Primary pulmonary hypertension

This issue of the JRCPL includes an account of a clinico-pathological conference presented by a distinguished pathologist who is also the subject of the conference, Professor Julia Polak, a very brave lady (pages 225–30). Primary pulmonary hypertension (PPH) was first described by Romberg in 1891, and only now are we beginning to understand this rare disease. It affects 1–2 per million people in Western countries, most often young women, and is almost universally fatal. Presentation is late, with advanced pulmonary vascular obstructive disease. The recent surge of interest in PPH is partly due to the increase in the number of patients presenting with the disease following treatment with appetite suppressant drugs such as fenfluramine. Fenfluramine and dexfenfluramine were withdrawn by the Federal Drug Administration in September 1997, following reports of the association between these drugs and PPH and later, valvular heart disease (the drug was withdrawn after the clinico-pathological conference presented in this issue was held). Other work that has recently given prominence to the disease includes the localisation of the gene for familial PPH to chromosome 2q31.32. Only 6% of cases are familial. The disease is inherited in an autosomal dominant manner, with incomplete penetrance and shows genetic anticipation. On a more positive note, several studies now report that chronic prostacyclin therapy improves both the quality of life and survival.

Pathogenesis

The pathogenesis of PPH is unknown but the disease is thought to develop in those with a genetic predisposition to respond adversely to a variety of stimuli, instigating a cascade of cell-signalling pathways that eventually lead to pulmonary vascular obstructive disease. It can be associated with autoimmune disease, hepatic cirrhosis with portal hypertension, and infections including HIV. Other identifiable trigger factors include the appetite suppressant drugs aminorex fumarate (which resembles amphetamine, adrenaline, and ephedrine), fenfluramine and phentermine (chemical congeners of amphetamine and structurally similar to aminorex), and dexfenfluramine (the d-isomer of fenfluramine). Aminorex was released in 1965; the number of patients presenting with PPH having taken the drug peaked in 1969, the drug was withdrawn in 1968, and by 1972 the incidence had fallen to the pre-1967 level. European countries in which aminorex was not available, like the UK, did not experience an increase in the number of new cases of PPH during the same time period. The first symptoms generally appeared 6–12 months after first taking the drug. Mortality was 20% at the time of the outbreak, the average survival after diagnosis being three and a half years. By 1979, of the 102 cases reported by Gurtner, half had died and the majority of survivors were severely disabled. By 1985, the disease appeared to have regressed in half the survivors, but this could be an optimistic assessment. The clinical and pathological findings in patients with PPH who had taken aminorex were indistinguishable from those in patients with the disease who had not taken the drug.

History repeated itself 20 years later when the number of new cases of PPH increased in association with the introduction of fenfluramine and dexfenfluramine, first in France and then in the USA. The time course of the disease is similar to that following treatment with aminorex, but it can be extremely short – only 23 days in a recent case report in which both fenfluramine and phentermine had been prescribed; the patient died eight months later. An international multi-centre trial published in 1996 confirmed that the use of appetite suppressants, primarily derivatives of fenfluramine, was associated with the development of PPH, the risk being similar to that associated with taking aminorex. Professor Polak took fenfluramine for more than three months, 22 years before she presented in severe right heart failure. In retrospect, she had become symptomatic within three years, but was thought to have asthma, as are most patients with PPH. Moreover, Professor Polak had a child after taking the drug, which may have increased the risk of developing the disease. Was Professor Polak exposed to one trigger or a sequence of triggers? Certainly she could not have survived with plexogenic pulmonary arteriopathy for over 20 years. If fenfluramine was indeed the initial trigger, then it probably induced medial hypertrophy and some intimal proliferation (which is the extent of the pulmonary vascular disease in some patients who die with PPH), and further stimuli led to further damage. But finally, was taking fenfluramine so long ago really responsible for Professor Polak’s illness? Based entirely on circumstantial evidence, the verdict is probably ‘yes’.

The mechanism of action of aminorex fumarate and fenfluramine is not understood but there are clues that provide insight into the pathogenesis of other forms of PPH not caused by these drugs. Perfused into the isolated rat lung, these drugs and dexfenfluramine induce a dose dependent increase in pulmonary pressure. They inhibit potassium current in patch clamped pulmonary arterial smooth muscle cells taken from the respiratory arteries of the lung, and dexfenfluramine causes reversible membrane depolarisation, like hypoxia. These findings offer a

