Editorial

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Primary pulmonary hypertension

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In 1952 Paul Wood[1] described primary pulmonary hypertension as a "relatively rare disease, usually encountered in women between 20 and 30, but may be met at any age and in either sex. . . . Patients with primary pulmonary hypertension are rarely seen until the disease is far advanced, symptoms being late in onset. . . . The course is rapidly downhill to death within two years in the majority of cases". At necropsy the small pulmonary arteries and arterioles showed proliferative changes distinguishable from the organised thrombi characteristic of thromboembolic pulmonary hypertension. None of his clinical cases of primary pulmonary hypertension was disproved at necropsy, confirming his opinion that primary pulmonary hypertension was a disease in its own right, whatever the cause.[2]

Acknowledging that it is frequently impossible for the clinician to distinguish thromboembolic from idiopathic pulmonary hypertension, a committee convened by the World Health Organisation[3] defined three pathological types of pulmonary hypertension which may appear to the clinician to have no known cause: recurrent thromboembolism, primary veno-occlusive disease, and plexogenic pulmonary arteriopathy. In practice, the term primary pulmonary hypertension is frequently reserved for plexogenic pulmonary arteriopathy, as Paul Wood had intended. The term plexogenic pulmonary arteriopathy was adopted because the plexiform lesion was thought to be characteristic of primary pulmonary hypertension, but this is not so, being absent in about 30% of cases.[4] The pulmonary vascular lesions in primary pulmonary hypertension are identical to those seen in congenital heart disease with a left to right shunt and pulmonary hypertension, but are more severe, and the incidence of plexiform lesions, occluded arteries, and dilatation lesions is higher. Even in advanced cases, however, it may not be possible to demonstrate a plexiform lesion, particularly in a lung biopsy and the term non-plexogenic plexogenic arteriopathy is sometimes used to describe such a case. This clumsy and misleading term is best avoided: the alternative "vasoconstrictive pulmonary hypertension" has at least the merit of indicating a fundamental abnormality of the pulmonary vasculature.

Primary pulmonary hypertension can occur in families, when it has the same clinical and pathological features as in the non-familial form.[5]

It has been suggested that the majority, possibly all cases of primary pulmonary hypertension, are thromboembolic in origin, despite the different pathological features in the two conditions.[6] In addition to causing mechanical obstruction, chronic thromboembolism has been thought to initiate vasoconstriction and the development of plexogenic pulmonary arteriopathy, but there is as yet little evidence that this attractive hypothesis applies to the pulmonary circulation[7–10] despite the tantalising relation between thrombosis and constriction of vascular smooth muscle in the systemic circulation. Thrombotic or thromboembolic lesions are occasionally associated with the lesions of plexogenic pulmonary arteriopathy (5·5% of cases in one series[6]), but this finding probably indicates the development of thromboemboli in the later stages of plexogenic pulmonary arteriopathy. Clotting abnormalities do not usually occur in patients with primary pulmonary hypertension and, even when they do, microemboli are not always present in the lung.[11]

Sadly, it is usually the pathologist who distinguishes between thromboembolic and plexogenic pulmonary arteriopathy at necropsy. The clinician sorely needs more information about possible sources of emboli if he is to distinguish the two disorders successfully. Dr James's elegant pathological studies suggest that the right antrum atrii dextri is probably a fairly common and unsuspected source of pulmonary microemboli.[12] Knowledge of possible sites of thrombus formation is increasingly important in view of recent developments in cross-sectional echocardiography and platelet scintigraphy. These two techniques are already used to detect thrombi within the left ventricle.[13] They complement each other since cross-

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sectional echocardiography identifies a mass while indium-111-labelled platelets locate a thrombus and reflect its activity. The right atrial appendage can be seen by cross-sectional echocardiography either from a suprasternal view[14] or by tilting the transducer anteriorly from a standard four chamber aortic root cut, but whether it is possible to identify a mass within the appendage is at present uncertain. Within the lung itself, surface scintillation counting using autologous radio-labelled platelets has been used to demonstrate platelet sequestration in adults with acute respiratory failure.[15] This technique might help distinguish thromboembolic from plexogenic pulmonary arteriopathy. The early diagnosis of thromboembolic pulmonary hypertension is essential if the patient is to have a reasonable chance of responding well to anticoagulants, with or without the addition of vasodilator drugs. The majority of patients present too late. In a recent study from the Mayo Clinic the mean pulmonary vascular resistance was 28 Wood units/m^2 in a group of patients with primary pulmonary hypertension, 76% of whom were later shown to have peripheral pulmonary arterial thrombotic occlusion.[16] Long term anticoagulation improved the chance of five year survival but 75/100 patients died within five years of presentation.

