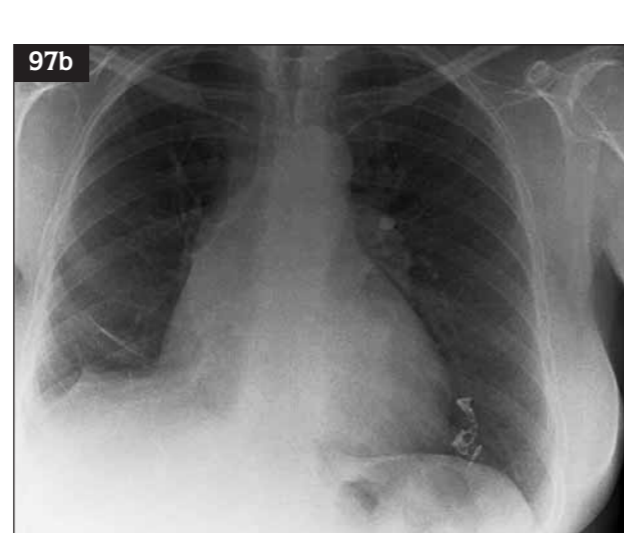
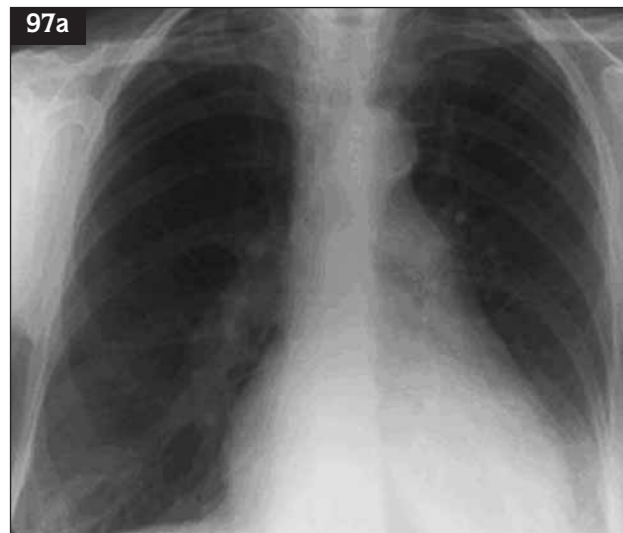


PRIMARY PULMONARY HYPERTENSION

PPH affects 1–2 per 1,000,000 individuals and is twice as common in women as in men. Endothelial and smooth muscle cell proliferation in pulmonary arterioles leads to thickening of the walls and the formation of plexiform lesions that occlude the vascular lumen. *In situ* thromboses contribute to the occlusion. Ultimately these changes lead to an increased pulmonary vascular resistance, right ventricular hypertrophy, dilatation, and failure. If untreated, the median survival is less than 3 years. Heart–lung transplantation is the only cure, but in recent years administration of vasodilators, particularly prostacyclin analogues, has been shown to greatly improve survival.

PPH remains a diagnosis of exclusion, though this may alter with the recent delineation of the molecular basis of familial PPH (which is due to germ-line mutations in the *BMPR2* gene). PPH may be precipitated by exposure of susceptible individuals to specific toxins, such as appetite suppressant drugs and rapeseed oil. Pathological processes highly similar to those in PPH occur in patients with collagen vascular diseases, HIV infection, and portal hypertension. Many individuals ‘susceptible’ to the development of PPH in these clinical settings will have mutations in *BMPR2*, but the degree to which these agents should be viewed as triggers of PPH rather than causative agents in their own right remains a subject of research.



97 Chest radiographs in pulmonary hypertension patients. Note hilar prominence due to enlarged pulmonary arteries, and enlarged cardiac silhouette in **b**. Patient **b** also has pulmonary arteriovenous malformations which have been treated by right lower lobectomy and embolization: embolization coils are evident in the left lower zone

CLINICAL FEATURES

Patients with pulmonary hypertension present with progressive breathlessness out of proportion to the severity of any precipitating underlying respiratory or cardiac disease.

