PERSONAL PRACTICE

Cystic fibrosis

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The median age at death from cystic fibrosis has increased from six months in 1959 to 17 years in 1986.¹ It is assumed, although proof is lacking, that this improved survival is the result of the liberal use of better antibiotics, closer attention to nutrition and improved pancreatic enzyme supplements, more successful management of meconium ileus, increased ascertainment of milder forms of the disease, and the development of special centres. In the past, incurability was both an attitude of mind and a self fulfilling prophecy, and the notion of early demise insidiously undermined treatment and sapped therapeutic zeal. The greatest change has been a more positive approach. Regrettably, enthusiasm to treat has not been matched by good quality clinical trials, which are hampered by the highly variable nature of the disease, the complexity of clinical scoring systems, and by a system of medical research that encourages short term single centre projects (often carried out by passing registrars whose real interests are not research) when the major need is for longer term multicentre studies of therapeutic approaches. As a result, the modern management of cystic fibrosis remains largely unvalidated. Heated debate about the value of cystic fibrosis centres, the reasons for better survival in certain towns and countries, and the usefulness of neonatal screening are the legacy of poor data. There is a danger that hopes for a cure arising out of research in molecular biology may impede more down to earth objective evaluation of current and future treatment strategies.

Suspecting the diagnosis

Common modes of presentation are described elsewhere.² Unfamiliar presentations are: (i) meconium plug syndrome (most cases do not have cystic fibrosis); (ii) failure to thrive, anorexia, and vomiting accompanied by low serum potassium, chloride and sodium concentrations with a metabolic alkalosis (the biochemical features of pseudo-Bartter's syndrome)—cystic fibrosis may escape early detection in such infants because of an associated low sweat concentration of sodium³; and (iii) failure to thrive with hypoalbuminaemia and anaemia.

Making the diagnosis

The total absence of one or more major features, which are malabsorption due to pancreatic insufficiency, chronic suppurative lung disease, and failure to thrive, make one especially

cautious in the interpretation of the results of sweat tests. Supportive, but not diagnostic evidence are: an abnormal chest radiograph, finger clubbing, the presence of *Staphylococcus aureus* or mucoid *Pseudomonas aeruginosa* in the sputum or a cough swab, an increase in faecal fat excretion, or a sibling with cystic fibrosis. Some patients (less than 10% seen locally, but up to 38% in one Canadian series⁴) have sufficient pancreatic function for normal digestion, so that even the most sophisticated direct pancreatic function testing with triple lumen tube infusion of the duodenum can only exclude pancreatic insufficiency, and not cystic fibrosis itself.⁴ The final diagnosis hinges on the accurate performance and correct interpretation of the sweat test.

The standard procedure in sweat testing is for sweating to be stimulated by pilocarpine iontophoresis to achieve the accurate collection of at least 100 mg of sweat.² Sweat sodium and chloride concentrations are below 40 mmol/l in normal children, and lie between 80 and 125 mmol/l in most children with cystic fibrosis.² Values between 40 and 80 mmol/l are an indication for repeat sweat testing at a cystic fibrosis centre, together with a detailed examination of the clinical features to unravel the cause of the respiratory or gastrointestinal pathology, or both. Other possible conditions associated with raised sweat electrolytes are listed elsewhere.²

Up to 10% of patients with cystic fibrosis referred to regional centres are found to have an alternative diagnosis.^{5,6} The main reasons for these errors are disregard of the clinical features or the lack of them, incorrect performance of the sweat test, and faulty interpretation of the results. Some practical suggestions are:

(i) Ensure that the test is performed by one experienced technician who is familiar with the technique and its problems, the most common errors being loss of sweat by evaporation leading to a falsely high result, and faulty technique causing pain and burns. Delegation to junior staff or medical students is inappropriate. Special caution is required where a hospital performs the test infrequently (that is, less than once a week).

