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SPECIAL ARTICLE

# Historical compilation of cystic fibrosis☆

**Salvador Navarro**

*Retired senior consultant, Servicio de Gastroenterología, Institut de Malalties Digestives i Metabòliques, Hospital Clínic, Barcelona, Spain*

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**KEYWORDS**
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**Abstract** Cystic fibrosis is the most common life-shortening recessively inherited disorder in the Caucasian population. The genetic mutation that most frequently provokes cystic fibrosis (ΔF508) appeared at least 53,000 years ago. For many centuries, the disease was thought to be related to witchcraft and the ''evil eye'' and it was only in 1938 that Dorothy H. Andersen characterized this disorder and suspected its genetic origin. The present article reviews the pathological discoveries and diagnostic and therapeutic advances made in the last 75 years. The review ends with some considerations for the future.


**PALABRAS CLAVE**
Fibrosis quística;
Historia;
Prueba del sudor;
Terapia génica;
Trasplante pulmonar

## Recopilación histórica de la fibrosis quística

**Resumen** La fibrosis quística es la enfermedad con herencia autosómica recesiva más frecuente en la población caucásica que produce una merma de la vida. La mutación genética que más frecuentemente la provoca (ΔF508) parece que hizo su aparición hace unos 53.000 años. La enfermedad se relacionó durante siglos con la hechicería y el «mal de ojo», y no fue hasta 1938 en que Dorothy H. Andersen la describió como una entidad con personalidad propia y sospechó su origen genético. En este artículo se presenta una revisión de los descubrimientos fisiopatológicos y de los avances diagnósticos y terapéuticos que se han desarrollado a lo largo de estos tres cuartos de siglo. Finalmente, se plantean algunas consideraciones que deberán tenerse en cuenta en el futuro.


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*E-mail address:* 6119snc@comb.cat

## Introduction

Despite the low incidence—one in 2000–4000 live births—within the pancreatic pathology group, and although prevalence varies depending on ethnic background and region of origin, cystic fibrosis (CF) is the most common autosomal recessive genetic disease in the Caucasian population. It is the result of mutations in the cystic fibrosis transmembrane regulator gene (CFTR), which causes abnormally viscous secretions in the cells of different epithelia. Mutations in this gene, consisting of 27 exons, are located on the long arm of chromosome 7. Frequency in healthy carriers is considered to be 1/30,[1] giving some idea of the magnitude of the problem.

This multi-organ disease is classically characterized by a triad that includes lung impairment (chronic obstructive disease with bronchiectasis and repeated infections), pancreatic impairment (exocrine insufficiency) and abnormal sweat test results. It also has various other clinical manifestations, such as nasal polyps, azoospermia, chronic liver disease, cholelithiasis, diabetes mellitus and pancreatitis. Malnutrition and delayed growth are commonly observed in these patients. Up to 10–15% of neonates with CF have bowel obstruction at the level of the terminal ileum, a complication known as meconium ileus.

Although prognosis is difficult to establish, it has been improving over the years as its pathogenesis becomes better understood and different therapeutic advances—as will be discussed throughout this article—are applied. Thanks to these breakthroughs, patient survival improved from 14 to 20 years between 1968 and 1977. Nevertheless, a recent study has predicted that the average life expectancy in children born in 2010 and diagnosed with CF will be 37 years old for women and 40 years old for men, if the mortality rate observed during that year remains the same. However, it is speculated that survival could exceed 50 years if mortality continues to fall at an annual rate of 1.8%, as happened between 2000 and 2010.[2] These data indicate the importance that this disease will acquire among the adult population in the coming years, especially if we take into account that a number of less serious clinical forms are not suspected in childhood but are later diagnosed in adulthood.

Despite these favourable expectations, CF remains a cause of major suffering for both patients and their families, as it frequently results in prolonged hospitalization, significantly shortens life spans and often leads to death in very young individuals.[3]

## The evidence

According to the estimates of geneticist Xavier Estivill (1955; Barcelona, Spain), the antiquity of the most common mutation in CF (ΔF508) dates back some 53,000 years, while other less common mutations, such as G542X and N1303K, originated at least 35,000 years ago.[4] Thus, determining the origins of this disease requires its historical background to be examined.

