CYSTIC FIBROSIS

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

Goals

- Basic defect
- Pathophysiology
- Clinical signs and symptoms
- Therapy

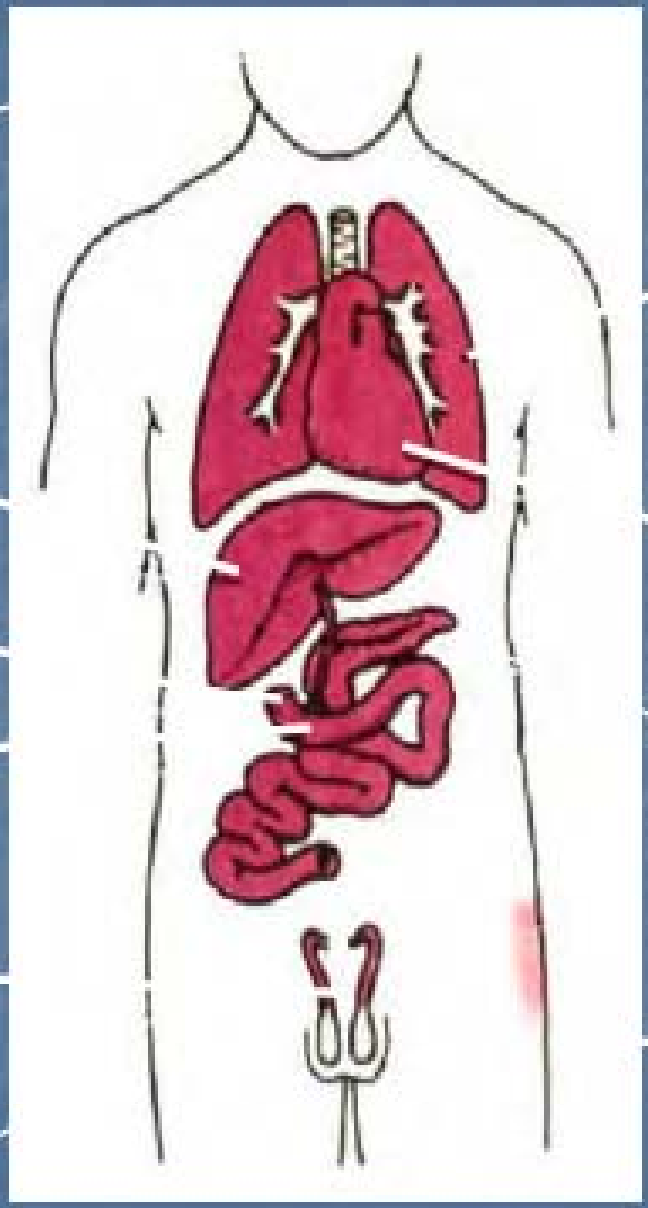
What is Cystic Fibrosis?

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

Clinical Presentation

- Chloride channel defect in exocrine glands
- Thick secretions
- Recurrent pneumonia
- Pancreatic insufficiency
- High salt content in sweat
- Male infertility

Multiorgan System Manifestations of CF



Rhinosinusitis
Nasal polyposis

- Lung abscess
- Chronic bronchitis
- Bronchiectasis
- Honeycomb lung
- pneumothorax
- hemoptysis

•Secondary biliary cirrhosis
• 5% have liver dysfuction as bile ducts obstruct

Malabsorption

Cor pulmonale

Meconium ileus in newborns

• 65% obstruction blocks digestive enzymes – may cause diabetes
•Chronic pancreatitis

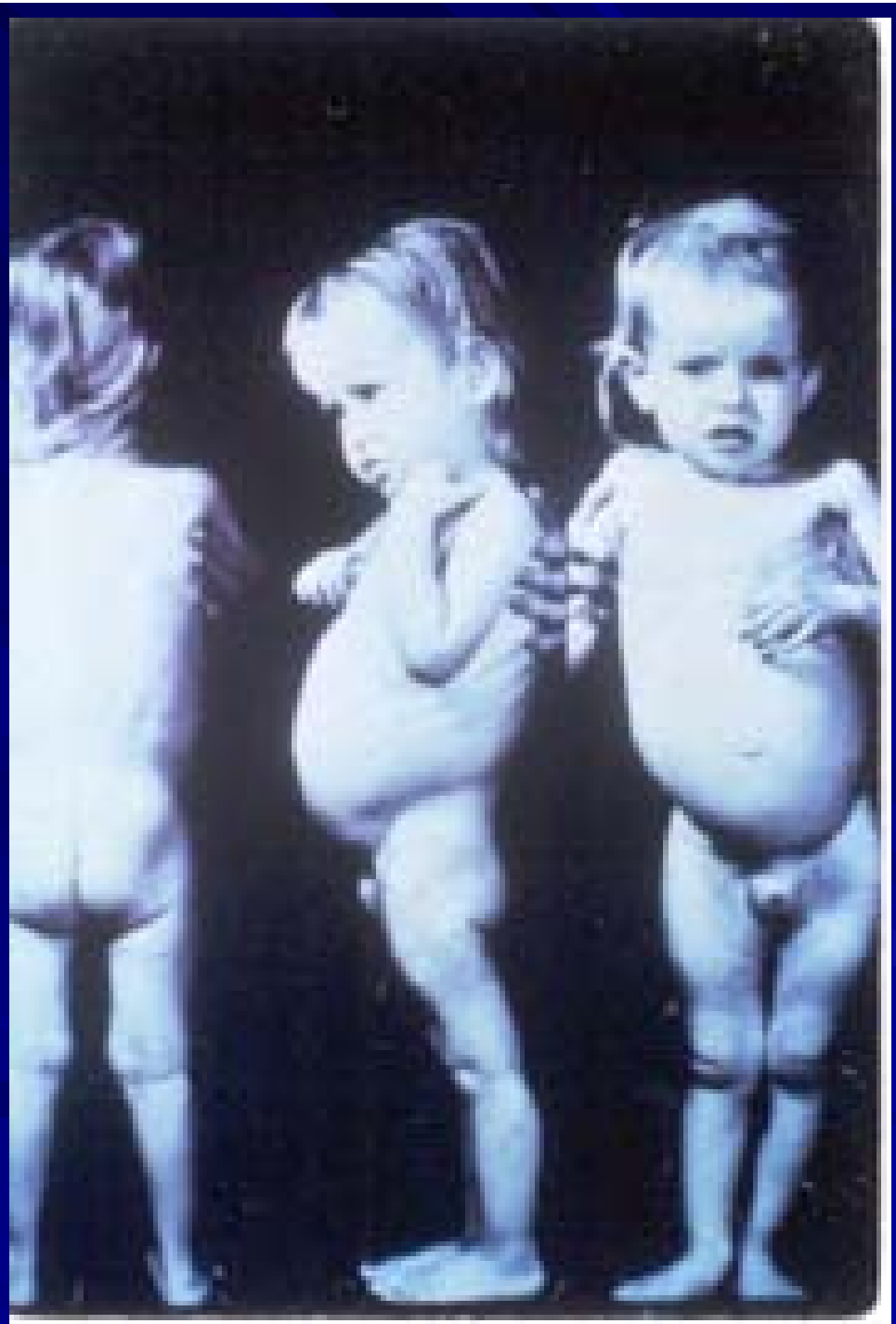
Obstructed vas Deferens- 95% male sterility.
Cervical plugs may effect female fertility

Abnormal sweat electrolytes

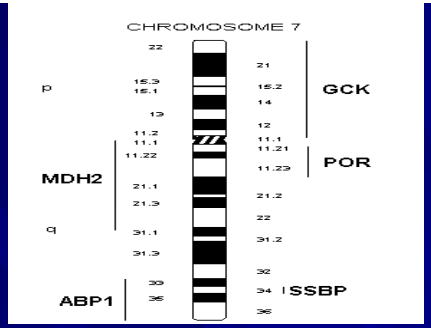
Rectal prolapse

“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”

