

A History of Cystic Fibrosis

You are in >The thirties

A History of Cystic Fibrosis by Dr James Littlewood OBE, June 2009

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Pancreatic malabsorption as distinct from coeliac disease – “fibrocystic disease of the pancreas”

The major advance towards the end of the Thirties was the clear description of “fibrocystic disease of the pancreas” by Dorothy H Andersen, from the Pathological Laboratory, Babies Hospital and the Department of Pathology, Royal College of Physicians and Surgeons, Columbia University, New York in a paper she read at a joint meeting of the American Pediatric Society with the Society for Pediatric Research on May 5th 1938 (Andersen, 1938 below).

Prior to the Thirties there had been isolated case reports of children with the clinical features of intestinal malabsorption considered to be due to pancreatic insufficiency; in some cases this suggestion was supported by the presence of pancreatic histological changes at autopsy – a feature that eventually led to the recognition of cystic fibrosis as a distinct clinical entity. Some of the children also had severe respiratory problems. Many reports contained autopsy details as most affected children died in infancy for there were no antibiotics available until the mid-Forties; even sulphonamides, which were of limited value in CF, were not available until the end of the decade. A further problem was that death in infancy from pneumonia or gastroenteritis even in non-CF infants in the Thirties was a relatively frequent occurrence.

During the Thirties further small series of children were reported who had intestinal malabsorption with evidence of pancreatic abnormalities. A number of authors noted that children with coeliac disease were not uniform and some had definite pancreatic abnormalities – usually noted at autopsy (Parmalee, 1935 below; Hess & Saphire, 1935 below). In 1952 Martin Bodian, pathologist at the Hospital for Sick Children, Great Ormond Street, London, comments that Dorothy Andersen’s classic 1938 paper (Andersen, 1938 below) was, in part, the result of her gradually collecting details of her own patients with pancreatic abnormalities and similar patients published by previous authors or made available by colleagues. With this information she was able to build up a picture of a specific condition in which a pancreatic lesion was often associated with steatorrhoea and respiratory disturbances (Bodian, 1952 below). During the Thirties other workers were reaching the same conclusions as Andersen at much the same time; these included in 1938 Blackfan and May (1938 below) who reported 35 cases of fibrocystic disease from among 2500 paediatric autopsies; these authors gave credit to Kenneth Wolbach to whom they attributed the first description of the typical pancreatic lesion and for the suggestion that the changes may be due to an abnormal secretion within the pancreatic ducts (Blackfan & Wolbach, 1933 below). There were others who recognised the clinical features of CF as distinct from coeliac disease (Parmalee, 1935; Hess & Saphire, 1935; Harper, 1938; Rauch et al, 1939 - all below). Although the first clear description of CF has been attributed to Fanconi (Fanconi et al, 1936 below) by some European clinicians, he described only two patients and the paper did not lead to a general recognition of the condition as did that of Dorothy Andersen in 1938.

At the end of the Twenties there had been an observation made that eventually led to one of the most important medical advances of all time – an advance, that when eventually developed, was to have a major influence on the survival of children with cystic fibrosis. In 1929 Alexander Fleming, the microbiologist at St Mary’s Hospital in London, observed inhibition of a growth of *Staphylococcus aureus* on a culture plate by a Penicillin mould which had contaminated the plate (Flemming, 1929 above). Flemming did little more with his discovery at the time but at the end of the Thirties this initial observation eventually led to the development of penicillin by Howard Walter Florey and his colleagues in Oxford. In 1940 a pure extract of penicillin was produced from the mould *Penicillium notatum* by the chemist Ernest Boris Chain. Until the availability of penicillin and subsequently other antibiotics, infants with CF rarely survived beyond early childhood.

1930 Harper M. Two cases of congenital pancreatic steatorrhoea with infantilism. *M J Aust* 1930; 2:663-664.

Margaret Harper (1879-1964) was a distinguished paediatrician at the Royal Alexandra Hospital for Children, Sydney. She reported two children with typical clinical features and stools characteristic of



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pancreatic malabsorption; both children died of bronchopneumonia and the one autopsied had typical pancreatic changes of cystic fibrosis (also Harper, 1938 when she described 8 further children; also 42 more in 1948. Both below).

In the Australian Dictionary of Biography it notes of Margaret Harper, that “She painstakingly experimented with infant diets and won international repute for discovering the difference between coeliac disease and cystic fibrosis of the pancreas in 1930”. This is not entirely true but she clearly described children whose malabsorption syndrome was due to pancreatic abnormalities - both the clinical features and pathological findings. However, it was not until Dorothy Andersen's paper in 1938 (below) that CF was clearly identified as a specific disorder.

1931 Leipmann H, Hoffman H. Investigation of a case of pancreatic insufficiency. *Zeit Kinderheilk* 1931; 50:212-223. (German).