The first suspected reference to the disease is in an Irish proverb from the end of the fifteenth century, which says: ''Woe to that child who tastes salty when kissed on the forehead. He is bewitched and soon must die''.[5] Such children were considered to be afflicted with the ''evil eye'' and it was assumed that they would die prematurely. In 1606, a reference to the disease also appeared in the book *Diez previlegios para mugeres preñadas*, by Juan Alonso y de los Ruyzes de Fontecha (1560–1620; Daimiel, Spain), professor of medicine at the University of Alcalá de Henares (Madrid, Spain) (Fig. 1).[6]

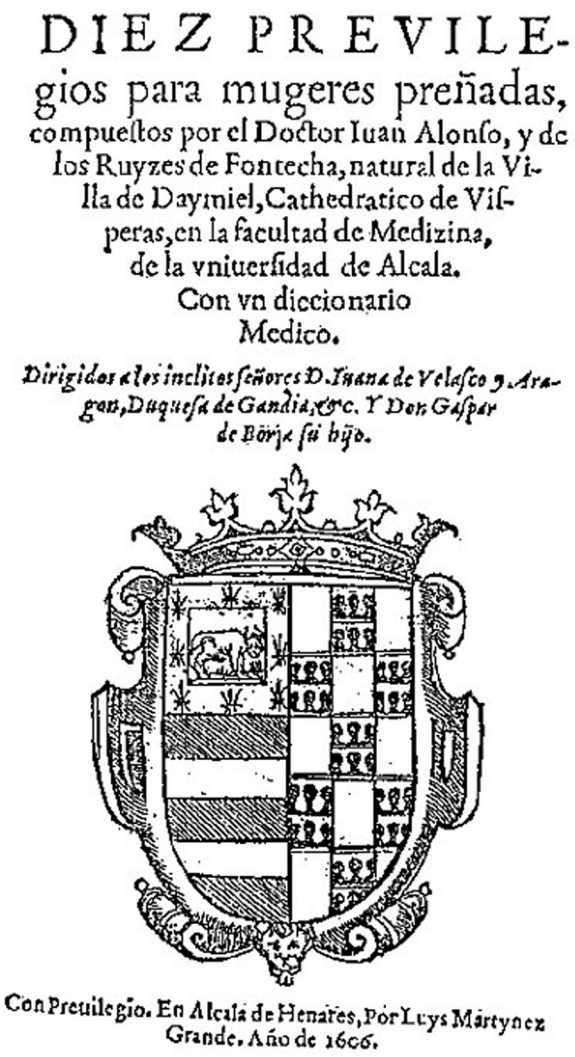
DIEZ PREVILE-
gios para mugeres preñadas,
compuestos por el Doctor Iuan Alonso, y de
los Ruyzes de Fontecha, natural de la Vi-
lla de Daymiel, Cathedratico de Vis-
peras, en la facultad de Medizina,
de la vniuersidad de Alcala.
Con vn diccionario
Medico.
Dirigidos a los inclites señores D. Iuana de Velasco y Ara-
gon, Duquesa de Gandia, &c. Y Don Gaspar
de Borja su hijo.
Con Preuilegio. En Alcalá de Henares, Por Luys Martynez
Grande. Año de 1606.

**Figure 1** Bookcover of *Diez previlegios para mugeres preñadas*, by Juan Alonso y de los Ruyzes de Fontecha (1560–1620; Daimiel, Spain), professor of medicine at the University of Alcalá de Henares (Madrid, Spain).

The first pathological description was probably made in 1595, when Pieter Pauw (1564–1617; Amsterdam, the Netherlands), professor of botany and anatomy at Leiden University, performed an autopsy on a supposedly bewitched 11-year-old girl, who had presented malnutrition and hectic fever for 8 years. In her abdomen he found a swollen pancreas, scirrhous and bright white in colour, and therefore considered that the cause of death had been the pancreas. He also observed signs of pericarditis, which, we know today, appear in certain cases of CF.[7] The second case was reported in 1673 by Georg Seger, who treated a 3-year-old girl in the city of Thorn (today Torun, Poland) for fever, vomiting and prolonged undernourishment. The autopsy was conducted by