Chapter 36: Cystic fibrosis

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Cystic fibrosis is an autosomal recessive disease which affects approximately one in 2000 children born in the UK (Kuzemko, 1986). It is thought to be due to a primary gene defect which, although not yet precisely identified, appears to lie on the long arm of chromosome number 7 (Wainwright et al, 1985). The disease is commonest in people of European caucasoid origin and its incidence is highest in countries populated by peoples of this genetic background. The disease is seen less frequently in Asians and in Negroes and is extremely rare in Chinese peoples.

The basic defect is not yet known precisely, but the clinical and diagnostic features stem almost entirely from the abnormalities of exocrine glandular secretions which occur throughout the body. The systems most affected clinically are the respiratory system and the digestive tract. There is also a high level of sodium in the sweat which can be used for specific diagnostic purposes (Gibson and Cooke, 1959). The disease is life-long and results in progressive deterioration of pulmonary function with age. It may also be associated with major problems in other systems such as the liver leading to cirrhosis, and the reproductive system causing infertility in males. These aspects are discussed in more detail later.

Antenatal diagnosis and screening

Antenatal diagnosis is presently available in two forms, either as an amniocentesis at 18-20 weeks' gestation or by chorionic villus sampling at 8-10 weeks. At amniocentesis, phenylalanine inhibitable intestinal alkaline phosphatase activity is measured; its activity is less inhibited than in normal individuals. This test, if positive, carries a reliability approaching 92% (Brock et al, 1985). If negative there is a 3% chance of the infant being affected. More recently, chorionic villus sampling has become possible using new DNA genetic probes which can be used at 8-10 weeks of gestation (Farral et al, 1986). This, however, requires familial gene mapping of both parents and affected children before pregnancy begins. If the test proves positive it is highly reliable with an overall false negative rate of less than 5% and a false positive rate of less than 0.04%.

Neonatal screening for cystic fibrosis is also available utilizing the presence of an elevated plasma immunoreactive trypsin which can be measured on dried blood spot (Guthrie) test cards in the neonatal period (Kuzemko and Heeley, 1983). This substance remains elevated for approximately the first 3 months of life, after which it drops to normal or low values. This test is therefore useful for screening in the neonatal period and early infancy but is not of help subsequently. Screening with this technique in the UK has shown an incidence of approximately one in 2100 live births. The false positive rate is less than 0.05% on initial testing and drops to less than 0.001% on repeat testing. The false negative rate is also extremely low (Kuzemko, 1986).

The sweat test remains at present the only definitive diagnostic test. This is performed with the use of pilocarpine iontophoresis and the collection of sweat thereafter for sodium or chloride analysis (Gibson and Cooke, 1959). Classically, a value of these substances in excess of 70 mmol/L on a sample weighing in excess of 100 mg is diagnostic in the presence of
appropriate clinical symptoms. However, the concentration of sodium in sweat tends to rise naturally with age and may also be elevated to the higher end of the normal range in patients with asthma. In some of these cases it may be extremely difficult to make the diagnosis (Hodson et al, 1983) and pancreatic function tests may have to be performed to aid in the diagnosis. The virtual absence of pancreatic bicarbonate and low levels of the enzymes trypsin, lipase and amylase are typical of the patient with cystic fibrosis (Hadborn et al, 1968).

**Presentation**

*N Neonatal*

Cystic fibrosis may present in many different forms. The early presentations in the neonatal period are shown in Table 36.1.

<table>
<thead>
<tr>
<th>Table 36.1 Neonatal presentation</th>
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<tr>
<td>Prenatal diagnosis</td>
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<tr>
<td>Meconium ileus</td>
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<tr>
<td>Meconium perforation and peritonitis</td>
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<tr>
<td>Obstructive jaundice</td>
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<tr>
<td>Neonatal screening - raised immunoreactive trypsin</td>
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<td>Positive sweat test (sibling with cystic fibrosis).</td>
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Meconium ileus is the commonest presenting feature in this period. This will be the mode of presentation in 10-15% of all cases of cystic fibrosis (Donnison, Schwachman and Gross, 1966). Babies with this condition fail to pass stools after birth and rapidly develop abdominal distension secondary to intestinal obstruction which is caused by the sticky inspissated faecal material. These changes have been noted as early as 20 weeks by ultrasound *in utero*, some babies even develop intrauterine perforation. Treatment is usually surgical and may involve resection of the small bowel followed by end-to-end anastomosis (Dinwiddie, 1983). Some cases may respond to simple gastrografin enema. Particular attention should be paid to the baby's general condition in the perioperative period since they are prone to lower respiratory tract infection following ventilation. They may also develop infections either in the chest or due to septicemia and may have particular nutritional difficulties until bowel function is restored. Those who present with meconium ileus now have almost as good a prognosis as those who present in later life (Wilmott et al, 1983).