A report of a child with evidence of intestinal malabsorption, laboratory evidence of pancreatic insufficiency and also keratomalacia. There was improvement with nutritional therapy but no evident benefit from Pankreon (a pancreatic extract). The passage of oil from the anus was a feature – a very typical sign of pancreatic steatorrhoea. Although there was marked steatorrhoea there was adequate carbohydrate absorption – also a feature of CF. The authors reviewed previously reported cases of pancreatic insufficiency in childhood and noted that the condition was rare.

Almost certainly this infant had cystic fibrosis. The passage of yellow-orange oil with the stools is very suggestive, in fact virtually diagnostic, of pancreatic steatorrhoea.

1931 Daffinee RW, Higgins HL, Mallory TB. Corneal ulcers and roughened conjunctivae associated with fat intolerance. *N Engl J Med* 1931; 204:1264-1267. A white male infant aged six months had spots on his eyes noted by the mother also weight loss. He died of bronchopneumonia one month later and at one stage was excreting 40% of his dietary fat intake (70% of which was neutral fat). Autopsy showed almost complete atresia of the cystic duct and histologically “extremely marked disease of the pancreas” - practically all the acinar tissue had disappeared. The lungs showed multiple abscesses. Mallory, the author who was the pathologist, writes “in the later stages of the disease he had a definite pancreatic lack whatever the original cause may have been”.

There can be little doubt that this infant had CF although there are a number of reports suggesting that severe stenosis or even atresia of the pancreatic duct may be the primary cause of the clinical syndrome.

1932 Parsons LG. Celiac disease. *Rachford Memorial Lectures. Am J Dis Child* 1932; 43:1293.

Leonard Parsons (1879-1950) was Professor of Paediatrics in Birmingham, UK. This is a long article describing the current situation regarding coeliac disease drawing on the author's experience of 73 children - 21 were from the Boston Children's Hospital “through the kindness of Dr Kenneth Blackfan”. Parsons advised against diagnosing coeliac disease unless there were more than 2 g of fat daily in the faeces – usually there was considerably more - up to 20 g; also the percentage of fat in the stools may reach 80% - the normal upper limit being 25%. There is a detailed clinical commentary with attention to the nutritional deficiencies.

The mortality of only 10.6%, in the pre-antibiotic era, suggests that there were few infants with CF included in this series. In discussing the morbid anatomy Parsons mentions that “in two or three cases some excess of fibrous tissue or small-celled infiltration around the ducts of the pancreas has been found”. However, most authors had not found pancreatic changes at autopsy in children with coeliac disease. “In coeliac disease the pancreatic juice is normal because the fats in the stool are split normally; furthermore, specimens obtained by duodenal intubation have shown the presence of trypsin, amylase and lipase in normal amounts – when estimated by the method of McClure, Wetmore and Reynolds”. However, Parsons observed that Fanconi apparently believed “that the diastatic ferments function poorly” in coeliac disease.

So in this very detailed paper by one of the UK's leading paediatricians, most of the discussion centred on what was almost certainly gluten induced coeliac disease; the possibility that some cases were due to pancreatic abnormality was discussed only briefly but dismissed. In later work some degree of pancreatic insufficiency was reported to occur in untreated coeliac disease but this was only temporary and considered to be due to substrate protein deficiency associated with the malnutrition (Carroccio A et al, *Gut* 1991; 32:796-799).

1932 Van Creveld S. Pancreatic fat stool of children. *Ned Tidjschr Geneesk* 1932; 76:3741-3755. (German).

“In describing some morbid cases the question is extensively discussed in how far fat stool in children may be caused by a primary pancreatic affection. Especially the differential diagnosis between intestinal infantilism and pancreatic fat stool is stressed; a case of the latter condition is described.”

1932 Siwe S. On the exocrine function of the pancreas and the results of their omission. A case of almost total agenesis of the exocrine portion of the pancreas. Deutsche Arch Klin Med 1932; 173:339-358. (German).

A child with feeding problems from the age of six months and cough from 19 months died aged two years. She had been born prematurely and had foul stools, poor development and a large abdomen. She died from varicella and bronchitis. The pancreas had well-preserved islets in contrast to almost total degeneration of the exocrine portion of the gland. There was rickets and mild cirrhosis and a fatty liver (details from Andersen, 1938 below).

This patient was accepted by Dorothy Andersen as having CF although rickets is very rare in cystic fibrosis; however, it is more likely to occur if there is liver disease (Scott J et al, 1977 below).

1933 Blackfan KD, Wolbach SB. Vitamin A deficiency in infants. J Pediatr 1933; 3:679-706.

Kenneth Blackfan (1883-1941) was Associate Professor of Pediatrics at Johns Hopkins, then Professor of Pediatrics at Cincinnati and at Harvard from 1923 to 1941. He apparently 'mentored' both Louis Diamond and Sydney Farber. In 1941 he died of lung cancer at the age of 58 – at the height of his career. The Children's Hospital in Boston is on Blackfan Street - named after him. This is an interesting account primarily of early vitamin A deficiency, in which there was considerable interest at the time. In 13 infants and young children, 11 of whom were eventually autopsied, vitamin A deficiency was reported. Epithelial metaplasia due to vitamin A deficiency was considered an important predisposing factor to infection by causing – "loss of protective powers of the epithelium due to diminished or absent mucus secretion and loss of ciliary motion". Six of the 11 infants autopsied had extensive pancreatic lesions (later recognised as typical of CF), that the authors correctly attributed to inspissation of secretion in the ducts.

