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Cystic Fibrosis

- Richard H. Simon
  Pulmonary and Critical Care Medicine
  Department of Internal Medicine

Fall 2008

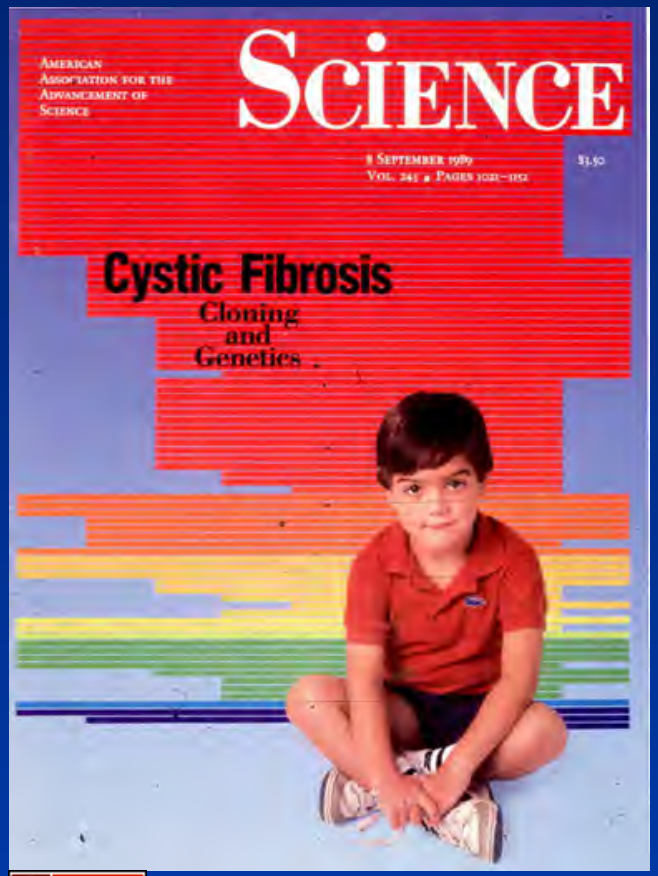
University of Michigan
Medical School

Objectives

- Understand:
  - The genetic nature of cystic fibrosis (CF)
  - The pathophysiology of CF lung disease
- Know how to diagnose CF
- Learn the basic approach to treating CF lung disease

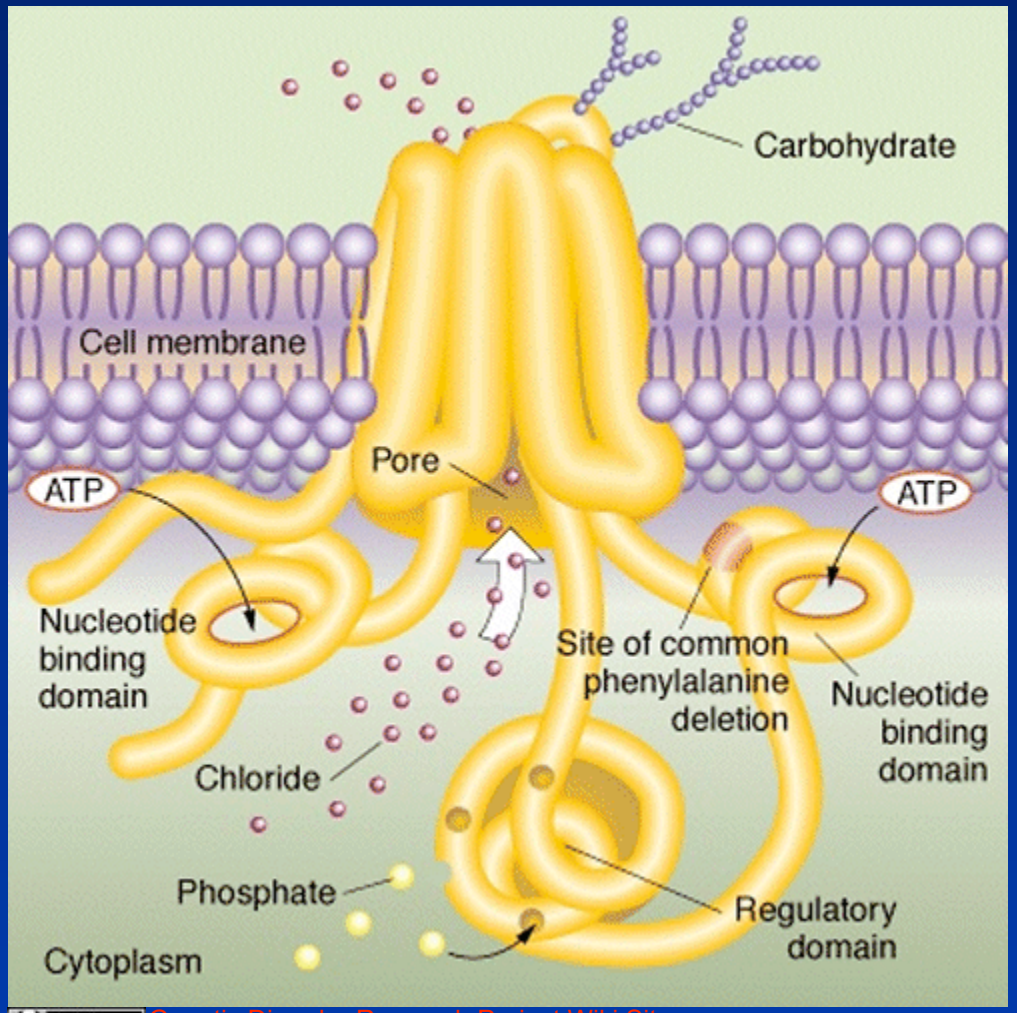
Cystic Fibrosis

- Inherited disease
  - Autosomal recessive
- Gene cloned in 1989: "CFTR"
  - Cystic Fibrosis Transmembrane conduction Regulator
- 1601 mutations in CFTR known to cause CF
- An extensive amount of information is known about CFTR



FAIR USE Science, September 1989

Schematic Representation of CFTR



 Genetic Disorder Research Project Wiki Site

Pathophysiology of CF

CFTR Dysfunction

?

Disease manifestations

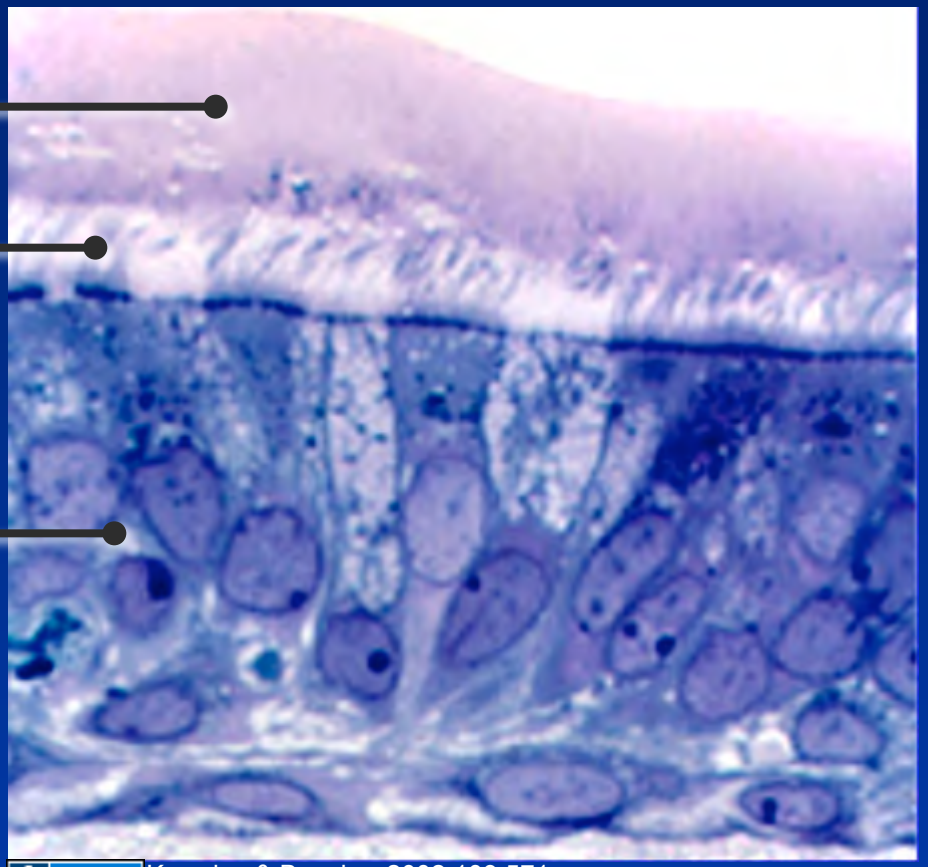
- Lungs
- Sinuses
- Pancreas
- Liver
- Bones
- Vas deferens