In plexogenic pulmonary arteriopathy the appearance of the peripheral pulmonary arteries suggests that the primary abnormality is vasoconstriction. Experimental studies suggest that intense vasoconstriction can lead to fibrinoid necrosis of the muscular pulmonary arteries,[17] a change thought to precede the development of the plexiform lesions.[18] If vasoconstriction is indeed responsible for plexogenic pulmonary arteriopathy it must be far more severe than is usually seen in man because hypoxia is a potent vasoconstrictor agent and yet leads only to medial hypertrophy, without progression to the more advanced lesions seen in plexogenic pulmonary arteriopathy.[19] The incidence of primary pulmonary hypertension, however, appears to be greater at altitude than at sea level,[20] suggesting that hypoxia may increase susceptibility in those predisposed to develop "vasoconstrictive" primary pulmonary hypertension. A possible link between vasoconstriction in the systemic and pulmonary circulations is suggested by the development of plexogenic pulmonary arteriopathy in some patients with Raynaud's phenomenon.[21]

In the late 1960's an epidemic of plexogenic pulmonary arteriopathy was associated with ingestion of the appetite suppression drug, aminorex fumarate.[22] Only about three out of every 1000 patients taking the drug developed pulmonary hypertension, however,[23] and there appeared to be no relation either between the dose administered and the risk of developing pulmonary hypertension or between the dose and the increase in pulmonary arterial pressure. Again, these observations suggest that aminorex, like hypoxia, instigated the development of primary pulmonary hypertension in susceptible individuals. Genetic factors that determine the amount of pulmonary arterial smooth muscle affect the vasoconstrictor response to hypoxia in different animal species[24] while in man racial factors may be important.[25] Individual susceptibility in man may be related to the amount of pulmonary vascular smooth muscle one happens to have been born with, but resolution of the problem awaits improved understanding of the fundamental properties of vascular smooth muscle.

The association between pulmonary hypertension and aminorex fumarate reopened the debate about dietary pulmonary hypertension. It has not been possible to induce pulmonary hypertension in animals with aminorex fumurate or other appetite suppressant drugs.[26] Ingestion of the seeds of *Crotalaria spectabilis*, however, produces pulmonary hypertension in all rats to which it is given. The pyrrolozidine alkaloids are metabolised in the liver and their products have first a hepatotoxic effect and then a pulmonary hypertensive effect.[27] The concept of dietary pulmonary hypertension is attractive and might eventually explain the association between portal and pulmonary hypertension, but at the moment it is of little practical value beyond warning against using new drugs too readily.

The epidemic of aminorex induced plexogenic pulmonary arteriopathy had one encouraging feature: in some patients withdrawal of the provoking stimulus lead to a symptomatic and haemodynamic improvement in the patient's condition[28 29] Spontaneous reversal of primary pulmonary hypertension can also occur.[30 31] These observations encourage one to hope that the early treatment of primary pulmonary hypertension might retard or even halt progression of the disease. In general, however, response to chronic treatment has been inconsistent and disappointing. A wide range of drugs with different modes of action have been tried, including sublingual isoprenaline,[32] diazoxide,[33] phentolamine,[34] hydralazine,[35] and, more recently, nifedipine[36] and long term oxygen administration. The poor response probably indicates the severity of the pulmonary vascular obstructive disease present when the treatment is started. Different series report a mean pulmonary vascular resistance ranging from 15 to 20·7 units/m^2 at the time the diagnosis was made.[2 32 33 37] Had these patients had congenital heart disease they would usually have been considered inoperable. Since patients with primary pulmonary hypertension usually have more severe pulmonary vascular disease than patients with congenital heart disease perhaps it is not surprising that the response to chronic vasodilator therapy is fre-

quently unsatisfactory. The variation in response to therapy in patients who showed a similar response to the injection of the drug into the pulmonary artery at the time of cardiac catheterisation probably reflects structural differences in the pulmonary vasculature at the onset of treatment and individual differences in susceptibility to the drug.