The authors noted that "The pancreatic lesions were all identical and presumably representing a disease entity. At first we regarded the pancreatic changes as the result of vitamin A deficiency (as did Dorothy Andersen for some years). As the same condition has been found scores of times without other evidences of vitamin A deficiency and since it is not constant even in vitamin A deficiency, we must consider the two are not necessarily connected". The photomicrograph of pancreas (figure 1) is typical of the changes seen in CF for which Blackfan & May (1938 below) gave credit to Wolbach for the first clear description.

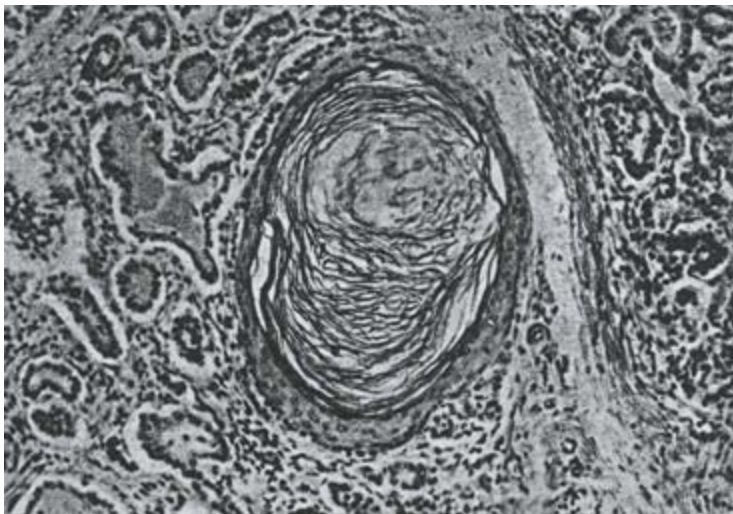


Figure 1: Photomicrograph of pancreas. From the paper with permission.

The authors continue "The pancreatic lesion referred to is characterised by dilatation of acini and ducts, by inspissated secretion, atrophy of the acini, lymphoid and leukocyte infiltration of some degree and fibrosis. Our preliminary studies indicate that the pathogenesis of this striking pancreatic affection resides in the production of an abnormal secretion which inspissates and leads to distension and atrophy of ducts and acini. It is reasonable to assume that this pancreatic lesion, if extensive, may be responsible for failure to utilise fats and hence vitamin A in the presence of an adequate intake".

The authors concluded that vitamin A deficiency was not infrequent and should be suspected without regard to the characteristic eye signs; histological evidence of vitamin A deficiency may appear in infants who appear to be receiving an adequate intake; they postulate that some factor or factors interfering with storage or utilisation of this vitamin lessens the availability of the supply essential for normal nutrition; certain diagnostic criteria to identify at an early stage are mentioned

and vitamin A deficiency should be considered as a general systemic disease rather than as a local disease of the eye.

1933 Greenberg J. An attempt to reproduce coeliac disease experimentally in young animals by excluding the external pancreatic secretion from the intestine. *Yale J Biol Med* 1933-34; 6:121-153.

In this paper there is a previously unreported case described of an infant aged 11 months in whom a completely fibrotic pancreas was found. The very title of this paper suggests that the differentiation between coeliac disease and CF was still far from clear.

1934 Huet GJ. A case of Herter's infantilism with chronic lung involvement. *Maandschr v Kindergeneesk* 1933-34; 3:343-350. (Dutch).

A boy aged 10 years who had chronic diarrhoea died of bronchopneumonia. There had been feeding difficulty in the infancy and a chronic cough from the age of six years. His development was generally poor, his stools fatty and he had chronic chest infection. Autopsy showed purulent bronchitis with dilation of the bronchi and fibrosis of the lungs. There was marked atrophy of pancreatic acini and hypertrophy of the islets; also fatty degeneration and cirrhosis of the liver. Tuberculosis had been suspected during life but was ruled out.

This patient is mentioned by Andersen (1938 below) and undoubtedly had cystic fibrosis.

1935 Anke H. A case of congenital pancreatic insufficiency. *Munchen Med Wochen* 1935; 82:1787-1789.

A boy aged 14 years with clinical evidence of congenital pancreatic malabsorption with steatorrhea; he had typical "butter stools" containing an excess of neutral fat. There were no significant chest problems – he even did well in the Hitler Youth movement!

