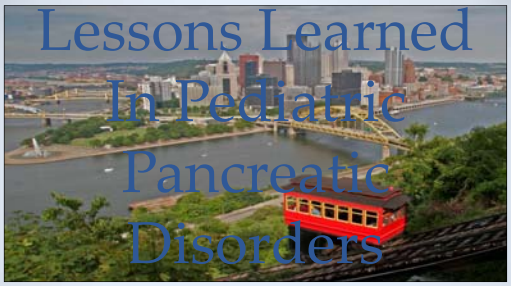
Lessons Learned In Pediatric Pancreatic Disorders



Mark E. Lowe, MD PhD
Professor and Vice-Chairman of Pediatrics
Children's Hospital of Pittsburgh of UPMC

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

Peter Durie

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

1904 Bramwell B. Pancreatic infantilism: remarkable improvement (growth of body and sexual development) as a result of the administration of pancreatic extract. Trans Medico-chi Soc Edin 1904; 23; 162. Clinical Studies 1904; 2:348-352. Edinburgh. R and R Clark.

"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".

Cystic Fibrosis

1930's

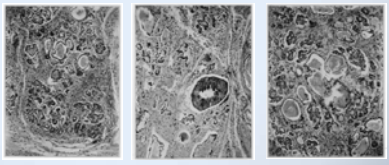
CYSTIC FIBROSIS OF THE PANCREAS AND ITS RELATION TO CELIAC DISEASE

A CLINICAL AND PATHOLOGIC STUDY

DOROTHY H. ANDERSEN, M.D.

NEW YORK

Dorothy Andersen



Cystic Fibrosis

1940's

PANCREATIC FUNCTION AND DISEASE IN EARLY LIFE. I. PANCREATIC ENZYME ACTIVITY AND THE CELIAC SYNDROME[1]

By SIDNEY FARBER, HARRY SHWACHMAN, AND CHARLOTTE L. MADDOCK

(From The Children's Hospital, The Infants' Hospital, and the Department of Pathology, Harvard Medical School, Boston)

(Received for publication April 20, 1943)

Harry Shwachman

di Sant'Agnese PA, Andersen DH. Celiac Syndrome IV. Chemotherapy in infections of the respiratory tract associated with cystic fibrosis of the pancreas; observations with penicillin and drugs of the sulphonamide group, with special reference to penicillin aerosol. Am J Dis Child 1946; 72:17-61.

Paul di Sant'Agnese

Cystic Fibrosis

1950's

Darling RC, **di Sant'Agnese PA**, Perera GA, Andersen DH. Electrolyte abnormalities of the sweat in fibrocystic disease of pancreas. Am J M Sc 1953; 225:67-70.

di Sant'Agnese PA, Darling RC, Perera GA, Shea E. Sweat electrolyte disturbances associated with childhood pancreatic disease. Am J Med 1953; 15:777-784.

di Sant' Agnese PA, Darling RC, Perera GA, Shea E. Abnormal electrolyte composition of the sweat in cystic fibrosis: Clinical significance and relationship to the disease. Pediatrics 1953; 12: 549-563.

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

Holsclaw DS, **Grand RJ**, **Shwachman H**. Massive haemoptysis in cystic fibrosis. Pediatrics 1970; 75:829-838.

Keating JP, Feigin RD. Increased intracranial pressure associated with probable vitamin A deficiency in cystic fibrosis. Pediatrics 1970; 46:41-46.

Shwachman H, **Lebenthal E**, Khaw P-T. Recurrent acute pancreatitis in patients with cystic fibrosis with normal pancreatic enzymes. Pediatrics 1975; 55:86-94.

Farrell PM, Bieri JG, Fratantoni JF, Wood RE, **di Sant'Agnese PA**. The occurrence and effects of human vitamin E deficiency. J Clin Invest 1977; 60:233-241.

- Search for CF factor

Cystic Fibrosis

1980's

diSant'Agnese PA, Hubbard VS and Lowe ME. Recent developments in clinical and basic research in cystic fibrosis. Monograph Pediatr 1981:14:1-25.

Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping

Johanna M. Rommens, Michael C. Iannuzzi, Bat-sheva Kerem, Mitchell L. Drumm, Giorgi Melmer, Michael Dean, Richard Rozmahel, Jeffery L. Cole, Dara Kennedy, Noriko Hidaka, Martha Zsiga, Manuel Buchwald, John R. Riordan, Lap-Chee Tsui, Francis S. Collins

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

John R. Riordan, Johanna M. Rommens, Bat-sheva Kerem, Noa Alon, Richard Rozmahel, Zbyszko Grzelczak, Julian Zielenski, Si Lok, Natasa Plavsic, Jia-Ling Chou, Mitchell L. Drumm, Michael C. Iannuzzi, Francis S. Collins, Lap-Chee Tsui

Identification of the Cystic Fibrosis Gene: Genetic Analysis

Bat-sheva Kerem, Johanna M. Rommens, Janet A. Buchanan, Danuta Markiewicz, Tara K. Cox, Aravinda Chakravarti, Manuel Buchwald, Lap-Chee Tsui

Cystic Fibrosis

1990's

Decade of gene therapy

Explosion of *CFTR* polymorphisms identified

Improvements in care

Fibrosing colonopathy was first recognized

Cystic Fibrosis

New Milleneum

The Development of Chemical Modulators of CFTR Function

Wilschanski M, Famani C, Blau H, Rivlin J. Augarten A, Vital A, Kerem B, Kerem E. A pilot study of the effect of gentamicin on nasal potential difference measurements in cystic fibrosis patients carrying stop mutations. Am J Resp Crit Care 2000; 161:860-865.

Wilschanskli M et al. Chronic ataluren (PTC 124) treatment of nonsense mutation cystic fibrosis. Eur Respir J 2011; 38:59-69.

Accurso FJ, Rowe SM, **Durie PR**, Konstan MW, Dunitz J, Hornick DB, Sagel SD, Boyle MP, Uluer AZ, Upadhyay D, Ramsey BW, Freedman SD, Dong Q, Ahmed AM, Stone AJ, Olson ER, Ordenez CL, Clancy JP, Campbell PW, Ashlock MA. Interim results of Phase IIa study of VX-770 to evaluate safety, pharmokinetics and biomarkers of CFTR activity in cystic fibrosis subjects with G551D. Pediatr Pulmonol 2008; Suppl 31: 267 page 295.

Ramsey BW. Davies J. McElvaney NG. Tullis E. Bell SC. Drevinek P. Griese M. McKone EF. Wainwright CE. Konstan MW. Moss R. Ratjen F. Sermet-Gaudelus I. Rowe SM. Dong Q. Rodriguez S. Yen K. Ordonez C. Elborn JS. VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Eng J Med 2011; 365:1663-1672. **Ivacaftor**

Cystic Fibrosis

New Milleneum

Rodgers CS, Stoltz DA, Meyerholz DK, Ostedgaard LS, Rokhlina T, Taft PJ, Rogan MP, Pezzulo AA, Karp PH, Itani OA, Kabel AC, Wohlford-Lenane CL, Davis GJ, Hanfland RA, Smith TL, Samuel M, Wax D, Murphy CN, Rieke A, Whitworth K, Uc A, Starner TD, Brogden KA, Shilyansky J, McCray PB Jr, Zabner J, Prather RS, Welsh MJ. Disruption of the CFTR gene produces a model of cystic fibrosis in newborn pigs. Science 2008; 26; 321(5897):1837-1841.

Cystic Fibrosis

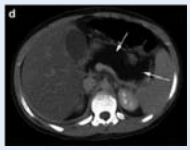
The Future

- 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

- **Shwachman H**, Diamond LK, Oski FA, Khaw K-T. The syndrome of pancreatic insufficiency and bone marrow dysfunction. J Pediatr 1964;65:645-663.
- Bodian M, Sheldon W, Lightwood R. Congenital hypoplasia of the exocrine pancreas. Acta Paediatr 1964;53:282-293.

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

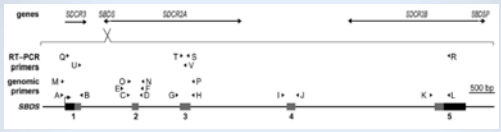
Maja Popovic[1,4], Sharan Goobie[1,4], Jodi Morrison[1], Lynda Ellis[2,3], Nadia Ehtesham[1], Nicole Richards[1], Graeme Boocock[1,4], Peter R Durie[2,3,5] and Johanna M Rommens*[1,4]

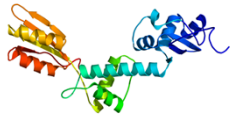
2003

Mutations in *SBDS* are associated with Shwachman–Diamond syndrome

Graeme R.B. Boocock[1,2], Jodi A. Morrison[1], Maja Popovic[1,2], Nicole Richards[1], Lynda Ellis[3,4], Peter R. Durie[3,4] & Johanna M. Rommens[1,2]

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
  - Decreased protein load in the acinar cells
  - No fibro-inflammatory disease
- Improved understanding of SBDS function
  - Why are some organs affected more than others?

