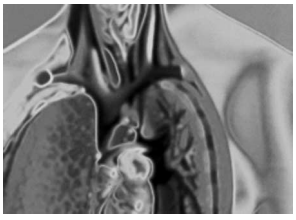
CHAPTER 10



Cystic Fibrosis

Introduction

Cystic fibrosis is the most common potentially lethal inherited disease of white people. **It affects about 1 in 2500 live births** in the UK and is inherited in an autosomal recessive manner. About **1 in 25 of the population is a carrier** of the disease.

The basic defect

Cystic fibrosis is a result of a defect in a gene on the long arm of chromosome 7 which codes for a 1480-amino-acid protein, named **cystic fibrosis transmembrane conductance regulator (CFTR)**. More than 800 mutations of this gene have been identified but the most common is designated ΔF508, in which mutation of a single codon of the gene results in the loss of phenylalanine ('delta F') at position 508 of the protein. CFTR functions as a **chloride channel** in the membrane of epithelial cells and the primary physiological defect in cystic fibrosis is reduced chloride conductance at epithelial membranes, most notably in the respiratory, gastrointestinal, pancreatic, hepatobiliary and reproductive tracts. In sweat ducts, failure of reabsorption of chloride ions results in elevated concentrations of chloride and sodium in the sweat, a characteristic feature of the disease and the basis for the sweat test used in diagnosis.

Lungs

In the bronchial mucosa failure of chloride transport results in **secretions of abnormal viscosity** which interfere with mucociliary clearance mechanisms and the **high salt content** of airway surface fluid **inactivates defensins** which are naturally occurring antimicrobial peptides on the epithelial surface. There is some evidence that the CFTR also has a role in the normal uptake and processing of *Pseudomonas aeruginosa* from the respiratory tract. Patients with cystic fibrosis also have abnormal mucus glycoproteins which act as binding sites such that **bacteria adhere to the mucosa** and proliferate. Thus, the gene defect results in dysfunction of CFTR and predisposes to severe chronic lung infection by a variety of mechanism at the cellular level. The inflammatory response is unable to clear the infection and a vicious cycle of **infection** and **inflammation** develops, progressing to lung damage, **bronchiectasis**, **respiratory failure** and **death**.

Gastrointestinal tract

In the **pancreas** the abnormal ion transport results in the plugging and obstruction of ductules with progressive destruction of the gland. The pancreatic enzymes (e.g. lipase) fail to reach the small intestine and this results in **malabsorption** of fats with steatorrhoea and failure to gain weight. Progressive destruction of the endocrine pancreas may cause **diabetes**. Abnor-

malities of bile secretion and absorption cause an increased incidence of **gallstones** and **biliary cirrhosis**. Sludging and desiccation of intestinal contents probably accounts for the occurrence of **meconium ileus** (neonatal intestinal obstruction) in about 10% of babies with cystic fibrosis, and for the development of **distal intestinal obstruction syndrome** (meconium ileus equivalent) in older children and adults.

Clinical features (Fig. 10.1)

Infants and young children

About 10% of children with cystic fibrosis present at birth with **meconium ileus**, a form of intestinal obstruction caused by inspissated viscid faecal material resulting from lack of pancreatic enzymes and from reduced intestinal water secretion. More than half of children affected by cystic fibrosis have obvious malabsorption by the age of 6 months with **failure to thrive** associated with abdominal distension and copious offensive stools from **steatorrhoea** as a result of malabsorbed fat. **Rectal prolapse** occasionally occurs. Recurrent **respiratory infections** rapidly become a prominent feature with cough, sputum production and wheeze.

Older children and adults

Respiratory disease (Fig. 10.2)