Haemoptysis occurs as a result of the increased pulmonary capillary pressure. Patients may have anginal chest pains due to ischaemia of the hypertrophied RV. Examination should suggest the presence of PH: cyanosis, a resting tachycardia, elevated JVP with prominent a and v waves, RV heave, and a loud pulmonary second sound – masked if tricuspid regurgitation develops – all suggest the presence of significant PH. Peripheral oedema and ascites may be present. Additional signs will reflect the nature of any precipitating disease.

INVESTIGATIONS AND DIAGNOSIS

Routine tests performed in breathless patients which should suggest the possibility of PH include:

- Chest radiograph: the first radiographic sign of significant PH is usually enlarged main pulmonary arteries (the right lower pulmonary artery should be < 16 mm wide [97]). ‘Pruning’ of peripheral vascular markings may be evident. Although right ventricular hypertrophy and dilatation may be present, this may not be apparent from the radiographic cardiac silhouette until late in the disease.

- ECG: features of right atrial and ventricular hypertrophy will be evident including RBBB, P pulmonale, T wave inversion in V1–4, and the full S1Q3T3 pattern (91).
- Arterial oxygen saturation and blood gases: severe hypoxaemia ($\text{SaO}_2 < 90\%$, $\text{PaO}_2 < 8 \text{ kPa}$) will usually be evident, accompanied by low normal PaCO_2 .
- Thoracic CT scan: The most obvious abnormality occurs if the cross sections of the aorta and main pulmonary artery trunk are compared: the diameter of the pulmonary artery should be significantly less than that of the aorta, but in PH the pulmonary artery trunk diameter may equal or exceed the aortic diameter (98). A relative paucity of peripheral vascular markings may be evident. The hypertrophied or dilated right-sided chambers, with associated septal abnormalities, should be evident, and a pericardial effusion may be present.
- Lung function: in the absence of additional respiratory disease, spirometry (FEV_1 , VC, and FEV_1/VC ratio) and lung volumes (TLC, RV) should be normal, except in late stages of the disease. The crucial abnormality is seen on assessment of gas transfer: the TLCO and KCO will be severely reduced (< 70% predicted), reflecting the reduced microvascular bed available for gas exchange.



98 Thoracic CT scan in patient with severe pulmonary hypertension. Note that the contrast-filled pulmonary artery trunk (small arrow) has a diameter exceeding that of the aorta (large arrow) at the same level

SPECIALIZED TESTS TO DIAGNOSE AND QUANTIFY PH

Echocardiography

Wall thickness and overall dimensions of the right-sided cardiac chambers on two-dimensional echocardiography will suggest the presence of PH. A simple test to support the diagnosis can be performed by Doppler analysis of the tricuspid regurgitant jet of blood (detectable even if not evident on clinical examination). The maximum flow velocity of the jet depends on the pressure gradient across the valve: as the right atrial pressure can be estimated from the JVP, the right ventricular pressure and hence pulmonary artery pressure can be estimated. Additional specialized tests are also performed.

Cardiac catheterization

Direct pressure measurements are made using a pulmonary artery catheter; pulmonary arterial and right-sided cardiac chamber pressures are measured directly by appropriate catheter tip placement. Pulmonary venous pressure is measured during brief balloon occlusions of the pulmonary arterial flow. Catheterization allows a calculation of the cardiac output (using Fick's haemodilution method) and the pulmonary vascular resistance, which is important in determining the prognosis. Finally, catheterization allows a therapeutic test of the response of the pulmonary circulation to acute administration of vasodilator substances (see below).

MANAGEMENT

Any reversible cause or factor exacerbating PH should be treated. Patients should avoid strenuous exercise, pregnancy, and high altitude, which can further increase pulmonary arterial pressure. Administration of long-term oxygen in severely hypoxaemic patients and anticoagulation each prolong survival. In patients with severe PH due to chronic thromboembolic disease with proximal obstruction, surgical thromboendarterectomy may be possible, and carries a lower mortality than heart–lung transplantation, the only ‘cure’.

In recent years administration of vasodilators, particularly prostacyclin analogues, has been shown to improve survival greatly in PPH. The effect of prostacyclin therapy on exercise tolerance varies from inhibition of deterioration to up to a 30% improvement on the pre-treatment baseline. The approval of the endothelin antagonist, bosentan, for PPH offers another option for improving haemodynamics and vascular remodelling in this condition.