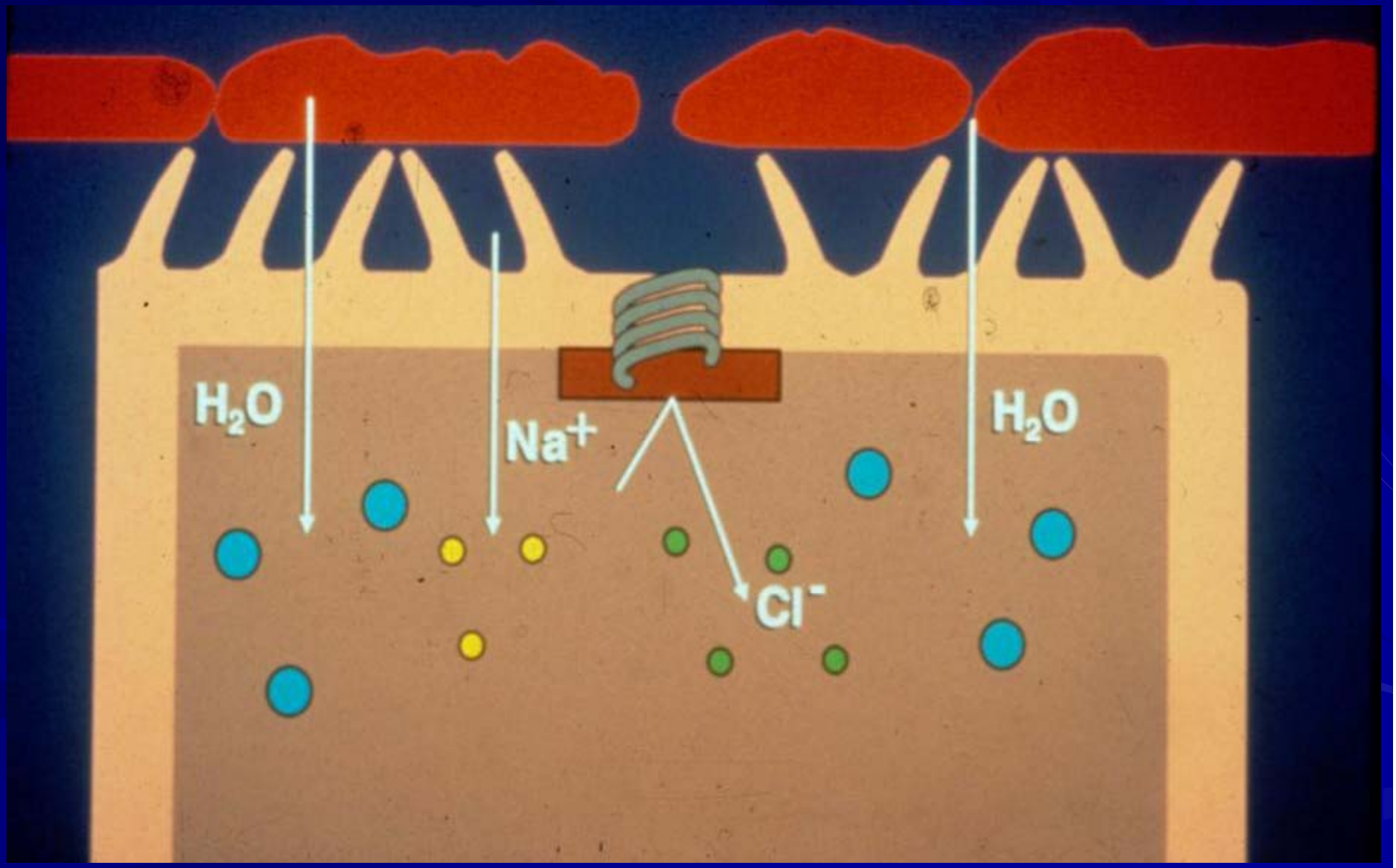


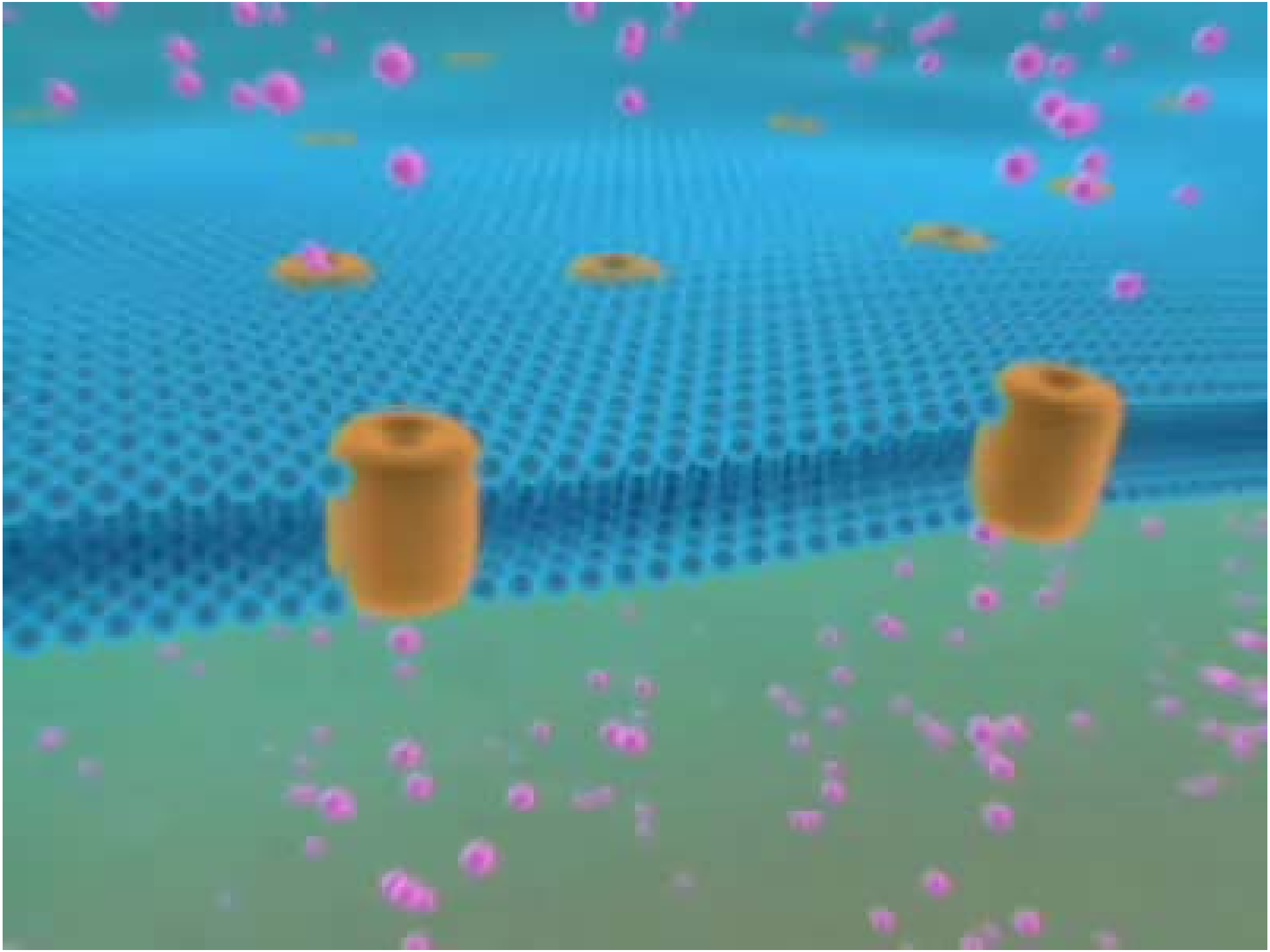
Genetics of CF



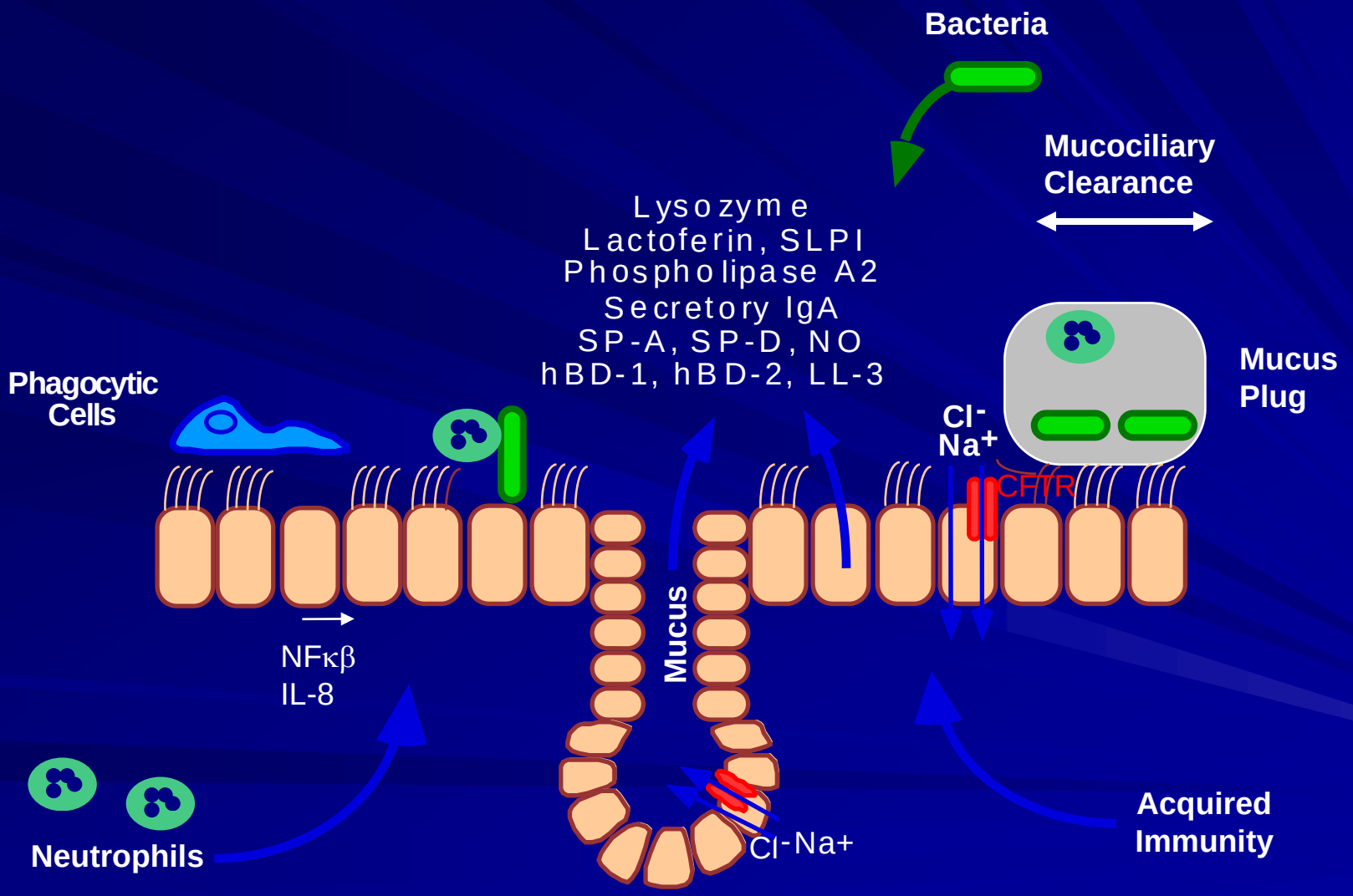
- Most common lethal genetic disease in Causasians
  - 30,000 affected individuals in US
  - 27,000 in Europe
- CFTR - cAMP regulated chloride channel located in apical membrane of glandular epithelium
  - Encodes for a protein of 1480 amino acids
  - Defective ion transport
  - Class defects
  - Long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

Ion Transport



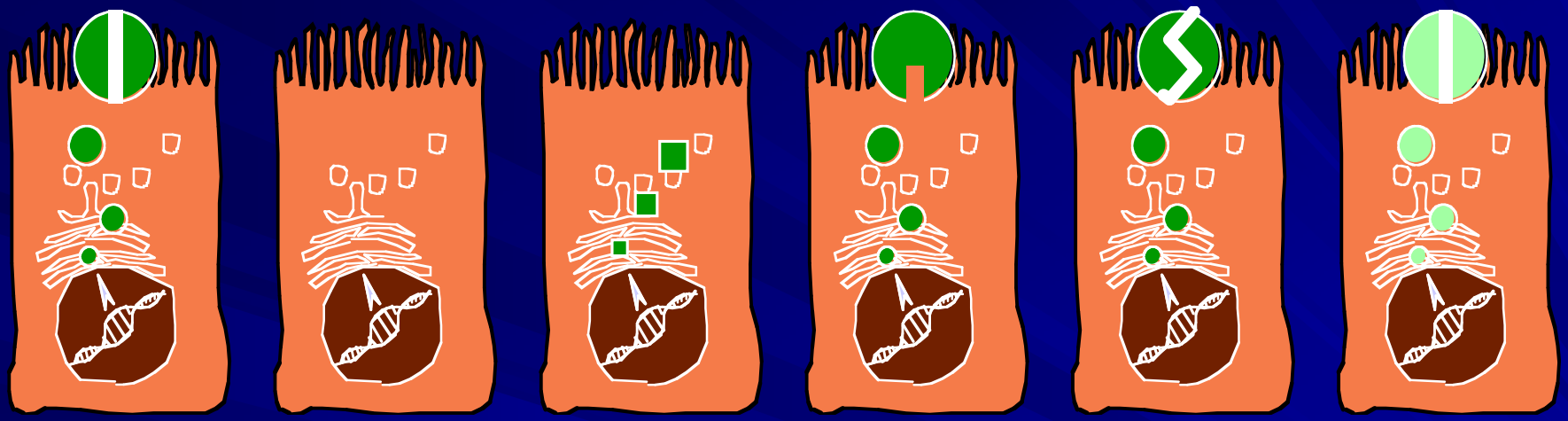


The Cystic Fibrosis Airway

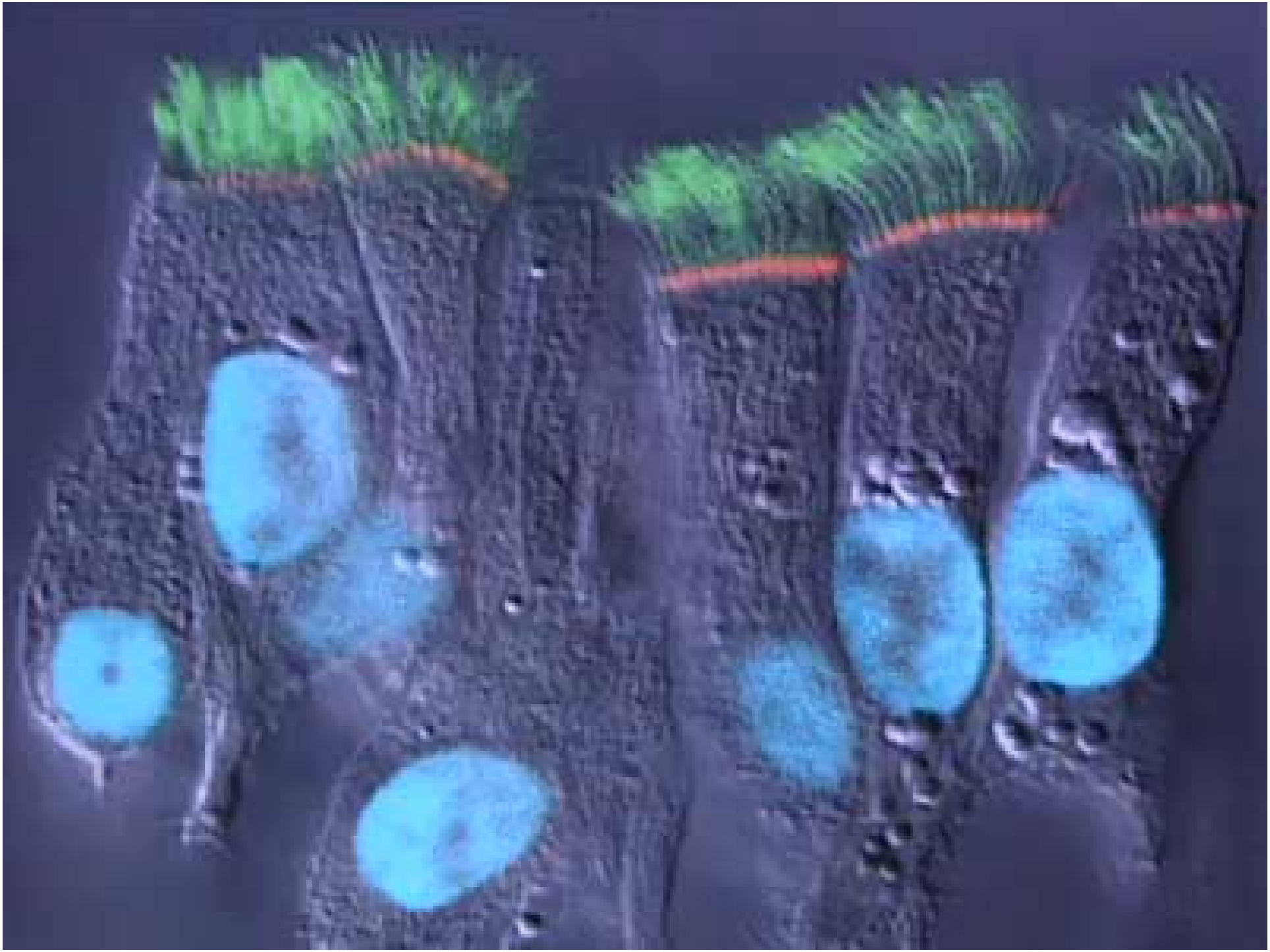


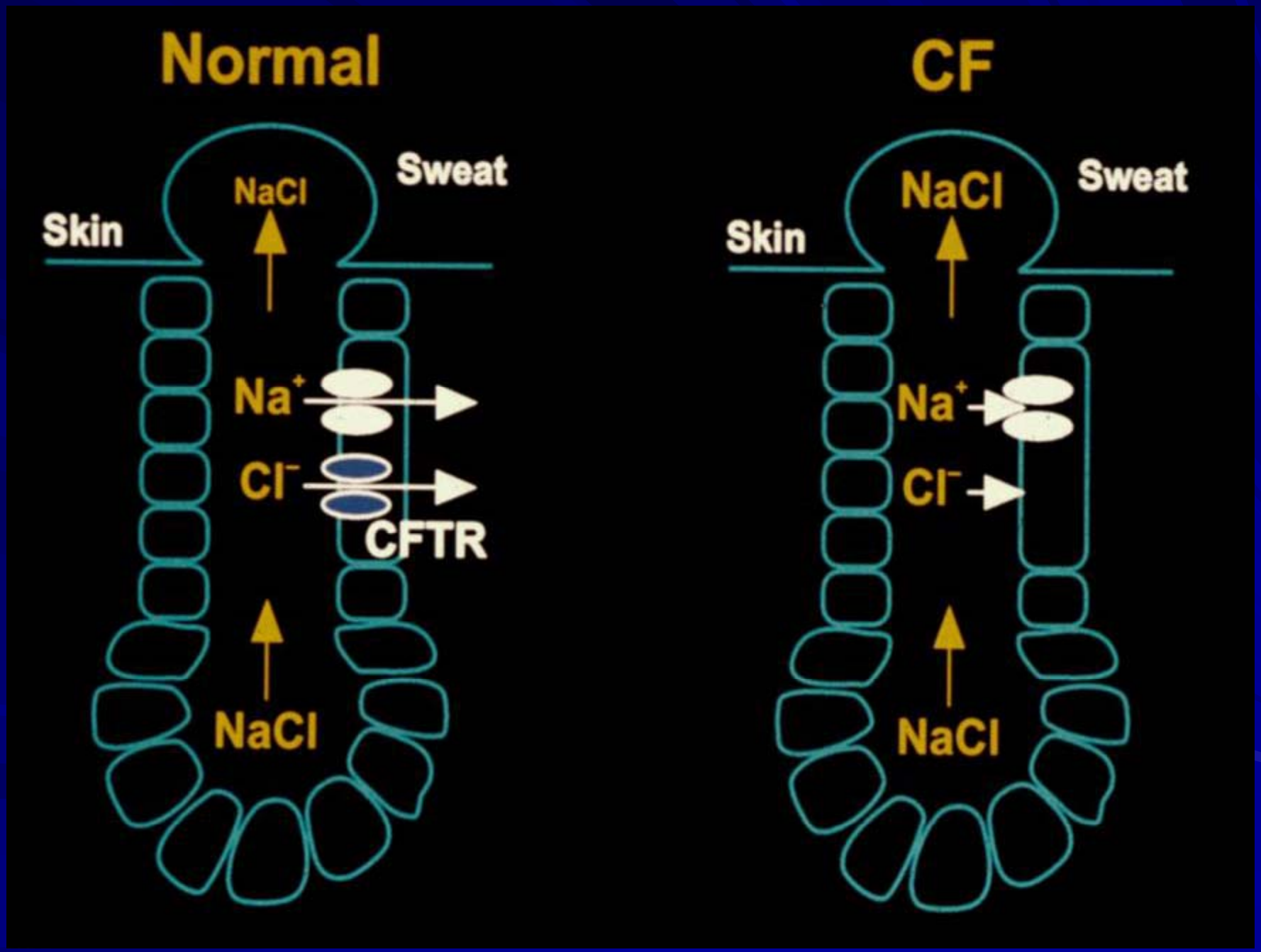
Used with permission - R. Gibson, 2004.

