

Primary pulmonary hypertension

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Primary pulmonary hypertension (PPH) is a rare disorder with an incidence of one to two cases per million people per year in Western populations. It is a progressive disease usually affecting the arterial side of the pulmonary circulation and, if untreated, progresses to severe pulmonary hypertension and, finally, right heart failure. Characteristically, and because of the vague nature of the symptoms, PPH may take up to 18 months to diagnose and, following diagnosis, the median survival is under two years. The disease is most common in women (ratio 1.7:1) and the mean age at the time of diagnosis is in the mid 30s. This bleak picture of PPH has been transformed over the last decade, partly because of better diagnostic techniques allowing earlier diagnosis and also because of new treatments, in particular the use of continuous intravenous prostacyclin. It is now realised that vasoconstriction of the pulmonary vascular bed is not the primary cause of PPH but occurs in association with marked histological changes. These histological changes are seen not only in PPH but also in severe pulmonary hypertension in association with other disorders such as HIV infection, connective tissue disease, and the use of appetite suppressant drugs. The realisation that primary or unexplained pulmonary hypertension was the end of a spectrum of several diseases causing severe pulmonary hypertension has lent a new impetus to the understanding of the disease and prompted a major symposium sponsored by the World Health Organisation held in Evian, France, in September 1998. At this symposium were gathered clinical scientists from all over the world with an interest in pulmonary hypertension and the result was a consensus about classification of pulmonary hypertension, the pathobiological methods of screening, risk assessment, and treatment. The first part of this review considers the clinical aspects of pulmonary hypertension, in particular the classification of pulmonary hypertension, the pathology, methods of screening for pulmonary hypertension, assessment of patients who are known to have pulmonary hypertension, and treatment of the disease. The second part focuses on what is and is not known about the pathobiology of pulmonary hypertension and how clinical and basic science may lead us to a further understanding of this enigmatic series of conditions. It is clear that the future is exciting in the world of pulmonary vascular medicine, and we are

probably at the threshold of major new developments in pathobiological understanding and the treatment of vascular disease which may have ramifications outside the world of the lung.

Clinical

CLASSIFICATION OF PULMONARY HYPERTENSION

In the past, pulmonary hypertension has been classified as either primary (unexplained) or secondary. However, included in secondary pulmonary hypertension were a wide ranging number of causes such as left heart dysfunction, hypoxic lung disease, left to right shunt, and liver disease. This classification was therefore unsatisfactory, particularly when it was realised that both the pathological abnormalities and the treatment may be similar in patients with a severe pulmonary hypertension from whatever cause. This realisation has prompted a new nosology and a new classification. The new classification proposed at the WHO meeting in 1998¹ is shown in table 1.

RISK FACTORS FOR PULMONARY HYPERTENSION

From the classification shown in table 1 it is clear that there are various risk factors for severe pulmonary hypertension. However, it is extremely important to assess the level of risk and hence the likelihood that a patient with a given condition will develop pulmonary hypertension. This is important both on the grounds of conservation of resources and cost. A detailed analysis of the pathobiology and suggested mechanisms of pulmonary hypertension is presented in the next section but the group at the WHO provided a useful classification of risk which can be used as a basis for screening patients who may develop pulmonary hypertension (table 2). We can define a risk factor for pulmonary hypertension as a factor that may either be necessary for causation or facilitate the development of the disease. Sometimes, of course, it is not possible to determine whether a factor was present prior to the onset of pulmonary hypertension, in which case it is described as an associated condition—that is, a condition that co-exists with pulmonary hypertension and therefore implies a common risk factor. The Risk Factor Subcommittee headed by Lucien Abenheim rated risks on the basis of the strength of their association with pulmonary hypertension. *Definite* indicates an association based on several different observations and often including a

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Table 1 WHO classification of pulmonary hypertension¹

Diagnostic classification

1. Pulmonary arterial hypertension

1.1 Primary pulmonary hypertension

(a) Sporadic

(b) Familial

1.2 Related to:

(a) Collagen vascular disease

(b) Congenital systemic to pulmonary shunts

(c) Portal hypertension

(d) HIV infection

(e) Drugs/toxins

(1) Anorexigens

(2) Other

(f) Persistent pulmonary hypertension of the newborn

(g) Other

2. Pulmonary venous hypertension

2.1 Left sided atrial or ventricular heart disease

2.2 Left sided valvular heart disease

2.3 Extrinsic compression of central pulmonary veins

(a) Fibrosing mediastinitis

(b) Adenopathy/tumours

2.4 Pulmonary veno-occlusive disease

2.5 Other

3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Sleep disordered breathing

3.4 Alveolar hypoventilation disorders

3.5 Chronic exposure to high altitude

3.6 Neonatal lung disease

3.7 Alveolar-capillary dysplasia

3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1 Thromboembolic obstruction of proximal pulmonary arteries

4.2 Obstruction of distal pulmonary arteries

(a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)

(b) In situ thrombosis

(c) Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature

5.1 Inflammatory

(a) Schistosomiasis

(b) Sarcoidosis

(c) Other

5.2 Pulmonary capillary haemangiomas

Functional assessment*

(A) Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

(B) Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(C) Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(D) Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

*Modified after the New York Heart Association functional classification.¹

major study; *very likely* indicates a similar series of observation or a general consensus amongst experts; *possible* indicates an association based on case reports, registries such as the National Institute of Health Registry of Primary Pulmonary Hypertension, and expert opinions; and *unlikely* indicates risk factors that have been proposed but for which no additional evidence has been forthcoming.

SCREENING FOR PULMONARY HYPERTENSION

Since PPH usually takes two years to diagnose, median survival is only a further two years, and the prognosis probably depends on making a diagnosis when the pulmonary circulation is compliant and responsive to vasodilator therapy, it is very important to try to make the diagnosis as early as possible. On the other hand, a full assessment of the pulmonary circulation involves right heart catheterisation which is an invasive procedure. Clearly, a

balance has to be drawn between the need to make an early diagnosis (the benefits of early use of vasodilators, though likely, are not yet established) and the risks of the diagnostic techniques that are to be used. The advent of widely available echocardiography has transformed our ability to screen patients for pulmonary hypertension. Other techniques such as cardiopulmonary exercise testing, magnetic resonance imaging, and spiral CT scanning are also likely to play an increasing part in the future in the diagnosis of pulmonary hypertension.

Who to screen

If we are to screen for pulmonary hypertension it is very important to focus screening on those who are most likely to have the disease and most likely to benefit from treatment of the disease. Major associations with pulmonary hypertension are as follows.

- (1) Family history. The genetics of pulmonary hypertension is dealt with below but it has been clear for some time, since the early studies in Nashville, USA, that a significant proportion of patients (approximately 6–10% of cases) have a family history of pulmonary hypertension. There are probably at least two genes of which the first to be discovered was PPH 1 (locus 2q 31–32). Familial pulmonary hypertension is inherited as an autosomal dominant with incomplete penetrance, suggesting that screening at least first degree relatives may be fruitful.² It is suggested that first degree relatives should be screened by trans-thoracic echocardiography at the time of the diagnosis of the index case and at any time in the future should they develop symptoms consistent with pulmonary hypertension.
- (2) Connective tissue disease. Some 10% of patients with PPH have Raynaud's phenom-

Table 2 WHO classification of risk for pulmonary hypertension¹

A. Drugs and toxins

1. Definite

● Aminorex

● Fenfluramine

● Toxic rapeseed oil

2. Very likely

● Amphetamines

● L-tryptophan

3. Possible

● Meta-amphetamines

● Cocaine

● Chemotherapeutic agents

4. Unlikely

● Antidepressants

● Oral contraceptives

● Oestrogen therapy

● Cigarette smoking

B. Demographic and medical conditions

1. Definite

● Sex

2. Possible

● Pregnancy

● Systemic hypertension

3. Unlikely

● Obesity

C. Diseases

1. Definite

● HIV infection

2. Very likely

● Portal hypertension/liver disease

● Collagen vascular diseases

● Congenital systemic-pulmonary cardiac shunts

3. Possible

● Thyroid disorders

enon. It is also known that patients with connective tissue disease—in particular the CREST variant of systemic sclerosis but also other conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE)—are susceptible to pulmonary hypertension and, indeed, up to 40% of patients with CREST will die of the pulmonary hypertension.³ It is therefore recommended that transthoracic echocardiography is performed annually in patients with systemic sclerosis and those with other connective tissue diseases are screened should they develop appropriate symptoms.

(3) Appetite suppressants. It is ironic that the second WHO symposium on PPH should be held at the time of the second epidemic of pulmonary hypertension associated with appetite suppressant usage. The first WHO symposium 25 years ago was held following an epidemic of pulmonary hypertension in Europe in association with the appetite suppressant agent aminorex fumarate.⁴ The more recent association between appetite suppressant drugs and pulmonary hypertension has occurred since the widespread use of fenfluramine and dexfenfluramine. Perhaps, luckily, the association was discovered quite early and the prevalence is not nearly as high as it was for aminorex.⁵ At present we do not believe it is useful to screen patients who have taken an appetite suppressant for resting pulmonary hypertension since the incidence is low (approximately 1 in 20 000 among a population who have used the drugs for three months) even though the relative risk is high.

(4) Portal hypertension. Patients with liver disease may develop either right to left shunting⁶ or pulmonary hypertension. Pulmonary hypertension seems only to occur where there is also portal hypertension, suggesting that cirrhosis on its own is not sufficient.^{7–9} It is only necessary to screen patients with cirrhosis if they are being considered for liver transplantation, in which case it becomes mandatory.

(5) HIV infection. The association between pulmonary hypertension and HIV infection has been known for a number of years.^{10–11} Since these patients will probably have several other important reasons for ill health, it is not recommended that they are screened for pulmonary hypertension but they should be offered echocardiography if appropriate symptoms develop.

(6) Drug use. There seems to be an association between both L-tryptophan and 5-hydroxytryptamine uptake inhibitors and pulmonary hypertension. The mechanisms are not understood and at present no recommendation can be made about screening.

(7) Thyroid disease. There is a known link between underactive thyroid and PPH.¹² It is not recommended that patients with hypothyroidism are screened for pulmonary hypertension but clearly patients with pulmonary hypertension should have thyroid function tests.