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possible explanation for the initial rise in pulmonary arterial pressure in susceptible individuals. The anorectic action of fenfluramine is mediated via the action of serotoninergic pathways in the brain16. Experimental studies show that it promotes rapid release of serotonin, inhibits its uptake, and may have receptor agonist activity16. Phentermine impairs serotonin uptake by the lung17. Serotonin is a powerful vasoconstrictor agonist which is present in excess in patients with PPH of unknown aetiology18. In such patients, platelet storage of serotonin was reduced. Serotonin is released from neuroendocrine cells and in Professor Polak's case, as in other patients with PPH, foci of cell aggregates were present. An elevated plasma serotonin appears to be a primary abnormality in that the abnormality persists after successful lung transplantation18. Yet it seems unlikely that an increase in the circulating level of serotonin could, in itself, cause PPH, since the high levels seen in the carcinoid syndrome are not associated with PPH. Rather, endothelial or smooth muscle cell handling of serotonin may be abnormal in PPH. Most recently, abnormalities in the voltage gated potassium channels (Kv) have been described in the pulmonary arterial smooth muscle cells of three patients with PPH, abnormalities not found in secondary pulmonary hypertension19. The attenuated potassium channel gene transcription and decreased mRNA stability of Kv channel α subunits were thought to account for the reduction in whole cell potassium current found in these cells. This is an exciting study. The activation of voltage gated potassium channels determines membrane potential and is therefore a critical determinant of cytoplasmic free Ca2+ and hence of vascular tone. Abnormal voltage gated potassium channel activity may be important in the pathogenesis of PPH.

Irrespective of the initiating trigger, the endothelium probably plays a crucial role in the pathogenesis of the disease, influencing both vasoconstriction and structural remodelling, functions that are inseparable. Vasoconstrictor agents such as endothelin are also vascular smooth muscle mitogens, while vasodilator agents such as prostacyclin and nitric oxide can be antiproliferative and antiinflammatory. Two of the most powerful intrinsic vasodilators are thought to be deficient in patients with PPH: prostacyclin and nitric oxide. Dilatation lesions may show a decrease in expression of endothelial nitric oxide synthase (eNOS), as in the clinicopathological conference on pages 225–3019. More importantly, the presence of eNOS does not necessarily imply normal eNOS activity. In patients with PPH, the amount of exhaled nitric oxide has been shown to be normal at rest but fails to increase on exercise20. This probably reflects both endothelial dysfunction and the reduction in endothelial surface area that occurs with advancing obstructive disease. The blood vessels show dense immunostaining for vascular endothelial growth factor in the plexiform lesions, and frequently in the endothelial cells overlying intimal proliferation in the small muscular arteries. It is possible that the vascular endothelial growth factor is having an angiogenic effect on the plexiform lesions while stimulating the production of nitric oxide in the smooth muscle cells. Other metabolic indicators of endothelial dysfunction include an excess of circulating thromboxane in relation to prostacyclin, elevated endothelin levels and coagulation abnormalities22,23. The role of platelet aggregation in the pathogenesis of PPH is unknown, but elevated fibrinopeptide A levels indicate that thrombosis occurs in situ and thrombosis is frequently evident in the established disease at autopsy24. As noted above, an abnormally high release of serotonin from aggregating platelets is thought to account for the elevated plasma serotonin found in these patients18. Anticoagulation therapy increases survival25. The rationale for giving chronic vasodilator therapy is that a reduction in vasoconstriction will not only alleviate symptoms but will retard the progression of vascular disease from medial hypertrophy to plexogenic arteriopathy. This applies particularly to chronic intravenous prostacyclin therapy.

Treatment

Treatment for PPH is treatment for life. The therapeutic regime has to be tailored to meet the needs of each individual, and adjusted as and when required according to changes in clinical and haemodynamic status. Optimising the management of these patients markedly improves quality of life and survival. Conventional treatment consists of giving anticoagulants and oral vasodilator therapy, usually a calcium channel blocker, and supplemental domiciliary oxygen. Warfarin, rather than aspirin or dipyridamole, is recommended to prevent thrombosis in situ25. The desirability of using chronic vasodilator therapy is assessed at cardiac catheterisation by the acute response to a vasodilator drug. Chronic vasodilator treatment can have an adverse effect and precipitate or worsen right heart failure in those with unfavourable haemodynamics, who have a high fixed pulmonary vascular resistance. Drugs used for testing responsiveness include acetylcholine, nitric oxide, adenosine and prostacyclin. Acute responsiveness to prostacyclin is assessed by giving incremental doses of the drug. A positive response to a vasodilator is taken as a decrease in mean pulmonary arterial pressure of 20% or more with no change in cardiac index. Cardiac catheterisation can be hazardous in these patients in whom the cardiovascular system is so brittle.

Recent studies have shown that chronic intravenous prostacyclin therapy is more effective than oral vasodilator therapy26–28. The most important determinants of survival are age and the acute response to prostacyclin. A study by Barst and colleagues26 reported a five-year survival of 88% in children under six, compared with 25% for older children29. In a group of children who responded satisfactorily to prostacyclin at catheterisation, the five-year survival was 86%, compared with 33% for non-responders26. Some patients who do not respond to acute vasodilator therapy can respond satisfactorily to chronic therapy but need close supervision. Also, some patients who do not respond to oral chronic vasodilator therapy can be treated with intravenous prostacyclin to good clinical and haemo-
dynamic effect with increased survival\(^2\). Problems associated with continuous intravenous prostacyclin therapy include abrupt interruption of the infusion which is usually noticed very rapidly, causing fatigue and occasionally syncope. Rarely, death supervenes, presumably due to a pulmonary hypertensive crisis. Less dramatic complications include discomfort at the catheter site, bleeding, infection and thrombotic episodes. Patients can become very tolerant of prostacyclin, requiring constant, aggressive, upward adjustment of the dosage. Clinical and haemodynamic improvement is generally sustained. Some patients, given prostacyclin as a bridge to transplantation, have improved to such an extent that they are being treated long-term with intravenous prostacyclin rather than being transplanted\(^2,3\). In these patients, prostacyclin appears to be acting primarily by structurally remodelling the pulmonary vasculature rather than acting as a pulmonary vasodilator. While the reduction in pulmonary vascular resistance achieved by long-term calcium channel blockers does not increase with time, a study published in January 1998 demonstrated that long-term intravenous prostacyclin therapy achieves a greater reduction in resistance than is achieved at the outset by acute vasodilator testing\(^27\). The duration of treatment is not known but, on present evidence, it should be continued indefinitely.