Molecular Consequences of CFTR Mutations

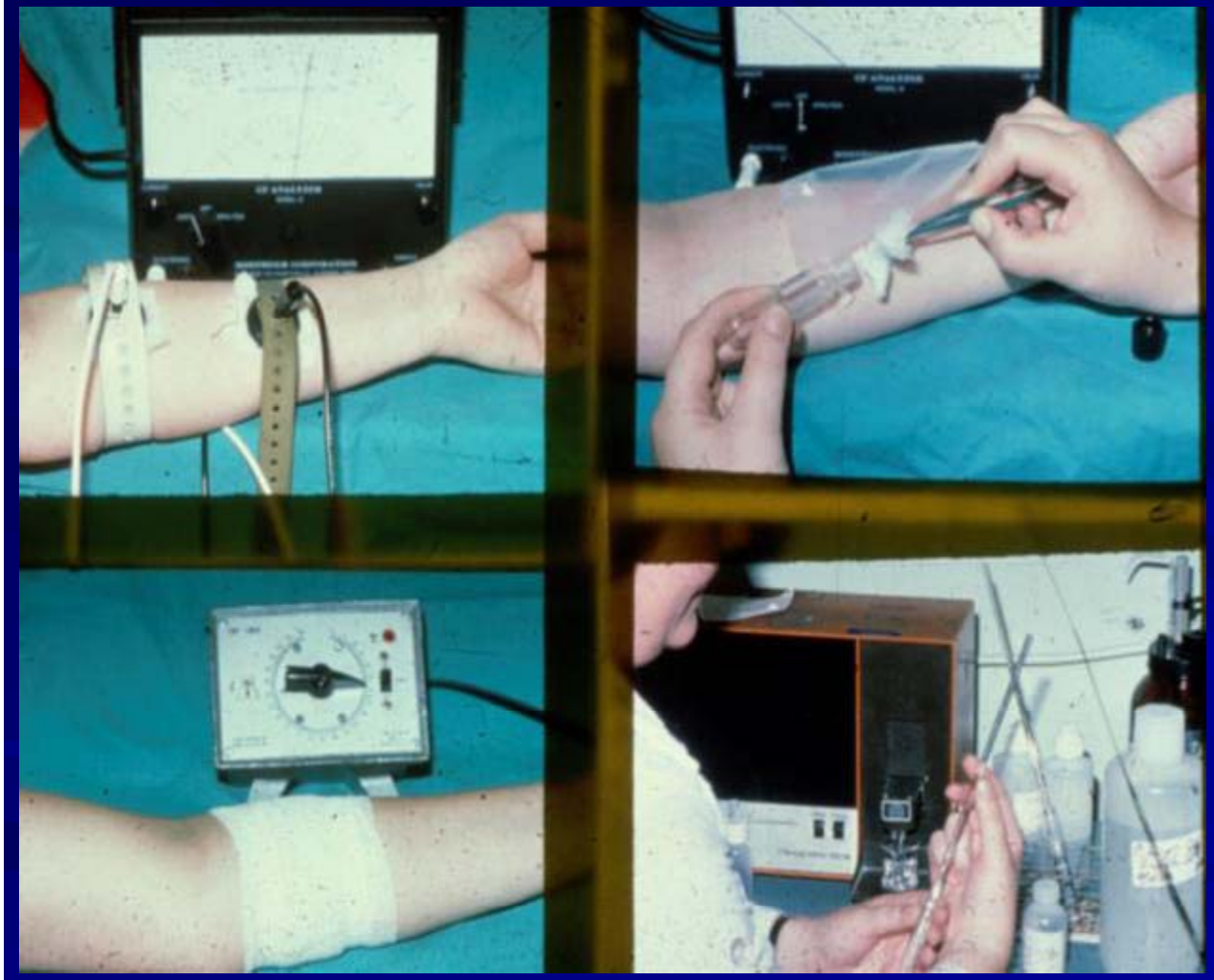


Normal	I	II	III	IV	V
	No synthesis	**Block in processing**	**Block in regulation**	**Altered conductance**	**Reduced synthesis**
	Nonsense G542X	Missense	Missense G551D	Missense R117H	Missense A455E
	Frameshift 394delTT	AA deletion ΔF508			Alternative Splicing 3849+10kbC–>T
	Splice junction 1717-1G–>A				




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

The sweat test (Chloride)



Normal

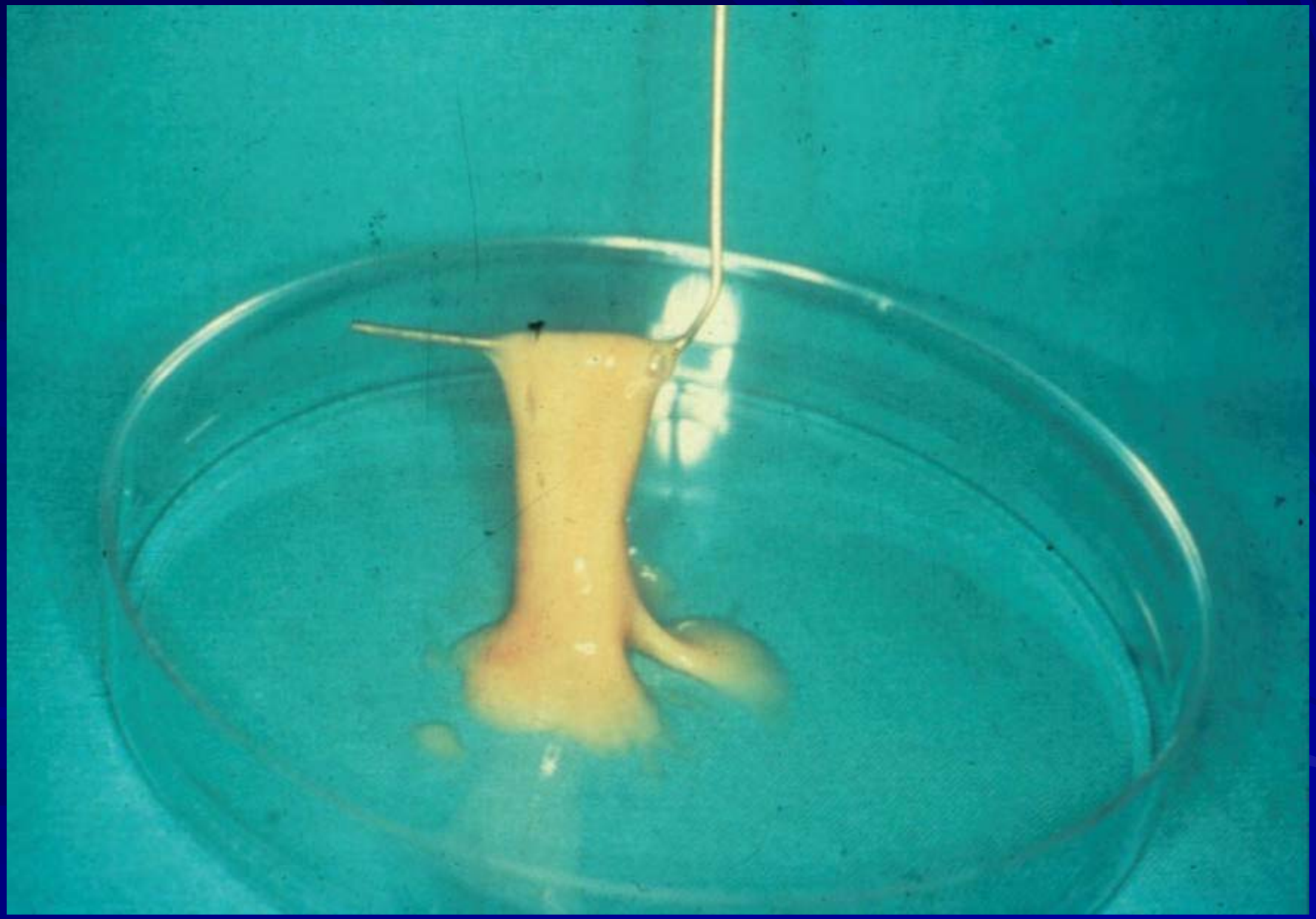
Under 40 mEq/L

Borderline

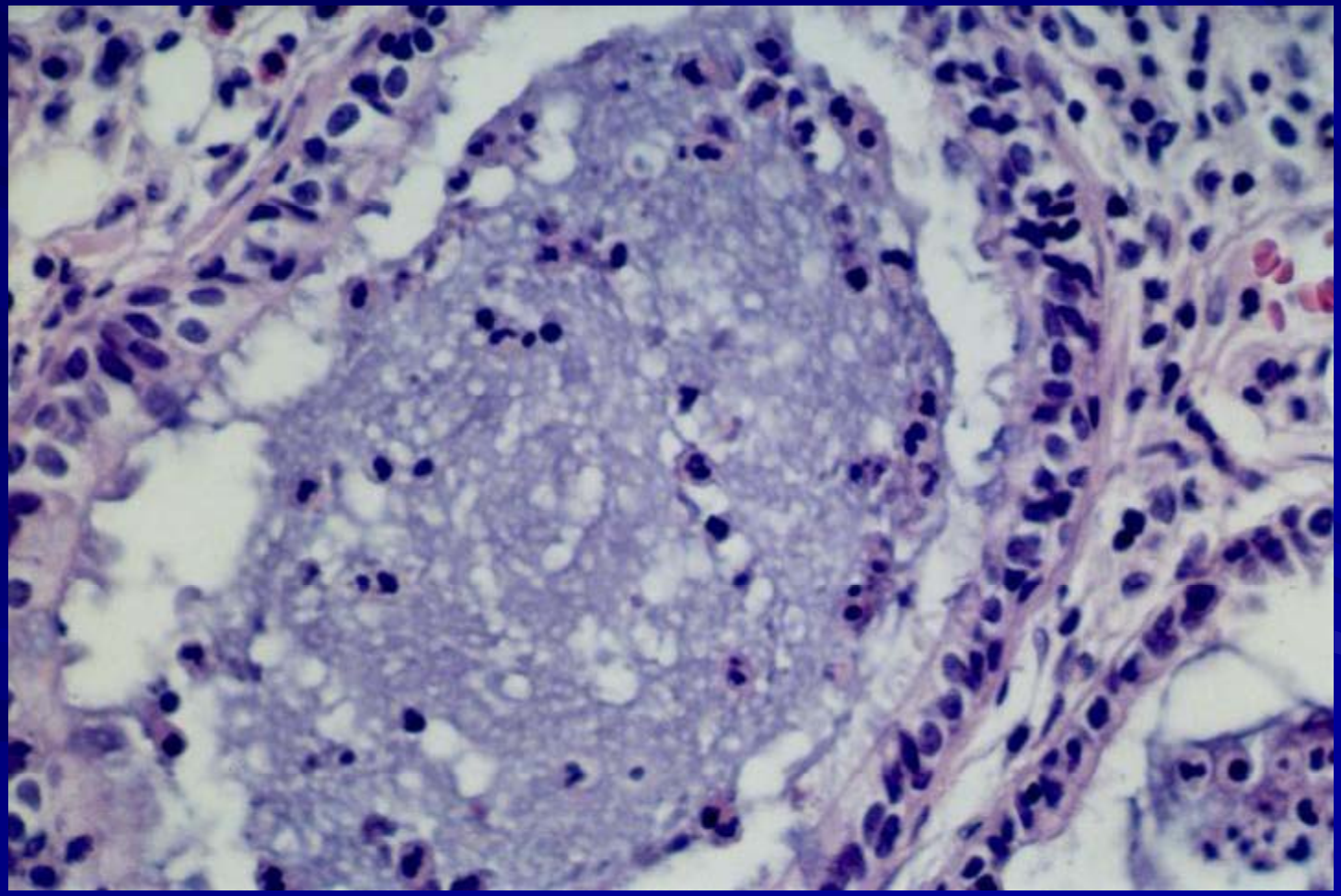
40-60 mEq/L

Positive

Over 60 mEq/L



Airway Mucous Plugging, Infection, and Inflammation in Cystic Fibrosis

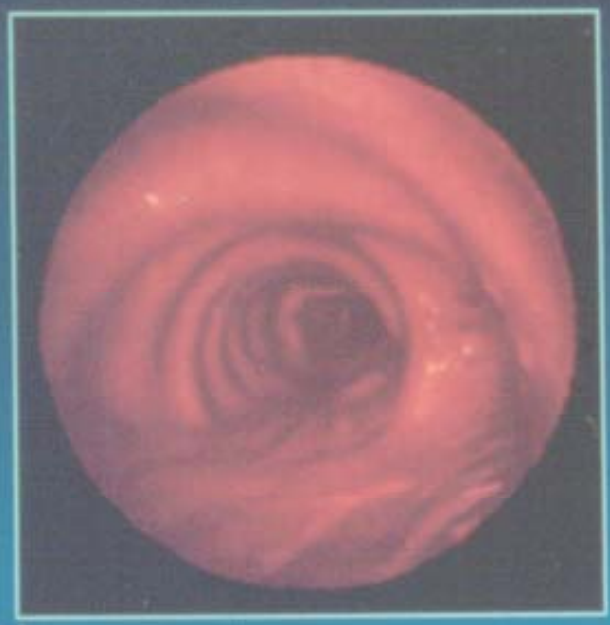


Used with permission – J. Wagener, 2004.