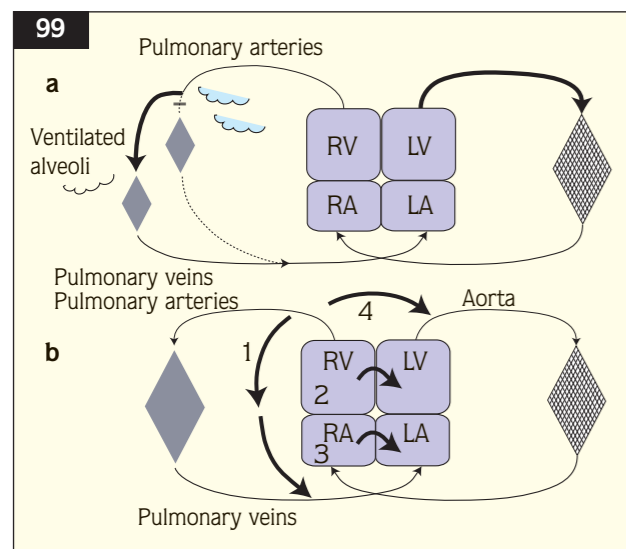
PULMONARY ARTERIOVENOUS MALFORMATIONS AND RIGHT-TO-LEFT SHUNTS

Physiological shunts are essential for the maintenance of ventilation and perfusion relationships; if alveoli are not aerated owing to airway obstruction, oedema fluid or other pathology, then physiological hypoxic vasoconstriction diverts pulmonary blood flow to other aerated areas (99a). In pathological right-to-left shunts, pulmonary arterial blood is not diverted to other areas of the lung, but instead returns direct to the left atrium (99b).

Pathological right-to-left shunts occur most commonly in pulmonary arteriovenous malformations (PAVMs). Intrapulmonary right-to-left shunts are also seen in the hepatopulmonary syndrome in patients with severe liver disease. In Eisenmenger's syndrome, due to reversal of left-to-right shunts of congenital heart disease, the right-to-left shunts are nonpulmonary (99b).

Capillary-free communications between the pulmonary and systemic circulations have two important clinical consequences:

- Pulmonary arterial blood passing through these right-to-left shunts cannot be oxygenated, leading to hypoxaemia.



99 Shunts. (a) Physiological intrapulmonary shunting due to hypoxic vasoconstriction (dotted line bars) directs pulmonary arterial flow to aerated regions of the lung, and does not result in a right-to-left shunt; (b) Right-to-left shunts due to intrapulmonary (1) or intracardiac (reversed VSD [2] or ASD [3]) communications, or a reversed patent ductus arteriosus (4). ASD, atrial septal defect; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, ventricular septal defect

- The absence of a filtering capillary bed allows particulate matter to reach the systemic circulation, where it impacts in other capillary beds causing clinical sequelae, particularly in the cerebral circulation.

Massive right-to-left shunts may be recognized by the clinical triad of profound central cyanosis, digital clubbing, and polycythaemia.

PULMONARY ARTERIOVENOUS MALFORMATIONS

PAVMs are abnormal intrapulmonary vascular structures that develop postnatally (usually in puberty). PAVMs occur sporadically, but over 90% of PAVMs occur in association with the inherited disorder hereditary haemorrhagic telangiectasia (HHT, or Osler–Weber–Rendu syndrome). The discussion below focuses on these noniatrogenic PAVMs, in which historical mortality rates ranged from 4 to 40%. PAVMs also occur in patients in whom cyanotic congenital heart disease has been corrected by surgically-generated cavopulmonary or atriopulmonary shunts.

CLINICAL FEATURES

Approximately 50% of patients have no respiratory symptoms at the time of presentation, even with physical signs, such as cyanosis, clubbing, a vascular bruit, or abnormal chest radiographs. The commonest symptom is dyspnoea, but this may not be appreciated until after the condition has been treated. PAVM patients even tolerate worsening hypoxaemia on exercise well, reflecting their low pulmonary vascular resistance and ability to generate a supranormal cardiac output, which may increase further on exercise. Pleuritic chest pain of uncertain aetiology occurs in up to 10% of patients. A similar percentage experience haemoptysis, which may be due to accompanying endobronchial telangiectasia. The majority of patients with PAVMs will have personal or family evidence of underlying HHT, though this may require careful questioning.

