CYSTIC FIBROSIS

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Office of Health Economics
12 Whitehall London SW1A 2DY

No 79 in a series of papers on current health problems published by the Office of Health Economics. Copies are available at £1.00
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ISSN 0473 8837

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Office of Health Economics

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Introduction

Cystic Fibrosis (CF) is the most common genetically determined disease in Britain. Each year about 400 infants are born with the disorder and of these probably less than 25 per cent will survive into their 30s.

It is not historically clear when the study of CF began. While the American National Cystic Fibrosis Foundation (1971) maintains that the first descriptions of the disease were recorded in 1905 by Landsteiner and in 1912 by Garrod, it also acknowledges that the disorder was not described as a discrete entity until the 1930s. Numerous clinical manifestations associated with the disease and the varying degree of severity between patients probably caused confusion with other diseases for a considerable period of time. The first year that cystic fibrosis (or cystic fibrosis of the pancreas as it was then called) was distinguished from other diseases with similar clinical manifestations is claimed to be 1934.

During the short history of the disease, the prognosis for CF has shown a marked improvement. Whereas survival was measured in months when the disease was first described, most patients in developed countries now survive childhood, with a mean life span in specialist CF centres of between 20 and 25 years. The reasons for this improvement reflect a consortium of factors: earlier diagnosis, the availability and appropriate use of effective antibiotics and improved patterns of health care. They have not only been effective in prolonging life but equally important, advances in these areas of management of the disease have resulted in notable improvements in the quality of life for CF patients.

Much has been learned about the disease over the past fifty years but many fundamental problems remain unsolved. The precise biochemical fault that causes CF is still unknown, there is no known cure for the disease and until recently there was no reliable method suitable for routine use to diagnose the disease at an early stage (that is *in utero*). Furthermore, the increase in life expectancy enjoyed by CF patients has inevitably brought new problems and challenges for the sufferers themselves and those involved with them. In recent months, however, scientists and researchers have announced a significant discovery, namely the identification of the location of the gene defect causing CF. This information raises new hope for those affected by the disease and their families.

This paper looks at the nature and management of CF, the improvement in prognosis, the possibilities for prevention and social and economic considerations.

The nature of the disease

An inherited disease manifested in the exocrine glands, CF is characterised by chronic pulmonary disease, pancreatic enzyme deficiency and abnormal sweat electrolyte levels. The exocrine glands include those which secrete mucus, saliva and sweat to their outer surfaces. In a patient with CF they produce mucus that is thick, viscous and sticky and obstructs the ducts of the organ in which they are located. The precise underlying cause of this abnormality is unknown but the increase in viscosity has been variably attributed to a lack of water, alterations of electrolyte and calcium concentrations and abnormal organic constituents. The disease affects most organs in the body (Table 1) but it is the severity of pulmonary disease which to a large extent determines the morbidity and mortality associated with the condition.

Although structurally normal at birth, the lungs of patients with CF are subject to recurrent infections and chronic mucus hypersecretion. Figure 1 illustrates the typical chronology of pulmonary complications that occur. The abnormally viscid mucus initiates a vicious circle whereby the cilia of the tracheobronchial tree are unable to move the tenacious mucus, initially causing obstruction of the smaller bronchi and bronchioles and impairing the normal ciliary cleansing processes whereby germs and dust are expelled from the lungs and breathing passages. This may lead to infection, especially in the first instance, with the pathogens Haemophilus influenzae and Staphyloccocus aureus resulting in bronchitis and bronchiolitis.[1] The glands then produce more secretions in an attempt to clear the infection. Hypertrophy and hypersecretion of the mucus secreting bronchial glands add to the accumulation of secretions, and obstruction of the airway. Completion of this process leads to partial or total collapse of the lung (segmental or lobar atelectasis). The gradual accumulation of viscid secretion interferes with the normal process of mucociliary clearance, whereby the cilia of the tracheobronchial tree move the mucus. In addition, ventilation and the cough mechanism are adversely affected allowing further collection of secretions.

The inflammatory reaction and infection destroy the ciliated epithelium and permanently impair the cleansing of the tracheobronchial tree. This in turn leads to bronchiestasis,[2] and finally the formation of fibrosis, abscesses and cysts which constitute reservoirs of infection that continue to affect other areas of the lung.

1 Bronchiolitis is the name given to bronchitis affecting the finest bronchial tubes.

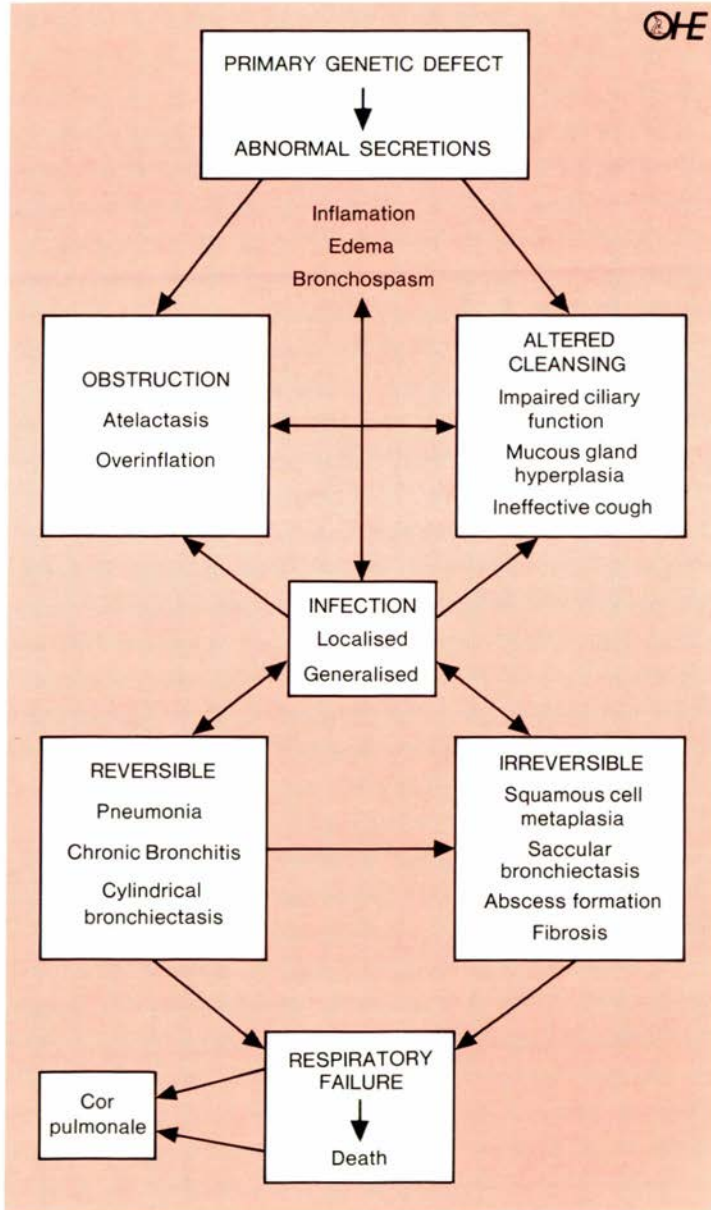
2 Bronchiectasis is the condition characterised by dilation of the bronchial tree.

Table 1 **Organ involvement in cystic fibrosis.**

Organ	*Pathogenesis*	*Clinical manifestations*	*Usual onset*	*Frequency*
Lung	Obstruction/infection	Bronchiectasis	All ages	Near 100%
		Bronchitis		
		Pneumonia		
		Pneumothorax	Usually	Occasional
		Haemoptysis	older child	Occasional
Upper airway	Obstriction/infection	Sinusitis	All ages	50%
		Nasal polyps		10–15%
Bowel	Intestinal obstruction	Meconium ileus	Birth	6–25%
		Meconium ileus equivalent	Late childhood	Common
		Intussusception		
		Hypoalbuminaemia oedema	All Ages	Occasional
		Rectal prolapse	Younger child	Occasional
Pancreas	Inspissation/obstruction/fibrosis	Malabsorption	Usually at birth	80–90%
		Diabetes	Older	1–5%
Liver	Obstruction/fibrosis	Subclinical cirrhosis	All ages	25–50%
		Portal hypertension	Late childhood	2%
		Neonatal jaundice	Infancy	Occasional
Gall bladder	Obstruction	Cystic duct obstruction	All ages	20%
		Small gall bladder		
Reproductive tract	Vas deferens obliteration	Sterility	Birth	98%
	Thick vaginal secretions	Decreased fertility	Older child	Common
		Hydrocele, hernia	All ages	Occasional
Sweat glands	Abnormal sweat electrolytes	Salt loss	Birth	Near 100%
		Heat prostration	All ages	Occasional
Salivary glands	Abnormal electrolyte concentrations		All ages	Near 100%
Retina	Hypoxia, exudative retinopathy	Visual disturbance	All ages	Rare
Ears	Pharyngeal-middle ear obstruction	Conductive hearing loss	All ages	Occasional
Heart	Hypoxia, broncho-pulmonary anastomosis	Cor pulmonale	All ages	Common
		Fibrosis		Rare
Bones		Hypertrophic osteoarthropathy	All ages	Rare
Extremities		Clubbing	All ages	Common

Source Phelan P D *et al*, (Ed) Respiratory Illness in Children. Blackwell Scientific Publications. Second Edition 1982.