*Infancy*

The common modes of presentation in infancy are shown in Table 36.2. The most frequent presentation is with a combination of failure to thrive, recurrent loose stools despite a large appetite, and frequent respiratory tract infections (Goodchild and Dodge, 1985a). Many infants are misdiagnosed as having food allergy or intolerance or possibly coeliac disease. The stools are typically pale, fatty and frequent. They tend to float and have an offensive pungent penetrating odour which can be virtually diagnostic.
A less common presentation is with anaemia and hypoproteinaemia secondary to the nutritional deficiencies (Neilson and Larsen, 1982). The baby frequently tastes salty when kissed and this too may be an important diagnostic clue. Rectal prolapse may result from the frequent loose stools and cystic fibrosis should always be considered in the infant who presents with this problem. Treatment is usually successful when the appropriate diagnosis is made and dietary management is commenced. In hot countries excessive salt loss through the sweat may result in major electrolyte imbalance or heat exhaustion with associated hyponatraemia and hypokalaemia (Kessler and Anderson, 1951).

**Table 36.2 Presentation in infancy**

- Failure to thrive
- Recurrent loose stools
- Recurrent lower respiratory tract infection
- Anaemia and oedema
- Rectal prolapse
- Heat exhaustion.

A number of infants will present with recurrent respiratory infections or persistent respiratory symptoms after common viral infections such as bronchiolitis. If there is a productive cough, evidence of persistent hyperinflation or indrawing of respiratory muscles which continues after the acute phase is passed, this diagnosis should certainly be considered and a chest X-ray should be performed. A small number of patients will present with staphylococcal pneumonia and empyema and again cystic fibrosis should be considered in this group. The prognosis for children who present with these forms of pulmonary infection in infancy is not always as poor as might be thought since the lung is rapidly growing and developing at this stage and, if it can be protected from further major insult, there is considerable room for recovery for a period of time.

**Childhood and adolescence**

A number of patients will present in later childhood, adolescence or even in adult life with symptoms due to cystic fibrosis. These patients tend to have a milder form of the illness as seen clinically, at least initially. The different presentations seen at this stage are shown in Table 36.3.

**Table 36.3 Presentation in childhood and adolescence**

- Recurrent wheeze, cough and purulent sputum production
- Nasal polyps and sinusitis
- Biliary cirrhosis
- Meconium ileus equivalent
- Diabetes mellitus
- Heat exhaustion
- Male infertility.

Cystic fibrosis should certainly be considered in this group of patients particularly when symptoms are persistent or recurrent. Some of these cases are detected when a sibling
is diagnosed as having cystic fibrosis and the rest of the family is reviewed. Some will have atopic features and may be thought to have asthma which can be particularly difficult to control, or have frequent respiratory infections. Suspicion should also be raised when there is evidence of chronic bronchial line shadowing on the chest X-ray or if there is any suggestion of finger clubbing when there is no other obvious reason for this. Allergic disorders, including rhinitis and asthma, are common in patients with cystic fibrosis (Wilmott, 1985) and this may obscure the diagnosis in some cases. A small number of patients with cystic fibrosis appear virtually asymptomatic, these are usually the siblings of known cases who, on screening with a sweat test, have high sweat sodium values. They represent one end of the spectrum of the illness and there must undoubtedly be a number of people who have the illness but who have virtually no symptoms and are never diagnosed.

**Management**

Management of the patient with cystic fibrosis is complex because it is a multisystem disease which therefore needs the involvement of a number of disciplines. Attention should not only be paid to the purely medical aspects, but also to the psychological, social, genetic, educational and occupational implications of the illness. While the diagnosis and management of the complications are best dealt with in a specialized cystic fibrosis clinic, much of the patient's care can now be undertaken by other sympathetic and involved hospital practitioners and family doctors. As more and more patients enter adult life in reasonable health, the value of combined care between hospital and general practitioner is greater than ever before.