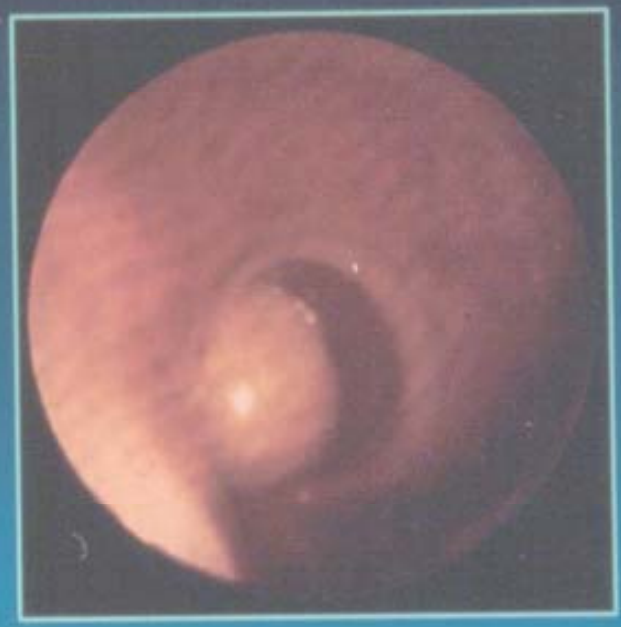
CF Lung: End-Stage Bronchiectasis

Bronchoscopic Views of Normal and CF Airways

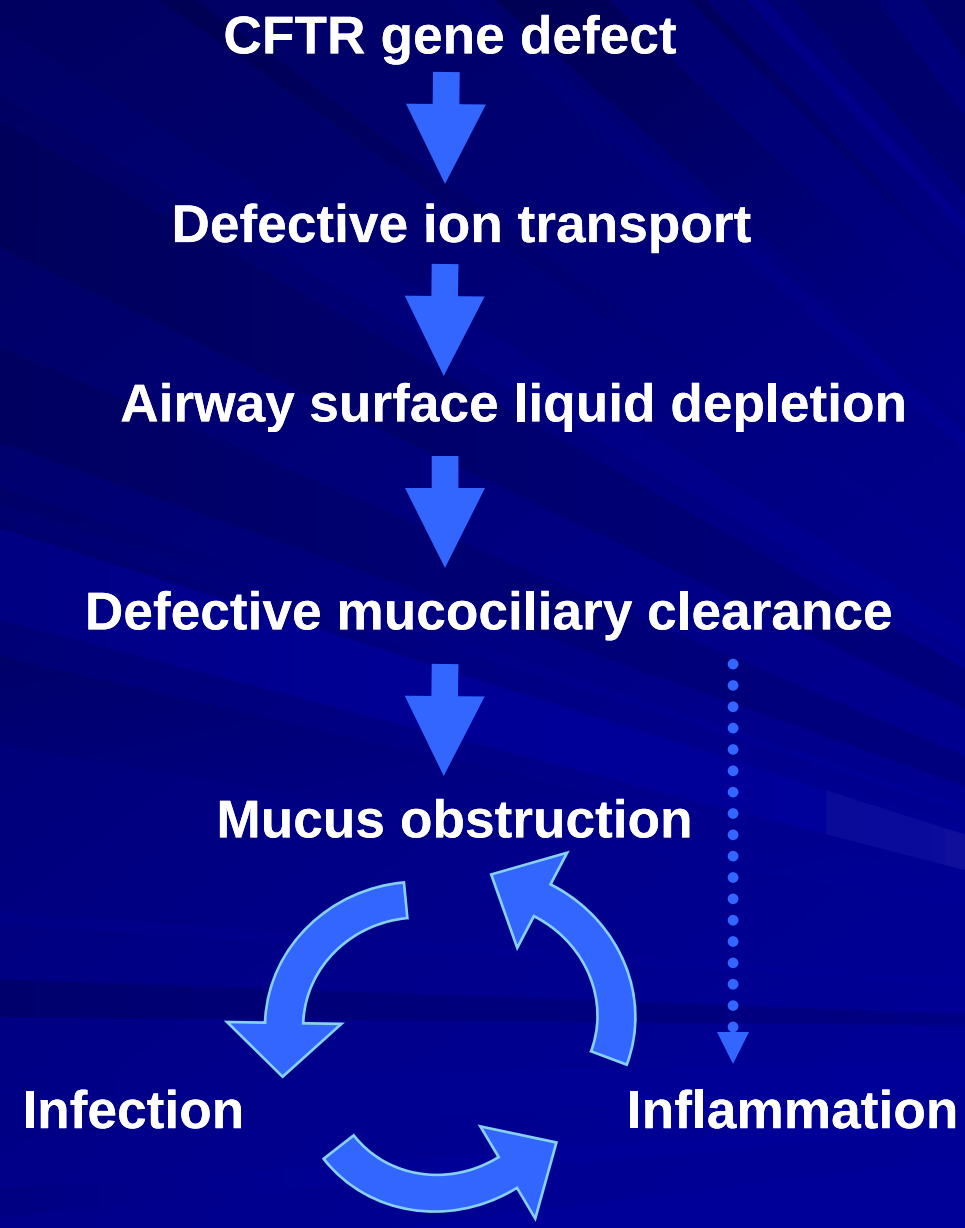
Normal



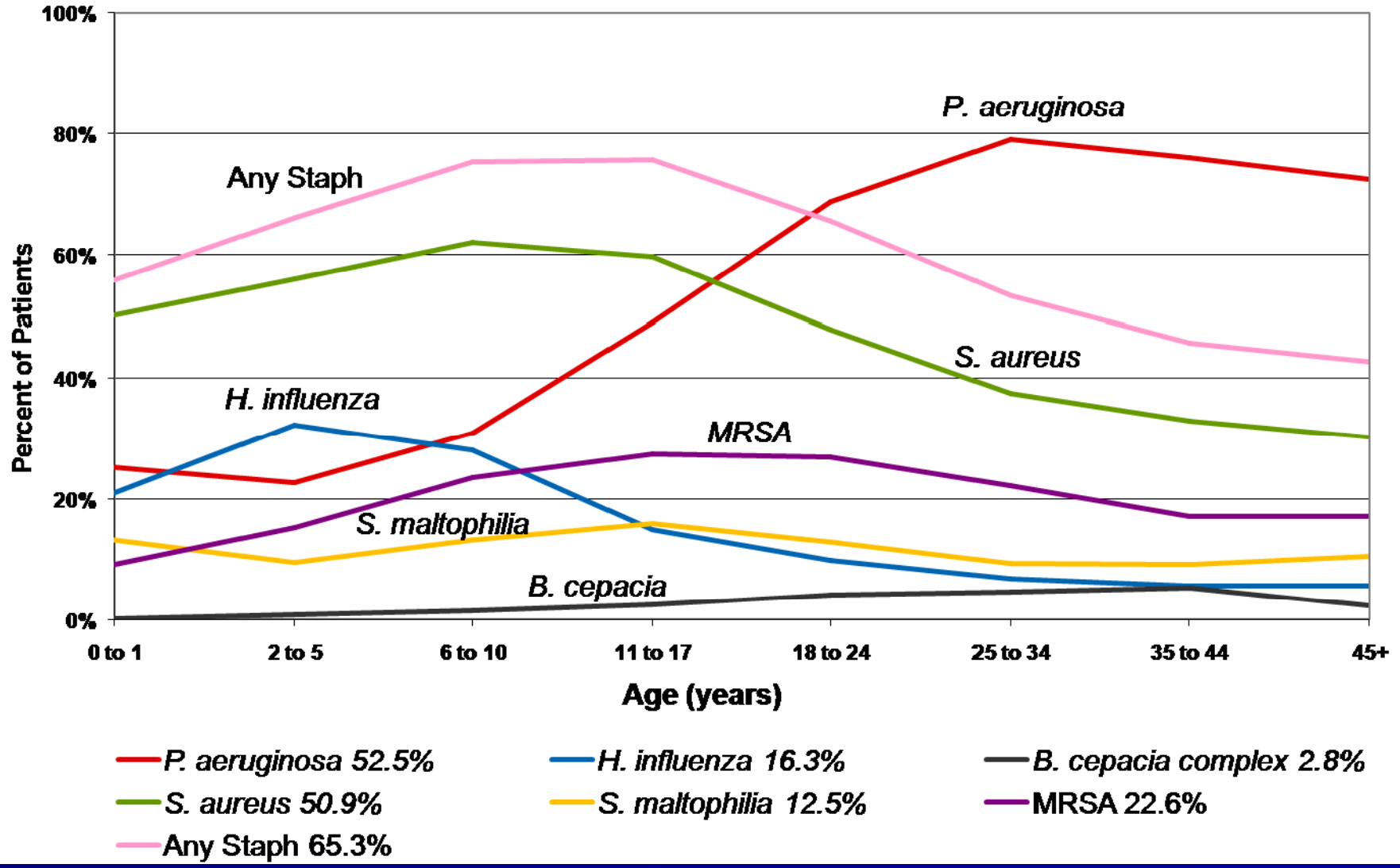
CF



CF Pathophysiology



Age-Specific Prevalence of Respiratory Infections in CF Patients, 2008



Source: Cystic Fibrosis Foundation Patient Registry, 2008 Annual Data Report

Natural History of Acquisition of *Pseudomonas aeruginosa*

Mucoid *P. aeruginosa*

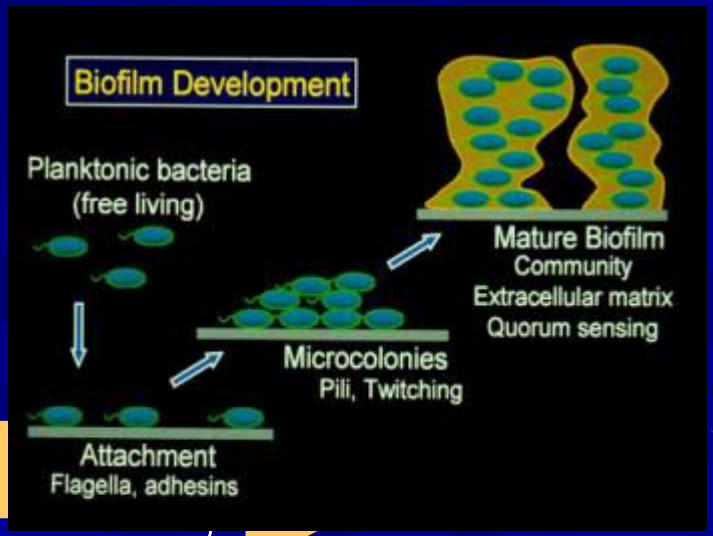
Birth

1st *Pa* + culture

2nd *Pa* + culture

Pa negative culture

Persistently *Pa* + cultures



Intermittent infection

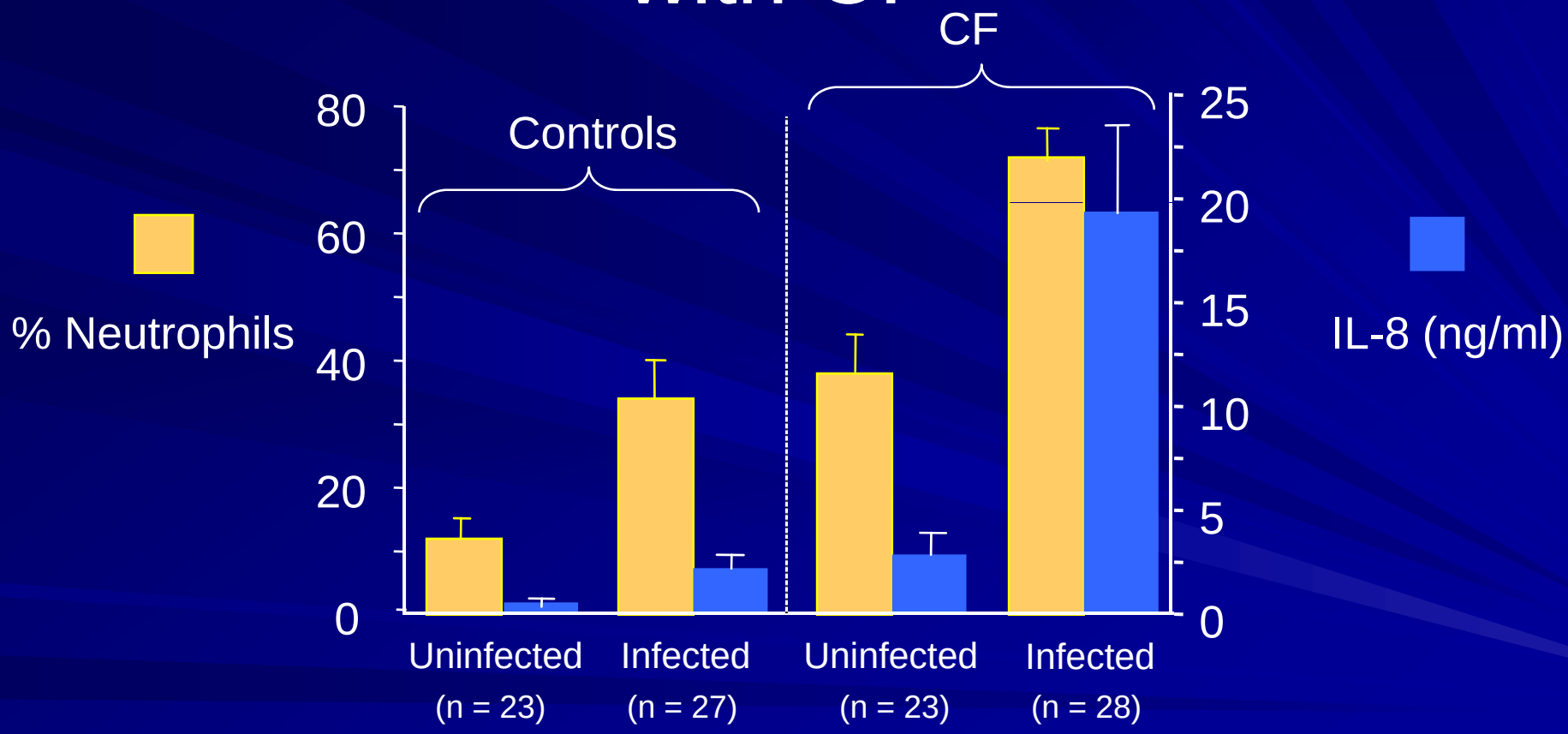
Chronic infection

Eradication

Pulmonary Exacerbations

Chronic Suppressive Therapy

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.

