Cystic fibrosis

Cystic fibrosis (**CF**) is a genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine.[1][5] Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections.[1] Other signs and symptoms may include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in most males.[1] Different people may have different degrees of symptoms.[1]

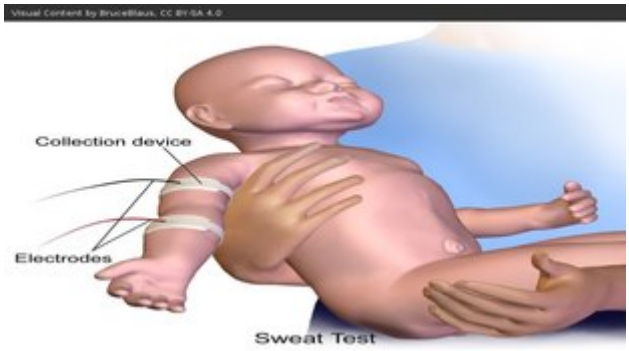
CF is inherited in an autosomal recessive manner.[1] It is caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[1] Those with a single working copy are carriers and otherwise mostly healthy.[3] CFTR is involved in the production of sweat, digestive fluids, and mucus.[6] When the CFTR is not functional, secretions which are usually thin instead become thick.[7] The condition is diagnosed by a sweat test and genetic testing.[1] Screening of infants at birth takes place in some areas of the world.[1]

There is no known cure for cystic fibrosis.[3] Lung infections are treated with antibiotics which may be given intravenously, inhaled, or by mouth.[1] Sometimes, the antibiotic azithromycin is used long term.[1] Inhaled hypertonic saline and salbutamol may also be useful.[1] Lung transplantation may be an option if lung function continues to worsen.[1] Pancreatic enzyme replacement and fat-soluble vitamin supplementation are important, especially in the young.[1] Airway clearance techniques such as chest physiotherapy have some short-term benefit, but long-term effects are unclear.[8] The average life expectancy is between 42 and 50 years in the developed world.[4][9] Lung problems are responsible for death in 80% of people with cystic fibrosis.[1]

Cystic fibrosis	
Other names	Mucoviscidosis
 Clubbing in the fingers of a person with cystic fibrosis	
Specialty	Medical genetics, pulmonology
Symptoms	Difficulty breathing, coughing up mucus, poor growth, fatty stool[1]
Usual onset	Symptoms recognizable ~6 month[2]
Duration	Life long[3]
Causes	Genetic (autosomal recessive)[1]
Diagnostic method	Sweat test, genetic testing[1]
Treatment	Antibiotics, pancreatic enzyme replacement, lung transplantation[1]
Prognosis	Life expectancy between 42 and 50 years (developed world)[4]
Frequency	1 in 3,000 (Northern European)[1]

CF is most common among people of Northern European ancestry and affects about one out of every 3,000 newborns.[1] About one in 25 people is a carrier.[3] It is least common in Africans and Asians.[1] It was first recognized as a specific disease by Dorothy Andersen in 1938, with descriptions that fit the condition occurring at least as far back as 1595.[5] The name "cystic fibrosis" refers to the characteristic fibrosis and cysts that form within the pancreas.[5][10]

Contents



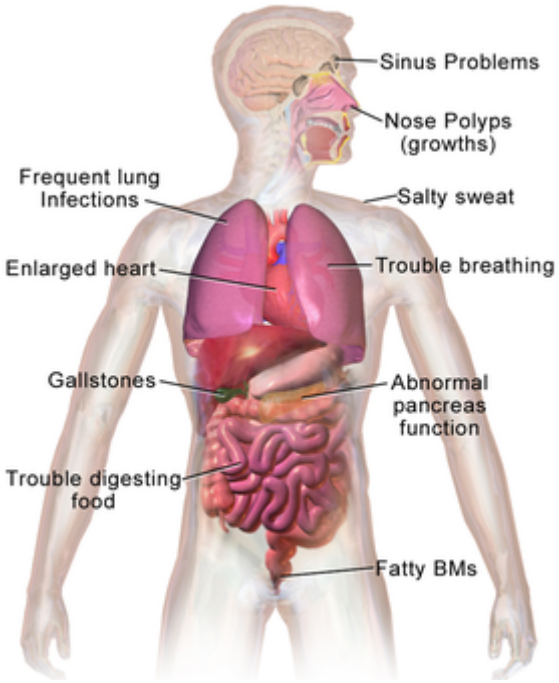
Play media

Video summary (script)

Signs and symptoms

The main signs and symptoms of cystic fibrosis are salty-tasting skin,[11] poor growth, and poor weight gain despite normal food intake,[12] accumulation of thick, sticky mucus,[13] frequent chest infections, and coughing or shortness of breath.[14] Males can be infertile due to congenital absence of the vas deferens.[15] Symptoms often appear in infancy and childhood, such as bowel obstruction due to meconium ileus in newborn babies.[16]

As the children grow, they exercise to release mucus in the alveoli.[17] Epithelial cells in the person have a mutated protein that leads to abnormally viscous mucus production.[13] The poor growth in children typically presents as an inability to gain weight or height at the same rate as their peers, and is occasionally not diagnosed until investigation is initiated for poor growth. The causes of growth failure are multifactorial and include chronic lung infection, poor absorption of nutrients through the gastrointestinal tract, and increased metabolic demand due to chronic illness.[12]

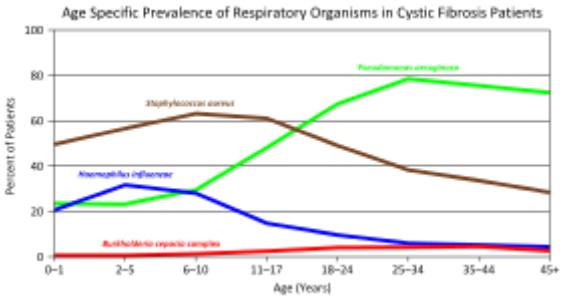


Health problems associated with cystic fibrosis

In rare cases, cystic fibrosis can manifest itself as a coagulation disorder. Vitamin K is normally absorbed from breast milk, formula, and later, solid foods. This absorption is impaired in some cystic fibrosis patients. Young children are especially sensitive to vitamin K malabsorptive disorders because only a very small amount of vitamin K crosses the placenta, leaving the child with very low reserves and limited ability to absorb vitamin K from dietary sources after birth. Because factors II, VII, IX, and X (clotting factors) are vitamin K–dependent, low levels of vitamin K can result in coagulation problems. Consequently, when a child presents with unexplained bruising, a coagulation evaluation may be warranted to determine whether an underlying disease is present.[18]

Lungs and sinuses

Lung disease results from clogging of the airways due to mucus build-up, decreased mucociliary clearance, and resulting inflammation.[19][20] Inflammation and infection cause injury and structural changes to the lungs, leading to a variety of symptoms. In the early stages, incessant coughing, copious phlegm production, and decreased ability to exercise are common. Many of these symptoms occur when bacteria that normally inhabit the thick mucus grow out of control and cause pneumonia.