Figure 1 **Lung disease in cystic fibrosis.**



Complications include rupture of a cyst causing pneumothorax, in which air enters the pleural cavity and haemoptysis which means the patient coughs up blood. Eventually, respiratory insufficiency, cardiac failure (*cor pulmonale*) or both may lead to death.

A similar process in the upper airway causes chronic pansinusitis in many CF patients. The lining of the air passages which covers the thin bony plates at the entrance to the nose, the nasal turbinates, are frequently swollen, and the development of recurrent nasal polyps occurs in 10–15 per cent of patients with CF.

It was the post mortem appearances of the pancreas full of cysts and fibrosed that originally led to the label of cystic fibrosis of the pancreas. Lack of pancreatic enzyme activity was used, and still is used as a diagnostic indicator for involvement of the pancreas. Although research has demonstrated that about 15 per cent of patients with CF have measurable pancreatic enzyme activity, the majority exhibit symptomatic steatorrhoea – the cardinal feature of insufficient secretions from the pancreas. The biochemical control of secretion from the pancreas which is transported through a duct system into the gut, is disordered with sticky secretions resulting in the blockage of the duct system and destruction of the gland tissue. Enzyme deficiency results in varying degrees of malabsorption, especially of protein and fat, which has to be monitored and managed throughout the patient's life.

Some infants with CF exhibit severe manifestations in the first week of life, whereas a few may not exhibit symptoms until adolescence or even later. Despite such variations, however, nearly all patients with CF eventually have symptoms of both pulmonary infection and pancreatic insufficiency. Table 2 illustrates the important clinical manifestations and physical signs of CF in different age groups.

Diagnosis

The exceptionally high salt content of sweat, common to all children with CF, forms the basis of the most reliable diagnostic test for the condition. Most methods used for the sweat test are based on the quantitative iontophoresis technique described by Gibson and Cooke (1959). Sweating is stimulated by the passage of a galvanic current through a solution of the compound pilocarpine, applied to the skin underneath an electrode. The sweat is then collected and analysed for sodium and chloride concentrations. Table 3, which is a summary of the sweat test results for 252 children with CF and 252 controls, obtained by Shwachman and colleagues (1981), illustrates that the concentration of sodium and

Table 2 **Important clinical manifestations and physical signs of cystic fibrosis in different age groups.**

- Newborn
  - Meconium ileus, atresia, plug
  - Prolonged neonatal jaundice
- Infant
  - Pulmonary
    - Failure to thrive
    - Bronchiolitis, rhonci
    - Chronic cough, retractions, respiratory distress
    - Pulmonary infiltrates especially right upper and right middle lobe atelectasis
    - Clubbing
    - *Staphylococcus aureus* or *Pseudomonas* on culture
  - Gastrointestinal
    - Failure to thrive
    - Chronic diarrhoea
    - Rectal prolapse
    - Abdominal distention
    - Edema, anaemia
    - Vitamin deficiencies
  - Others
    - Salt loss
    - Bulging fontanelle
    - Gastroesophageal reflux, etc
- Older child
  - Pulmonary
    - Sinusitis, nasal polyps
    - Asthma, wheezing, rhonci
    - Bronchiectasis, rales
    - Hyperinflation
    - Clubbing, arthropathy
    - Hemoptysis
    - Pneumothorax
    - Cor pulmonale
    - Growth failure
  - Gastrointestinal
    - Malabsorption syndrome
    - Growth failure, delayed puberty
    - Meconium ileus equivalent
  - Others
    - Portal hypertension
    - Pancreatitis
    - Heat prostration
    - Intussusception, etc
- Adults
  - Glucose intolerance, diabetes
  - Sterility in males
  - Microgallbladder, gallstones, etc

Table 3 **Sodium, chloride and potassium values in CF children and controls**

	CF patients			*Controls*		
	Sodium	*Chloride*	*Potassium*	*Sodium*	*Chloride*	*Potassium*
Mean	111.190	115.330	22.930	28.514	28.025	10.339
SD	11.987	12.112	2.488	6.079	6.048	2.365
n	252.0	252.0	252.0	252.0	252.0	252.0
Minimum	75.4	78.6	13.8	15.9	7.7	6.0
Miximum	144.6	148.2	29.6	45.9	43.4	16.9

Source Shwachman H, Mahmoodian A and Neff R K (1981), *J Paediatr.* 98, 576.

chloride in the sweat of CF patients is four times as high as the normal.

Despite recognition as potentially one of the most accurate diagnostic tests in medicine, however, the improper use of the sweat test in some instances has led to diagnostic errors, with serious and psychological consequences. In 1978 Smalley and her colleagues described 14 children in whom the diagnosis of CF had been made incorrectly on the basis of the initial sweat test producing misleadingly high results. In a more recent study, David and Phillips (1982) reported seven patients seen over three years who had been wrongly diagnosed.

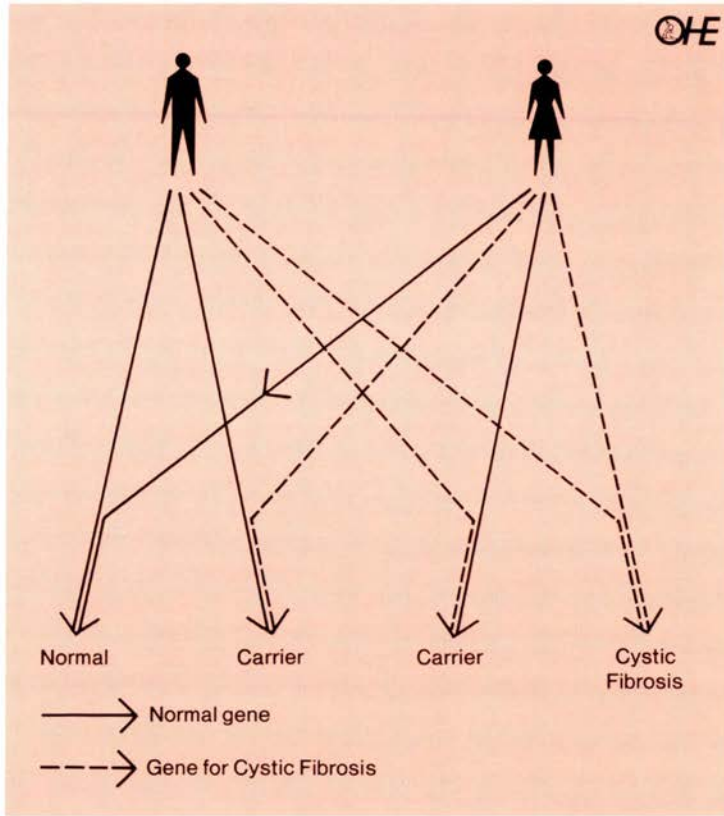
In the latter study misleadingly high initial sweat tests were found in only three of the seven patients. In the remainder the diagnostic error was the result of either disregarding normal sweat test results, or failure to carry out any sweat test at all or disregard for the absence of the typical clinical features. Some indication of the serious psychological effect misdiagnosis may have is demonstrated by the sending of four of these children to special schools for the physically handicapped. These findings emphasise the need for an abnormal sweat test to be considered within the context of the overall clinical picture.

Lack of pancreatic enzyme activity is frequently used as a second diagnostic sign. Symptoms of malabsorption in children, such as poor weight gain despite increased appetite, frequent bulky, foul and semi-formed stools, rectal prolapse and failure to thrive, are all suggestive of CF. In about 10 to 15 per cent of cases the disorder presents itself in the newborn period as meconium ileus – obstruction of the small bowel by impacted meconium, often requiring surgical relief. This is not to be confused with 'meconium ileus equivalent' which frequently occurs later in the lifespan of a CF patient and comprises small intestinal obstruction. Chronic or recurrent symptoms in the upper or lower respiratory tract such as chronic cough, chronic sinusitis, nasal polyposis, asthma-like symptoms, bronchitis and the presence of Staphylococcus aureus, Haemophilus influenzae or Pseudomonas aeruginosa in the sputum may also be indicative of CF, especially in children.

Genetics and frequency

CF is an autosomal recessive condition, meaning each CF patient has inherited a CF gene from each parent (Figure 2). Thus it is not sex-linked and there is no difference in the frequency of occurrence between the sexes. About one in twenty of the general popu-

Figure 2 **Manner of inheritance in cystic fibrosis.**



lation are carriers of the CF gene and when the abnormal gene is present in both parents there is a one in four chance that each offspring will inherit CF. If the infant inherits a gene for cystic fibrosis from one parent and a corresponding normal gene from the other, the infant will, of course, be free of the disorder but will be a carrier of the CF gene which may be passed on to the next generation. If the infant inherits normal genes from both parents he or she will have neither CF nor carry the CF gene.