The overall progress, normal growth, lack of respiratory problems are against this boy having CF although he could have had atypical CF due to unusual so-called "mild" mutations. However, the "butter stools" would suggest pancreatic malabsorption and could indicate that he had "congenital lipase deficiency", later described in two families, each with two affected children by Sir Wilfred Sheldon (1901-1983), paediatrician at The Hospital for Sick Children, Great Ormond Street, London (*Arch Dis Child* 1964; 39:268-71). Both of these children had severe steatorrhea, a tendency for oil to ooze from the anus, but satisfactory growth, absent or low pancreatic lipase but normal amylase and proteolytic enzymes in the pancreatic juice. A similar patient was described by Garrod & Hurlley (1912 above).

1935 Parmalee AH. The pathology of steatorrhea. *Am J Dis Child* 1935; 50:1418 - 1428.

Parmalee described the evidence, present in some children, associating pancreatic disease with coeliac syndrome. He described two further children. A girl who died aged 14 years had early feeding problems, fat intolerance with rancid fatty stools, a protuberant abdomen, bronchitis and eventually bronchopneumonia; at autopsy her pancreas showed the typical changes of cystic fibrosis. Another girl who died aged four years had poor weight gain and the appearances of intestinal malabsorption. At autopsy the pancreas was typical of CF with a narrow duct which was queried as atretic.

"Congenital steatorrhea" and "pancreatic steatorrhea" obviously referred to infants who had CF and differed from the usual picture of coeliac disease in their early onset, excessive amount of neutral fat in the stools and the uniformly fatal outcome. There were constant changes in the pancreas at autopsy – "marked fibrosis and great diminution of secretory gland tissue in the pancreas, also bronchopneumonia".

This paper is mentioned frequently in the literature as making a major contribution to clarifying the situation regarding the various conditions classified as coeliac disease by correlating the clinical and pathological picture.

1935 Hess JH, Saphire O. Celiac disease: Chronic intestinal Indigestion. A report of three cases with autopsy findings. *J Pediatr* 1935; 6:1-13.

This is a frequently quoted paper from Chicago describing three infants with pancreatic insufficiency and severe pancreatic fibrosis at autopsy with distension of the ducts, also liver involvement and bronchopneumonia with abscess formation. There is an interesting account of the published views on the aetiology of coeliac disease, noting that only some authors describe associated pancreatic lesions. The present authors concluded that "If, by the use of special staining methods, it is not possible to demonstrate fibrosis in the pancreas, then it must be conceded that the symptom complex of coeliac disease has not one definite pathological entity.....Because of our findings we must insist, however, that in every instance of coeliac disease the pancreas should be studied with the before mentioned special methods before pronouncing it normal".

Here was further evidence that coeliac disease was really a syndrome comprising more than one

condition and good advice to always exclude pancreatic abnormality. Cystic fibrosis was gradually emerging as a specific entity.

1936 Dodd K. Intestinal obstruction due to meconium ileus in a newborn infant. *J Pediatr* 1936; 9:486-491.

Katherine Dodd of Nashville notes that “from time to time there have appeared in the literature reports of obstruction due apparently to no tumour or congenital malformation of the gastrointestinal tract but to an accumulation of mucilaginous meconium in the tract itself”. There is usually no mention of meconium ileus even in the more complete textbooks. This infant had signs of intestinal obstruction, developed bronchopneumonia and died at 10 days. There was tenacious grey material in the ileum and colon. “The only other organ showing marked changes was the pancreas” which showed marked changes of interstitial pancreatitis, cellular infiltration and dilatation of some ducts and acini” – in fact was typical of cystic fibrosis.

A review of the literature revealed 21 similar reported cases – the five who recovered were well having passed a large meconium plug and they probably had “meconium plug syndrome” and not cystic fibrosis. The rest had fatal obstruction due to abnormal bowel contents. In five cases abnormalities were found in the pancreas where this was examined (Kornblith et al, 1929 above; Landsteiner, 1905 above). Dodd suggested that the failure of pancreatic secretion or bile to reach the gastrointestinal tract during fetal and neonatal life was at least part of the cause of meconium ileus.

1936 Fanconi G, Uehlinger E, Knauer C. Das Coeliakie-syndrom bei angeborener zystischer Pankreasfibromatose und Bronchiektasien. *Wien Med Wchnschr* 1936; 86:753-756. (Celiac syndrome with congenital cystic fibromatosis of the pancreas and bronchiectasis).

Guido Fanconi (1892-1979), was Professor of Paediatrics in Zurich from 1929-1965 and a pioneer of modern scientific paediatrics (figure 2). Although this publication is considered by some Europeans to be the first clear description of CF, it is a brief report of only two children who died aged 10 months and three years with ‘coeliac syndrome’, purulent bronchitis and bronchiectasis. The pancreatic changes were quite typical of those later described in cystic fibrosis. “The changes in the lungs and pancreas, two vital organs, are so profound that their failure appears understandable”.

