EDITORIAL

Pulmonary hypertension, mechanisms and treatment

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Pulmonary hypertension is a common complication of chronic left ventricular and hypoxic lung disease. In both conditions, its development carries a poor prognosis and greatly limits the effectiveness of medical treatment. Primary pulmonary hypertension (PPH) is, by contrast, very rare but a schedule of treatments has now been identified to help patients at different stages of this disease; and when medical treatment fails, transplantation is available. Transplantation surgery has offered an opportunity for improved survival together with enhanced quality of life. However, this treatment is limited to just a few patients as a result of scarcity of donors. There remains, therefore, a need to identify the underlying mechanisms of these diseases, in the hope that new treatments can be developed. A previous review series in the Journal has already highlighted new insights into clinical and basic knowledge of major conditions associated with pulmonary hypertension [1–5]. However, certain areas have not been covered by the previous series.

In this new review series, in an attempt to fill this gap, we have drawn upon four areas of active research. In the first article of the series, VOELKEL and TUDER [6] consider the factors responsible for the growth and remodelling of the pulmonary vascular bed. A particular feature of this part of the review is the interest in an inflammatory process either as a contributory mechanism or one which results from the initial "injury" to the pulmonary vascular bed. In the article by VOELKEL and TUDER [6], we are reminded that there have been major advances in the understanding of systemic vascular disease, particularly in the interaction between inflammatory cells and the remodelling of the vascular wall.

It is possible that the gene or genes responsible for familial PPH are concerned with the regulation of the factor or factors responsible for the structural remodelling. It may, therefore, present a valuable area of research to consider candidate genes for this form of the disease.

The second article by CHAOUAT *et al.* [7] bridges the fields of basic mechanisms and treatments for severe pulmonary hypertension. They have reviewed the role of thrombosis in the development of these diseases. Clearly, in the later stages of most forms of pulmonary hypertension extensive thrombosis occurs. Whilst this is probably secondary to the underlying vascular injury, a therapeutic

intervention with anticoagulant treatment has an impressive effect on the survival of the patient. It is possible to conclude that the progression of the disease is linked to this phenomenon.

In addition to thrombosis, it is important to appreciate that inherited forms of thrombophilia, *i.e.* enhanced or hypercoagulable states, account for over 40% of patients who experience recurrent deep vein thrombosis and pulmonary emboli. The discovery that the molecular mechanism underlying resistance to activated protein C is an amino acid substitution on factor V in the coagulation cascade has opened up methods for screening patients for this tendency, without resort to functional assays which cannot be undertaken whilst the patient is still receiving Warfarin anticoagulation treatment. It will be interesting to see whether this abnormality is more common in those patients with thromboembolic pulmonary hypertension than in PPH patients.

Secondary forms of thrombophilia are also becoming more important, particularly when resulting from the presence of anticardiolipin antibodies. It is still unclear whether this is a cause or a consequence of vascular disease. Unique epitopes are often exposed in vascular injury, which could lead to the development of these auto-antibodies.

In the third article, Brenot and Kneussl introduce the current approach to the treatment of PPH. This has become systematic over the last decade as a result of the pioneering work of Valentine Fuster and the National Institutes of Health (NIH) teams of clinical scientists, who have separately described the natural history of the disease. From this had developed a staged medical treatment plan. The patients with the least advanced disease receive anticoagulants and, when tolerated, they can also be treated with high doses of calcium channel blockers. This combination can enhance quality of life and improve survival.

In the more severe stages of the disease, continuously infused intravenous prostacyclin (PGI₂) not only improves survival but can restore a good quality of life. Of interest, this is the only treatment for which a randomized controlled trial has been undertaken. Perhaps this might encourage the health purchasing agencies to consider employing this expensive treatment.

There is a growing awareness that transplantation of lung or heart-lung is not providing the answer to long-term survival in PPH. For reasons that are unclear, patients with PPH have a very high incidence of chronic lung rejection leading to either marked organ dysfunction or death.

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Finally, we are fortunately able to include an article which covers the development of pulmonary hypertension in patients with sleep apnoea syndrome. This draws upon a very broad experience of the study of hypoxia occurring during sleep and offers guidance on therapeutic approaches.

Our understanding of pulmonary hypertension has enormously advanced over the last decade. Not only has the diagnosis been simplified but there are new treatments which enhance survival and quality of life. New and more effective treatments are anticipated as we delve deeper into the underlying mechanisms of the disease.

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