Atrial septectomy has been shown to improve survival in adults with recurrent syncope who have a bad prognosis\(^32\), and is also used in children. In exercise-induced syncope, the systemic circulation dilates and cardiac output cannot be sustained. However, in the presence of a right to left shunt at atrial level, output is maintained and the right heart chambers are decompressed. Following blade atrial septectomy, the one and two year survival rate in adults improved from 54% and 42% respectively to 87% and 76%\(^2\). Syncope was abolished. Atrial septectomy can be used as a bridge to transplantation, and ought to be a helpful adjunct to medical treatment, particularly if used earlier in less moribund patients.

Patients who fail to respond to medical treatment require transplantation and this also means treatment for life until the problem of graft rejection is solved. Results of this treatment are improving (18 month survival: 57% for heart–lung and 64% for double-lung transplant\(^33\), but donors remain scarce, so it is essential to optimise medical treatment and to find better ways of doing so. The aetiology of PPH is probably multifactorial. However, based on our present understanding, it is logical to presume that the development of selective receptor antagonists to endothelin, thromboxane and serotonin, modulating potassium channel activity and improving nitric oxide and prostacyclin delivery systems, will all play a part in controlling the progression of pulmonary vascular disease and in remodelling the pulmonary vasculature.

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Ethical review of research in the NHS: the need for change

This issue of the JRCPL features two papers by Holley and Foster (pages 238–41 and 242–5) that describe data relevant to the process of ethical approval of multi-centre research. The previous issue also included a paper documenting the experiences of one set of researchers who had to apply to a very large number of local research ethics committees (LRECs)².

Delay in obtaining ethical approval is potentially very damaging to the UK commercial sector, and may drive large-scale clinical trials to other countries with a more rapid ethical review process; this is bad for both UK research and the UK economy. Moreover, unnecessarily delaying good research of potential benefit to the public is itself unethical. Indeed, when in 1991 the Department of Health formally put the responsibility for ethical review of research in the NHS on health authorities, it also emphasised that part of the role of a research ethics committee (REC) was positively to encourage good research.

Following extensive consultation, a new system of multi-centre research ethics committees (MRECs) was implemented when the Department of Health published HSG (97)23. A similar document was published in Scotland, where an MREC started work in April 1997. The eight English MRECs (one in each of the English NHS regions) were all in operation by the autumn of that year. An MREC in Wales has now been appointed and will start considering applications shortly. The rapid introduction of the system has been helped by the fact that many of the appointed members have substantial LREC experience.

From the start, the system was designed to be uniform across the UK. All MRECs use a common application form (derived largely from the common application form that LRECs in the South and West Region had already devised), and have a common constitution, standard operating procedures and administrative documentation (including a common database). The chairmen and administrators meet to share problems and ideas. Minor changes in the system, when necessary, are adopted by all the MRECs.

But will these new MRECs solve the problems previously highlighted? In theory they should, but the commissioning and initial working of MRECs have revealed a number of severe problems in the structure and process of ethical review of research in the NHS. MRECs have the responsibility of reviewing the ethics of the research protocol (which includes the content of the patient information sheet and consent form), and advising the NHS about whether the research is ethical. The advice from any one MREC has authority throughout the UK. Herein lies perhaps the major problem that has been encountered: a reluctance (and occasionally outright refusal) of some LRECs to accept the opinion of another REC (in this case the MREC).

In their papers, Holley and Foster provide some historical background that helps us to understand this attitude of total independence. Many RECs had already been established prior to 1991, particularly following the publication of the various guidelines by the Royal College of Physicians from 1967 onwards. In 1991 the Department of Health presented a framework for LREC operation and authority within the NHS, and placed this firmly with health authorities. Ethical approval of research in the NHS was no longer a matter of good practice, but a formal policy requirement.

Since that time, however, there has been no substantial updating of regulations regarding RECs, although some helpful advice has been issued on specific points. Nor has there been, in many parts of the country at least, much communication between LRECs, even within the same health district. Increasingly, and unsurprisingly, LRECs had evolved their own patterns of working and devised their own solutions to problems, in order to cope with a rapidly expanding workload, while still remaining – to a greater or

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