

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 (GM-CSF) with trials of recombinant GM-CSF 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

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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 anastomotic 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.

Immunosuppression

The introduction of cyclosporine in the late 1970s as a highly effective and safe immunosuppressant heralded renewed interest in lung transplantation. Pivotal to success was a change in focus toward developing heart-lung transplantation which ensured a viable blood supply to the tracheal anastomosis via coronary – bronchial anastomoses. The Stanford group under Norman Shumway's direction perfected the surgical approach in the experimental laboratory and by 1981 felt ready to enter the clinical arena.

In 1982 the group reported success in three patients with advanced pulmonary hypertension. These recipients were chosen because logic at the time argued that the lack of preoperative sepsis would make them more likely to survive the procedure. It is ironic to note that in the modern era of lung transplantation it is now recognised that patients with pulmonary hypertension represent the most challenging group with which to achieve success.

Indications for transplantation

From these modest beginnings lung transplantation has developed over 25 years into a well established treatment option for a wide range of common respiratory conditions including chronic obstructive pulmonary disease, lung fibrosis and perhaps most notably cystic fibrosis. There is now a thriving worldwide programme of paediatric transplantation. It is truly a remarkable medical success story. Moreover, advances in surgical technique have permitted the re-introduction of isolated lung transplantation either as single, bilateral or lobar transplantations. Isolated lung transplantation is now by far the most common surgical approach in the modern era. Over 20,000 lung and heart lung transplantations have now been performed worldwide.

Research and development

Research and development at the beginning of clinical progress was predominantly focused on surgical techniques, methods of lung preservation and diagnosis of allograft rejection. Establishing the safety and efficacy of transbronchial lung biopsy in confirming the diagnosis of acute lung rejection was an important development affording a reliable means of differentiating this process from acute infection of the graft. The physiology of the transplanted lungs was fully characterised in detail including demonstration that the pattern of breathing, awake, asleep or on exercise in recipients did not differ significantly from normal despite denervation.

The international community recognised the value of collaboration in the field of lung transplantation and led by the International Society for Heart and Lung Transplantation established a comprehensive registry and database to facilitate audit/research and encourage multicentre clinical trials. Today there are many such clinical studies taking place worldwide alongside collaborative research efforts using modern molecular science. The development of international consensus

guidelines for lung transplant referral in 1998, revised in 2006, set a benchmark for collaboration in the field of organ transplantation

Current issues

Recent research and development has largely focused on improving the medical management of lung transplant recipients and therefore outcomes by elucidating the mechanisms which lead to early acute vascular injury and late chronic graft dysfunction. During follow-up of successful recipients it was recognised that many developed progressive irreversible airflow obstruction which was shown on lung biopsy to be due to obliterative bronchiolitis. Initially thought to be a manifestation of chronic allograft rejection alone it is now recognised to represent allograft dysfunction as a consequence of diverse insults including infections and gastrointestinal reflux. It remains the most important barrier to improving long-term outcomes of lung transplantation and is a major focus of research worldwide.

Despite this complication, the last 30 years has witnessed remarkable improvements in results. Recipients now enjoy high quality of life post-transplantation and an expectation of greatly improved survival with 40% surviving over 10 years. The cost effectiveness of the procedure has been established. The growth of lung transplantation has also enabled an increased focus and insight into several orphan lung diseases including idiopathic pulmonary hypertension and lymphangioleiomatosis.

The shortfall in donor organs compared with the number of potential recipients remains a continued vexed issue and limits availability to highly selected recipients. There are continued approaches to extend the pool of potential donor organs including the use of lungs from donors following cardiac arrest (non-heart beating donors) and the use of lobes from living donors. Continued efforts to increase organ donation from patients with brain stem death must remain a priority. Xenotransplantation remains an elusive challenge for the future.

Summary

The last 30 years have seen lung transplantation grow from a procedure associated with absolute failure to one which now offers excellent outcomes for patients with advanced lung disease. It has brought much needed hope and is truly a remarkable story of medical advancement in the field of respiratory medicine.