Respiratory infections in CF varies according to age.

Green = *Pseudomonas aeruginosa*
Brown = *Staphylococcus aureus*
Blue = *Haemophilus influenzae*
Red = *Burkholderia cepacia* complex

In later stages, changes in the architecture of the lung, such as pathology in the major airways (bronchiectasis), further exacerbate difficulties in breathing. Other signs include coughing up blood (hemoptysis), high blood pressure in the lung (pulmonary hypertension), heart failure, difficulties getting enough oxygen to the body (hypoxia), and respiratory failure requiring support with breathing masks, such as bilevel positive airway pressure machines or ventilators.[21] *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are the three most common organisms causing lung infections in CF patients.[20] The most common infection involves bacterial strain mutation to form a biofilm-forming and sustaining mucoid

strain on the lung epithelium, which can result in downstream mechanisms that progress the infection.[22] In addition to typical bacterial infections, people with CF more commonly develop other types of lung disease.

Among these is allergic bronchopulmonary aspergillosis, in which the body's response to the common fungus *Aspergillus fumigatus* causes worsening of breathing problems. Another is infection with *Mycobacterium avium* complex, a group of bacteria related to tuberculosis, which can cause lung damage and does not respond to common antibiotics.[23] People with CF are susceptible to getting a pneumothorax.[24]

Mucus in the paranasal sinuses is equally thick and may also cause blockage of the sinus passages, leading to infection. This may cause facial pain, fever, nasal drainage, and headaches. Individuals with CF may develop overgrowth of the nasal tissue (nasal polyps) due to inflammation from chronic sinus infections.[25] Recurrent sinonasal polyps can occur in 10% to 25% of CF patients.[20] These polyps can block the nasal passages and increase breathing difficulties.[26][27]

Cardiorespiratory complications are the most common cause of death (about 80%) in patients at most CF centers in the United States.[20]

Gastrointestinal

Prior to prenatal and newborn screening, cystic fibrosis was often diagnosed when a newborn infant failed to pass feces (meconium). Meconium may completely block the intestines and cause serious illness. This condition, called meconium ileus, occurs in 5–10%[20] of newborns with CF. In addition, protrusion of internal rectal membranes (rectal prolapse) is more common, occurring in as many as 10% of children with CF,[20] and it is caused by increased fecal volume, malnutrition, and increased intra–abdominal pressure due to coughing.[28]

The thick mucus seen in the lungs has a counterpart in thickened secretions from the pancreas, an organ responsible for providing digestive juices that help break down food. These secretions block the exocrine movement of the digestive enzymes into the duodenum and result in irreversible damage to the pancreas, often with painful inflammation (pancreatitis).[29] The pancreatic ducts are totally plugged in more advanced cases, usually seen in older children or adolescents.[20] This causes atrophy of the exocrine glands and progressive fibrosis.[20]

The lack of digestive enzymes leads to difficulty absorbing nutrients with their subsequent excretion in the feces, a disorder known as malabsorption. Malabsorption leads to malnutrition and poor growth and development because of calorie loss. Resultant hypoproteinemia may be severe enough to cause generalized edema.[20] Individuals with CF also have difficulties absorbing the fat-soluble vitamins A, D, E, and K.[30]

In addition to the pancreas problems, people with cystic fibrosis experience more heartburn,[30] intestinal blockage by intussusception, and constipation.[31] Older individuals with CF may develop distal intestinal obstruction syndrome when thickened feces cause intestinal blockage.[30]

Exocrine pancreatic insufficiency occurs in the majority (85% to 90%) of patients with CF.[20] It is mainly associated with "severe" CFTR mutations, where both alleles are completely nonfunctional (e.g. ΔF508/ΔF508).[20] It occurs in 10% to 15% of patients with one "severe" and one "mild" CFTR mutation where little CFTR activity still occurs, or where two "mild" CFTR mutations exist.[20] In these milder

cases, sufficient pancreatic exocrine function is still present so that enzyme supplementation is not required.[20] Usually, no other GI complications occur in pancreas-sufficient phenotypes, and in general, such individuals usually have excellent growth and development.[20] Despite this, idiopathic chronic pancreatitis can occur in a subset of pancreas-sufficient individuals with CF, and is associated with recurrent abdominal pain and life-threatening complications.[20]

Thickened secretions also may cause liver problems in patients with CF. Bile secreted by the liver to aid in digestion may block the bile ducts, leading to liver damage. Over time, this can lead to scarring and nodularity (cirrhosis). The liver fails to rid the blood of toxins and does not make important proteins, such as those responsible for blood clotting.[32][33] Liver disease is the third-most common cause of death associated with CF.[20]

Endocrine

The pancreas contains the islets of Langerhans, which are responsible for making insulin, a hormone that helps regulate blood glucose. Damage of the pancreas can lead to loss of the islet cells, leading to a type of diabetes unique to those with the disease.[34] This cystic fibrosis-related diabetes shares characteristics that can be found in type 1 and type 2 diabetics, and is one of the principal nonpulmonary complications of CF.[35]

Vitamin D is involved in calcium and phosphate regulation. Poor uptake of vitamin D from the diet because of malabsorption can lead to the bone disease osteoporosis in which weakened bones are more susceptible to fractures.[36] In addition, people with CF often develop clubbing of their fingers and toes due to the effects of chronic illness and low oxygen in their tissues.[37][38]