It is estimated that around 400 new CF cases are diagnosed each year in the United Kingdom, with approximately 6,000 sufferers in 1984. Data on the frequency of CF depend on two types of ascertainment, each of which has limitations (Raeburn 1983). The first

Table 4 **Calculated carrier frequency and reported incidence for different reported incidences of cystic fibrosis.**

Reported Incidence	*Country*	*Carrier Frequency*	*Authors*
1/1654	UK	1/20	Prosser 1976
1/1675	Switzerland	1/20	Kaiser *et al* 1976
1/2358	UK	1/24	Hall & Simpkiss 1968
1/2650	Italy	1/26	Righetti *et al* 1976
1/3800	USA	1/31	Wright & Morton 1968
1/5000	Israel	1/35	Levin 1963
1/8000	Sweden	1/45	Selander 1962

Source Raeburn J A, Genetics and Genetic Counselling in Hodson M E, Norman A P and Batten J C (eds) Cystic Fibrosis, Ballière Tindall, London 1983.

approach, which is based on data collected from hospital or clinical registers or the records of abnormal sweat test results, indicates the frequency of symptomatic disease which was sufficient to raise suspicion of the diagnosis. This approach tends to underestimate the frequency of CF relying greatly on the level of awareness amongst doctors. The second approach depends on data obtained from infant screening programmes. Unless the screening test identifies an abnormality which is directly due to the CF gene, this will also produce an inaccurate estimate. Taking these possible sources of inaccuracy into account, the addition of CF cases identified by screening to those identified by clinical means has demonstrated that in Britain the incidence of CF ranges from 1 in 1,600 to 1 in 2,300 births.[3] This means that CF is the most common genetic disorder affecting children in Great Britain. Throughout the world, CF is predominantly restricted to Caucasians. The incidence in non-white populations is much lower, although not as thoroughly documented (Table 4).

Prognosis

In 1969 survival data were published which compared life tables for 128 children with CF between 1964 and 1968 with similar tables for the preceding 20 years (George and Norman 1969). Figures 3a and 3b, and 4a and 4b demonstrate a marked improvement in prognosis over these two time periods.

Focusing on the group of children with CF not presenting as meconium ileus (obstruction of the bowel) for the period 1964–68,

3 The most frequently quoted figure for the incidence of CF lies somewhere between these two estimates, at 1 in 2,000.

Figure 3a **Cystic fibrosis – survival rates.**

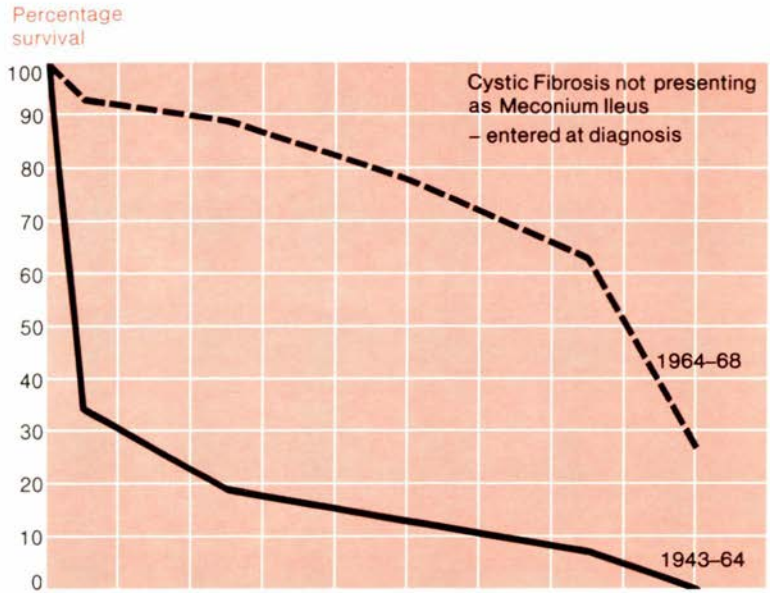


Figure 3b **Cystic fibrosis – survival rates.**

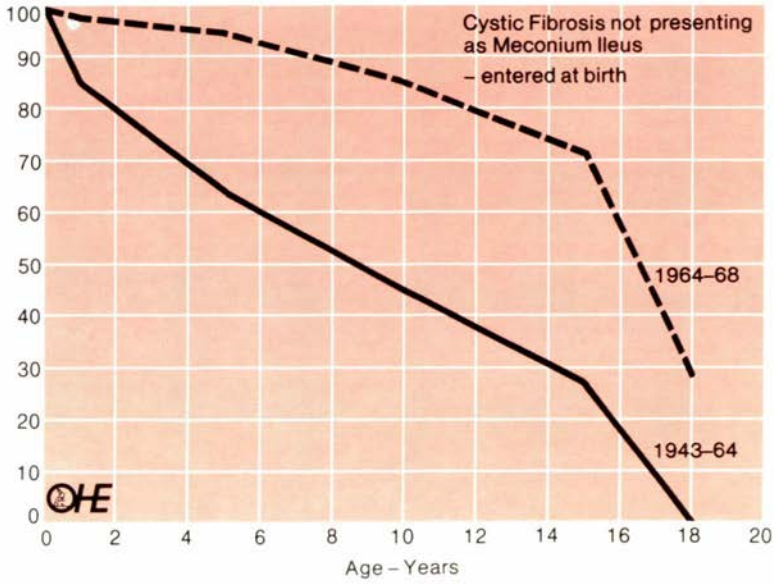


Figure 4a **Cystic fibrosis – survival rates.**

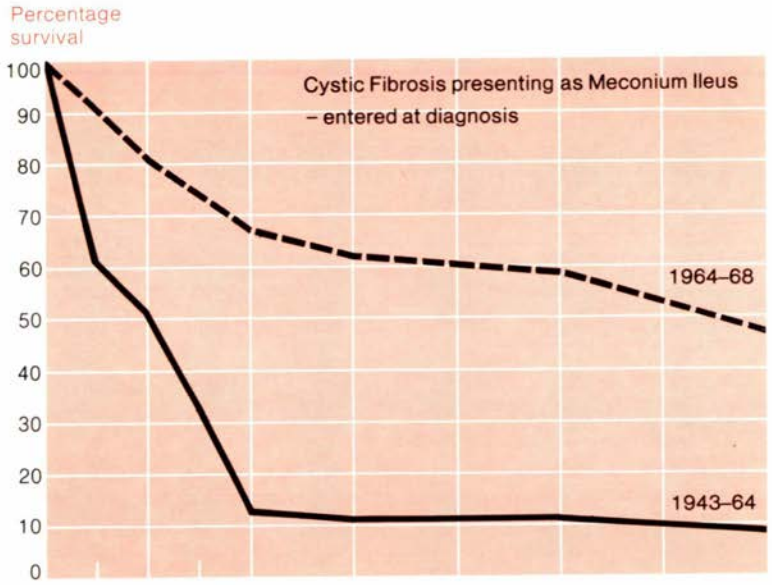
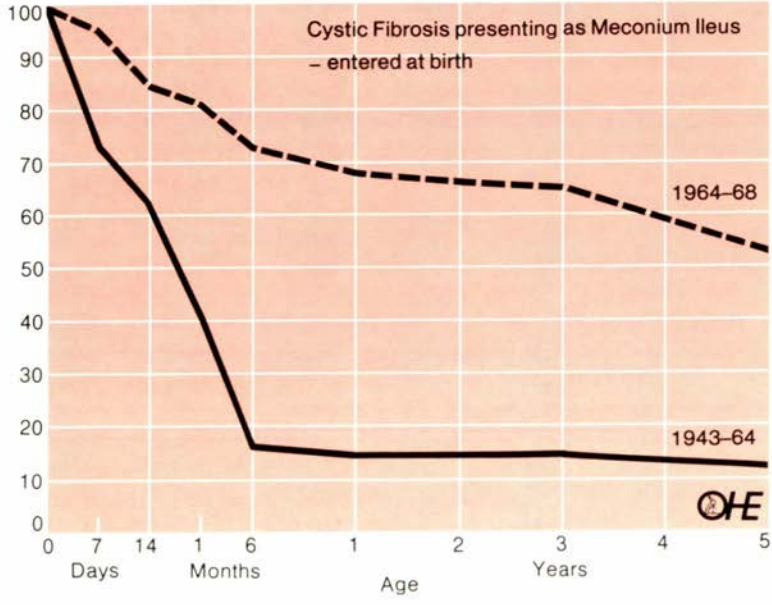


Figure 4b **Cystic fibrosis – survival rates.**



the difference in survival rates between those entered at birth and those entered at diagnosis is small, reflecting the effect of early diagnosis and treatment. For example, at two years of age, the survival rate for those entered at diagnosis is 93 per cent as compared with 98 per cent for those entered at birth. At 10 years of age the survival rate at diagnosis is 77 per cent and 85 per cent at birth, and at 18 years the corresponding figures are 26 per cent and 30 per cent.