How to screen

Clearly, it is not appropriate for all patients at risk to have a transthoracic echocardiogram. In low risk individuals particular attention should

be paid to clinical features that might indicate the development of pulmonary hypertension, though these are often enigmatic, particularly when patients have other more urgent symptoms and signs associated with their primary disorder. Typically, patients complain of breathlessness on exertion with no other important symptoms and few cardiopulmonary signs. The clinical symptoms and signs of pulmonary hypertension are described below but, unfortunately, by the time the typical clinical features develop, there is usually advanced disease so a patient with exertional breathlessness of no known cause and few clinical signs should be considered as having pulmonary hypertension until proved otherwise. Basic additional investigations should include the following:

(1) Chest radiograph: this may show an enlarged heart and enlarged main pulmonary artery. The experienced observer may notice peripheral pruning of the pulmonary vasculature.

(2) Electrocardiogram: this may show evidence of right atrial and right ventricular hypertrophy, right axis deviation and strain.

(3) Blood tests: these depend on the history; there may be a need to measure HIV status, thyroid function, autoantibodies, or to look for evidence of underlying liver disease.

(4) Transthoracic echocardiogram: this non-invasive investigation is the screening method of choice and is widely available in most centres. It will demonstrate the presence of pulmonary hypertension (by measure of tricuspid regurgitant jet velocity and relationship of acceleration time to ejection time in the pulmonary outflow tract), right ventricular overload (increase in right ventricular size), and other indices (see below). It may also help to determine the underlying diagnosis by showing the presence of clot, shunt, or evidence of left ventricular disease. A weakness of echocardiography is that the investigation is usually done at rest whereas at least 70% of pulmonary circulation must be obstructed before the resting pulmonary artery pressure rises. It is likely in the future that echocardiography will be enhanced and amplified by making measurements on exercise or following passive leg raising which increases venous return to the right heart.¹³ If pulmonary hypertension or evidence of right ventricular dysfunction is discovered on echocardiography, the next consideration is how often to repeat the test or, indeed, whether to proceed to right heart catheterisation. These questions have not been answered but in high risk individuals it would seem reasonable to repeat the echocardiogram every year and to arrange cardiac catheterisation when the pulmonary artery systolic pressure as measured by echocardiography rises above 40 mm Hg.

PATHOLOGY OF PULMONARY HYPERTENSION

The pulmonary vasculature has both similarities to and differences from the systemic circulation. The similarities include an arterial structure which consists of an intima composed of endothelial cells, a media composed of

smooth muscle cells, and adventitia composed of protein matrix secreted by adventitial fibroblasts. A major difference between the two circulations is that the pulmonary circulation is a high flow, low pressure system with a remarkable degree of compliance to cope with cardiac outputs that may rise sixfold with heavy exercise. Furthermore, the pulmonary vessels must be thin walled to allow gas exchange but must be sufficiently well supported so as not to rupture. A further important difference between the two circulations is the response to hypoxia. The systemic circulation dilates to hypoxia whereas the pulmonary circulation constricts. Hypoxic pulmonary vasoconstriction is a reflex that has been known about since 1946¹⁴ but is still not fully understood, nor is the relationship between the vasoconstriction/remodelling that occurs following hypoxia and that which accompanies PPH. At present the consensus is that hypoxic pulmonary vascular damage is different. However, patients with severe pulmonary hypertension (which is rare in pulmonary hypertension caused by hypoxia) have underlying histological abnormalities which may vary slightly depending on aetiology but show a remarkable degree of similarity.

PPH is characterised by intimal fibrosis, in situ thrombosis, and hypertrophy of the smooth muscle cells of the media and is divided into three pathological types: plexogenic arteriopathy, thrombotic arteriopathy, and pulmonary veno-occlusive disease.¹⁵ The plexogenic form (approximately 50% of cases) has the worst prognosis and is associated with the plexiform lesion, an unusual pathological entity consisting of a mass of disorganised vessels associated with endothelial cells, smooth muscle cells, and myofibroblasts. This may represent an angiogenic response to underlying vascular injury. In the thrombotic form there is similar pulmonary vascular histology but, in addition, multiple thrombi are present. These thrombi give the abnormal patchy appearance seen in a ventilation perfusion scan and may be a consequence of endothelial injury. They may also explain why anticoagulants improve survival in these patients. Pulmonary veno-occlusive disease (less than 10% of patients) appears to be a separate entity with intimal proliferation of the intrapulmonary veins rather than arteries. Although very rare, it is important to make the diagnosis because treatment with intravenous vasodilators such as prostacyclin can be fatal. The mechanisms underlying the pathological appearances seen in severe pulmonary hypertension are not fully understood but are considered below.

ASSESSMENT OF PULMONARY HYPERTENSION

Clinical assessment of pulmonary hypertension involves three separate intellectual processes. Firstly, we need to look for and understand the cause of the pulmonary hypertension; secondly, we need to evaluate pulmonary haemodynamics and their effect on pulmonary and cardiac function; and thirdly, we need to assess patients for responsiveness to vasodilator therapy whether by oral calcium channel blockers or by continuous intravenous vasodilators.

Making the diagnosis

Important clinical features include breathlessness with no other obvious cause, specific signs of pulmonary hypertension (loud pulmonary second sound, right ventricular heave, pulmonary flow murmur), signs of right heart dysfunction (raised jugular venous pressure, V waves in the neck, hepatic pulsation, swollen ankles) and signs of co-existent disease (primary pulmonary, cardiac, or liver disease or evidence of venous thrombosis or connective tissue, thyroid or HIV disease). Chest radiography (fig 1) is of limited benefit but may show enlargement of the heart or main pulmonary artery or peripheral pruning of vessels. Electrocardiography may show right atrial or right ventricular hypertrophy, right axis deviation, and strain. Pulmonary function tests may indicate underlying lung disease but in "pure" pulmonary hypertension spirometric tests and lung volumes are usually normal but the carbon monoxide transfer factor is usually low, consistent with a low pulmonary capillary blood volume. The ventilation-perfusion scan (fig 2) may show the presence of mismatched defects indicating possible underlying thromboembolism, but defects may also be seen in pure intrinsic vascular disease, particularly the thrombotic variant. The ventilation scan will be normal but the perfusion scan may show patchy loss consistent with vascular obstruction. Computed tomographic (CT) scanning is needed to exclude parenchymal lung disease but volume scans of the central pulmonary arteries after injection of contrast may help to demonstrate major intravascular clot (fig 3). Echocardiography is the most useful non-invasive investigation. Transthoracic echocardiography will show a dilated right heart or right ventricular hypertrophy with evidence of pulmonary hypertension such as a decrease in the ratio of acceleration time to ejection time or an increase in tricuspid regurgitant wave velocity. In addition, echocardiography will show any left to right shunts and in the future it may be used to evalu-

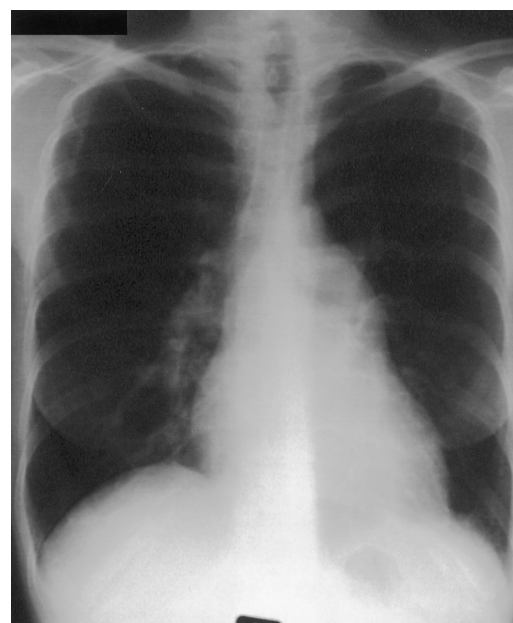


Figure 1 Chest radiograph from a patient with PPH showing the enlarged main pulmonary artery and enlarged heart.

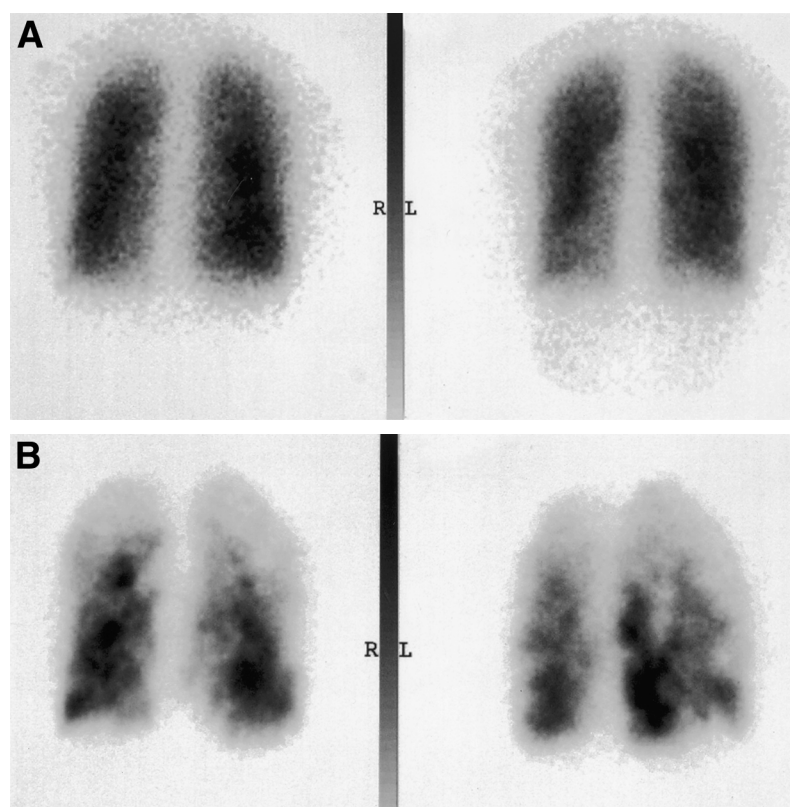


Figure 2 Ventilation-perfusion scan from the patient in fig 1 showing (A) normal ventilation but (B) patchy loss of perfusion due to vascular obstruction. Pulmonary embolism should be excluded.