Persistent cough and purulent sputum characterise the development of **bronchiectasis**. Progressive lung damage is associated with the development of digital clubbing and progressive **airways obstruction**, sometimes associated with wheeze. Serial measurements of forced expiratory volume in 1 second (FEV_1) give an indication of the severity and progression of the disease. Some patients show a significant asthmatic component with reversible airways obstruction and some develop colonisation of the bronchi by *Aspergillus fumigatus* and may show features of allergic bronchopulmonary aspergillosis (see Chapter 9). Initially, the typical organisms isolated in sputum cultures are ***Staphylococcus aureus***, *Haemophilus influenzae* and *Streptococcus pneumoniae*. By teenage years many have become infected with mucoid strains of ***Pseudomonas aeruginosa***. ***Burkholderia cepacia*** is a Gram-negative plant pathogen which causes onion rot. It was initially thought that this organism was not pathogenic to humans but in the 1980s it became apparent that patients with cystic fibrosis were vulnerable to this bacterium and that infection could spread from patient to patient in an epidemic way, particularly amongst children with cystic fibrosis in close social contact in holiday camps, for example. The clinical course of patients with *Burkholderia cepacia* infection is very variable but some show an accelerated rate of decline in lung function and some develop a fulminant necrotising pneumonia, the so-called **'cepacia syndrome'** (Fig. 10.3). It is now recognised that there are many different strains of this bacterium but *Burkholderia cepacia* genomovar III is associated with the worst prognosis. Because of the potential for transmission of infection between patients with cystic fibrosis it is now standard practice to segregate patients with different infections such that they attend different clinics and wards, and social contact between patients with cystic fibrosis is discouraged.

As the cycle of infection and inflammation progresses, lung damage worsens with deteriorating airways obstruction, destruction of lung parenchyma, impairment of gas exchange and the development of **hypoxaemia**, **hypercapnia** and **cor pulmonale**. The persistent pulmonary inflammation provokes hypertrophy of the bronchial arteries, and **haemoptysis** becomes common. Occasionally, when severe bleeding occurs, therapeutic embolisation of the bronchial arteries may be required. **Pneumothorax** occurs in about 5–10% of patients with advanced disease and may require prompt tube drainage. Pleurodesis may be required for recurrent pneumothoraces but this should be performed with care so as not to compromise future potential lung transplantation.

