Seminar

Pulmonary embolism

Samuel Z Goldhaber

Pulmonary embolism (PE) is a common illness that can cause death and disability. It is difficult to detect because patients present with a wide array of symptoms and signs. The clinical setting can raise suspicion, and certain inherited and acquired risk factors predispose susceptible individuals. D-dimer concentration in blood is the best laboratory screening test, and chest CT has become the most widespread imaging test. Treatment requires rapid and accurate risk stratification before haemodynamic decompensation and the development of cardiogenic shock. Anticoagulation is the foundation of therapy. Right-ventricular dysfunction on echocardiography and higher than normal concentrations of troponin identify high-risk patients who might need escalation of therapy with thrombolysis or embolectomy even if the blood pressure is normal on presentation. When patients are admitted to medical wards or when patients undergo surgery, their physicians should prescribe prophylactic measures to prevent PE. After hospital discharge, prophylaxis should continue for about a month for patients at high risk of thromboembolism.

Pulmonary embolism (PE) is a common, potentially life-threatening cardiopulmonary illness that has only recently attracted the attention of the general public, when a healthy young woman died of PE shortly after a flight from Australia to the UK. Although PE can be difficult to diagnose, early recognition is important because prompt medical or surgical intervention can be life-saving. Therefore, physicians, health-care providers, and the public need to understand the rapidly progressing advances in PE epidemiology, pathophysiology, diagnosis, treatment, and prevention strategies. The interdisciplinary nature of PE means that knowledge about this disease can no longer be consigned to the domain of specialists.

Epidemiology

Although PE and deep venous thrombosis (DVT) can be notoriously difficult to diagnose,[1] hospital admission rates for venous thromboembolism (VTE) increased in the UK in the 1990s.[2] Despite challenges in detection of VTE, cohort studies show consistency in incidence estimates among western populations. In the Brest district of France, the annual incidence was 1·83 per 1000.[3] In Olmsted County, MN, USA, the most recent annual incidence estimate was 1·22 per 1000 among adults.[4] In the Longitudinal Investigation of Thromboembolism Etiology, which combined two separate US cross-sectional studies totalling 148 054 person-years, the annual incidence was 1·45 per 1000.[5] If the annual incidence of recognised VTE is 1·50 per 1000, and if only one of every three cases of VTE is detected, the USA, with a population of almost 300 million, has about 450 000 recognised incident cases and 900 000 unsuspected incident cases, totalling about 1 350 000 VTE cases each year.

Mortality from recognised PE is higher than generally acknowledged. In a population-based cohort study from Olmsted County, the 30-day mortality rate after PE or DVT was 28%.[6] In the International Cooperative Pulmonary Embolism Registry of 2454 consecutive patients from 52 institutions in seven countries, the 3-month mortality rate was 17·4 %.[7] In a Japanese registry of 533 patients with PE, the in-hospital mortality rate was 14·0%.[8] Many patients die from underlying comorbid disorders, especially cancer and cardiorespiratory diseases.[9] The mortality from PE in registries such as the international one mentioned above, which enrol consecutive patients without any exclusions, is far higher than that in selective registries such as the Prospective Investigation of Pulmonary Embolism Diagnosis, in which the 1-year mortality rate from PE was 2·5%.[10] In an overview of 1302 patients in five clinical studies of PE, 19 died of PE and there were 11 other sudden deaths, giving a low overall mortality rate of only 2·3%.[11]

Risk factors

Understanding of risk factors for VTE[12,13] will increase the likelihood that DVT and PE can be diagnosed and prevented. These factors include environmental, natural, and hormonal influences (panel 1).

Travel

Long-haul air travel is a rare (0·4 cases per million passengers) risk factor for massive PE.[14] The risk increases substantially with flight distances of 5000 km or more.

Search strategy and selection criteria

I subscribe to about 15 journals in internal medicine, cardiology, haematology, and pulmonary disease. I use a "tear and file" system to track relevant articles. To ensure that I have not missed important articles in other journals, I check the venous thrombosis articles weekly on the AMEDEO web page. For selection in this seminar, I searched MEDLINE (1993–2003) with the search terms "pulmonary embolism" and "clinical" and "OVID full text". I chose mostly recent articles published in 2000–2003. I emphasised papers from journals with high impact factors that add critical knowledge to this field. I also included 22 articles recommended by the reviewers of this seminar.

