



The Joseph Levy Memorial Lecture

and

The Ettore Rossi Medal Lecture

***Looking back over 40 years
and what the future holds***

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As the recently appointed Chairman of the UK Cystic Fibrosis Trust, I am most grateful for the invitation from CF Worldwide to give the Joseph Levy Memorial Lecture in our 40th Anniversary Year. I am also most appreciative of the honour bestowed on me by colleagues in the European Cystic Fibrosis Society in awarding me the Ettore Rossi medal – Professor Rossi was the founder of that society. Both Mr Joseph Levy and Professor Ettore Rossi, in their quite different ways, made very great contributions to improving the lives of people with cystic fibrosis.

Mr Joseph Levy CBE BEM and the Cystic Fibrosis Research Trust



The UK Cystic Fibrosis Research Trust was formed in 1964 on the initiative of the late Mr John Panchaud, whose daughter Caroline had cystic fibrosis. Mr Joseph Levy CBE BEM was Chairman of the CF Research Trust for 20 years, from soon after its formation in 1964 until 1984 when his son, Mr Peter Levy OBE succeeded him; Peter Levy continues as one of our Trustees. Many in the UK CF community, patients, parents and professionals, have reason to be grateful to Joseph Levy, to Peter and the Levy family for their continuing and generous support in many areas.

One of the first Trustees was Caroline's grandfather, Mr Percy Lovely and he with John Panchaud enlisted further distinguished Trustees including Lord Crook and Joseph Levy. Their inaugural meeting was held at the Mansion House in London on the 20th February 1964. Joseph Levy and John Panchaud soon became the leaders on the fundraising side and, according to Sir Robert Johnson, "*set about the seemingly impossible task of raising funds for research into something of which scarcely anyone had heard*". (Johnson, 1984). And what a success they made of it even though there were so few children with CF surviving then that very few people had even heard of the condition.

Professor Ettore Rossi 1915-1999



Professor Ettore Rossi qualified as a doctor in 1940 and became Professor and Chairman of the Department of Paediatrics of the University of Berne, Switzerland in 1956 until he retired in 1985. A consideration of his *curriculum vitae* describes a paediatrician and scientist who was really larger than life – a giant of European paediatrics (Vassella et al, 1995). He was one of the central figures involved in the development of many areas of paediatrics in Europe, including cystic fibrosis. In 1969 he became the first Chairman of the European Working Group on Cystic Fibrosis (later to become the European Cystic Fibrosis Society). I met him only briefly on a few occasions - one incident left me with a lasting impression of his kindness and humanity. At an International CF Conference when chairing a plenary session, he had no hesitation in informing one presenter, of a study involving children in numerous needle biopsies of the liver, in no uncertain terms, precisely what he thought of the ethics of the study! He was obviously held in high regard by those who knew him and described as an enthusiastic teacher, a serious hard working paediatrician and a superb medical friend - "*the beloved father of hundreds of paediatricians in the whole world*" (Schoni, 1999).



Often in the past progress in CF organisations has been initiated and made by parents, relatives or friends who have refused to accept the *status quo* – as we will see later. John Panchaud was one parent who was determined to do something to improve the UK situation. In 1963 a meeting with Dr David Lawson, a paediatrician whose daughter had CF, resulted in the formation of the UK CF Research Trust.

The original Medical/Scientific Committee of the CF Research Trust was chaired by David Lawson and included Dr Archie Norman (whose clinic John Panchaud's daughter Caroline attended at Great Ormond Street in London). Soon after this Sir John Batten, who started the first clinic for adults with CF at the Royal Brompton London in 1966, joined the Committee.

Mr Ron Tucker OBE – first Director of the CF Research Trust



Over the past 40 years there have been very many people who have contributed to the development of the CF Research Trust, as it was first known, but the first Executive Director, Mr Ron Tucker OBE, deserves special mention. His contribution to the development of the work of the Trust is legendary from the time of his appointment in 1965 to his retirement in 1984. I can vouch personally for Ron's boundless enthusiasm, refusal to take "no" for an answer, constant encouragement and practical help to those of us developing regional CF services such as ours at St James's in Leeds (Littlewood & Kelleher, 1989).



HRH Princess Alexandra – Patron of CF Trust from 1968 to the present

The CF Trust has been very fortunate that, as early as 1968, at a time when no one had heard of CF or the CF Research Trust, HRH Princess Alexandra kindly agreed to become the Patron of the charity – which, at that time, was struggling for recognition. We are most grateful for her 36 years of continuous patronage and support.

Looking back over 40 years

Even though Henry Ford maintained that "*History is more or less bunk*", an anniversary is an appropriate time to look back at the history of cystic fibrosis – to review what has been achieved, the lessons learned and where we should be going – for in medicine "*Intelligence is learning by experience*".

I look back from the perspective of a general paediatrician who, some 30 years ago during the Seventies, gradually became increasingly involved in the challenge of improving the medical care people with cystic fibrosis, when I had been a doctor for almost 20 years and working in paediatrics for over 15 years. Perhaps this rather later involvement allows me to view the early progress with some degree of objectivity. Certainly, even in the Seventies, in any one city there were very few children with CF who survived to require treatment for many years.

Improving outlook at the cost of burdensome treatment

Change in the outlook for people with CF since I qualified in 1956 has been quite remarkable; and particularly since 1980, progress, both in understanding the basic defect itself and the control of its secondary effects, has been particularly impressive, culminating in the eventual identification of the CF gene in 1989 (Rommens et al, 1989; Riordan et al, 1989; Kerem et al, 1989).

The more effective treatments over the past 20 years, for the chest and intestinal malabsorption have significantly improved the quality and length of life for most people with CF from early childhood to middle age, although even the best treatment we can offer still does not achieve even a near-normal quality or length of life. The unremitting life long demands on family life, time, emotions and finance for a family are still huge and difficult for those not closely involved to fully appreciate. Also these improvements in outlook have only been achieved by imposing on the patients and their families ever more complex, demanding and expensive regimens of treatment. Hence, it is obvious that, now the basic defect has at last been identified, it is logical and appropriate to increase our efforts to improve or even correct the basic defect, in order to ease the almost intolerable burden of the present day treatment.

PROGRESS THROUGH THE DECADES



THIRTIES

The first clear description

The first clear description of cystic fibrosis (CF) was 66 years ago, in 1938, by Dr Dorothy Andersen, the pathologist at the New York Babies Hospital. Although there had been reports of infants who almost certainly had cystic fibrosis prior to Andersen's paper, "*Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study*", was the first report which clearly defined CF as a

clinical entity (Andersen, 1938). She reported the clinical and pathological findings in 49 children, describing the characteristic neonatal meconium ileus, intestinal and respiratory complications and many other features of CF – particularly the characteristic pancreatic histology. The histology of the respiratory epithelium, which showed squamous metaplasia, resembled that seen in vitamin A deficiency and, for some years, Andersen continued to support the role of vitamin A deficiency, secondary to the intestinal malabsorption, as a major factor contributing to the pathogenesis (Andersen, 1949).

FORTIES

“Mucoviscidosis” - a generalised, recessively inherited disorder

Although few doctors had heard of CF in the Forties, Dr Sydney Farber, Chief of Pathology at The Children’s Hospital, Boston, recognised CF as being a generalised disorder affecting organs other than the pancreas and in 1943 introduced the term “mucoviscidosis”. Farber was a colleague of the legendary Dr Harry Shwachman, who with Dr Paul di Sant’Agnese of New York, were two leading authorities on CF in the USA for many years. Farber accurately summarized the secondary consequences of the CF defect as - *“the respiratory tract damage therefore depends on primary obstruction by thick mucus, failure of proper lubrication of ciliated epithelium and secondary staphylococcal infection”* (Farber, 1943).

Dorothy Andersen and her paediatric colleague Dr Hodges (later to be succeeded by Paul di Sant’Agnese), investigating 113 families, concluded that there was a Mendelian recessive mode of inheritance - *“the disease, although hereditary, requires more than one factor for expression”* (Andersen & Hodges, 1946); others agreed (Bodian, 1952).

Treatment with emphasis on early intervention

Although sulphonamides (so-called M&B) became available in the Thirties, there were no antibiotics until the mid-Forties. The treatment focused heavily on nutrition as there was still a widespread belief that malnutrition, and in particular vitamin A deficiency with its effect on the morphology of the respiratory epithelium (squamous metaplasia), in some way contributed to the expression of the genetic defect. Andersen advised *“a low fat, high protein diet with a liberal allowance of vegetables, fruits and sugar and moderate restriction of starch. Supplementary vitamin A is essential and pancreatin and vitamin B complex are given”* (Andersen, 1945). In 1946, di Sant’Agnese also stressed the importance of diet and attributed the improved prognosis to *“An appropriate diet begun promptly and continued consistently, use of sulphadiazine during the stage of chronic cough and the use of nebulised penicillin”* – although he later concluded that *“sulfa drugs were totally ineffective”*! In 1943 di Sant’Agnese had obtained a small quantity of penicillin from the US army and treated children with CF with *“dramatic”* results, whether the antibiotic was given by aerosol (only 20,000 units given 7 times daily – adherence is not mentioned!) or by intramuscular injection – the most common pathogen then being a penicillin-sensitive *Staphylococcus aureus* (di Sant’Agnese et al, 1946). The need for early treatment before too much lung damage represents the subsequent experience of many CF clinicians (Mearns, 1972).

Undoubtedly, the Second World War and the demands of other diseases accounted for the lack of publications on CF from Europe during the Forties.

FIFTIES

The sweat test revolutionises diagnosis



The major clinical advance during the Fifties was the recognition of the increased salt content of the sweat in cystic fibrosis by Paul di Sant’Agnese. The observation of heat prostration in infants with CF during the New York heat waves of 1948 and the early Fifties (Kessler & Andersen, 1951) led to his subsequent demonstration of the excessive salt content of the sweat (di Sant’Agnese et al, 1953). The sweat test was a major advance permitting accurate diagnosis when CF was suspected; diagnosis of CF had previously involved demonstration of pancreatic abnormality by obtaining duodenal juice and demonstrating low levels of enzymes in a child with clinical features of malabsorption. Diagnosis by sweat analysis became more practicable, accurate, safer and more generally available when sweating was stimulated by the pilocarpine iontophoresis rather than various potentially dangerous methods of heating the patients (Gibson & Cooke, 1959). However, unless the test is performed accurately by experienced personnel disastrous

diagnostic mistakes will and have occurred (Smalley et al, 1978; Shaw & Littlewood, 1987; Cystic Fibrosis Foundation Patient Registry, 1996).