On comparing survival rates over the two time periods for those entered at diagnosis, there is a notable improvement. Whereas the survival rate was just 34 per cent at one year of age in 1943–64, the corresponding figure for 1964–68 is 93 per cent. At five years of age the survival rate is 19 per cent (1943–64) versus 89 per cent (1964–68).

For those children with CF presenting as meconium ileus the picture is similar. The gap in survival rates between those entered at diagnosis and birth is small. Comparison of survival over the two time periods for those entered at diagnosis shows an improvement from 33 per cent for the first period to 75 per cent in the second time period. Similarly for those entered at birth the corresponding figure is 41 per cent as against 81 per cent. This improvement in prognosis continues throughout the first five years of life, as indicated in Figures 4a and 4b.

A publication in 1975 by Robinson and Norman indicated that the improvement in life expectancy enjoyed by patients with CF continued over the next five years. They compared survival rates obtained from life tables of 215 children attending the Hospital for Sick Children during the five years from January 1969 to December 1973, with the two previous series. For the group not presenting with meconium ileus, 97 per cent were alive at five years, compared with 89 per cent during the previous five-year period and 19 per cent in the earliest survey. Of those presenting with meconium ileus 79 per cent were alive at five years compared with 54 per cent and 13 per cent respectively. More recent data covering the period 1974–79 indicate that survival rates for patients presenting with meconium ileus have improved appreciably (Wilmott *et al* 1983).

There seems good reason to expect that life expectancy will continue to improve, although survival data for more recent years are less complete. It is not possible to distinguish between those diagnosed at birth and those diagnosed later in life or between those presenting with meconium ileus and those not, when using routine mortality data. It is hoped that the results of a recent survey of CF by the British Paediatric Association (BPA) will provide more accurate and recent data relating to life expectancy, differen-

tial mortality and age of diagnosis. The working party has identified over 4,500 patients and preliminary data suggest an 80 per cent survival to age 13 years and 50 per cent survival to age 20 years or more. It has been estimated that 1,000 additional patients will enter the 'adult' group during the next 5 years (15 years of age and over).

The reasons for the improvement in prognosis remain somewhat uncertain although a more comprehensive and consistent treatment regimen (notably the use of effective antibiotics, efficient physiotherapy and dietary management) together with earlier diagnosis and treatment and an increased awareness of the nature of the illness among the medical profession are thought to be significant factors. Much of the debate has focused on the second of these three elements, namely the argument that the earlier the diagnosis the more favourable the prognosis. It is, of course, reasonable to argue that the earlier the diagnosis, the earlier the treatment to combat pulmonary complications. However, it does not necessarily follow that those with CF who are diagnosed later are at a significant disadvantage. Some manage well despite the delay, although this probably reflects the fact that the disorder may take a milder form in those presenting late. Furthermore, it must be remembered that each patient is unique, responding to treatment and life as a whole in his/her own individual way.

Ornstein and his colleagues (1977) attempted to test directly the hypothesis that early treatment improves prognosis. They examined 16 sibling pairs with CF. Younger siblings' conditions were diagnosed during the first year of life, usually before the onset of pulmonary disease and older siblings' conditions were diagnosed after one year of age and after the onset of pulmonary disease. Although the sibling pairs received similar treatment, comparison at seven years of age showed that the young siblings had significantly better chest X-ray scores, total clinical scores, residual lung volumes and ratios of residual volume to total lung volume. Younger siblings also required fewer hospital admissions to control their lung disease. Thus the results of this study suggest that in general earlier treatment is beneficial for patients with CF. This conclusion is supported by recent research by Wilcken and Chalmers (1985) who examined the effects of neonatal diagnostic screening on CF-related morbidity. Their study revealed that the number of days spent in hospital, the number of separate admissions and the number of patients ever admitted to hospital during the first two years of life were considerably smaller for patients in whom CF was diagnosed by screening than those in whom the

diagnosis was indicated by symptoms.

Warwick (1982) looked at the effects of early diagnosis and CF centre care on the prognosis for survival with CF. Using data from a long-term follow-up study of early diagnosed CF cases from the CF centre at Case Western Reserve University (CWR), Cleveland, Ohio, where a prophylactic pulmonary therapy has been used since the 1950s, he reported an expected 20 year survival of 60 per cent of the entire group. However, when the patients were segregated into those who had a chest X-ray within the range of normal at the time of diagnosis or achieved such an X-ray within one year, and those who did not, two very different rates of survival were found. In the first group, which consisted mainly of early diagnosed patients for whom prophylactic pulmonary therapy was practicable the expected 20 year survival was 93 per cent. This is in sharp contrast to the second group, where significant lung disease was present at the time of diagnosis, and the expected 20 year survival was merely 40 per cent.

Warwick also reported a significant difference in prognosis between those treated at a CF centre and those seen at hospitals where care was given by individual physicians. Data from the entire globe for the years 1949–66 showed that in the absence of a CF centre life expectancy to four or five years was 50 per cent. By contrast, the addition of a CF centre to the CF care team increased that 50 per cent survival to 21 years in the USA. Table 5 shows percentage survival for various countries where CF centres are established.

These observations from around the world of the benefits of early diagnosis and centre treatment are supported by data from Denmark. In 1981 it was reported in Denmark there was a doubling of survival of all patients treated at the CF centre in Copenhagen as compared to patients treated exclusively at other departments (Schiøtz, Hoiby and Flensborg).

Table 5

	Percentage survival for CF where CF centre is established	*Source*
USA	50% survival to 21 years	Cystic Fibrosis Foundation, 1978
Switzerland	62% survival to 12 years	Kraemer *et al*, 1979
Canada	50% survival to 22 years	Cystic Fibrosis Foundation, 1978
Sweden	42% survival to 22 years	Kollberg H, 1982
Netherlands	48% survival to 20 years	Holdsaw D S, 1980
Australia	65% survival to 19 years	Phelan P D, 1979
Denmark	75% survival to 21 years	Schiøtz P O, 1981

Figure 5 **Location of large CF centres.**

Phelan and Hey (1984) compared the prognosis for CF in England and Wales with that in the state of Victoria, Australia. The incidence of CF is similar in the two locations but mortality rates were reported to be two to three times lower in every age group in Australia than in England and Wales. Phelan and Hey attribute this to centralisation of treatment, with 90 per cent of children and adolescents managed in the one clinic in Victoria.

The national distribution of CF centres in Britain is demonstrated in Figure 5. Large CF centres tend to be located in places of high population density and university or teaching hospital centres and thus appear to be distributed fairly evenly throughout the UK. The British Paediatric Working Party on CF was set the task of assessing the advantages and disadvantages of regional centres for CF. The background to their investigation was the recent publication of a number of reports indicating a marked difference in survival between different countries and different centres, with the general implication that the best results are achieved in large centres with specialist CF services.

The arguments in favour of such centres include the availability of specialist services with experienced medical and ancillary staff, access to large numbers of patients facilitating research by both basic research workers and clinicians conducting epidemiological and therapeutic studies and administrative advantages. The disadvantages of providing care in specialist centres include expense, travel and inconvenience for those living a distance from the centre, the theoretical risk of cross-infection between patients, and the possibility that when emergency treatment is required at a local hospital, staff may be unfamiliar with the patient and not experienced in managing CF. In addition, the heavy workload imposed upon CF centres carries physical and emotional demands.

The BPA made a number of recommendations with regard to the establishment of more CF centres, not necessarily by expansion but by means of redeployment and earmarking of staff and facilities in some centres. At the moment 16 hospitals throughout Britain have more than 50 patients with CF, who may travel long distances from local hospitals for periods of expert care. However, the DHSS remains to be persuaded that special funds should be allocated for CF centres.

Management of the disease

The palliative nature of the treatment of CF reflects the absence of knowledge of the basic biochemical abnormality. Thus, effective treatment, which is not restricted to medical aspects of care but includes physchological, social, genetic, educational and occupational aspects, is aimed at the complications of the disease. Treatment begins at the time of diagnosis and continues throughout the life span of the patient. The basic management of the condition is founded upon the objectives and methods first described by Anderson in 1949: to prevent or control pulmonary disease and ensure optimal nutrition. The extreme variability, however, in the degree of involvement and severity between one sufferer and another means optimal treatment must be highly individualised and aimed at ensuring as good a quality of life as possible in addition to prolonging life. Inadequate treatment, on the other hand, may serve merely to prolong life in a state of discomfort and misery.

Respiratory disease is the most serious manifestation of CF, accounting for much of the morbidity and almost all of the mortality associated with the disease. To a large extent the management of respiratory disease and pulmonary complications determines the life span and the quality of life of the individual. Thus treatment is aimed at two goals: the prevention and control of infection and the removal of bronchial secretions.