CF Lung Function

PULMONARY FUNCTION TESTS:

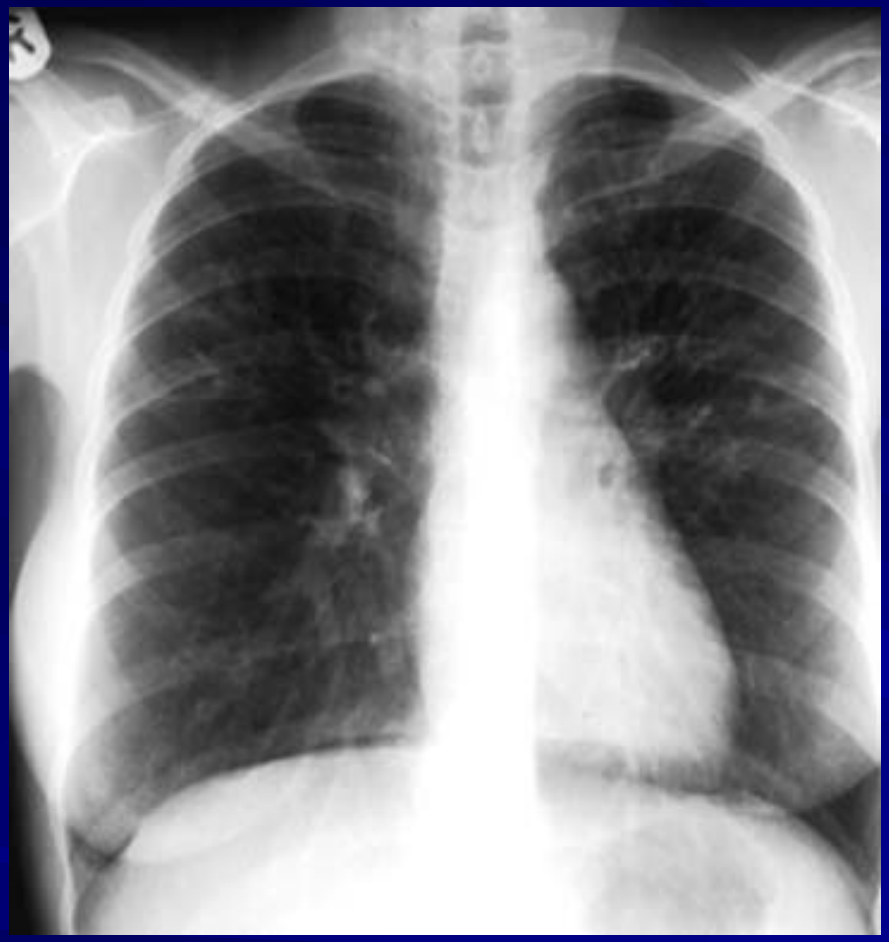
	NORMAL	MILD	MODERATE	SEVERE
FEV_1	NL	NL	↓ (70%)	↓↓ (40%)
FEF_{25-75}	NL	↓(70%)	↓↓ (40%)	↓↓↓ (20%)
MEFV				
VC	NL	NL	↓	↓↓
TLC	NL	NL or ↑	NL or ↑	↓
RV/TLC	25%	↑ (35%)	↑↑ (50%)	↑↑↑ (70%)
PaO_2	NL	↓ (94)	↓↓ (85)	↓↓↓ (60)
$PaCO_2$	NL	NL	NL	↑↑

Presentation (CF PANCREAS)

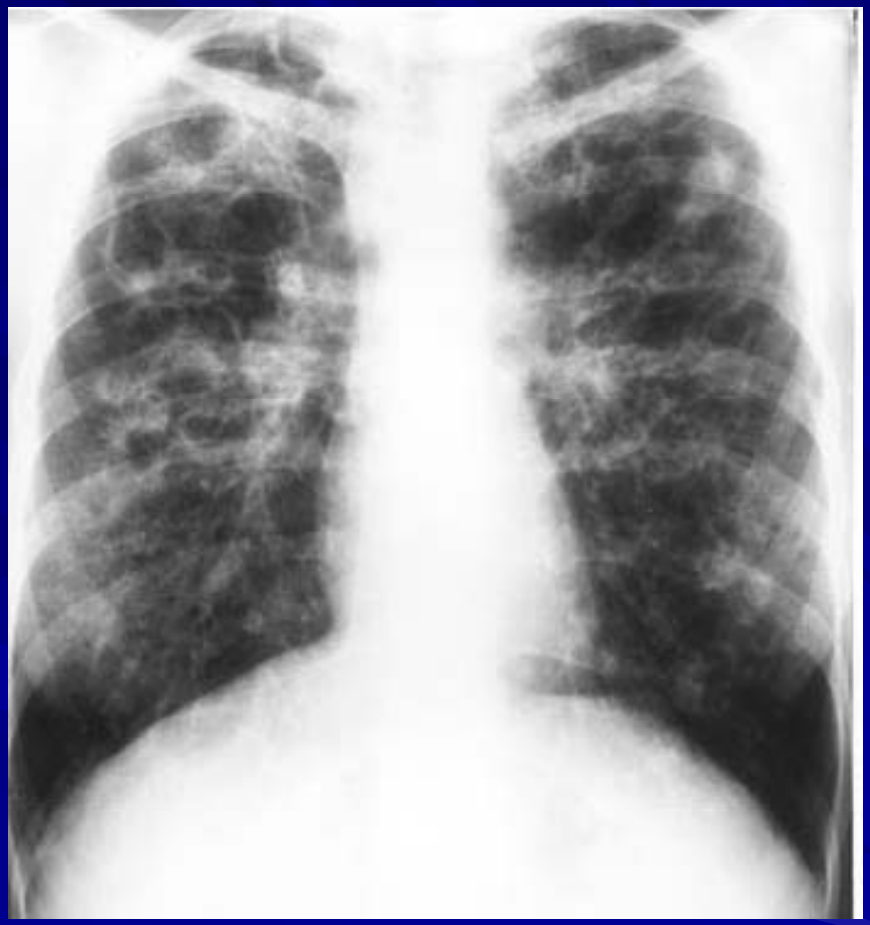
C Chronic respiratory disease
F Failure to thrive
P Polyps
A Alkalosis, metabolic
N Neonatal intestinal obstruction
C Clubbing of fingers
R Rectal prolapse
E Electrolyte ↑ in sweat
A Aspermia / absent vas deferens
S Sputum – S.aureus/P.aeruginosa