Patients with clinically silent right-to-left shunts are still at risk of major complications. Haemorrhage from the PAVMs may be fatal during pregnancy, and catastrophic embolic cerebral events (cerebral abscess and embolic stroke) and transient ischaemic attacks occur in patients regardless of the degree of respiratory symptoms.

INVESTIGATIONS AND DIAGNOSIS

Most PAVM patients are hypoxaemic, reflecting their right-to-left shunt, but the differential diagnosis of

hypoxaemia is wide, and the degree of hypoxaemia may be subtle, even in the presence of clinically significant PAVMs. Formal diagnostic methods are based on noninvasive techniques to image the PAVMs and/or detect the right-to-left shunt.

Thoracic imaging

Chest radiographic appearance ranges from apparent normality, particularly if PAVMs are small or in the lower lobes where they can be obscured by a hemidiaphragm, through prominent bronchovascular markings, to the classical rounded mass with visible feeding or draining vessels. Helical CT scans detect smaller lesions (100a) and usefully exclude other diagnoses in hypoxaemic patients.

Right-to-left shunt quantification

Flow through anatomical intrapulmonary shunts can be detected and quantified by impaired oxygenation following inhalation of 100% oxygen for 20 minutes, or by a standard perfusion scan. The latter assesses the distribution of ^{99m}technetium-labelled albumin macroaggregates which should impact in the pulmonary capillary bed, but can pass through shunt vessels (100b). Quantifying the activity from the kidneys compared to the total dose injected provides the means for accurate quantification of the shunt. Contrast echocardiography can be used to detect the shunt, and allows exclusion of intracardiac shunting.

MANAGEMENT

PAVM complications can be limited if the condition is recognized and treated, with transcatheter embolization therapy offering the safest method of treatment. In experienced centres there are proven

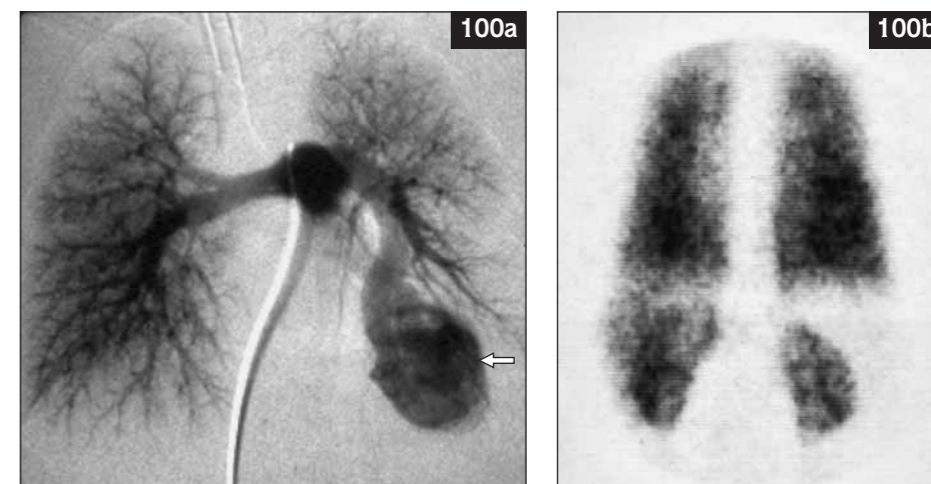
long-term physiological benefits of embolization, with excellent safety profiles, and this has supported the trend towards earlier treatment of the asymptomatic patient, accompanied by clinical screening of high-risk groups. In addition, prophylactic antibiotics are recommended at the time of dental and surgical procedures to reduce the risk of brain abscess. However, many PAVM patients remain undiagnosed, or under regular follow-up in respiratory units without consideration of intervention.

THE IMPORTANCE OF RECOGNIZING UNDERLYING HHT

Diagnosis and treatment of any PAVM is only one part of the management of a PAVM patient, more than 90% of whom will have underlying HHT, and it is crucial for the patient and their family that the physician is alert to this possibility. HHT is more commonly recognized by the consequences of abnormal dilated vessels developing in the systemic circulation, leading to epistaxes, mucocutaneous telangiectasia, and iron deficiency anaemia secondary to chronic gastrointestinal and/or nasal haemorrhage. Large arteriovenous malformations also occur in several systemic vascular beds, such as the cerebral, spinal, and hepatic circulations. Current clinical criteria for a definitive diagnosis of HHT require the presence of three out of four key features, namely: (1) spontaneous recurrent epistaxis; (2) telangiectases at characteristic sites; (3) a visceral manifestation; and (4) an affected first-degree relative.