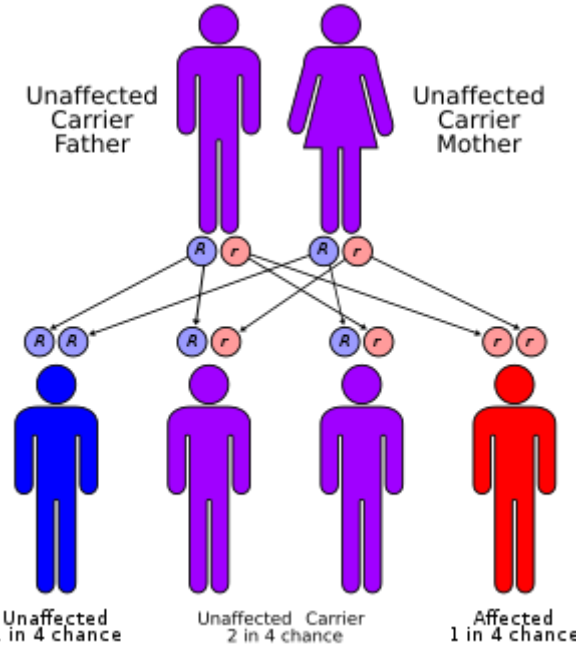
Infertility

Infertility affects both men and women. At least 97% of men with cystic fibrosis are infertile, but not sterile and can have children with assisted reproductive techniques.[39] The main cause of infertility in men with CF is congenital absence of the vas deferens (which normally connects the testes to the ejaculatory ducts of the penis), but potentially also by other mechanisms such as causing no sperm, abnormally shaped sperm, and few sperm with poor motility.[40] Many men found to have congenital absence of the vas deferens during evaluation for infertility have a mild, previously undiagnosed form of CF.[41] Around 20% of women with CF have fertility difficulties due to thickened cervical mucus or malnutrition. In severe cases, malnutrition disrupts ovulation and causes a lack of menstruation.[42]

Causes

CF is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator (*CFTR*). The most common mutation, ΔF508, is a deletion (Δ signifying deletion) of three nucleotides[43] that results in a loss of the amino acid phenylalanine (F) at the 508th position on the protein. This mutation accounts for two-thirds (66–70%[20]) of CF cases worldwide and 90% of cases in the United States; however, over 1500 other mutations can produce CF.[44] Although most people have two working copies (alleles) of the *CFTR* gene, only one is needed to prevent cystic fibrosis. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is considered an autosomal recessive disease.[45]

The *CFTR* gene, found at the q31.2 locus of chromosome 7, is 230,000 base pairs long, and creates a protein that is 1,480 amino acids long. More specifically, the location is between base pair 117,120,016 and 117,308,718 on the long arm of chromosome 7, region 3, band 1, subband 2, represented as 7q31.2. Structurally, the *CFTR* is a type of gene known as an ABC gene. The product of this gene (the CFTR protein) is a chloride ion channel important in creating sweat, digestive juices, and mucus. This protein possesses two ATP-hydrolyzing domains, which allows the protein to use energy in the form of ATP. It also contains two domains comprising six alpha helices apiece, which allow the protein to cross the cell membrane. A regulatory binding site on the protein allows activation by phosphorylation, mainly by cAMP-dependent protein kinase.[21] The carboxyl terminal of the protein is anchored to the cytoskeleton by a PDZ domain interaction.[46] The majority of CFTR in the lung's passages is produced by rare ion-transporting cells that regulate mucus properties.[47]



Cystic fibrosis has an autosomal recessive pattern of inheritance

In addition, the evidence is increasing that genetic modifiers besides *CFTR* modulate the frequency and severity of the disease. One example is mannan-binding lectin, which is involved in innate immunity by facilitating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease, as well as an increased burden of chronic bacterial infections.[20]

Carriers

Up to 1 in 25 individuals of Northern European ancestry is considered a genetic carrier. The disease appears only when two of these carriers have children, as each pregnancy between them will have a 25% chance of producing a child with the disease. Although only about 1 of every 3,000 Caucasian newborns has CF, there are more than 900 known mutations of the gene that causes CF. Current tests look for the most common mutations.[48]

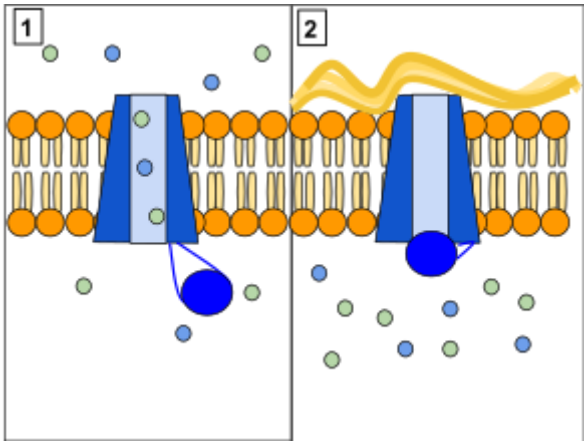
The mutations screened by the test vary according to a person's ethnic group or by the occurrence of CF already in the family. More than 10 million Americans, including 1 in 25 Caucasian Americans, are carriers of one mutation of the CF gene. CF is present in other races, though not as frequently as in Caucasian individuals. 1 in 46 Hispanic Americans, 1 in 65 African Americans, and 1 in 90 Asian Americans carry a mutation of the CF gene.[48]

Pathophysiology

Several mutations in the *CFTR* gene can occur, and different mutations cause different defects in the CFTR protein, sometimes causing a milder or more severe disease. These protein defects are also targets for drugs which can sometimes restore their function. ΔF508-CFTR, which occurs in >90% of patients in

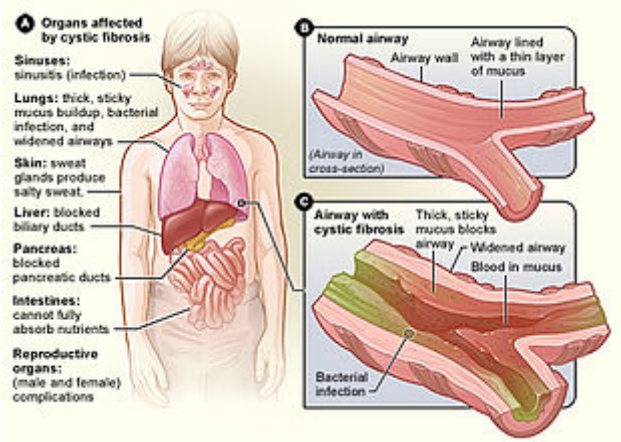
the U.S., creates a protein that does not fold normally and is not appropriately transported to the cell membrane, resulting in its degradation.

Other mutations result in proteins that are too short (truncated) because production is ended prematurely. Other mutations produce proteins that do not use energy (in the form of ATP) normally, do not allow chloride, iodide, and thiocyanate to cross the membrane appropriately,[49] and degrade at a faster rate than normal. Mutations may also lead to fewer copies of the CFTR protein being produced.[21]



The CFTR protein is a channel protein that controls the flow of H_2O and Cl^- ions in and out of cells inside the lungs. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the buildup of thick mucus in the lungs.