Antibiotics have been identified as the most important factor in extending the life span of CF patients, although consensus of

Table 6 **Antibiotics commonly used in the treatment of cystic fibrosis.**

To combat Staphylococcus aureus	Erythromycin Flucloxacillin Fusidic acid
To combat Haemophilus influenzae	Amoxycillin Chloramphenicol
To combat Pseudomonas aeruginosa	Azlocillin Carbenicillin Cefsulodin Ceftazidime Gentamicin Netilmicin Piperacillin Ticarcillin Tobramycin

opinion over the best way to administer them has yet to be established. Differences in approach are based on various periods and modes of administration (oral, intravenous, aerosol inhalation).

A number of suitable antibiotics are now available (Table 6) with the preferred method of use varying between CF centres, and individual physicians. The choice of antibiotic is largely determined by the nature of the invading organism and for this reason it is necessary to take frequent sputum cultures.

A variety of pathogens have been identified in the sputum of CF patients, with the most common being Staphylococcus aureus, Haemophilus influenzae and Pseudomonas aeruginosa (Table 7). Staphylococcus and Haemophilus are the organisms commonly presenting in the early phase of the disease process whilst Pseudomonas is more common at a later stage. Interestingly, Pseudomonas aeruginosa seems to have a predilection for CF patients and in recent years there has been a rise in the rate of colonisation with Pseudomonas aeruginosa. The reasons for this are not entirely clear but may be related to the extensive use of antibiotics to suppress other pathogens. Although a harmful organism, Staphylococcus is responsive to treatment whereas it is virtually impossible to eradicate Pseudomonas aeruginosa once established.

The tendency in recent years towards more frequent use of intravenous antibiotics reflects, among other factors, the improve-

Table 7 **Common and uncommon pathogens.**

Bacteria	
Common	Staphylococcus pyogenes Pseudomonas aeruginosa Haemophilus influenzae
Uncommon	Klebsiella pneumoniae Legionella pneumophila Anaerobic species Mycobacterium tuberculosis and other mycobacteria
Fungi	Aspergillus fumigatus
Viruses	Respiratory syncytial virus Influenza parainfluenza virus Rhinovirus Etc.
Others	Mycoplasma pneumoniae Chlamydia

Source Batten J C and Matthew D J, The Respiratory System in Hodson M E, Norman A P and Batten J C (eds) Cystic Fibrosis, Ballière Tindall, 1983.

ment in intravenous therapy in the form of the heparin lock. This enables discontinuous therapy via a relatively inconspicuous intravenous site, total mobility and exercise, full postural drainage and leave from hospital for school or employment.[4] This compares with an armboard, continuous infusion, confinement to bed or room and impairment in carrying out physical activity or postural drainage, which was common practice just a decade ago.

Equally important in the prevention of lung infection is effective physiotherapy. This is started as soon after diagnosis as possible. Its purpose is to mobilise and remove the bronchial secretions and hence to aid respiration and slow down the course of infection. Physiotherapy is normally introduced by a member of the professional team and is then taken over by the patient and family and continued throughout the patient's life.

Postural drainage, whereby the patient is placed in various positions allowing gravity to drain secretions from the lungs, assisted by chest clapping and vibration, is recommended two to four times daily. The frequency depends both on the degree of pulmonary involvement of the individual and a realistic estimation of the time and energy each patient and his/her family can commit. The importance of adequate and consistent physiotherapy should, however, not be underestimated, being one of, if not the most, important factor in preventing respiratory infection and in aiding antibiotics to eradicate the infection once it has occurred.

Physical exercise, breathing exercises and effective coughing are encouraged to make the best use of the lungs and to keep the respiratory tract clear. Older children and adults are encouraged to learn the forced expiration technique (FET) whereby a small breath is taken in and then, with the mouth open, air is squeezed out of the lungs. FET can be carried out independently by the patient and thus without help from family and friends. Besides being an efficient means of clearing excess bronchial secretions, FET provides an important degree of independence for the individual. Aimed at encouraging patients to partake in as much physical exercise as they feel able to manage, some CF centres have organised swimming and horse riding clubs. Such activities also play an important role in the psychological and social aspects of care, aiding the very important normalisation of the child.

The need to control and prevent infection underlines the need for immunisation in patients with CF. Vaccination against whooping cough (pertussis) and measles is most important as both these infections may result in lung damage. Other routine vaccinations,

4 In some cases intravenous therapy can be maintained at home.

such as diphtheria, tetanus, poliomyelitis, rubella and BCG are also important. In addition, annual immunisation against influenza should be considered especially at times when epidemics threaten and the strain is known so that a specific vaccine can be given.

The role of inhaled mucolytic therapy in the early prevention of lung disease remains to be clarified, although mucolytic agents are sometimes administered with the aim of reducing the viscosity of the sputum. These agents, which act by increasing the water content of the sputum directly or by osmosis, by enzymic action or by the splitting of sputum glycoprotein disulphide bonds, are usually administered by intermittent aerosol inhalation.

Bronchodilator treatment is used in some circumstances to improve air flow obstruction. Studies have demonstrated, however, that it is successful in only a minority of patients and may cause a significant deterioration in a few (Landau and Phelan 1973, Pitcher-Wilmott *et al* 1981).

Despite the tendency among clinicians and researchers to concentrate on the pulmonary manifestations of the disease, nearly all patients with CF suffer alimentary disorders of some kind. Usually they are unpleasant and occasionally fatal. As with the lungs, the impact of the digestive disorder varies from patient to patient and age to age, and hence treatment has to be adapted to the needs of the individual.

The digestive disorders associated with CF are generally a consequence of one or two factors. The first is pancreatic enzyme deficiency which causes malabsorption and hence nutritional impairment and the second is the effect of chronic chest disease. Management of digestive complaints can broadly be discussed under three headings: pancreatic enzyme replacement, vitamin supplementation and dietary management. Focusing on the first of these, the administration of pancreatic supplements with each meal and snack is the mainstay of treatment for pancreatic malabsorption. A number of preparations are available and in various forms – powders, capsules, granules and tablets. The type of product and dosage has to be tailored to the needs of each patient such that steatorrhoea is minimised and nutrition is maximised.

Turning to vitamin supplementation, pancreatic insufficiency may result in malabsorption of fat soluble vitamins, notably vitamins A, D, E and K. Although the signs of vitamin A and D deficiency are very rare, it is common practice to give these vitamins in twice the normal dosage. Vitamin K supplementation is given in cases where liver disease, a feature of CF in 25 per cent of cases, leads to blood clotting dysfunction. Unfortunately as the age of CF patients increases, so does the incidence of liver dysfunction

and in some patients it can be their major problem. CF is now an important cause of hepatic cirrhosis and portal hypertension in adolescence and young adults. The need for vitamin E supplementation has still to be confirmed, although neurological signs associated with low concentrations of vitamin E have been reported in a few patients with CF (Muller *et al* 1983).

Most patients with CF are underweight and whilst this is partially attributable to chest infection, it is usually accompanied by some malnutrition as well, meaning dietary management is an important aspect of treatment. High intake of proteins and calories in addition to regular pancreatic and vitamin supplements is recommended. Nutritious snacks between meals are also an important source of extra calories. In addition, medium chain triglycerides, oils and fats derived from coconut oil, may be used as dietary supplements to provide extra calories or as partial replacement of the usual long chain dietary fat. In those patients who fail to gain weight and/or have persistent frequent stools, despite pancreatic enzyme supplements, cimetidine or ranitidine may occasionally be helpful to reduce gastric acid production, for acid inactivates pancreatic enzymes.

Whilst pancreatic exocrine insufficiency is generally regarded as the second most important manifestation of CF, causing malabsorption it may also lead to meconium ileus equivalent which itself causes much suffering. Other gastrointestinal complications, include gall stones, recurrent acute pancreatitis, intussusception and duodenal ulcer at an age when they would otherwise be unexpected. Thus the management of gastrointestinal disease in CF is of equal importance to that of pulmonary disease.

The possibilities for prevention

Until recently virtually nothing was known about the primary cause of CF. After several decades of research by biochemical, physiological and immunological methods scientists and researchers failed to unearth the basic defect. However, the discovery at the end of 1985 of the location of the CF gene has raised new hopes and represents a significant breakthrough.

Research groups in London, Copenhagen, Toronto and Salt Lake City, Utah have found that the gene defect causing CF is located in the middle of the human chromosome number seven. The research groups have discovered other genes which surround the CF gene and can be followed through families where the disease occurs. Those reported by the London and Salt Lake City

Table 8 **Approaches to the prevention of genetic disease**

1.	Mutagen control
2.	Population screening and prospective counselling
3.	Retrospective counselling
4.	Maternal screening
5.	Prenatal diagnosis
6.	Neonatal screening

Source Adapted from Weatherall D J. The impact of a new method of gene analysis on screening for genetic disease, in The Value of Preventive Medicine, Ciba Foundation Symposium, 1985 110.

research groups are such close neighbours that they are inherited with the cystic fibrosis gene every time. The London group, based at St Mary's Hospital, Paddington, have found three genes from chromosome seven which are co-inherited and are known as 'markers', since they mark the position of the CF mutation. Researchers from Toronto and Salt Lake City, Utah have described two further markers and scientists are now working together to develop a set of markers surrounding the CF defect.