PAVMs may be the first sign of HHT in the presenting patient, and may be the only feature of HHT evident in patients through their thirties, forties, fifties, and beyond. Mucocutaneous telangiectasia are often subtle. Furthermore, the majority of patients

100 Pulmonary arteriovenous malformations. (a) Angiographic appearances of pulmonary arteriovenous malformations (arrowed); (b) Perfusion scan demonstration of a 40% right-to-left shunt: note the abnormal signal from kidneys, spleen, and liver. Angiogram in (a) was performed by Dr James Jackson



will not volunteer a personal or family history of nosebleeds unless specifically asked, and allowed time to check with relatives. Detailed management of the nonpulmonary aspects of HHT is beyond the scope of this text. The importance for the family is that relatives of PAVM patients are likely to have HHT and PAVMs, and be at risk of paradoxical emboli and other complications. Diagnosis of HHT within the family allows presymptomatic screening for PAVMs and treatment before the catastrophic cerebral or haemorrhagic consequences ensue.

HEPATOPULMONARY SYNDROME

Thirty to seventy percent of cirrhotic patients develop intrapulmonary vascular dilatations resulting in right-to-left shunting. The hepatopulmonary syndrome (HPS) was first described as a triad of cirrhosis, clubbing, and cyanosis associated with normal heart and lungs. The syndrome is now defined by the presence of liver disease, an increased $P(A-a)O_2$ breathing room air, and evidence of intrapulmonary vascular dilatations. The anatomical basis appears to be due to dilatation of smaller vessels than usually discussed as representing PAVMs, and embolization therapy is rarely an option. The hypoxaemia and impaired gas transfer recover post-liver transplantation.

Table 68 Causes of haemoptysis

- Malignancy
 - Inflammation
 - TB
 - Bronchiectasis including cystic fibrosis**
 - Suppurative pneumonia**
 - Aspergilloma**
 - Pulmonary emboli
 - Cardiac causes of pulmonary hypertension
 - Acute left ventricular failure**
 - Mitral stenosis**
 - Vasculitis
 - Anticoagulation
 - Iatrogenic
 - Haematological disorders
 - Trauma
 - Aortic aneurysm
 - Other rare pulmonary causes
- Common causes are shown in **bold**

HAEMORRHAGIC CONDITIONS

HAEMOPTYSIS AND MAJOR HAEMORRHAGE

Bleeding can originate from the pulmonary or systemic bronchial circulations. Important causes of haemoptysis are listed in *Table 68*. Pulmonary infarction following pulmonary emboli, and acute inflammatory processes such as suppurative pneumonias, commonly cause less substantial haemoptysis. Major haemorrhage is more likely if abnormal bronchial and pulmonary vascular structures are present.

Abnormal vasculature commonly develops as a result of chronic infective processes. Hypertrophied systemic vessels occur following chronic lung inflammation and infection; conditions such as bronchiectasis and aspergillomas lead to hypertrophied and tortuous bronchial arteries, and transpleural collaterals from intercostal, axillary, and inferior phrenic arteries. Pulmonary artery aneurysms at high risk of rupture, occur particularly in the walls of tuberculous cavities (Rasmussen's aneurysms), lung abscess, and following endovascular seeding from endocarditis and in intravenous drug abusers.

Management of life-threatening haemoptysis

Haemoptysis is life-threatening owing to the possibility of asphyxiation occurring long before systemic hypotension develops. To reduce the risk of asphyxiation, attempts can be made to keep the blood in one lung by nursing the patient on the side suspected of bleeding. Patients should be given high-flow oxygen and fluid, to maintain haemodynamic stability. Expert anaesthetic and ICU support is needed urgently to permit emergency intubation.

Ideally patients should be haemodynamically resuscitated, investigated to assess the site and likely cause of bleeding, then treated. The chest radiograph is extremely helpful in suggesting the side and probable cause – there may not be time for a CT scan. Rigid bronchoscopy under general anaesthesia allows confirmation of the side of bleeding and bronchial suction. However, resuscitation should not delay therapeutic interventions which may be life-saving, even if the bleeding site and diagnosis were not formally established before the procedure was undertaken.

