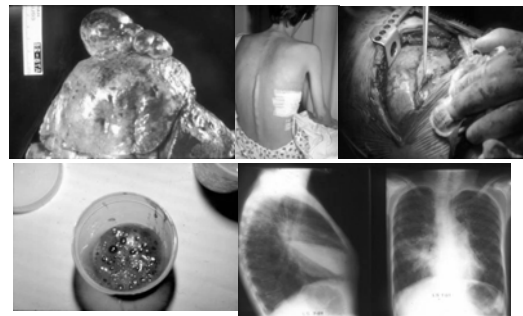
CF Pneumothorax



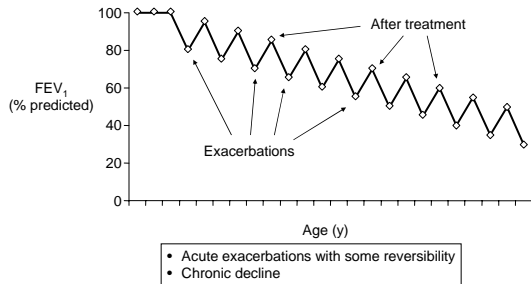
BLEBS



CF: Pulmonary Complications



Exacerbations Contribute to the Deterioration of Lung Function



CF: Respiratory management

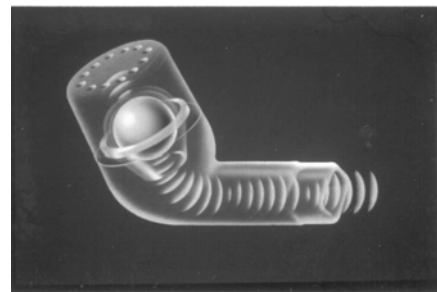
- Regular visits to CF Center
- Airway clearance
- Mucus thinners (DNase, hypertonic saline)
- Antibiotics(PO-IV-Aerosol)
- Anti inflammatory drugs



Airway Clearance

- CPT
 - Vest
 - Flutter
 - ACB
- ISSUES**
- Reflux
 - Risk factor for *Pa*
 - Adherence

CF Flutter



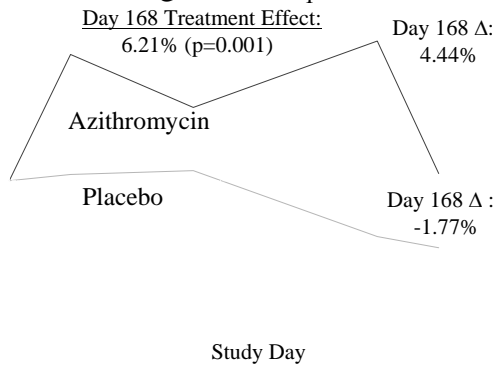
Anti-inflammatory Rx

- 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. pneumoniae* 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

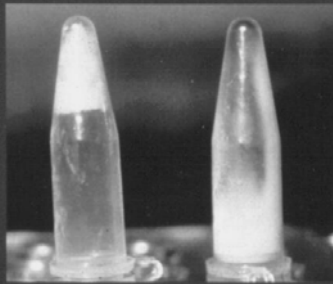
Relative Change in FEV₁ % Predicted



DNase

- Recombinant DNase
- Hydrolyzes DNA
- Aerosolized

Pulmozyme Increases the Pourability of Cystic Fibrosis Sputum



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

Treating Airway infections

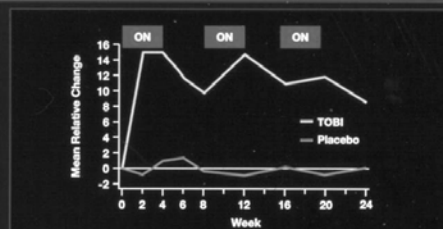
- Prophylactic treatment
 - prevent colonization
- Exacerbations
 - improves lung function
 - reduces inflammation
 - decreases bacterial density
- First isolates
 - may delay colonization

Antibiotics

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

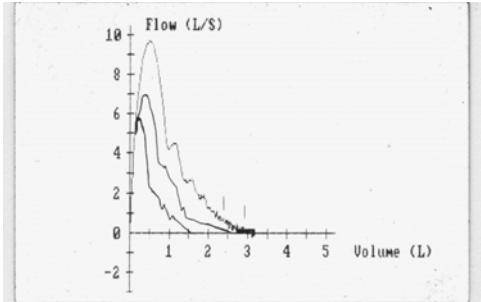


Mean Relative Change in FEV₁ % Predicted (002 Study)



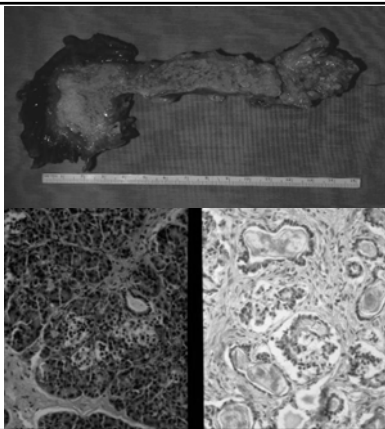
Bonney DR. Presented at the Eleventh Annual North American Cystic Fibrosis Conference, October 25-31, 1997, Nashville, Tennessee.

CF PFT's



CF: Gastrointestinal Disease

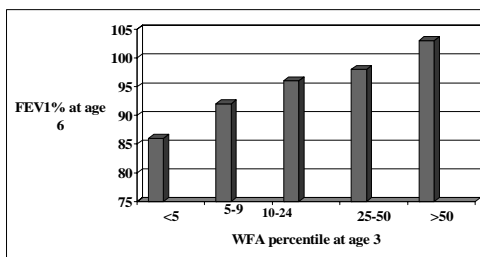
- Pancreatic insufficiency/malabsorption
- Lipo-soluble vitamin deficiency
- Failure to thrive
- Neonatal intestinal obstruction (15%)
- Recurrent distal intestinal obstruction
- Biliary stasis



CF: Pancreas-malabsorption

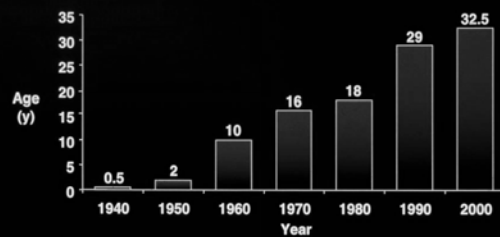


Nutrition and CF



Konstan et. Al. Pediatr Pulmonol 2000

Median CF Survival Age, 1940-2000



Data from Cystic Fibrosis Foundation, Bethesda, Md. Available at http://www.cf.org/infodisplayation_files/frame.htm#fs00015.htm.