Few early publications on cystic fibrosis

In 1958 Shwachman and Kulczycki published their classic review of experience with 105 patients. This paper included a description of the Shwachman-Kulczycki clinical scoring system, which, although somewhat outdated today, by the much-improved condition of patients, is still widely used despite many other suggested clinical scores (Conway & Littlewood, 1996). They described an improving outlook for children with CF and noted that survival into adult life was occurring with increasing frequency in their clinic (Shwachman & Kulczycki, 1958). The experience from the Fifties was summarised in a further review (Shwachman, 1960). Therapy to thin secretions included iodides, also intramuscular or inhaled pancreatic trypsin, oral streptokinase or streptodornase, carbon dioxide inhalations and nocturnal mist tent therapy using 10% solution of propylene glycol and 3% sodium chloride.



Antibiotics (chlortetracycline or oxytetracycline) were recommended for infections and continuously only for those who were chronically infected and large doses combined with chloramphenicol or erythromycin for more severe infections but were seldom given intramuscularly. Resistant Staphylococci and the appearance of Pseudomonas were, even then, emerging problems. Aerosol antibiotics, penicillin and streptomycin or neomycin and polymyxin, were added for more severe infections (Shwachman, 1960).

Through the Fifties as more antibiotics became available (chlortetracycline, oxytetracycline, chloramphenicol and erythromycin) paediatricians, parents and patients were becoming more familiar with both their obvious good but disappointingly frequent unwanted effects. The numerous side effects resulting from the unusual often repeated and prolonged use of antibiotics were reported at a later date e.g. allergic reactions, renal, eye problems and many others (Shwachman, 1983).

Evidence of the beneficial effect of pancreatic enzyme therapy became available though not all clinicians were impressed (Harris et al 1955) and many patients were unable to tolerate a normal fat intake even with enzyme supplements.

Physiotherapy techniques ‘imported’ from the UK

Postural drainage had long been the traditional treatment for children with bronchiectasis in the UK and this had been introduced into the treatment of children with CF from the time of diagnosis in Dr Winifred Young’s clinic the UK in 1950 (Mearns, 1993). The English methods of physiotherapy were used (Doyle, 1959) and commended by Shwachman on a number of occasions (Shwachman, 1960). Jocelyn Reed was said to be the first person to recommend, *“clapping and pressure vibrations during expiration are the most effective forms of mechanical stimulus to eliminate secretions”* (Reed, 1952). However, not all CF physicians were convinced of the value of physiotherapy – *“The ritual of carefully positioning the patient to drain every segment separately is usually an exercise in futility”* (Docter, 1981)!

LeRoy Matthews’s “comprehensive and prophylactic (preventive) treatment programme” – a major milestone in CF care

Dr William Wallace, Chairman of Paediatrics at the Babies and Children’s Hospital, Cleveland had been approached in 1957 by a parents’ organisation - the “Cousins Club” - one of whom had already lost a child and had another deteriorating from cystic fibrosis. They asked Dr Wallace to start a “research orientated treatment programme for CF” which they would fund.



To develop this Dr Wallace appointed a young paediatrician, Dr LeRoy Matthews, to plan and initiate the “comprehensive and prophylactic (preventive) treatment programme” for the treatment of cystic fibrosis (Doershuk, 2001).

The comprehensive and prophylactic treatment program subsequently developed incorporated many of the components now regarded as essential for modern CF centre care e.g. early correct diagnosis, a comprehensive programme to deal with all the aspects of the disease and data collection to validate the impact of the treatment on morbidity and survival (Matthews et al, 1964; Doershuk et al, 1964; Doershuk et al, 1965).

Important components of the treatment programme included regular physiotherapy, regular monthly respiratory cultures to guide antibiotic therapy, special microbiology techniques for CF sputum, regular nebulised treatment using phenylephrine as decongestant and propylene glycol as a mucolytic. The use of mist tents was the only major component recommended, which is not used today. Mist tent therapy was a popular form of treatment in the USA in the Sixties. Arranging for the child with CF to sleep in a fine mist seemed a reasonable way of attempting to relieve mucoid impaction of the airways and reduce the viscosity of the sputum. In 1967 objective evidence of the positive value of mist tent therapy was published by respected paediatricians in the USA (Matthews et al, 1967), subsequent studies failed to confirm significant fluid deposition below the larynx and the treatment was finally discontinued after further studies showed little or no lung deposition (Norman, 1971; Chang et al, 1973).

Some of the other CF Centres started in the Fifties

In Canada, CF clinics were started by Dr Alan Ross at Montreal Children's 1957, by Dr Douglas Crozier at the Hospital for Sick Children, Toronto in 1958 and by Dr William Cochrane at the Halifax Children's Hospital, Nova Scotia - later taken over by Dr Terence Gillespie in 1966. In the UK there were few CF Centres until the Eighties. In London there were Winifred Young's from 1950 and Archie Norman's at Great Ormond Street in London. In 1953 Dr Charlotte Anderson started her clinic in Australia and later moved to Birmingham in the UK. Although Sir John Batten's



adult CF clinic started in the mid-Sixties at the Royal Brompton in London, in most parts of the UK there was no demand for adult CF care as there were virtually no adults with cystic fibrosis. David Lawson, at Carshalton Hospital in Surrey UK, was also treating increasing numbers of children with CF and making a major contribution to clinical research and the CF organisations. In



Denmark most patients were treated at a main CF Centre in Copenhagen from 1968 where it was shown later that the outlook could be improved in chronically infected patients by more aggressive treatment with regular courses of intravenous antibiotics (Schiotz et al, 1981; Jensen et al, 1989).

Respiratory function tests

There were early reports of the use of pulmonary function testing (West et al, 1954; Mearns, 1968), which allowed more accurate documentation of the patients' declining lung function. Although many paediatric respiratory units eventually had access to sophisticated respiratory function laboratories and reported in detail the characteristics of the CF lung disease, the availability of simple respiratory function testing in the form of the Wright's Peak Flow Meter, the first bellows Vitalograph from the mid-Sixties and later electronic Vitalograph spirometers proved adequate for many CF Centres in the UK, including our own in Leeds and their ease of use and interpretation made a major contribution to routine patient care. Respiratory function tests for pre-school children and infants have remained, even to the present, the province of the researcher and clinical physiologist but do confirm the early changes in the lungs of CF infants (Ranganathan et al, 2002). A chest X-ray and respiratory function tests were to become basic information for assessment of a patient's progress (Chrispin & Norman, 1974).

THE SIXTIES

The start of CF organisations

During the Sixties more national CF organisations were formed, usually following pressure from parents and engendering a collaborative approach between the medical community and the CF families.

The US National CF Research Foundation (later the CF Foundation) had been formed in 1955, and the Canadian CF Foundation in 1959. In 1964 the UK "CF Research Foundation Trust" was formed as a charitable organisation to raise funds for research, later renamed the "CF Research Trust" and finally, when increasing research funds went to support clinical care during the Eighties, the scientists requested the title be amended to the "CF Trust". Subsequently, national CF organisations formed in many countries where the cystic fibrosis was identified; their programmes covered welfare, support, advocacy, clinical care, professional education and research, depending on the local stage of development (Morrison & Morrison, 1993).

In 1960 there was the first meeting in European Working Group on Cystic Fibrosis in Vienna, which was instigated by Professor Rossi of Berne; eventually in the Nineties, this group became the European Cystic Fibrosis Society and holds a major CF conference every year.

In 1965 the International Cystic Fibrosis (Mucoviscidosis) Association (the predecessor of CF Worldwide) was formed in Paris under the medical chairmanship of Paul di Sant' Agnese. Its aims were to improve the care of children and adults who had cystic fibrosis, to foster research and to disseminate information. This was the start of the International CF (ICFMA) now CF Worldwide meetings, which occur every 4 years.

Sweat tests and jejunal biopsies for diagnosis of infants and children with malabsorption

Impressed by Dr Tom McKendrick's sweat test study, which he was performing when I was a junior doctor at Great Ormond Street Children's Hospital, London in 1963, on returning to Leeds I purchased a sweat-testing box (McKendrick, 1962). So by the late Sixties with accurate sweat tests by our biochemist, Mr Alan Steele, and our recently introduced paediatric jejunal biopsy service in 1968, virtually all infants and children with malabsorption could be accurately diagnosed (Littlewood, 1995a).

More accurate description of exocrine pancreatic function in cystic fibrosis

The name of Beat Hadorn is closely associated with accurate pancreatic function tests in CF describing the pancreozymin–secretin stimulation test. He showed that in CF there was a reduced volume of stimulated pancreatic juice and abnormally low bicarbonate levels even in those few people with CF who had sufficient residual pancreatic function to achieve normal fat absorption (Hadorn et al, 1968). Later non-invasive faecal chymotrypsin levels (Brown et al, 1988) and faecal elastase 1 measurements have simplified the diagnosis of pancreatic insufficiency (Cade et al, 2000).

Outlook for patients still very poor in the Sixties

Through the Sixties, although there were reports of an improving outlook from a few centres, most affected children still died within a few years and no one had a clue as to the nature of the basic defect and relatively few people were researching the problem. Sir Robert Johnson recalls the situation facing CF families in the UK in the Sixties - *"the general picture here was of ignorance and distress, unmitigated by hope or practical effective action"*. As a young paediatrician in the Sixties I can certainly vouch for that.

THE SEVENTIES

A new attitude in some places

During the Seventies there was a definite change in attitude in some clinics where individual doctors were gaining experience in treating more patients who were surviving for longer. The details and impressive results of LeRoy Matthew's comprehensive treatment programme, which started in 1957, were published in 1964 (Matthews et al, 1964; Doershuk et al, 1964) and the methods of management and treatment they used eventually formed the basis of the CF Foundation's network of CF Centres in the USA from 1961.

As early as 1972, Drs Margaret Mearns and Winifred Young at the Queen Elizabeth Hospital in London published encouraging results of their meticulous clinical and microbiological follow-up and treatment reflecting their care in the Sixties (Mearns, 1972). These were further indications that vigorous meticulous treatment of the secondary effects of the basic defect at an early stage could significantly improve prognosis. From the 1950s their young patients had received prophylactic erythromycin and nebulised neomycin and intensive physiotherapy – before 1957 they had 50 infants who, at a year, had no significant trouble and who, at 5 years, were still considered to be free of bronchitis (Mearns, 1969).