In all, over twenty scientists pursued the gene for five years before this breakthrough was announced. Blood samples were taken from over 200 children with CF and their families in many countries to follow the inheritance of the disease, which only occurs when the CF gene is inherited from each parent. It is hoped that one consequence of this discovery will be the development of new tests to identify the two million or so carriers of the gene for CF.

Table 8 outlines the various approaches to the prevention of genetic disease. The possibilities for prevention related to CF will be considered under five headings; prospective genetic counselling, prenatal diagnosis, neonatal screening, retrospective counselling and the prevention of complications.

Prospective genetic counselling involves screening large populations and then offering appropriate advice about marriage. In the case of CF this entails detection of the CF gene for the identification of CF carriers. As noted above, it is hoped that in view of the recent developments suitable carrier detection tests will soon be available. In the past no test has been shown to identify 100 per cent of known heterozygotes[5] in a blind study.

Prospective genetic counselling is particularly useful in the management of a CF family. If a CF patient should marry it is

5 Carriers of one defective gene, as opposed to a pair.

clearly important to know the carrier status of their spouse. Similarly carrier detection tests would be beneficial to identify which siblings of a CF patient are carriers so that the risk to their future children can be assessed, and if necessary the spouse can be tested. The frequence of the CF gene is also such that pre-pregnancy carrier testing of normal couples without a family history of CF would be of value, provided a simple, accurate and inexpensive carrier detection test was available.

Prenatal diagnosis or antenatal screening is primarily restricted to conditions such as spina bifida and Down's syndrome considered to be of such severity that termination of pregnancy is indicated. Attempts to recognise the CF foetus in early pregnancy have so far been largely confined to parents who are known to be CF carriers, that is those who have already produced a CF child. For many years there has been a search for methods which can diagnose CF prenatally and recently Brock and colleagues (1985) in Edinburgh have been successful in developing such a test.

Their method involves the analysis of amniotic fluid obtained from around the developing baby by needle puncture through the uterus. Amniotic fluid is procured at 17–18 weeks of pregnancy and the proportion of alkaline phosphatase which is of intestinal origin is measured. This isoenzyme is markedly decreased in amniotic fluid when the foetus has CF. For babies born into families where a previous child has CF results have given a high degree of accuracy for prediction of the CF foetus.

Whilst the development of this test is undoubtedly a step forward, it is nevertheless based on a secondary manifestation in the disease. The recent discovery of the location of the gene for CF, however, has important implications for future prenatal diagnosis. Having located the gene, vigorous attempts will now be made to identify the gene itself and to find out what it produces. This in turn, will enable the development of a prenatal test that avoids the need for family studies and is based on the primary gene defect.

Neonatal screening is generally restricted to conditions for which there is a useful therapy. The value of screening for CF in neonates has been the centre of debate for several years. The lack of a cure, and the lack of adequate proof of efficacy of early treatment of CF have together undermined the case for screening. Set against this, however, is the obvious advantage of enabling appropriate treatment to begin *before* serious pulmonary disease becomes established. In addition the diagnosis of CF in the neonatal period enables earlier genetic counselling to be given to the parents of the affected child possibly preventing the birth of a second affected foetus.

Table 9 **Neonatal screening test for the detection of cystic fibrosis.**

Method	*Comment*
The Palm Test	No value during first 2 months of life. Low cost. No prospective.
Meconium albumin tests (B-M test).	Low cost. Rapid. High rate of false negative (25%) and some false positive results.
Meconium lactase activity	Improves specificity of the B-M test. Adds to cost.
Faecal trypsin assay	Low cost. High rate of false negative results especially when pancreatic function is adequate.
Blood immunoreactive trypsin (IRT)	High sensivitity and specificity. Low rate of false negative results reported. Requires central laboratory facilities. Average cost.

Source Kuzemko J A, Heeley A F, Diagnostic Methods and Screening. In Hodson M E, Norman A P, Batten J C (eds) Cystic Fibrosis, Ballière Tindall 1983.

Table 9 describes the neonatal screening tests available, and comments on their suitability for use. The ideal test is one which is specific to CF, sensitive, cheap and painless. That is, no babies would be identified as having CF who do not, and all babies who have the disease would be detected. At present, there is no national policy towards routine screening for CF, although it is performed routinely in a few centres. It has been suggested that screening should be restricted to a limited number of centres until a procedure is fully standardised and pilot prospective studies have been performed to assess the efficacy of early diagnosis and treatment. Preliminary reports suggest that the outcome for babies detected by screening is more favourable than those recognised by symptoms, although further studies and longer follow up are required.

The importance of *retrospective genetic counselling* should not be underestimated. It is not enough simply to warn parents of a CF child that there is a 1 in 4 risk to further CF children. The mechanism of inheritance needs to be clearly and simply explained and emphasis placed on the fact that the 1 in 4 chance of recurrence in siblings is theoretical and all pregnancies carry the same risk. The counsellor should point out the various options relating to further children which the parents of a CF child face, and try to dispel any feelings of guilt or shame there may be within the family. As the patient with CF grows older the emphasis of counselling will gradually shift from the parent to the patients. It is clearly impor-

tant for the CF patient to talk about the disease, to understand more about it and to come to terms with its particular implications in their own family.

The possibility for prevention can finally be considered in terms of the *prevention of complications* – both medical and psychological. There is pressing need to develop new and improved ways to prevent pulmonary complications and pancreatic malabsorption, and to improve existing methods, as well as to develop new approaches, into the psychological aspects of the management of CF.

It is clear that at present there are no effective means of primary prevention suitable for routine use – carrier detection and intervention before pregnancy – although research may soon offer such possibilities. The developments in the latter half of 1985 undoubtedly have important implications for carrier detection and subsequent genetic counselling, prenatal diagnosis and even potentially for national treatment. In the meantime, secondary prevention, in the form of genetic counselling and the prevenion of complications, is a realistic means of prevention which can help to reduce the frequency of CF and minimise psychological difficulties.

Social aspects

Despite the positive trend in prognosis, the diagnosis of CF is still a catastrophe for the family. It is difficult for parents to accept the fact that their child has inherited a chronic disease for which there is no known cure and furthermore that they are faced with the prospect that future offspring could be similarly affected. Thus the diagnosis can cause problems in the closest of families and the most stable of marriages. It is for this reason that the psychological and social aspects of CF care are most important if the management of the patient and the family is to be successful. And, like the medical aspects of treatment, the emotional and social aspects should begin immediately after diagnosis and then continue throughout the patient's life to be followed up within the family after the patient's death.

Much of the literature and research on the psychological problems associated with CF is anecdotal in nature. It has, however, become apparent that over the last 10 years there has been a notable change in the reactions of children and their families, such that many are able to cope remarkably well with the stresses of a chronic condition. Earlier studies on the emotional state of child-

ren with CF suggested that emotional disturbance was frequent and often severe. The reasons for this apparent change lie partly in the nature of the earlier studies, which were based either on small numbers or on a particular cultural group, and partly in the notable improvement in life expectancy which has undoubtedly changed the expectations and attitudes of children and parents.

The fact that more and more CF sufferers can now reasonably expect to enjoy adolescent life has nevertheless brought new problems and challenges. The problems that everyone faces on reaching adolescence and adulthood, such as educational choices, establishment of relationships and the necessary adjustment to new environments and decisions concerning jobs and marriage are likely to make special demands on the person with CF. In particular, a teenager with CF, like all teenagers, may go through a rebellious phase when physiotherapy, medication and diet are refused. He may be embarrassed when people comment on his continual cough and when he has to tell his friends about his illness.

Despite recognition of these difficulties, studies of adolescents and young adults indicate that many of them are psychologically well-adjusted to their illness. In 1981 Bywater interviewed 27 patients aged 12–16 years with CF and found that all of them appeared to be well-adjusted. None had special problems at school, they were not socially isolated and family relationships seemed good. Comparison with a group of healthy adolescents and their mothers showed, however, that the patients had a slight tendency towards depression.

The psychosocial adjustment of patients with CF is evidenced by the observation of 183 adolescents and young adults attending the Brompton Hospital Cystic Fibrosis Unit. Table 10 shows their occupations, with only three being too ill to work. Under 12 per

Table 10 **Occupations of adolescents and adults attending the Brompton Hospital Cystic Fibrosis Unit, March 1982.**

Students (school and university)	61
Unemployed (too ill to work)	3
Unemployed (unable to find suitable work)	13
Housewife	9
In employment	97
Total	183

Source Norman A P and Hodson M E, Emotional and Social Aspects of Treatment, In Hodson M E, Norman A P and Batten J C (eds) Cystic Fibrosis, Ballière Tindall 1983.

cent of those available for work, excluding housewives and students, were unemployed. These figures are all the more encouraging when one takes the problem of mass unemployment into consideration which means that not all young people who are physically fit can find employment. Care should be taken, however, in interpreting the Brompton data as they are based on a small selected sample of CF patients.