Gastrointestinal disease

About 85% of patients with cystic fibrosis have

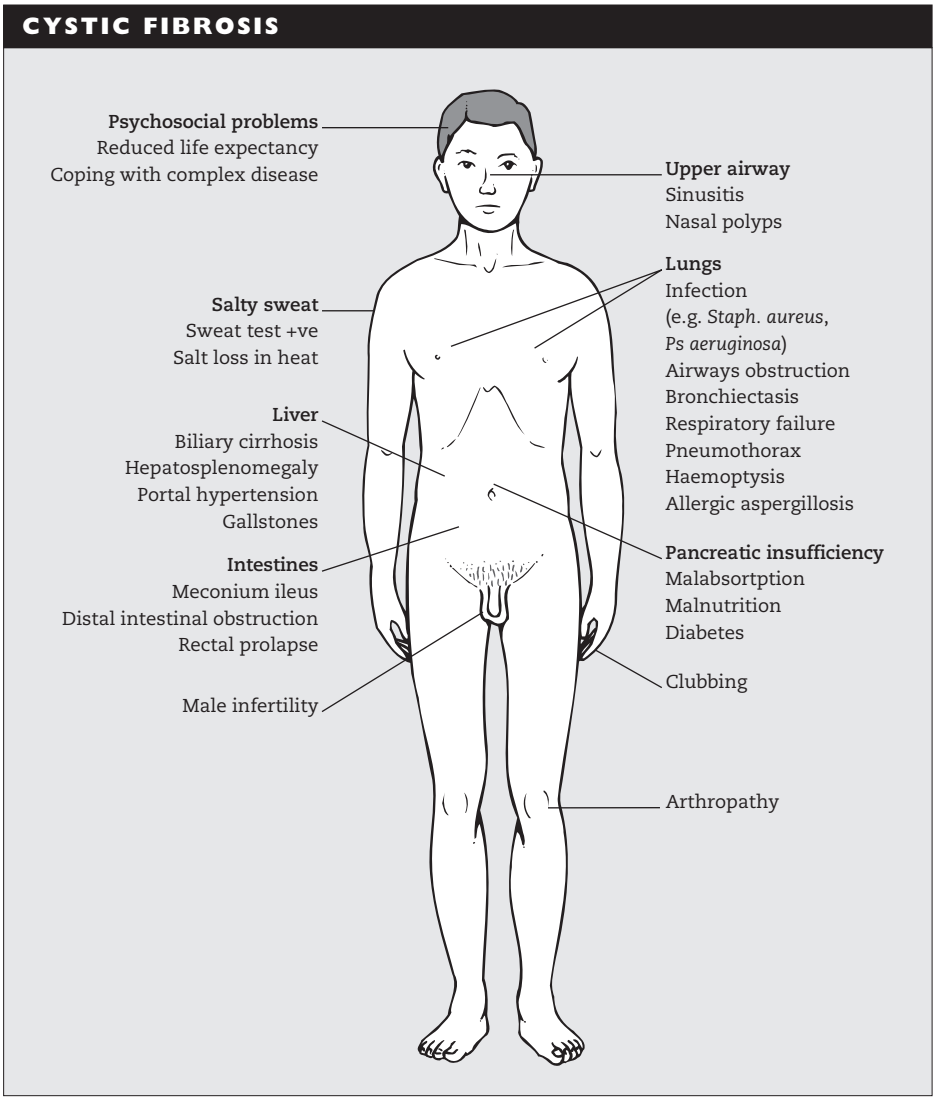


Fig. 10.1 Clinical features of cystic fibrosis. Cystic fibrosis is a multisystem disease resulting from mutations of the gene which codes for a protein, cystic fibrosis transmembrane conductance regulator (CFTR), which functions as a chloride channel on epithelial membranes. Failure of chloride conductance results in abnormal secretions and organ damage in the respiratory, pancreatic, hepatobiliary, gastrointestinal and reproductive tracts.

pancreatic insufficiency with **malabsorption of fat** because of lack of lipase. Unless these patients receive adequate pancreatic enzyme supplements they develop steatorrhoea with frequent bulky offensive stools and failure to gain weight. Progressive destruction of the endocrine pancreas is manifest by an increasing incidence of **diabetes** as these patients get older. A variety of **hepatobiliary abnormalities** occur including fatty liver, gallstones and

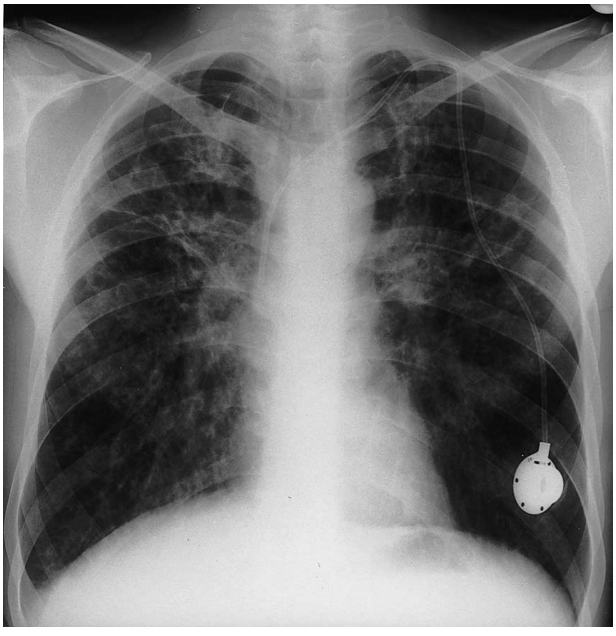


Fig. 10.2 Chest X-ray of this 37-year-old man with cystic fibrosis shows hyperinflation, peribronchial thickening, cystic bronchiectasis and perihilar fibrosis. A Portacath central venous system is in place with the access port situated subcutaneously in the left lower chest. He has chronic *Pseudomonas aeruginosa* infection and receives about three courses of intravenous ceftazidime and gentamicin at home each year. His forced expiratory volume in 1 second is 1.5L (42% of predicted) and his general condition and lung function have remained stable over the last 5 years on treatment including long-term nebulised colistin, nebulised deoxyribonuclease, physiotherapy and nutritional supplements.