David Lawson

recommended early and continuous anti-staphylococcal antibiotic treatment, which seemed sensible and we adopted in Leeds for our few screened infants (Lawson, 1969; Lawson, 1972). Further development of the Specialist CF Centres occurred in some countries but there were few in the UK.

“Cystic fibrosis – a not-so-fatal disease”

However, during the Seventies, it was encouraging that in many countries the tide really seemed to be turning. Dr Douglas Crozier, who, in 1958, had started the CF clinic at the Hospital for Sick Children, Toronto, exemplified this new approach (Crozier, 1974). I was influenced by Crozier's article - *“Cystic fibrosis – a not so fatal disease”*- in which he gave advice, based on his considerable experience in Toronto, which clearly described the modern approach to management now adopted in many CF Centres including our own in Leeds i.e. *“Success of treatment will depend on a complete assessment of the patient and then continuing attempts to obtain normal bodily function and maintain it”*. From the early Seventies, Crozier abandoned the traditional low fat diet believing that *“to deprive the child with cystic fibrosis, who usually has very little subcutaneous fat, of this important nutrient seems ridiculous”*. As early as 1972, Crozier changed his patients to a high saturated fat diet of whole milk, butter, eggs, and animal fats which did require the patients to take 60 -100 Cotazym pancreatic enzyme capsules each day (Crozier, 1974). Later, the significantly superior nutritional state and longer survival of Toronto patients than those in the rest of Canada and also in Boston, was attributed to their better nutritional state (Corey et al, 1988).

The Danish CF Centre approach improves the prognosis

This lack of acceptance of the *status quo* approach was also evident in the Danish CF Clinic in Copenhagen, established as a CF Centre in 1968, (Szafl et al, 1983) where, since 1963, 80% of the country's 225 patients were treated. In 1976 they realised that chronic *Pseudomonas aeruginosa* infection and its severity, as judged by the number of precipitins in the patient's serum, was closely associated with the prognosis (Høiby, 1977). Professor Neils Høiby's work on precipitins influenced our subsequent interest in *Pseudomonas* antibodies in our Leeds patients and these were studied in detail by Dr Moira Brett (Brett et al, 1986; Brett et al, 1988; Brett et al, 1992) and are still used in the clinic (Pond et al, 1994; Lee et al, 2004a). Høiby's work resulted in the introduction of the Danish policy of regular 3-monthly 2-week courses of intravenous antibiotics for those patients chronically infected with *Pseudomonas* in 1976 (Schiotz et al, 1981; Szafl et al, 1983; Jensen et al, 1989) and cohort isolation which separated patients with *Pseudomonas aeruginosa* from those without the infection (Høiby & Pedersen, 1989); their improving results were later reflected in an impressive increase in survival (Frederiksen et al, 1996).

The late Dr Christian Koch and Professor Neils Høiby and their colleagues in Copenhagen have had a major influence on the care of people with cystic fibrosis and their aggressive approach to treatment, general caring attitude, and practically useful and influential contributions to the CF literature have been a major influence on many of us involved with CF care (Littlewood, 1997).

Improvement in nutritional diagnosis and treatment

As survival improved through the Seventies there was an increasing interest in the chronic nutritional problems as the nutritional state and growth of surviving children deteriorated with their increasing chest involvement (Berry et al, 1975). Typical nutritional advice at the time for infants and children with CF was that *“the general attitude should be liberal rather than restrictive and rigid. The aim should be for an acceptable compromise between troublesome steatorrhoea and severe restriction of dietary fat”* (Gracey, 1975).

In an attempt to improve absorption by dietary manipulation, Dr Allan, a general paediatrician from Macclesfield in England, popularised a nutritional supplement consisting of beef serum protein hydrolysate, a glucose polymer and medium chain triglycerides – the so called “Allan Diet” on which there were increased rates of weight gain (Allan et al, 1973). A subsequent study from Cincinnati, lent further support to the beneficial effect of the “Allan Diet” (Berry et al, 1975). Although another trial from Wales reported some improvement in 10 of 28 patients treated with the diet for 12 months, the authors' conclusions were that *“such an unpleasant and expensive diet should be restricted to a few selected cases, rather than given as routine treatment”* (Yassa et al, 1978). However, the new acid resistant pancreatic enzymes were soon to become available permitting most patients a normal fat intake – and providing a more acceptable way of increasing their energy intake.

Essential fatty acids and cystic fibrosis

Abnormalities of fatty acid (EFA) had been noted by many authors from the Sixties to the present (Kuo et al, 1962; Strandvik et al, 2001) and even suggested as a primary metabolic abnormality. Professor Bob Elliott in New Zealand reported an unusual clinical course in a child with CF treated with IV infusions of soya oil emulsion, which contains mainly linoleic acid (Elliott & Robinson, 1975) and in further treated children (Elliott, 1976). These reports caused considerable interest at the time and Rosenlund also reported some fall of sweat sodium levels with this treatment (Rosenlund et al, 1977). An abnormality of prostaglandin metabolism was suggested (Chase et al, 1978). In a subsequent controlled trial, 10 children were given either infusions of 20 ml/kg of 10% Intralipid or the calorific equivalent infusions of 10% glucose on alternate weeks for a year (Chase et al, 1979a). "Cumulative analysis" showed a greater improvement in the test group although numbers seemed hardly adequate. This is said to be the first double blind study of nutritional intervention in cystic fibrosis. Interestingly, the precise role of essential fatty acids is yet to be determined but correcting the essential fatty acid imbalance between docosahexanoic and linoleic acid has been reported to modify the pancreatic histological abnormalities in CF mice (Freedman et al, 1999); also the imbalance is also present in the tissues of people with cystic fibrosis (Freedman et al, 2004).

Energy intake commonly inadequate when analysed by dietitians and nutritionists

A number of important studies in the late Seventies and early Eighties measured the actual energy intake of people with cystic fibrosis. Contrary to the traditional impression, that people with CF had voracious appetites, when their intakes were actually measured professionally by nutritionists or dietitians, it was evident that many consumed less energy even than that recommended for healthy children of their age (Chase et al, 1979b). It is disappointing that subsequent studies have continued to show many people with CF in the UK continue to have suboptimal energy intakes (Littlewood et al, 1984; Littlewood et al, 1988; Littlewood, 1993).

Towards the end of the Seventies, there was an important paper supporting the suggestion that a good nutritional state was associated with a better prognosis (Kraemer et al, 1978).

The main lesson appeared to be that the dietitian was an essential member of the CF team.

SEVENTIES

Science

By the late Seventies three abnormal "factors" had been recognised in the serum of people with CF and their presence had been the subject a great deal of research and speculation - they were the Spock factor (Spock et al, 1967), the Mangos factor (Mangos et al, 1967) and the Lieberman factor (Lieberman et al, 1979). Spock reported ciliary dyskinesia when the serum of people with CF was added to a preparation of fresh water mussels and observed under the microscope. Much effort went into attempting to identify this "CF factor". However, despite a great deal of research neither isoelectric focusing (Wilson et al, 1977) nor using gels from isoelectric focusing to raise antibodies (Manson & Brock, 1980) permitted accurate identification. Mangos and co-workers reported a factor in saliva that inhibited resorption of sodium from rats' parotid duct. Lieberman identified a lectin-like factor in the blood of people with CF that disappeared with antibiotic treatment and was postulated to stimulate excessive mucus production, reacting with its glycoprotein to cause its precipitation and increased viscosity (Lieberman et al, 1979). Dr Lynne Reid, former chairman of UK Research and Medical Advisory Committee, who had moved from London to Harvard, reviewed her extensive research into bronchial mucus and its glycoproteins in cystic fibrosis but was unable to draw any definite conclusions, which had a bearing on the aetiology (Reid, 1981).

In summary, although some progress was made in a few Centres in controlling the secondary effects of the CF defect during the Seventies, scientific progress was limited and neither the location of the CF gene nor the mechanisms of its serious pathophysiological effects were known.

THE EIGHTIES

Major advances in clinical care – more meetings

From 1959 to 1986 there were annual meetings of the North American CF Club and from then the CF Foundation and Canadian CF Foundation have organised excellent annual North American CF Conferences, attendance at which has become a high priority for all responsible

for advising on CF care on both sides of the Atlantic. As a general paediatrician with an increasing involvement in CF, my first experience of a major international CF conference was the 8th International CF Congress held at the Royal York Hotel, Toronto in 1980. I presented work, carried out in collaboration with Professor Monty Losowsky and Dr Jerry Kelleher of our University Department of Medicine in Leeds, on the disappointingly low fat soluble and normal water-soluble vitamins status of our few children with CF whom we believed were receiving adequate vitamin supplements (Littlewood et al, 1980; Congden et al, 1981). This was the start of a long and productive collaboration with this and other departments in our large hospital, St James's in Leeds. We encouraged many of our colleagues to apply their particular skills to the problems of cystic fibrosis. In most parts of the UK we did not have CF Centres, such as that in Toronto, staffed by CF Teams of professionals and it became obvious to me that the organisation of CF care in many, but by no means all, parts of N. America, Europe and Australia appeared to be somewhat ahead of that available to many people in the UK - even in 1980. I returned home determined to improve and expand our small CF clinic in Leeds.

The philosophy of a comprehensive treatment programme recommended by LeRoy Matthews and his colleagues, Harry Shwachman and subsequently by Crozier and others, had a major influence on our approach in Leeds from the mid-Seventies. An all-encompassing treatment programme seemed the obvious answer to the optimal management of a serious, permanent, progressive, multi-system disorder where appropriate treatment appeared to be one of the main determinants of health and survival. Attendance at the 8th International Cystic Fibrosis Congress, Toronto in 1980 and meeting many professionals involved in such programmes certainly fired the flames of enthusiasm to do likewise!

Development of the Leeds CF Service – early neonatal CF screening

In 1975 we had started a small monthly CF clinic in Leeds with the paediatric outpatients nurse, physiotherapist and dietitian (Littlewood & Kelleher, 1989) and in the same year introduced neonatal CF screening, with the BM Meconium test, at our maternity unit for the 3000 newborns for whose paediatric care I was responsible (Evans et al, 1981). Despite the reported unreliability and eventual abandonment of this test in most other countries, we continued to use this method and, by performing the test in the laboratory rather than by overworked midwives on the wards, we achieved an acceptable false negative rate of around 12% (Littlewood et al, 1995b) until eventually we changed to the immunoreactive trypsin + DNA in 1996 (Shapiro et al, 1999).