The results of a follow-up study from the US of 75 patients aged 18 years and over with CF, published in 1979, (Sant'Agnese and Davis) again reinforces the view that adolescents and young adults appear well-adjusted to their condition. Of the 38 surviving patients, 69 per cent (27 patients) were either at work, attending school or undertaking housewife responsibilities full-time. The group included a physician, several engineers, teachers, a political assistant, several sales people and two manual labourers. Six other patients were at work or attending school part-time. As the authors of the report are careful to point out, however, the data do not reveal the difficulties frequently encountered by these people, including interrupted schooling for hospitalisation, selection of occupations compatible with future reduction in physical capacity and the use of holidays for hospitalisation with consequent reduction of time for rest and recreation.

It is to be expected that some patients with a chronic disease such as CF will be isolated and socially deprived. However, many appear to be successful at interpersonal relations as reflected in Table 11 which illustrates the social status for the same patients attending the Brompton Hospital. From a total of 83 women 25 are married, compared with nine out of 100 men, suggesting that for some reason female patients find it easier to find a partner than males. Despite the stress caused by a chronic condition, the

Table 11 **183 Patients March 1982 – social data.**

	Females (83)	Males (100)
Married	25	9
Single	53	89
Divorced	1 (remarried)	1 (remarried)
Engaged	5	2
Children	6 plus 2 adopted	1

Source Norman A P and Hodson M E, Emotional and Social Aspects of Treatment. In Hodson M E, Norman A P and Batten J C, (eds) Cystic Fibrosis, Ballière Tindall 1983.

Brompton data suggest that most marriages are intact. In addition, six mothers have borne children.

However, with improved survival, increasing numbers of patients are reaching their productive years and problems associated with sexual function and reproduction are being encountered more and more frequently. Young men often become distressed when they discover that they are unlikely to produce children of their own. There is a need for careful and sympathetic counselling to explain that fertility, although unlikely, is possible and that sexual activity is not affected. Fertility among females with CF is often reduced, the thick cervical mucus possibly presenting an impediment to the passage of spermatozoa. Pregnancy presents a significant hazard for both mother and offspring because of the potential adverse effect of pregnancy on pre-existing pulmonary disease. Furthermore, there is the probability that the offspring may lose a parent prematurely. An additional problem lies in the increased risk of producing a child with CF, 1 in 40, if the father is of unknown genetic status, versus 1 in about 2,000 in the general population.

There is no doubt that the increase in life expectancy enjoyed by many CF patients today has resulted in new challenges and problems. This underlines the need to ensure as good a quality of life as possible for CF victims as opposed to merely extending life in a state of misery. The healthy person has enough stress in adolescence but the frustrations of the problems of CF, the challenges of marriage, child bearing, child rearing, further education and work are particularly severe. Moreover, they present the counsellor with a new set of problems, as reflected in a comment made by the opening speaker at the '1000 years of CF' conference at the University of Minnesota in 1981. He said 'I once spent a considerable amount of time extolling the virtues of adoption to a premarital adolescent CF girl only to be confronted at a later time with the onerous duty of filling out a form from an adoption agency, attesting to the now pulmonary crippled, married young woman's ability to care for or raise a baby.'

Economic aspects

Estimates of the cost of a disease, either to society or to an individual must be treated with caution. Indicators such as lost national or personal income or years of productive activity can be misleading in that they tend to overstate the cost of diseases which predominantly affect those of working age and underestimate the costs of conditions which chiefly affect the elderly.

The task of costing CF is complicated by the absence of specific reference to the disease in routine sources of data on which estimates of cost are usually based. Under these circumstances, it is necessary to turn to alternative measures, such as a recently published budgeting exercise (Lamb and David 1985) carried out at Booth Hall Children's Hospital in Manchester, to obtain some useful guidelines with which to work. The immediate disadvantage of using this kind of information is that it relates to a specific hospital and its applicability on a national basis is subsequently open to question.

In the study cited above, each consultant was firstly asked to categorise his patients according to their clinical condition. The cost per in-patient stay at 1982–83 prices for each health care group for one paediatrician is demonstrated in Table 12. For CF the estimated figure is £1,606, being seven times greater than that for asthma and over 11 times more than that for respiratory infection.

Table 12 **Cost of treating patients in each health care group for one paediatrician per hospital admission.**

No	*Health care group*	*Cost (£)*
1	Asthma	229
2	Bronchiolitis	414
3	Croup	114
4	Respiratory infection	140
5	Viral illness	89
6	Febrile convulsion	192
7	Fever of unknown origin	231
8	Feeding difficulties	303
9	Failure to thrive	354
10	Poisoning	94
11	Eczema	1,273
12	Cystic Fibrosis	1,606

Source Lamb S M and David T J, 1985. *British Medical Journal*, 290, 650–651.

Table 13 **Health care group 12 (cystic fibrosis): average resources consumed per admission.**

Resource		*Quantity*	*Units*
Consultant	(time spent)	6	Hours
Registrar	(time spent)	5	Hours
Senior house officer	(time spent)	10	Hours
Nurses	(time spent)	40	Hours
Physiotherapist	(time spent)	28	Hours
Social worker	(time spent)	0.1	Hours
Dietician	(time spent)	4	Hours
Medical/surgical equipment		10	Units
Ceftazidime		50	Grams
Intravenous fluids		240	Hours
Duration of stay		10	Days
Terbutaline aerosol canister		192	Puffs
Nebuhaler		0.8	Units
Vivonex		2	Packets
Triosorbon		6	Packets
Medium chain triglyceride oil		1	Litre
Ceres margarine		2	Tubs
Ketovite tablets		42	Tablets
Ketovite syrup		70	ml
Pancrease		280	Capsules
Oral-N-acetyl-cysteine		6	Ampoules
Ultrasound liver scan		0.5	Examinations
Chest radiograph		0.75	Examinations
Barium swallow radiographs		0.02	Examinations
Liver function test		1	Test
Urea and electrolytes		2	Test
Sweat electrolytes		0.04	Test
Y-Glutamyl transpeptidase		0.1	Test
Full blood count		1	Test
Prothrombin time		0.1	Test
Sputum culture		10	Test
Nasal smear for eosinophils		0.05	Test
Total IgE		0.15	Test
Secretarial time		2	Hours
General services		10	Days

Source Lamb S M and David T J, 1985, *British Medical Journal*, 290, 650–651.

Table 13 represents a 'resource recipe' or list of the average resource requirements per admission for CF. There is good reason to assume a high degree of accuracy in the compilation of this list as reflected by the efforts of those concerned to cross-check the data and also to ask other members of the medical team – registrars, senior house officers, nurses, physiotherapists, dieticians and medical illustrators – to estimate resource recipes for the basis of comparison. The cost per in-patient stay for patients with CF was based on an average length of stay of 10 days.

The CF unit at this particular hospital is attended by 100 patients. The projected figure for the number of admissions for these patients for 1985 is 123. Using this information, estimated annual hospital in-patient costs for the treatment of CF at Booth Hall Children's Hospital are around £197,538.

Application of the estimated cost per in-patient visit to the general population with CF suggests that overall hospital in-patient costs for the disease are just under £12 million. Although accounting for a very small proportion of total NHS hospital expenditure the cost per individual in-patient visit, as already indicated, is comparatively high. This is further evidenced by comparisons with hospital in-patient costs for, say, back pain (OHE, 1985). The cost per in-patient stay for CF is nearly twice as much even though the average length of stay for back pain is two and a half days longer than that for CF. By contrast, total in-patient cost for sufferers of back pain is nearly five times greater than that for CF at £58.8 million. This is chiefly explained by the difference in numbers of in-patient visits. For back pain sufferers the appropriate figure is 63,000 whereas for patients with CF it is probably less than 7,500.[6]

The accuracy of such estimates must be considered in the light of a number of uncertainties on which they are based. One would expect the hospital costs for CF to be high, given the nature of the management of the disease and daily requirements. The particularly high costs of Booth Hall Children's Hospital are partly attributable to the availability and use of a relatively new but expensive antibiotic, ceftazidime. The availability of this compound, has resulted in a treatment policy whereby children with CF whose lungs are colonised with pseudomonas are admitted every three months for a 14-day course of intravenous antibiotics. This has inevitably increased the number of admissions and the cost of treating the disease, with ceftazidime accounting for 25 per cent of this hospital's medicine bill.

An advantage of the use of ceftazidime is that it need be given only three times a day. This has led the adult clinic in Manchester to permit self-administration of ceftazidime at home after treatment has been initiated in hospital, in selected cases. Children in Peterborough have been similarly treated at home with the assistance of general practitioners and trained nurses. Home therapy inevitably results in considerable savings in hospital costs.