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

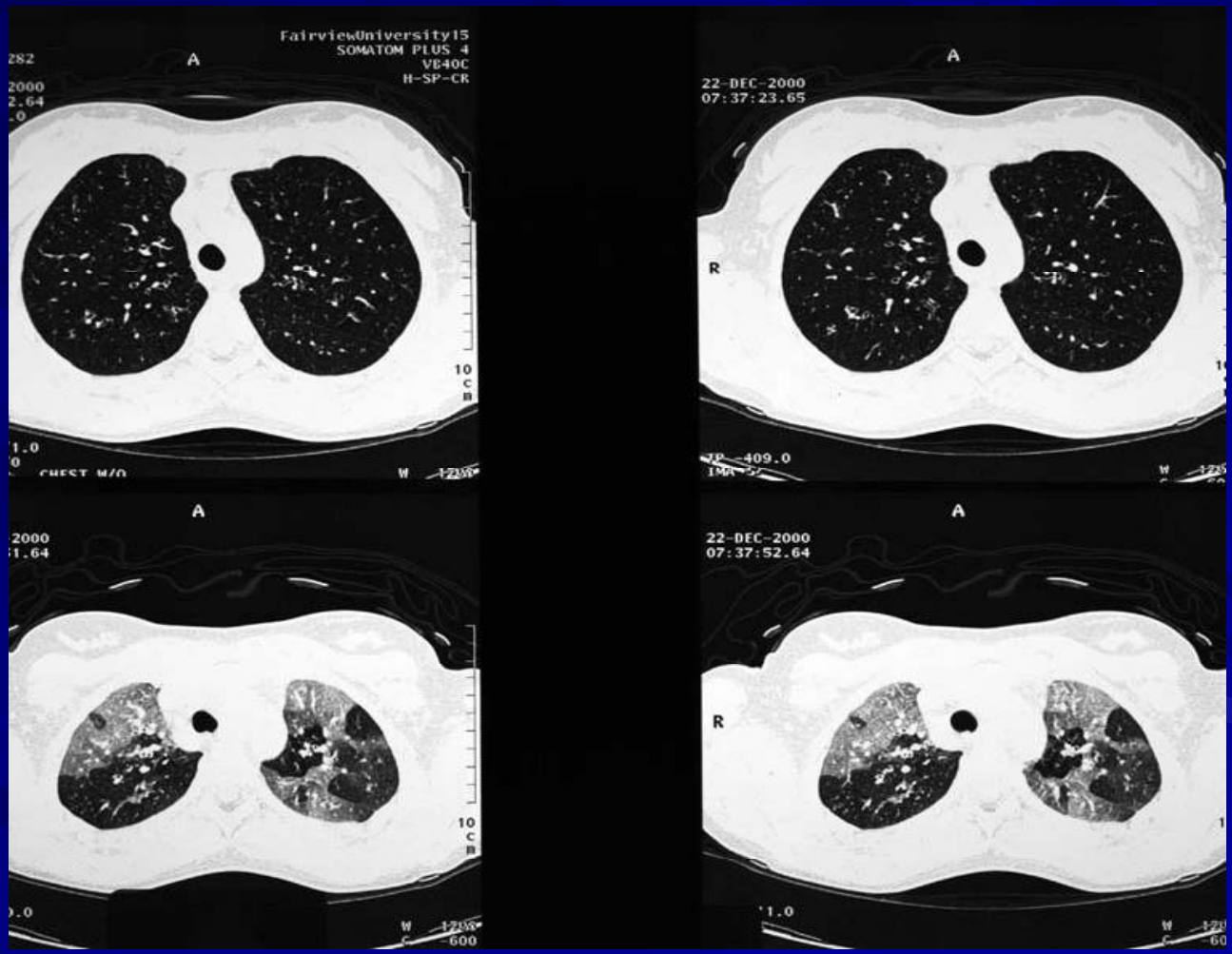


CF mild disease: hyperinflation, increased markings

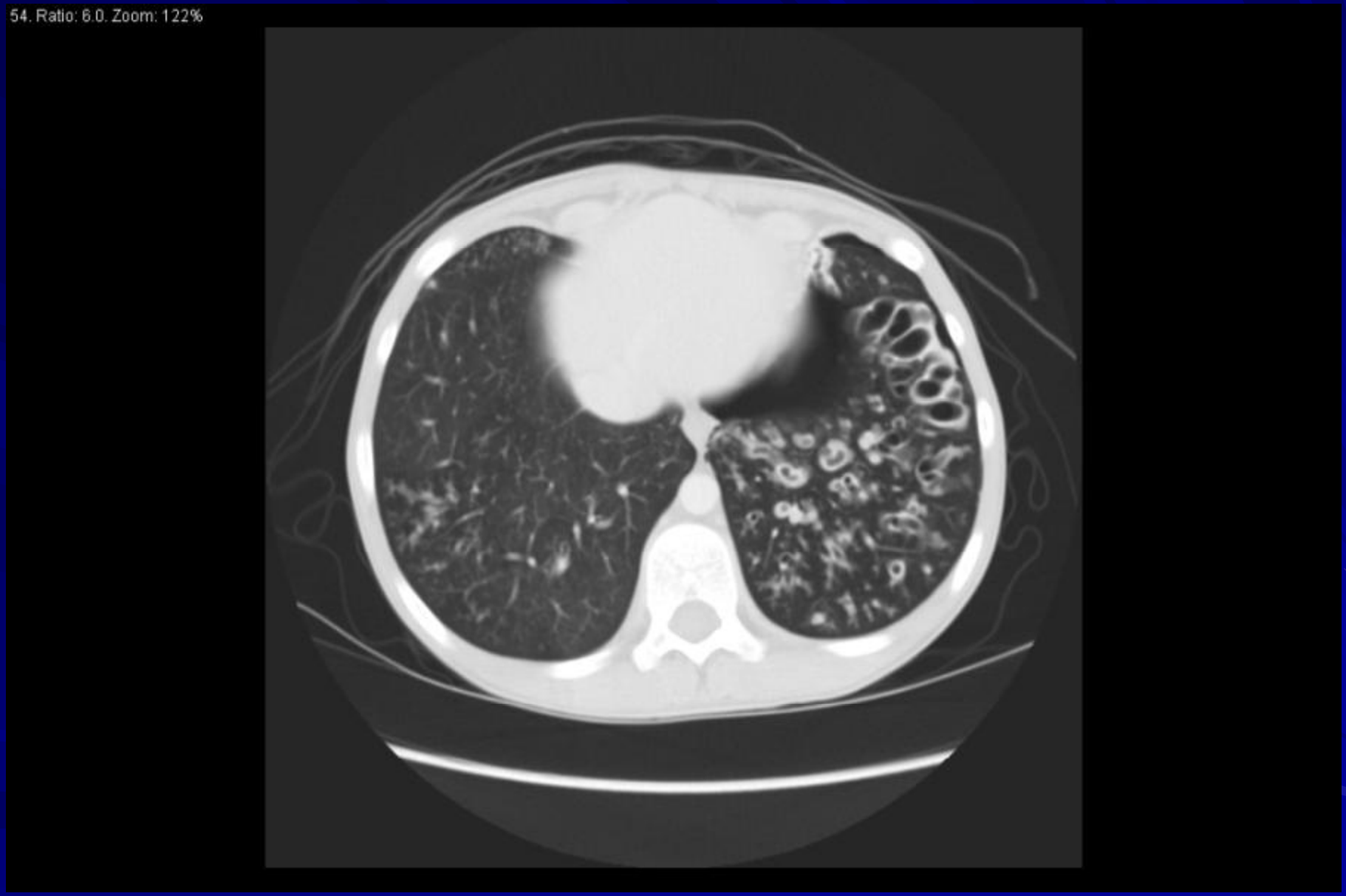


CF advanced disease: with bronchiectasis

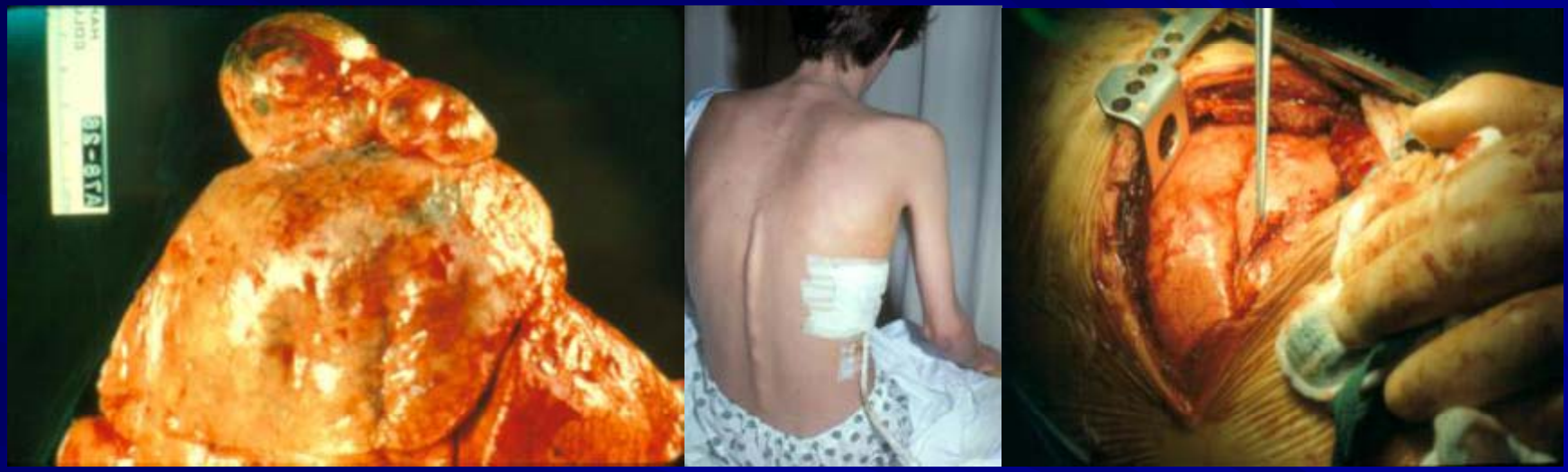
High-Resolution Inspiratory and Expiratory CT Scan in 12 year old

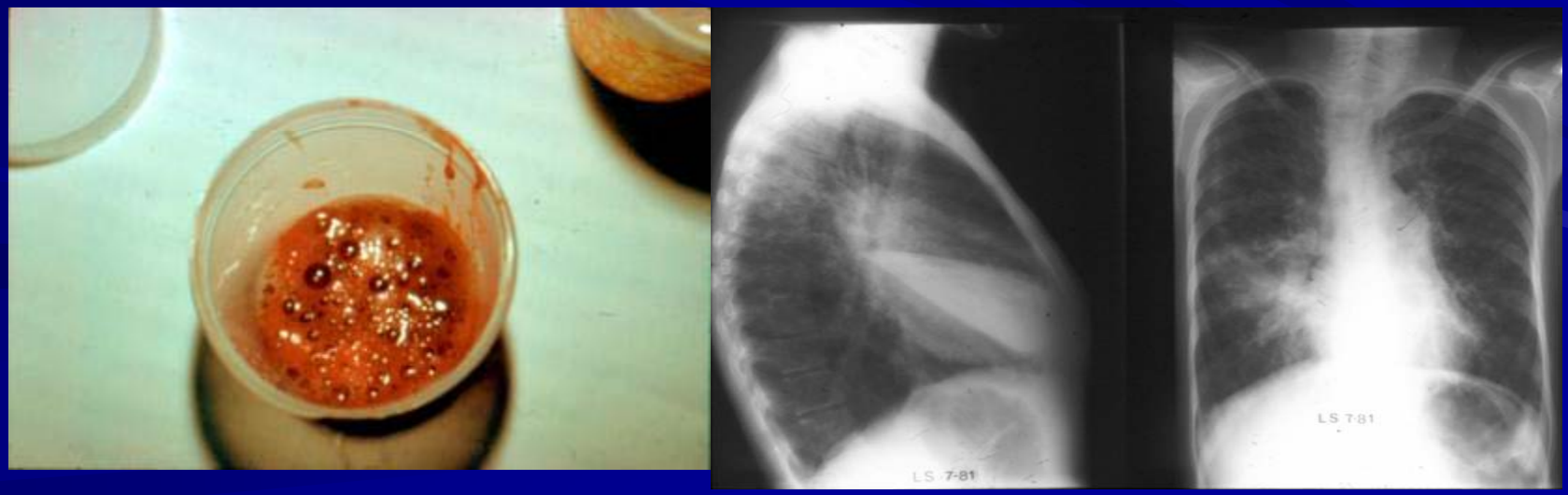


Used with permission - C. Milla, 2004.


54. Ratio: 6.0. Zoom: 122%

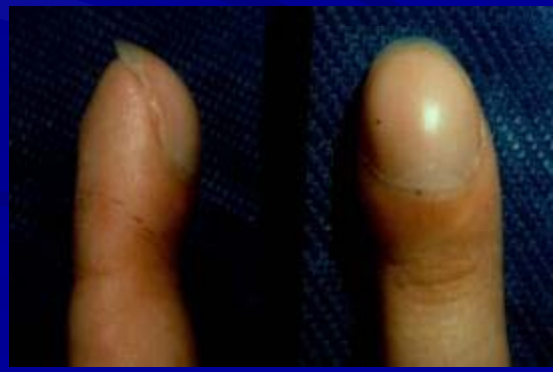
CF: Pulmonary Complications



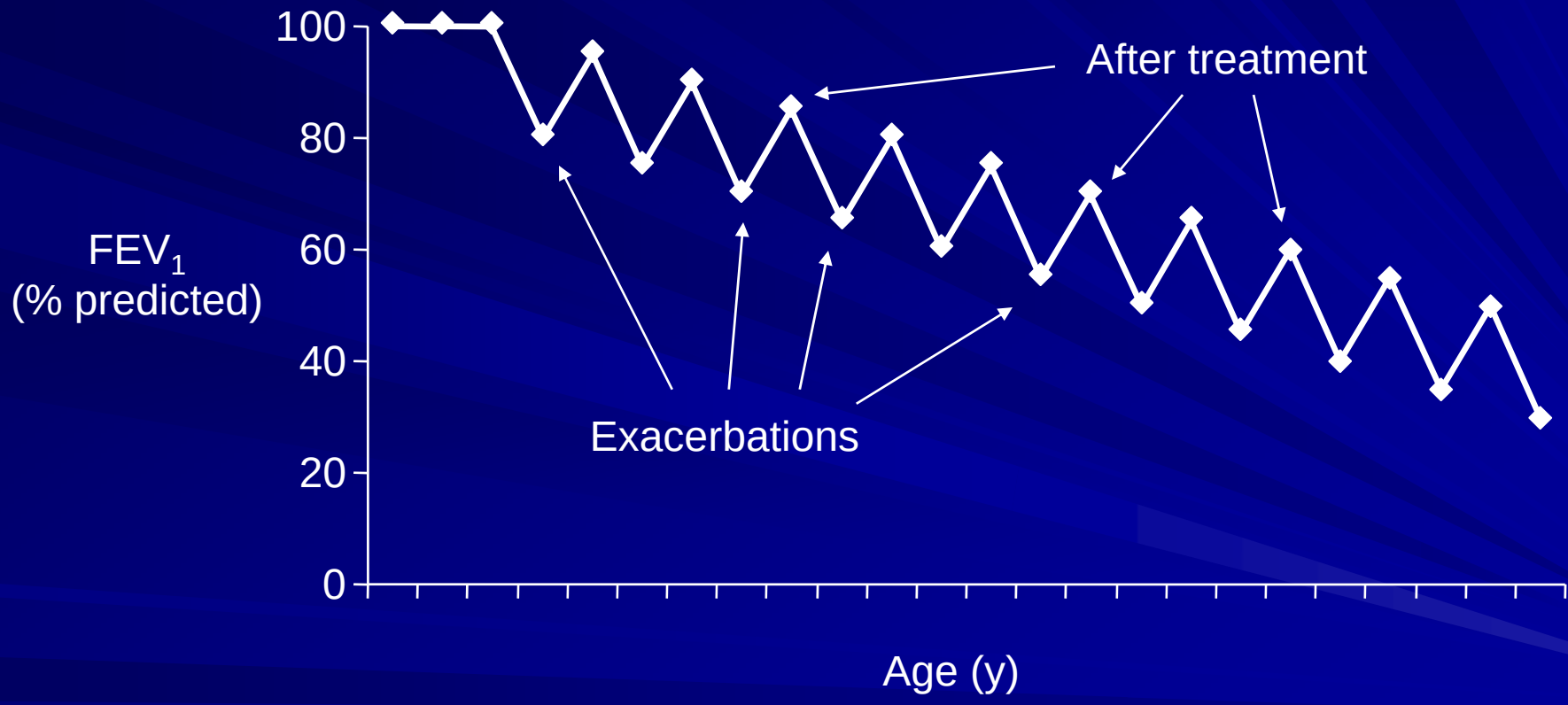


Hypertrophic osteoarthropathy

- Clubbing
- Periostial new bone formation
- Proliferation of skin and osseous tissue at distal parts of extremities



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 agents

Airway Clearance

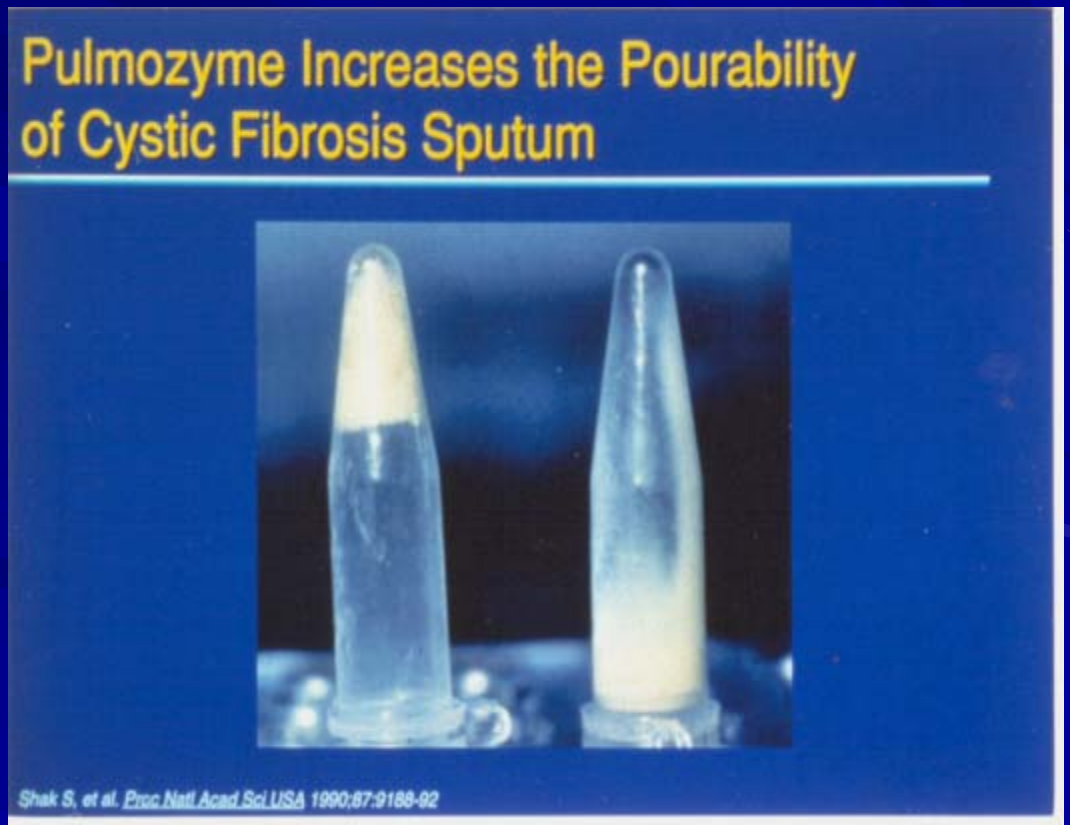
- CPT
- Vest
- Flutter
- ACB

Airway Clearance

- Chest Physical therapy
- Vest – mechanical percussion
- Flutter, Acapella
- Breathing techniques : ACB
- Exercise