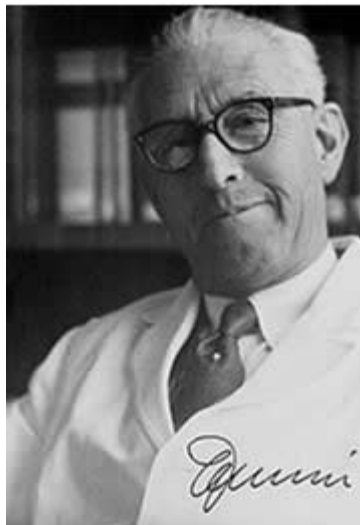


Figure 2: Guido Fanconi (1892-1979). From Wikipedia.

Martin Bodian quotes a 1928 publication of Fanconi’s (1928 *Beih. Jb. Kinderhkl* 21) as noting cases of coeliac disease starting in early infancy and often associated with bronchitis but surprisingly Fanconi did not mention this in his 1936 paper which is so frequently quoted in Europe as the first description of cystic fibrosis.

Speaking in 2008, Walter Hitzig, the distinguished immunologist from Zurich, recalls (referring to this paper) that “My teacher Guido Fanconi, in his usual enthusiasm, presented a “new disease” to the Swiss paediatricians in 1936. However, one of the doctors questioned its importance in his daily practice. Fanconi’s answer: “Oh certainly it is important – I have seen already 3 cases!” of course earned him a big laughter in the audience! And today the syndrome described as Pankreas-Fibrose, now called cystic fibrosis, is considered to be the most frequent hereditary disease in the Caucasian population, and no doubt every paediatrician must diagnose it”.

Lynn Taussig describes meeting Knauer, the third author, after this paper was published. Apparently the two children described in Knauer’s doctoral thesis in 1935 were the two described in this

paper. The next year Fanconi, Uehlinger and Knauer published this paper. He notes that the first name on the paper was now Fanconi’s. Maurice Super mentions that there was controversy between Fanconi and Wangenstein “who thought the condition might be something unique to the cantons in which Fanconi worked”. The hereditary genetic nature of CF was not suspected at this time.

Fanconi published a number of papers on various aspects of intestinal malabsorption and other aspects of paediatrics between 1921 and 1956 mostly in German or French. He was referred to in one article as a “Jack of all trades” – as were many of the paediatricians of the time. Reviewed objectively, none of these publications, with the possible exception of this 1936 paper, made any major or original contribution to the understanding or definition of cystic fibrosis. However, Fanconi made other very important contributions; in 1929 he described hereditary panmyelopathy known as Fanconi’s anaemia, in 1941 he deduced that polio was spread via the gastrointestinal route rather than by droplets and apparently predicted that Down’s syndrome was due to a chromosome

abnormality 20 years before trisomy 21 was discovered.

1936 Meltzer S. Meconium ileus. *Canad Med Ass J* 1936; 34:186.

A single case report by Sara Meltzer, a pathologist in Winnipeg – the second infant in the family to die of neonatal obstruction. Abnormal meconium was noted but pancreas was not examined and the infant died on the first day. She mentions a similar case report by Kornblith & Otani 1929 (above) where there was stenosis of the duct of Wirsung (the main pancreatic duct) also twins seen by Sydney Farber with occlusion of the pancreatic duct and pancreatic fibrosis (also Dodd, 1936 above).

1936 Garsche R. Clinical forms and pathogenesis of pancreatic insufficiency in older children. *Z Kinderheilk* 1936; 58:434-455. (German).

An infant with feeding problems from 6 months who died aged four years and six months after developing chest problems. He had failure to gain weight, with large foul stools, protuberant abdomen, and alternate hunger and anorexia. The cause of death was pneumonia. The pancreas showed fibrosis with replacement of acinar tissue with fat and concretions. The liver was fatty with mild biliary cirrhosis (mentioned by Andersen as having CF, 1938 below).

1938 Burger P. Cas rare d'ileus du nouveau-ne par epaississement du meconium. (A rare case of ileus in the newborn with inspissation of meconium). *Gynec et Obstet* 1938; 37:176-177.

A case of neonatal intestinal obstruction with pancreatic changes at autopsy. Almost certainly meconium ileus attributed to some abnormality in the secretions of the liver or pancreas.

1938 Thomas J, Schultz FW. Pancreatic steatorrhoea. *Am J Dis Child* 1938; 56:336-343.

This study from Chicago identified 10 previous reported cases of pancreatic steatorrhoea (Garrod & Hurlley, 1913; Miller & Perkins, 1920; Clarke & Hadfield, 1924; Harper, 1930; Siwe, 1932, Hess & Saphir, 1935; Parmalee, 1935 – all above). The authors report an emaciated boy who died aged five years with progressive chest infection and steatorrhoea. There was typical CF histology of an atrophic and markedly fibrosed pancreas. There is a footnote that Margaret Harper had published a report of 8 more cases since this present paper was submitted (Harper 1938, below)

Another author collecting examples of infants who had similar clinical and histological features and suggesting they had a specific condition.