The description of the immunoreactive trypsin test for neonatal CF screening by Crossley and Elliot from New Zealand was a major advance (Crossley et al, 1979). The method was subsequently used as the basis for a number of successful neonatal CF screening programmes during the Eighties e.g. East Anglia in the UK (Heeley et al, 1982), New South Wales (Wilcken & Chalmers, 1985), Colorado (Hammond et al, 1991) and Wisconsin (Farrell et al, 2001) and others.

First Leeds nutritional study prompted start of Comprehensive CF Assessments

Undoubtedly the result of this small late Seventies, was a major factor in “Comprehensive CF Assessments” at other areas where our treatment was improvement (Littlewood et al, 1984; 1993). As our first assessments areas where treatment could be service for other paediatricians’ patients in the city and surrounding Yorkshire region (population 3.5 million). The paediatricians agreed, (some rather reluctantly!) and naturally sent their most severely affected patients to see if we could help. So in the early Eighties our little team at St James’s went up a very steep learning curve treating many severely affected children. More than 600 children have been subsequently had at least one Comprehensive Assessment at Leeds; they came from Leeds, the surrounding Yorkshire Region, other parts of the UK and a few from overseas. The service has continued to the present day (Conway et al, 2003). We have described the development of the service in detail elsewhere (Littlewood



nutritional survey, carried out in the our starting regular so-called St James’s in Leeds to determine any suboptimal and to identify potential for Littlewood et al, 1988; Littlewood appeared to be so useful in revealing improved, I suggested we provide the

& Kelleher, 1989) but it is important to acknowledge the crucial continuing cooperation of numerous willing colleagues of many disciplines with their diverse skills and enthusiasm, in the environment of such a large teaching hospital as St James's; their involvement was a major factor in the successful development of the service.

CF Assessment results reflected the condition of UK children with CF

In 1988, at the International CF Congress in Sydney, we reported the results of Comprehensive Assessments on the first 250 patients seen at our Regional Paediatric CF Centre in Leeds between May 1980 and September 1987. Unfortunately, the picture was one of significant under-treatment as evidenced by incorrect diagnosis (3%), under-treated chest infection as evidenced by remarkable response to a course of intravenous antibiotics (30%), physiotherapy judged by our physiotherapists to be ineffective (60%), an energy intake which, on detailed analysis, fell below the recommended (75%), insufficient or old outdated pancreatic supplements (40%) and subnormal fat-soluble vitamin levels (60%) to mention only the main areas (Littlewood et al, 1988). It was encouraging the majority of families took the simple advice, implemented the recommendations and came for follow-up assessments, on average 15 months after their first attendance. There were significant improvements in many areas following the advice after the first visit e.g. significant improvement in weight for age occurred in the 0-5, 5-10 and the over 15 year olds.

Data collection and patient registries developed to deal with increasing information

Data collection was becoming increasingly important both on a national and local CF centre basis as had been recommended by LeRoy Matthews. The CF Foundation's patient registry, developed by Dr Warren Warwick from 1964 onwards, had demonstrated a rise in median survival from 14 years in 1968 to 20 years in 1977 (Warwick & Pogue, 1969). Also Archie Norman published a number of papers between 1967 to 1975 recording the improving prognosis in the UK (Norman, 1967; George & Norman, 1969; George & Norman 1971; Robinson & Norman, 1975). In 1977 Dr Mary Corey had started data collection at the Toronto CF clinic and has been making major contributions in this field consistently since then. At the 1980 Toronto International CF Congress she reported a median survival of Toronto patients of over 30 years, far better than reported by other North American centres (Corey, 1980). Later she reported that the clinical state and survival of the patients were significantly better in Toronto than in Boston and Canada as a whole (Corey et al, 1988). Most countries now have a national CF database – in 1995 the UK CF Database based at Dundee (www.cystic-fibrosis.org.uk) replaced the original UK CF Survey started by the original UK CF Working Party in 1982 that finally reported in 1997 (Dodge et al, 1997). The availability of computers in CF clinics for this purpose from the early Eighties revolutionised this area of management and clinical research (Miller & Littlewood, 1984; Littlewood AE, 1997).

Marked differences between CF Centres – “a matter of degree rather than kind”

It became clear, and is still very obvious both from clinical experience and CF Registries, that there were striking differences in the condition of patients attending different, but recognised and accredited, CF Centres. The study of Woods and Piazza reflected care throughout the Seventies at three recognised US CF Centres where median survivals were very different at 9.5, 18.1 and 22.8 years. Analysis showed differences reflected the closeness of supervision (number of clinic visits) and intensity of treatment (days of intravenous antibiotics) the patients received (Woods & Piazza, 1988).

In 1960, Dr Terrence Gillespie, the CF Centre Director from Halifax, Nova Scotia questioned why the results were so much better in LeRoy Mathews's CF centre in Cleveland than in Halifax, Nova Scotia as both clinics prescribed similar treatment. After he had worked in both places he concluded, “*the fundamental difference (in the treatment) was a matter of degree rather than kind. Dr Matthews had developed the concept of starting full treatment on the day of diagnosis on every patient, regardless of the clinical condition*” (Gillespie, 2001). This seems to be the most likely explanation for these persisting differences, which remain a major cause for concern.

Data in Phelan and Hey 1984 paper prompts 1982 UK Working Party on CF

CF Centre care was already well established in Victoria, Australia to the extent that a paper published in 1984, reporting on patients during the Seventies and before, showed significantly

better survival in Victoria, than in England and Wales (Phelan & Hey, 1984). These results prompted the formation of the British Paediatric Association UK Working Party on Cystic Fibrosis (WPCF) chaired by Professor John Dodge, who had already been to Australia and observed the treatment there. The purpose of the WPCF was to report on the situation regarding CF care in the UK. The WPCF instigated the UK Survey in 1982, supervised by John Dodge, to determine the situation in the UK at that time. There were some 3870 patients in the UK, many saw only their local paediatrician and less than half (46.5%) attended one of the 16 clinics in the UK treating more than 50 patients. The Working Party's eventual recommendations regarding CF Centre care were that every person with CF should have some contact with a Specialist CF Centre either by full attendance or, in the case of children, an alternative would be some form of shared care (UK CF Working Party Report, 1982; Dodge et al, 1988). It is surprising that these findings and recommendations were at first rejected (but fortunately later reluctantly accepted) by the Council of the British Paediatric Association, who, at that time, questioned the need for CF Centres still believing that any competent paediatrician should be able to treat cystic fibrosis!

Fortunately, despite the attitude of a few general paediatricians and the British Paediatric Association, Ron Tucker and the CF Research Trust, gradually financed the appointment of an increasing number of doctors (CF Research Fellows), CF Nurses, Physiotherapists and Dietitians in the UK hospitals where CF Centres were developing – they were the key members of staff in the developing CF Centres. Some were funded directly by the Joseph Levy Foundation and many by the UK CF Trust's first Clinic Support and Improvement Grants. Many families in the UK opted to attend a CF Centre for all their care and voted with their feet, which were firmly pointed in the direction of a CF Centre by Ron Tucker, the Executive Director of the CF Trust!

Drs LeRoy Matthews and Carl Doershuk, Professor Rossi and others in Europe, had recognised the value of a specialist team approach in the Sixties. Unfortunately, it took well over 20 years for some paediatricians to appreciate and act on this.

Major advances in clinical care during the Eighties

There was a gradual increase in the use of nebulised anti-Pseudomonal antibiotics for patients chronically infected with *Pseudomonas aeruginosa* following Professor Margaret Hodson's important paper on the use of nebulised gentamicin and carbenicillin in stabilising the condition of adults chronically infected with *P.aeruginosa* (Hodson et al, 1981). This was a major advance for these patients some initial reservations regarding the development of bacterial resistance to aminoglycosides.

We were still worried about antibiotic resistance, but tired of accepting that initial colonisation with *P. aeruginosa* would inevitably progress to chronic infection, and therefore revived the use of colomycin, an old antibiotic from the Sixties. Colomycin was no longer used but was very active against Pseudomonas, and seemed safe to use as a possible nebulised treatment to try and eradicate early Pseudomonas. To our surprise, and against current teaching, a modest half megaunit of nebulised colomycin twice daily did eradicate early *P. aeruginosa* thus delaying or preventing chronic *P. aeruginosa* infection (Littlewood et al, 1985). Subsequent clinical progress, cultures and antibody studies confirmed that eradication had taken place (Brett et al, 1986; Brett et al, 1988; Brett et al, 1992; Pond et al, 1994). The feasibility of early eradication was later confirmed in a controlled trial from Denmark using nebulised colomycin and oral ciprofloxacin (Valerius et al, 1991) and subsequently by many others, so that early eradication gradually became established practice. The introduction of early eradication of Pseudomonas infection from the early Eighties is now having an obvious effect on the prevalence of chronic *P. aeruginosa* infection in those Centres where it was introduced in the Eighties e.g. it has now fallen to below 4% in children in both the Leeds (Lee et al, 2004a) and the Copenhagen CF Centres (Frederiksen et al, 1997; Fredericksen et al, 1999).

The earlier, more frequent and more "professional" use of intravenous antibiotics at all stages of infection (Rabin et al, 1980) was a major development e.g. where oral treatment has failed to eradicate the organism or reverse a new symptom (usually a new cough) even though the patient is not ill. Choosing two antibiotics with expert microbiological support, ensuring

adequate blood levels, allowing for the altered pharmacokinetics in CF and related to the stage of the infection all became routine in CF Centres. Also intensive courses of intravenous antibiotics became routine treatment for exacerbations of chest infection (Conway et al, 1985) or as regular three-monthly courses in patients who were chronically infected with *P. aeruginosa* (Jensen et al, 1989). New anti-pseudomonal antibiotics became available giving clinicians wider choice (azlocillin 1980, piperacillin 1982, netilmicin 1982, ceftazidime 1983, aztreonam 1986, and oral ciprofloxacin 1986). Improved delivery systems and intravenous access e.g. totally implantable venous access devices (Cassey et al, 1988; Essex-Cater et al, 1989), EMLA local anaesthetic cream to apply before venepunctures (which many children would rate as one of the more important advances of the decade!), butterfly cannulas, long lines, constant intravenous infusion pumps (to maintain IV lines for many days at slow flow rates in small children). The increasing reliance on and more frequent use of intravenous antibiotics resulted in an increasing use of home intravenous antibiotics supervised by more specialised CF staff – usually CF Nurse Specialists (Rucker & Harrison, 1974; Winter et al, 1984; Gilbert et al, 1988; Stern, 2001).

