Recent advances in cystic fibrosis

A conference on ‘Recent Advances in Cystic Fibrosis’ was held at the Royal College of Physicians on 7 and 8 December 1992.

Intensive research following the discovery of the cystic fibrosis (CF) gene in 1989 has expanded understanding of the pathophysiology of the disease. Genetic and ion-transport researchers no longer move independently along parallel tracks but feed and fuel each other. Greater understanding of the basic defect at cellular and genetic level is spawning potential new treatments, all of which need full clinical evaluation. Meanwhile, routine day-to-day care continues to improve steadily. It is timely to take stock of the current situation. The conference aimed to highlight recent scientific advances, to review their impact on patient care, and to provide a patient’s view.

Sir John Batten (London) surveyed the literature on CF, from the report of familial congenital steatorrhea in the Quarterly Journal of Medicine of 1912, via Anderson’s definitive paper on CF in 1938 and the introduction of the diagnostic sweat test following the death from heatstroke of a number of babies in New York in the hot summer of 1957, all of whom had CF, to present-day therapeutic triumphs. Even in the 1960s, prognosis was generally so poor that few believed that intensive care for CF was justified. The history of CF is one of dogged treatment regimens punctuated by the occasional leap forward, eg the introduction of powerfully effective anti-pseudomonal antibiotics, the realisation of the importance of correcting malnutrition with a normal to high fat diet, the growth of specialised CF centres, the recent advances in the understanding of the biochemistry and genetics of CF. Today the possibility of transferring, by viral vector, the genetic code for the normal CF protein to patients’ respiratory tracts, and the 60% to 70% two-year survival after lung transplantation, are bright lights at the end of what was, not so many years ago, a long and dark tunnel.

What is CF?

Professor Dodge (Belfast) emphasised that CF is a multisystem disease capable of varied manifestations and a plethora of complications in many organs. The kernel of his message was that more physicians are needed, perhaps formally trained and accredited in CF, who can detect CF disease at an early stage, whatever its expression, and treat it with the best available medication. The spectrum of CF-associated illness is greater than was previously realised, including sweat test negative individuals, and perhaps even men whose only manifestation of the CF gene is congenital bilateral absence of the vas deferens.

Biochemistry and genetics

Dr Harris (Oxford), Dr Alton (London) and Dr Santis (London) outlined the scientific background of ion transport and the structure and function of the CF gene. Dr Dorin (Edinburgh) introduced her mouse model of CF, and Professor Williamson (London) summarised the prospects for gene therapy.

Over 250 mutations of the CF gene have been analysed. A single deletion, delta F508, coding for phenylalanine, accounts for 67% of cases. Only 30 of the identified mutations have been found on more than 10 chromosomes.

The product of the CF gene, the cystic fibrosis transmembrane protein regulator (CFTR), acts as a chloride channel in the apical membrane of the cell. The abnormal protein product of the delta F508 mutation fails to reach its preferred site of action and remains ineffective within the intracellular milieu. (One therapeutic possibility, if the mutant protein retains some function, is to facilitate its transport to the apical membrane where even reduced biochemical activity may be effective).

The gene’s structure has been defined but much remains to be determined about its function. Does it have activities other than working as a chloride channel? How is its expression regulated? What are the important areas of the gene beyond the coding region? The genotype explains only in part the phenotype. There is a highly significant correlation between genotype and exocrine pancreatic function but a much less clear relationship with respiratory function. What other influences are at work? We know that there are alternative, calcium-dependent chloride channels. These not only offer the possibility for pharmacological intervention, but their varied expression may also explain the different clinical pictures seen in the same genotype.

Dr Alton (London) focused on the basic defect in the CF sweat duct as the impermeability of the cell membrane to the chloride ion. In vitro work has shown the CF gene to be crucial for cAMP mediated chloride movement. In the respiratory tract the effect of this is exacerbated by the two-to-threefold increase in sodium absorption. Water follows sodium, causing the ciliary mucus to dry out and thicken: lung pathology and infection ensue.