Figure 3 Computed tomographic (CT) angiogram of the patient in fig 1 showing large pulmonary arteries and absence of intravascular clot.

ate right ventricular performance by an index of myocardial performance.¹⁶⁻¹⁹

Echocardiography is measured at rest and it would be useful to make echo-doppler measurements on exercise but this remains difficult. Cardiopulmonary exercise testing has been examined. The simplest cardiopulmonary exercise test is a six minute walk and the results correlate with pulmonary haemodynamics and long term survival.²⁰ It has also been claimed that measurements of gas exchange during exercise correlate with pulmonary artery pressure.^{21 22} Other non-invasive techniques which may be of use include magnetic resonance imaging (MRI) to evaluate right ventricular function.²³

All these non-invasive investigations are useful in helping to point to the underlying diagnosis and the extent of pulmonary hypertension. However, for definitive assessment

right heart catheterisation is necessary. This should only be done at a designated pulmonary hypertension centre (see below) since the investigation and, in particular, the administration of vasodilators carries a significant risk in inexperienced hands. It is usually possible to conduct all relevant investigations at a single sitting, reducing the necessity for further catheterisation. These should include exclusion of shunt, measurement of pressures and cardiac outputs, pulmonary angiography, and measurement of vasodilator responsiveness. Right heart catheterisation is usually performed using a Swan Ganz triple lumen thermodynamic catheter inserted under fluoroscopic control via the right femoral vein. These catheters may be difficult to manipulate through a hypertrophied right heart and are not easy to pass up the superior vena cava in order to measure oxygen saturations at different positions in the right heart to identify a shunt. A multipurpose catheter is usually used for this purpose. The following pressures are measured: right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary artery occlusion pressure. These measurements should be made with the glottis open at functional residual capacity to reduce the effect of intrapulmonary pressure swings on pressure. Cardiac output is measured in triplicate by thermodilution and the measurements are repeated after administration of 100% oxygen if there is concomitant hypoxaemia and after exercise if pressures appear to be normal. Selective pulmonary angiography is also performed should there be any doubt from the ventilation-perfusion scan about the presence or absence of thromboembolism (fig 4).

This procedure carries an increased risk in patients with pulmonary hypertension because of sudden rises in pressure in hypertensive non-compliant vessels and the flow rates of contrast medium are usually reduced when pulmonary hypertension is present. Finally, a vasodilator study is done with continuous measurement of systemic arterial pressure and pulmonary artery pressure, heart rate, and heart rhythm while the vasodilator is administered. Vasodilator studies are risky in inexperienced hands because, if pressures start to fall, patients can undergo cardiac arrest from which they often cannot be resuscitated. It is therefore important to be able to recognise the early signs of a dangerous change in haemodynamics such as fall in systemic pressure, rise in heart rate, or failure of cardiac output to rise. Several vasodilators have been used including inhaled nitric oxide,²⁴ adenosine,^{25 26} high dose calcium antagonists²⁷ and prostacyclin,²⁸ with adenosine, nitric oxide, and prostacyclin being the most popular for repeat vasodilator trials.²⁹ Nitric oxide and prostacyclin^{25 30 31} have the advantage of being very short acting so their effects can be reversed should the patient's condition deteriorate. Ideally, following a vasodilator there should be a fall in pulmonary artery pressure accompanied by a rise in cardiac output. This is not always the case and often there is a rise in cardiac output with no change in pulmonary artery pressure. The sig-

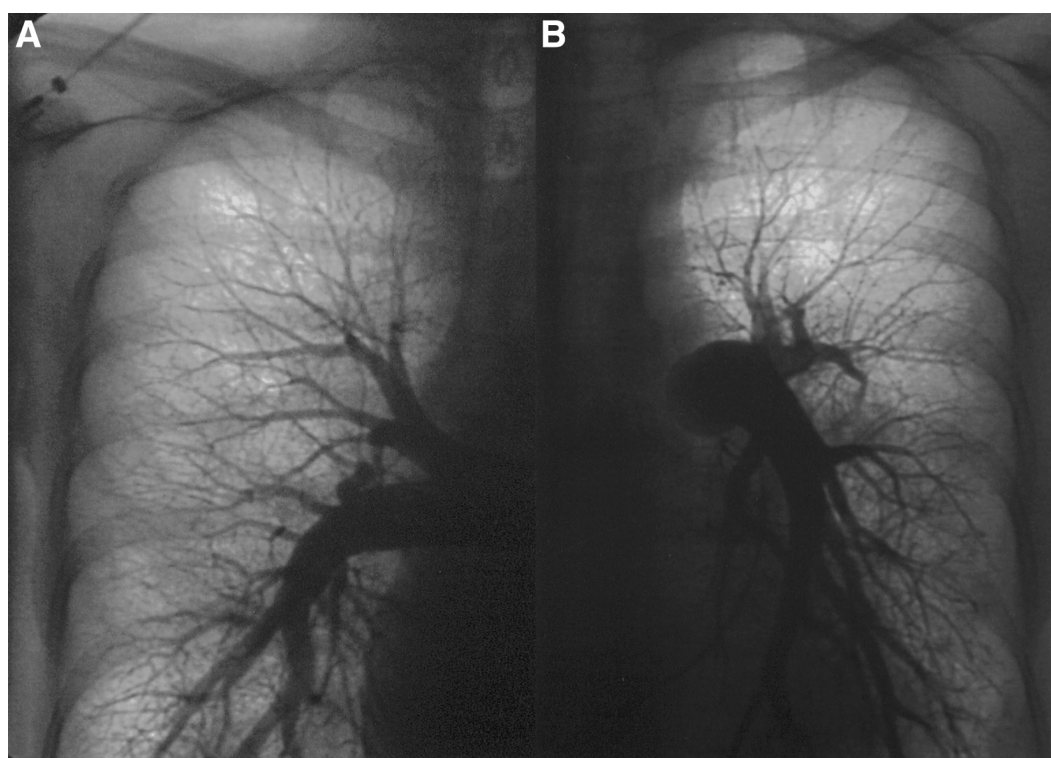


Figure 4 (A) Right and (B) left selective pulmonary angiograms from the patient in fig 1 showing large central pulmonary vessels but peripheral pruning and no evidence of pulmonary embolism.

nificance of these haemodynamic changes is not fully understood but, where there is an appropriate haemodynamic response—that is, a fall in pulmonary artery pressure with a rise in output—the prognosis is much better. Unfortunately, only 30% of patients fall into this category.

All the investigations of pulmonary hypertension are done with the patient resting. However, since the usual complaint is of exertional breathlessness, there may be mechanisms for assessing a patient's response to exercise and the effect of treatment on that response in the future. Promising methods include cardiopulmonary exercise testing (see above) and continuous pulmonary artery pressure measurement using the new manometer tipped catheters.³²

TREATMENT OF PULMONARY HYPERTENSION: GENERAL POINTS

Treatment of pulmonary hypertension centres round the treatment of an underlying cause if present and treatment of the pulmonary hypertension itself. The underlying causes that should be recognised and treated include hypoxic lung disease, thromboembolic pulmonary hypertension, HIV infection, thyroid dysfunction, connective tissue disease, left to right shunts, and left ventricular dysfunction. If underlying causes have been searched for and excluded or treated, an assessment must be made of the risks versus benefits of treating the pulmonary hypertension itself. The current consensus would be that treatment of mild pulmonary hypertension (mean pressure less than 30 mm Hg) is probably not advisable with the current therapeutic agents. Where severe pulmonary hypertension exists, the choice of treatment lies between calcium channel block-

ers and continuous intravenous prostacyclin together with anticoagulants.

TREATMENT OF SEVERE PULMONARY HYPERTENSION

This section deals only with severe intrinsic pulmonary vascular disease—that is, where the disease affects the vessels rather than a vascular response to other disease; the treatment of chronic obstructive pulmonary disease, left heart dysfunction, or left to right shunt will not be discussed. It concentrates on the treatments that have been evaluated for PPH, pulmonary hypertension associated with connective tissue disease, and pulmonary hypertension in association with portal hypertension. By far the greatest literature is in PPH where the issues surrounding treatment have become somewhat clearer and a consensus is beginning to emerge.³³ The theoretical basis for the use of vasodilators in pulmonary hypertension has been reviewed elsewhere³⁴; this paper concentrates on studies that have shown benefit in the pulmonary circulation including anticoagulants, vasodilator therapy, immunosuppressive therapy, inotropes, and the surgical creation of intracardiac shunt for therapeutic purposes.

Anticoagulants

It has been known for a number of years that long term treatment with warfarin improves the prognosis in PPH. This is true even for patients who do not respond to conventional vasodilators. For example, Rich *et al* showed that anticoagulants doubled survival in non-responders from 31% to 62% at three years.³⁵ When anticoagulants are combined with a vasodilator they provide an additional benefit so it is standard practice in pulmonary vascular units to give anticoagulants to patients with

resting pulmonary hypertension (usually mean PAP >30 mm Hg) unless there is a contraindication. The benefits of treating very early pulmonary hypertension are not yet established (see above). The reason for the benefit of anticoagulants is not clear, although it is presumed that they prevent in situ thrombosis which occurs particularly in the thrombotic variant of PPH and is seen in lung tissue at necropsy in patients dying from pulmonary hypertension.³⁶ This raises the issue of the difference between so-called “chronic thromboembolic pulmonary hypertension” and “primary pulmonary hypertension with thrombosis”, but that distinction is outside the scope of this review. The goal of treatment should be to achieve an international normalised ratio (INR) of 2.

Since we know that prostacyclin can increase exercise tolerance over that seen with anticoagulants without causing vasodilation (see later), it is possible that the improved exercise capacity is due to its anti-platelet activity in which case other forms of anti-thrombotic agents may be useful in the future. There is some evidence that thromboxane synthetase inhibition may be helpful³⁷ and perhaps other agents will provide even greater benefit, in particular the newer heparins and heparin-like compounds.