The protein created by this gene is anchored to the outer membrane of cells in the sweat glands, lungs, pancreas, and all other remaining exocrine glands in the body. The protein spans this membrane and acts as a channel connecting the inner part of the cell (cytoplasm) to the surrounding fluid. This channel is primarily responsible for controlling the movement of halogens from inside to outside of the cell; however, in the sweat ducts, it facilitates the movement of chloride from the sweat duct into the cytoplasm. When the CFTR protein does not resorb ions in sweat ducts, chloride and thiocyanate[50] released from sweat glands are trapped inside the ducts and pumped to the skin.



Additionally hypothiocyanite, OSCN, cannot be produced by the immune defense system.[51][52] Because chloride is negatively charged, this modifies the electrical potential inside and outside the cell that normally causes cations to cross into the cell. Sodium is the most common cation in the extracellular space. The excess chloride within sweat ducts prevents sodium resorption by epithelial sodium channels and the combination of sodium and chloride creates the salt, which is lost in high amounts in the sweat of individuals with CF. This lost salt forms the basis for the sweat test.[21]

Most of the damage in CF is due to blockage of the narrow passages of affected organs with thickened secretions. These blockages lead to remodeling and infection in the lung, damage by accumulated digestive enzymes in the pancreas, blockage of the intestines by thick feces, etc. Several theories have been posited on how the defects in the protein and cellular function cause the clinical effects. The most current theory suggests that defective ion transport leads to dehydration in the airway epithelia, thickening mucus. In airway epithelial cells, the cilia exist in between the cell's apical surface and mucus in a layer known as airway surface liquid (ASL). The flow of ions from the cell and into this layer is determined by ion channels such as CFTR. CFTR not only allows chloride ions to be drawn from the cell

and into the ASL, but it also regulates another channel called ENac, which allows sodium ions to leave the ASL and enter the respiratory epithelium. CFTR normally inhibits this channel, but if the CFTR is defective, then sodium flows freely from the ASL and into the cell.

As water follows sodium, the depth of ASL will be depleted and the cilia will be left in the mucous layer.[53] As cilia cannot effectively move in a thick, viscous environment, mucociliary clearance is deficient and a buildup of mucus occurs, clogging small airways.[54] The accumulation of more viscous, nutrient-rich mucus in the lungs allows bacteria to hide from the body's immune system, causing repeated respiratory infections. The presence of the same CFTR proteins in the pancreatic duct and sweat glands in the skin also cause symptoms in these systems.

Chronic infections

The lungs of individuals with cystic fibrosis are colonized and infected by bacteria from an early age. These bacteria, which often spread among individuals with CF, thrive in the altered mucus, which collects in the small airways of the lungs. This mucus leads to the formation of bacterial microenvironments known as biofilms that are difficult for immune cells and antibiotics to penetrate. Viscous secretions and persistent respiratory infections repeatedly damage the lung by gradually remodeling the airways, which makes infection even more difficult to eradicate.[55]

Over time, both the types of bacteria and their individual characteristics change in individuals with CF. In the initial stage, common bacteria such as *S. aureus* and *H. influenzae* colonize and infect the lungs.[20] Eventually, *Pseudomonas aeruginosa* (and sometimes *Burkholderia cepacia*) dominates. By 18 years of age, 80% of patients with classic CF harbor *P. aeruginosa*, and 3.5% harbor *B. cepacia*.[20] Once within the lungs, these bacteria adapt to the environment and develop resistance to commonly used antibiotics. *Pseudomonas* can develop special characteristics that allow the formation of large colonies, known as "mucoid" *Pseudomonas*, which are rarely seen in people who do not have CF.[55] Scientific evidences suggest the interleukin 17 pathway plays a key role in resistance and modulation of the inflammatory response during *P. aeruginosa* infection in CF.[56] In particular, interleukin 17-mediated immunity plays a double-edged activity during chronic airways infection; on one side, it contributes to the control of *P. aeruginosa* burden, while on the other, it propagates exacerbated pulmonary neutrophilia and tissue remodeling.[56]

Infection can spread by passing between different individuals with CF.[57] In the past, people with CF often participated in summer "CF camps" and other recreational gatherings.[58][59] Hospitals grouped patients with CF into common areas and routine equipment (such as nebulizers)[60] was not sterilized between individual patients.[61] This led to transmission of more dangerous strains of bacteria among groups of patients. As a result, individuals with CF are now routinely isolated from one another in the healthcare setting, and healthcare providers are encouraged to wear gowns and gloves when examining patients with CF to limit the spread of virulent bacterial strains.[62]

CF patients may also have their airways chronically colonized by filamentous fungi (such as *Aspergillus fumigatus*, *Scedosporium apiospermum*, *Aspergillus terreus*) and/or yeasts (such as *Candida albicans*); other filamentous fungi less commonly isolated include *Aspergillus flavus* and *Aspergillus nidulans* (occur transiently in CF respiratory secretions) and *Exophiala dermatitidis* and *Scedosporium prolificans* (chronic airway-colonizers); some filamentous fungi such as *Penicillium emersonii* and *Acrophialophora fusispora* are encountered in patients almost exclusively in the context of CF.[63] Defective mucociliary clearance characterizing CF is associated with local immunological disorders. In addition, the prolonged

therapy with antibiotics and the use of corticosteroid treatments may also facilitate fungal growth. Although the clinical relevance of the fungal airway colonization is still a matter of debate, filamentous fungi may contribute to the local inflammatory response and therefore to the progressive deterioration of the lung function, as often happens with allergic bronchopulmonary aspergillosis – the most common fungal disease in the context of CF, involving a Th2-driven immune response to *Aspergillus* species.[63][64]

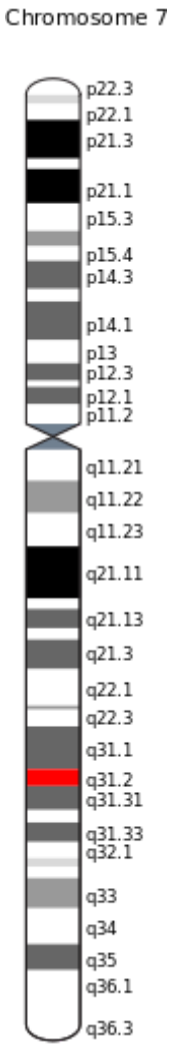
Diagnosis

Cystic fibrosis may be diagnosed by many different methods, including newborn screening, sweat testing, and genetic testing.[65] As of 2006 in the United States, 10% of cases are diagnosed shortly after birth as part of newborn screening programs. The newborn screen initially measures for raised blood concentration of immunoreactive trypsinogen.[66] Infants with an abnormal newborn screen need a sweat test to confirm the CF diagnosis.