**Pulmonary disease**

**Pathology**

The major changes in the lungs occur as a consequence of bacterial colonization resulting in persistent infection. This also leads to the production of increasingly viscid pulmonary secretions which are difficult to clear and result in marked airway obstruction with further infection and subsequently bronchiectasis (Tomashefski, Vawter and Reid, 1983). Initially there is a low grade chronic bronchitis and bronchiolitis, but as the disease progresses the airways become more permanently distorted, thickened and damaged by the infective process. This leads to areas of collapse with microabscess formation and other areas of overinflation and air trapping. The bronchial walls typically become thickened and this produces the classical signs seen on the chest X-ray (Chrispin and Norman, 1974). As a consequence of this chronic state, airway obstruction, which can result in wheezing, also occurs and this may have, in addition, an underlying allergic or asthmatic basis. It is important to test the patient for bronchodilator responsiveness if he is wheezing since not all bronchodilators work effectively in patients with cystic fibrosis (Mitchell et al, 1978). As the disease progresses the more common pathogens, particularly *Staphylococcus aureus* and *Pseudomonas aeruginosa*, may become permanent residents of the lower respiratory tract (Wilmott et al, 1983). These assume varying degrees of pathogenicity, but often result in the need for frequent or continuous antibiotic treatment to suppress their activity.

Upper respiratory tract problems are also common in cystic fibrosis and include chronic sinusitis, allergic rhinitis and frequently nasal polyposis (Drake-Lee and Pitcher-Wilmott, 1982). These are due to a combination of chronic infection and sometimes
underlying allergy. The nasal polyps tend to grow slowly but ultimately result in significant nasal obstruction with breathing difficulties and recurrent headaches. When removed they tend to return again and many patients require repeated surgery for this problem.

**Management of the lung**

Management of the pulmonary complications is aimed at minimizing the effect of chronic infection, clearing the lung of the viscid secretions and treating any underlying asthma which may be present. The major modes of pulmonary management are shown in Table 36.4.

**Table 36.4 Pulmonary management of cystic fibrosis**

Chest physiotherapy
Forced expiratory technique (FET)
Physical exercise
Antibiotics - intermittent or continuous
Antifungal agents
Bronchodilators
Sodium cromoglycate (Intal)
Steroids - oral or inhaled
Inhaled mucolytics.

Physiotherapy is the most important part of treatment for the lung and is required on a daily basis in virtually all cases (Hodson and Gaskell, 1983). The frequency and timing will depend on each patient. It is important to continue this on a regular basis because it prevents the accumulation of secretions and allows the patient to be physically trained in receiving this treatment. This is particularly important when an infection supervenes and the frequency and intensity must be increased. When the patient regularly produces sputum, physiotherapy should be carried out three times daily for 10-15 minutes. Older children and adults can successfully perform their own physiotherapy using the forced expiratory technique (FET) (Pryor et al, 1979). This is a special method of chest percussion, postural drainage and coughing which is successful in clearing sputum once it has been properly demonstrated by an appropriately trained physiotherapist. Physical exercise is helpful in the management of the lung, but does not replace physiotherapy as a means of clearing the lung secretions (Geddes, 1984). Any underlying exercise-induced wheezing should also be treated with beta-agonists or with sodium cromoglycate.

**Antibiotics**

Antibiotic therapy is frequently required for lung infection in patients with cystic fibrosis. The antibiotics may be administered by different regimens including continuous therapy throughout life with antistaphylococcal agents, antibiotic therapy in the early years to reduce colonization with *Staphylococcus* or other pathogens, or intermittent therapy during exacerbations of respiratory infection (Table 36.5) (Goodchild and Dodge, 1985b). The most common present practice is to administer antibiotics as required in relation to symptoms and the presence of significant pathogens. Recent studies have demonstrated an increase in bacterial induced symptoms, even during intercurrent viral infections (Stroobant, 1986), so it is important to cover these with antibiotics as well.
Table 36.5 Antibiotics in cystic fibrosis

<table>
<thead>
<tr>
<th>Antistaphylococcal</th>
<th>flucloxacillin</th>
<th>erythromycin</th>
<th>trimethoprim</th>
<th>fusidic acid</th>
<th>chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other antibiotics</td>
<td>amoxycillin</td>
<td>cephalosporins</td>
<td>doxycycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipseudomonas agents</td>
<td>gentamicin</td>
<td>tobramycin</td>
<td>amikacin</td>
<td>carbenicillin</td>
<td>cefotaxime</td>
</tr>
</tbody>
</table>

The two major pulmonary pathogens in cystic fibrosis are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Pitt, 1986). These often become permanent residents of the lower respiratory tract and when they are persistently cultured from the sputum it is virtually impossible to eradicate them. Treatment is therefore aimed at suppressing their activity and reducing their effect on the production of chronic bronchiectasis.