Calcium channel blockers

Over the last 10 years calcium channel blockers have been shown to improve morbidity and survival in patients with PPH.^{27–38} Calcium channel blockers are a heterogeneous group of compounds but it is the dihydropyridine blockers that have been used in patients with pulmonary hypertension, the rationale being that their principal action is on vascular smooth muscle. Their depressant effect on myocardial contractility is the principal limitation to their use. They are used in very high doses—for example, diltiazem up to 720 mg daily and nifedipine up to 300 mg daily. Although studies have shown that high doses are necessary, proper dose response relationships have never been shown and it is difficult to choose a dose for a given patient. The drugs are potentially dangerous and should not be given without formal vasodilator studies. Only patients who respond to acute vasodilator testing should be treated with a calcium antagonist. Once treatment is started, patients must be very closely monitored in hospital to ensure that they do not deteriorate. Patients may develop heart failure and, if this is not identified early, they can deteriorate rapidly. For these reasons treatment with a calcium antagonist should ideally only be initiated by those with appropriate experience in a pulmonary vascular unit.

The mechanism of action of calcium antagonists is presumed to be that of vasodilation but they may have other actions such as reduction in smooth muscle cell replication or effects on cell growth of other pulmonary vascular cells. Adverse effects of calcium antagonists include systemic hypotension, hypoxaemia due to increased ventilation-perfusion mismatching,

right ventricular dysfunction, cardiogenic shock, arrhythmias, and death. However, there is now good evidence that calcium antagonists in combination with anticoagulants can produce five year survivals of the order of 90% in patients who respond to an acute vasodilator trial, so it appears that they may slow or abolish the underlying pathophysiological process as well as providing vasodilatation.

Current medical treatment for severe pulmonary hypertension is now so effective in those who respond acutely that it is preferable to heart/lung transplantation. It is hoped that calcium channel antagonists with less detrimental effect on myocardial contractility may be developed for use in PPH. At present calcium channel antagonists remain the oral drug of choice as vasodilators in severe PPH. Their benefit in pulmonary hypertension secondary to other conditions such as connective tissue disease has not been established.³⁹

Other vasodilators

Many other vasodilators have been used in PPH, reflecting the fact that none is perfect. These include diazoxide,⁴⁰ captopril,^{41–42} and hydralazine.⁴³ At present calcium channel blockers remain the drug of choice despite their problems. Newer vasodilators such as potassium channel openers may become available in the future but they have not yet been evaluated in pulmonary hypertension. Specific potassium channels are present in pulmonary vascular smooth muscle cells and these may well be the avenue by which hypoxia causes pulmonary vasoconstriction.

Nitric oxide has been successfully used as an acute vasodilator in patients with pulmonary hypertension but at present the need for it to be delivered in a continuous gaseous form means that it is not really an option for long term treatment. Nitric oxide donors are being developed which could be used both orally and by inhalation and this may be the future for these compounds. They are of particular interest because of the known endothelial cell dysfunction in PPH.

Inotropic agents

Since right heart dysfunction is a sequel of severe pulmonary hypertension due to the increased outflow impedance of the right ventricle, it would appear logical to use inotropes once maximum vasodilation has been achieved, particularly if there is concomitant use of calcium channel blockers which are known to be negatively inotropic. No large clinical trials have looked at the use of directly acting inotropes in precapillary pulmonary hypertension, but a recent study using digoxin showed an improvement in cardiac output and a fall in sympathomimetic amines in pulmonary hypertension.⁴⁴ While there are few data on the benefit of inotropic agents, there is considerable evidence that other agents such as β blockers and ACE inhibitors used to treat biventricular heart failure of ischaemic origin may cause deterioration and should not be used. The co-existence of pulmonary hypertension with portal hypertension may be a special case, perhaps because a vasodilator may

affect both circulations. There is anecdotal evidence of benefit for isosorbide mononitrate in a patient with pulmonary hypertension associated with portal hypertension due to hepatitis C virus.⁴⁵ She responded to intravenous prostacyclin and, since isosorbide is commonly used for portal hypertension, was given isosorbide 40 mg twice daily. The second catheterisation six months later showed a beneficial effect on pulmonary haemodynamics.

Prostacyclin

The largest literature on the use of vasodilators in severe pulmonary hypertension relates to prostacyclin and analogues. Prostacyclin is a natural vasodilator produced by the endothelial cells of the circulation. Rubin *et al* first showed that prostacyclin induces vasodilation in patients with PPH.⁴⁶ Higenbottam then used it as a bridge to transplantation in a young woman with severe pulmonary hypertension. She was restored from being bed bound to an active life while awaiting transplantation.⁴⁷ It was not until 1990 that the drug was assessed in a large group of patients by Rubin *et al*.⁴⁸ They showed a reduction in pulmonary artery pressure of more than 10 mm Hg in six of 10 patients who completed an eight week study and the benefits of continuing therapy were seen up to 18 months. Continuous intravenous prostacyclin also produced benefits over conventional treatment when used in PPH. Barst *et al* for the Primary Pulmonary Hypertension Study Group conducted a 12 week prospective trial comparing continuous intravenous prostacyclin with conventional therapy (anticoagulation and calcium antagonists) in 81 patients with severe pulmonary hypertension. Those receiving continuous prostacyclin showed an improvement in exercise tolerance whereas those on conventional treatment showed a fall over 12 weeks. There were also improvements in haemodynamics consistent with the view that improved haemodynamics were responsible for the improvement in exercise tolerance.²⁰ They then looked at the effects of longer term prostacyclin (more than one year) in 27 patients with primary and secondary pulmonary hypertension who had demonstrated a mean reduction of 27% in pulmonary vascular resistance with an intravenous vasodilator.⁴⁹ The rate of infusion of prostacyclin was increased by, on average, 2.4 ng/kg body weight per minute per month. Twenty six of the 27 patients showed improvements in both symptoms and haemodynamic measurements with a mean fall in pulmonary vascular resistance of 53%. Of interest was the fact that the mean fall in pulmonary artery pressure over the study period was greater than that seen acutely with maximal doses of intravenous adenosine. This suggests that long term prostacyclin has effects other than those of simple vasodilation, presumably causing some reversal of the histological changes in the vessels of the pulmonary circulation. These studies have changed the whole basis of how we view severe pulmonary hypertension. We used to believe that prostacyclin was simply a vasodilator and therefore could only prevent further worsening of the disease.

It is now clear that the disease process can be reversed and it is tempting to speculate that the histological changes are also reversed. However, a major hazard with continuous intravenous prostacyclin therapy is that it requires an indwelling Hickman line and pump. The indwelling line carries the risk of infection, catheter clot, catheter breakage, and catheter dislodgement. Patients must be taught scrupulous aseptic technique, how to make up their own drug, and to attach the syringes. Another problem is that, should supply cease for any reason, they can develop life threatening pulmonary hypertension and die. Thus, all patients must be given a back up syringe system. It would clearly be preferable if the drug could be given in other ways and there is evidence that prostacyclin and its analogues can, like nitric oxide, be given by inhalation.⁵⁰⁻⁵²

Iloprost has similar effects to prostacyclin when given intravenously⁵³ but, although it has a longer half life, this confers no real advantage over prostacyclin when given intravenously. However, its long half life may be of benefit because it can be given via a nebuliser and a large prospective trial of inhaled iloprost is being considered for later this year. Other analogues with different half lives have been tried by other routes or are under investigation including continuous subcutaneous infusion, but the results have not yet been reported. Clearly, the best route for administering these agents would be orally and oral beraprost, a prostacyclin analogue, has been tried in small groups of Japanese patients but it is not yet available for clinical use.⁵⁴⁻⁵⁵

The principal problem with prostacyclin is its cost which, for the average UK patient, is between £40 000 and £60 000 a year. Clearly, this is a major burden for any health authority (health board in Scotland) and thus there is a need to centralise the use of prostacyclin to a limited number of pulmonary vascular units spread around the UK.

Surgical methods

Atrial septal defects (ASD) with left to right shunts are a cause of pulmonary hypertension. However, in situations where severe pre-capillary pulmonary hypertension develops, the creation of an artificial ASD is a possible treatment. There have been no formal clinical trials of atrial septostomy but a number of centres have performed the procedure with evidence of benefit.⁵⁶⁻⁵⁸ The rationale for atrial septostomy is that unloading the right heart and improving pre-load to the left heart via the atrial septal defect will improve cardiac output. Oxygen content of arterial blood falls but, as cardiac output rises, oxygen delivery should improve. The treatment is not yet standardised but can be performed by either balloon or blade septostomy. It can be considered in patients with recurrent syncope or right heart failure despite maximum medical therapy when no other therapeutic option exists apart from transplantation. Clearly, this treatment should only be undertaken in centres with experience of septostomy and severe pulmonary hypertension.

Transplantation

Before the improvement in medical treatment for severe pulmonary hypertension, heart/lung or lung transplantation was the standard approach for severe intractable pulmonary hypertension and, in some centres, a large proportion of transplants were for this diagnosis. With over 1000 patients worldwide having received either single lung, double lung, or heart/lung transplantation, there is considerable experience of transplantation for pulmonary hypertension. Surprisingly, there appears to be little difference in the effectiveness of one operation over another although patients undergoing single lung transplantation for pulmonary hypertension have fared slightly less well than those having a single lung transplant for other conditions. A detailed analysis of the costs and benefits of transplantation is outside the scope of this article but at present we can expect a one year survival of 70% and a three year survival of 50–60% in patients with pulmonary hypertension. These figures are slightly worse than those for aggressive vasodilator therapy in “responders”. The principal problems with transplantation are the need for continuous immunosuppression and the development of late complications such as bronchiolitis obliterans. The better results with medical treatment make the timing of referral to a transplant centre more difficult. In general, however, if patients are failing to improve on medical treatment they should be considered for referral for transplantation; they can always be evaluated and referred back to the pulmonary vascular centre if not thought to be sufficiently ill for a transplant at the time of evaluation. There are a number of reviews of strategy regarding the timing of transplantation in pulmonary hypertension but the future of conventional transplantation is bleak because donors are in very short supply.^{59–61} Despite adequate facilities in most Western countries, the principal rate limiting step is the availability of donor organs. This has prompted some live donations from living relatives but the associated moral and ethical dilemmas are considerable. There is a possibility that animal donors such as the pig may be available in the future once the immunological problems are conquered but, once again, there are ethical issues and fears of cross infection.