(ii) Measure both sodium and chloride. Discrepancies of more than 20 mmol indicate the need for further testing. The sodium concentration tends to be slightly lower than the chloride in patients with cystic fibrosis, and the reverse in normal subjects. The sum of the sodium and chloride values usually lies above 140 mmol/l. Testing the sodium alone may result in the diagnosis being missed in infancy

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when the sweat may exhibit a high concentration of potassium and normal concentration of sodium.³

(iii) Beware the trap of believing one result in favour of another because it fits with the perceived diagnosis. An example is the patient with a sweat sodium of 51 and 45 mmol/l. A third result was 86 mmol/l and cystic fibrosis was incorrectly diagnosed, disregarding the two previous results not in the range for cystic fibrosis.

(iv) Normal teenagers and adults have higher sweat sodium concentrations than normal children, and 5 to 10% of normal adults have values greater than 60 mmol/l.

Genetics and screening

Referral to the genetic clinic is best made soon after the diagnosis of the first affected child. A calm appraisal of the issues is precluded if a pregnant mother is referred to the genetic clinic as an emergency. Antenatal diagnosis is now possible by analysis of fetal DNA obtained from a chorionic villus biopsy specimen, and in the small proportion of families where this test is uninformative, a less specific test of amniotic fluid for microvillar enzymes can be carried out.

Measurement of the serum immunoreactive trypsin is a useful screening test in the newborn period with only about 1 in 30 000 false negative results, but false positive results (0.3% false positive on first test) mean the diagnosis cannot be made on the results of this test alone.⁷ Screening would abolish late diagnosis, but remains controversial.

Monitoring of patients

Close monitoring of bacterial pathogens in the sputum is a prerequisite for rational antibiotic treatment. Specimens of sputum or throat swabs can be sent by post to the laboratory regularly (for example, every two weeks), enabling the prompt recognition of new pathogens or the emergence of antibiotic resistance.

Visits to the clinic are customarily recommended every six to 12 weeks to monitor the patient's progress, to detect complications or lapses in adherence to treatment, and to continue parent and patient education in the management of the disease. Routine monitoring includes weight, height, lung function tests, occasional checks on the parents' physiotherapy technique, and a six monthly chest radiograph.⁸ An annual abdominal ultrasound examination can be used to detect the development of cirrhosis (untreatable), enlargement of the spleen (also detectable by abdominal palpation) indicating portal hypertension, and gall stones (usually asymptomatic in children). The value of information obtained from ultrasound scans is offset by the annual parental alarm generated by a test that detects largely incurable complications.

Vaccination

There is a special need to ensure that pertussis and measles vaccinations are not delayed (for

example, because the patient has a cough). Influenza can be catastrophic, and there is a case for giving annual influenza vaccination to all patients, giving a half dose to children aged 1 to 3 years (despite the fact that the vaccine is not licensed for use in children under 4 years of age). Deterioration in respiratory function after chicken pox⁹ has led us to use intravenous acyclovir 10 mg/kg/dose, three times daily for five days, starting at the onset of the rash. Eventual exposure is inevitable so there is little point in giving zoster immune globulin after discovery of contact with chicken pox, but it would be helpful if varicella vaccine became freely available. A controlled trial of polyvalent pseudomonas vaccine showed that it failed to prevent pseudomonas colonisation or modify the progress of the disease.¹⁰

Antibiotics

Concern about antibiotic resistance, a lack of objective evidence of efficacy, and high cost have all been used as arguments against the routine use of antibiotics. As one of the main aims of treatment is to prevent lung damage, however, there is no logic in waiting until the patient is coughing up large volumes of purulent sputum or has a high fever. We actively seek respiratory pathogens by frequent sputum culture, and the antibiotic policy is determined by the state of the patient and the pathogens that are isolated.

(i) *Haemophilus influenzae*

As soon as *H influenzae* has been isolated, we prefer to treat with antibiotics (for example, amoxycillin) rather than wait for new symptoms. Amoxycillin resistance necessitates the addition of clavulanic acid or the use of erythromycin.

(ii) *S aureus*

The main aim of giving lifelong oral flucloxacillin is to prevent staphylococcal pneumonia during an intercurrent viral infection. Even with huge doses of flucloxacillin (for example, 3 g four times daily to a 10 year old) combined with fusidic acid (for example, 250 to 500 mg four times a day to a 10 year old), eradication of *S aureus* from the sputum is almost impossible to achieve with antibiotics given orally. Aggressive intravenous regimens using a combination of clindamycin and fusidic acid¹¹ may have a place in the treatment of patients with symptoms in whom *S aureus* is repeatedly recovered from the sputum despite oral antistaphylococcal antibiotics.