The following three papers were regarded by di Sant'Agnes and Andersen in 1959 as simultaneously describing cystic fibrosis although, Dorothy Andersen's 1938 paper is usually taken as the first clear description of cystic fibrosis.

1938 Harper MH. Congenital steatorrhoea due to pancreatic defect. *Arch Dis Child* 1938; 13:45-56.

Further to her 1930 report of two children with steatorrhoea (Harper, 1930 above), Margaret Harper of Sydney reported a further eight children with features compatible with cystic fibrosis. Congenital steatorrhoea, abnormal glucose tolerance curves and characteristic pancreatic lesions in all the 4 who were autopsied; 8 of the 10 who died had bronchopneumonia. "The passage of fatty stools from birth (particularly "butter stools") with failure of nutrition, the diagnosis of congenital defect of the pancreas can reasonably be made".

Subsequently Margaret Harper reported 42 children with pancreatic steatorrhoea from the Royal Alexandra Hospital for Children, Sydney (Harper, 1949 below).

The orange-yellow oil in, on and around the stools is now recognised as a typical and frequent feature of untreated cystic fibrosis. The discussion in this paper reviews previous reported cases with particular emphasis on the characteristics of the stools. A visit to the ward sluice to inspect the stools of children on the ward was a usual part of the paediatric ward round even in the Sixties and considered to be an essential part of the full evaluation of an ill child just as was chemical testing and microscopy of the urine by the ward doctor.

1938 Andersen DH, Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. *Am J Dis Child* 1938; 56:344-399.

Although many infants had already been reported who, in hindsight, obviously had cystic fibrosis, this was the first clear detailed clinical and pathological description of a large series of affected infants in English. Dorothy Andersen reported 49 patients - 20 from her hospital and others from colleagues and the literature. She described the neonatal intestinal obstruction, intestinal and respiratory complications and many other features – but particularly the characteristic pancreatic

histology (figures:3 and 4). Salient points from the original description are as follows - "In 45 of the cases the pancreas presented a microscopic picture which is described by the term cystic fibrosis. The acini contain secretions of various sizes, and the acinar cells were flattened to form a thin epithelial wall around them. The smaller concretions were surrounded by relatively normal cells, which occasionally contained eosinophil granules.....The size of the cysts varied in each case but large ones were not often noted in the youngest infants. Surrounding the acini and also the lobules there were moderate to large amounts of fibrous tissue, the quantity varying roughly with the age of the child.....The islets of Langerhans were usually normal in number and appearance."

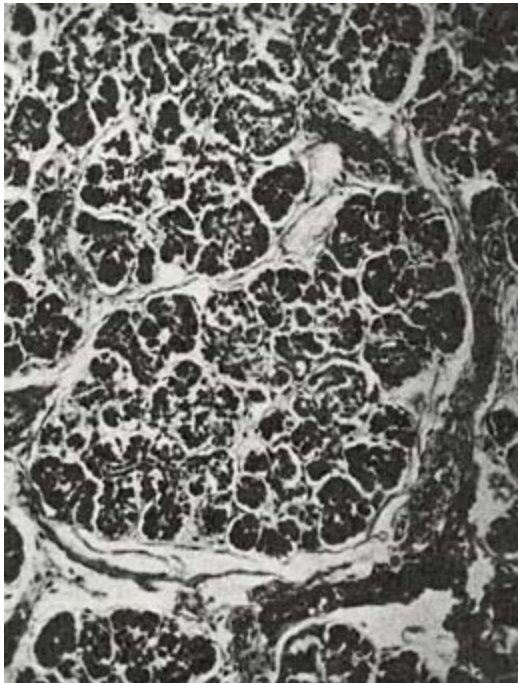


Figure 3: Pancreas of non-CF newborn aged 3 days. With permission.



Figure 4: Pancreas of CF newborn aged 6 days. With permission.

Andersen likened much of the epithelial histology to that found in vitamin A deficiency which for some years she regarded as the primary cause of the systemic features of the condition; this causation was never substantiated although she continued to support this theory for some years. The paper contains an excellent tabulated review of the previously reported cases and describing her paper Martin Bodian (1952 below) writes - "such a clear account of the symptoms that it enabled many cases to be recognised that had hitherto been missed, and aroused such interest that it was followed by a shoal of case reports and confirmatory reviews" which appeared during the Forties (many are described below).