Pathobiology of severe pulmonary hypertension

There are many associations and risks for severe intrinsic pulmonary hypertension including congenital shunts, HIV infection,^{62–64} anorexigens,^{65–69} portal hypertension,⁷⁰ autoimmune disease,^{71–74} hypoxia, and there is the familial form of the disease. Despite the large number of associated risks and causes for severe pulmonary hypertension, there is a surprising similarity in the histological change seen in the pulmonary vessels. Preliminary data also suggest surprising similarities in the response to treatment, particularly to intravenous prostacyclin which, whether or not it causes vasodilation when given acutely, may result in a fall in pressures long term which

suggests that it is working as an anti-growth factor and reversing the vascular remodelling process. At present no common underlying mechanism has been found to link all these conditions but it is likely that one will be found in the future. One question is the link between vasoconstriction and remodelling. Does vasoconstriction lead to remodelling and does vasodilation lead to de-remodelling? It is tempting to say that this is the case because many vasoconstrictors are also growth factors and many vasodilators are anti-growth factors, allowing us to postulate cell growth–vasomotor coupling.⁷⁵ To find a common mechanism it is worth looking at the cellular make up of the pulmonary vessels and to consider the possible factors, whether physical or inflammatory, to which they might be exposed and the ways in which they might respond. Firstly, however, we must consider how genetic predisposition might dictate the cellular response to extrinsic factors.

GENETICS OF PULMONARY HYPERTENSION

It is clear that genetic analysis is going to play an important part in elucidating the pathobiology of PPH. The familial form of the disease appears to depend on inheritance of one or perhaps two PPH genes.^{76–77} Approximately 100 families worldwide with familial PPH have been identified including 72 in the USA, eight in the UK, and 10 in Australia. Overall, the incidence of familial pulmonary hypertension is approximately 6%. Inheritance appears to be via vertical transmission, suggesting a single dominant gene. It is not sex linked and is likely to be an autosomal dominant gene with incomplete penetrance. The syndrome can skip generations and having the gene confers only a 10–20% likelihood of developing the disease. The first gene ascribed to PPH (given the code PPH1) has been localised to seven million base pairs at 2q 31–32.⁷⁸ Genetic anticipation appears to occur with successive generations developing the disease slightly earlier than the preceding generation. Most recently, a family study in the UK has discovered a gene outside the 2q 31–32 region, suggesting heterogeneity of the genetic basis of familial PPH but further details are needed. At present the proteins coded by the PPH gene(s) are unknown.

As well as familial PPH there is also evidence of association particularly with autoimmune diseases suggesting co-inheritance. For example, approximately 10% of patients with PPH have Raynaud's phenomenon and up to 40% of patients with autoimmune disease, particularly the CREST variant of systemic sclerosis, have pulmonary hypertension. No genetic basis for this association has been determined but co-association provides further evidence to suggest an immunogenetic basis for the disease.

PATHOBIOLOGY OF CELLULAR CHANGE IN SEVERE INTRINSIC PULMONARY HYPERTENSION

Changes are seen in each of the three main cell types that make up the pulmonary vessels (for review see Wagenwoort¹⁵). In the intima there is intimal thickening and fibrosis. In the media

there is increased muscularity leading to the increased thickness of the muscular arteries and also muscularisation of arterioles which do not normally have a muscular coat. There is also increased connective tissue and extracellular matrix, particularly in the larger muscular arteries. In the adventitia there is an increase in matrix protein probably due in part to fibroblast proliferation (fig 5).

Endothelial cells

The endothelial cells form the intima of pulmonary arteries and are usually one layer thick. The endothelium is considered to be the front line in response to haemodynamic changes in the circulation and may also be the concert leader in terms of directing the remodelling process that occurs in response to haemodynamic change, inflammation, injury and circulating agents. The endothelium is a source of vasoconstrictors (endothelin 1 and thromboxane) and vasodilators (prostacyclin and nitric oxide). It is useful to think of the tone of a vessel as being determined by the balance of the vasodilators and vasoconstrictors. The vasoactive agents may also be responsible for cellular remodelling (see above) so that disease of the pulmonary circulation can be considered as an imbalance between vasoconstrictor/growth factors and vasodilator/anti-growth factors. We know, for example, that there is nitric oxide deficiency in pulmonary hypertension induced by appetite suppressants.⁷⁹ There is impairment of endothelium mediated pulmonary vasodilation in patients with both PPH and systemic sclerosis,^{80 81} suggesting a reduction in vasodilator capacity, an increase in vasoconstrictor capacity, or a change in the balance between the two. There is evidence for all of these. For example, decreased nitric oxide concentrations have been found in the exhaled air of patients with pulmonary hypertension with systemic sclerosis⁸² and patients with PPH have shown reduced expression of nitric oxide synthase,⁸³

an increase in circulating endothelin 1⁸⁴ and 5-hydroxytryptamine,⁸⁵ and an imbalance between vasoconstrictors and vasodilators was seen in patients with pulmonary hypertension of different causes.⁸⁶ Changes in nitric oxide production are thought to be responsible for the abnormal arteriovenous connections seen in patients with cirrhosis of the liver. In these patients the physiological vasodilation of pulmonary capillaries may possibly be due to excess nitric oxide production resulting in right to left shunts and hypoxaemia. In contrast, some patients with cirrhosis, usually those with portal hypertension, develop pulmonary hypertension. The mechanism remains unknown but has been reviewed by Herve *et al.*⁷⁰

Endothelin 1 is a powerful pulmonary vasoconstrictor although its role in the physiological control of the pulmonary circulation is unknown. It appears to have little influence on acute vasoconstriction as seen with hypoxic pulmonary vasoconstriction but it may have a role in conditions causing prolonged severe intrinsic pulmonary hypertension where its slow onset of action may be more relevant. There is evidence of increased expression of endothelin 1 in patients with pulmonary hypertension.⁸⁴

Media

The media is composed of smooth muscle cells which, in patients with PPH, become hypertrophied and the muscularisation then extends into previously non-muscular areas. In addition, there is laying down of extracellular matrix. The changes in the media may be orchestrated from the endothelium or may be due to changes in potassium channels in the cells⁸⁷ or to increased circulating vasoconstrictors such as serotonin.^{85 88}

Adventitia

The adventitia is composed of matrix proteins including collagen and elastin secreted by fibroblasts. There may be fibroblast proliferation and differentiation and an increase in matrix proteins. These changes are likely to be due to physical factors such as stretch and changes in pressure⁸⁹ or hypoxia.^{90 91}

Conclusions

It is clear that, for intrinsic pulmonary vascular hypertension to develop, there must be a complex interaction between various elements. There are genetic factors which may be a single PPH gene (the protein product of which is not yet identified) or co-inheritance of other genes such as those responsible for connective tissue disease. Inheritance of these genes may or may not lead to pulmonary hypertension and it is possible that additional factor(s) such as physical injury (hypoxia, shear stress, pressure and flow), inflammation (autoimmune disease, HIV disease, local injury (thrombosis)) or circulating toxins (appetite suppressants) are necessary to trigger a process which involves vasoconstriction and cellular remodelling. A complex interplay of vasodilators, vasoconstrictors, growth factors, and anti-growth factors may be necessary to produce the final

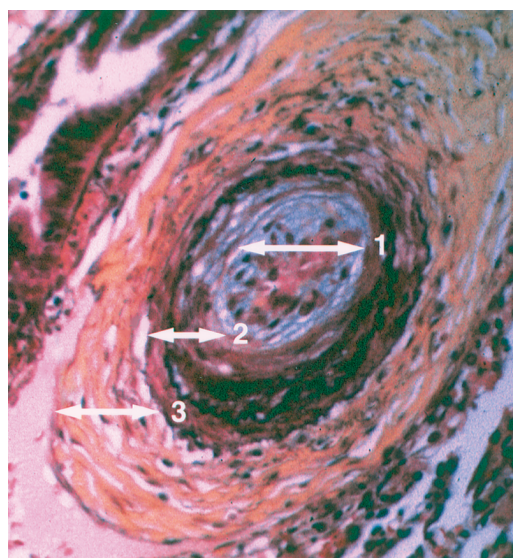


Figure 5 Cross section of a pulmonary artery (approximately 125 μ m) in a patient with severe pulmonary hypertension showing thickening of all three layers of the vessel. Possible mechanisms for these changes are suggested. 1=intima; 2=media; 3=adventitia.

histological change seen in fig 5, but which factors are present early in the disease and which are a consequence of the disease process is not yet clear. It is likely that, in the next 10 years, the genetic and physiopathological basis underlying severe pulmonary hypertension will be understood. Hopefully, this will lead to a radical change in treatment and a further improvement in morbidity for a devastating set of diseases which often affect young people.

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Bronchiolitis obliterans organising pneumonia associated with the use of nitrofurantoin

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Abstract

The spectrum of nitrofurantoin lung injury continues to widen. The case histories are presented of two patients who developed lung disease associated with the use of nitrofurantoin with histological features of bronchiolitis obliterans organising pneumonia (BOOP), a rare but recognised form of drug induced injury. The two middle aged women presented with respiratory symptoms after prolonged treatment with nitrofurantoin. Both had impaired lung function and abnormal computed tomographic scans, and their condition improved when nitrofurantoin was withdrawn and corticosteroid treatment commenced. The favourable outcome in these two patients contrasts with the fatal outcome of the two other reported cases of nitrofurantoin induced BOOP. We suggest that the previous classification of nitrofurantoin induced lung injury into "acute" and "chronic" injury is an oversimplification in view of the wide variety of pathological entities that have subsequently emerged.

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Keywords: bronchiolitis obliterans organising pneumonia; drug induced pulmonary disease; nitrofurantoin

An increasing number of drugs are recognised as causing lung injury and the spectrum of their adverse effects is widening. A recognised but uncommon form of drug induced lung disease is bronchiolitis obliterans organising pneumonia (BOOP).¹ We report two cases of nitrofurantoin induced pulmonary disease with histological features of BOOP.

