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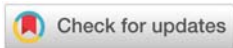
Received: 21 February, 2019

Accepted: 06 March, 2019

Published: 07 March, 2019

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Review Article

The History of Cystic Fibrosis

Abstract

Humans have died from CF for thousands of years, while, the first clear references to the disease extend back only a few centuries. It was recorded in popular ancient folklore from Northern Europe which ensured that if you kissed a child with a salty taste, it was said to be "hexed" and would die an early death.

In 1936 Professor Guido Fanconi established a relationship between celiac disease and cystic fibrosis of the pancreas and bronchiectasis and wrote about it in his work entitled "*Familial Pancreatic Cystic Fibromatosis with bronchiectasis*". Studying 47 families with patients suffering from this disease, Andersen and Hodges in 1946 concluded that for families, the situation was concordant with autosomal auto recessive inheritance.

Discovery of the sweat electrolyte defect in 1953 and standardization of the sweat test in 1959 allowed identification of milder cases. The pillars of care established then (attention to nutrition, airway clearance, treatment of lung infection) remain today.

In 1985, the gene for chromosome 7 was identified and at the end of the decade it was patent that CF was caused by poor functioning of the chloride channel dependent on cAMP. This was confirmed with the identification of the gene and its protein product (CFTR) in 1989 through the positional cloning of Lap-Chee Tsui and John Riordan (Toronto) on the same number of Science together with Francis S Collins (Michigan). In 1991, it was demonstrated that the protein CFTR forms a chloride canal and that it needs ATP hydrolysis to open. This afforded new diagnostic tests, opportunities for research, and prospects for using the gene as therapy.

In the 1980s, scientists discovered that poor functioning of the epithelial tissue was common for all organs affected by CF. Specifically, it revealed that the patients' epithelial were impermeable to the chloride ion [1]. In 1983, PM. Quinton [2], (University of California) explained that the reason for the salty sweat in patients with CF was due to the inability of the epithelial tissue to absorb chloride and as a result, it was impossible for sodium to be absorbed from the light of the conduit causing excessive retention of those ions in sweat leading to them being abnormally salty. By 1983, Quinton marked a change in the investigation of the disease with the discovery that the main issue with CF was a defective reabsorption of chloride at the level of the epithelial cells of the epithelial gland. [3]

In 1985, the gene for chromosome 7 [4] was identified and at the end of the decade it was patent that CF was caused by poor functioning of the chloride channel dependent on cAMP. This was confirmed with the identification of the gene and its protein product (CFTR) in 1989 through the positional cloning of Lap-Chee Tsui and John Riordan (Toronto) on the same number of Science [5-7] together with Francis S Collins (Michigan). In 1991, it was demonstrated that the protein CFTR forms a chloride canal [8] and that it needs ATP hydrolysis to open [9].

With the identification of the CFTR gene, new pathways of investigation have been opened [10] including the use of genetically modified rats in 1992 [11-13] and 1993 [14] and 1995 [15], as well as mutational studies and functional analyses of the CFTR protein in epithelial cells. It is important to highlight that the different murine models of CF have intestinal diseases but do not develop respiratory problems. However, there are two strains of rats that do show respiratory problems. In 1997, G. Kent et al., described the phenotype of a congenic strain of "knock-out" rats, a congenic strain of back-crossing that developed early pulmonary illnesses spontaneously and progressively characteristic of fibrosis, inflammation and problems with the mucociliary clearance [16]. More recently, one rat has been developed that specifically overexpresses the sodium ENaC canal in the respiratory epithelium to demonstrate that the transport of sodium per se may cause pulmonary illness similar to that of cystic fibrosis [17]. The increase in the absorption of sodium in these rats led to an increase in the concentration of mucus, which caused a severe and spontaneous pulmonary illness comparable to CF, with inflammation through neutrophils, obstruction of mucus and little bacterial elimination which makes these rats a better model for the study of pulmonary issues of CF.

Before the 20th century

Marvin J. Allison [18] (1921–2015), The North American doctor and paleopathologist, famous for his studies in Chile and the discovery that tuberculosis existed in pre-Columbian America, wrote in 1979 [19], that understanding the history of a disease leads to its reduction or even eradication.