To some extent, however, this is counteracted by the fact that

6 This figure is derived by multiplying the estimated number of CF sufferers, 6,000 by the average annual figure for the number of hospital admissions, 1.23.

the assumed rate of hospitalisation for the general population with CF is taken to be 1.23 times per annum, with an average length of stay of 10 days. In practice, it is extremely difficult to calculate the average annual number of admissions for a disease such as CF which exhibits varying degrees of severity throughout its course and may require frequent periods of hospitalisation at some points in time and fewer hospital visits at others. The length of stay also varies considerably depending on the clinical status of the patient, the treatment required and very often home circumstances.

The cost of outpatient consultations constitutes a possibly even greater drain on resources. In the absence of routine national data, it is again difficult to estimate these costs. Nevertheless, the number of outpatient visits is likely to be relatively high, given that nearly all patients with CF need to make regular outpatient visits to enable the physician to monitor their state of health.

The economic implications of CF are not, of course, confined to the in-patient and outpatient costs imposed upon the NHS. Until the last decade or so, few patients were expected to reach adolescence or adulthood and thus contribute towards the output of the economy. Taking the average income in all industries and services in 1984 as a base line, and assuming that patients with CF lose an average of 47 years of working life, the indirect costs of CF, as measured by future lost national income, are estimated to be around £582 million for 1984.

Again, the accuracy of this estimate is questionable, since many patients with CF are now able to work and thus contribute something towards national output. Furthermore, the estimate is based on an average annual increase in income of 5 per cent over the next 47 years which could be an overestimate or underestimate depending on the changes in the economic climate.

The personal and social costs of CF are even less easy to quantify than the overall burden on society. There is little doubt, however, that the expense of caring for a child or adult with CF – or indeed any chronic disease – remains a considerable drain on family resources. A special diet is often costly, as is medication, and travel to and from hospital has become increasingly expensive, thereby increasing the financial burden. In some circumstances patients are entitled to a variety of state benefits to cover such expenses, such as Attendance Allowances and Supplementary benefit. For those over sixteen years of age, prescriptions have to be paid for and there are at present no exemptions, unlike other chronic diseases such as diabetes.[7]

7 CF patients may purchase a four or twelve month prepaid 'season ticket' which covers the cost of all prescriptions.

In addition to these kinds of costs, CF almost always results in severe personal hardship with substantial intangible or social costs. In some cases this relates to physical difficulties which prevent participation in certain activities and for some employment. In others it relates to social handicaps which prevent the sufferers themselves and those involved with them from enjoying normal social activities. Very often one parent is prevented from going to work by the very fact that he or she is needed to help provide physiotherapy, special meals and general care and support for the chronically sick child. The physical appearance of the child is often inhibiting and can result in social isolation and deprivation. Furthermore, as the prognosis for patients with CF has improved, the personal costs incurred as a consequence of inability to reproduce and the prospect for those couples with children that one parent may die prematurely before their child has reached independent status, is not easily quantified but represents an important element of the overall cost of the disease.

One further category of cost which should be considered is that of research. Throughout the world there are a number of voluntary societies which raise money for research into CF and work to improve conditions for sufferers from chronic illness. In the United Kingdom, by far the greatest amount of money for research comes from the funds of the Cystic Fibrosis Research Trust (CFRT). In 1984 research expenditure by CFRT was almost two-thirds of a million pounds and it was expected that this figure would be exceeded in 1985.The significant increase in knowledge obtained through this research and that of similar organisations in other countries has undoubtedly brought substantial rewards, as reflected by the remarkable improvement in life expectancy and quality of life, and the recent formation of the Association of Cystic Fibrosis Adults.

The Medical Research Council supports research into CF to a limited extent, although facilities for research workers with external support are available in NHS hospitals. In addition, there is some industrial research carried out, for example, by pharmaceutical companies in the development of new and improved formulas.

Finally, it should be acknowledged that the increase in life expectancy has important economic implications in respect of the consequential increase in expenditure on CF patients. Since their treatment now extends over many years the expense of caring for a CF patient is by implication increased. Given the limited availability of resources, increased expenditure in one area of health

care, in this case CF, inevitably results in fewer resources available for alternative health care activities.

Conclusion

The significant increase in knowledge obtained through research in Britain and abroad has led directly and indirectly to a notable improvement in life expectancy for patients with CF. Just 50 years ago survival was measured in months rather than years, whereas today many patients survive into adolescence and adult life. Despite this achievement, however, many fundamental problems associated with the disease remain unsolved. Above all, the disorder is a life threatening disease for which, as yet, there is no cure.

The 1979 report of the 'First Fifteen Years' by the Cystic Fibrosis Research Trust sets out the long-term aims of research into CF. The four main aims are depicted as the identification of the basic biochemical abnormality, the development of tests for detection of the affected foetus in early pregnancy, the development of tests for carrier detection and the development of mass infant screening tests.

As indicated earlier in the text, some progress has been made in most of these areas, and the developments at the end of 1985 have raised new hopes for prenatal diagnosis, carrier detection and improved treatment. For many years research has been confused by conflicting evidence and proposals but it is hoped that the latest discoveries will enable the gene responsible for causing CF to be identified.

In an attempt to identify the basic biochemical fault, past research efforts have focused on specific abnormalities identified in the blood and biological fluids known collectively as the 'CF factors'. In addition, several researchers have identified the so-called CF protein. Current evidence suggests, however, that the CF protein is not a primary product of the basic gene defect. In a letter to *Nature*, van Heyningen and colleagues (1985) suggest that their serum protein is derived from chromosome one, whereas the latest evidence indicates that the CF gene is on chromosome number seven. Other specific areas of research include the investigation of abnormalities of CF cells in culture, enzyme activities of CF cells and membrane studies of CF. The possibility of a defect in the immune and complement systems has also been closely examined since recurrent infection is an important feature of progressive pulmonary involvement.

In recent years recombinant DNA technology has been developed so that there are now ways to study genes directly at the molecular level. For diseases where the affected gene product is known, it has proved possible to isolate the gene as a DNA recombinant and to study the molecular pathology directly. To be successful for CF it is necessary to have a strategy to isolate a specific gene probe that can recognise the defective gene in CF.

The three research groups from London, Toronto and Salt Lake City have produced radioactively labelled DNA probes that delineate regions of human DNA close enough to the CF gene to be inherited preferentially with it in some families. Once the abnormal gene is isolated and the basic defect is unearthed, new avenues in prevention, treatment and cure may eventually lead to elimination of the disease.

A high degree of success has already been achieved in the diagnosis of CF in the unborn baby. Brock's test for prenatal diagnosis detects the disease correctly in 95 per cent of cases and the technique has been adopted in Paris. The implications of a suitable test to detect CF at an early stage of pregnancy are widespread, allowing the mother to opt for termination of pregnancy, if desired. At the moment, however, a foetus is tested for CF only if a couple has already produced a child with CF and hence are known to be carriers. It is unlikely that such a strategy will lower the incidence of the disease. The only way to prevent the birth of most children with CF would be to test all pregnant women and if necessary their sexual partners for the gene, and then offer prenatal diagnosis for pregnancies found to be at risk. As an alternative to screening and abortion an additional long-term aim must be to find a cure for the disease.

Some progress has been made towards the development of a suitable method to identify unaffected carriers of the CF gene. Unfortunately, none of the test systems has yet proved sufficiently reliable for routine clinical use. Yet, given the high frequency of the disease, an accurate and inexpensive carrier detection test would no doubt be of considerable value. As noted above it is hoped that reliable tests for carrier detection will soon be developed as a consequence of the latest discoveries.

Further advances in all these areas will undoubtedly open up new horizons in the treatment, prevention and cure of CF. Significant improvements in life expectancy have, in the meantime, already been achieved. And yet, whilst the mean life span is now between 20 and 25 years, in recognised CF centres, probably less than 25 per cent survive into their 30s. To repeat, CF is the commonest genetically determined disorder in Britain. When com-

pared with, say, the thalidomide tragedy which affected a *total* of between 400 and 500 babies in Britain, public awareness of CF is astonishingly limited. Few people are aware that it is an inherited disease which for the same number every year reduces life expectancy to about 20 years and, for many, results in years of suffering and distress.

This report suggests that the history of CF is moving into a new phase. Whilst recognising that it is still a very serious disorder with a high risk of early death, emphasis is now placed on early diagnosis and active treatment in the likelihood of patients progressing through infancy and childhood to adolescence and early adulthood. However, optimistic predictions about CF research should be made with caution. In the past, affected families, many of whom are active in support of the research effort, have suffered the distress of too many false hopes. Nevertheless, there seems considerable hope that the basic defect in CF will be identified during the next few years.

In the meantime, centres of excellence for the treatment of CF patients can achieve improvements in the quality and length of life, when compared with the outcome achieved in non-specialist settings. This argues strongly for the provision of a larger number of such centres under the NHS. At present less than half (46.5 per cent) of CF patients are on the records of such centres.

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