(iii) *P aeruginosa*

With the exception of oral ciprofloxacin, the use of which is curtailed by the swift development of permanent resistance, all antipseudomonas antibiotics have to be given by injection (or inhalation). In the past this meant that treatment was confined to acute severe deteriorations with fever. In many units, including ours, this expectant policy has been replaced by a regimen of three monthly courses of intravenous antibiotics for 10 to 14 days in any patient in whom

P. aeruginosa has been recovered from the sputum on more than one or two occasions, regardless of symptoms.¹² It is claimed that such treatment has improved survival,¹³ but this has not been proved.

With careful training of parents, intravenous antibiotics can safely be given at home in many cases, thereby avoiding eight weeks in hospital each year.¹⁴ First line antipseudomonas antibiotics are ceftazidime, semisynthetic penicillins (for example, ticarcillin) and the aminoglycosides (for example, tobramycin, aiming for a serum concentration of 10 to 12 µg/ml, 15 minutes after intravenous injection). Tobramycin is generally given in combination with another agent, and all are given by intermittent injection. Continuous infusion of ceftazidime (75 mg to 300 mg/kg/day) achieves higher and more constant serum concentrations than intermittent injection, a theoretical advantage which merits further study.¹⁵

Microbial resistance to ceftazidime, aminoglycosides, or penicillins is often temporary. Daily sputum sampling during intravenous treatment enables rapid detection of resistance, and a quick change of antibiotic. The increased renal clearance of the penicillins and aminoglycosides in cystic fibrosis, and the need for antibiotics to penetrate pus filled cavities, areas of poor perfusion, and mucopolysaccharide encapsulated strains of *P. aeruginosa*, all require high antibiotic dosage if treatment is to be effective.

P. aeruginosa cannot be eradicated from the sputum of those with advanced bronchiectasis. Frequent sampling of respiratory secretions, however, commonly shows the presence of *P. aeruginosa* in infancy, sometimes before the isolation of *S. aureus* or the development of radiological changes. In such patients it is common to find that the organism becomes impossible to recover from the sputum after one or more courses of intravenous antibiotics. It is reasonable to discontinue regular intravenous antibiotics if pseudomonas has not been recovered for six to 12 months, being prepared to start treatment again if and when the organism reappears.

Inhaled antibiotics, given immediately after physiotherapy, have usually been regarded as second best, and their role is uncertain. It is possible that inhaled antibiotics may diminish frequent relapses requiring intravenous antipseudomonas antibiotics in those with severe lung disease. Drawbacks to the twice daily inhalation of gentamicin 80 mg and carbenicillin 1 g are the time required to administer the drugs by nebuliser, the development of antibiotic resistance, and adverse reactions. A currently popular alternative is colistin,¹⁶ 1 to 2 million units twice daily; the risks of systemic absorption causing renal damage or deafness are unknown but probably small.

(iv) Other strains of pseudomonas

The recovery of *Pseudomonas cepacia* may be associated with a particularly poor prognosis.¹⁷ Response to antibiotic treatment is poor even if the organism is sensitive in the laboratory, and the best hope is that cessation of antipseudomas

treatment may lead to replacement by *P. aeruginosa*. *P. cepacia* is universally resistant to colistin, and a theoretical worry is that the use of colistin may encourage colonisation by *P. cepacia*. The laboratory will occasionally isolate other strains, such as *Pseudomonas fluorescens*, *malophilia*, *paucimobilis*, *putida*, or *stutzeri*, but it is not clear whether these are respiratory pathogens.