Organ transplantations heart-lung, double lung and liver

A major advance, for those who had reached the end stages of their disease, was the successful introduction of heart-lung transplantation in 1985 (Yacoub et al, 1990; Scott et al, 1988). The possibility of successful treatment in what were previously the terminal stages of the condition had a major influence on both prognosis and the treatment of severely affected individuals. The first results of heart-lung transplantations were quite remarkable and were related both to surgical skills, concentrated medical expertise in assessment and after care and also to more successful immunosuppressive therapy to prevent rejection of the transplanted organs. Later double lung transplants became more popular (Pasque et al, 1990) and are now the most commonly performed operation. Living donor lung transplants have proved successful in some centres and will be an obvious choice for some families (Cohen & Starnes, 2001)

Liver transplantation has been used successfully in patients with CF and the results are surprisingly good. Lung function, far from deteriorating as a result of the long operation has improved in some patients (Mieles et al, 1989; Noble-Jamieson et al, 1994). Successful heart-lung-liver transplantations (Noble-Jamieson et al, 1996) and lung-liver transplantations have also been performed (Couetil et al, 1995; Couetil et al, 1997).

New techniques of physiotherapy

Various new devices and techniques for physiotherapy of CF were described and evaluated during the Eighties (Pryor et al, 1979; Webber, 1986; Tyrell et al, 1986; Webber, 1990;) and an increasing proportion of people with CF received effective treatment from physiotherapists experienced in cystic fibrosis. Many parents told me they found the hour they spent with the physiotherapist to be one of the most valuable parts of the Comprehensive Assessment at our Leeds Centre (Morton et al, 1988; Worthington & Kelman, 1996). Subsequently increasing attention has been paid to the value of exercise (Webb et al, 1995). Also, particularly in the USA, the therapy vest has proved very popular with many patients (Hansen & Warwick, 1990; Arens et al, 1994; Langenderfer, 1998) although, rather surprisingly, is rarely used in the UK. This is one of a number of interesting differences between N. American and European practice – another being the different approach to use of early nebulised antibiotics for early *Pseudomonas aeruginosa*.

Acid resistant pancreatic enzymes – the major nutritional advance

The nutritional state of many patients continued to improve initially largely due to the increasing involvement of dietitians as part of most CF teams allowing identification and then appropriate correction of the inadequate energy intake by individual advice and resumption of a normal or high fat intake (MacDonald, 1984; Littlewood, 1986; Littlewood & MacDonald, 1987).

A normal fat intake was made possible by the availability in the early Eighties of the new acid resistant enzymes Pancrease and Creon which, in most patients, were dramatically more effective than the older unprotected preparations (Holschlaw & Keith, 1980; Beverley et al, 1987). Undoubtedly these new enzymes were probably the major advances in treatment

during the Eighties and markedly improved not only the nutrition but also the lives of the many patients who had previously had uncontrolled and severely handicapping unpleasant bowel symptoms particularly with fatty foods.

Other advances in nutrition

For the more severely affected patients enteral feeding, first by the nasogastric route (Bradley et al, 1979) and then by gastrostomy (Shepherd et al, 1980; Levy et al, 1985; Shepherd et al, 1986) allowed nutritional rehabilitation of those with severe malnutrition allowing reasonable nutritional state to be maintained even in many of the most severely affected patients e.g. those awaiting heart-lung transplantations.

Fat-soluble vitamin deficiencies were identified and re-identified and corrected by appropriate doses of suitable supplements (Sitrin et al, 1987; Kelleher et al, 1987; Rayner et al, 1989; Stamp & Geddes, 1993)

The first effective medical treatment for CF related liver disease

In 1989 Dr Carla Colombo reported the beneficial effect of regular ursodeoxycholic acid treatment in improving CF related liver disease. This was an exciting prospect for, up to that time, there was no specific treatment for those with liver involvement (Colombo et al, 1990). Subsequent experience has confirmed the importance of this treatment.

Increasing need for Centres dealing with adults

As the population of people with CF in the UK increased as a result of these improvements in treatment, Paediatric CF Centres developed in most large cities. Towards the end of the Eighties Adult Centres gradually appeared to accommodate the increasing number of children who were now reaching adulthood (Conway & Littlewood, 1990; Conway, 1998). Also arrangements for transition from paediatrics to these adult centres received, and continues to receive, increasing attention.

EIGHTIES

Science - from possible membrane transport problem to CFTR and the gene

At the 1980 Toronto International CF Congress, there was a poster suggesting that abnormal epithelial electrolyte transport may reflect the primary defect - *"the existence of an extraordinarily active sodium absorption could explain some of the clinical findings of CF e.g. hyper viscous mucus as being caused by excessive absorption of NaCl and water"* (Hopfer et al, 1980). Then, in 1981, Dr Michael Knowles and colleagues, from the University of North Carolina, USA, demonstrated an abnormal potential difference in the nasal mucosa of patients with CF thus providing more direct evidence of a primary epithelial dysfunction (Knowles et al, 1981); this was further supported by subsequent demonstration of the abnormality being already present in newborns with cystic fibrosis indicating the abnormality was primary rather than secondary to circulating CF factors or other substances. In 1983 Dr Paul Quinton, who himself has CF, showed that the chloride impermeability he had demonstrated in sweat glands was the basis for the raised sweat electrolytes in patients with cystic fibrosis (Quinton, 1983). These were the most important advances to date in understanding the basic defect as a membrane transport problem.

Search for and identification of the CF gene

From the early Eighties various groups, including Professor Bob Williamson's at St Mary's in London, attempted to identify the CF gene by using 'reverse genetics', as the protein was unknown. They studied families with more than one affected child. In 1985 with this technique Eiberg, in Copenhagen, demonstrated a linkage to the enzyme paraoxinase, which exists in two forms but was present in the same form in 90% of CF siblings (Eiberg et al, 1985). In the same year, Professor Lap-Chee Tsui from Toronto, in a series of mouse hybrid experiments, demonstrated a marker on chromosome 7 linked to both paraoxinase and cystic fibrosis (Tsui et al, 1985). Two other markers, known to be on chromosome 7, were closely linked to CF, the Met oncogenes, Met H and Met D from Dr Ray White in Salt Lake City (White et al, 1985) and the DNA probe pJ3.11 from Bob Williamson's laboratory in London (Wainwright et al, 1985). These findings were published in the same edition of Nature on 29th November 1985.

In 1989 the CF gene was headed by Professor Lap-Chee Professor Jack Riordan and conductance regulator (Kerem et Riordan et al, 1989). These di Sant'Agnes Prize of the CF ceremony at the North American



eventually identified by teams Tsui, Dr Francis Collins and termed the cystic fibrosis al, 1989; Rommens et al, 1989; workers were awarded the Paul Foundation at a memorable CF Conference.

Practical benefits following the identification of the gene

Unfortunately in the early years following the identification of the gene there were rather unrealistic expectations regarding the prospects for gene therapy and that application of the new discovery would change clinical care within a short time. Since 1989 well over 1000 different mutations have been described and there have been a number of practical benefits for the patients and their families. Carrier detection, accurate antenatal diagnosis and incorporation of DNA testing into many neonatal screening programmes have been major advances. Attempts to correlate phenotype and genotype have proved less successful than at first expected but the major influence of environmental factors has been a major confounding factor. However, the definite correlation of so-called "mild" mutations with preservation of pancreatic function and better clinical condition is now well established (Kristidis et al, 1992). The vast majority of people homozygous for DF508 are pancreatic insufficient and many of those with an R117H mutation are pancreatic sufficient (Cystic Fibrosis Mutations Database). Also, certain mild mutations are associated with late presenting disease often with normal pancreatic function and normal or near normal sweat electrolytes (Cutting, 2000). An association of congenital bilateral absence of the vas deferens (CBAVD) in infertile males has been associated with a high incidence of CF mutations (Chillon et al, 1995), some with two mutations the most common being DF508/R117H - somewhat blurring the edges of the traditional CF diagnosis. More recently a significant proportion of people with pancreatitis, but who do not have CF, have been found to be carriers of a CF mutation (Cohn et al, 1998).

THE NINETIES

Clinical care

The improvement in clinical care, which characterised the Eighties, continued through the Nineties thanks to the staff at the now established CF Centres. There have been a number of notable additions to the treatments available in addition to further validation of existing treatments. However, the provision of "optimal care", which is complex and very expensive, for all people with CF, particularly in the UK, has proved increasingly difficult, not least due its very high cost (Littlewood & Cross, 2000). Inadequate funding is still a major factor in preventing the provision of optimal care in the UK and seems to be a greater problem here than in some other countries, as judged by the relatively fewer proportion of patients receiving the more expensive drugs.

Cross-infection between people with CF - a new major problem

In 1979 *Pseudomonas* (now *Burkholderia*) *cepacia* was first reported in North America and thereafter reports of this new pathogen with the potential to spread between patients and cause serious illness occurred with increasing frequency both in North America (Isles et al, 1984; Thomassen et al, 1985) and later from the UK (Simmonds et al, 1990). At first some clinicians were slow to accept that cross-infection between patients occurred until the early Nineties when this was established beyond any doubt (LiPuma et al, 1990; Govan et al, 1993). The severity and fatal nature of the associated illness in a proportion of infected patients with CF and its propensity to spread between patients has led to a radical change in both clinic practice and the social habits of people with cystic fibrosis. CF Camps – so popular in N. America and so appreciated by some patients from the UK - were a source of infection and eventually abandoned (Pegues et al, 1994). Eventually, in 1993, the Infection Control Group of the CF Trust recommended strict segregation of patients infected with *Burkholderia cepacia*. This was the start of the era of cross-infection control, which was to revolutionise the whole attitude to infection and cross-infection and social contact in CF Centres and in the community.