The history of cystic fibrosis (CF) is as old as humankind [20]. Until its recognition as an entity within the medical community, deaths caused by CF were commonly attributed to different reasons and still may be in underdeveloped countries. Thus, the exact number of people with cystic fibrosis existing in the world today [21], remains a matter of speculation. A lack of adequate diagnoses and treatment also makes survival difficult and the number of carriers may continue to increase.

It is difficult to pinpoint the origin of CF because, as it is a genetic disease, it may have existed from the beginning of humanity. X. Estivill et al. [22], estimated that CF may have appeared in Europe some 52,000 years ago, even if the population was genetically different to our reality society.

Long before CF was recognised as a pathological entity, it was recorded in popular ancient folklore from Northern Europe which ensured that if you kissed a child with a salty taste, it was said to be “hexed” and would die an early death, as noted by Quinton [23]. Similarly, one German text written in the 15th century (Codex Latinus Monacensis 849) [24], – more of a grimoire or manual for necromancy and divination written in Latin – records the blessing “*Wider Elbe*” against the illnesses of “bewitched” children. The codex recommended licking the nose of the supposedly bewitched child to determine if it had a salty taste or not – *so sint es dyelbe*. This was the first written documentation relating a salty taste with a possible illness, commonly known today as cystic fibrosis.

In Spain, around the year 1606, a description related to this subject was found in literary medicine during the Spanish Golden Age written by Juan Alonso y de los Ruices de Fontecha, more commonly known as Juan Alonso de Fontecha (Daimiel, Ciudad Real, 1560– Alcalá de Henares, 1620). Fontecha was a Spanish doctor, obstetrician, pharmacologist and writer. During his time as a professor of medicine at the University of Alcalá, he wrote in his book entitled *Diez Privilegios para Mugeres Preñadas* [25], that one’s fingers would taste salty after rubbing the forehead of a bewitched child. Additional references to a salty taste and enchanted children can be seen in European literature during the 17th century.

The first macroscopic and pathological description of the process can most likely be attributed to the Dutch anatomist and botanist Peter Pauw (1564–1617). In Leiden, in the year 1595 during his time as rector at the University, he carried out an autopsy on an eleven-year-old girl and described the pancreas as enlarged, hardened and gleaming white in colour after having cut and opened it; he concluded that the cause of death was the pancreas. His work demonstrated the relationship between superstition or bewitchment and the organic cause of the disease. Additional documentation was recorded by the

Dutch anatomist Gerardus Leonardus Blasius (1627–1682), who in 1677 wrote in his book of strange observations [26], about the cirrhotic pancreas of a nine-year-old boy.

One of the very first “medical records” [27], was carried out by Georg Seger (Nuremberg 1629– 1678) in what is known today as Thorun, Poland in 1673. He gathered information on a three-year-old girl recording her fever, vomiting, diarrhoea, difficulties gaining weight and prolonged malnutrition. The autopsy of the small patient – practiced in the height of what was known as Gimnasium Anatomicum – showed a hardened and cirrhotic pancreas.

Nils Rosén von Rosenstein (1706, Sexdrega–1773, Uppsala), eminent Swedish paediatrician and professor in Uppsala in 1740, worked with C. Linnaeus in his book about childhood diseases in 1764 [28]. There he described a medical profile within the general section called “*Fluxus Coeliasus*” characterised by the presence of diarrhoea, dystrophy, weakness and a lack of improvement; however, those who were ill had a voracious appetite. He also described swelling in the hands and feet as well as a distended abdomen with a hardened pancreas. They were most likely all sick with CF. Among other developments, he introduced the use of quinine and variolation or immunization in Sweden against smallpox [29]. The works of N. Rosén were widely translated and his work entitled *The Diseases of Children and their Remedies* (1776) [30], was considered the first form of podiatry to be widely accepted and used.

Carl Von Rokitansky (1804, Hradec Králové, Bohemia – 1878, Vienna) –located in the thriving Vienna of 1838– described the results of one of the thousands of autopsies he practiced. This autopsy involved a seven-month-old foetus with no signs of postnatal life, in which he detected a perforation in the small intestine and a large presence of meconium in the peritoneum with an inflammatory reaction. This was presumably what is now known as Meconium Ileus. Rokitansky, founder and promoter of The Second Viennese Medical School, focused on using the scientific method, developed a method of autopsy known as the Rokitansky technique, which is still a standard method used today, based on an “in situ” examination of the viscera [31].

