Problem 3.05

CF

CFTR
(CF Transmembrane Conductance Regulator)
7q31 gene locus
Apical membrane of exocrine epithelial cells
pKA cAMP (SNS) activated Cl channel (others are Ca [PSNS])
Involved in salt & water balance

pKA = Protein Kinase A
IRT = Immunoreactive Trypsin
ASL = Airway Surface Liquid
ICF = Intracellular Fluid
Ile = Isoleucine
Phe = Phenylalanine
CF = Cystic Fibrosis
△F508 = Phe (F) Amino Acid #508 changed
7q31 = Chromosome 7, long arm (q) pos 31 on gene, p = short arm

- Named after fibrous cysts found in pancreas
- Autosomal Recessive
- △F508
  - 1/25 carriers (caucasian)
  - 1/2500 incidence (caucasian)
  - 50% homozygous
  - 40% heterozygous
- Severity correlates with pancreatic function & sweat Cl not respiratory
- Life expectancy 35 yrs (M > F)

CF

Abnormal CFTR

Genetic Defect
- △F508 70%
(3 base pair deletion → Phe for Ile)
(Most common)

Impaired ability to pump Cl into or out of exocrine gland lumen
- 2° modification
- 1° secretion not effected

1° Secretion
- Ca operated Cl Channel
- Cl into lumen
- **Not** by CFTR

No 2° Mod. → CFTR cannot pump Cl **from** lumen to ICF → Sweat remains Salty @ rest & with Exercise (Isotonic) → Sweat Test
- Gold standard
- Cl > 60 mmol/L

Sweat Gland

Males Sterile (Accounts for 1-2% of cases) ← Congenital Bilateral Agenesis of the Vas Deferens (esp w 5T)

Subfertile Females

90%

↑ Semen viscosity ← Epididymis

Biliary Cirrhosis

Liver & Gall Bladder

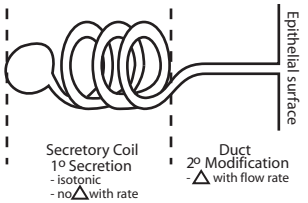
↓ Bile salts → ↓ Dietary fat absorption → ↓ Fat soluble vitamins (A, D, E, K)

Weight Loss

Steatorrhoea (fat malabsorption) Pistachio green (protein malabsorption)

Stool

Exocrine Gland (Submucosal or Sweat)



Atypical Gastric Reflux ← Obstruction ← ↑ Mucus viscosity ← Small Intestine

Infants → - Meconium Illeus - Meconium Plug Syndrome

- Chronic Sinusitis - Polyps ← Nose

Respiratory Epithelium (upper airway only)

Pancreas

Endocrine → DM (5%)

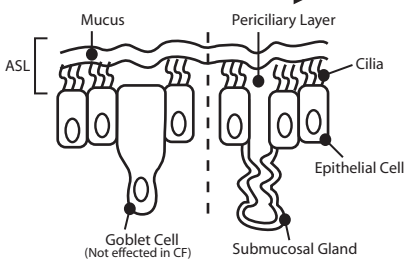
Exocrine → ↓ Enzymes (Lipase, amylase, trypsin chymotrypsin) → ↓ Absorption of fats, protein & carbs

Respiratory Virus

RSV → Histamine, LTC4, IgE

Rhinovirus → Bradykinin, IL1, IL6, IL8

Mucociliary Escalator



Trachea & Bronchi (Alveoli not effected)

Mucus

Goblet Cell
- Exocytosis)
- Absent in tertiary bronchioles
- Not effected in CF

Submucosal Gland
- Exocrine)
- Absent in terminal bronchioles

Secretory granules

Respond to 1° initiating stimulus

Responds to ANS

CFTR does not pump Cl **into** lumen

CFTR does not inhibit Na absorption channel

↓ Na & Cl within lumen

↓ H_2O in lumen

↑ Mucus viscosity

↓ ASL (Regulated by mucus contact with cilia)

Impaired Mucociliary Transport → Mucus Accumulation (Excessive)

Damage to Respiratory Epithelium

Cough Reflex → Chronic Productive Cough

Bronchial Plugging → Small aiway closure → Atelectasis
- CXR changes
- Resp crackles

Provides excellent medium for micro-org growth

↑ Bacterial adherence

Opportunistic Infection

Colonisation by non-commensal flora

Atypical Infections
- Staph. aureus
- Haem. Influenza

Immune Response (often damaging)

Immune Complexes Proteolytic Enzymes Oxygen Radicals

Lung Parenchymal Injury → Bronchiectasis (CF most common cause in West)

Haemoptysis Clubbing Inspiratory crackles

Cor Pulmonale ← Pulmonary Hypertension

Cavitation

CXR → Spirometry
- ↓ TLC

Respipratory Failure

DEATH

Lung Transplant

Spirometry
- ↓RV
- ↓FRC
- ↑TLC
- ↑FEV_1

Problem

↑ Mucus

Pseudomonas aeurigonosa
- Gram -ve
- Found in soil, water, plants, animals
- Rx aggressively (IV Antibiotics)
- Common nosocomial infection
- Not common in "normals"
- Dx by sputum culture & Abs

Pyocyanin
- Sweet odour
- Blue green sputum

CXR
Bilateral bronchopneumonia with pleural effusion common

Chronic Colonisation ← Persistance

Worse Prognosis

Bronchial Hyperreactivity/ Asthma

Common Dx in infancy via faliure to thrive

Sweat gland Cl not pumped *from* lumen
Resp glands Cl not pumped *out of* lumen

94% of newborns with CF detected
- Guthrie heel prick test (@ 4 days)
- Dx via IRT
- Amniocentesis

Dx: sweat test, pancreatic test, DNA

Mucus is only formed in upper airway
- Goblet cells and submucosal glands

Serous exocrine glands pump Na, Cl and H_2O into lumen making the mucus more fluid