the British Thoracic Society (BTS) in 1982, reflecting the gradual melding together of these two historical strands of the profession. The BTS has played a major role in developing the specialty over the last 25 years and led the way in many areas including clinical governance, training, and lobbying for smoking cessation services and better services for patients.

In the 1960s, today's manpower figures for respiratory medicine were unimaginable. There were around eight respiratory senior registrars in the country, compared to 275 specialist registrars now, and far fewer chest consultants. Many consultants in district general hospitals were single-handed until recently, despite extremely high workloads. The four UK chairs in respiratory medicine in 1984 have now expanded at least tenfold.

Back to the future

I entered respiratory medicine at an exciting time when expectations were high. Many of these expectations have been fulfilled, in part at least. Several conditions can be, and are, prevented, some are cured and most patients with chronic respiratory conditions can expect a better quality of life. There have also been some major disappointments. The eradication of TB was in sight in the 1980s but due to AIDS and multi-drug resistance, it is now a bigger problem than ever worldwide. The five-year mortality for lung cancer has improved little despite progress in diagnosis and treatment, and the reduction in particulate air pollution has had less effect on the incidence of COPD than was hoped.

The factors underpinning the successes during the last 40 years are various and include individual innovators and inventers, new drugs from the pharmaceutical industry, leadership in ensuring that good practices are widespread and a strong track record of research. The UK has played a major role in clinical, epidemiological and physiological research throughout my career, much of it pragmatic and feeding through directly to patient care. The increase in research in cell and molecular biology and clinical genetics, in conjunction with good clinical research, holds the promise of more fundamental benefits for patients in the future.

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CURRENT KEY DEVELOPMENTS

Cystic fibrosis

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Background

By the end of the 1960s cystic fibrosis (CF) was established as a rare and fatal disease of childhood defined by recessive inheritance, pancreatic insufficiency, lung infections and a positive sweat test. Since so few children with CF lived past their teens the associated diabetes, liver disease and male infertility attracted little attention. Scientists avoided CF as it was poorly funded, poorly understood and advances seemed unlikely. Nevertheless, shining through this gloom were rare beacons of optimism, a few enthusiastic paediatricians had given aggressive treatment with dietary supplements and antibiotics and shown that CF need not always progress rapidly to death.

The first adult CF clinic in the UK started at the Brompton Hospital in 1966. New pancreatic enzyme formulations, new antipseudomonal antibiotics, and physiotherapy techniques led to a shift in attitudes. More importantly CF families set up national bodies (Cystic Fibrosis Research Trust in the UK and Cystic Fibrosis Foundation in the USA) to raise money for research, educate CF parents and press for higher standards of care. Interested clinicians were converted into CF specialists, attendance at a CF centre became the norm and scientists were attracted into the field by the new money and astonishing advances in molecular genetics. Specialising in CF became fashionable and meetings, previously sad and poorly attended, began to buzz. Progress, excitement and optimism were in the air and the journals were full of advances: neonatal screening, prenatal diagnosis, high fat diets with acid resistant pancreatic enzymes, regular intravenous (iv) and nebulised antibiotics, all cascaded into print. The scientists joined in and after a few false starts – serum CF factors and spurious immune defects – progress was rapid: defective ion transport linked the sweat gland to the lungs and pancreas (1981) and the new techniques of chromosome walking and jumping helped identify the CF

gene (1989). Analysis of the gene led to definition of the protein CF transmembrane receptor which turned out to be the chloride channel. International CF meetings now attracted thousands and there was riotous delight as Francis Collins, one of the team leaders, announced the identification of the CF gene with a song he had written accompanied by a small guitar.

New treatments

New treatments followed, not always because of the new science but rather because of a concerted effort by clinicians, CF groups and small pharmaceutical companies – although rare, life-long treatment of CF could provide reasonable returns and new therapies might be extended to other more common airway diseases. First came deoxyribonuclease (DNase), a recombinant human protein that reduced sputum viscosity and improved lung function. Then came Tobi®, a new nebulisable formulation of tobramycin. Nebulised antibiotics had been used for 20 years in Europe but it needed a link up between the CF Foundation and a small pharmaceutical company to fund a series of definitive clinical trials. At the same time major progress in lung transplantation restored a few to normal life and gave hope to many more.

New devices

Alongside all of this, and just as important, were the new devices. Nasogastric feeding tubes were replaced by small bore percutaneous endoscopic gastrostomy tubes – better and kinder. Permanent iv access by subcutaneous ports made iv antibiotic treatment easier. Positive pressure iv infusion devices allowed treatment to continue at home or at work and improved topical lung delivery systems – rapid nebulisers and dry powder inhalers simplified inhaled treatment and enhanced compliance. Positive pressure and oscillatory devices assisted physiotherapy and non-invasive ventilators palliated symptoms for advanced lung disease and bridged a few to transplantation.

All these technical advances coincided with and contributed to a revolution in the delivery of care. Cystic fibrosis centres built up multidisciplinary teams made up of specialist nurses, physiotherapists, dieticians, pharmacists and microbiologists. National and international guidelines defined standards of staffing, monitoring, treatment and cross infection. Cystic fibrosis databases added to knowledge of epidemiology and allowed comparisons between individual clinics and different countries so providing evidence of optimal care. The CF community pioneered patient advocates, expert patients, peer review of CF centres, and the CF organisations became formidable political lobbyists, fundraisers and directors of research.

New problems

All this energy, progress and enthusiasm have improved the lives of people with CF far beyond the expectations of the 1960s but inevitably new problems have been identified:

- longer life means more time to develop complications as diabetes, osteoporosis, sexual and psychological difficulties are now a routine part of CF care
- cross infection has plagued a few centres and new antibiotic resistant pathogens are becoming an increasing problem
- costs of care are escalating
- the intensity of treatment is becoming more burdensome and the risks of long-term side effects are steadily increasing.

All these are challenges for the future to be set against the gains that are now so visible. Now CF is no longer a miserable, fatal childhood disease but instead is a lifelong medical condition with an estimated prognosis of at least 40 years and rising. Those with CF are able to work normally and raise families albeit with a major burden of treatment and uncertainty about the future. A massive and well coordinated research effort is under way. High throughput screening of tens of thousands of chemical entities should find new ion transport drugs and gene therapy (proof of principle already published) is developing steadily. Further progress will follow. Cystic fibrosis as a lifelong condition will remain but CF as a disease is on its way out.

Genetic predisposition to chronic obstructive pulmonary disease: advances in α_1-antitrypsin deficiency and the serpinopathies

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Alpha$_1$-antitrypsin deficiency is the only widely accepted genetic factor that predisposes smokers to chronic obstructive pulmonary disease (COPD). Most individuals with COPD have normal levels of α_1-antitrypsin but 1–2% are homozygous for the severe Z deficiency allele (Glu342Lys). This mutation causes α_1-antitrypsin to be retained within the endoplasmic reticulum of hepatocytes as periodic acid Schiff (PAS) positive inclusions. Work over the past 15 years has elucidated the mechanism by which the mutant protein is retained within the liver and has provided new insights into the pathobiology of the liver and lung disease associated with α_1-antitrypsin deficiency. Biochemical, biophysical and crystallographic studies have shown that the Z mutation of α_1-antitrypsin causes the protein to undergo an aberrant conformational transition and form chains of ordered polymers.[1–3] These ordered polymers are not detected by the unfolded protein response[4] and are only partly cleared by autophagy. Their retention within hepatocytes causes cell damage that presents clinically as neonatal