Bronchodilators and steroids

Wheezing is a common feature of cystic fibrosis. It may be caused by acute infection, in which case antibiotic treatment may help, or it may be due to bronchial hyper-reactivity, a common feature of cystic fibrosis. Response to β_2 stimulants is variable, and there are a number of patients with intermittent or persistent wheezing in whom there is little or no response to inhaled β_2 stimulants, ipratropium bromide, disodium cromoglycate, or inhaled or systemic steroids. The onset of, or increase in, asthmatic symptoms, accompanied by fever, an increased eosinophil count, and the presence of pulmonary infiltrates, suggest the development of allergic bronchopulmonary aspergillosis. Skin prick tests or blood tests for specific IgE antibodies are of little diagnostic value as they are positive in a high proportion of all severely affected patients with cystic fibrosis, but a negative test may be helpful by pointing away from the diagnosis. Some patients respond to bronchodilators alone, but if not then oral steroids are effective.

The use of prednisolone carries a risk of provoking insulin dependent diabetes mellitus, an especially unfortunate complication in an already handicapped patient. Impaired carbohydrate tolerance (seen in up to 40% of patients) leading to insulin dependent diabetes mellitus is seen in 1 to 2% of those with cystic fibrosis under 16, but occurs in up to 7% of adults.¹⁸ The suggestion that prednisone given on alternate days may help lung function in mildly affected patients requires confirmation before it can be recommended.¹⁹

Nutrition

Faecal nutrient losses, poor appetite, respiratory infection, and increased energy expenditure explain why patients require above average energy intakes.²⁰ Low fat diets have now been replaced by diets high in fat, protein, and carbohydrate. The new pH sensitive enteric coated microsphere preparations of pancreatic enzymes Creon (Duphar Laboratories) and Pancrease (Ortho-Cilag) have achieved substantially improved fat absorption, accompanied by diminished abdominal distension, stool odour, and number of bowel actions.²¹ Of the two formulations, Creon has a greater lipase content (8000 units BP per capsule, compared with 5000 units BP in Pancrease)²² and its retail price is lower (£22.99 for 100 capsules, compared with £25.57 in June 1989). The previous goal of fewer bowel actions has been replaced by trying to achieve a normal (5 g/day) faecal fat excretion, and this is usually possible with

between five and 20 capsules of enzyme microspheres/meal. Where enzyme supplements fail to abolish abnormal fat loss in the stool, it can sometimes be achieved with the addition of oral ranitidine twice daily or, failing that, taurine supplements* (500 mg twice daily), the mode of action of which is unclear.²³

Breast milk is usually suitable for infants with cystic fibrosis. For formula fed infants, maximal intake of nutrients with a minimal need for pancreatic supplements can be achieved with a casein hydrolysate milk formula to which is added a fat emulsion and additional carbohydrate (appendix 1). For older patients who stop gaining weight and have poor appetites, weight gain can sometimes be achieved by giving nutritional supplements based on skimmed milk powder; examples are Complan (Farley) or Build-Up (Carnation). Suitable carbohydrate supplements are Maxijul (Scientific Hospital Supplies), Caloreen (Roussel), or Polycal (Cow and Gate) and a suitable medium chain triglyceride supplement is Liguinen (Scientific Hospital Supplies). Finally there are flavoured food supplements, for example, Fresubin (Fresenius) or Fortisip (Cow and Gate). Short or long term nocturnal enteric feeding with a peptide based feed (appendix 2), occasionally causes remarkable benefit to general health but can also be an intolerable burden, and the indications for such treatment have yet to be established.²⁰ Where nocturnal feeding is successful and is planned for long term use, the need for a nasogastric tube can be avoided by the simple procedure of an incisionless gastrostomy.²⁴

Although it is common practice to give multivitamin supplements such as Ketovite (Paines and Byrne), and fluoride tablets where the tap water has a low fluoride content, the need for water soluble vitamins is doubtful.²⁰ The need for supplements of fat soluble vitamins is uncertain. Asymptomatic conjunctival xerosis, possibly the result of vitamin A deficiency, has recently been reported in three children with cystic fibrosis, and this is a topic that merits further study.²⁵

Severe deficiencies of vitamin D and K are rare in cystic fibrosis. Vitamin E deficiency causing haemolytic anaemia and only partly reversible spinocerebellar degeneration and peripheral neuropathy is a rare complication of cystic fibrosis, found particularly in patients with liver disease or who have had ileal resection. The risk of vitamin E deficiency merits the routine use of vitamin E supplements in a dose of 45 mg to 200 mg/day. The optimum dose and the role for monitoring serum concentrations are uncertain.