Case 1

A 34 year old female non-smoker with recurrent urinary tract infections presented with increasing dyspnoea and cough over several months. She had been taking nitrofurantoin 50 mg at night for more than two years. She had no other significant exposures and was on no other medications. Examination was normal. The chest radiograph showed diffuse bi-basal reticulonodular shadowing. Baseline blood tests were normal, except for ANA 1:1280, with a diffuse staining pattern. Lung function tests showed forced expiratory volume in one second (FEV₁) of 2.09 l with forced vital capacity (FVC) of 2.33 l (predicted 3.18/4.04). Carbon monoxide transfer factor (TLCO) was reduced to 67% predicted. High resolution computed tomographic (HRCT) scans of the thorax showed patchy peribronchial interstitial

thickening, especially of the medium and small sized bronchi, with very little fibrosis. Open lung biopsy specimens showed that many respiratory bronchioles were distorted and largely occluded by fibroblastic tissue with associated mucus plugging and outgrowth of respiratory epithelium into surrounding alveolar tissue, consistent with BOOP. In the absence of other factors a diagnosis of nitrofurantoin induced pulmonary disease was made and the drug was discontinued. Prednisone 30 mg per day, gradually reducing over nine months, resulted in significant symptomatic improvement, significant improvement in lung function (FEV₁ 3.56 l, FVC 4.20 l, TLCO 82% predicted), and considerable but incomplete clearance of interstitial changes on the HRCT scan.

Case 2

A 50 year old female non-smoker with recurrent urinary tract infections gave a two month history of worsening dyspnoea, fatigue, anorexia, and cough with fevers and night sweats for three weeks. There was no history to suggest an underlying connective tissue disorder. She had been taking nitrofurantoin 50 mg at night regularly for one year. On examination she was tachypnoeic and tachycardic with bi-basal "velcro" crackles. Arterial blood gas measurements showed hypoxia (Pao₂ 6.5 kPa) with a wide alveolar-arterial gradient (9.1 kPa). Blood count and renal and liver function were normal, erythrocyte sedimentation rate (ESR) was 81 mm/h, and the ANA was 1:1640 with anti dsDNA negative. Lung function tests showed FEV₁ of 0.82 l and FVC of 0.84 l (predicted 2.87 and 3.77 l, respectively). TLCO could not be measured because of breathlessness. An HRCT scan of the thorax showed patches of "ground glass" opacity, interstitial fibrosis with traction bronchiectasis, and scattered areas of dense consolidation (fig 1). Transbronchial biopsy specimens showed loose immature fibrous tissue within air spaces and incorporated into the interstitium, a patchy interstitial infiltrate of mixed inflammatory cells including lymphocytes, plasma cells, and a few eosinophils, and prominent hyperplasia of type II pneumocytes. Pieces of airway wall showed inflammation with peri-airway fibrous and outgrowth of respiratory epithelium into fibrotic lung tissue. The appearance was consistent with BOOP/diffuse alveolar damage. The diagnosis of nitrofurantoin induced pulmonary disease was made; the drug was withdrawn and prednisone 40 mg daily reducing slowly to baseline 10 mg daily was given over three months. At three months a repeat

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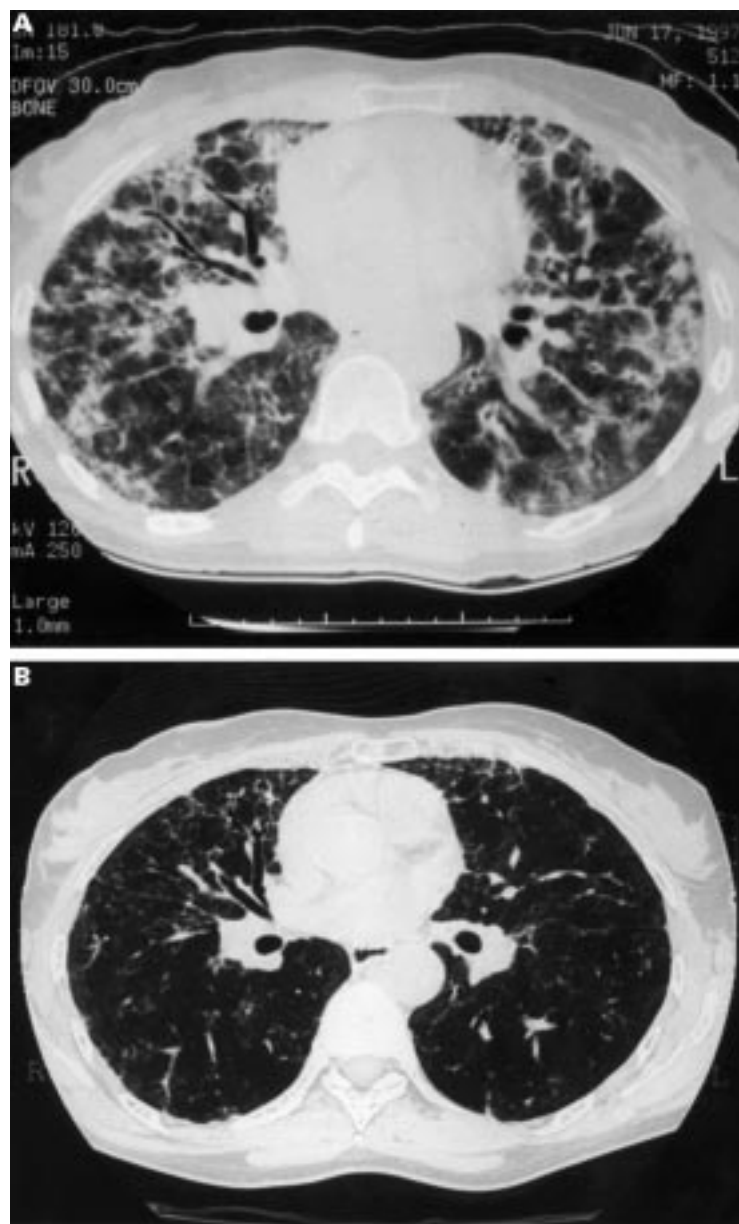


Figure 1 (A) Mid thoracic HRCT scan in case 2 showing small residual areas of normal lung, extensive interstitial fibrosis with traction bronchiectasis most marked in the right middle lobe, patchy ground glass opacity, and areas of dense consolidation. (B) Equivalent HRCT scan three months after withdrawal of nitrofurantoin and commencement of treatment with prednisone showing extensive but incomplete clearance of abnormalities.

HRCT scan showed marked reduction of the ground glass opacities and areas of consolidation, but with persistent interstitial fibrosis. Repeat lung function tests showed FEV₁ had improved to 2.88 l (100% predicted) with FVC 2.89 l (77% predicted) and TLC 66% predicted. The patient was subsequently weaned off oral steroids with no clinical, radiological, or physiological evidence of relapse.

Discussion

We conclude that both patients had nitrofurantoin induced pulmonary disease on the grounds that there was a lack of an alternative explanation for their lung disease and a good response to drug withdrawal and treatment with an oral corticosteroid. We acknowledge that BOOP of other causes may respond well to

corticosteroid treatment, but there was no disease recrudescence on steroid reduction and withdrawal. The establishment of a firm aetiological relationship would require re-challenge with nitrofurantoin. This was considered inappropriate in view of the severity of pulmonary impairment on presentation and the residual and irreversible changes on the HRCT scan.

Relatively few pharmaceutical agents have been associated with BOOP. These include amiodarone, acebutalol, nilutamide, cephalosporins, barbiturates, and cocaine.² There are only two previously reported cases of BOOP attributable to nitrofurantoin use.³ Both patients were elderly ex-smokers with symptoms of 3–4 weeks duration and both responded well to initial corticosteroid treatment, but rapid tapering led to an irreversible decline and death after failure to respond to increased steroid dosage. Details of drug treatment were not included in the report.

The course of the disease in our patients was rather different. Both were maintained on medium to high dose prednisone initially, gradually reducing over months, and the duration of treatment may have been important in terms of the improved outcome. They were weaned off oral steroids without clinical, radiological, or physiological evidence of relapse.

Nitrofurantoin induced pulmonary disease may present in many forms including BOOP, diffuse alveolar damage, vasculitis, interstitial fibrosis, pleural and airways disease, and pulmonary haemorrhage.¹ A final common toxic pathway has not been postulated. Nitrofurantoin induced pulmonary disease may result from immune mediated injury^{3,4} or via hydroxyl radical generation with subsequent free oxidant damage.⁵ The reduced incidence with the addition of the antioxidant ascorbic acid to nitrofurantoin preparations⁵ and results of in vitro studies⁶ suggest that this and other antioxidants may significantly reduce toxicity.

Initial reports suggested that the duration of nitrofurantoin treatment dictated the disease pattern. The “acute” reaction was characterised by marked constitutional symptoms including rash, fever, arthralgia, fatigue, together with pulmonary symptoms of dry cough and dyspnoea.^{3–5} The “subacute” and “chronic” forms were more insidious, with increased eosinophil count, raised ESR, and vasculitis and interstitial inflammation on histological examination, consistent with a type III immune response.^{3,4} Increased immunoglobulin levels, hepatic transaminases and ANA titres (the so called “drug induced lupus syndrome”^{7,8}) was associated with a degree of irreversible fibrosis. Some early reports of biopsy specimens from a patient with nitrofurantoin induced lung disease⁵ which predate the recognition of idiopathic BOOP as an independent entity are suggestive of a BOOP-like pattern. Cohen³ suggested that BOOP may be a precursor to chronic lung fibrosis, an early and potentially reversible phase in the spectrum of fibrosing lung disease. However, both patients in this report had residual radiological abnormalities although the remaining functional abnormalities were minor. The subsequent variety of

pathological entities now shown to be caused by nitrofurantoin suggests that these early categorisations are an oversimplification.

The initial interest in nitrofurantoin induced lung disease has waned as more suitable less toxic agents have been found for chronic urinary infections. However, the drug remains generally available in spite of its high toxic profile and clinicians need to be aware of the spectrum of associated lung disease.