In many cases, a parent makes the diagnosis because the infant tastes salty.[20] Immunoreactive trypsinogen levels can be increased in individuals who have a single mutated copy of the *CFTR* gene (carriers) or, in rare instances, in individuals with two normal copies of the *CFTR* gene. Due to these false positives, CF screening in newborns can be controversial.[67][68]

Most U.S. states and countries do not screen for CF routinely at birth. Therefore, most individuals are diagnosed after symptoms (e.g. sinopulmonary disease and GI manifestations[20]) prompt an evaluation for cystic fibrosis. The most commonly used form of testing is the sweat test. Sweat testing involves application of a medication that stimulates sweating (pilocarpine). To deliver the medication through the skin, iontophoresis is used, whereby one electrode is placed onto the applied medication and an electric current is passed to a separate electrode on the skin. The resultant sweat is then collected on filter paper or in a capillary tube and analyzed for abnormal amounts of sodium and chloride. People with CF have increased amounts of them in their sweat. In contrast, people with CF have less thiocyanate and hypothiocyanite in their saliva[69] and mucus (Banfi et al.). In the case of milder forms of CF, transepithelial potential difference measurements can be helpful. CF can also be diagnosed by identification of mutations in the CFTR gene.[70]

People with CF may be listed in a disease registry that allows researchers and doctors to track health results and identify candidates for clinical trials.[71]



The location of the *CFTR* gene on chromosome 7

Prenatal

Women who are pregnant or couples planning a pregnancy can have themselves tested for the *CFTR* gene mutations to determine the risk that their child will be born with CF. Testing is typically performed first on one or both parents and, if the risk of CF is high, testing on the fetus is performed. The American College of Obstetricians and Gynecologists recommends all people thinking of becoming pregnant be tested to see if they are a carrier.[72]

Because development of CF in the fetus requires each parent to pass on a mutated copy of the *CFTR* gene and because CF testing is expensive, testing is often performed initially on one parent. If testing shows that parent is a *CFTR* gene mutation carrier, the other parent is tested to calculate the risk that their children will have CF. CF can result from more than a thousand different mutations.[45] As of 2016, typically only the most common mutations are tested for, such as ΔF508[45] Most commercially available tests look for 32 or fewer different mutations. If a family has a known uncommon mutation, specific screening for that mutation can be performed. Because not all known mutations are found on current tests, a negative screen does not guarantee that a child will not have CF.[73]

During pregnancy, testing can be performed on the placenta (chorionic villus sampling) or the fluid around the fetus (amniocentesis). However, chorionic villus sampling has a risk of fetal death of one in 100 and amniocentesis of one in 200;[74] a recent study has indicated this may be much lower, about one in 1,600.[75]

Economically, for carrier couples of cystic fibrosis, when comparing preimplantation genetic diagnosis (PGD) with natural conception (NC) followed by prenatal testing and abortion of affected pregnancies, PGD provides net economic benefits up to a maternal age around 40 years, after which NC, prenatal testing, and abortion have higher economic benefit.[76]

Management

While no cures for CF are known, several treatment methods are used. The management of CF has improved significantly over the past 70 years. While infants born with it 70 years ago would have been unlikely to live beyond their first year, infants today are likely to live well into adulthood. Recent advances in the treatment of cystic fibrosis have meant that individuals with cystic fibrosis can live a fuller life less encumbered by their condition. The cornerstones of management are the proactive treatment of airway infection, and encouragement of good nutrition and an active lifestyle. Pulmonary rehabilitation as a management of CF continues throughout a person's life, and is aimed at maximizing organ function, and therefore the quality of life. At best, current treatments delay the decline in organ function. Because of the wide variation in disease symptoms, treatment typically occurs at specialist multidisciplinary centers and is tailored to the individual. Targets for therapy are the lungs, gastrointestinal tract (including pancreatic enzyme supplements), the reproductive organs (including assisted reproductive technology), and psychological support.[66]

The most consistent aspect of therapy in CF is limiting and treating the lung damage caused by thick mucus and infection, with the goal of maintaining quality of life. Intravenous, inhaled, and oral antibiotics are used to treat chronic and acute infections. Mechanical devices and inhalation medications are used to alter and clear the thickened mucus. These therapies, while effective, can be extremely time-consuming. Oxygen therapy at home is recommended in those with significant low oxygen levels.[77]

Antibiotics

Many people with CF are on one or more antibiotics at all times, even when healthy, to prophylactically suppress infection. Antibiotics are absolutely necessary whenever pneumonia is suspected or a noticeable decline in lung function is seen, and are usually chosen based on the results of a sputum analysis and the person's past response. This prolonged therapy often necessitates hospitalization and insertion of a more permanent IV such as a peripherally inserted central catheter or Port-a-Cath. Inhaled therapy with antibiotics such as tobramycin, colistin, and aztreonam is often given for months at a time to improve

lung function by impeding the growth of colonized bacteria.[78][79][80] Inhaled antibiotic therapy helps lung function by fighting infection, but also has significant drawbacks such as development of antibiotic resistance, tinnitus, and changes in the voice.[81] Inhaled levofloxacin may be used to treat *Pseudomonas aeruginosa* in people with cystic fibrosis who are infected.[82] The early management of Pseudomonas aeruginosa infection is easier and better, using nebulised antibiotics with or without oral antibiotics may sustain its eradication up to 2 years.[83]

Antibiotics by mouth such as ciprofloxacin or azithromycin are given to help prevent infection or to control ongoing infection.[84] The aminoglycoside antibiotics (e.g. tobramycin) used can cause hearing loss, damage to the balance system in the inner ear or kidney failure with long-term use.[85] To prevent these side-effects, the amount of antibiotics in the blood is routinely measured and adjusted accordingly.

All these factors related to the antibiotics use, the chronicity of the disease, and the emergence of resistant bacteria demand more exploration for different strategies such as antibiotic adjuvant therapy.[86] No trials have been published that examine the effectiveness of antibiotics for pulmonary exacerbations is people with cystic fibrosis and Burkholderia cepacia complex.[87]

Other medication

Aerosolized medications that help loosen secretions include dornase alfa and hypertonic saline.[88] Dornase is a recombinant human deoxyribonuclease, which breaks down DNA in the sputum, thus decreasing its viscosity.[89] Dornase alpha improves lung function and probably decreases the risk of exacerbations but there is insufficient evidence to know if it is more or less effective than other similar medications.[90] Denufosol, an investigational drug, opens an alternative chloride channel, helping to liquefy mucus.[91] Whether inhaled corticosteroids are useful is unclear, but stopping inhaled corticosteroid therapy is safe.[92] There is weak evidence that corticosteroid treatment may cause harm by interfering with growth.[92] Pneumococcal vaccination has not been studied as of 2014.[93] As of 2014, there is no clear evidence from randomized controlled trials that the influenza vaccine is beneficial for people with cystic fibrosis.[94]