Airway Cross Sectional View

Mucus layer

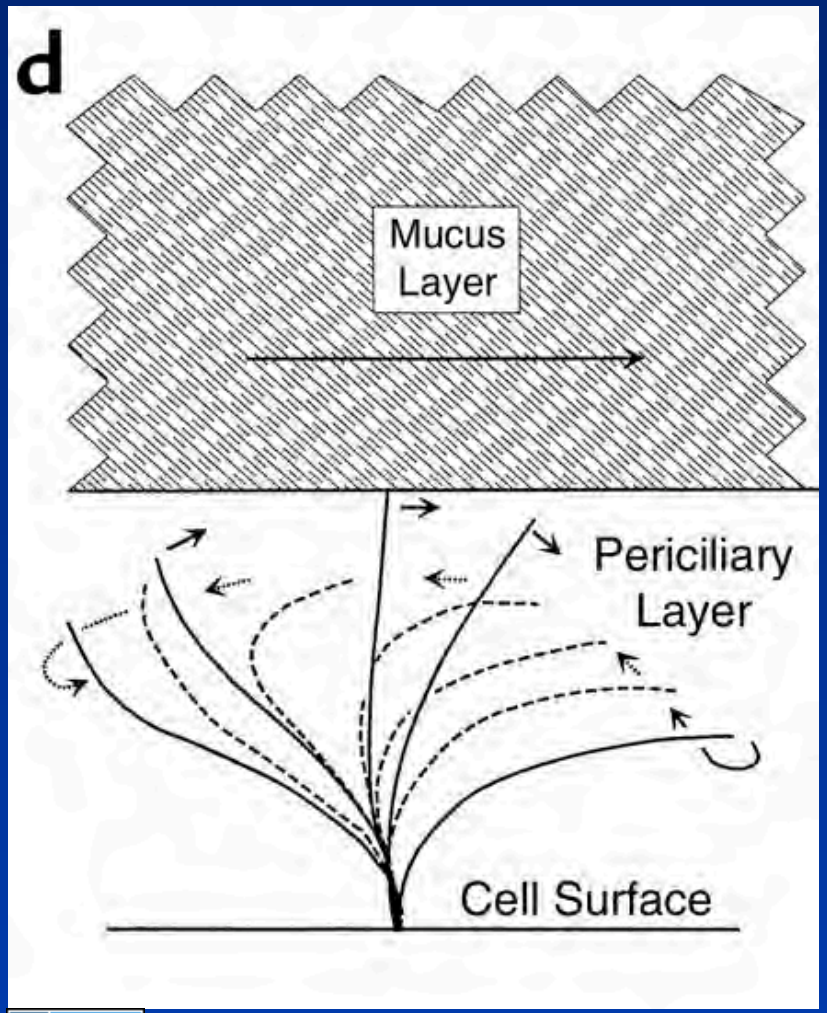
Pericellular layer with cilia

Epithelial cell layer



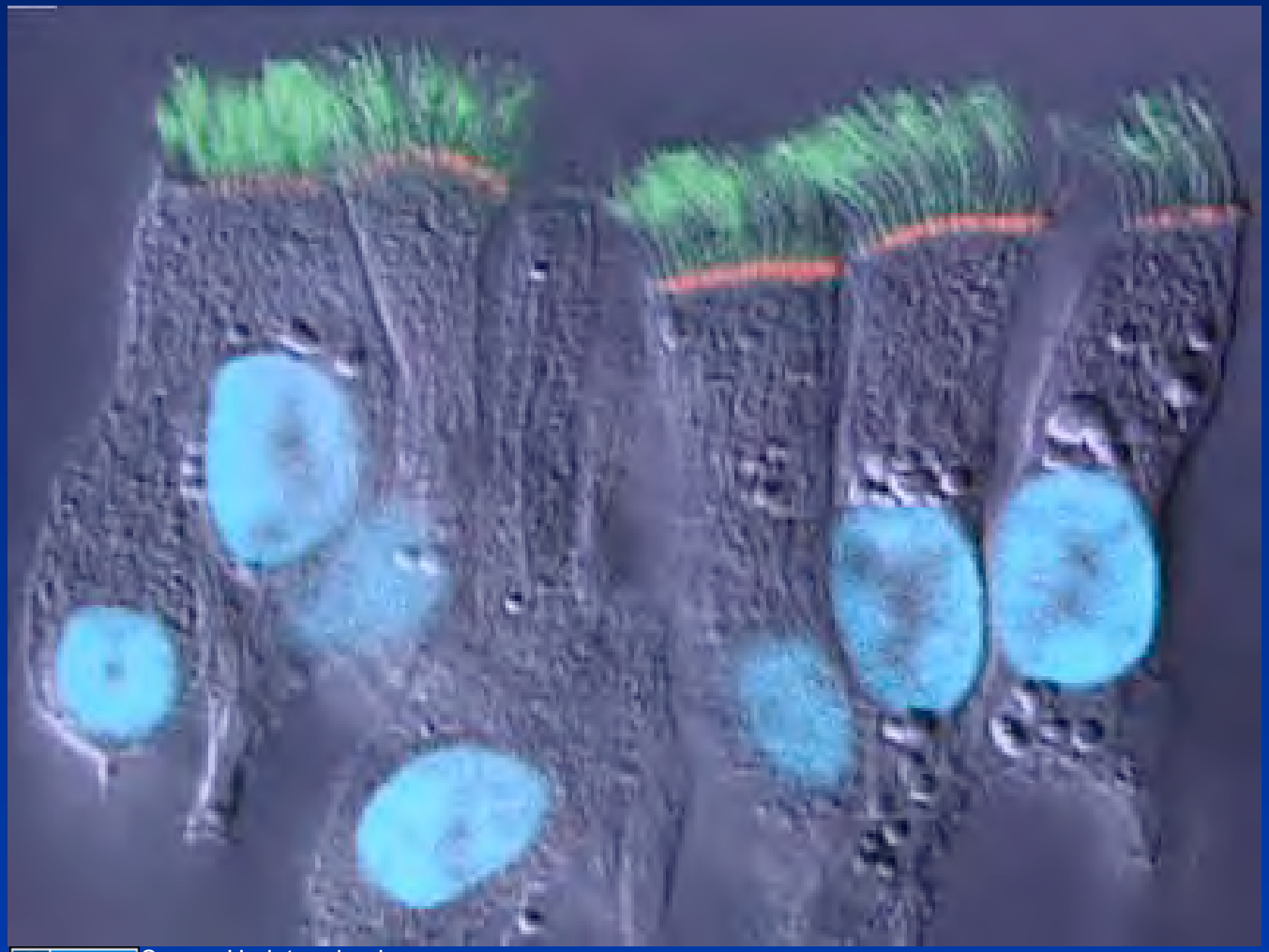
PD-INCL Knowles & Boucher 2002;109:571

Required Geometry for Effective Mucociliary Clearance

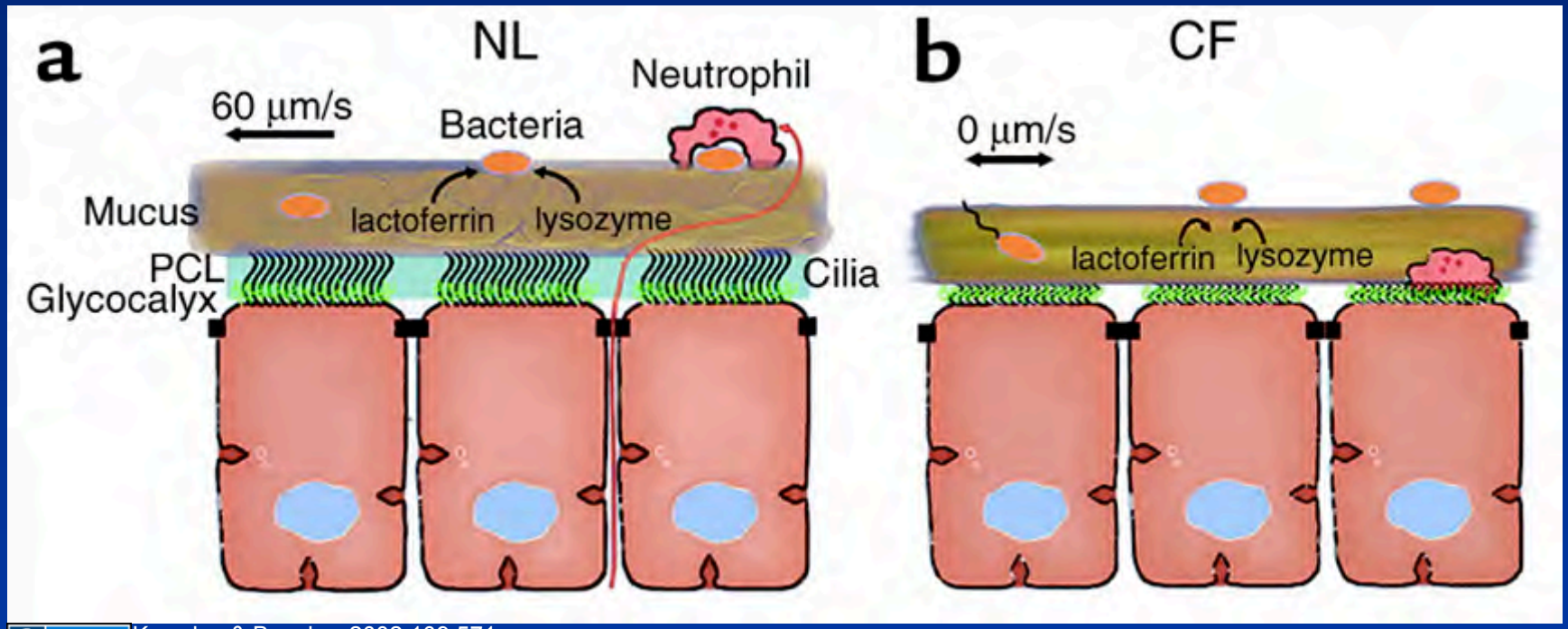


 Knowles & Boucher 2002;109:571

Pathophysiology of CF Lung Disease

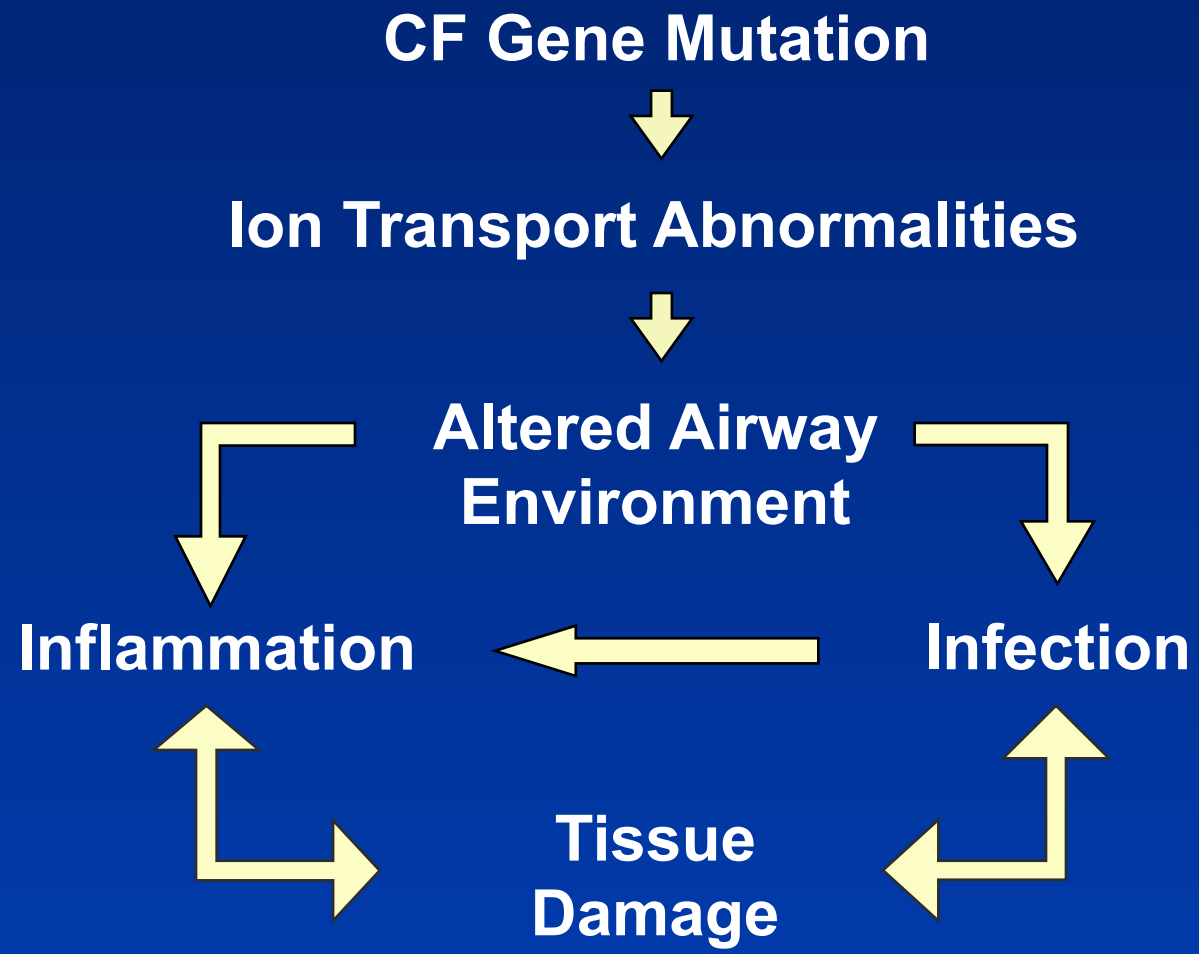


Consequences of CFTR Deficiency on Airway Clearance



PD-INEL Knowles & Boucher 2002;109:571

Pathophysiology of CF Lung Disease



Pathophysiology of CF Lung Disease

CF Gene Mutation

↓

Recurrent Bronchitis

↓

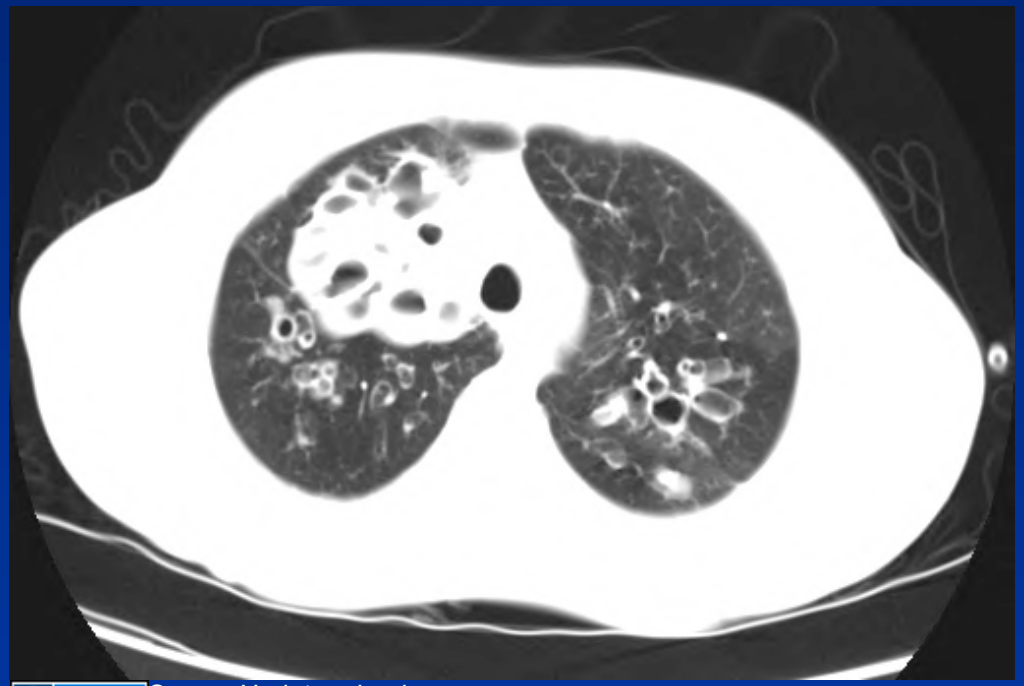
Bronchiectasis

↓

Chronic Respiratory Failure

↓

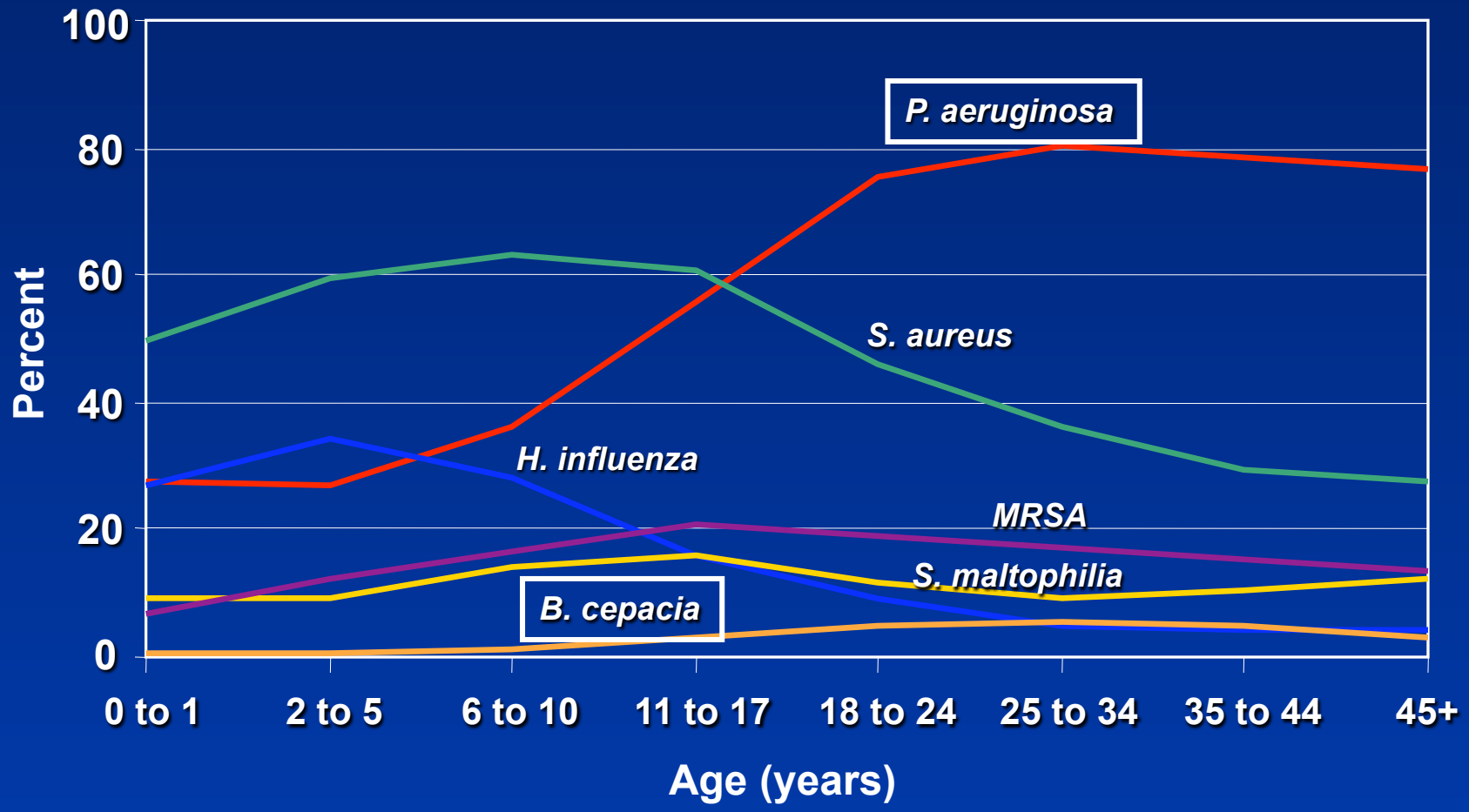
Death



PD-INEL Source Undetermined

PD-INEL R. Simons

Prevalence of Infections in CF Patients