Figure 5: Dorothy Andersen

Dorothy Andersen (1901-1963) (figure 5) was the pathologist at the Babies Hospital at the Columbia Presbyterian Medical Center in New York. She had a wide range of interests and made contributions in many other areas of medicine. She was said to be a rugged individualist, a paediatric clinician, pathologist, a research chemist – also apparently a roofer and carpenter, happy to make her own home improvements! Eventually over 600 children with CF were referred to her in New York; she involved Dr. Paul di Sant'Agnese, eventually another leader in the CF field, to provide paediatric care for her patients as she was primarily a pathologist. Dr Phillip Farrell of Wisconsin lists 4 reasons for the referral of so many children to her in New York. First was this seminal 1938 publication, second a combination of her reputation and her arrogance (she is alleged to have said she was the only person in the world who knew about cystic fibrosis in the late Thirties and Forties!), third the desperation of parents and fourth New York was the one place people could reach easily in those days. Described as "windblown"

(1901-1963). From Wikipedia.

by friends and detractors alike, Dorothy Andersen was considered quite a character. She is said to have kept a particularly untidy lab, holding semi-annual "glüg" parties there, in honour of her Scandinavian heritage. She was a niece of Hans Christian Andersen. She was a bright compassionate and sensitive scientist who was also a chain smoker and died of lung cancer at the age of 62 years.

In 1950 Milton Graub, a paediatrician who eventually became President of the US CF Foundation, suspected his two year old son had CF and describes how he called Dr Andersen on a Sunday morning and found her working in her laboratory. She listened to the medical history and saw his son the next day. The diagnosis was much more difficult and was made primarily on the clinical features plus analysis of the duodenal secretions. These were done and the diagnosis of cystic fibrosis of the pancreas was established. Since Dr Andersen was a pathologist she referred his son Lee for further clinical care to Dr Paul di Sant'Agnese. "He was a pediatric specialist and a delight – soft spoken, reassuring and supportive" (from Doershuk CF, 2001. below).

1938 Blackfan KD, May CD. Inspissation of secretion and dilatation of ducts and acini, atrophy and fibrosis of the pancreas in infants. A clinical note. J Pediatr 1938; 13:627-634.

Over a period of 15 years, examination of the pancreas in over 2,800 paediatric necropsies in Boston disclosed 35 examples of a well-defined pathologic lesion the existence of which was unsuspected during life. The lesion was characterised by inspissation of secretion, dilatation of the ducts and acini, atrophy and fibrosis. Only seven showed the stratified epithelium characteristic of vitamin A deficiency. The need for further information concerning the absorption of fat and especially nitrogen as well as pancreatic enzymes as an aid to diagnosis was suggested. The average age of death was 8 months.

Blackfan & Wolbach (1933 above) from a study of the lesion in the large amount of material available, in regard to pathogenesis, had observed "Our preliminary studies indicate that the pathogenesis of this striking pancreatic affection (figure 6) resides in the production of an abnormal secretion which inspissates and leads to distension and atrophy of the ducts and acini" (See also Blackfan & Wolbach, 1933 above; May CD 1943 below).

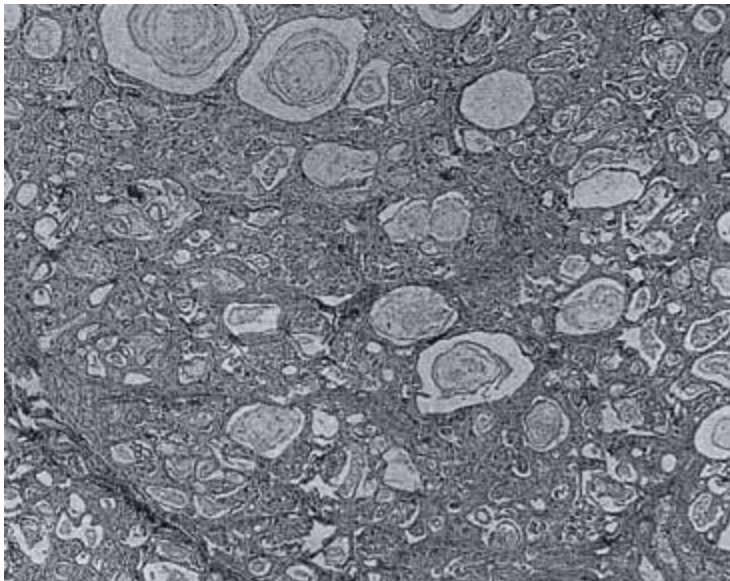


Figure 6: Pancreas - Inspissated secretion, dilation of the ducts and acini, atrophy and fibrosis. From paper with permission.

Dr. Charles D. May (1908 - 1992) was a paediatrician, an expert on childhood nutritional disorders and a leading figure in the United States paediatric world at the time. He qualified at Harvard Medical School in 1935. In World War II he served in the Army Medical Corps, returning to research at Harvard Medical School in 1946. May became an Associate Professor of Pediatrics at the University of Minnesota from 1947 to 1952, and subsequently held senior positions in Iowa, New York and Denver. He was succeeded as head of the Nutrition Clinic in Boston in 1947 by Harry Shwachman (of whom a great deal more later) who had worked with him before the war when May was the chief resident. Shwachman many years later recalled that "May's interest in CF was limited because he didn't have a laboratory...and he wrote a textbook on CF because he wanted to write down his experience before he left the clinic. He went to England with an army unit and gave a lot of lectures in London at Great Ormond Street Clinic in London. And Dr Norman who was in charge

of that clinic told me that he learned all he knew about CF from Dr May. And I had been May's right hand man for a number of years so it was logical that I take over the clinic when he left" (Fanos JH. 2008 Am J Med Genet Part A 146A:284-293).