Mucolytic agents

- Recombinant DNase
- Hypertonic saline

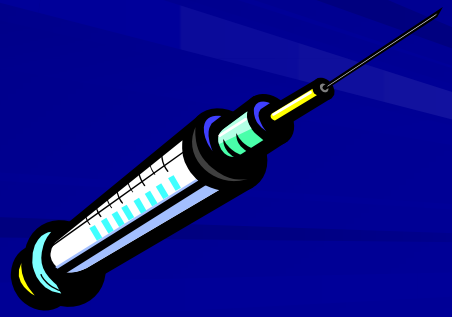


Treating Airway infections

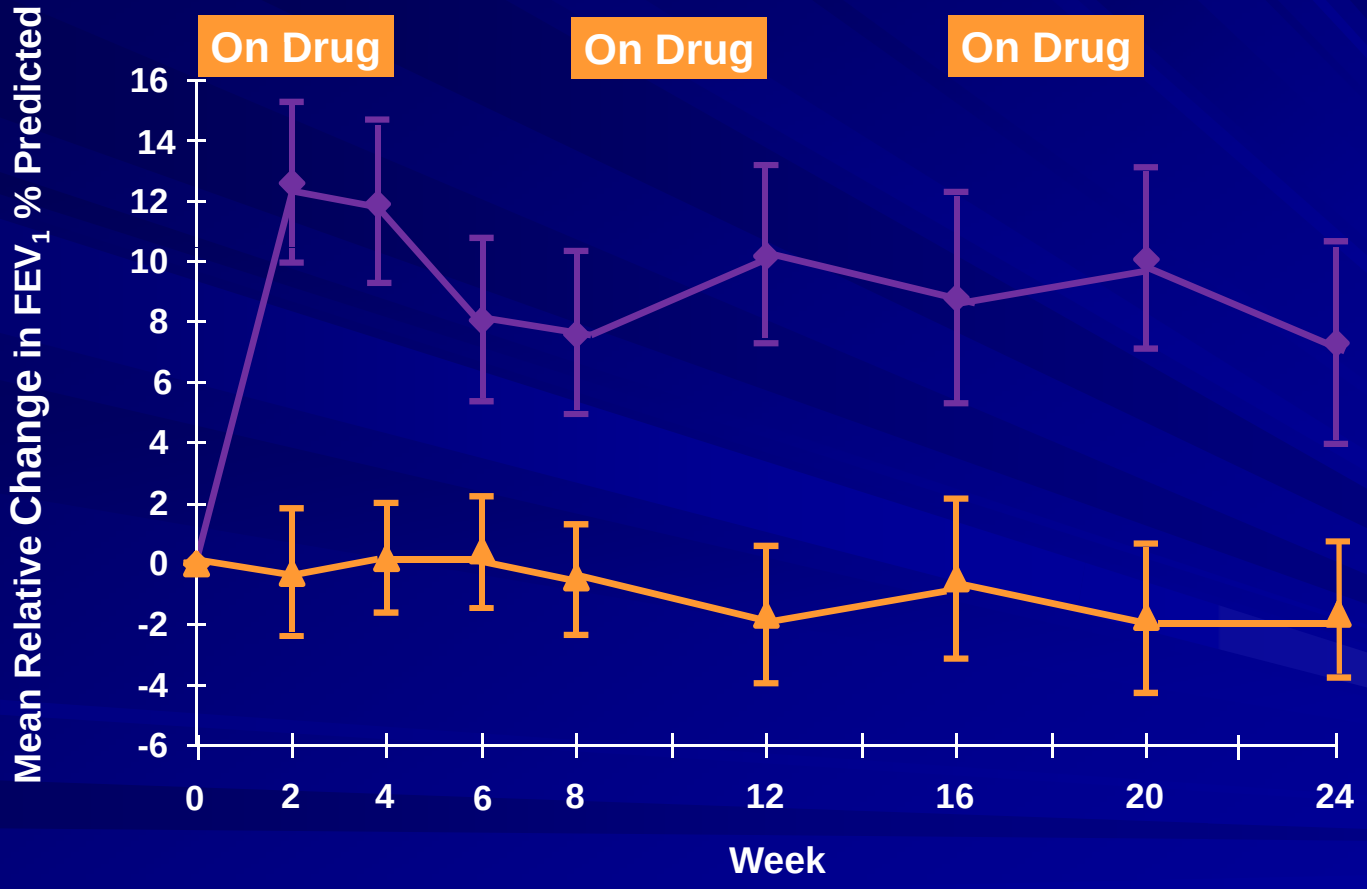
- Prophylactic treatment
  - prevent colonization
- Exacerbations
  - improves lung function
  - reduces inflammation
  - decreases bacterial density
- First isolates
  - may delay colonization