Lancet 2004; **363:** 1295–305

Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA (S Z Goldhaber MD)

Correspondence to: Dr Samuel Z Goldhaber, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA (e-mail: sgoldhaber@partners.org)

Passengers at particularly high risk include those older than 50 years, and individuals with a history of previous VTE, thrombophilia, limitation of mobility, cancer, or large varicose veins.

Obesity

The magnitude of risk associated with obesity is related to the body-mass index. The Nurses' Health Study identified risk factors for PE among a cohort of initially healthy female nurses, with 1 619 770 person-years of follow-up.[15] The relative risk of PE was 1·7 (95% CI 1·1–2·7) for those with a body-mass index of 25·0–28·9 kg/m^2 and 3·2 (1·7–6·0) for those with a body-mass index of 29·0 kg/m^2 or higher. In the International Cooperative Pulmonary Embolism Registry, the proportion of patients with a body-mass index of 29·0 kg/m^2 or higher was 29%.[7] Even in Japan, with a much leaner population than western countries, a prospective PE registry found that body-mass index was 25·3 kg/m^2 or higher in 34% of cases.[8]

Panel 1: Risk factors for PE

Environmental
- Long-haul air travel
- Obesity
- Cigarette smoking
- Hypertension
- Immobility

Natural
- Increasing age

Women's health
- Oral contraceptives, including progesterone-only and especially third-generation pills
- Pregnancy
- Hormone replacement therapy

Medical illness
- Previous PE or DVT
- Cancer
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Inflammatory bowel disease
- Antipsychotic drug use
- Chronic in-dwelling central venous catheter
- Permanent pacemaker
- Internal cardiac defibrillator
- Stroke with limb paresis
- Nursing-home confinement or current or repeated hospital admission
- Varicose veins

Surgical
- Trauma
- Orthopaedic surgery, especially total hip replacement, total knee replacement, hip fracture surgery, knee arthroscopy
- General surgery, especially for cancer
- Gynaecological and urological surgery, especially for cancer
- Neurosurgery, especially craniotomy for brain tumour

Thrombophilia
- Factor V Leiden mutation
- Prothrombin gene mutation
- Hyperhomocysteinaemia (including mutation in methylenetetrahydrofolate reductase)
- Antiphospholipid antibody syndrome
- Deficiency of antithrombin III, protein C, or protein S
- High concentrations of factor VIII or XI
- Increased lipoprotein (a)

Non-thrombotic
- Air
- Foreign particles (eg, hair, talc, as a consequence of intravenous drug misuse)
- Amniotic fluid
- Bone fragments, bone marrow
- Fat
- Cement

Women's health

Oral contraceptives, pregnancy, and postmenopausal hormone replacement therapy raise the risk of PE. Inherited prothrombotic states further increase the risk.

First-generation oral contraceptives contained more than 50 μg oestrogen. They were associated with an alarming increase in the frequency of massive PE and were withdrawn from the market in 1989. Second-generation oral contraceptives, containing less than 50 μg oestrogen, were introduced in the USA in 1967, but an excess, albeit lower, risk of VTE persisted. Third-generation oral contraceptives contain newer progestagens, such as desogestrel or gestodene, which improve acne and hirsutism. However, they cause adverse haemostatic changes, including acquired resistance to activated protein C[16] and therefore increase the risk of VTE more than second-generation pills. Increasing age and cigarette smoking further increase the thrombotic risk among users of oral contraceptives.[17]

Despite the increased relative risk of VTE from oral contraceptives, the absolute risk of fatal PE is low. In a New Zealand study, the absolute risk of death from PE in current users was estimated as one per 100 000 woman-years. Among the women who died, the median age was 29 years. The risk of fatal PE was twice as high among women taking third-generation oral contraceptives.[18]

A history of PE or DVT is an absolute contraindication to oral contraceptives. Relative contraindications include a strong family history of VTE or an inherited prothrombotic state, such as factor V Leiden or the prothrombin gene mutation. Whether women with a family history but no personal history of VTE should be screened for prothrombotic states is controversial. Overall, oral contraceptives are safe and effective. The absolute risk of VTE is very low.