Staphylococci may be treated with intensive oral therapy but in severe cases hospital admission is required for intravenous treatment. *Pseudomonas* requires parenteral therapy, either in hospital or at home, and this is usually given in the form of two antibiotics, an aminoglycoside in combination with either a ureidopenicillin, such as azlocillin or a third generation cephalosporin such as ceftazidime. The usual treatment period is for 2 weeks and this is combined with intensive physiotherapy and nutritional support. Recently, aerosol antibiotics have been used more frequently for the treatment of Pseudomonas infections with some success and selected patients with chronic symptoms may well benefit from this form of treatment on a daily basis at home, either for short periods or even continuously for a period of many months (Hodson, Penketh and Batten, 1981). Ciprofloxacin is a new oral antipseudomonas agent which has been used in this situation but resistant organisms have already emerged.

Inhaled mucolytic agents may be helpful in those with particularly thick or viscid sputum and there is some evidence that these may be particularly useful when combined with inhaled antibiotic therapy (Heaf, Webb and Matthew, 1983). Whenever possible, the response to this treatment should be measured by the use of lung function tests as, in some cases, the lung function deteriorates when these agents are given.

Wheezing is a common feature in the lung disease of cystic fibrosis and may be due to airway obstruction secondary to infection. Many cases, however, have associated asthmatic
symptoms and these should be treated vigorously with the usual agents, including beta-
agonists, theophylline, sodium cromoglycate and steroids if necessary (Wilmott, 1985). Again,
the response to the treatment should be assessed by lung function tests whenever possible.

Other pulmonary complications which may be encountered include haemoptysis, seen
more commonly in the adolescent or adult patient with more advanced lung disease (Batten
and Matthew, 1983). Most cases will stop bleeding spontaneously but occasionally
bronchoscopy followed by angiography and embolization of the vessel may be necessary.

Pneumothorax is not uncommon in adults and requires treatment with the usual
measures including high oxygen concentration if tolerated, intercostal chest drainage and
pleurodesis or pleurectomy after a period of 7-10 days if the lesion has not resolved (Penketh
et al, 1982).

Advanced cases show evidence of cor pulmonale and this will require treatment with
diuretics and more intensive treatment of the underlying lung infection. Its onset is usually
associated with worsening of the prognosis.

Alimentary problems

Abnormalities of bowel function are one of the major features of cystic fibrosis.
Eighty-five per cent of patients have clinically abnormal pancreatic function and require
pancreatic enzymes in varying quantities. The features of the disordered bowel function may
present in a number of different ways including the following: meconium ileus (10-15%),
steatorrhoea with pale, offensive, fatty stools in the presence of large appetite, and third,
aemia and hypoproteinaemia secondary to nutritional deficiency. Abnormalities of the bowel
have been seen in utero as early as 18 weeks and also form the basis of the microvillar
enzyme tests based on the intestinal alkaline phosphatase which may be measured in amniotic
fluid obtained by amniocentesis (Brock et al, 1985).

Meconium ileus

Babies with meconium ileus usually present with intestinal obstruction in the first 24-
48 hours of life. They often require surgery to remove areas of necrotic bowel and to aid in
the release of the sticky, viscid meconium which has caused the intestinal obstruction. A
number of babies respond to treatment with gastrografin enema, but the remainder require
operative surgery. It is important to maintain the baby's nutrition at this time until bowel
function is restored and this may be undertaken with intravenous feeding or enteral feeds
including breast milk where possible, low fat high carbohydrate formula or Pregestemil if
necessary (Dinwiddie, 1983). Most of these children will require pancreatic supplements from
an early age and the dose of these should be modified to result in normal weight gain and
growth and in the passage of normal stools which do not contain an excess of fat. All infants
will require vitamin supplementation including A, B, C, D and usually E.