Antibiotics

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



Phase 3 TSI Trial: Mean Relative Change in FEV_1 % Predicted



Ramsey BW et al. N Eng J Med 1999

Konstan and Saiman
NACFC 2009; Plenary Session II

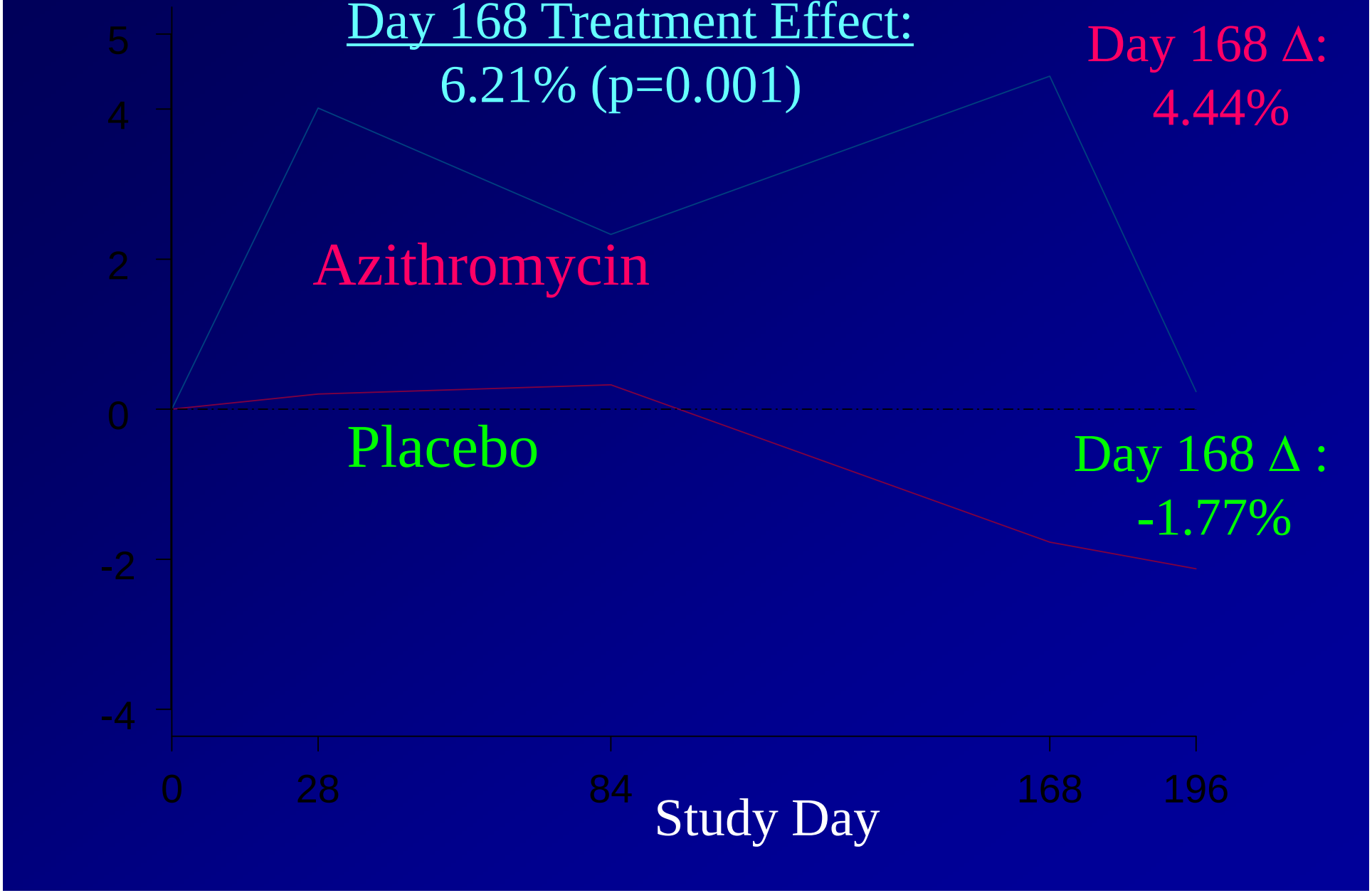
Anti-inflammatory Rx

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

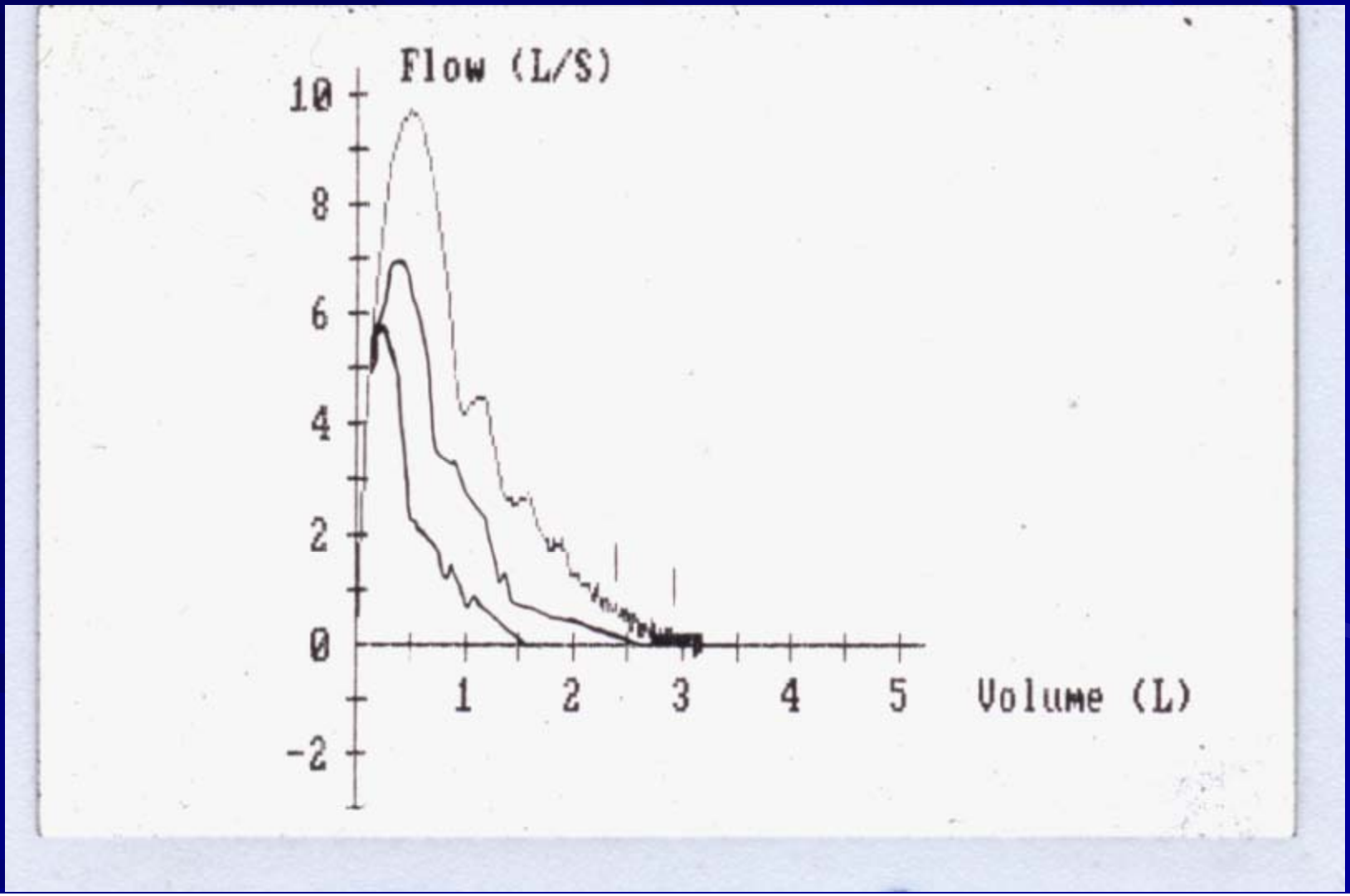
ISSUES

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

Relative Change in FEV_1 % Predicted

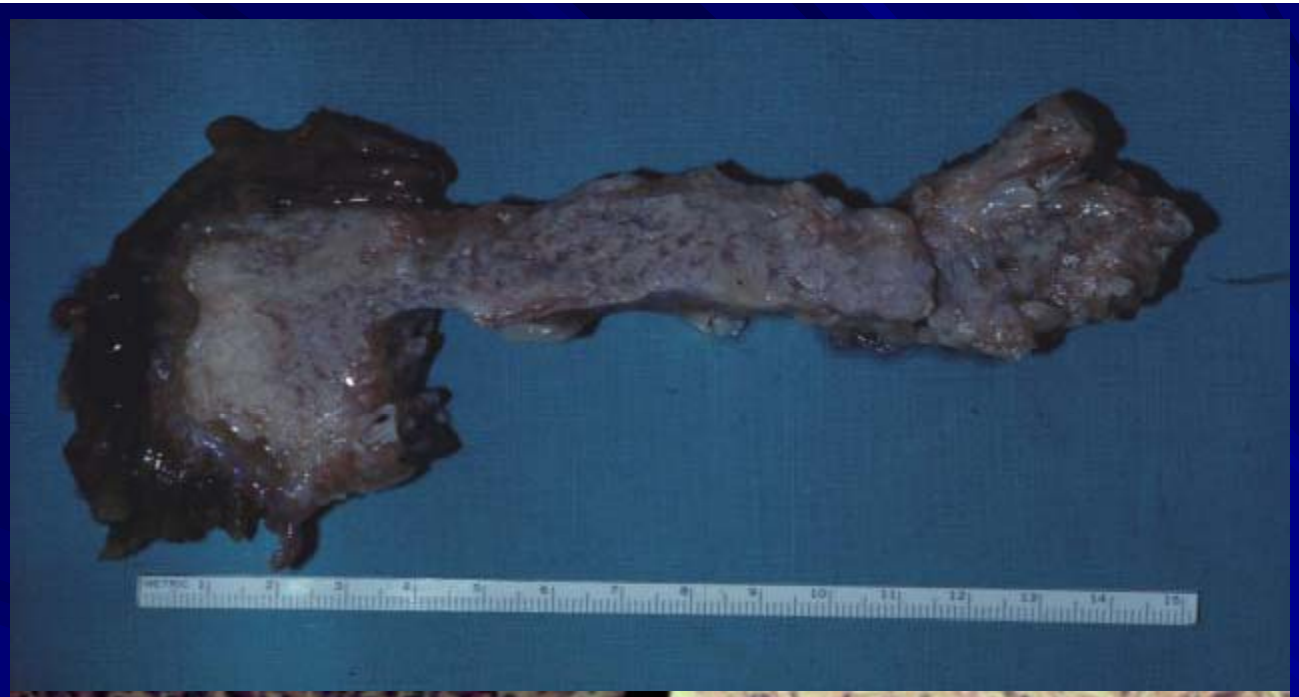


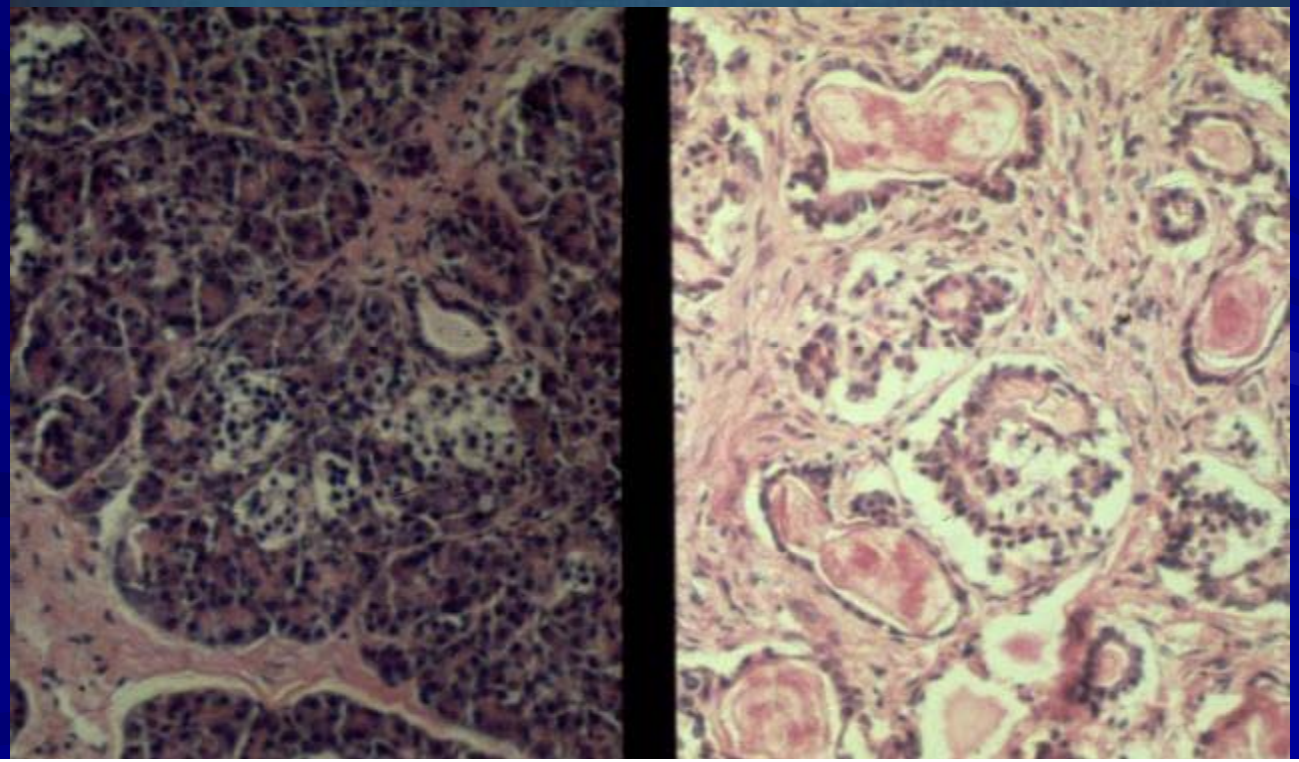
CF PFT's



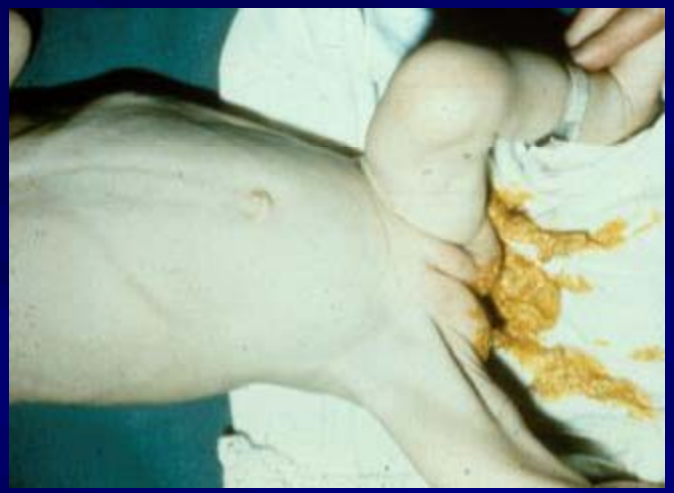
CF: Gastrointestinal Disease

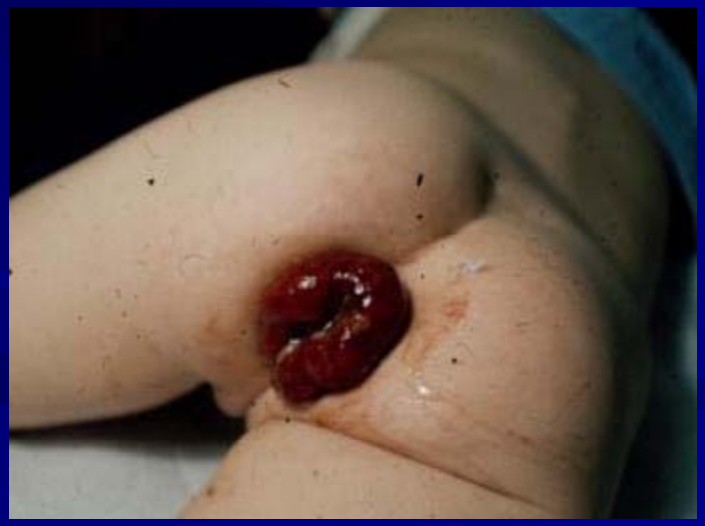
- Pancreatic insufficiency/malabsorption
- Lipo-soluble vitamin deficiency (ADEK)
- Failure to thrive - hypoproteinemia and edema
- Neonatal intestinal obstruction (15%)
- Recurrent distal intestinal obstruction
- Biliary stasis - portal hypertension 2-5% pts

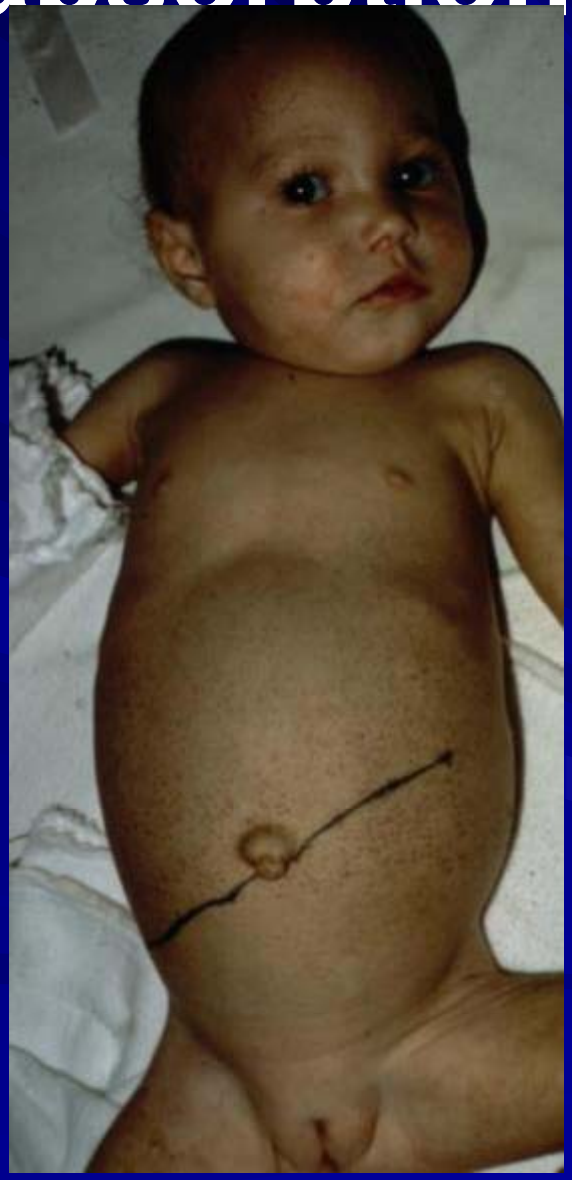


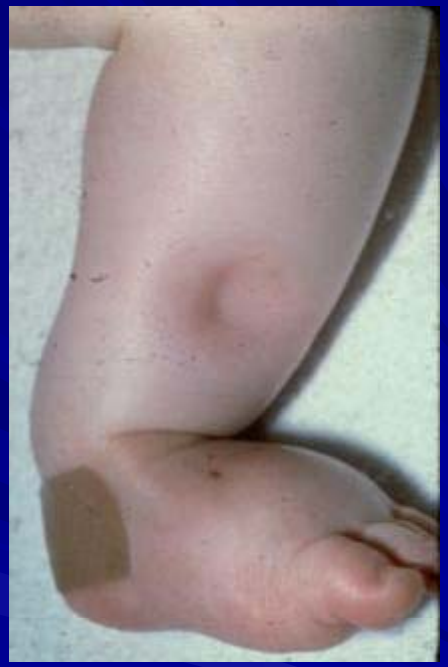


CF: Pancreas-malabsorption



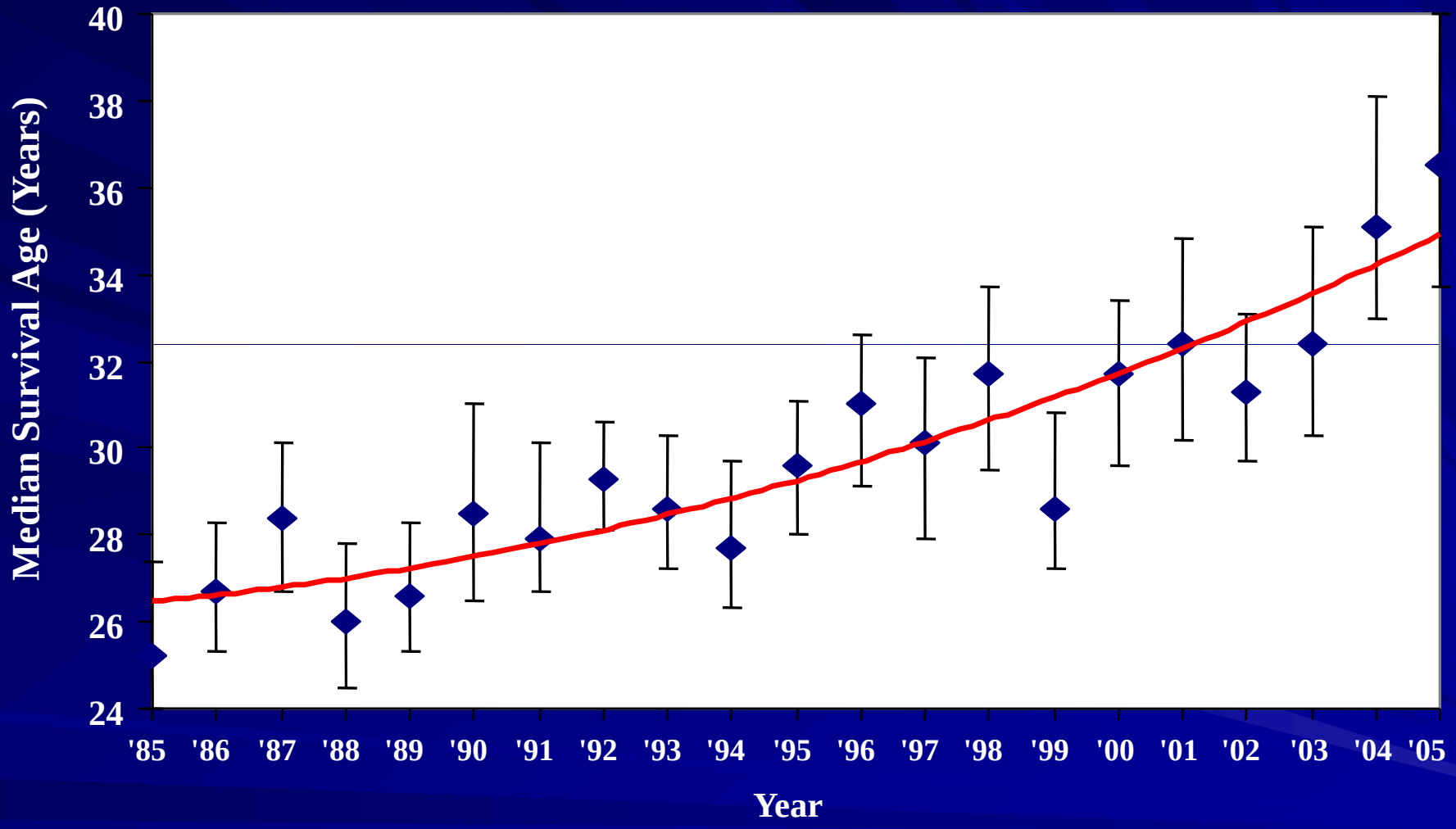






Median Predicted Survival Age, 1985-2005

(with 95 percent confidence bounds)



As of August 2006, the median predicted survival is 36.5 years for 2005.

Newborn screening

- 2009- all States in US & EU
- Advantages
  - Early diagnosis and intervention
  - Genetic screening
  - Improved nutrition
- Risks
  - False results
  - Cost and anxiety
  - CFMA
- Models
  - IRT/IRT
  - IRT/DNA

Pediatric Asthma

- Reversible airway obstruction
- Triggers: allergies, weather changes, exercise, environmental triggers
- Cough, wheeze, shortness of breath
- Lower airway obstruction

Bronchiolitis

- RSV
- Mucous plugging secondary to airway debri
- Minimal reversibility
- Obstructive pattern