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LETTERS TO THE EDITOR

Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis

McCaffery *et al*¹ conclude that "antistaphylococcal treatment achieves sputum clearance of *Staphylococcus aureus* in patients with cystic fibrosis . . ." and that prophylactic treatment in young children is "... likely to be of clinical benefit". These positive conclusions are based on the results of a study which has important methodological problems. Neither the introduction nor the methods section of this review state what hypotheses the review set out to test, the criteria used to decide whether a study was suitable for inclusion, outcomes to be studied in the review, or methods used to assess the methodological quality of included studies. Systematic reviews differ from narrative reviews in that they test hypotheses using a methodology which is well described.² The authors have described their search strategy, which is based on that developed by the Cochrane Collaboration, to identify randomised controlled trials. The authors have, however, included a number of studies in their review which are not randomised controlled trials. It is not clear from the information provided whether their search strategy is sensitive enough to identify all possible relevant studies.

The authors base their conclusions on the results of just two randomised controlled trials, involving only 66 children, with a maximum follow up of two years.^{3,4} All of these children were under seven years of age (most under two years) and had upper respiratory samples taken, not sputum. Of the other studies described as randomised, one used alternate allocation (and so was not randomised)⁵ and one reported further outcomes in patients included in one of the randomised controlled trials.⁶ Only two randomised controlled trials actually reported the prevalence of *S aureus* in respiratory secretions. The larger study by Weaver *et al*⁶ reported that the prevalence of *S aureus* was reduced with prophylaxis but

"clearance" was not achieved from nose and throat swabs.

The important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer symptoms, improved lung function, and prolonged survival. None of the studies described in the review addressed these issues nor, indeed, the concern that prophylactic antibiotics may encourage chronic pulmonary infection with organisms such as *Pseudomonas aeruginosa* or multiply resistant *S aureus*. A Cochrane review addressing this intervention is currently being undertaken by two of us (AS and SW) and this will have the advantage that it will be regularly updated to incorporate new studies. Only when further properly designed studies have been completed and included in an up to date systematic review will we be able to evaluate whether antistaphylococcal antibiotic prophylaxis is "... likely to be of clinical benefit".

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AUTHORS' REPLY Smyth *et al* have listed a number of features that they regard as being essential to systematic reviews. In particular, they suggest that systematic reviews should always test hypotheses. However, a clear understanding of the existing evidence is necessary for the generation of valid hypo-

theses and, in our view, this is best achieved by systematic reviewing. Indeed, many important systematic reviews published in major clinical journals do not specifically test hypotheses, but study the current evidence in order to identify the state of existing knowledge and to define areas for further research.^{1,2} This objective is consistent with the view of the authors of the Cochrane Collaboration Handbook who recognise that systematic reviews can have different motivations, one of which is the resolution of conflicting evidence.³ Indeed, it is probably difficult to define systematic reviews as formally as Smyth *et al* (and others) have proposed as the science of systematic reviewing is undergoing continuous development. More systematic reviews are being performed now than ever before (a Medline search looking for "systematic review" in titles and abstracts presents 4158 citations in the last 10 years, 1538 (37%) of which are in the last two), with reviewers defining their methods according to the problem in question.

Again, because of the nature of the field being studied, we had purposely not defined stricter criteria for study selection or drawn up a preselected list of outcomes of interest. As the area under investigation was largely unknown, we felt such criteria could limit our search. Also, in the absence of any significant background information, we were uncertain if such a choice of outcomes could be made objectively. Indeed, if we had arbitrarily drawn up a list of outcomes that were of interest to us, we would have missed a number of outcomes that others had used and which could be of potential interest to readers when designing clinical trials in the future. We did not use quality scores because there is little objective evidence to support the use of quality scoring in systematic reviews.⁴ Many of the scoring systems have not been developed with sufficient rigour⁴ and could add the analyst's bias to the results.⁵ A recent review of a random sample of 240 meta-analyses showed that less than half assessed trial quality.⁶ However, we note that newer techniques such as meta-regression may provide better alternatives in the future.

As we were principally interested in randomised controlled trials (RCTs), we used a search strategy that has been well validated for the recall of such trials. However, as before,⁷ we wanted to present an analysis of outcomes of both RCTs and non-RCTs because we felt this would make our conclusions more objective. Again, this approach is supported by the authors of the Cochrane Collaboration Handbook.⁸ Smyth *et al* state quite rightly that the important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer

symptoms, improved lung function, and prolonged survival. However, this should not inhibit the use of laboratory based outcomes which could influence clinical decision making until appropriate clinical data are available. Indeed, given the high predictive value of oropharyngeal cultures in children for identifying pathogens in bronchoalveolar lavage fluid (sensitivity and specificity of 90%),⁸ we feel the evidence we have defined in support of clearance of *Staphylococcus aureus* from the upper or lower respiratory tract with anti-staphylococcal antibiotics does suggest that this therapeutic intervention is likely to be of clinical benefit, although we strongly support their argument that properly designed studies are needed to confirm this hypothesis.

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Therapeutic ratio of inhaled fluticasone

I read with interest the recent article by Meijer and colleagues on the effects of inhaled fluticasone and prednisolone on clinical and inflammatory parameters in patients with asthma.¹ Rather than focusing on the differences between oral and inhaled corticosteroid, I believe that a more important finding is the effect of a fourfold increase in the dose of fluticasone on the therapeutic ratio. For airway parameters there were no significant differences in the effects on bronchial hyperresponsiveness to methacholine and adenosine monophosphate or on sputum eosinophils between fluticasone in doses of 500 µg and 2000 µg per day. However, for systemic bioactivity markers there were significant differences between the two doses of fluticasone on serum cortisol levels and blood eosinophils. Taken together these findings suggest that, at least for effects on airway hyperresponsiveness and inflammation, the therapeutic ratio for fluticasone declines sharply above a watershed dose of 500 µg per day. This result is perhaps not surprising, given the high glucocorticoid

topical potency for in vitro anti-inflammatory activity with fluticasone.²

It is also important to point out that the study by Meijer *et al* was performed using fluticasone delivered via a Diskhaler dry powder inhaler device, which delivers a twofold lower respirable fine particle dose than a fluticasone propionate pressurized metered dose inhaler.³ This is due to the larger particle size from the fluticasone dry powder inhaler. Hence, increasing the nominal dose of fluticasone dry powder may result in a proportionately greater delivery of larger particles to the central airways and consequently to a less than expected impact on small airway inflammation. The lower fine particle dose of fluticasone dry powder will also result in reduced lung bioavailability, as shown by a fivefold lower degree of adrenal suppression compared with the same nominal dose of fluticasone delivered via a pressurized metered dose inhaler with spacer device.⁴ The use of fluticasone in a dose of 500 µg/day via a dry powder inhaler would therefore explain the absence of any significant suppression of blood eosinophils or serum cortisol in their study. This does not mean that fluticasone propionate dry powder in a dose of 500 µg/day is not systemically bioavailable, as recently published data with this dose of fluticasone given via a Diskhaler reported significant suppression of 24 hour urinary cortisol excretion (33% reduction) and peripheral blood lymphocyte glucocorticoid receptor mRNA expression (71% reduction) during steady state dosing in asthmatic patients.⁵

Another finding in the study by Meijer *et al* was the relatively greater effect on bronchial hyperresponsiveness to adenosine monophosphate than to methacholine challenge with both oral and inhaled corticosteroid after two weeks. Similar findings have been reported after two weeks of treatment with inhaled budesonide powder in a dose of 1600 µg/day.⁶ The authors not unreasonably suggested that adenosine monophosphate responsiveness might be more sensitive to changes in airway inflammation than methacholine. However, the treatment period was relatively short and one cannot exclude the possibility that the effects on methacholine hyperresponsiveness might have been proportionately greater with a longer duration of treatment, as has been reported in previous studies.^{7,8} It is also conceivable that differences in bronchial hyperresponsiveness between the doses of inhaled fluticasone may have become apparent with a longer duration of treatment.

Finally, it is important not to extrapolate the results of the study by Meijer *et al* on patients with relatively mild asthma to more severe asthmatic patients in whom altered airway geometry may cause a reduction in lung delivery and lung bioavailability from narrowed peripheral small airways. Also, their results may be specific to the unique drug/device interaction of fluticasone propionate given via the dry powder inhaler, and further studies are needed to look at the dose-response relationship for the therapeutic ratio using more efficient delivery systems such as a pressurized metered dose inhaler with spacer.

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AUTHORS' REPLY We thank Dr Lipworth for his interest in our article.¹ Although we found no significant dose difference in PC₂₀ adenosine monophosphate and methacholine or in sputum eosinophils over a two week period between the two doses of fluticasone, the trends suggested a favourable effect of 2000 µg compared with 500 µg per day for every parameter measured, and there was, indeed, a significant dose response effect on sputum levels of ECP. It is well known that the dose response curve for inhaled steroids in general is very shallow at conventional and higher doses, and we agree that from our data this seems to apply to fluticasone also. From our study, in which only two doses of fluticasone were used, we are careful not to overinterpret where the decline in the therapeutic ratio starts with this drug.

We are aware that the respirable fraction of fluticasone in the dry powder formulation is lower than in the pressurized metered dose inhaler, although the suggested magnitude of the difference is debatable using data from Dr Lipworth's own group.² Unfortunately, in humans we still have considerable problems in separating the effects of common drugs on the large and the small airways, and the remarks by Dr Lipworth on the site of delivery are intuitively correct but, we believe, unproven as far as the clinical effects are concerned. There is no doubt that the dry powder formulation has systemic bioavailability and we clearly demonstrate this. We accept the notion that, with more sensitive markers of bioavailability, an effect might have been demonstrable also with the dose of 500 µg per day. The clinical relevance of this still needs to be determined even after so many years of using inhaled steroids.