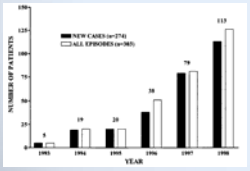
Pancreatitis

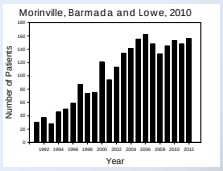
Acute

Recognition that kids have pancreatitis

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

M. James Lopez, MD, PhD





Hereditary Pancreatitis

WEST VIRGINIA, TENNESSEE

HEREDITARY PANCREATITIS: THREE NEW KINDREDS AND A CRITICAL REVIEW OF THE LITERATURE

John Kattwinkel, M.D., Allen Lapey, M.D., Paul A. di Sant'Agnese, M.D., William A. Edwards, B.S., with the assistance of Mary P. Hufty

From the Pediatric Metabolism Branch and Digestive and Hereditary Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland

Genes and Acute Recurrent and Chronic Pancreatitis

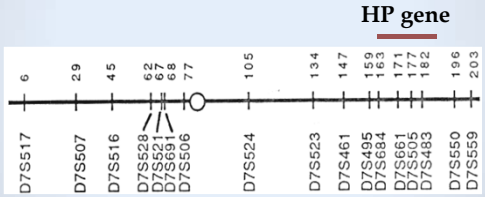
1996

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

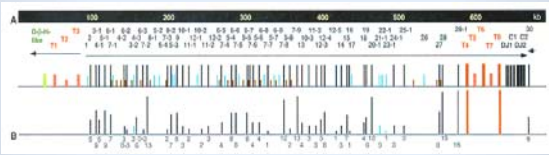
David C. Whitcomb[1,2,3], Michael C. Gorry[3,4], Robert A. Preston[3,4], William Furey[5], Michael J. Sossenheimer[1], Charles D. Ulrich[6], Stephen P. Martin[6], Lawrence K. Gates, Jr[7], Stephen T. Amann[8], Phillip P. Toskes[8], Roger Liddle[9], Kevin McGrath[9], G. Uomo[10], J. C. Post[3,11,12] & Garth D. Ehrlich[3,4,11,12]

Genetic Linkage Map for Hereditary Pancreatitis Gene

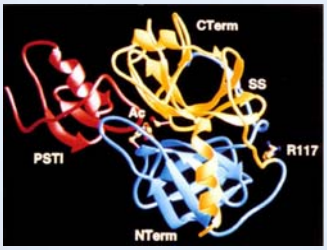
Chromosome 7



Human β T Cell Receptor Locus



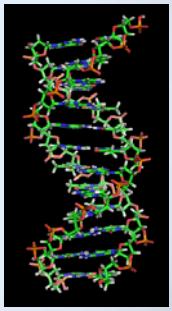
Cationic Trypsinogen



Cationic trypsinogen complexed with PSTI

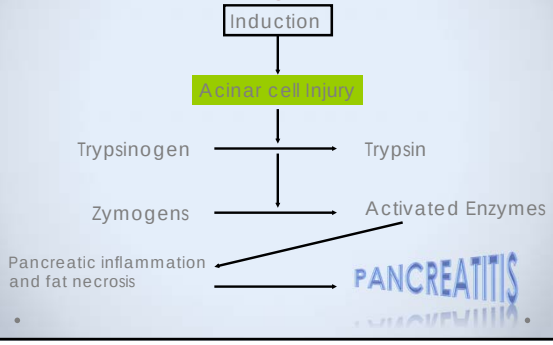
Genetics of Chronic Pancreatitis

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



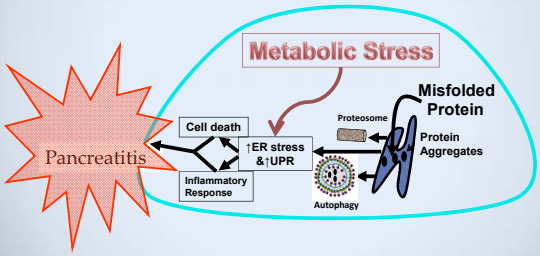
Pathophysiology

Autodigestion



Pathophysiology

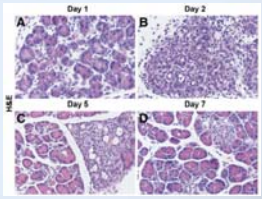
ER Stress and Unfolded Protein Response



Pathophysiology

Regeneration

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



INSPPIRE

- Consortium of 14 Pediatric Centers
  - USA
  - Canada
  - Israel
  - 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