In 1850, Alois Bednar (1816, Potter stein, Bohemia–1888, Vienna) Austrian paediatrician and chief physician at the city orphanage in Vienna, as well as associate professor at the University, applied Rokitansky’s techniques to childhood illnesses and described a similar case in a new-born living child that died after six days of life [32]. Roughly coinciding in time, medical teams in England described and published similar information.

20th century

Controversy still exists today about who the first description of cystic fibrosis should be attributed to in the modern era. Following DA Christie and EM Tansey [33], Blackfan and Wolbach (1933) [34], were considered to have the first scientific description of cystic fibrosis in the 20th century. However, pancreatic illnesses and bronchiectasis were not attributed to

anything other than a Vitamin A deficiency. It was not until the year 1936, when Professor Guido Fanconi published an article entitled “*Das Coeliacum bei Angeborener zystischer Pancreasfibromatose und Bronchiektasen*” that a relationship was established between celiac disease and cystic fibrosis of the pancreas and bronchiectasis and wrote about it in his work entitled “*Familial Pancreatic Cystic Fibromatosis with bronchiectasis*” [35]. G. Fanconi (1892, Poschiavo, Suiza-1979, Zurich) developed his career as a paediatrician in the Children’s Hospital in Zurich; in 1934 the first case of cystic fibrosis of the pancreas was described, at least retrospectively, in a thesis written under his direction and almost a decade beforehand, in 1928, he published his observations concerning “celiac syndrome” in a group of children with digestive symptoms starting from breastfeeding and associative respiratory illness [36].

The first descriptive correlation between the practice and histopathology of cystic fibrosis as an independent entity was carried out by Dorothy Andersen, (Dorothy Hansine Andersen 1901, Asheville, North Carolina – 1963, New York) a pathologist at Columbia Presbyterian Medical Center in New York and professor. In 1938, she communicated in May (American Pediatric Society) and published in August a detailed review of the signs of the disease, including its association with meconium ileus calling it “*cystic fibrosis of the pancreas*” “*the diagnosis of cystic fibrosis of the pancreas can be made with certainty only by examining the duodenal contents for pancreatic enzymes or by microscopic examination of the pancreas*”. Even though it was still associated with a vitamin A deficiency [37]. This theory was sustained throughout many years without sufficient scientific evidence [38]. Her work was carried out on deceased patients at the Babies’ Hospital. The following year she made the first diagnosis in vivo on a patient with cystic fibrosis. This diagnosis was difficult for both patient and doctor because it was based on the quantification of pancreatic enzymes in duodenal secretions according to where the duodenal catheter was placed. In those days, the diagnosis was given based on the information already known, pancreatic insufficiency and chronic pulmonary involvement.

By 1944 it was clear for those few doctors that were interested that cystic fibrosis not only affected the pancreas, but it also affected other organs, such as the lungs, with exocrine solution. Therefore, the name was not entirely appropriate and Sidney Farber (1903, Buffalo – 1973, Boston), a professor of pathology at Harvard Medical School in Boston coined the term “mucoviscidosis” on his findings observed in the autopsies of deceased patients who had what was beginning to be called cystic fibrosis. He defined it as a systematic illness did not affect just one organ [39].

From that point on, it seemed evident that the bronchial “mucoviscidosis” had a lot to do with the pathogens in CF. A fortunate medical coincidence led to the development of new antibiotics at the end of the 1940s with the discovery of penicillin by Sir Alexander Fleming in 1929 [40]. At the time, he was working in St. Mary’s Hospital in London. Fleming discovered penicillin, but it was not available for clinical

use and was restricted on account of its difficulty for mass production until 1941.

Studying 47 families with patients suffering from this disease, Andersen and Hodges (1946) [41], concluded that for families, the situation was concordant with autosomal recessive inheritance. Although Andersen continued to believe “*the pulmonary infection is the result of the nutritional deficiency*”, this was the first time that a clear method was established, based on clinical evidence, that CF was a recessive illness according to Mendelian patterns.

In 1952, Bodian developed the pathogenic theory stating that lesions observed in the pancreas, lungs, liver and different channels were due to thick abnormal secretions that blocked the excretory pathways of the exocrine glands [42]. He described focal biliary cirrhosis for the first time, a pathognomonic lesion of CF in the liver.