When available, emergency angiography and embolization are usually preferable to emergency thoracic surgery, because of the poor condition of the patient, and the extensive nature of disease when inflamed pleura and transpleural collaterals are present. Unless there are reasons to suspect a pulmonary vascular origin, bronchial angiography and embolization with polyvinyl alcohol particles is usually undertaken first.

Immediate control of bleeding is achieved in the majority of cases, allowing careful discussion of long-term management in a nonemergency situation over the ensuing weeks and months – re-bleeding is likely if the causative pathology is not removed.

ALVEOLAR HAEMORRHAGE AND PULMONARY VASCULITIDES

Alveolar haemorrhage has important consequences for gas exchange whether or not haemoptysis is present. Alveolar haemorrhage is characteristic of pulmonary vascular involvement in the small vessel vasculitides (*Table 69*). Many other rarer primary systemic vasculitides affect the lung vasculature, though pulmonary manifestations are predominantly nonvascular and are discussed in Chapters 7 and 11 (Wegener's disease) and 7 (Churg–Strauss syndrome). Alveolar haemorrhage also occurs in Goodpasture's syndrome, in which the basement membrane is damaged by anti-glomerular basement membrane (anti-GBM) antibodies.

CLINICAL FEATURES

Patients present with dyspnoea, haemoptysis, fever, chest radiograph changes suggestive of alveolar

oedema, and hypoxaemia. The diagnosis is not easy to make, particularly as they are rare (each < 40 cases per million population), and the clinical features of alveolar haemorrhage in an acute inflammatory disorder with elevated CRP and ESR strongly resemble those of pneumonia. Clues to the presence of alveolar haemorrhage and a systemic vasculitic syndrome are obtained from the multi-system involvement, the pattern of disease, the presence of haematuria or urinary activity (casts) on microscopy, and the failure to respond to antibiotics.

The chest radiograph and CT scan both display diffuse alveolar infiltrates, and HR CT scanning using 1 mm slices reveals more disease than is apparent on the chest radiograph. The cardinal sign of alveolar haemorrhage on pulmonary function tests is a supranormal gas transfer factor (DL_{CO} or K_{CO} > 150% predicted) that begins to return to the usual low/normal values soon after commencing treatment. Bronchoscopy can be helpful, as bronchoalveolar lavage should detect haemosiderin-laden macrophages. Diagnostic anti-neutrophil cytoplasmic (ANC) antibodies or anti-GBM antibodies are often present, but lung or renal biopsy may be needed to confirm the diagnosis.

Table 69 Primary vasculitides and alveolar haemorrhage syndromes

	LARGE VESSEL Takayasu's arteritis	SMALL VESSEL Wegener's granulomatosis	OTHER Microscopic polyangiitis	Churg–Strauss syndrome	Goodpasture's syndrome
Histological features	Medium/large pulmonary arteries	Necrotizing, granulomatous vasculitis	Capillaritis	Eosinophilic, necrotizing and granulomatous vasculitis	Basement membrane injury
Alveolar haemorrhage	Rare	10%	50%	< 5%	++
Other respiratory symptoms	Usually nil	ENT disease (nasal, sinuses)		Long-standing asthma & rhinitis	Smoking or hydrocarbon triggers
Key non-respiratory disease features	Aorta and branches 'pulseless disease'	Either sex FS glomerulonephritis Systemic features	Either sex Glomerulonephritis (haematuria) Systemic features	Females Eosinophilia Systemic features Cardiac disease	Males Glomerulonephritis
Antibody associations	Usually negative	c-ANCA positive	p-ANCA	p-ANCA	Anti-GBM
Mortality	< 10%	10–20%	10–40%	Low	Low if promptly treated
Treatment	Steroids	Cyclophosphamide and steroids +/- plasmapheresis		Steroids (+/- cyclophosphamide)	Cyclophosphamide, steroids + plasmapheresis

