Lessons Learned In Pediatric Pancreatic Disorders
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Outline and Objective
- Cystic Fibrosis
- Shwachman-Diamond
- Pancreatitis: acute and chronic
- To take a journey from the early years to the present and to describe advances and lessons learned and to predict the future

Cystic Fibrosis
The Early Years

1595 Pieter Pauw Professor of Botany and Anatomy at Leiden
"I conducted an autopsy on an 11-year old girl said to be bewitched. She had strange symptoms for eight years. Death had been caused by the pancreas which was oddly swollen... It was scirrhous. When it was removed the interior was found to be brightly colored, a kind of hard white viscous mass. The little girl was very thin, worn out by hectic fever."

1848 "If it tastes salty when someone is kissed on the brow, then this person is hexed"
1857 "The child will soon die whose brow tastes salty when kissed."
Cystic Fibrosis

The Early Years


"I claim that there is a distinct variety or form of infantilism which is due to disease of the pancreas and that this, the pancreatic form of infantilism, as I have ventured to term it, can be cured by administration of pancreatic extract. I consider that it is a distinct clinical entity - a disease which has not hitherto been recognised or described".

1930's

Dorothy Andersen

Cystic Fibrosis

1940's

Harry Shwachman

Cystic Fibrosis

1950's


Presented the paper at the APS meeting in 1953. Not a single question.

Showed data to Jas Juno, the leading sweat physiologist. He responded “impossible” and left the room.

Shared data with Shwachman who recognized the importance and published a large follow-up series in 1954 corroborating the findings.

Cystic Fibrosis

1960's

- Growth of CF foundations world-wide
  - US foundation started in 1955

- Clinical progress
  - Develop paradigms of good clinical care
  - Increasing use of the sweat test

- Research focus
  - Search for agents to dissolve viscous mucous

Cystic Fibrosis

1970's

- Improvements in clinical care

- Search for CF factor
Cystic Fibrosis

1980's


Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping

Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA

Identification of the Cystic Fibrosis Gene: Genetic Analysis

Cystic Fibrosis

1990's

Decade of gene therapy

Explosion of CFTR polymorphisms identified

Improvements in care

Fibrosing colonopathy was first recognized

Cystic Fibrosis

New Millenium

The Development of Chemical Modulators of CFTR Function


Cystic Fibrosis
New Millenium


Cystic Fibrosis
The Future

- Improved therapy for gastrointestinal manifestations of CF
- Better methods for monitoring malabsorption
  - New, less invasive methods to accurately measure steatorrhea
  - Improved pancreatic enzyme replacement therapies
- Continued development of treatments to correct CFTR dysfunction
  - Strategies to pay for the therapies
- Therapies to regenerate the exocrine pancreas

Shwachman-Diamond Syndrome


Pancreatic insufficiency
Normal Sweat Test
Anemia
Thrombocytopenia
Neutropenia
Short stature
Autosomal recessive disorder
Shwachman-Diamond Syndrome

2002
Fine mapping of the locus for Shwachman-Diamond syndrome at 7q11, identification of shared disease haplotypes, and exclusion of TPST1 as a candidate gene
Maja Popovic1,2, Sharan Groh8,4, Svob Morison6, Lynda Ellis8,5, Nicky Treharne3, Nicole Richard7, Graham Swinyard4,7, Peter R Dove6,8 and Johanna M Forreston4,7

2003
Mutations in SBDS are associated with Shwachman-Diamond syndrome
Graham R Vine1,2,3, Max A Morrison1, Maja Popovic1,2, Nicky Richard7, Lynda Ellis8,5, Peter R Dove6,8 and Johanna M Forreston4,7

Shwachman-Diamond Syndrome

29 kDa protein
Broadly expressed
Facilitates release of eukaryotic initiation factor 6 from the 60S ribosome subunit
Defective ribosomal assembly

Shwachman-Diamond Syndrome

• Better understanding of the clinical spectrum

• Understanding the pathophysiology of the pancreatic disease
  o Decreased protein load in the acinar cells
  o No fibro-inflammatory disease

• Improved understanding of SBDS function
  o Why are some organs affected more than others?
Pancreatitis

Acute

Recognition that kids have pancreatitis

The changing incidence of acute pancreatitis in children: A single-institution perspective

Morville, Barmada and Lowe, 2010

Hereditary Pancreatitis

Genes and Acute Recurrent and Chronic Pancreatitis

1996

Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene

Genetic Linkage Map for Hereditary Pancreatitis Gene

Chromosome 7

HP gene

Human β T Cell Receptor Locus

Cationic Trypsinogen

Cationic trypsinogen complexed with PSTI
Genetics of Chronic Pancreatitis

- 1998: CFTR
- 2000: SPINK1
- 2006: CASR and CEL
- 2008: CTRC
- 2013: CPA1

Pathophysiology

Autodigestion

Activation of digestive enzymes

Trypsinogen → Trypsin

Zymogens → Activated Enzymes

Pancreatic inflammation and fat necrosis

ER Stress and Unfolded Protein Response

Metabolic Stress

Pancreatitis

Misfolded Protein

Protein Aggregates

Ectodomain

Pancreatitis

Inflammatory Response

Ectodomain
Pathophysiology
Regeneration

Regeneration after cerulein induced pancreatitis
From: Fendlich et al. Gastroenterology, 2008;135:621-31

INSPPIRE
• Consortium of 14 Pediatric Centers
  o USA
  o Canada
  o Israel
  o Australia

• Focus on acute recurrent and chronic pancreatitis
• R21 funding (Aliye Uc, MD is the PI)
• 203 patients recruited in about 7 months

Future Directions
• Improved understanding of the patient population
• Better understanding about pathophysiology
• Therapies to prevent acute recurrent pancreatitis
• Therapies to prevent or reverse fibrosis and to stimulate pancreatic regeneration for chronic pancreatitis