 Cystic Fibrosis Foundation Patient Registry Data. 2005

Natural History of CF Lung Infections

- *Ps. aeruginosa* or *B. cepacia* complex species persist in the lung
- True infection, not "colonization"
- Difficulty in eradicating infection:
  - Intrinsic antibiotic resistance
  - Acquired antibiotic resistance
  - Poor antibiotic penetration into secretions
  - Alginate produced by mucoid Ps. (biofilms)
  - CF-related defects in mucosal (but not systemic) defenses

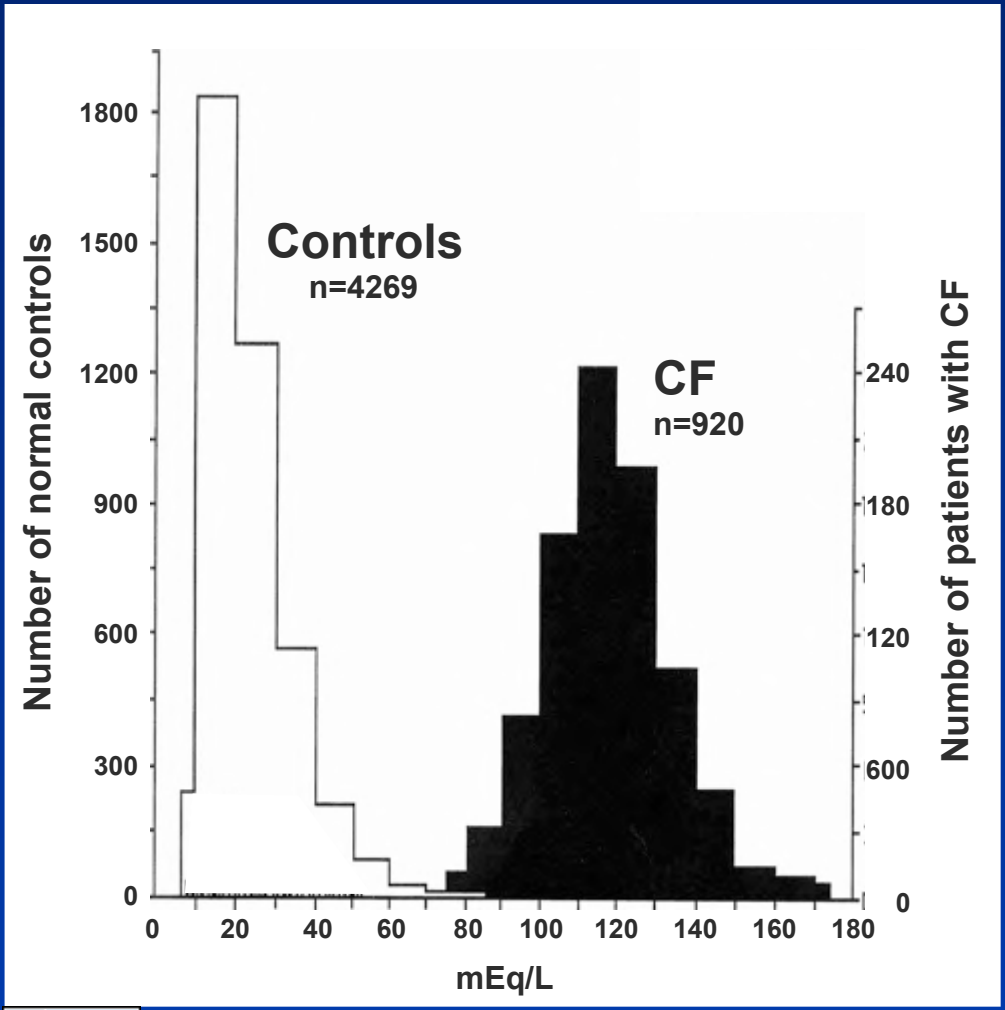
Diagnostic criteria for cystic fibrosis
Part 1: Clinical Manifestation of Disease

- **At least one of the following:**
  1) **One or more clinical manifestations of CF**
     - **Meconium ileus**
     - **Chronic bronchitis / bronchiectasis**
     - **Chronic infection of the paranasal sinuses**
     - **Pancreatic insufficiency**