In pregnancy, the risk of PE increases with time, and most cases of VTE occur during pregnancy rather than post partum. Increasing maternal age and caesarean-section delivery increase the likelihood of VTE.[19] Inherited prothrombotic states are associated with obstetric complications[20] and with late fetal loss.[21]

The Women's Health Initiative is a randomised placebo-controlled primary prevention trial that enrolled 16 608 women to assess the major benefits and risks of postmenopausal hormone replacement therapy.[22] The trial used a combined oestrogen and progesterone preparation that is most commonly prescribed in the USA. Though the trial duration was planned to be 8·5 years, the study was stopped early because overall health risks exceeded benefits after an average of 5 years of follow-up. The hazard ratio for PE in the treated group was twice that for controls. The absolute excess risk of PE was 8·0 per 10 000 woman-years. In a meta-analysis of 12 studies, the relative risk of VTE was 2·1 among current users and was highest (3·5) during the first year of use.[23]

Selective oestrogen-receptor modulators such as raloxifene increase the risk of PE. In a study on prevention of breast cancer, 7705 postmenopausal women were

assigned raloxifene or placebo; by 40 months of follow-up the rate of PE was three times higher in patients assigned raloxifene than in those assigned placebo (0·3% *vs* 0·1%). The rate of DVT was also three times higher (0·7% *vs* 0·2%).[24]

Oestrogen agonists-antagonists such as tamoxifen are used to treat or prevent breast cancer. In a trial of 7152 women randomly assigned tamoxifen or placebo, the VTE rate was 2·5 times greater in the tamoxifen group (1·20% *vs* 0·47%).[25]

Cancer

In patients with known cancer who develop VTE, recurrence and bleeding complications are common with conventional heparin followed by oral anticoagulation.[26] Low-molecular-weight heparin as monotherapy without oral anticoagulation can halve the rate of recurrence compared with oral anticoagulation.[27]

Cancer, occult at the time of PE diagnosis in many cases, predisposes to PE. In the Swedish Cancer Registry, the risk of discovering a newly diagnosed cancer was increased for at least 2 years after the diagnosis of VTE.[28] However, when such cancers are discovered, they generally become apparent at an advanced stage and confer a poor prognosis.[29] Cancer should be suspected, especially in patients who have idiopathic VTE and recurrence during follow-up.[30]

Thrombophilia

Inherited and acquired risk factors for PE commonly interact. In most inherited thrombophilias, impaired neutralisation of thrombin or failure to control thrombin generation causes VTE.[31] To help define the role of heritability of the prethrombotic state, quantitative genetic-model fitting for hypercoagulability was done among participants in the St Thomas' UK Adult Twin Registry.[32] There was a high degree of heritability for markers of coagulation and inhibition of fibrinolysis, indicating substantial genetic control over fibrin formation and fibrinolysis.

Factor V Leiden is an autosomal dominant single point mutation (G→A) that brings about resistance to activated protein C and an increased predisposition to VTE (roughly three times). The carrier frequency ranges from 3% to 7%, and the mutation is especially prevalent in northern European people.[33] Among participants in the Physicians' Health Study, the carrier frequency was 5·3% for white Americans, 2·2% for hispanic Americans, 1·2% for African Americans, 0·45% for Asian Americans, and 1·2% for native Americans.[34] There is conflicting evidence on whether patients with VTE and factor V Leiden have an increased rate of recurrence after anticoagulation is discontinued compared with individuals who do not have this mutation.[35,36]

A single point mutation (G→A at position 20210) has been identified in the prothrombin gene, which causes an increased risk of VTE.[37] As with factor V Leiden, inheritance is autosomal dominant. However, the magnitude of the effect is slightly less than that of factor V Leiden.[38]

Hyperhomocysteinaemia is associated with VTE and is most commonly caused by an acquired nutritional deficiency of folate exacerbated by inadequate intake of vitamin B_{12} or vitamin B_6. Folate antagonists, such as methotrexate and phenytoin or vitamin B_6 antagonists, such as oestrogens, tobacco, or theophylline, also raise homocysteine concentrations. Impaired renal function can cause hyperhomocysteinaemia because homocysteine is predominantly metabolised by the kidneys.[39]

The antiphospholipid antibody syndrome, an acquired disorder, is the most ominous hypercoagulable state for PE. Anatomically large and recurrent VTE is the most common clinical manifestation of this syndrome, but increases in antibodies to cardiolipin are also associated with myocardial infarction, stroke, and first-trimester miscarriage.[40]