Physiotherapy

A zealous commitment to chest physiotherapy is a universal feature of treatment, but practices vary more than any other aspect of cystic fibrosis management. In Britain physiotherapy

is based on percussion, postural drainage, and the forced expiratory technique (huffing), whereas in many European countries patients are trained to perform the Belgian or German forms of 'autogenic drainage' in which a form of controlled breathing is supplemented by the use of inhalations of moisture, breathing against a positive expiratory pressure, and the forced expiratory technique.²⁶ The advantages of the latter approach comprise patient independence (percussion is eschewed) and greater flexibility tailored to the needs of the patient, but as with all forms of physiotherapy there is need for objective evaluation. It is not clear whether daily and prolonged (30 minutes or more) running or cycling can replace physiotherapy, but the clinical benefits to patients sufficiently committed to vigorous exercise can be impressive.

Complications

Pneumothorax affects up to 20% of teenagers and adults with cystic fibrosis. Recurrences are common, and may require chemical pleurodesis or pleurectomy, though the resulting adhesions may prevent subsequent heart-lung transplantation.²⁷ Mild haemoptysis is common and responds to antibiotic treatment of the underlying chest infection. More severe episodes warrant the exclusion of coagulation defects resulting from liver disease or hypersplenism, and may stop only after blood transfusion and bronchial artery embolisation. Alveolar hypoventilation may lead to hypoxic pulmonary hypertension and cor pulmonale, which has a poor prognosis. Digoxin is no use, but diuretics are of some value for cardiac failure.

Gall stones or sludge in the gall bladder are detectable in up to 10% of children with cystic fibrosis but are asymptomatic, and cholecystitis and biliary colic are mainly confined to those over 16 years of age. Ten to 25% of children develop bile duct obstruction with abnormal mucus, and possibly also stenosis of the common bile duct causing focal biliary fibrosis, the precursor to the development of cirrhosis which affects about 5% of patients by adult life.²⁸ The main complications of cirrhosis are bleeding oesophageal varices and hypersplenism. The standard advice has been to ignore varices until they bleed. The exception is in the patient with varices and thrombocytopenia caused by hypersplenism in whom the first variceal bleed is likely to be fatal, and there may be a case for splenic embolisation in such patients.

Meconium ileus equivalent has almost disappeared with the use of pancreatic enzyme microspheres, and nowadays seems to be mainly associated with insufficient doses of enzymes. The features are colicky abdominal pain, and a faecal mass in the right iliac fossa, plus constipation and sometimes intestinal obstruction. After appendicitis and intussusception have been excluded, mild cases can be treated with oral N-acetylcysteine (for example, 10 ml four times a day) or one or two doses of oral Gastrografin (50 to 100 ml, taken with 200 to 400 ml of water). Those with obstruction require intravenous

*Taurine capsules are made by Istituto Farmochimico Nativelle SPA, Firenze, Italy, and obtainable in the United Kingdom from Idis Ltd, 51 High Street, Kingston upon Thames, Surrey, KT1 1LD, tel 01-549-1355.

fluids, N-acetylcysteine or Gastrografin enemas, and occasionally operation.

Asymptomatic radiological opacity of the paranasal sinuses and underdevelopment of the frontal sinuses are almost universal in cystic fibrosis. Nasal polyps, present in 6% to 36% of patients, may cause nasal obstruction and distortion, but many patients have no symptoms and spontaneous resolution is well described. Operation is commonly followed by recurrence, and is best confined to those with troublesome symptoms who have failed to respond to steroid nose drops.

Arthritis beginning in the teens is seen in about 10% of young adults with cystic fibrosis. In about half this is caused by hypertrophic pulmonary osteoarthropathy, with radiological changes of periostitis in long bones, exacerbations during chest infections, a mean age of onset of 15 years, and only an initial response to non-steroidal anti-inflammatory drugs. In most of the remainder the symptoms are the result of episodic arthritis with painful joint swelling, stiffness (often accompanied by fever and erythema nodosum), and a mean age of onset of 11 years. The attacks last no more than four days and generally respond well to non-steroidal anti-inflammatory drugs.