We agree that the improvement in hyperresponsiveness with steroid treatment can continue for much longer than the improvement in forced expiratory volume in one second (FEV₁).³ The concept that the improvement in methacholine hyperresponsiveness might continue for a longer period than that of

adenosine is interesting, but we are unaware of any data to substantiate this. In fact, in a study by Weersink and colleagues, the same difference between the two bronchoconstrictor agents held true for six weeks instead of the two weeks of fluticasone treatment in the current study.⁴

It is interesting to debate whether the insufficient effect of inhaled steroids in patients with severe asthma is due to lower availability in the peripheral airways, as Dr Lipworth suggests, or, for instance, to a decreased sensitivity to steroids—either *per se* or as a result of increased inflammation and associated cytokine load.⁵ The suggestion by Dr Lipworth should result in a relatively better effect of systemic steroids compared with inhaled steroids, especially in the more obstructed patients, but this does not agree with our clinical impression. In fact, the finding of a superior effect of the inhaled corticosteroid over oral prednisolone (30 mg for two weeks) in our study rather suggests a contrary mechanism, perhaps compatible with a higher effectiveness of the lipophilic compound fluticasone at the level of the epithelium and (sub)mucosa than of systemic prednisolone, even if only in the larger airways. Nevertheless, we are careful not to extrapolate our findings beyond the devices and population studied. There are, however, in addition to ours, a few other studies which suggest that inhaled corticosteroids may have an effect at least as great as prednisolone in asthma exacerbations.^{6,7}

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“Systematic review” of asthma education studies

We were disappointed that Sudre *et al.*¹ felt there was insufficient documentation and excessive variability in studies of education programmes for adults with asthma published between 1979 and 1998. We feel that their conclusion is largely because they did

not perform a rigorous systematic review of papers in this area.

Systematic reviews of research evidence are undoubtedly invaluable scientific activities. They establish whether scientific findings are consistent and can be generalised across populations, settings, and other variations. Systematic reviews should be based on the “gold standard” of published randomised clinical trials. However, in the 77 trials reported Sudre *et al.* included 35 studies which were not randomised controlled trials. They also give no information about which interventions were found to have statistically significant effects. They include a study which simply asked patients whether they preferred audiovisual information or written information and did not have any intervention,² a study which has not been published,³ and interventions assessing the use of psychotherapy⁴ and yoga⁵ for asthma patients, which seem outside the criteria for inclusion in the review. Another four studies they include are excluded from the Cochrane reviews of patient education^{6,7} on the grounds that they are not educational intervention studies. It is therefore not surprising that in 81% of projects assessed the background educational theory was not mentioned and few projects had a patient’s needs assessment performed.

While we accept that many of the studies reviewed had missing information on the form and duration of education, we are concerned that some of these studies may be being misquoted. As an example, our own randomised controlled trial on personalised patient education for asthma delivered in four booklets over three months (reference 65) is incorrectly quoted as consisting of “a 10 minute encounter with a physician”.⁸ We are concerned that other studies referenced may also have been incorrectly classified.

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- 8 Osman LM, Abdalla MI, Beattie JAG, *et al.* Reducing hospital admission through computer supported education for asthma patients. Grampian Asthma Study of Integrated Care (GRASSIC). *BMJ* 1994;308:568–71.

AUTHORS’ REPLY Drs Douglas and Osman correctly state that we did not perform a systematic review of the efficacy of education

programmes, but neither did we claim to do so. Our goal, clearly stated in the title, was to describe the objectives, methods, and content of education programmes. In fact, we renounced conducting a meta-analysis of the effectiveness of programmes when we realised the extent of the variability of educational interventions. Averaging the proverbial apples and oranges did not make much sense. Our study suggests that, not only is the number of fruit species greater than anticipated (variability between programmes), but you cannot always tell one from the other (insufficient description of programmes). The latter finding implies that even a systematic review aimed at identifying features associated with greater effectiveness is not feasible. Such an endeavour would be further complicated by the fact that variables used to assess efficacy vary from one evaluation study to the next. In our opinion, standardisation of both programme descriptions and evaluation methods would foster progress in patient education.

While randomised controlled trials are the gold standard for assessing efficacy, *all* studies reporting an educational intervention should describe in sufficient detail what that intervention consisted of. We therefore included in our review all studies that had an educational component, regardless of the evaluation design.

We admit that we used a broad definition of education as “any attempt to provide the patient with knowledge or personal skills to reduce the impact of asthma on health”. The educational content varied among programmes (this is one of our main points) and could include drug management, environmental control, relaxation, yoga, etc. The paper by Partridge¹ provides an interesting description of an education programme in an asthma clinic, its weaknesses, and attempts at correcting these. As for including work published only as a dissertation, this may be considered an advantage rather than a drawback by some meta-analysts. We maintain that all studies that we reviewed included an explicit educational component and doubt that changing eligibility criteria to exclude a small subset of studies would much alter our general conclusions.

We stand corrected about the incomplete reference to the Grassic intervention in the discussion section of our paper.² In our database this programme was described more accurately as follows (partial data): number of training sessions: 4 (counting one 10 minute session in person and three mailed booklets); duration of training period: 3 months; delivery of education by: *physician and self-help*; educational setting: *individual*; training tools: *booklet*; training method: *lecture/vertical teaching*. Had we conducted an effectiveness review we would have no doubt singled out this study as by far the largest trial of asthma education, and one that did achieve clinical benefits for its patients. More such research studies are needed.

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- 1 Partridge MR. Asthma education: more reading or more viewing? *J R Soc Med* 1986;79.
- 2 Osman LM, Abdalla MI, Beattie JAG, *et al.* Reducing hospital admission through computer supported education for asthma patients. Grampian Asthma Study of Integrated Care (GRASSIC). *BMJ* 1994;308:568–71.

BOOK REVIEWS

Case Presentations in Clinical Tuberculosis Davies PDO, Ormerod LP. (Pp 320; £29.99). Edward Arnold. ISBN 0 340741 597.

This text is a thorough but concise overview of clinical tuberculosis presented as a well structured series of cases with clearly reproduced radiographs, computed tomographic scans, and slides. Each case is complemented by a short pertinent discussion clarifying any points of interest or debate. A carefully chosen chapter layout sequentially introduces the reader to the most challenging and interesting aspects of the disease and also provides an easy reference framework.

The authors' obvious wealth of experience allows readers with a more limited exposure to learn something of the more unusual manifestations of infection, including an extensive range of extrapulmonary and multisystem disease. The complex matter of antituberculous treatment in the emergent group with drug resistant mycobacterial infection, comorbidity, or compliance problems is tackled in some depth, highlighting potential pitfalls and explaining, in a real clinical context, the reasons behind the decisions made.

The difficulties associated with the diagnosis and management of tuberculosis in patients with human immunodeficiency virus are well illustrated, but not exhaustively covered, in a chapter whose commentary sections are particularly full and instructive.

Most of the 120 featured case presentations have a short list of affiliated references aimed to guide, rather than delineate in detail, further research of the points of interest raised.

The format of the book ensures an enjoyable and pragmatic approach to learning about tuberculosis, thus making it directly relevant to all those involved in the medical care of patients with the condition, especially at a training level. It would be an ideal accompaniment to existing formal textbooks.—ILJ

Anti-Inflammatory Drugs in Asthma. Sampson AP, Church MK, eds. (Pp 288, hardback). Switzerland: Birkhauser, 1999. ISBN 3 7643 5873 4

This is one of a series of publications under the collective heading "Progress in Inflammation Research" to which some of the European heavyweights in asthma research have contributed chapters. All the asthma drugs are included with the notable exception of the anticholinergic agents, although I found the title a little misleading as the in vivo

anti-inflammatory effects of some of the drugs discussed remains contentious. However, from the opening chapter it becomes apparent that investigations into the pathophysiology of, and the effects of treatment on, asthma have played an important part in defining the inflammatory mechanisms. The "commonly" used asthma medications are discussed initially with Peter Barnes giving an erudite synopsis of the anti-inflammatory effects of corticosteroids. The next two chapters deal with the putative anti-inflammatory effects of phosphodiesterase inhibitors and β_2 adrenoceptor agonists, although the chapter on phosphodiesterase inhibitors concentrated on the different isoenzymes and thus was heavy going with little discussion of their anti-inflammatory effects and no concluding summary. Despite theophylline being available for at least 40 years, I was struck by the paucity of clinical data available regarding its efficacy and in vivo anti-inflammatory effect (if at all). This is presumably because it is not profitable for pharmaceutical companies to investigate the drug further. The mast cell stabilisers are considered next, and the last third of the book deals with leukotriene antagonists and discusses other novel potential anti-inflammatory agents including anti-IgE agents, cytokines and adhesion molecule antagonists.

Several of the chapters are interesting and well written with well laid out tables and graphs, although some have several annoying typographical errors. The book does provide a good summary of the anti-inflammatory effects of present and potential future asthma medications and would act as a good reference source for departments or individuals with an interest in this field.—JB

NOTICES

Cardiovascular Disease Prevention V

A conference entitled "Cardiovascular Disease Prevention V" will be held on 4–7 April 2000 at the Conference Centre, Kensington Town Hall, London. For further information contact The Secretariat, Hampton Medical Conferences Ltd, 127 High Street, Teddington, Middlesex TW11 8HH, UK. Telephone +44 (0)181 977 0011. Fax +44 (0)181 977 0055. email hmc@hamptonmedical.com

British Association for Lung Research

The British Association for Lung Research (BALR) Spring Meeting entitled "Inflammation Control: A Goal for the Millennium" will

be held on 18 April 2000 at the Wills Hall, University of Bristol. For further information contact Dr Lynne Armstrong, The Lung Research Group, University of Bristol Medical School Unit, Southmead Hospital, Westbury on Trym, Bristol BS10 5NB, UK. Telephone +44 (0)117 959 5348. Fax +44 (0)117 959 5018. email Lynne.Armstrong@bristol.ac.uk

CORRECTIONS

UK Pulmonary Vascular Units

In the list of UK Pulmonary Vascular Units given at the end of the review article on "Primary pulmonary hypertension" by A J Peacock which appeared in the December issue of *Thorax* (1999;54:1107–18), the address for Dr Simon Gibbs should have included the Imperial College School of Medicine which includes Hammersmith, Brompton and Harefield hospitals.

Atrial septostomy in pulmonary vascular disease

In the editorial entitled "Role of atrial septostomy in the treatment of pulmonary vascular disease" by R J Barst which appeared on pp 95–6 of the February issue of *Thorax*, there was an error in figure 1. The correct version is reproduced below, showing that in "non-responders" the PAP is *increased* or unchanged. The publishers apologise for this error.