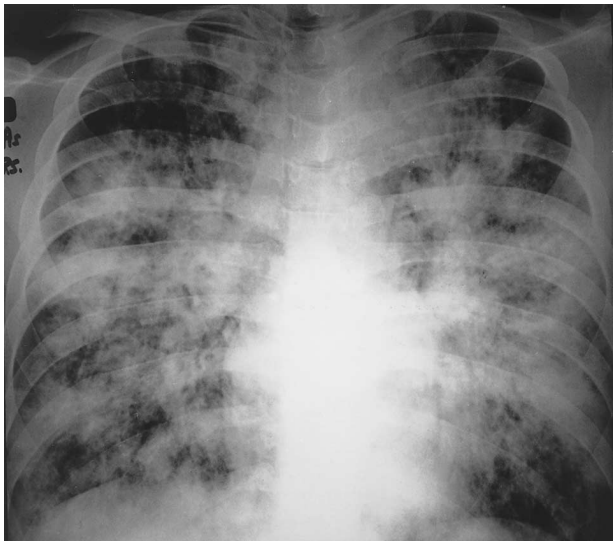


Fig. 10.3 'Cepacia syndrome': chest X-ray of this 23-year-old man with cystic fibrosis shows the typical appearance of 'cepacia syndrome' with fulminant bilateral necrotising pneumonia. He had acquired *Burkholderia cepacia* genomovar III infection 7 years previously during an outbreak of infection amongst patients with cystic fibrosis attending a holiday camp. His lung function showed an accelerated rate of decline in the years after infection and he then developed a severe exacerbation that failed to respond to treatment and progressed to a fatal fulminant pneumonia over a 2-week period.

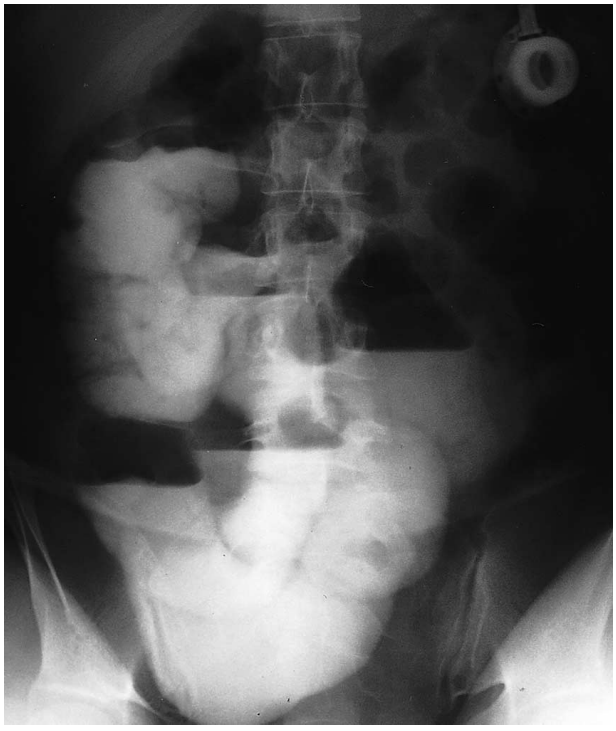


Fig. 10.4 Meconium ileus equivalent. This 31-year-old woman with cystic fibrosis was admitted to hospital complaining of abdominal distension, colicky pain and constipation. A mass of inspissated faecal material was palpable in the right iliac fossa. Erect abdominal X-ray (after taking Gastrografin) shows distended loops of small bowel containing multiple fluid levels. A diagnosis of meconium ileus equivalent (distal intestinal obstruction syndrome) was made and she was treated with Gastrografin (orally and by enema), *N*-acetylcysteine orally, intravenous fluids, followed by flushing of the bowel using balanced intestinal lavage solution.

focal biliary fibrosis, and about 5% of patients develop multinodular cirrhosis with hepatosplenomegaly, portal hypertension, oesophageal varices and liver failure. **Distal intestinal obstruction syndrome** (meconium ileus equivalent) (Fig. 10.4) results from inspissated fatty semi-solid faecal material obstructing the terminal ileum. A number of factors contribute to the development of this complication including malabsorption of fat, disordered intestinal motility and dehydrated intestinal contents resulting from defective intestinal chloride transport. The clinical features vary depending on the severity of the obstruction. Typically, the patient suffers recurrent episodes of colicky abdominal pain and constipation, and there is often a palpable mass in the right iliac fossa. In severe cases complete intestinal obstruction may develop with abdominal distension, vomiting and multiple fluid levels in distended small bowel on an erect X-ray of abdomen. It is treated by administration of the radiocontrast Gastrografin (sodium diatrizoate). This agent has detergent properties which allow it to penetrate the inspissated fatty material and its hypertonicity then draws fluid into the faecal bolus. In the absence of complete obstruction the bowel can be flushed using balanced intestinal lavage solution. Other measures include rehydration, stool softeners (e.g. lactulose) and *N*-acetylcysteine which probably acts by cleaving disulphide bonds in the mucoprotein faecal bolus. Prevention of recurrence requires adequate pancreatic enzyme supplements, avoidance of dehydration and sometimes use of laxatives.