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Prospects for gene therapy

Professor R Williamson (London) stated that it is no longer necessary to defend the concept of somatic gene therapy. CF is an ideal model for such treatment:

- the gene is available. One correct copy of the appropriate cell will result in a normal phenotype;
- the lungs are accessible to nebulised delivery;
- it is likely that only a minority of cells needs to be corrected to achieve a normal consistency of the respiratory mucus.

The attenuated adenovirus is a suitable vector. It will target and enter the appropriate cells which will then express the viral genome containing information for the manufacture of a properly functioning CFTR. Three proposed pilot programmes involving adenoviral vector systems in human subjects have received approval in the USA. Many questions need to be answered, not least whether patients will be able to receive repeated treatment courses without mounting an immune response to the virus which would prevent it from successfully entering the cell.

Population screening

Professor Brock (Edinburgh) discussed the ethics of screening for CF, and the best model for the task. Screening in early pregnancy was put forward as the best option. It is the least likely to be biased in favour of the higher social classes, notwithstanding that late antenatal booking is more a feature of the socially deprived, and could be integrated easily into existing NHS treatment programmes. The points considered were whether to screen couples as a single unit: ie, only screening the account for the second partner if the first is positive, and only proceeding to counselling if both are positive, or to screen the woman first and offer her partner screening if appropriate. The main advantages of the former are that it provokes less anxiety and makes fewer demands on counselling time.

Infection and the lungs

Professor Shale (Cardiff) and Dr Govan (Edinburgh) gave a detailed account of the pathophysiology of the lung disease. Lung damage results not only from the direct effect of bacteria, usually Pseudomonas aeruginosa and Staphylococcus aureus, but also from the florid immune response to these infectious agents. The immune system, frustrated by its inability to remove the microcolonies of mucoid P aeruginosa, produces an excess of free elastase in the lung with consequent chilotoxic effects, increased mucus secretion, mucosal injury, and connective tissue destruction. The continuous stimulus to the immune system and release of inflammatory mediators converts a physiological to a pathophysiological reaction. The exact place of prophylactic oral antibiotics, early use of nebulised antibiotics, and anti-inflammatory agents is still to be determined. The role of viral and fungal infection in CF respiratory exacerbations requires further definition. Controversy accompanies Pseudomonas cepacia: is it a pathogen or a disease marker? Should we segregate P cepacia carriers from other CF patients?

Management of CF

Lung disease

Dr Hodson (London) espoused the use of nebulised antibiotics as maintenance therapy and described the Brompton home-care service. Without doubt, more CF treatment will take place in the patients’ homes: the home-care intravenous antibiotic treatment programmes are rapidly expanding, and patients so treated will soon outnumber those admitted. While missing the benefits of hospital physiotherapy and daily medical review, patients treated at home benefit from the greater independence and comfort.

Other recent advances in the management of lung disease are the use of nasal ventilation as a holding procedure in patients awaiting lung transplant, and the promising early trials of nebulised DNase in temporarily improving lung function.

Extrapulmonary disease

Dr Littlewood (Leeds) concentrated on the management of diabetes mellitus, liver disease, and male infertility from among the many extrapulmonary manifestations of CF.

Diabetes: Between 10% and 30% of CF adults are likely to develop diabetes and it will be missed in its early stages if not regularly and assiduously screened for. Dr Littlewood stressed the importance of performing glucose tolerance tests in older patients. The overall clinical state is worse in those who progress to frank diabetes even before hyperglycaemia becomes overt. A high-energy diet is advised. An unlimited amount of carbohydrate should be given but in a similar distribution each day to allow reasonable adjustment of insulin dosage.

Liver disease: Some 20% of patients have evidence of liver disease, ranging from focal biliary fibrosis to cirrhosis. All patients need at least yearly screening by liver function tests and ultrasound scan. Other aetologies having been excluded, liver disease in CF should be treated with ursodeoxycholic acid and taurine. There is no reason to delay intervention once liver abnormalities have been detected.