     - **Salt loss syndromes**
     - **Male infertility due to congenital bilateral absence of the vas deferens**
  2) **Positive newborn screening test**
  3) **History of CF in a sibling**

Diagnostic Criteria for Cystic Fibrosis
Part 2: Laboratory evidence of CFTR abnormality

- **At least one of the following:**
  1) **Elevated sweat chloride test**
  2) **Identification of a mutation in each CFTR gene known to cause CF**
  3) **In vivo demonstration of characteristic abnormalities in ion transport across nasal epithelium (not widely available)**

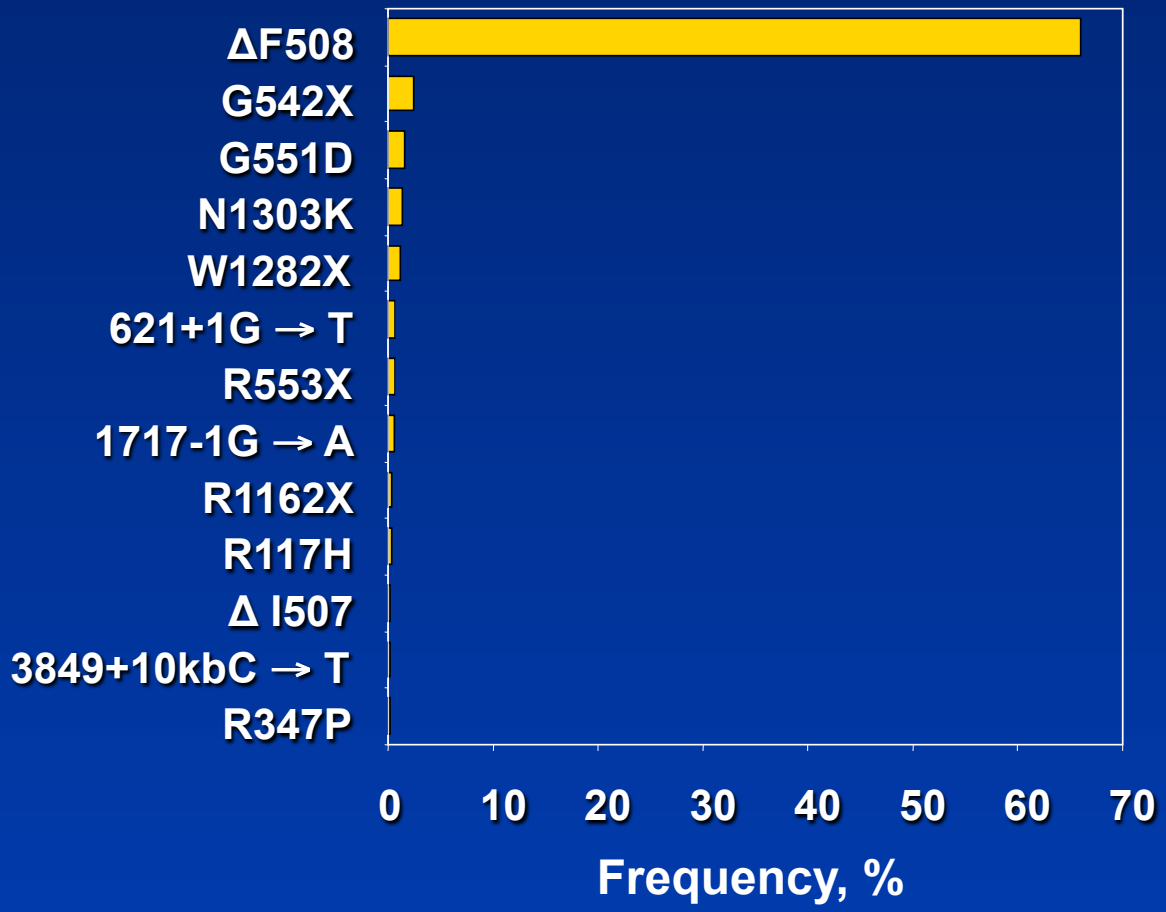
Sweat Test for Diagnosis of CF



Shwachman H, Mahmoodian A. Mod Prob Pediatr 1967;10:158

Use of Genotyping to Diagnose CF

Population Frequency of Specific CFTR Mutations Causing CF



- 1601 CFTR mutations known to cause CF
- Only 25 mutations have a frequency ≥ 0.1%