Ivacaftor is a medication taken by mouth for the treatment of CF due to a number of specific mutations responsive to ivacaftor-induced CFTR protein enhancement.[95][96] It improves lung function by about 10%; however, as of 2014 it is expensive.[95] The first year it was on the market, the list price was over $300,000 per year in the United States.[95] In July 2015, the U.S. Food and Drug Administration approved lumacaftor/ivacaftor.[97] In 2018, the FDA approved the combination ivacaftor/tezacaftor; the manufacturer announced a list price of $292,000 per year.[98] Tezacaftor helps move the CFTR protein to the correct position on the cell surface, and is designed to treat people with the F508del mutation.[99]

In 2019, the combination elexacaftor/ivacaftor/tezacaftor was approved for CF in the United States.[100] It is used in those that have a f508del mutation.[100] The list price in the US is going to be $311,000 per year.[101]

Ursodeoxycholic acid, a bile salt, has been used, but an updated Cochrane review concluded there was insufficient data to show if it was useful.[102]

Procedures

Several mechanical techniques are used to dislodge sputum and encourage its expectoration. One technique is chest physiotherapy where a respiratory therapist percusses an individual's chest by hand several times a day, to loosen up secretions. This "percussive effect" can be administered also through specific devices that device chest wall oscillation or intrapulmonary percussive ventilator. Other methods such as biphasic cuirass ventilation, and associated clearance mode available in such devices, integrate a cough assistance phase, as well as a vibration phase for dislodging secretions. These are portable and adapted for home use. Chest physiotherapy is beneficial for short-term airway clearance.[8]

Another technique is positive expiratory pressure physiotherapy that consists of providing a back pressure to the airways during expiration. This effect is provided by devices that consists of a mask or a mouthpiece in which a resistance is applied only on the expiration phase.[103] Operating principles of this technique seems to be the increase of gas pressure behind mucus through collateral ventilation along with a temporary increase in functional residual capacity preventing the early collapse of small airways during exhalation.[104][105]

As lung disease worsens, mechanical breathing support may become necessary. Individuals with CF may need to wear special masks at night to help push air into their lungs. These machines, known as bilevel positive airway pressure (BiPAP) ventilators, help prevent low blood oxygen levels during sleep. Non-invasive ventilators may be used during physical therapy to improve sputum clearance.[106] It is not known if this type of therapy has an impact on pulmonary exacerbations or disease progression.[106] It is not known what role non-invasive ventilation therapy has for improving exercise capacity in people with cystic fibrosis.[106] During severe illness, a tube may be placed in the throat (a procedure known as a tracheostomy) to enable breathing supported by a ventilator.

For children, preliminary studies show massage therapy may help people and their families' quality of life.[107]

Some lung infections require surgical removal of the infected part of the lung. If this is necessary many times, lung function is severely reduced.[108] The most effective treatment options for people with CF who have spontaneous or recurrent pneumothoraces is not clear.[24]

Transplantation

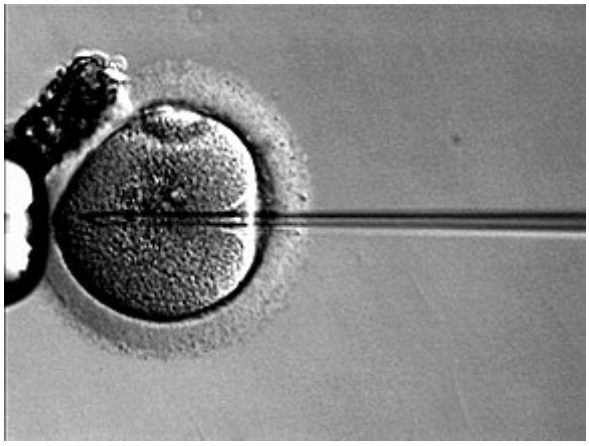
Lung transplantation often becomes necessary for individuals with CF as lung function and exercise tolerance decline. Although single lung transplantation is possible in other diseases, individuals with CF must have both lungs replaced because the remaining lung might contain bacteria that could infect the transplanted lung. A pancreatic or liver transplant may be performed at the same time to alleviate liver disease and/or diabetes.[109] Lung transplantation is considered when lung function declines to the point where assistance from mechanical devices is required or someone's survival is threatened.[110]

Other aspects

Newborns with intestinal obstruction typically require surgery, whereas adults with distal intestinal obstruction syndrome typically do not. Treatment of pancreatic insufficiency by replacement of missing digestive enzymes allows the duodenum to properly absorb nutrients and vitamins that would otherwise be lost in the feces. However, the best dosage and form of pancreatic enzyme replacement is unclear, as are the risks and long-term effectiveness of this treatment.[111]

So far, no large-scale research involving the incidence of atherosclerosis and coronary heart disease in adults with cystic fibrosis has been conducted. This is likely because the vast majority of people with cystic fibrosis do not live long enough to develop clinically significant atherosclerosis or coronary heart disease.

Diabetes is the most common nonpulmonary complication of CF. It mixes features of type 1 and type 2 diabetes, and is recognized as a distinct entity, cystic fibrosis-related diabetes.[35][112] While oral antidiabetic drugs are sometimes used, the recommended treatment is the use of insulin injections or an insulin pump,[113] and, unlike in type 1 and 2 diabetes, dietary restrictions are not recommended.[35]



Intracytoplasmic sperm injection can be used to provide fertility for men with cystic fibrosis

There is no strong evidence that people with cystic fibrosis can prevent osteoporosis by increasing their intake of vitamin D.[114] Bisphosphonates taken by mouth or intravenously can be used to improve the bone mineral density in people with cystic fibrosis.[115] When taking bisphosphates intravenously, adverse effects such as pain and flu-like symptoms can be an issue.[115] The adverse effects of bisphosphates taken by mouth on the gastrointestinal tract are not known.[115]

Poor growth may be avoided by insertion of a feeding tube for increasing food energy through supplemental feeds or by administration of injected growth hormone.[116]

Sinus infections are treated by prolonged courses of antibiotics. The development of nasal polyps or other chronic changes within the nasal passages may severely limit airflow through the nose, and over time reduce the person's sense of smell. Sinus surgery is often used to alleviate nasal obstruction and to limit further infections. Nasal steroids such as fluticasone propionate are used to decrease nasal inflammation.[117]

Female infertility may be overcome by assisted reproduction technology, particularly embryo transfer techniques. Male infertility caused by absence of the vas deferens may be overcome with testicular sperm extraction, collecting sperm cells directly from the testicles. If the collected sample contains too few sperm cells to likely have a spontaneous fertilization, intracytoplasmic sperm injection can be performed.[118] Third party reproduction is also a possibility for women with CF. Whether taking antioxidants affects outcomes is unclear.[119]