Infertility: The advent of epididymal sperm aspiration has given new hope to CF males. Sperm so harvested can fertilise, but no egg fertilised by CF sperm has as yet been successfully reimplanted.
Physiotherapy

Dr Webb (Manchester) emphasised the essential role of the physiotherapist in CF care, and reviewed the various physical techniques available. The physiotherapy requirements of each CF patient need frequent reassessment. A flexible approach to the changing needs of the individual should be adopted. What is the place of exercise in a physiotherapeutic regimen for CF? Exercise makes patients feel better, but it does not improve their performance in respiratory function tests. We do not know if it improves longterm survival. Such studies have not been, and probably cannot be, done. Dr Webb’s own work shows clearly that exercise should complement chest physiotherapy (postural drainage and clapping) and not replace it; the latter is more efficient at clearing the lung of sputum.

Nutrition

Dr Weller (Birmingham) made two straightforward points in relation to nutrition in CF.

1. No CF child should be malnourished or suffer suboptimal growth.
2. All patients should see a dietician specialising in CF at every outpatient or ward visit.

Research has shown that the most effective way to increase energy intake is by intensive dietary counselling. Minimal nutritional support must include a high fat and high energy diet, fat-soluble vitamin supplements, salt supplement when necessary, and the proper use of enteric coated microsphere pancreatic enzyme preparations. For those whose weight-for-height percentage remains stubbornly below 85%, or whose weight falls rapidly after inpatient treatment, enteral feeding by nasogastric or gastrostomy tube should be considered. This should only be undertaken in centres with the necessary expertise.

Cystic fibrosis in adults in the UK

Dr Walters (Birmingham) gave an eloquent account of the social, educational and workplace achievements of adult CF patients. She provided cogent evidence for the advantages to patients of CF centres, and urged that the adult needs of the older CF sufferer should be met.

Organ transplantation

Dr Higgenbottom (Papworth) reviewed the successes of the Papworth transplant programme, with one-year survival at about 80%. Absolute contraindications to transplantation are now few: eg, severe liver disease, mycetoma involving the pleura, and active tuberculosis. Early postoperative deaths are mostly due to infection, and late problems to obliterator bronchiolitis. Surgeons in the USA and in the Newcastle centre in the UK prefer the sequential single lung transplant operation. At Papworth, a heart-lung block transplant is preferred. The major problem is donor supply: between 40% and 60% of patients accepted for transplant will die while on the waiting list.

State of the art

Professor Boucher (University of North Carolina), gave the ‘State of the Art’ lecture. He asked: ‘Can we protect the lung against deterioration by judicious use of new agents that might normalise fluid movements and secretions?’ Amiloride should theoretically maintain water in the respiratory mucus by blocking the surface cells’ ability to take up sodium. Early trials with inhaled amiloride showed a less steep fall in forced vital capacity (FVC) in patients on active treatment compared to those on placebo when all other routine maintenance therapy was stopped. Subsequent studies have shown no benefit from amiloride therapy when it is used as an adjunct to, rather than a replacement of, regular medication. It is unlikely to represent a significant therapeutic advance on its own.

Professor Boucher was enthusiastic about the therapeutic possibilities of the candidate chloride secretagogues, of which UTP seems the most promising. This acts by increasing intracellular calcium and opening accessory chloride channels. Together with amiloride, it might maintain the hydration of the airway mucus.

Concluding remarks

In the final lecture Dr Geddes (London) sounded a note of caution. He reminded us that there are still many unanswered questions concerning the use in CF of gene therapy, amiloride and UTP, anti-inflammatory agents, antibiotics, and immunotherapy. When properly applied, routine treatment is now so successful that it is difficult to achieve better results even with the addition of effective new drugs. In the field of transplant surgery he suggested that the only answer to the shortfall in donor organ supply is to look at the possibility of using animal lungs. After all, very good use of pig insulins has been made without serious ethical controversies.

The conference was attended by 58 delegates. It was disappointing that not more of the paediatricians and adult physicians from outside the main centres who care for only small numbers of CF patients had made the effort to attend. The meeting was well organised and thoughtfully planned, and was an excellent way to keep abreast of the many recent advances in CF care.