1953 marked an important year for the understanding of CF with the detection of the abnormalities in sweat glands by Paul di Sant’Agnese. Di Sant’Agnese (1914–2005)– together with Harry Schwachman and Dorothy Andersen– founded the Cystic Fibrosis Foundation and Cystic Fibrosis Care in the United States at Columbia University Medical Center in New York. In 1946, he was also the first to use inhaled penicillin as a treatment of CF [43]. In 1949, there was a large heat wave that led to many patients with CF to suffer from dehydration with hypochloremic alkalosis and prostrations due to the loss of salt, especially those that were breastfeeding. Di Sant’Agnese– at the time working with Andersen as a pathologist– investigated the cause of these excessive losses and came to the conclusion that it was due to the abnormal elimination of chlorine through sweat. This led to the development in 1952 of what is still used today as a diagnostic test for CF, the test that quantifies electrolytes in sweat, known as the sweat test [44]. This opened the door for investigations to identify the main issue of the disease [45]. Before the discovery of this test, CF was diagnosed through duodenal intubation which demonstrated pancreatic insufficiencies in line with previous findings. The most effective method of diagnosing CF was by determining the amount of sodium in one’s sweat. Originally, patients underwent high temperatures to induce sweat, which was not without risk; however, in 1959, utilising *pilocarpine iontophoresis* designed by Gibson and Cook [46], this could be done safely. Lewis E. Gibson and Robert E. Cooke of the department of Paediatrics at Johns Hopkins Medical School published their findings in 1959. Gibson (1927–2008) joined R. Cooke’s team at Johns Hopkins and was subsequently the director of different study groups on CF until he retired from teaching paediatrics at Loyola University Stritch School of Medicine in Chicago and Director of his centre for CF in 1996. Robert Edmond Cooke (1920–2014) was a paediatrician deeply involved in American healthcare reform during both the John F. Kennedy administration– a close collaborator and friend of the family– and the Lyndon B. Johnson administration.

During the 50s and 60s, although the fundamental cause of the lesions was unknown, different clinical methods were set up. Shwachman (Boston, 1910–1986) was the first to publish

that 15% of patients did not have any pancreatic issues and established a system of ranking clinical severity [47], that is still used [48].

Newborns with meconium Ileus had a bleak prognostic as close to 50% died. The implementation and publication, in 1957 at The Children's Hospital of Philadelphia, used a technique called an ileostomy, developed by Bishop and Koop [49], which helped them to save many lives. A decade later in 1969, Doctor Helen Noblett (Royal Children's Hospital, Melbourne) utilised enemas of amidotrizoate meglumine (Gastrografin®) for uncomplicated meconium ileus, which led to the cure for children without having to undergo surgery [50].

Other advances in the field of pharmacology contributed to the survival of those who were ill such as penicillin resistant to beta-lactamase and the introduction of enteric-coated pancreatic enzymes that impede the inactivation of lipase because of chloric acid in the stomach.

The autosomal inheritance pattern of CF was clearly indicated by the group at Harvard in 1956, with Fred Allen as the geneticist [51] and verified by PM Connealy, in 1973 [52].

In the 1980s, scientists discovered that poor functioning of the epithelial tissue was common for all organs affected by CF. Specifically, it revealed that the patients' epithelial were impermeable to the chloride ion [53]. In 1983, PM. Quinton [54] (University of California) explained that the reason for the salty sweat in patients with CF was due to the inability of the epithelial tissue to absorb chloride and as a result, it was impossible for sodium to be absorbed from the light of the conduit causing excessive retention of those ions in sweat leading to them being abnormally salty. By 1983, Quinton marked a change in the investigation of the disease with the discovery that the main issue with CF was a defective reabsorption of chloride at the level of the epithelial cells of the epithelial gland [55].

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With the identification of the CFTR gene, new pathways of investigation have been opened [62] including the use of genetically modified rats in 1992 [63-65], and 1993 [66] and 1995 [67], as well as mutational studies and functional analyses of the CFTR protein in epithelial cells. It is important to highlight that the different murine models of CF have intestinal diseases but do not develop respiratory problems. However, there are two strains of rats that do show respiratory problems. In 1997, G. Kent et al. described the phenotype of a congenic strain of "knock-out" rats, a congenic strain of back-crossing that developed early pulmonary illnesses

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