It is likely that May gave the first lecture on CF in the UK at the Royal Society of Medicine during his time in the US army (May, 1943 below). Later he held the Chair of Pediatrics at the University of Iowa where later he chaired the first scientific meeting of the National CF Research Foundation in 1955 which was attended by most of the few US paediatricians involved in CF care. Also, around 1953, he was one of the clinicians to observe that *Pseudomonas aeruginosa* was usually involved when persisting pulmonary infection was present. According to Warren Warwick, May also authored seminal work on pancreatic enzymes.

1938 Davie TB. Massive replacement of the pancreas by adipose tissue. J Path Bact 1938; 46:473.

A severely retarded child who died at four years had massive fat replacement of the pancreas with sparing of the islands of Langerhans, considered to have been present since early infancy. Some patients with obstruction of the pancreatic ducts develop massive fat replacement and others show atrophy of the pancreas; it is not clear whether primarily due to obstruction of the pancreatic duct. The classical experiments of MacCallum ligating the pancreatic duct of dogs which eventually led to the isolation of insulin and the persistence of the islets were discussed (Banting & Best, 1922 above). Apparently liver failure is likely with massive fatty replacement if there is secondary infection. The author considers the present case supports the view that life can continue in the absence of exocrine pancreatic secretion.

1939 Andersen DH. Cystic fibrosis of the pancreas, vitamin A deficiency and bronchiectasis. J Pediatr 1939; 15:763-771.

This Mead Johnson Award lecture was presented before the American Academy in 1939. Dorothy Andersen's 1938 paper (above) was attracting considerable attention and here she describes how she became involved in the study. Andersen notes that pancreatic deficiency in childhood had been considered infrequent but believed it was the recognition rather than the disease that was unusual! Her interest had been aroused by a child considered to have coeliac disease yet who died of bronchopneumonia following an operation – at autopsy the pancreas was found to be composed of small and large cysts and a few tubules embedded in a mass of fibrous tissue. She became convinced that the pancreatic lesion was the cause of the symptoms and so began a search for similar cases. In 1000 autopsies at the Babies Hospital, New York, the pancreas had been examined in 650 and in 20 this showed evidence of fibrosis; most had died of pneumonia aged less than 6 months (comparable to 8 month age of death of Blackfan & May's series (1938 above). She obtained further cases from the literature and colleagues to a total of 49 which formed the basis of her 1938 seminal publication (Andersen, 1938 above).

Fourteen of the 49 children with CF that Andersen reported in 1938 showed histological evidence of vitamin A deficiency – in particular, epithelial changes characteristic of vitamin A deficiency. Also seven of 12 cases of vitamin A deficiency in the literature who had post mortems had pancreatic lesions (Blackfan & Wolbach, 1933 above).

For some years Andersen considered that many of the extra-gastrointestinal clinical manifestations of CF were due to vitamin A deficiency secondary to the severe malabsorption caused by the primary pancreatic abnormality. Andersen also emphasised the importance of demonstrating a very low titre or absence of trypsin from the duodenal juice in making the diagnosis. At this time the cause of the condition was quite unknown and the hereditary aspects had not yet been recognised.

1939 Rauch S, Litvak AM, Steiner M. Congenital familial steatorrhoea with fibromatosis of pancreas and bronchiolectasis. J Pediatr 1939; 14:462-490.

These authors wrote - "We propose to describe what we consider a clinical entity. Because of its apparent familial incidence, its congenital nature, its association with respiratory symptoms, and the post-mortem findings we suggest the term congenital familial steatorrhoea with fibromatosis of the pancreas and bronchiolectasis".

There is a very detailed report of previously reported cases with details of two new children who died aged seven months and two and a half years from bronchopneumonia. Post mortem on one showed the typical pancreatic changes of cystic fibrosis. The authors classified steatorrhoea into "idiopathic" which included true idiopathic celiac disease and the "pancreatogenous variety" as follows - "A review of the reported cases in the literature leaves the impression that steatorrhoea, excluding the acquired forms in adults of pancreatic inflammation or lithiasis, or those in which pathology of the lacteals is found, may be divided into idiopathic and pancreatogenous forms. The former includes celiac disease and sprue, tropical and non-tropical".

This paper was obviously published at the same time as Andersen's 1938 paper and the authors comment - "Since this paper was completed, the article of Dr Dorothy Andersen "Cystic fibrosis of the pancreas and its relation to celiac disease" (1938 above) and that of Dr John Thomas and Dr

FM Schultz "Pancreatic steatorrhoea" appeared in the August 1938 issue of the American Journal of Diseases of Children" (1938 above).

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