Despite advances in laboratory diagnosis of hypercoagulability, predisposing thrombophilic states are identifiable in only a minority of patients with VTE. Therefore, the most important action is to obtain a careful family history. Patients and their families should be reassured that some asymptomatic carriers of prethrombotic genetic risk factors will never develop clinical evidence of PE or DVT. There is no published evidence to support screening of first-degree relatives of patients with thrombophilia.[41]

Pathophysiology

Venous stasis and endothelial damage predispose to VTE, especially among patients with underlying hypercoagulable states. Those with previous PE or DVT are particularly susceptible to recurrences. Most cases of PE result from thrombi that originate in the pelvic region or deep veins of the leg. When venous thrombi become dislodged from their sites of formation, they move through the venous system to the pulmonary arterial circulation. Extremely large emboli can lodge at the bifurcation of the pulmonary artery, forming a "saddle embolus". More commonly, however, a pulmonary vessel of second, third, or fourth order is affected. In rare cases, thrombi in the axillary, subclavian, or other arm veins embolise to the pulmonary arteries.[42]

PE can have the following pathophysiological effects: increased pulmonary vascular resistance resulting from vascular obstruction, neurohumoral agents, or pulmonary-artery baroreceptors; impaired gas exchange caused by increased alveolar dead space from vascular obstruction and hypoxaemia from right-to-left shunting, as well as impaired transfer of carbon monoxide due to loss of gas exchange surface; alveolar hyperventilation owing to reflex stimulation of irritant receptors; increased airway resistance resulting from bronchoconstriction; and decreased pulmonary compliance caused by lung oedema, lung haemorrhage, and loss of surfactant.

Right-ventricular dysfunction

The haemodynamic response to PE depends on the size of the embolus, coexisting cardiopulmonary disease, and neurohumoral activation. Pulmonary-artery obstruction and circulating neurohumoral substances decrease the pulmonary vascular bed and cause an increase in right-ventricular afterload. As right-ventricular and pulmonary-artery pressures rise, the right ventricle dilates, becomes hypokinetic, and ultimately fails. Progressive right-heart failure leads to reduced forward cardiac output and is the cause of death from acute PE in most cases.

Sudden increases in right-ventricular pressure adversely affect left-ventricular function because of the anatomical juxtaposition of the two ventricles and ventricular interdependence. Moderate right-ventricular hypertension can displace the interventricular septum towards the left ventricle, resulting in decreased left-ventricular diastolic filling and end-diastolic volume. The subsequent reduction in coronary-artery perfusion pressure to the overloaded right ventricle can cause progressive right-ventricular ischaemia and failure. Ultimately, right-ventricular infarction, circulatory arrest, and death can ensue.[43]

Diagnosis

Clinical suspicion

Diagnosis of PE poses a major challenge because classic symptoms and signs are not present in many cases. PE can present with subtle findings in young, previously healthy patients who have excellent cardiac reserve. With increasing age, PE tends to masquerade as other illnesses such as acute coronary syndrome or exacerbation of chronic obstructive pulmonary disease. Accurate diagnosis of PE is particularly difficult when patients present with two concurrent illnesses, such as obvious pneumonia plus occult PE or obvious congestive heart failure plus occult PE. Such patients may not improve clinically despite appropriate treatment for the apparent illness, until the PE is also recognised and treated.

Detection of PE begins with consideration of VTE as a diagnostic possibility. The clinical scenario is crucial in assessing the likelihood of PE. Wells and colleagues[44] have developed a rapid seven-feature bedside assessment that is useful because almost half of their study patients could be classified as "PE unlikely". The researchers designated a score of 4·0 or less as PE unlikely. In this low-risk group, only about 5% of patients were subsequently found to have PE. The seven features are: clinical signs and symptoms of DVT (3·0 points); an alternative diagnosis is less likely than PE (3·0 points); heart rate above 100 bpm (1·5 points); immobilisation or surgery in the previous 4 weeks (1·5 points); previous DVT or PE (1·5 points); haemoptysis (1·0 point); and cancer, being treated currently or within the previous 6 months or palliative (1·0 point).