Physical exercise is usually part of outpatient care for people with cystic fibrosis.[120] Aerobic exercise seems to be beneficial for aerobic exercise capacity, lung function and health-related quality of life; however, the quality of the evidence was poor.[120]

Prognosis

The prognosis for cystic fibrosis has improved due to earlier diagnosis through screening and better treatment and access to health care. In 1959, the median age of survival of children with CF in the United States was six months.[121] In 2010, survival is estimated to be 37 years for women and 40 for men.[122]

In Canada, median survival increased from 24 years in 1982 to 47.7 in 2007.[123] In the United States those born with CF in 2016 have an expected life expectancy of 47.7 when cared for in specialty clinics.[124]

In the US, of those with CF who are more than 18 years old as of 2009, 92% had graduated from high school, 67% had at least some college education, 15% were disabled, 9% were unemployed, 56% were single, and 39% were married or living with a partner.[125]

Quality of life

Chronic illnesses can be very difficult to manage. CF is a chronic illness that affects the "digestive and respiratory tracts resulting in generalized malnutrition and chronic respiratory infections".[126] The thick secretions clog the airways in the lungs, which often cause inflammation and severe lung infections.[127][128] If it is compromised, it affects the quality of life (QOL) of someone with CF and their ability to complete such tasks as everyday chores.

According to Schmitz and Goldbeck (2006), CF significantly increases emotional stress on both the individual and the family, "and the necessary time-consuming daily treatment routine may have further negative effects on quality of life".[129] However, Havermans and colleagues (2006) have shown that young outpatients with CF who have participated in the Cystic Fibrosis Questionnaire-Revised "rated some QOL domains higher than did their parents".[130] Consequently, outpatients with CF have a more positive outlook for themselves.

Furthermore, many ways can improve the QOL in CF patients. Exercise is promoted to increase lung function. Integrating an exercise regimen into the CF patient's daily routine can significantly improve QOL.[131] No definitive cure for CF is known, but diverse medications are used, such as mucolytics, bronchodilators, steroids, and antibiotics, that have the purpose of loosening mucus, expanding airways, decreasing inflammation, and fighting lung infections, respectively.[132]

Epidemiology

Cystic fibrosis is the most common life-limiting autosomal recessive disease among people of European heritage.[134] In the United States, about 30,000 individuals have CF; most are diagnosed by six months of age. In Canada, about 4,000 people have CF.[135] Around 1 in 25 people of European descent, and one in 30 of Caucasian Americans,[136] is a carrier of a CF mutation. Although CF is less common in these groups, roughly one in 46 Hispanics, one in 65 Africans, and one in 90 Asians carry at least one abnormal *CFTR* gene.[137][138] Ireland has the world's highest prevalence of CF, at one in 1353.[139]

Mutation	Frequency worldwide[133]
ΔF508	66%–70%[20]
G542X	2.4%
G551D	1.6%
N1303K	1.3%
W1282X	1.2%
All others	27.5%

Although technically a rare disease, CF is ranked as one of the most widespread life-shortening genetic diseases. It is most common among nations in the Western world. An exception is Finland, where only one in 80 people carries a CF mutation.[140] The World Health Organization states, "In the European Union, one in 2000–3000 newborns is found to be affected by CF".[141] In the United States, one in 3,500 children is born with CF.[142] In 1997, about one in 3,300

Caucasian children in the United States was born with CF. In contrast, only one in 15,000 African American children suffered from it, and in Asian Americans, the rate was even lower at one in 32,000.[143]

Cystic fibrosis is diagnosed in males and females equally. For reasons that remain unclear, data have shown that males tend to have a longer life expectancy than females,[144][145] but recent studies suggest this gender gap may no longer exist perhaps due to improvements in health care facilities,[146][147] while a recent study from Ireland identified a link between the female hormone estrogen and worse outcomes in CF.[148]

The distribution of CF alleles varies among populations. The frequency of ΔF508 carriers has been estimated at one in 200 in northern Sweden, one in 143 in Lithuanians, and one in 38 in Denmark. No ΔF508 carriers were found among 171 Finns and 151 Saami people.[149] ΔF508 does occur in Finland, but it is a minority allele there. CF is known to occur in only 20 families (pedigrees) in Finland.[150]

Evolution

The ΔF508 mutation is estimated to be up to 52,000 years old.[151] Numerous hypotheses have been advanced as to why such a lethal mutation has persisted and spread in the human population. Other common autosomal recessive diseases such as sickle-cell anemia have been found to protect carriers from other diseases, an evolutionary trade-off known as heterozygote advantage. Resistance to the following have all been proposed as possible sources of heterozygote advantage:

- Cholera: With the discovery that cholera toxin requires normal host CFTR proteins to function properly, it was hypothesized that carriers of mutant *CFTR* genes benefited from resistance to cholera and other causes of diarrhea.[152] Further studies have not confirmed this hypothesis.[153][154]
- Typhoid: Normal CFTR proteins are also essential for the entry of *Salmonella* Typhi into cells,[155] suggesting that carriers of mutant *CFTR* genes might be resistant to typhoid fever. No *in vivo* study has yet confirmed this. In both cases, the low level of cystic fibrosis outside of Europe, in places where both cholera and typhoid fever are endemic, is not immediately explicable.
- Diarrhea: The prevalence of CF in Europe might be connected with the development of cattle domestication. In this hypothesis, carriers of a single mutant *CFTR* had some protection from diarrhea caused by lactose intolerance, before the mutations that created lactose tolerance appeared.[156]
- Tuberculosis: Another possible explanation is that carriers of the gene could have some resistance to tuberculosis.[157][158] This hypothesis is based on the thesis that *CFTR* gene mutation carriers have insufficient action in one of their enzymes – arylsulphatase - which is necessary for *Mycobacterium tuberculosis* virulence. As *M. tuberculosis* would use its host's sources to affect the individual, and due to the lack of enzyme it could not presents its virulence, being a carrier of *CFTR* mutation could provide resistance against tuberculosis.[159]

History

CF is supposed to have appeared about 3,000 BC because of migration of peoples, gene mutations, and new conditions in nourishment.[160] Although the entire clinical spectrum of CF was not recognized until the 1930s, certain aspects of CF were identified much earlier. Indeed, literature from Germany and Switzerland in the 18th century warned "*Wehe dem Kind, das beim Kuß auf die Stirn salzig schmeckt, es*

Dorothy Hansine Andersen first described cystic fibrosis in 1938.