Many vasodilator drugs have unpleasant and even dangerous side effects and should therefore be given only to the patients in whom the diagnosis is certain and in whom the disease is not so advanced that there is little hope of benefit. Recently, the use of open lung biopsy has been advocated in order to confirm the diagnosis of plexogenic pulmonary arteriopathy and to exclude generalised thromboembolic disease, veno-occlusive disease, and connective tissue disorders associated with pulmonary hypertension.[38 39] A biopsy should be helpful since the vascular lesions of plexogenic pulmonary arteriopathy affect the entire pulmonary vascular bed and therefore the biopsy should be representative of the whole. Patients with plexogenic pulmonary arteriopathy in whom the pulmonary vascular lesions are thought to be potentially reversible could then be treated with greater confidence and the clinical and haemodynamic response to treatment could be related to the structural changes present in the lungs at the onset.

At the moment the outlook for the majority of patients with primary pulmonary hypertension is grim. There are, however, several chinks of light amid the encircling gloom. In plexogenic pulmonary arteriopathy usually we cannot identify the agent provoking the disease. Nor can we treat the response of the lung rationally or effectively because we understand relatively little about the basic properties of vascular smooth muscle and the control of vascular tone. The past 20 years, however, have seen significant advances in the field of smooth muscle metabolism and physiology. The smooth muscle cell is no longer viewed as an isolated entity, but as part of a tissue in which the activity of the contractile protein within each cell is co-ordinated with that in adjacent cells and where the force generated by contraction changes the orientation of the connective tissue framework which the smooth muscle itself helps to produce.[40–43] Increasingly the function of the smooth muscle cell is seen to be related to that of adjacent structures. Acetylcholine mediated contraction of smooth muscle cells in the isolated rabbit aorta appears to depend on the presence of endothelial cells.[44] Focal proliferation of smooth muscle cells within the intima of systemic arteries is preceded by damage to the endothelial cells, which exposes the subendothelial layer to the mitogenic factors present in platelets and plasma.[45] The origin of these proliferating smooth muscle cells is uncertain, but in the pulmonary circulation, proliferating cells in the intima appear ultrastructurally to migrate from the media possibly through gaps in the internal elastic lamina, and to be derived from the less well differentiated myointimal or vasoformative cell.[17] Vascular tone is modified by many factors but sustained tonic contraction depends largely on transsarcolemmal influx of calcium through specific channels.[46] Slow calcium channel blockers, such as nifedipine, inhibit transmembrane flux and interfere with the release of intracellular bound calcium and by doing so reduce vascular tone.[47]

The pharmacology of vasodilator drugs is usually studied in systemic arteries, but the response of the pulmonary arteries is often found to be different in clinical practice, at least in degree. It is now clear that smooth muscle cells from different arteries are more specialised than had been supposed[48] and this emphasises the need for detailed studies on pulmonary vascular smooth muscle in the hope of developing a vasodilator drug with a selective action on the pulmonary circulation.

Advances in other fields have a more immediate clinical application. The increasing sophistication of certain non-invasive techniques will encourage investigation of patients with minimal or dubious symptomatology and help to assess the clinical progress and response to therapy in symptomatic patients in whom cardiac catheterisation carries a significant risk. Initially an intracardiac abnormality can be excluded using cross-sectional echocardiography. Both pulmonary arterial systolic pressure and pulmonary blood flow can now be measured non-invasively.[49 50] Unfortunately, there is as yet no reliable non-invasive technique available for the measurement of pulmonary vascular resistance.

Studies of the growth and development of the pulmonary circulation may well throw light on the pathogenesis of primary pulmonary hypertension. Some babies fail to adapt normally to extrauterine life and pulmonary hypertension persists after birth, sometimes with fatal results. It is conceivable that persistent pulmonary hypertension after birth represents one end of the spectrum. In other children, adaptation and growth may proceed more normally, but become insufficient to meet the demands made by somatic growth during childhood and adolescence. The majority of patients with primary pulmonary hypertension present in early adult life and presumably had an abnormal pulmonary vascular bed for some time before becoming symptomatic. In this context it is intriguing that the two fully documented cases of spontaneous reversal of primary pulmonary hypertension occurred during adolescence.[30 31] The pronounced female predominance in primary pulmonary hypertension may be the result not of the influence of female hormones on the development of

pulmonary hypertension, but of male hormones protecting boys with a similar reduction in pulmonary vascular reserve, perhaps by encouraging a more effective adolescent growth spurt.

At present we cannot prevent and can rarely hope to cure primary pulmonary hypertension of any pathological type, but the application of exciting advances in different branches of biology and medicine are beginning to suggest how patient management might be improved in the future.

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