Other complications

Nearly all **male patients are infertile** because of congenital bilateral absence of the vas deferens. The exact mechanism by which this complication occurs is not known but it has been suggested that it may result from resorption of the vas deferens after it has become

plugged with viscid secretions in fetal life. Females have near normal fertility although some abnormalities of cervical mucus are present. **Pregnancy** places additional burdens on the mother's health and is sometimes associated with a deterioration in the disease because of increased nutritional stress and impaired bronchial clearance. However, the main risk is of the mother failing to maintain all aspects of her own treatment as she focuses on the care of the baby.

Upper airway involvement causes troublesome **sinusitis** and **nasal polyps**. Cystic fibrosis **arthropathy** probably results from the deposition in joints of antigen–antibody complexes produced by the immune response to bacterial lung infections. Vasculitic **rashes** may also occur. In hot weather, patients with cystic fibrosis are at risk of developing **heat prostration** as a result of excess loss of salt in sweat. As these patients are living longer, a number of other complications are being described such as **osteoporosis** and **amyloidosis**. Patients with cystic fibrosis face major **social and emotional stresses** relating to their reduced life expectancy, outlook for employment, ability to form relationships and undertake marriage, and their general capacity to cope with a complex disease and its treatment.

Diagnosis

The diagnosis of cystic fibrosis is based upon the demonstration of **elevated sweat chloride** concentrations on a sweat test, in association with **characteristic clinical features** such as recurrent respiratory infections and evidence of pancreatic insufficiency. Nowadays the diagnosis is usually confirmed by the demonstration of **two known cystic fibrosis mutations** (e.g. ΔF508|ΔF508) on DNA analysis.

Sweat testing

In cystic fibrosis the ion-transport defect results in a failure to reabsorb chloride ions from the sweat, so that elevated sweat chloride and sodium concentrations are a characteristic feature of the disease. Sweating is induced by **pilocarpine iontophoresis**, the sweat is collected on filter paper and then analysed for sodium and chloride. Pilocarpine is placed on the skin of the forearm and a small electrical current is passed across it to enhance its penetration of the skin and stimulation of the sweat ducts. Meticulous technique is required to avoid evaporation of secretions or contamination. A sweat flow rate of at least 100μL/min is required for accurate analysis and sweat chloride levels above 60mmol/L on repeated tests are abnormal.

DNA analysis

The discovery of the cystic fibrosis gene in 1989 led to the development of **genotyping as an aid to diagnosis**. Genotyping can also be used to detect **carrier status**, and can be applied to chorionic villus biopsy material for **antenatal diagnosis**. However, there are more than 800 mutations of the cystic fibrosis gene currently identified and it is only possible to test for the more common mutations so that it can be difficult to exclude cystic fibrosis resulting from rare mutations. DNA analysis has established the diagnosis in some individuals with only mild clinical features, and this has extended our knowledge of the clinical spectrum of the disease to include some very rare older, less severely affected patients. Affected individuals have two gene mutations (e.g. ΔF508|ΔF508), one inherited from each of their parents. Carriers of the disease have only one abnormal gene, and do not show any evidence of the disease.

Screening

Early diagnosis of cystic fibrosis allows specific treatment to be commenced rapidly, and this is associated with an improved prognosis. Infants with cystic fibrosis have elevated serum **immunoreactive trypsin activity**. This can be measured on a single dried blood spot obtained on a Guthrie card as part of the neonatal screening programme for diseases such as phenylketonuria and hypothyroidism.

