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to be related to defective endothelial cell function [5]. To a lesser extent, it has also been reported in SLE, related to blood clotting are the possible targets for the antibodies [7]. Other proposed mechanisms acting in different patients with similar or different CTD are interstitial lung disease, vasculitis, intimal proliferation and medial thickening of the muscular arteries, and chronic recurrent thromboembolism. Emerging evidence provides a link between chronic inflammation and PH. Activation of endothelial cells with expression of MHC class II antigens, cellular infiltration with mononuclear cells and release of angiogenic cytokines are thought to lead to vascular damage and remodelling [8, 9]. These findings are strengthened by animal studies where chronic inflammation of the lungs can induce PH [10]. Whether this also occurs in CTD is unknown. A recent presentation of a RA patient with severe PH and arteriolar thickening, perivascular inflammation and venous sclerosis [11] suggests that this may be the case in at least some patients. Data point towards derangement of endothelial cells as being central to PH. A primary or secondary endothelial alteration occurring in or around a blood vessel could be the starting event. The excess of MHC DR*3, DR*W52 and DQ*2 antigens in children with unexplained PH [12] indicates that genetic factors may also play a part in the development of the disease. It could be that the damaged endothelium triggers a chronic

PULMONARY HYPERTENSION IN CONNECTIVE TISSUE DISEASES

Primary pulmonary hypertension (PPH) is a progressive disorder characterized by elevation in pulmonary artery pressure and pulmonary vascular resistance. Once the diagnosis has been established, patients have a progressive lethal course in usually no more than 5 years [1, 2]. Pulmonary hypertension (PH) occurring within connective tissue diseases (CTD) bears a strong resemblance to PPH and it is clinically, haemodynamically and prognostically indistinguishable from PPH. Most cases of PH associated with CTD are seen in systemic sclerosis (SSc) [3] and undifferentiated CTD [4]. To a lesser extent, it has also been reported in SLE, primary antiphospholipid syndrome (PAS), polymyositis/dermatomyositis, RA, and primary Sjögren's syndrome. There is a fair amount of knowledge available on PPH, how much of this knowledge applies to PH in CTD relies on how similar both are and how alike PH is in all CTD patients.

Potential mechanisms of PPH include vasoconstriction, thrombosis or an endothelial lesion. Recent information shows a decrease in prostacyclin synthesis felt to be related to defective endothelial cell function [5]. The presence of Raynaud's phenomenon in patients with CTD and PH suggests that vasoconstriction plays a role in its pathogenesis. In patients with SSc, PH may be due to extensive pulmonary interstitial fibrosis or a vascular lesion. In SSc, there are circulating platelet aggregates and elevated blood levels of platelet factor 4 that suggest a role for platelet aggregation in vascular injury [6]. However, the role of recurrent vasospasm in PH is still being debated. Mechanisms of production of pulmonary hypertension in other CTDs have not been fully delineated. In PAS, thromboembolic and nonthromboembolic pulmonary vascular disease are found. Phospholipids located either in endothelial membranes, involved in prostanoid synthesis, or related to blood clotting are the possible targets for the antibodies [7]. Other proposed mechanisms acting in different patients with similar or different CTD are interstitial lung disease, vasculitis, intimal proliferation and medial thickening of the muscular arteries, and chronic recurrent thromboembolism. Emerging evidence provides a link between chronic inflammation and PH. Activation of endothelial cells with expression of MHC class II antigens, cellular infiltration with mononuclear cells and release of angiogenic cytokines are thought to lead to vascular damage and remodelling [8, 9]. These findings are strengthened by animal studies where chronic inflammation of the lungs can induce PH [10]. Whether this also occurs in CTD is unknown. A recent presentation of a RA patient with severe PH and arteriolar thickening, perivascular inflammation and venous sclerosis [11] suggests that this may be the case in at least some patients. Data point towards derangement of endothelial cells as being central to PH. A primary or secondary endothelial alteration occurring in or around a blood vessel could be the starting event. The excess of MHC DR*3, DR*W52 and DQ*2 antigens in children with unexplained PH [12] indicates that genetic factors may also play a part in the development of the disease. It could be that the damaged endothelium triggers a chronic

inflammatory reaction which in turn perpetuates and furthers the vascular lesion [13]. Proof of additional or different mechanisms have not been presented as yet. It would be of interest to investigate the expression and upregulation of adhesion molecules and other surface antigens on pulmonary endothelial cells and the possible role of soluble factors and cell-to-cell contact in their regulation. Analysis of endothelial cells lining the neovascularisation for neo-antigens and homing receptors may be rewarding. It may be also helpful to know the role of hypertension itself in the progression and/or initiation of inflammation.

PH patients develop symptoms late in the disease course. This coincides with the presence of irreversible parenchimal lesions. Therapy would not be expected to be very successful at this stage. However, based on the speculation that vasoconstriction plays an important role in PH, vasodilators have been used in symptomatic patients. High oral doses of calcium-channel blocking agents are claimed to be effective in a selected group of PPH patients [14]. Therapies focused on decreasing platelet aggregation or restoring the imbalance between thromboxane and prostacyclin have also been advocated. Some workers suggest that continuous intravenous infusion of prostacyclin is beneficial in PPH [15]. Anticoagulants are deemed to increase survival [2]. Therapeutic experience in PH associated with CTD is meager. Combinations of corticosteroids and immunosuppressors are proposed for patients where immune mediated inflammatory pulmonary vascular lesions are suspected [11]. Vasodilators are recommended although, there is no clear evidence of their efficacy [16]. Recently, we have shown that chronic intravenous infusion of iloprost (prostacyclin-analogue) improves symptoms, and perhaps ventricular function, in severely affected patients [17]. Therapy with nitric oxide is experimental. Isolated lung or heart–lung transplantation is carried out sparingly and often not recommended. All these interventions have not altered the poor prognosis for this condition. If we are to improve therapy, considerably more information is required. Future clinical research in this field should be concentrated on CTD patients identified as at risk of PH, and detection of patients already affected by its early stages. Identification of these patients may allow prompt intervention to arrest further progression. Understanding the mechanisms of pulmonary vascular lesions in individual patients will serve to aid the design of rational approaches to reverse the disease. Meanwhile, observation and reporting of experience with new therapies will help to alleviate patient suffering.

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