Genotyping for CF Diagnosis

- Current commercial screening tests
  - Look for presence of between 25 - 100 mutations
  - These will detect a CF allele only ~90% of time
- For a group of patients with known CF, genotyping would be diagnostic in only ~81% of patients
- ∴ Screening for most common mutations is not as sensitive as sweat testing (98%) to diagnose classic CF

Genetic Diagnosis of CF

- Tests becoming commercially available for detecting mutations more broadly
  - PCR used to amplify all exons and surrounding splice sites
  - Heteroduplex formation screening and/or sequencing
  - Analysis for large deletions and duplications
  - Cost ~ $2,500

Acute Exacerbations of CF Lung Disease

- Symptoms
  - Increased cough with sputum production
  - Hemoptysis
  - Increased shortness of breath
  - Fever (not required)
  - Reduction in FEV1
  - Worsening infiltrates on chest x-ray (not required)

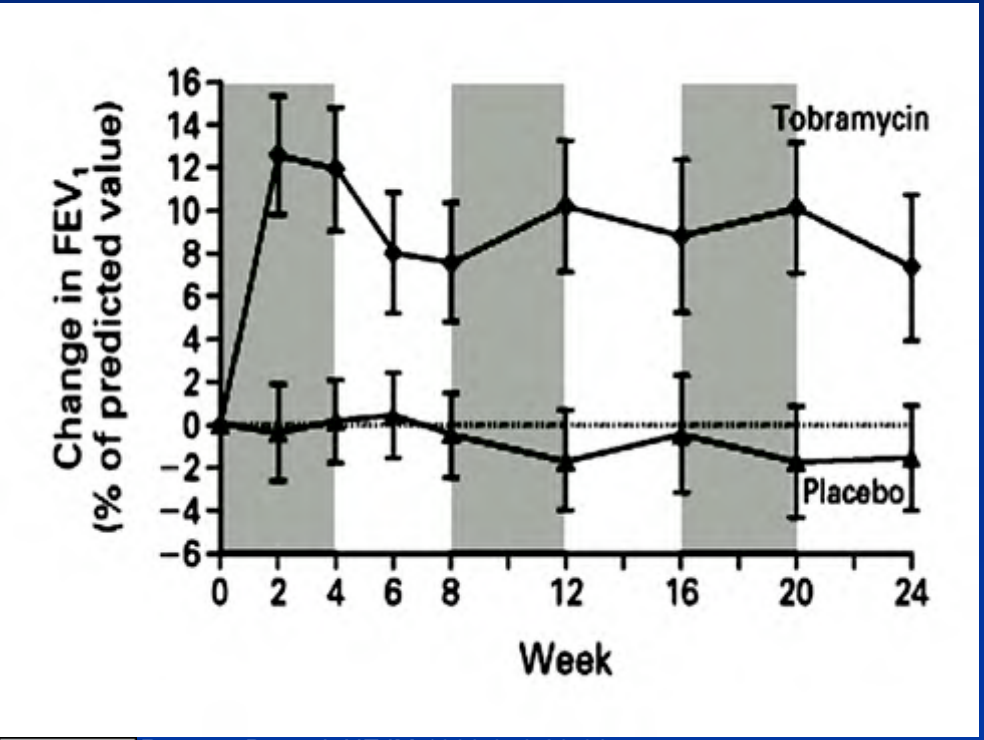
Acute Exacerbations of CF Lung Disease

- Antibiotic treatment
  - Oral antibiotics
    - If symptoms are mild, and
    - Bacteria are susceptible
  - Intravenous antibiotics otherwise

Management of Chronic Lung Disease in Cystic Fibrosis

Aerosolized Antibiotics

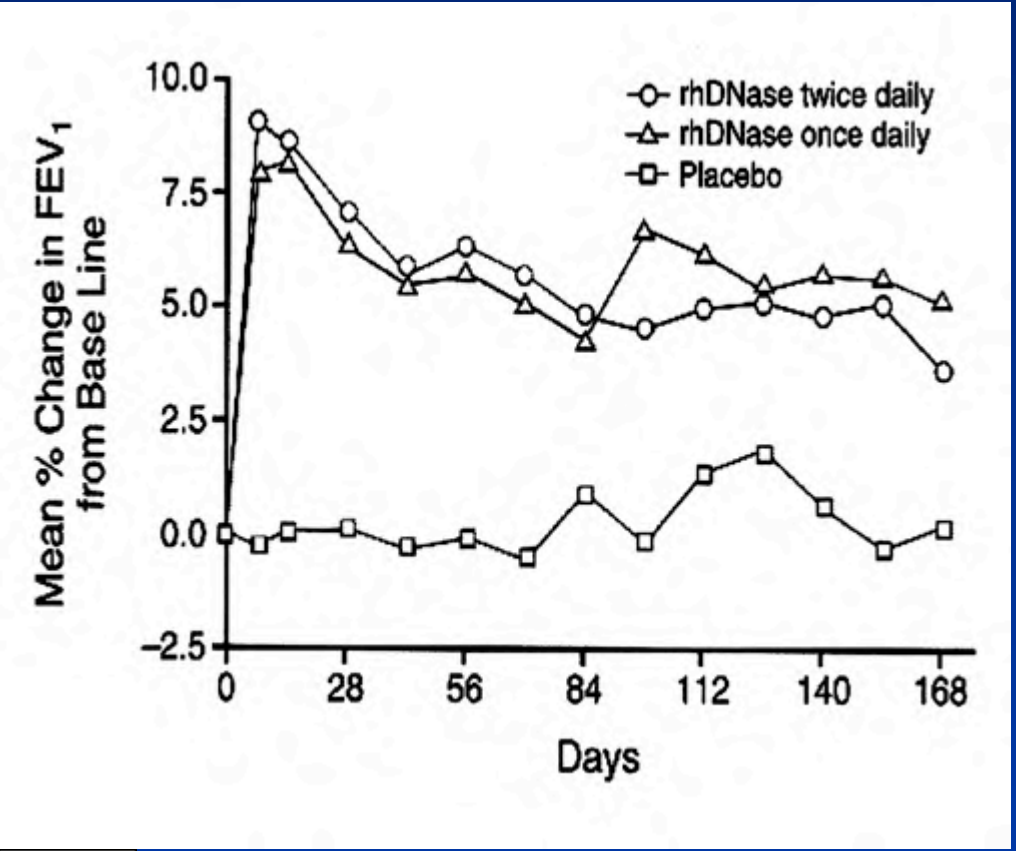
- High dose tobramycin proven for chronic infection
  - TOBI® 300 mg in 5 ml bid every other month



PD-INCL Ramsey B, et al. NEJM 1999;340:23-30

Mucolytic Therapy for CF

- DNase (Pulmozyme ®)
  - Chronic use improves FEV1 and causes fewer exacerbations



PD-INEL Fuchs HJ, et al. NEJM 1994;331:637-642

Bronchodilators in CF

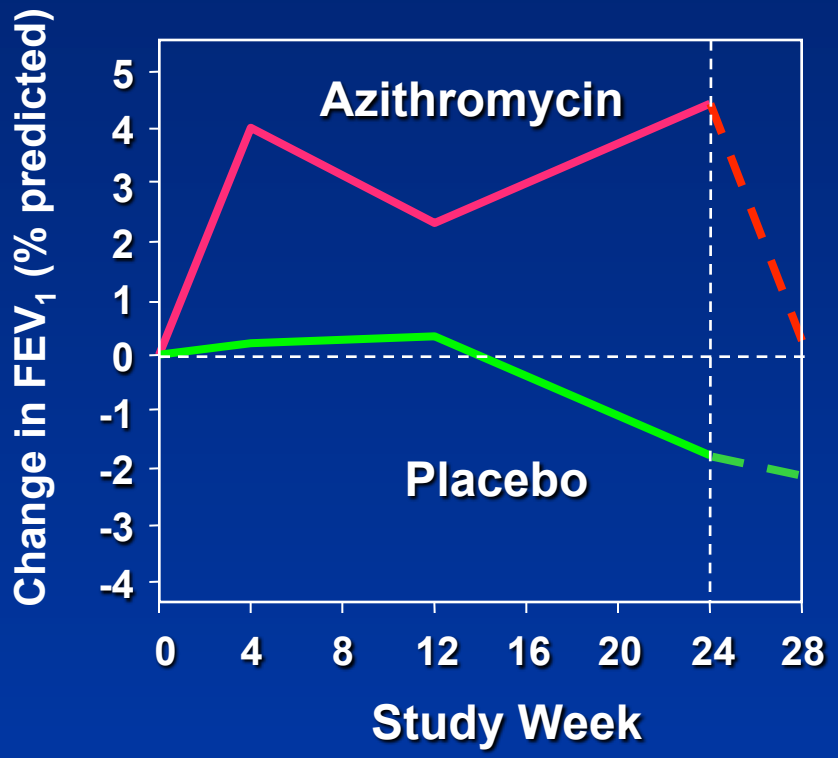
- No studies in acute exacerbations but routinely given
- Chronic use -- FEV1 improves acutely in some patients
  - β-adrenergic agonists (e.g. albuterol, salmeterol)
  - Anticholinergic agents (ipratroprium bromide, tiotroprium)