MANAGEMENT

The mainstay of treatment of these conditions is ventilatory support (oxygenation, noninvasive ventilation, or intubation) and prompt immunosuppression. Steroids are usually sufficient for Churg–Strauss syndrome, but more powerful immunosuppression is needed for Wegener's disease, microscopic polyangiitis, and Goodpasture's syndrome since, in these, untreated or steroid-treated disease leads to death from pulmonary or renal failure within a year in the majority of cases. Goodpasture's syndrome is treated by plasmapheresis to remove the offending antibody, followed by immunosuppression for remission-

maintenance. For Wegener's syndrome, cyclophosphamide at 2 mg/kg per day, plus prednisolone 1 mg/kg/day should lead to improvement within a month, though life-threatening pulmonary haemorrhage or renal failure may demand plasmapheresis. Once disease remission is achieved, relapse is common unless prolonged immunosuppression is given. Azathioprine or methotrexate are preferred to cyclophosphamide for remission-maintenance, owing to the severe side-effects of cyclophosphamide (bone marrow suppression and transitional cell carcinomas of the bladder in up to 5–10% of treated cases).

CASE STUDIES**CASE STUDY 1**

A 27-year-old woman presents with a 1-day history of acute left-sided pleuritic chest pain and a cough with blood-stained sputum. She is breathless walking upstairs.

Question: What two diagnoses should you have in mind?

Pneumonia, pulmonary embolus.

Question: What further history do you need?

Constitutional symptoms (e.g. fevers, sweats, chills) and risk factors for pulmonary emboli (immobility, previous events, family history).

She had flown back from Australia the previous week, and felt entirely well until the sudden onset of pain. She had recently started the contraceptive pill. She gives a family history of 'clots' but no other history of note. On examination, she is afebrile and coughing small amounts of blood. The JVP is elevated at 4 cm, BP 120/80 mmHg, pulse 95 bpm. Expansion is reduced on the right side of her chest and a squeaking sound is audible at the right base. Chest X-ray and ECG are normal. SaO₂ is 93% on room air. Blood is taken for FBC, U&E analysis, and arterial blood gases.

Question: Do you start heparin now?

Yes, but make sure you have an APTT and PTR result first.

Question: What is your preferred test?

CT scan with PE protocol (CT pulmonary angiogram).

The CT scan demonstrates thrombus in several segmental arteries.

Question: How long do you intend to anticoagulate her for?

At least 3 months.

CASE STUDY 2

You are referred a 40-year-old nonsmoking woman, whose chest radiograph displays a mass in the right lower zone. She was admitted following a minor stroke. She has had nosebleeds since admission, as did her daughter when visiting. On examination, she was cyanosed and clubbed, but otherwise looked well. There were resolving left upper motor neurone signs and no other feature of note except for some red spots on her lips.

Question: What is the differential diagnosis?

PAM due to hereditary haemorrhagic telangiectasia, complicated by a paradoxical embolic stroke, or lung cancer with cerebral metastases.

A CT scan is requested by your colleague who thinks she has lung cancer. This reveals large vessels entering the lobulated mass.

Question: What would you like to demonstrate on your next test?

A perfusion scan demonstrates activity in the kidneys, and the right-to-left shunt is estimated at > 20%.

Confirmation of right-to-left shunting.

Question: In addition to her routine stroke treatments, what two additional treatments does she need?

Antibiotic prophylaxis for dental, surgical, or other invasive procedures. Embolization of pulmonary arteriovenous malformations (performed by an experienced practitioner).

CASE STUDY 3

A 54-year-old nonsmoking man presents with breathlessness. He denies chest pain and was previously fit and well, although he was seeing the ear, nose, and throat surgeon for tests after a 'hole' developed in his nose. On examination, he has a mild pyrexia, the JVP is not elevated, BP is 130/80 mmHg, pulse 98 bpm. He is not cyanosed breathing room air, but the SaO₂ monitor reads 93%. There are bi-basal crackles on examination. The chest radiograph displays fluffy shadowing. The ECG is normal. Your colleague has sent bloods for FBC, U&E, glucose, clotting screen, and cardiac enzymes and is about to give him furosemide.

Question: What diagnosis is your colleague considering?

Pulmonary oedema.

Question: What diagnoses do you think are more likely?

Pulmonary haemorrhage secondary to Wegener's granulomatosis.

Question: What respiratory tests will help you with the diagnosis?

Gas transfer (K_{CO}, DL_{CO}) as part of lung function assessments.

Question: What other tests will help you make the diagnosis?

Urine microscopy for casts, bloods for CRP, ESR, and ANCA, and biopsy of the nose.