Increasing evidence of cross-infection with other organisms – *Pseudomonas aeruginosa*

The concept of cross-infection between people with CF with organisms other than *B. cepacia* had not been regarded as a major consideration with clinic staff other than in Copenhagen (although some parents had always worried) until the early Nineties; but this has now also become a major problem which almost dominates hospital practice and has had a major impact on the social lives of people with cystic fibrosis.

Cross-infection with so-called 'highly transmissible' strains of *Pseudomonas aeruginosa* has been increasingly reported (Cheng et al, 1996; Jones et al, 2001) and there are now many reports of cross-infection with *P. aeruginosa* in CF Centres – at times with serious consequences. These developments have had a major impact on the care and social lives of everyone with cystic fibrosis. Infection with certain types of *B. cepacia* may prove fatal in people with CF, and the highly transmissible strains of *P. aeruginosa* appear to be more difficult to treat (Jones et al, 2001).

As a result of these developments it is currently recommended that people with CF should be segregated according to their microbiological status and those with *B. cepacia* should also be segregated even from each other as those with less virulent genomovars may be infected by those with the more severe ones.

Other advances in treatment in the Nineties

Support for the routine use of prophylactic anti-staphylococcal antibiotics (flucloxacillin) in young children came from a controlled trial in screened CF infants in East Anglia in 1994 (Weaver et al, 1994). Now the Antibiotics Group of the UK CF Trust recommends the use of continuous flucloxacillin for the first 2 years of life for all infants with cystic fibrosis.

The use of macrolides (azithromycin) for patients chronically infected with *P. aeruginosa*, possibly as a result of their anti-inflammatory properties, has been a new widely introduced treatment following confirmation of their beneficial effect in a number of clinical trials (Equi et al, 2002; Saiman et al, 2003).

Intravenous antibiotics were increasingly used in less severely affected patients at a much earlier stage rather than as a last resort – central to modern treatment (*"a matter of degree rather than kind"*). More UK Centres, although remaining selective, are adopting the Danish 3-monthly IV antibiotic regimen for many of their chronically infected patients, even though the only trial available did not support the use of the regimen, probably due to the proportion of severely affected patients included (Elborn et al, 2000). The policy does seem to be reasonable for the reasons outlined by the team in Copenhagen (Page 8).

Recombinant human DNase (Pulmozyme) is an important new drug for inhalation and is the first really effective mucolytic, which is very effective in reducing the viscosity of the sputum and improving respiratory function in a significant proportion of people with cystic fibrosis (Shak et al, 1990; Fuchs et al, 1994). It is now an important and effective part of the daily treatment for many patients and there is now evidence that even mildly affected patients may benefit (Harms et al, 1998).

A special preparation of tobramycin for inhalation (TOBI) became available in the Nineties. Although inhaled amino glycosides (the IV preparations of gentamicin and tobramycin) have been widely used in the UK since Margaret Hodson's 1981 paper, an important, well-conducted controlled trial to confirm the beneficial effect of the special preparation of tobramycin for inhalation (TOBI) was welcome and this preparation is now increasingly used but limited by cost in the UK (Ramsey et al, 1999).

High strength pancreatic enzymes. Many patients, when taking a normal fat intake, did require a large number of enzyme capsules and it was not surprising that patients, and their professional advisers, welcomed the introduction of the new "high lipase enzymes" in 1992. However, in 1993 a new complication, fibrosing colonopathy, was observed in Liverpool and related to the very high doses some patients were taking (Smyth et al, 1994); subsequently further patients with strictures were reported from UK and the United States. Studies in the

UK (Smyth et al, 1995) and the US (FitzSimmons et al, 1997) showed a relationship with the very high doses of lipase achieved in some people with the new enzymes but differed on an association with the copolymer covering of some preparations. The problem has since receded in the UK following advice from the Committee on the Safety of Medicines to restrict the daily dose of lipase to 10,000 IU /kg/day (Littlewood, 1999), even though many people with CF, using brands which do not contain copolymer, still exceed this dose of enzymes (Mehta, 2001).

Other new problems have emerged as CF survival increases

With increasing survival, problems related to CF including diabetes mellitus, liver disease, osteoporosis, pregnancy and fertility have become increasingly common and another major management problem. New challenges beyond imagination of the early CF clinicians include the management of pregnancy in women with CF and treatment of infertility in men with cystic fibrosis. Also is it encouraging that even the problems of old age and CF are now being addressed (Warwick, 2003)

Diabetes mellitus – affecting an increasing number of adults

With increasing survival CF related diabetes mellitus (CFRDM) affects over 30% of adults with CF and during the Nineties there has been greater attention given to cystic fibrosis related diabetes mellitus. An important observation was that the gradual onset of glucose intolerance (in contrast to clinical diabetes mellitus) as judged by glucose tolerance tests, was associated with a worsening clinical course in the preceding years (Lanng et al, 1992; Lanng et al, 1995). Recently, the CF Foundation and the UK CF Trust have produced detailed documents dealing with CF related diabetes (Moran et al, 1999; UK Cystic Fibrosis Trust Diabetes Working Group Report, 2004).

Liver disease - the first effective treatment

Undoubtedly, the report of the use of ursodeoxycholic acid treatment (URSO) for CF liver disease, in a memorable presentation by Professor Carla Colombo in 1989, was a major advance in management (Colombo et al, 1990). Prior to this there had been no treatment for cystic fibrosis related liver disease other than reversing the changes of fatty infiltration by improving absorption and nutrition,

Osteoporosis

Although some patients with advanced disease had obvious X-ray changes of osteoporosis with kyphosis, vertebral collapse and an increased frequency of fractures (Aris et al, 1998), the availability of Dual Energy X-ray Absorptiometry (DEXA) scanning has allowed more accurate recognition in a greater proportion of people with cystic fibrosis. Better nutrition in childhood, more effective enzymes to improve intestinal absorption and regular monitoring of their effect; attention to energy, calcium and vitamin D intake and levels, should reduce the incidence and severity of osteoporosis with increasing age (Conway, 1999; Conway et al, 2000).

Pregnancy and fertility

New challenges include the management of pregnancy in women with CF, although the first pregnancy was reported in 1960, when the median age of survival was only 10 years (Siegel & Siegel, 1960). Subsequent reports have documented a gradual improvement in outcome (Gilljam et al, 2000; Edenborough, 2001). Infertility has been successfully treated in some men with CF by various techniques of sperm aspiration and subsequent *in vitro* fertilisation and a number of successful pregnancies have been reported (Schlegel, 1996; McCallum et al, 2000).

THE NINETIES

Science – consolidation and steady progress

Increasing expectations of patients and families that had developed through the Eighties culminated in the discovery of the CF gene in 1989 – and what a decade it had been when compared to the barren years prior to 1980! The Nineties began on a wave of enthusiasm, near euphoria, following the successful identification of the CF gene in 1989 (Rommens et al, 1989; Riordan et al, 1989; Kerem et al, 1989). Some patients and families considered that a cure had already been found! Also, the initial progress was encouraging. Two papers in

1990 reported correction of the CF defect in cultured CF cells by transfer of CFTR cDNA using viral vectors (Drumm et al, 1990; Rich et al, 1990). Thus, it was possible to correct the CF defect in cultured cells and subsequent experiments appeared to confirm that CFTR functioned as a chloride channel.

By 1992 three CF mouse models had been produced. The Cambridge mouse (Ratcliff et al, 1993) and the North Carolina Mouse had null mutations and were unable to produce any CFTR (Snowuart et al, 1992); the Edinburgh mouse did produce a little CFTR (Dorin et al, 1992). These mouse models were essential for further *in vivo* investigations of CFTR function and gene transfer.

There was a defect in chloride transport, excessive sodium absorption due to lack of inhibition of its absorption by CFTR (Stutts et al, 1995) with a net depletion in the water content of the airway secretion. This depletion, which was shown to be isotonic (Knowles et al, 1997), was excessively rapid which adversely affected mucus transport (Matsui et al, 1998).

Further research work concerned gene transfer into various cell lines and animal tissues using viral vectors. Immunological problems were less likely with non-viral vectors and the first *in vivo* successful gene transfer into the airways of CF mice was achieved using cationic liposomes (Hyde et al, 1993), which have subsequently been the preferred vector of the UK CF Gene Therapy Consortium working at London, Oxford and Edinburgh.

Studies of gene transfer in people with cystic fibrosis

In 1993, the first successful adenoviral mediated gene transfer was reported in a man with cystic fibrosis (Zabner et al, 1993). Subsequently nasal studies have been reported using viral vectors, which have achieved no evidence of significant gene transfer except with high doses causing inflammation (Knowles et al, 1995); also repeated applications leads to increasing inflammation and antibodies (Zabner et al, 1996; Flotte et al, 2003). Three studies from the UK, which involved application to the nose, used liposomes as the vector (Caplen et al, 1995; Gill et al, 1997; Porteous et al, 1997); another involved repeated nasal applications (Hyde et al, 2000) and the most recent from the Royal Brompton in London, involved transfer to both nose and lungs (Alton et al, 1999). Although progress has definitely been slower than originally expected, successful gene replacement therapy is still considered to be a reality within 5 to 10 years (Davies et al, 2001) and gene therapy and the investigation of more suitable vectors is now a high priority area of research for both the UK CF Trust and others.

Pharmacological treatments

An alternative strategy to gene therapy is to improve CFTR function by other means and a number of drugs are under investigation and showing promise as an alternative or complementary approach to treatment. Improved CFTR trafficking with some increase in CFTR function in the nasal epithelia of people with DF508 was achieved with oral sodium 4-phenylbutyrate (4-PBA) (Rubenstein & Zeitlin, 1998); other possibilities include genistein (Andersson & Roomans, 2000), and CPX (McCarty et al, 2002). Additional potential strategies include inhibition of sodium absorption by drugs such as amiloride or more active analogues (Rodgers & Knox, 1999) and activators of chloride secretion such UTP and INS 365 mediated through P2Y(2) extra cellular receptors (Noone et al, 2001).

More recent possibilities are the corrective effect of gentamicin in people with stop mutations (Wilschanski et al, 2003), of sildenafil on DF508 mutations (Dormer et al, 2003), curcumin on mice homozygous for DF 508 (Egan et al, 2004) and correction of fatty acid imbalance (Freedman et al, 1999; Freedman et al, 2004). Other possibilities have been reviewed recently (Rodgers & Knox, 2001).