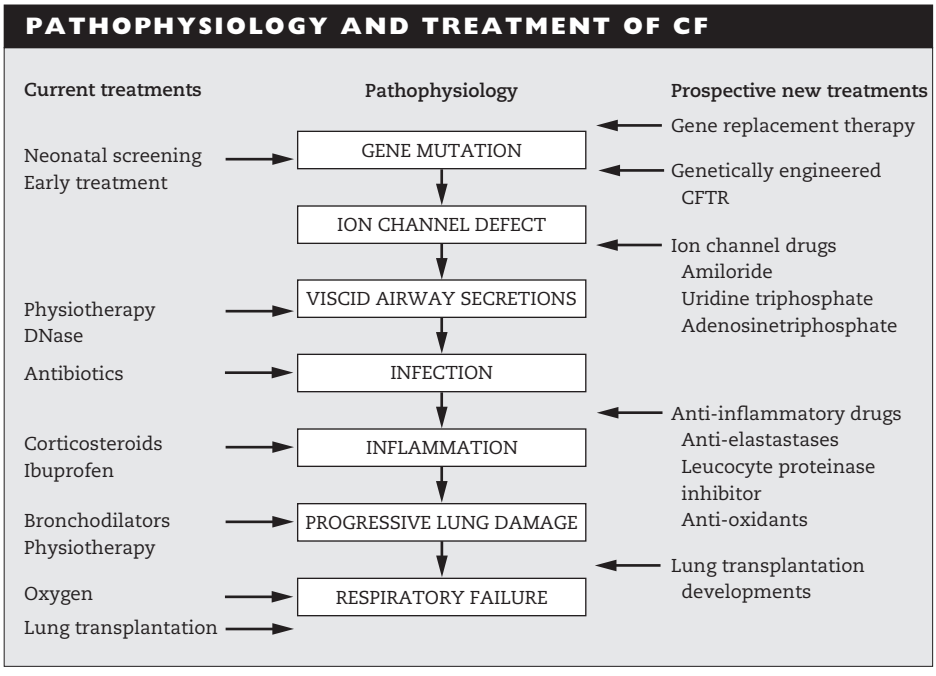


Fig. 10.5 Summary of pathophysiology and treatment of cystic fibrosis lung disease. The genetic defect results in a lack of cystic fibrosis transmembrane conductance regulator (CFTR) and abnormal chloride transport in airway epithelium. The resultant viscid secretions predispose to the acquisition and persistence of bacterial infection. The inflammatory response is unable to clear infection and a vicious cycle of infection and inflammation causes bronchiectasis and progressive lung damage, leading to respiratory failure and death, over a median period of 30 years. Key elements of treatment at all stages of the disease are nutrition, antibiotics, chest physiotherapy and psychosocial support. A variety of currently available and prospective treatments target the different pathophysiological stages of the disease to improve the outlook for patients with cystic fibrosis.

Treatment (Fig. 10.5)

Cystic fibrosis is a complex multisystem disease, and skills from several disciplines are needed in treating these patients. The optimal use of currently available treatments and the introduction of new treatments is best achieved by concentrating the care of these patients in regional **specialist centres**. The basic elements of treatment comprise clearance of bronchial secretions by **physiotherapy**, treatment of pulmonary infection by **antibiotics** and correction of nutritional deficits by use of **pancreatic enzyme supplements** and **dietary support**. Patients and their families require continuous encouragement and support in coping with this complex disease. The Cystic Fibrosis Trust acts as a focus of **information and support**, and coordinates fund raising for research.

Chest physiotherapy

The viscid purulent sputum results in airways obstruction, and clearance of airway secretions by chest physiotherapy is important at all stages of the disease. A variety of techniques can be used including **postural drainage** (using gravity-assisted positions to aid drainage), chest **percussion** and **positive expiratory pres-**

sure devices to aid dislodgement and expectoration of sputum from the peripheral airways. As patients mature it is important that they learn to perform bronchial clearance themselves. The 'active cycle of breathing technique' is often effective and popular with adult patients. This involves a **cycle of breathing control**, thoracic expansion exercises and the **forced expiratory technique** ('huffing') which releases secretions from peripheral bronchi. Exercise is an excellent adjunct to physiotherapy but should not replace it.

Antibiotics

Children with cystic fibrosis should be **immunised** against pertussis and measles as part of the childhood vaccination programme, and should receive annual influenza vaccination thereafter. They should avoid contact with people with respiratory infections and avoid inhalation of cigarette smoke. A variety of antibiotic strategies are used. *Staphylococcus aureus* is a major pathogen in the disease from early childhood and long-term continuous **flucloxacillin** is often used to suppress this infection. Further oral antibiotics are given during exacerbations in accordance with sputum cultures and sensitivity testing. Common pathogens include *Haemophilus influenzae* and *Streptococcus pneumoniae* which are usually sensitive to **amoxicillin**.