Later problems

Later abdominal complications may occur in infancy and childhood including
intussusception, adhesion obstruction, stricture formation at a previous anastomotic site and
low grade appendicitis. A few infants with cystic fibrosis present with rectal prolapse secondary to the malabsorption and this diagnosis should always be considered in young children with this condition.

Once weaned, the child should be given a diet with a normal fat content and the dosage of pancreatic supplements adjusted accordingly. The new enteric coated, acid resistant preparations, such as Creon and Pancrease, allow a higher lipase delivery to the duodenum and thus enable the fat content of the diet to be normal.

Another complication of cystic fibrosis in the older patient is meconium ileus equivalent, also termed distal intestinal obstruction syndrome. This presents with abdominal pain, distension and failure to pass stools. This results from inspissated stool obstructing the caecum in particular, although there is usually also significant generalized faecal loading present. Treatment is medical and consists of oral gastrografin or oral acetylcysteine. Recently a specialized non-absorbed electrolyte mix has proved successful in relieving symptoms (Cleghorn et al, 1986). If the patient fails to respond to these measures, then a gastrografin enema is usually successful. Enzyme therapy may need to be increased or decreased during the acute phase and readjusted again when the nutritional intake is restored. Those with chronic or recurrent symptoms may benefit from the use of cimetidine to diminish gastric acidity.

Other abdominal complications of cystic fibrosis include oesophageal varices in the presence of advanced liver disease and hypersplenism. These may result in recurrent haematemesis and, at present, treatment involves endoscopic sclerosis in order to prevent further bleeding episodes (Stamakis et al, 1982). About 15% of patients have liver disease of significance resulting in the longer term in biliary cirrhosis, ascites due to hypoproteinaemia and anaemia, neutropenia and thrombocytopenia because of hypersplenism. Those with significant liver disease will require additional vitamin K as part of their daily supplementation.

Other problems in cystic fibrosis

**Diabetes mellitus**

As many as 5% of older patients with cystic fibrosis may develop diabetes mellitus. A higher number will have abnormal glucose tolerance tests, although not clinical symptoms. This probably results from pancreatic fibrosis. It is more commonly seen in the adolescent or adult. Control of the diabetes is in the usual form with dietary measures and insulin if necessary. This clearly requires expert dietary advice.

**Arthropathy**

A small number of patients with cystic fibrosis complain of recurrent joint pains mainly affecting the larger joints and associated with low grade or minimal X-ray change. This may be secondary to their chronic inflammatory lung disease but the aetiology of this condition is not clear (Phillips and David, 1986). Treatment is usually conservative and symptomatic with drugs such as paracetamol, although the patient’s liver function should be checked before these are used on a chronic basis.
**Fertility**

Almost all cystic fibrosis males are infertile due to fibrosis of the vas deferens, reduced sperm count and motility. Male sexual activity is otherwise normal.

Many adult females with cystic fibrosis have produced normal, healthy children (Cohen, di Sant'Agnese and Friedlanders, 1980). They have significant reduction of overall fertility secondary to their chronic lung disease, and abnormalities of the mucus in the reproductive tract. The risk of a female with cystic fibrosis producing a child with this condition is one in 50. The breast milk of females with cystic fibrosis may be excessively salty and, if this is the case, breast feeding should be avoided.

**Psychological problems**

The psychological support of the family with cystic fibrosis is one of the most important parts of treatment. Because the patient has a chronic and life-limiting disease, much support has to be given by a number of health care professionals. There are marked effects on family life, both in terms of the patient's chronic ill health and also because of their need for frequent hospital visits and admissions and the time and expense that this involves. The psychological stress of the dying patient and the trauma of one or more family members being lost with the illness provides a great stress over an extended period. Sympathetic and supportive help and understanding is vital for these families on a long-term basis (Bywater, 1984).

**Prognosis**

The overall prognosis for patients with cystic fibrosis has greatly improved over the last 20 years. It is estimated that 60-70% of newborn infants with the illness may now expect to reach adult life (Wilmott et al, 1983) and 50% of those alive at 17 are still alive at the age of 30. Increasing numbers of older adults in their third and fourth decades are now being recorded. Many adults with cystic fibrosis have undertaken useful jobs and entered a wide variety of professions (Norman and Hodson, 1983).

The recent genetic advances in the location of the cystic fibrosis gene bring with them great promise for major changes in the understanding of the disease and the possibility of greatly improved treatments in the near future.