Adults with CF today

A recent survey of adults with CF by Dr Sarah Walters gave some idea as to the present situation for them in the UK (Walters, 2001). The average age of the 1246 responders was 25.5 years, 30% had partners, self rating was mild 29%, moderate 64% and severe 7%, 47% were in paid and 13% in voluntary work, health problems accounting for 42% of the unemployed and 40% being students. 58% had less than 2 weeks sick leave over the preceding year, The following medical problems were reported – diabetes 28%, arthritis 23%,

sinusitis 20%, infertility 19%, liver problems 14%, recurrent bowel problems and allergic bronchopulmonary aspergillosis 10%.

Concerns of CF families

A recent survey by the UK CF Trust on the main concerns of patients and their families found these were – the standard of care they receive, facilities and services available, person ultimately responsible for their care, who does what in shared care situation? Lack of specialist staff in smaller clinics at the local hospital, poor communication between professionals, inadequate adult services and cross-infection issues were other areas of concern.

WHAT THE FUTURE HOLDS

Early diagnosis in the first weeks by neonatal CF screening, early expert advice, support and monitoring by a specialist CF team, and early appropriate treatment of respiratory infection and malabsorption are now well-established and should be the right of all people with cystic fibrosis both now and in the future (Littlewood, 2000c).

In particular the increasingly successful aggressive conventional treatment should continue and be improved to ensure that as many people as possible will remain in good a condition to benefit from more specific treatments of the basic defect which are likely to be available within a few years.

- **Improvements in outlook with conventional treatment are likely to continue**

The effects of the improved treatment, which have occurred over the past two decades, are likely to be reflected in improved survival for the foreseeable future. In particular, the reduced proportion of people chronically infected with *P. aeruginosa* will reduce the number who will experience deterioration in their condition. Increased attention to nutrition after the introduction of neonatal screening and subsequent optimal nutritional management will also improve the nutritional state, growth and ultimate stature of people with cystic fibrosis. There may also be more specific pharmacological treatments, which will improve the outlook of many patients, and in the intermediate future gene replacement therapy is like to further improve the condition and, in the long-term, the survival of people with cystic fibrosis.

Despite involvement of expert dietitians and the availability of more effective pancreatic enzymes, chronic gastrointestinal problems of pain and distal intestinal obstruction syndrome are still relatively common in adults with CF, most of whom attend CF Centres primarily interested in respiratory problems. It is likely that more attention will be given to the gastrointestinal tract with consideration of perhaps methods of preserving the remaining endocrine pancreatic function which could delay the onset of diabetes mellitus; for although most children with CF already have pancreatic insufficiency, few have yet developed clinical diabetes. With regard to the malabsorption, it is likely that more detailed monitoring of both the malabsorption and gastrointestinal problems by established methods will occur with a more precise use of pancreatic enzymes in the many patients who continue to exceed the doses recommend by the UK Committee on Safety of Medicines. Also more detailed evaluation of distressing abdominal symptoms, rather than considering all to due to malabsorption, would lessen frequency of abdominal symptoms (Littlewood, 1992; Littlewood, 1995c; Littlewood & Wolfe, 2002). A reduction in the enzyme dose to recommended levels does not seem to be associated with an increase in symptoms or nutritional problems (Lowden et al, 1998) and satisfactory fat absorption is reported in clinics where the majority of patients do not exceed the recommended daily enzyme intake of less than 10,000 IU lipase /kg/day (Littlewood & Wolfe, 2000).

- **Greater proportion of care from Specialist CF Centre staff**

Virtually all advances in clinical care to the present time have occurred at Specialist CF Centres where there are sufficient patients and staff to identify and investigate the relevant problems. It is likely that further improvements in present treatment will continue to be made at CF Centres. For example, what is the best treatment for early *P. aeruginosa* when standard

inhaled and oral antibiotics fail? It is important to examine the circumstances where eradication fails and devise additional treatment strategies for these people accordingly and this requires the numbers that are treated a CF Centre (Lee et al, 2004b).

For another example, should all those who do become chronically infected with *P. aeruginosa* have 3-monthly courses of intravenous antibiotics with all the inconvenience, potentially serious side effects and great expense? The Copenhagen CF Centre introduced and has practiced this policy since 1976 (Pedersen et al, 1987) and the Danish results certainly do seem to be considerably better than most others (Frederiksen et al, 1996). These basic questions are central to management and really should be answered.

- **More user-friendly “conventional” treatment to control symptoms**

It is increasingly obvious that the detailed and demanding lifelong treatment required to maintain people with CF in the best possible condition, represents an almost unattainable regimen for many to continue year after year, particularly as adolescence approaches. It is likely that current treatment will be simplified, first by delaying the onset of chronic pulmonary infection and thus reducing the items of therapy required. Alternatively, the methods of delivering the present day treatment are likely to be simplified e.g. more efficient nebulisers and inhalers, powder rather than liquid delivery of inhaled drugs, assisted physiotherapy techniques, longer acting drugs reducing the doses needed and once rather than three times daily as has occurred with intravenous tobramycin (Smyth et al, 2003). Also increasing efforts to increase adherence from various psychosocial strategies are of increasing importance.

- **Increasing the number of transplants for people with cystic fibrosis**

This will remain a problem for the foreseeable future and it is reassuring that the problem is a high priority for the staff at the UK transplant centres and the situation is likely to improve. It is reassuring that the shortfall of transplants is not due to lack of funding but of donor organs the supply of which could possibly be improved by changes in donation arrangements and help at the donor's hospital and transplant centre.

- **New problems with increasing age – even growing old!**

The complexity of care and the new problems which have become more common with the increase in adults with CF e.g. diabetes, liver disease, osteoporosis, pregnancy and fertility problems, as well as complex psychosocial issues are better dealt with by the staff at a Specialist CF Centre. Already these disorders are receiving considerable attention at many CF centres and will become increasingly important, as there are an increasing proportion of adults with cystic fibrosis.

- **Agreed protocols of treatment**

Most countries, including the UK, now have agreed consensus documents for standards of care and routine managements and treatments derived from the views of expert committees, published data, Cochrane Reviews and other sources.

- **National and International Microbiological Reference Laboratories**

Management of infection will undoubtedly continue to be central to effective treatment and is likely to become even more important. It is almost certain that new unfamiliar pathogens will become an increasing problem – either those we already know in a more resistant form or new ones. These trends will need to be identified, acted upon and appropriate treatment strategies agreed as they arise. Cooperation between Centres will be required. There has been a tendency, on the part of some clinicians, to be slow to accept the pathogenicity of new organisms, if they have not personally observed their ill effects. This happened first with *B. cepacia*, and more recently with highly transmissible *P. aeruginosa*. Also with the tendency to travel abroad, organisms from one country may appear in another as happened with *B. cepacia*. Learning from past experience, it would be wise to consider all these strange-named newcomers as potentially pathogenic. It is clear that CF Reference Laboratories, as are already present in the UK, USA and some other countries, will be increasingly important in the years to come.

It is likely that clinical care will continue to improve but the established CF pattern, of new problems appearing when older ones recede, is bound to continue. Just as *P.aeruginosa*

replaced *S. aureus*, so, as the prevalence of chronic *P. aeruginosa* falls with successful early eradication, it is already apparent that *Aspergillus fumigatus* and *Stenotrophomonas maltophilia* are cultured more often. The annual rate of acquisition of new *P. aeruginosa* does not appear to change (Lee et al 2004b), even with strict segregation and good hygiene, as many new infections are acquired from the environment; but with early and more complete eradication, the prevalence of chronic Pseudomonas infection should continue to fall even further until either drugs or gene replacement therapy reduces the susceptibility of the patient's airways to infection or an effective vaccine is introduced - as seems a real possibility in the near future.

It is apparent that with early diagnosis and treatment, good nutrition, good hygiene, segregation and optimal early eradication antibiotic treatment, chronic infection can be and will be increasingly avoided or significantly delayed in the majority of children (Lee et al, 2004b). Certainly the hygienic and segregation policies with frequent expert microbiological monitoring, as recommended by the CF Foundation, UK CF Trust and other organisations will need to be enforced with increasing vigour and success by patients, families and professionals and everyone involved in CF care.

- **Stricter protocols for prevention of cross-infection, staff and facilities**

The consensus documents from both the CF Foundation and the UK CF Trust give clear guidance on the most effective way experts in the field consider are the best ways of reducing the risks of cross-infection and although these are difficult to accept by some families and even more difficult for some professionals, they are the best advice available at the present taking all factors into consideration (*Pseudomonas aeruginosa* infection in people with cystic fibrosis, UK Cystic Fibrosis Trust, 2001; Saiman et al, 2003; *Burkholderia cepacia* complex, UK Cystic Fibrosis Trust, 2004).

- **Increasing use of home care and CF Nurse Specialists**

With the increasing problem of cross-infection and fear of hospital acquired infection, home care by members of the multidisciplinary CF Team is likely to become more the rule with an considerable expansion in the role of the CF Nurse Specialist – again dependent on adequate funding. Expansion in this area would certainly be one of the most effective and cost-effective means of improving the standard of care of a significant number of people with CF as well as improving their quality of life and reducing their chances of cross-infection.

- **Carrier testing of relatives**

Although general population screening has not been generally successful, the investigation of relatives for carrier status should be generally available and, for those who requested it in the UK, is available through the National Health Service.

- **Pre-implantation diagnosis**

In vitro fertilisation using the eggs and sperms of parents who are known CF carriers, and subsequent selection of unaffected embryos, is more acceptable to many than antenatal diagnosis and if necessary termination of an early pregnancy, if they wish to avoid having a further child with cystic fibrosis (Ao et al, 1996; Polnay et al, 2002). This should be available to all couples that know they are carriers and is likely to be cost-effective in the long-term and should become generally available to more couples in due course.

- **Antenatal screening and diagnosis**

Antenatal screening is offered to all pregnant women in Edinburgh and has been available for over 10 years (Brock 1996; Murray et al, 1999). Not all prospective parents will wish to be screened for carrier status but it should, and I'm sure will, be available as a choice for all who want it in due course. Antenatal screening has been accepted in principle by the UK Government and is available in some parts of the United States. In Edinburgh, where antenatal CF screening has been routine since 1992, a significant reduction in the number of infants born with CF has occurred (Cunningham & Marshall, 1998); some reduction in the number of infants born with CF is a likely consequence of antenatal CF screening.