Anti-Inflammatory Treatment in CF

- Glucocorticoids
  - Oral (prednisone)
    - Preserves lung function, but too many adverse effects
  - Inhaled
    - Used for subgroup of with bronchial hyperreactivity (asthma) symptoms
- Ibuprofen
  - Beneficial for young patients
  - No evidence for improvement in adults

Macrolide Therapy for CF

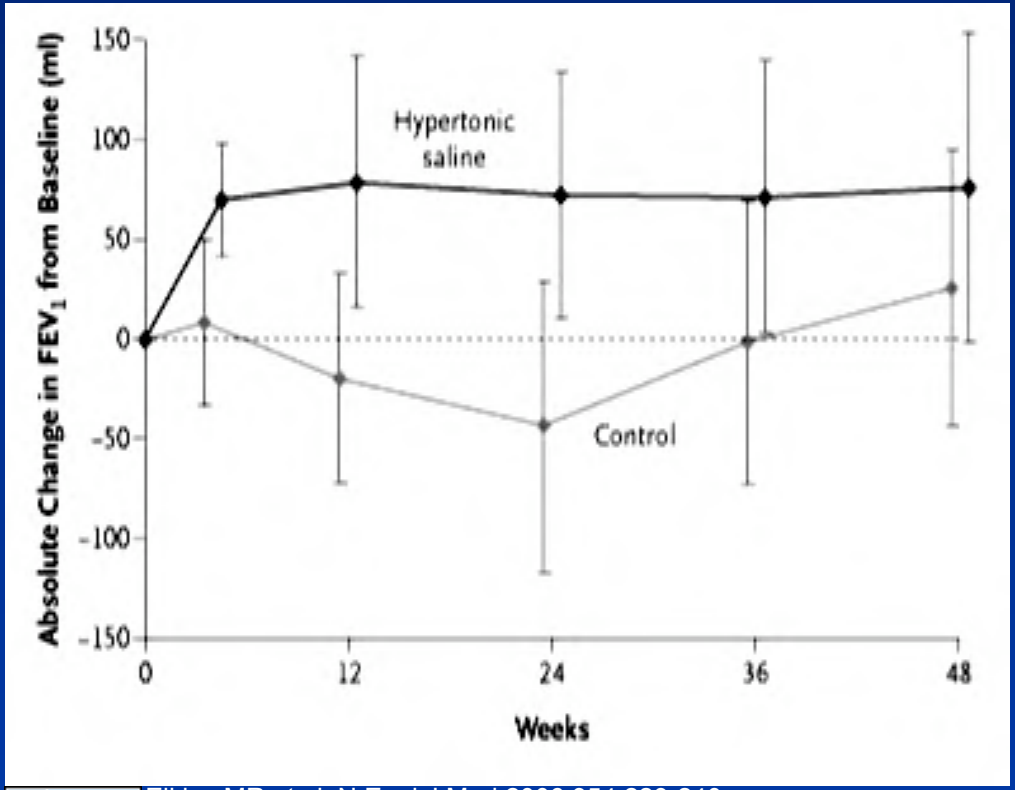
- Azithromycin in CF
  - Improved FEV1
  - Fewer exacerbations of CF lung disease
  - Uncertain mechanism of action
    - Anti-inflammatory?
    - Bacterial toxin or biofilm production?



PD-INEL Saiman L, et al. JAMA. 2003;290:1749-56

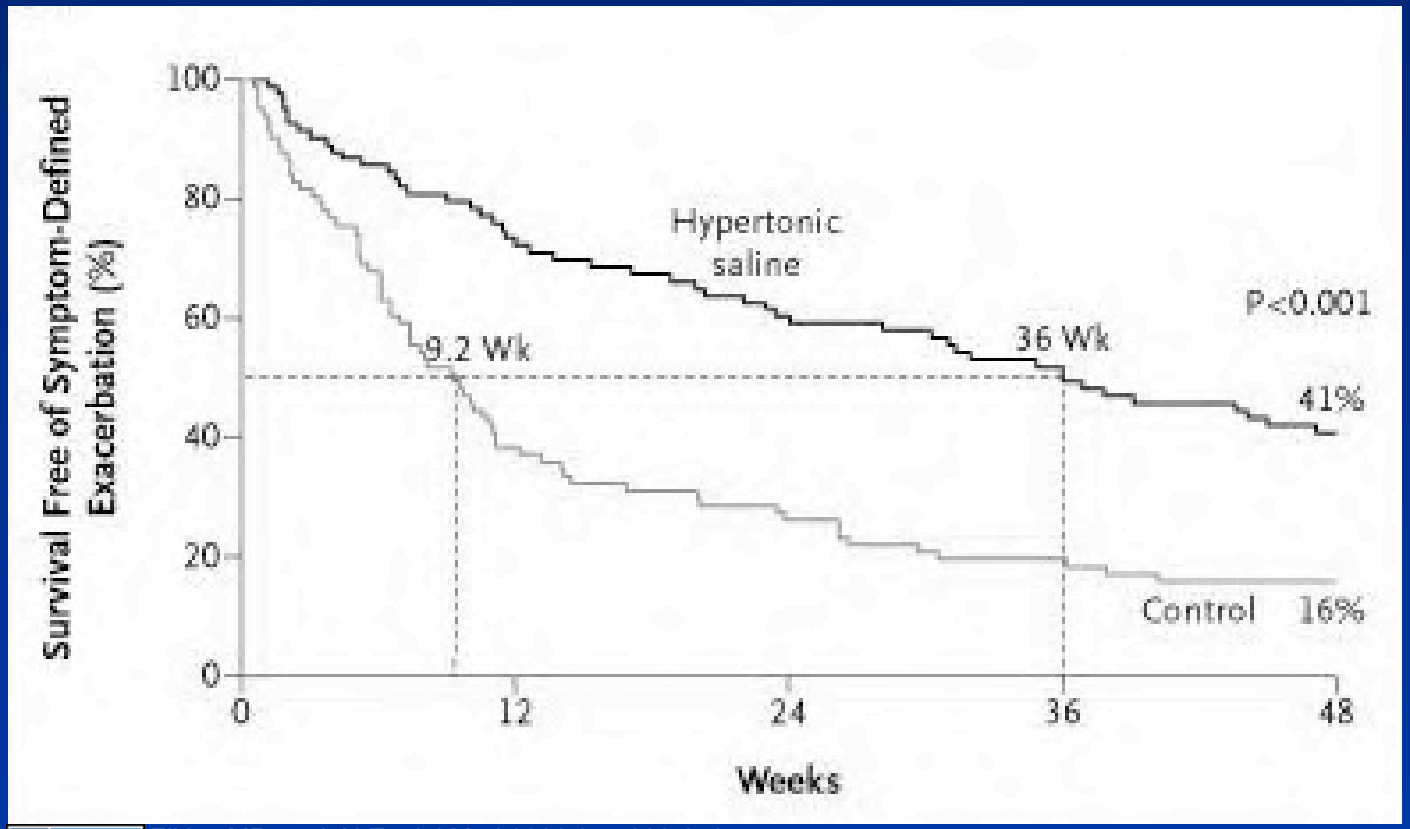
Nebulized Hypertonic Saline (7%)

- Effect on FEV1
  - Randomized, double-blind, placebo controlled trial
  - N = 164
  - Inhalation of 4 ml of 7% vs. 0.9% saline bid for 48 weeks



 Elkins MR et al. N Engl J Med 2006;354:229-240

Effect of 7% Saline on Frequency of Pulmonary Exacerbations



 Elkins MR et al. N Engl J Med 2006;354:229-240

Physiotherapy for CF

- No studies in acute exacerbations
  - But “standard of care” treatment
- Beneficial for chronic management

Physiotherapy Options for CF

- Flutter
- Acapella
- PEP
- Vest

Supplemental Oxygen

- Use same guidelines as COPD

Home Versus Hospital Therapy for Acute Exacerbation

- Home regimen must duplicate full hospital program
  - IV drugs
  - Physiotherapy
  - Nutrition
  - Et cetera
- Results from small studies showed mixed results