Infection with *Pseudomonas aeruginosa* becomes an increasing problem as children get older, and an important strategy in antibiotic therapy is to postpone for as long as possible the colonisation of the airways by this organism. Frequent sputum cultures are performed and intensive anti-pseudomonal antibiotic therapy is given when the organism is first isolated. This often comprises an **initial prolonged course of oral ciprofloxacin** and **nebulised colistin**. If this does not eradicate infection then **intravenous anti-pseudomonal antibiotics** are recommended. Eventually, chronic infection with *Pseudomonas aeruginosa* becomes established. Attempts at suppressing the effects of this infection involve long-term use of **nebulised antibiotics** such as colistin or tobramycin with additional courses of intravenous anti-pseudomonal antibiotics during infective exacerbations or when there is a decline in lung function. Usually an aminoglycoside (e.g. gentamicin, tobramycin) is given in combination with a third-generation cephalosporin (e.g. ceftazidime) or a modified penicillin (e.g. piperacillin). Treatment is usually given for 14 days and high doses are required to achieve adequate penetration of antibiotics into scarred bronchial mucosa because patients with cystic fibrosis have increased renal clearance of antibiotics.

Intravenous antibiotic treatment is often given **at home** by the patient after training. Where venous access is difficult a totally implanted central venous device can be inserted (e.g. Portacath). This comprises a central venous cannula connected to a subcutaneous port which is accessed by inserting a special non-cutting needle through the skin and the diaphragm of the subcutaneous chamber.

Burkholderia cepacia is usually resistant to many of the commonly used anti-pseudomonal antibiotics such as colistin, ciprofloxacin and aminoglycosides, but is often sensitive to ceftazidime or meropenem.

Bronchodilator medication

Some patients with cystic fibrosis have a reversible component to their airways obstruction, and benefit from bronchodilator drugs (e.g. salbutamol, terbutaline) and inhaled steroids (e.g. beclometasone, budesonide, fluticasone).

Deoxyribonuclease

The sputum of patients with cystic fibrosis contains high levels of DNA which is derived from the nuclei of decaying neutrophils. This makes the sputum very viscid and difficult to expectorate. Recombinant human deoxyribonuclease (Dnase/dornase alfa) is a genetically engineered enzyme which cleaves DNA. This recently developed treatment can be administered by nebulisation and improves the lung function and reduces the number of exacerbations in some patients.

Anti-inflammatory drugs

The inflammatory response is unable to eradicate infection and contributes to the progressive lung damage. Corticosteroid drugs (e.g. **prednisolone**) may have a beneficial effect but their use is limited by side-effects. High-dose **ibuprofen** may also be useful in reducing lung injury by inhibiting the migration and activation of neutrophils.

Nutrition

Pancreatic enzyme supplements (e.g. Creon, Pancrease, Nutrizym) are taken with each meal and with snacks containing fat. Enteric-coated preparations protect the lipase from inactivation by gastric acid, and use of antacid medication (e.g. omeprazole, lansoprazole) may improve effectiveness. The dose of enzyme is adjusted according to the dietary intake to optimise weight gain and growth and to control steatorrhoea. Use of high doses of pancreatic enzymes has been associated with the development of strictures of the ascending colon—so-called 'fibrosing colonopathy'—in a small number of children so that it is recommended that the dose of lipase should not exceed 10 000 U/kg/day. Supplements of **fat-soluble vitamins** (A, D, E) are routinely given.

Patients with cystic fibrosis suffer from nutritional deficiencies as a result of malabsorption and the increased energy requirements resulting from increased energy expenditure because of chronic lung infection. Most patients with cystic fibrosis require 120–150% of the recommended daily calorie intake for normal individuals, so that healthy eating for a patient with cystic fibrosis includes **high-energy foods** and frequent snacks between main meals. **Dietary supplements** (e.g. Fortisip, Scandishake) are useful when factors such as anorexia limit intake. In advanced disease **nocturnal enteral feeding** of high-energy formulas, through a nasogastric tube or gastrostomy, may be required.