ist verhext und muss bald sterben" or "Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon must die", recognizing the association between the salt loss in CF and illness.[160]

In the 19th century, Carl von Rokitansky described a case of fetal death with meconium peritonitis, a complication of meconium ileus associated with CF. Meconium ileus was first described in 1905 by Karl Landsteiner.[160] In 1936, Guido Fanconi described a connection between celiac disease, cystic fibrosis of the pancreas, and bronchiectasis.[161]

In 1938, Dorothy Hansine Andersen published an article, "Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: a Clinical and Pathological Study", in the *American Journal of Diseases of Children*. She was the first to describe the characteristic cystic fibrosis of the pancreas and to correlate it with the lung and intestinal disease prominent in CF.[10] She also first hypothesized that CF was a recessive disease and first used pancreatic enzyme replacement to treat affected children. In 1952, Paul di Sant'Agnese discovered abnormalities in sweat electrolytes; a sweat test was developed and improved over the next decade.[162]

The first linkage between CF and another marker (Paroxonase) was found in 1985 by Hans Eiberg, indicating that only one locus exists for CF. In 1988, the first mutation for CF, ΔF508 was discovered by Francis Collins, Lap-Chee Tsui, and John R. Riordan on the seventh chromosome. Subsequent research has found over 1,000 different mutations that cause CF.

Because mutations in the *CFTR* gene are typically small, classical genetics techniques had been unable to accurately pinpoint the mutated gene.[163] Using protein markers, gene-linkage studies were able to map the mutation to chromosome 7. Chromosome walking and chromosome jumping techniques were then used to identify and sequence the gene.[164] In 1989, Lap-Chee Tsui led a team of researchers at the Hospital for Sick Children in Toronto that discovered the gene responsible for CF. CF represents a classic example of how a human genetic disorder was elucidated strictly by the process of forward genetics.

Research

Gene therapy

Gene therapy has been explored as a potential cure for CF. Results from clinical trials have shown limited success as of 2016, and using gene therapy as routine therapy is not suggested.[165] A small study published in 2015 found a small benefit.[166]

The focus of much CF gene therapy research is aimed at trying to place a normal copy of the *CFTR* gene into affected cells. Transferring the normal *CFTR* gene into the affected epithelium cells would result in the production of functional CFTR protein in all target cells, without adverse reactions or an inflammation response. To prevent the lung manifestations of CF, only 5–10% the normal amount of CFTR gene expression is needed.[167] Multiple approaches have been tested for gene transfer, such as liposomes and viral vectors in animal models and clinical trials. However, both methods were found to be

relatively inefficient treatment options,[168] mainly because very few cells take up the vector and express the gene, so the treatment has little effect. Additionally, problems have been noted in cDNA recombination, such that the gene introduced by the treatment is rendered unusable.[169] There has been a functional repair in culture of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients.[170]

Phage therapy

Phage therapy is being studied for multidrug resistant bacteria in people with CF.[171][172]

Gene modulators

A number of small molecules that aim at compensating various mutations of the *CFTR* gene are under development. CFTR modulator therapies have been used in place of other types of genetic therapies. These therapies focus on the expression of a genetic mutation instead of the mutated gene itself. Modulators are split into two classes: potentiators and correctors. Potentiators act on the CFTR ion channels that are embedded in the cell membrane, and these types of drugs help open up the channel to allow transmembrane flow. Correctors are meant to assist in the transportation of nascent proteins, a protein that is formed by ribosomes before it is morphed into a specific shape, to the cell surface to be implemented into the cell membrane.[173]

Most target the transcription stage of genetic expression. One approach has been to try and develop medication that get the ribosome to overcome the stop codon and produce a full-length CFTR protein. About 10% of CF results from a premature stop codon in the DNA, leading to early termination of protein synthesis and truncated proteins. These drugs target nonsense mutations such as G542X, which consists of the amino acid glycine in position 542 being replaced by a stop codon. Aminoglycoside antibiotics interfere with protein synthesis and error-correction. In some cases, they can cause the cell to overcome a premature stop codon by inserting a random amino acid, thereby allowing expression of a full-length protein. Future research for these modulators is focused on the cellular targets that can be effected by a change in a gene's expression. Otherwise, genetic therapy will be used as a treatment when modulator therapies do not work given that 10% of people with cystic fibrosis are not effected by these drugs.[174]

Elexacaftor/ivacaftor/tezacaftor was approved in the United States in 2019 for cystic fibrosis.[175] This combination of previously developed medicines is able to treat up to 90% of people with cystic fibrosis.[173][175] This medications restores some effectiveness of the CFTR protein so that it can work as an ion channel on the cell's surface..[176]

Society and culture

- *Sick: The Life and Death of Bob Flanagan, Supermasochist*, a 1997 documentary film
- *65_Redroses*, a 2009 documentary film
- *Breathing for a Living*, a memoir by Laura Rothenberg
- *Every Breath I Take, Surviving and Thriving With Cystic Fibrosis*, book by Claire Wineland
- *Five Feet Apart*, a 2019 romantic drama film starring Cole Sprouse and Haley Lu Richardson

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External links

- Cystic fibrosis (https://curlie.org/Health/Conditions_and_Diseases/Genetic_Disorders/Cystic_Fibrosis/) at Curlie
- *cf (https://www.ncbi.nlm.nih.gov/books/br.fcgi?book=gene&part=cf)* at NIH/UW GeneTests
- Search GeneCards for genes involved in cystic fibrosis (https://www.genecards.org/cgi-bin/cardsearch.pl?search=cystic+fibrosis&search_type=kwd&mini=yes&speed=fast#results)
- Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/app)

Classification	**ICD-10**: E84 (http://apps.who.int/classifications/icd10/browse/2016/en#/E84) · **ICD-9-CM**: 277.0 (http://www.icd9data.com/getICD9Code.ashx?icd9=277.0) · **OMIM**: 219700 (https://omim.org/entry/219700) · **MeSH**:

	D003550 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D003550) · **DiseasesDB**: 3347 (http://www.diseasesdatabase.com/ddb3347.htm) · **SNOMED CT**: 190905008 (http://snomed.info/id/190905008)
External resources	**MedlinePlus**: 000107 (https://www.nlm.nih.gov/medlineplus/ency/article/000107.htm) · **eMedicine**: article/1001602 (https://emedicine.medscape.com/article/1001602-overview) · **Patient UK**: Cystic fibrosis (https://patient.info/doctor/cystic-fibrosis-pro) · CFTR-Related Disorders (https://www.ncbi.nlm.nih.gov/books/n/gene/NBK1250/) · **Orphanet**: 586 (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=586)