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

Simon R Johnson BSc DM MRCP
Reader in Respiratory Medicine, University Hospital, Queens Medical Centre, Nottingham
Email: simon.johnson@nottingham.ac.uk

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

typical of a rare disease, are attributed to a common condition.[2] In most cases clues to the correct diagnosis are present from the outset and delays in recognition are a source of frustration to patients and can result in loss of confidence in their doctors. Secondly, the optimal way to investigate these patients to confirm clinical suspicion may not be an invasive procedure and indeed it is important to avoid unnecessary investigations.

Finally, once the diagnosis of a rare disease is made patients often describe a feeling of 'isolation': their friends and family cannot empathise with them over a disease that they know nothing about. Their doctors may have seen only a few cases and may be unable to help with the difficulties experienced by a patient told that there is little information concerning prognosis and that treatments are unproven. Research into rare diseases also brings added difficulties; registries, networks and collaborations must be established to recruit sufficient patients to perform useful studies and funding for rare diseases is short. Despite these difficulties, however, significant progress has been made in certain rare diseases resulting in significant improvements for patients.

Improvements in the management of rare diseases have occurred in three main areas: recognition, support and specific therapies. In some cases patient advocacy via the internet has accelerated these advances with some rare disease charities being highly successful in raising awareness, providing research funds and in some cases changing government health policy. The LAM Foundation, an organisation for patients with the rare lung disease lymphangioleiomyomatosis (LAM), is one such example.[3]

Recognition of rare diseases, although still a challenge, in many cases can be facilitated by internet rare disease resources and the ease of contacting appropriate specialists irrespective of geographical location, leading to more rapid diagnosis and appropriate investigations. Rare disease registries have allowed large groups of patients to be formed which can provide valuable data on the clinical phenotype, survival, clinical trials and there are now many examples of research based biologic treatments for rare diseases.

Advances in basic science are now leading to new treatments. In alveolar proteinosis, a rare lung disease leading to respiratory failure caused by an accumulation of surfactant protein in the alveoli, it can be effectively treated by whole-lung lavage at specialist centres and is now recognised as a disease caused by an autoantibody to granulocyte/macrophage colony stimulating factor (GMCSF) with trials of recombinant GMCSF underway.[4] Lymphangioleiomyomatosis is caused by a defect in tuberin protein resulting in constitutive activation of the PI3 kinase/mammalian target of rapamycin (mTOR) pathway.[5]

The discovery that tuberin is an inhibitor of PI3 kinase/mTOR signalling has resulted in trials of mTOR inhibitors for LAM. Such advances have transformed the management of some rare diseases. In our own field, 10 years ago patients with LAM were told that nothing was known of the disease other than the life expectancy was around four years and that no active treatment was available. Patients diagnosed today can be given a more accurate prognosis, educated about their disease, how to recognise and avoid complications and can also obtain valuable support from other patients (via patients groups, eg www. lamaction.org). In addition, their physicians have easy access to state of the art medical information and of critical importance the patients may be included and managed as part of a clinical trial.

Thus, improvements in diagnosis and management of specific rare diseases have benefited a significant number of patients. Further this is a challenging and rewarding area for physicians interested in research and clinical care.

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Lung transplantation

Paul A Corris FRCP
Professor of Thoracic Medicine, Centre Freeman Hospital, Newcastle upon Tyne
Email: paul.corris@ncl.ac.uk

Background

Lung transplantation had a difficult birth and a tumultuous childhood but has blossomed into a settled and successful adulthood. Thirty years ago, the procedure seemed a dim and distant prospect as a viable treatment for patients dying prematurely with advanced lung disease. James Hardy of Mississippi, USA, was the first to attempt human lung transplantation in June 1963, though experimental work in this area had been ongoing since the early 1950s. His patient had locally advanced lung cancer and was in ventilatory failure with poor renal function. Technically the operation was satisfactory, however, success was short lived and he died 18 days later as a consequence of bronchial anastamotic breakdown and renal failure.

The next 15 years recorded 40 further attempts worldwide all of which failed, largely as a result of the apparent insuperable problems of bronchial anastomotic breakdown and sepsis. Recipients were often unsuitable with many in an unstable clinical state, intubated and with generalised infection. Immunosuppression in this era was limited and based on high doses of corticosteroids and azathioprine. By the 1970s interest in lung transplantation as a clinical prospect had waned, contrasting markedly with major developments in other solid organ transplantation.