Advanced disease

The clinical course of cystic fibrosis is very variable but an FEV_1 of less then 30% of the predicted value, for example, is associated with a 50% 2-year mortality rate. An awareness of the stage of the disease and the likely prognosis assists in planned management. Oxygen saturation should be measured by oximetry at each clinic visit in patients with advanced disease and when hypoxaemia develops domiciliary **oxygen** may alleviate the complications of respiratory failure. **Lung transplantation** is the main option to be considered for patients with advanced disease but the lack of donor organs severely limits the use of this treatment (see Chapter 20). Many patients will opt for a **palliative care** approach avoiding unpleasant interventions and focusing on measures which alleviate symptoms. Death is usually peaceful after a short coma due to ventilatory failure.

Prognosis (Fig. 10.6)

The prognosis of patients with cystic fibrosis has improved dramatically over the years. In the 1950s, survival beyond 10 years was unusual. Now the median survival is about 30 years and it is predicted to be at least 40 years for children born in the 1990s. There are now about 6250 patients with cystic fibrosis in the UK, of whom 40% are adults (aged 16 or over). Patients entering adulthood with cystic fibrosis face a number of problems, particularly relating to their chronic lung disease and reduced life expectancy (e.g. life insurance, choice of career, relationships, marriage, pregnancy, fertility). The improved survival of patients with cystic fibrosis has been attributed to a combination of factors including improved management of meconium ileus in neonates, earlier diagnosis, better dietary management and pancreatic enzyme supplementation and meticulous attention to physiotherapy and antibiotic treatments in specialist centres.

Prospective treatments

The identification of the cystic fibrosis gene in 1989 revolutionised our understanding of the detailed pathophysiology of this disease and

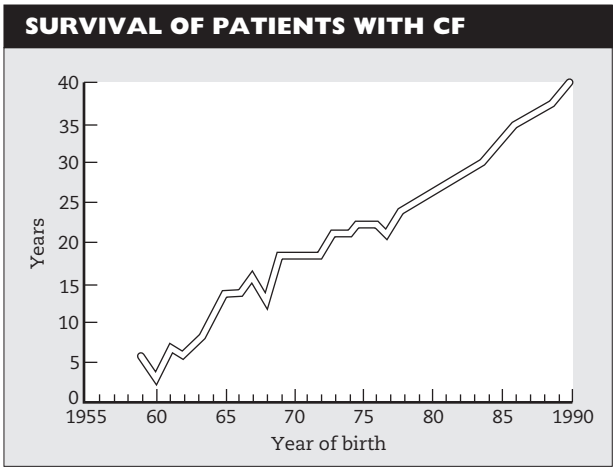


Fig. 10.6 Projected median survival of patients with cystic fibrosis by year of birth from 1959 to 1990. (Reproduced with permission from Elborn *et al.*, 1991.)

new treatments are being directed at each stage of the disease process. Perhaps the most exciting approach to treatment is the direct replacement of the defective gene by **gene therapy**. The DNA of CFTR has been cloned and has been given to patients in experimental trials using a vector such as a modified adenovirus or liposome to introduce the gene into epithelial cells. Expression of the gene can be detected by measuring transepithelial potential differences. However, many practical difficulties have to be overcome before gene therapy can be considered as a clinically effective treatment for patients.

New pharmacological approaches are being attempted to correct the **ion transport** defect by stimulating alternative chloride channels or inhibiting sodium channels. Nebulised amiloride has been shown to have a small effect in that regard, and newer agents such as adenosine triphosphate (ATP) and uridine triphosphate (UTP) are being assessed. **Nebulised DNase** represents a novel approach to reducing the viscosity of the sputum. This drug is currently available and improves the lung function and reduces the number of exacerbations in some patients. Attempts at modifying the inflammatory response involve the assessment of the role of some currently available (e.g. ibuprofen) and some novel **anti-inflammatory agents** (e.g. pentoxifylline, anti-elastases, serum leucocyte proteinase inhibitors (SLPIs)). Improvements in the field of **lung transplantation** offer the best hope for patients in the advanced stages of the disease. Advances in many different areas of scientific research are being brought into clinical practice in order to improve the outlook for patients with cystic fibrosis.

Further reading

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