The fatal outcome, male sterility, delayed sexual development, chronic ill health, the need for life long treatment, a desire for independence, and the genetic aetiology all contribute to the impressive social and psychiatric toll of this disease; this includes teenage rebellion, non-compliance with treatment, marital breakdown, and parental psychiatric disorder. Sensitive ward staff, liaison nurses, and social workers are the key to detecting problems that can otherwise be concealed for years.

A diminishing response to intravenous antibiotics in a child with advanced lung damage, or the onset of cardiac failure, are signs of a poor prognosis. It makes no sense to subject a child near death to the misery of futile and unpleasant treatment. Most families prefer terminal care at home. Oxygen helps to relieve dyspnoea, and may help the child to tolerate physiotherapy. Carbon dioxide narcosis cannot be relied upon to occur, and there should be no hesitation in giving opiates to distressed terminal patients. Heart-lung transplantation offers hope for a small number of patients for whom donor organs are available, but generates false optimism and disappointment for most.²⁷

The place of regional centres

Families sufficiently motivated to travel enormous distances to a regional centre cannot possibly be compared with those who require cajoling to attend a local hospital. The case for special centres in the United Kingdom is not strengthened by claims that do not allow for this fact.²⁹ Parents increasingly demand treatment in special centres, which are likely to have better laboratory and paramedical facilities (physiotherapy, dietetics), wards better geared to the needs of the patients, support from other children with cystic fibrosis and their parents, and a team approach. It is difficult for those

who see only the occasional case to provide up to date treatment without the backup of the facilities of a cystic fibrosis centre. The logical solution at present is for care at cystic fibrosis centres for those patients living nearby, or those wishing to travel. For the rest some sort of shared care is desirable. A challenge for paediatricians is to find adult chest physicians who are prepared to take a special interest in young adults with cystic fibrosis.

Conclusions

Whatever the reason, modern management has brought far longer survival and improved health during childhood. The price for survival into adult life is a considerable amount of medical intervention that impinges on the life of the patient and family. Many parents hope for a cure, but improvements in antibiotic and nutritional management are more realistic short term hopes.

Much of the current treatment of cystic fibrosis is based on dogma masquerading as science. Single centre studies cannot answer important therapeutic questions, such as the value of antipseudomonal or antistaphylococcal regimens. The energy devoted to endless arguments about whether patients ought to attend special centres would be better used to initiate a nationally coordinated multicentre study of specific therapeutic regimens. Highly successful precedents for this approach exist in the Medical Research Council trials of leukaemia treatment, and the United Kingdom Children's Cancer Study Group trials of solid tumour treatment.

Appendices

Appendix 1: Infant milk formula for cystic fibrosis: Pregestimil (Mead Johnson) 100 ml, to which is added 5 ml Liqueign (Scientific Hospital Supplies) and one Pregestimil scoop (3.4 g) of Maxijul (Scientific Hospital Supplies). This provides approximately 1 kcal/ml (0.0042 MJ/ml).

Appendix 2: Enteral feeding regimen: Pepti 2000 LF (Cow and Gate), containing short chain peptides (thus avoiding the need for pancreatic enzymes), maltodextrin, corn oil, medium chain triglyceride, vitamins and minerals, approximately 1 kcal/ml (0.0042 MJ/ml). Start with one sachet (126 g) dissolved in 500 ml water, and give by a Fortison Enteral Pump through a fine bore nasogastric tube, which is passed each bedtime. Either one can increase the volume as much as possible (limited by vomiting or nocturia) and then increase the concentration of the solution as much as possible, or one can aim to give a specific amount (for example, 30% of the recommended daily amount for energy).