- **Neonatal screening will continue to be introduced gradually**

The evidence and accumulated experience that screening is mandatory is now overwhelming and even in the UK, the Government agreed in 2001 to the introduction of neonatal CF screening in those parts of England where it is not yet routine. Fortunately, neonatal screening is gradually being introduced worldwide wherever CF occurs and economics allow (Southern & Littlewood, 2003). Failure to identify a serious condition at birth, whose outlook is so entirely dependent on early and appropriate treatment received, should now be regarded as suboptimal care to say the least (Littlewood, 1999).

It is difficult to predict the effect of these procedures on the eventual size of the CF population. Increase in survival would tend to increase and prevention of the birth of infants with CF would reduce the number of people with cystic fibrosis. It is understandable that termination of pregnancy has become less acceptable to couples as the prognosis for people with CF continues to improve and the prospect of more specific treatment becomes a more realistic possibility (Polnay et al, 2002). However, a fall in the number of newborns with CF has already been noted in East Anglia, a region of the UK where there has been neonatal screening for over twenty years (Heeley et al, 1982); perhaps due to an increased general awareness of cystic fibrosis (Green et al, 1993). Also in Leeds where neonatal screening has been routine since 1975, the incidence of CF between 1975 and 1985 was 1/2220 births and between 1996 and 2002 had fallen to 1/4307 (Conway et al, 2003).

- **Infertility treatment for men with cystic fibrosis**

The success of the various techniques of assisted conception, which have already resulted in successful pregnancies where the father has CF, are likely to become more successful and more readily available. Obviously to many men with CF this will be of major importance.

- **More clinical trials organised through CF Centres and CF Database**

With the inevitable future trials both of new conventional treatments and of drug or gene therapy for the basic defect, attendance at a CF Centre will be necessary for it will be through selected Centres that trials will be organised. Also registration on the national CF Database will be essential so that patients of appropriate age, sex and genotype can be identified. The CFF Therapeutics Development Programme is an example that it is likely others will follow.

- **Correction of persisting inequalities of care and funding problems**

The persisting inequalities of care so clearly revealed in the past and yet still so obviously still present as revealed by the CF registries in North America, the UK and elsewhere, are quite unacceptable. Consensus meeting and publications outlining the best available treatments, making the information available to all, and registries to monitor treatment received and the results will become routine. The value of national CF registries (which some busy clinicians find so irksome!) is now established and all patients (with their permission) will be registered. The role of the national CF organisations will be increasingly to identify and campaign to correct these inequalities after their expert groups have defined standards of care. Subsequently, they will ensure the application of their standards by regular accreditation (as already occurs in the USA), ideally in partnership with the Government or appropriate funding body.

- **Funding – a present and future problem**

Provision of the best available treatment for CF is very expensive and is likely to remain so and funding problems are a major obstacle to the delivery of optimal care in a number of countries and it is difficult to predict if this will be eased in the future. New treatments may be even more expensive? However, perhaps it should become increasingly unacceptable for those in prosperous countries to deny adequate care to those with the misfortune to have a serious life-threatening disorder such as cystic fibrosis. To achieve adequate provision by funding agencies or government must be a high priority for the next few years for all concerned - for inadequate funding is undoubtedly a major cause of inequalities of CF care in the UK and presumably elsewhere. There is no point in knowing what is required if there's no money to achieve it!

- **Appreciation of the major problems of families with a person with CF**

Even with the improved outlook for people with CF, having a family member with the condition remains a major and life-changing situation for the parents, siblings and other members of the family. Most professionals involved with CF care appreciate this and will continue to provide a sympathetic, high standard service for patients. It is important that the tendency to production line treatment, an increasing feature of our NHS, does not become common in CF care and that Centre staff, in particular Directors, continue to be always accessible whenever advice is required. Expert psychological advice can do much to assist patients and families to come to terms with their many and varied problems as they occur.

- **Major efforts to treat the basic defect – “to treat the cause rather than effects”**

The identification of the CF gene in 1989 presented a new opportunity - that of treating the cause rather than the secondary effects and we must now increase our efforts to take full advantage of this opportunity – indeed, major efforts are already in progress. A top priority must be a major effort to develop any specific treatment (“cure”), which shows promise as a treatment for the basic defect whether it is gene replacement, drugs, or other means. It is very likely that within 5 to 10 years, or even considerably sooner, either gene replacement or pharmacological treatment or both (perhaps depending on the patient’s particular mutations) will effectively normalise, or significantly improve, the disturbed physicochemical condition within the CF airways, so that much less treatment or even no other treatment will be required for the respiratory tract.

To the families and people with CF, progress seems to be painfully slow, even allowing for their understandably over optimistic hopes and expectations following the discovery of the CF gene in 1989. No one was clear in which direction to go before 1989. We now know the basic defect – unbelievable progress if viewed from before 1980 – so why is progress so slow they ask. When no one had any idea as to the basic defect, “good science” for science sake, which may have a bearing on CF, was acceptable although there were numerous blind alleys, which lead nowhere – yet they just might have lead to the cause. However, now we know the cause – admittedly still lacking some details on regulation etc – there is enough known to focus our research effort on its correction.

As occurred on the clinical side following the development of CF Centres, advances only really started to happen for the majority of patients when these CF Centres acquired many patients presenting the staff who then had the opportunity to identify, study and solve some of the many clinical problems. It cannot be over emphasised that virtually all significant clinical advances have been made at the Specialist CF Centres. The same joining of forces surely must happen with science and research, which must also be increasingly linked with clinical research. It is reassuring that this is already happening on a national and international level.

- **The UK CF Gene Therapy Consortium**

In the UK, in London, Oxford and Edinburgh, we are fortunate to have three of the leading CF gene therapy research teams in the world. We are aware that pharmacological approaches to treatment are the main focus of research in the USA. It was therefore decided to ask these three research groups to combine in their efforts with the promise of funding them for five years to permit continuity and cooperation to develop a compound to the stage of a Phase III trial within five years.

The concept of the UK CF Gene Therapy Consortium (UKGTC) was suggested by the Chief Executive of the UK CF Trust, Rosie Barnes, in 1999 after asking the scientists what they required to speed up the process, which seemed to many to be so painfully slow? They requested more senior scientists and technicians – experts, people to do the numerous experiments in the laboratories to move more projects forward at the same time. An important feature of the initiative was to guarantee regular funding and security to high quality scientists with proven track records in this field and also to avoid the delays caused by the search for piecemeal funding from the usual grant awarding bodies.

As many scientists still work in relatively small isolated groups, the formation of a combined working approach of a number of major centres, such as the UKGTC, is a definite step forward with the aim of much greater sharing, to a previously unpredicted extent, of ideas,

knowledge, resources and core facilities to speed progress and is already showing the advantages of such an arrangement. The members of the UK GTC are to be commended for their pioneering progress in putting progress in CF research before their career progress in many cases to make the UKGTC work. Also thanks should go to our quite exceptional Chief Executive, Rosie Barnes, for her vision and drive in bringing everyone together to form the UKGTC and her subsequent relentless efforts and those of her team to secure adequate funding. There has been some opposition to the recent changes in policy but it surely must be the right way to go when one considers the current situation. The progress of the UK GTC up to present has been very encouraging and praised by the new Scientific Advisory Board of independent experts at meetings of the UKGTC Steering Committee in 2002 and 2003.

- **The CF Foundation's Therapeutics Development Programme**

A major welcome initiative came from the USA CF Foundation in 1998 with their Therapeutics Development Programme designed to halve the time and reduce the cost of bringing new drugs to the patient. Either drugs which their drug-screening programme had identified or those identified by other means – some of which are already licensed. So all the complex machinery for conducting a large clinical trial in people with CF is in place. There is a specially trained network of CF Care Centres coordinated by the Children's Hospital and the Regional Medical Centre Seattle. Initiative has come from the CFF in the establishment of their clinical network to foster collaboration between the clinic, laboratories and industry and this is a major advance designed to speed introduction of new treatments (Goss et al, 2002).

A recent example of the value of such a system was the rapid response of the Cystic Fibrosis Foundation Therapeutics Inc. who with SEER Pharmaceutical, will fund a trial through the CF Foundations Therapeutics Development Programme to confirm or refute the interesting and potentially important possibility of curcumin, identified as having a corrective effect on the nasal potential difference of CF mice. Over 20 other compounds potentially useful compounds are under investigation by the CF Foundation.

- **High throughput screening for new CF therapies**

As part of the CFF initiative, high throughput screening is likely to identify active compounds, which can be brought as quickly as possible to trials in the CF patients. An automated method of analysing potential activity already identifying a small number of potentially active compounds from many thousands tested (Galietta et al, 2001).

CONCLUSION

I have endeavoured to cover some of the many aspects of the CF story as seen by a general paediatrician initially involved in other areas, who gradually became very involved in CF care and more recently has been working closely with the UK CF Trust. I have tried to highlight lessons from the past, such as the absolutely central role of Specialist CF Centres and the advantages of collaboration, and speculate on how developments will continue.

I thank all those friends and colleagues, too numerous to mention, who over the years have contributed to and now continue with the development of the Leeds Regional CF service. In recent years, since my retirement from the Leeds Centre, it has been a great pleasure to work with Rosie Barnes and her staff at the UK CF Trust. Last, but by no means least, thanks go to the hundreds of patients and parents who have proved such an inspiration and example over the years and who have uncomplainingly taken part in numerous clinical trials and research studies.

There has not been a time when there was more hope of major progress in CF care than the present, both in terms of clinical care, or drug and gene therapy, for even in 1989 after the identification of the CF gene, we realised that it would be some time before this major discovery would be translated into a treatment for patients. However, now, in contrast with the hopeless situation in the early years, the present state of knowledge, clinical care and scientific activity of highly regarded scientists would have been beyond belief even 20 years ago. In fairness to the early workers, there have also been massive advances in medicine, science and technology generally, many of which have facilitated the advances in CF research.

While research and improvement in diagnosis, treatment and provision for people in all stages of the condition will remain of the highest priority and will, of course, continue, it is abundantly clear that with the knowledge and progress that has been made up to the present, there must be an even greater concerted effort to modify, influence, treat or even cure the basic defect now this has been clearly identified. Progress both in the gene replacement and pharmacological areas is gaining momentum and I have no doubt that there should be a message of great encouragement and optimism from this meeting.

It has been a great privilege to receive these two honours and I thank the Levy family, CF Worldwide and the European CF Society most sincerely.

James Littlewood June 2004



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