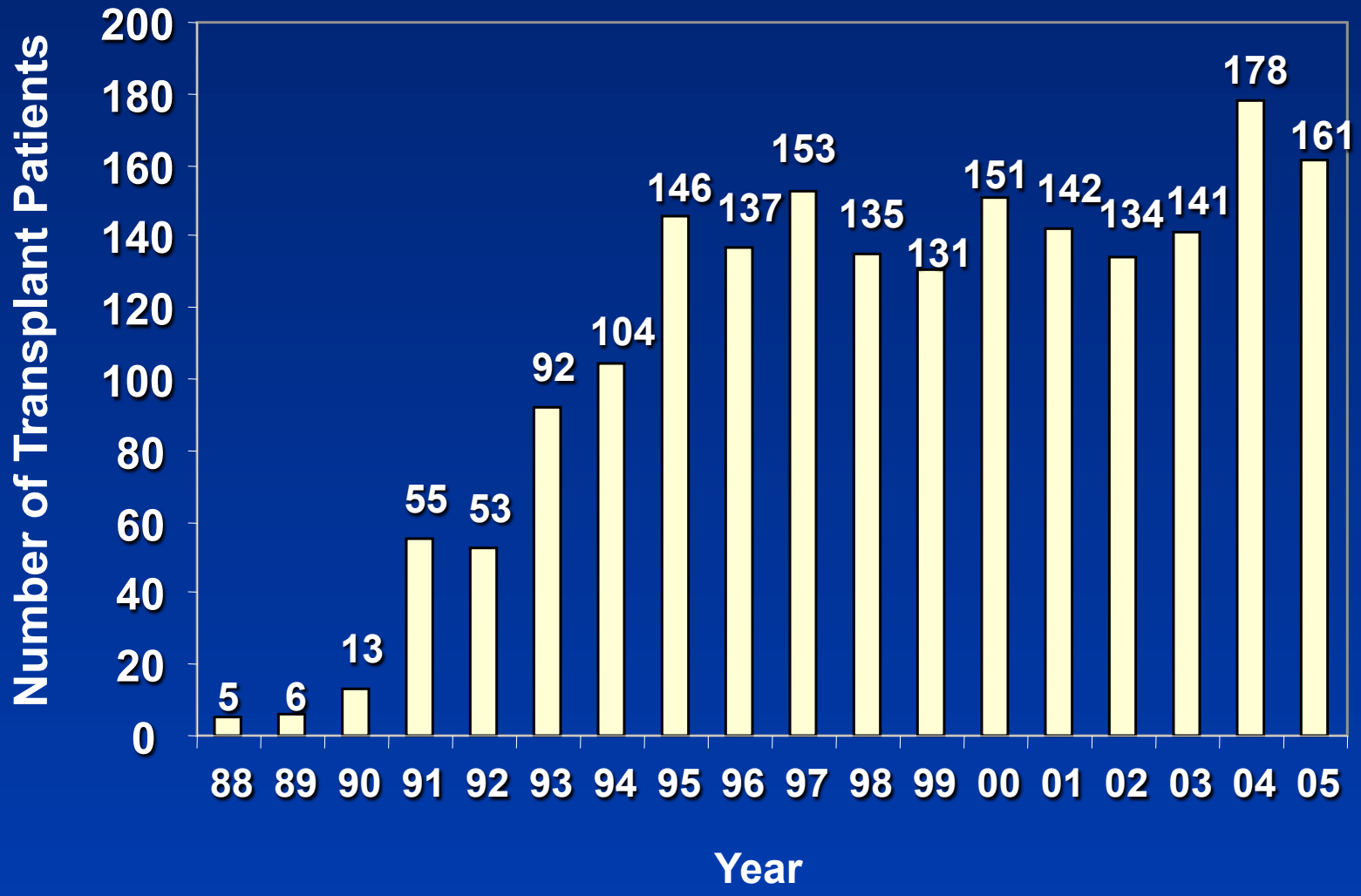
Assisted Ventilation in CF

- Past studies show very poor outcomes
- Non-invasive ventilation being used as a bridge to lung transplantation

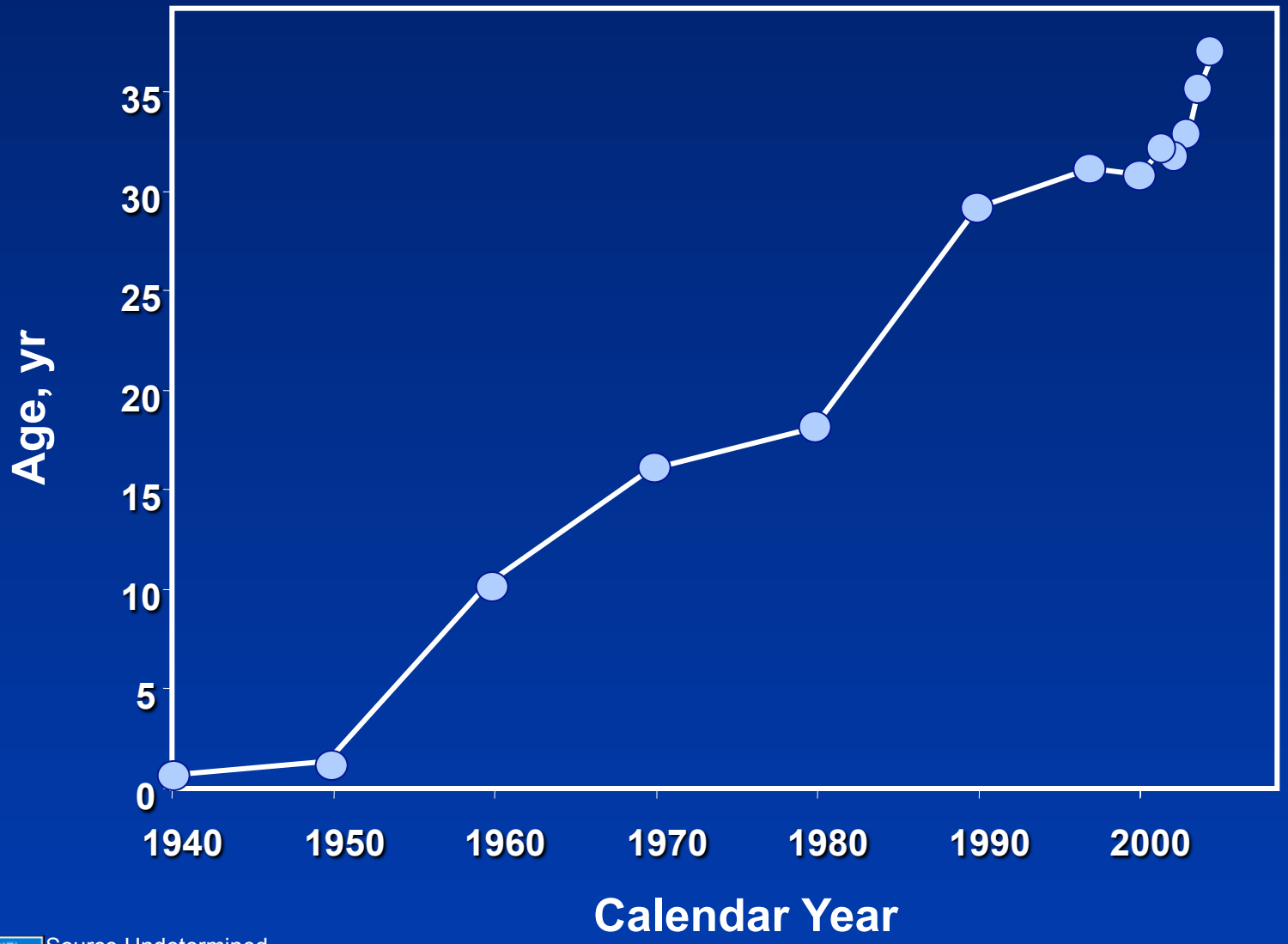
Lung Transplantation CF

- Bilateral lung transplantation
- Outcome similar to non-CF transplantation
- Problems
  - Long waiting lists
  - Many exclusions
- Living donor transplants