- 1 Britton JR. Effects of social class, sex, and region of residence on age at death from cystic fibrosis. *Br Med J* 1989;298:483-7.
- 2 Goodchild MC, Dodge JA. *Cystic fibrosis. Manual of diagnosis and management*. 2nd ed. London: Bailliere Tindall, 1985.
- 3 Devlin J, Beckett NS, David TJ. Elevated sweat potassium, hyperaldosteronism and pseudo-Bartter's syndrome: a spectrum of disorders associated with cystic fibrosis. *J R Soc Med* 1989; 82(suppl 16):38-43.
- 4 Durie PR, Forstner GG. Pathophysiology of the exocrine pancreas in cystic fibrosis. *J R Soc Med* 1989;82(suppl 16):2-10.
- 5 David TJ, Phillips BM. Overdiagnosis of cystic fibrosis. *Lancet* 1982;ii:1204-6.
- 6 Littlewood JM, Losowsky MS, Kelleher J. Sweat tests for cystic fibrosis. *Lancet* 1983;ii:183.
- 7 Ryley HC, Deam SM, Williams J, et al. Neonatal screening for cystic fibrosis in Wales and the West Midlands: 1. Evaluation of immunoreactive trypsin test. *J Clin Pathol* 1988;41:726-9.
- 8 Carty H. The chest radiograph in cystic fibrosis in children and the role of other radiological techniques. *J R Soc Med* 1987;80(suppl 15):38-46.

- 9 Macdonald NE, Morris RF, Beaudry PH. Varicella in children with cystic fibrosis. *Pediatr Infect Dis* 1987;6: 414-6.
- 10 Langford DT, Hiller J. Prospective controlled study of a polyvalent pseudomonas vaccine in cystic fibrosis—three year results. *Arch Dis Child* 1984;59:1131-4.
- 11 Littlewood JH. An overview of the management of cystic fibrosis. *J R Soc Med* 1986;79(suppl 12):55-63.
- 12 Phillips BM, David TJ. Management of the chest in cystic fibrosis. *J R Soc Med* 1987;80(suppl 15):30-7.
- 13 Szaff M, Holby N, Flensburg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection. *Acta Paediatr Scand* 1983;72:651-7.
- 14 David TJ. Intravenous antibiotics at home in children with cystic fibrosis. *J R Soc Med* 1989;82:130-1.
- 15 David TJ, Devlin J. Continuous infusion of ceftazidime in cystic fibrosis. *Lancet* 1989;i:1454-5.
- 16 Jensen T, Pedersen SS, Garne S, Heilmann C, Hoiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother* 1987;19:831-8.
- 17 Tablan OC, Martone WJ, Jarvis WR. The epidemiology of *Pseudomonas cepacia* in patients with cystic fibrosis. *Eur J Epidemiol* 1987;3:336-42.
- 18 Finkelstein SM, Wielinski CL, Elliott GR, et al. Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;112: 373-7.
- 19 Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;ii:686-8.
- 20 Durie PR, Pencharz PB. A rational approach to the nutritional care of patients with cystic fibrosis. *J R Soc Med* 1989;82 (suppl 16):11-20.
- 21 Beverley DW, Kelleher J, Macdonald A, Littlewood JM, Robinson T, Walters MP. Comparison of four pancreatic extracts in cystic fibrosis. *Arch Dis Child* 1987;62:564-8.
- 22 Whitehead AM. Study to compare the enzyme activity, acid resistance and dissolution characteristics of currently available pancreatic enzyme preparations. *Pharm Weekbl* 1988;10:12-6.
- 23 Belli DC, Levy E, Darling P, et al. Taurine improves the absorption of a fat meal in patients with cystic fibrosis. *Pediatrics* 1987;80:517-23.
- 24 Mago H, Chen C-L, Wesson DE, Filler RM. Incisionless gastrostomy for nutritional support. *J Pediatr Gastroenterol Nutr* 1986;5:66-9.
- 25 Vernon SA, Neugebauer MAZ, Brimlow G, Tyrell JC, Hiller EJ. Conjunctival xerosis in cystic fibrosis. *J R Soc Med* 1989;82:46-7.
- 26 David A. Autogenic drainage—the German approach. In: Pryor J, ed. *Respiratory care*. Edinburgh: Churchill Livingstone (in press).
- 27 Geddes DM, Hodson ME. The role of heart and lung transplantation in the treatment of cystic fibrosis. *J R Soc Med* 1989;82(suppl 16):49-53.
- 28 Bilton D, Fox R, Webb AK, Lawler W, McMahon RFT, Howat JMT. Pathology of common bile duct stenosis in cystic fibrosis. *Gut* (in press).
- 29 David TJ. The case for cystic fibrosis centres. *J R Soc Med* 1987;80(suppl 15):51-4.