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

hepatitis, cirrhosis and hepatocellular carcinoma.[5] It has become clear that this process also underlies the deficiency of other mutants of α_1-antitrypsin. The Siiyama mutation (Ser53Phe) is the most common cause of α_1-antitrypsin deficiency in Japan and the Mmalton (Δ52 Phe) variant is the most common cause of α_1-antitrypsin deficiency in Sardinia. Both mutations similarly favour the formation of polymers that are retained within hepatocytes as PAS positive inclusions.[3] Polymerisation also explains the mild deficiency of S (Glu264Val) and I (Arg39Cys) α_1-antitrypsin. In each case there is a striking genotype/phenotype correlation that can be explained on the basis of polymerisation. Those mutants that cause the most rapid polymerisation cause the most severe retention of protein within hepatocytes, the most profound plasma deficiency and the greatest risk of liver disease.

Proteinase inhibitors in the lung

Alpha$_1$-antitrypsin is one of the most important proteinase inhibitors within the lung. Emphysema associated with α_1-antitrypsin deficiency is widely believed to be due to uncontrolled action of the enzyme neutrophil elastase giving rise to tissue destruction. The situation is exacerbated as the Z mutation reduces the association rate between α_1-antitrypsin and neutrophil elastase by approximately fivefold. The inhibitory activity of Z α_1-antitrypsin can be further reduced as the Z mutation favours the spontaneous formation of α_1-antitrypsin loop-sheet polymers within the lung.[6] This conformational transition inactivates α_1-antitrypsin as a proteinase inhibitor, thereby further reducing the already depleted levels of α_1-antitrypsin that are available to protect the alveoli. Moreover the conversion of α_1-antitrypsin from a monomer to a polymer converts it to a chemoattractant for human neutrophils.[7,8]

The magnitude of the effect is similar to that of the chemoattractant C5a and present over a range of physiological concentrations. More recently a monoclonal antibody has been used to demonstrate the co-localisation of polymers of α_1-antitrypsin and neutrophils in emphysema associated with Z α_1-antitrypsin deficiency but not in emphysema in individuals with normal levels of α_1-antitrypsin.[9] Therefore the chemoattractant properties of polymers may combine with tobacco smoke to drive the progressive emphysema seen in individuals with α_1-antitrypsin deficiency.

Serpinopathies

Alpha$_1$-antitrypsin is the archetypal member of the serine proteinase inhibitor (or serpin) superfamily of proteins. They are all linked by a common molecular structure but they inhibit different target enzymes. The process of polymerisation also occurs spontaneously in association with mutants of other members of this family to cause intracellular hepatic retention and plasma deficiency. This results in deficiency of antithrombin, C1-inhibitor and α_1-antichymotrypsin that has been associated with thrombosis, angiooedema and COPD respectively. It also results in the plasma deficiency of heparin co-factor II but this has yet to be associated with a clinical phenotype. The process is perhaps most strikingly displayed in mutants of a neurone specific serpin, neuroserpin, to cause PAS positive intracerebral polymers that underlie the dementia familial encephalopathy with neuroserpin inclusion bodies or FENIB.[10] In view of the common molecular mechanism, these conditions have been grouped together as a new class of disease that has been called the serpinopathies.[3] The new insights provided by understanding serpin polymerisation has allowed the development of novel therapeutic strategies to block the aberrant conformational transition and so treat the associated disease.[3]

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Management of rare diseases in respiratory medicine

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General medicine comprises caring for patients with a fairly small number of common conditions and a much larger range of rare conditions. Medicine in any specialty will involve seeing patients with rare diseases. As a whole, rare diseases affect large numbers of patients, with up to 25 million Americans affected by 6,000 different conditions.[1] Diagnosis and optimal treatment is part of all physicians workload but such patients pose a series of challenges. Firstly, delays, sometimes of several years, in the diagnosis of rare conditions can occur when the symptoms, although