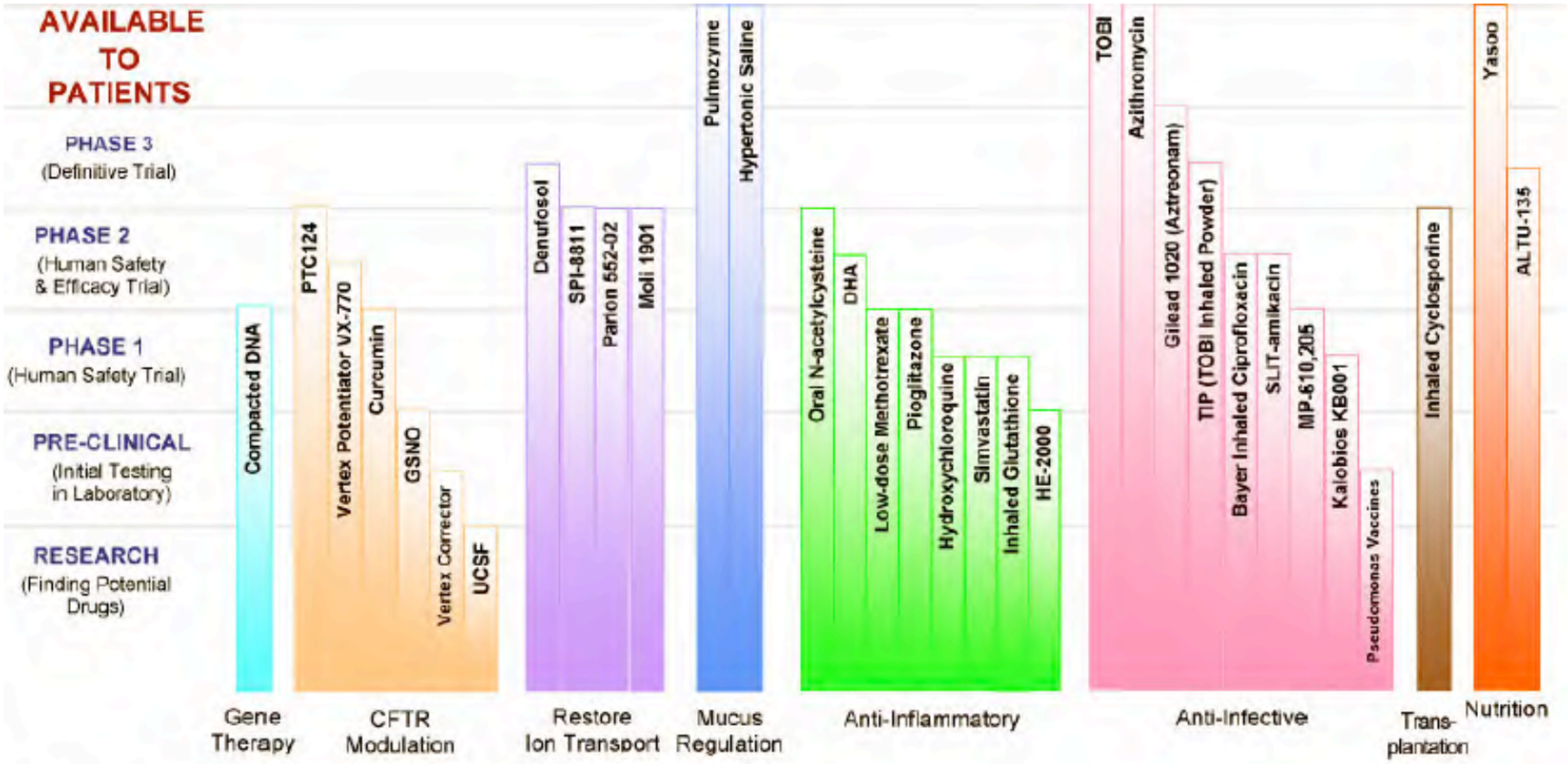
Number of CF Patients With Lung Transplants 1988 - 2005



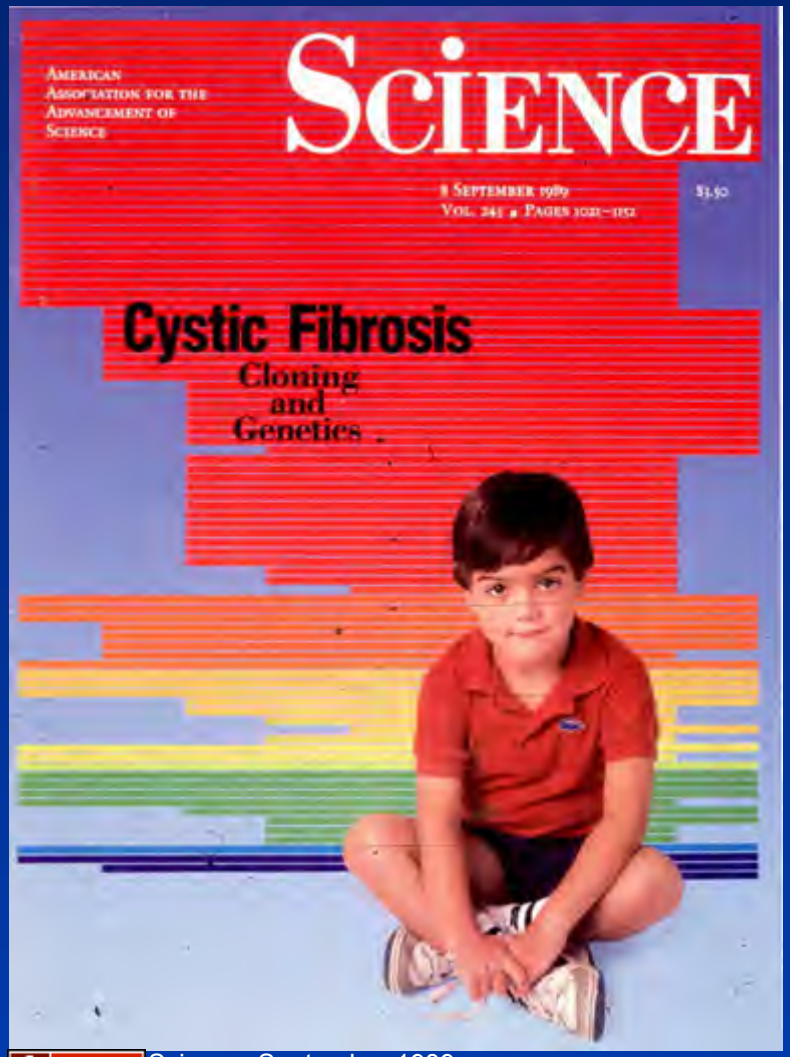
Median Predicted Survival for Cystic Fibrosis



New Therapies for CF Under Development – September 2007



Cystic Fibrosis 1989



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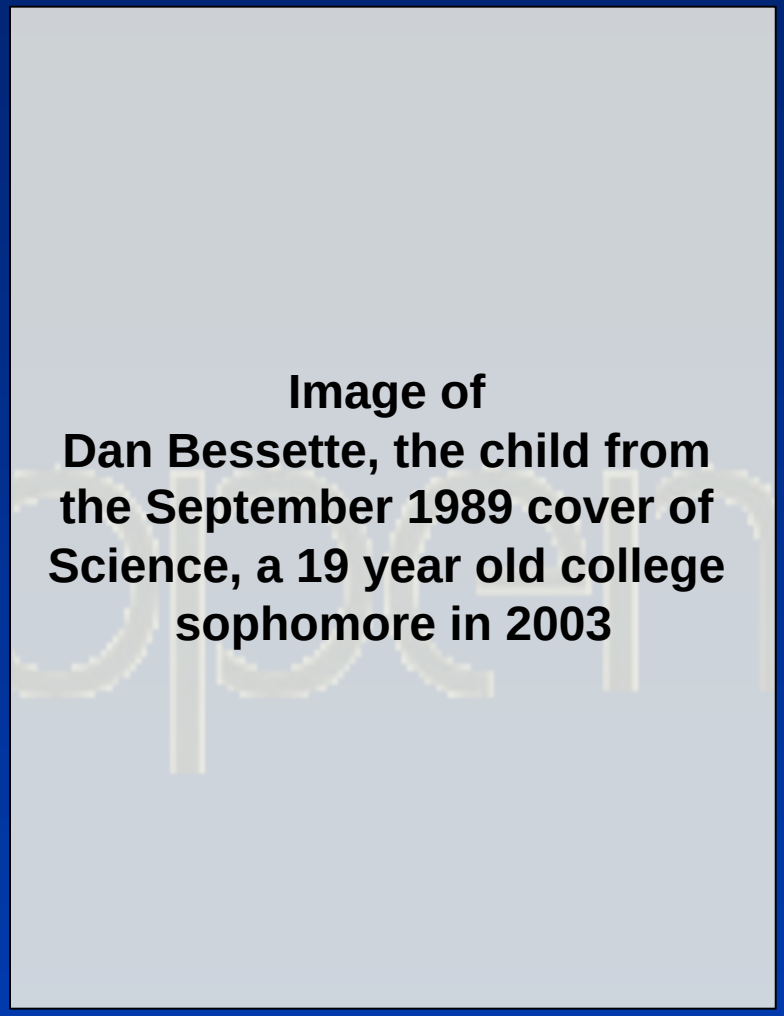
Clip of *Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping* from Science, September 1989, removed

Cystic Fibrosis Now



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- Simon RH. Treatment of CF lung disease. UpToDate, 2008.
- Davis P. Cystic Fibrosis Since 1938. Am J Respir Crit Care Med 2006;173: 475-482.

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 5: Science, September 1989

Slide 6: Genetic Disorder Research Project Wiki Site, http://runkle-science.wikispaces.com/Cystic+Fibrosis

Slide 8: Knowles & Boucher 2002;109:571

Slide 9: Knowles & Boucher 2002;109:571

Slide 10: Source Undetermined

Slide 11: Knowles & Boucher 2002;109:571

Slide 12: R. Simon

Slide 13: Source Undetermined; R. Simon

Slide 14: Cystic Fibrosis Foundation Patient Registry Data. 2005

Slide 18: Shwachman H, Mahmoodian A. Mod Prob Pediatr 1967;10:158

Slide 19: CF Genetic Analysis Consortium

Slide 25: Ramsey B, et al. NEJM 1999;340:23-30

Slide 26: Fuchs HJ, et al. NEJM 1994;331:637-642

Slide 29: Saiman L, et al. JAMA. 2003;290:1749-56

Slide 30: Elkins MR et al. N Engl J Med 2006;354:229-240

Slide 31: Elkins MR et al. N Engl J Med 2006;354:229-240

Slide 38: Source Undetermined

Slide 39: Source Undetermined

Slide 40: Source Undetermined

Slide 41: Science, September 1989