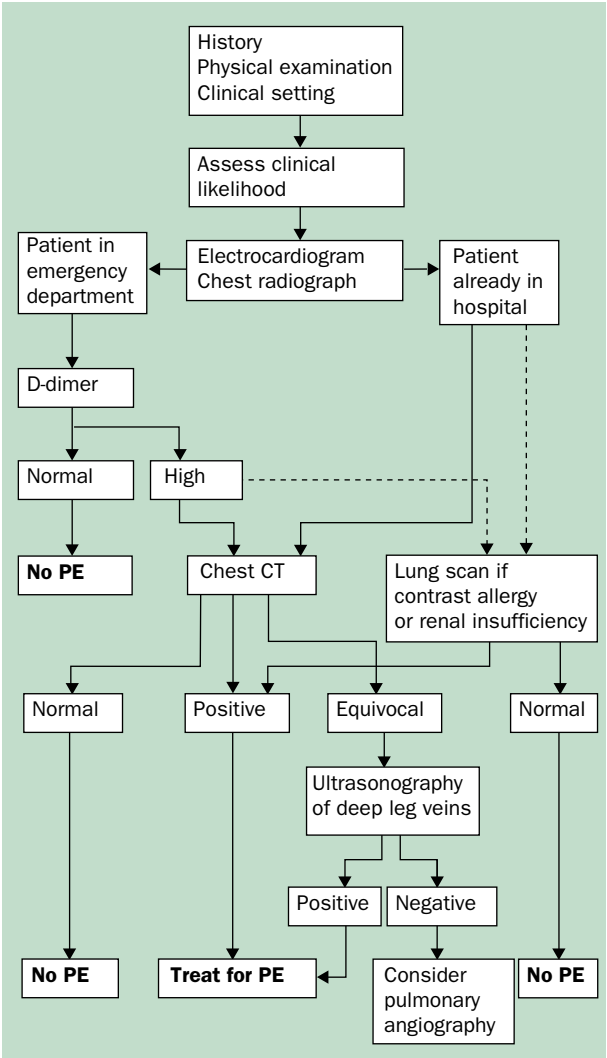


Figure 1: **Diagnostic algorithm for suspected PE**

For optimum diagnostic accuracy, symptoms and signs should be integrated with appropriate laboratory tests, including electrocardiography, chest radiography, and, when available, D-dimer testing. In many cases, no further diagnostic investigation is warranted. When appropriate, though, imaging tests, such as a chest CT or lung scan, should be done (figure 1).

Initial diagnostic studies

The electrocardiogram (figure 2) is useful to help exclude a myocardial infarction with ST-segment elevation and acute pericarditis. In patients with large PE, pulmonary hypertension and right-ventricular strain cause incomplete or complete right bundle-branch block, T-wave inversion in leads V1 to V4, an S wave in lead I, and both a Q wave and an inverted T wave in lead III.[45] A normal electrocardiogram is very unusual in patients with acute PE.

The chest radiograph cannot be used to diagnose or exclude PE. It is useful in the differential diagnosis because it can detect pneumonia, pneumothorax, rib fracture, and congestive heart failure. Common abnormalities in patients with large PE include cardiac enlargement, pulmonary-artery enlargement, and oligaemia of the embolised lung.[46] In patients with small PE, a small wedge-shaped density at the periphery of the lungs indicates pulmonary infarction—"Hampton's hump".

Laboratory studies

Testing of the arterial blood for hypoxaemia and calculation of the alveolar–arterial oxygen gradient have been basic tools in the investigation of PE for a long time. However, comparison of blood gas results with pulmonary angiography has shown that hypoxaemia is not specific and does not serve as a useful triage tool in patients with suspected PE.[47] Furthermore, the alveolar–arterial oxygen gradient is normal in about 20% of patients with angiographically proven PE.[48]

The D-dimer blood test has practical usefulness in the diagnostic investigation of some patients with suspected PE. Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin.[49] Among most patients with PE, endogenous fibrinolysis (which was clinically ineffective in preventing thromboembolism) results in a rise in the amount of D-dimer circulating in plasma. By contrast, a normal D-dimer concentration has a very high negative predictive value for excluding the diagnosis of PE. However, raised D-dimer concentrations are not specific for PE and are observed among patients with myocardial infarction, pneumonia, sepsis, and cancer, during the second and third trimesters of pregnancy, and after surgery. Therefore, this test is most useful in the setting of the emergency department, because most patients already in hospital have raised D-dimer concentrations.

At the Emergency Department of Brigham and Women's Hospital, we introduced a requirement that the D-dimer ELISA was done for all patients with suspected acute PE.[50] After a year, we found that 559 of 1106 D-dimer assays had raised results and 547 were normal. Only two patients with normal D-dimer concentrations had PE. Thus, the sensitivity of the D-dimer ELISA for acute PE was 96·4%, and the negative predictive value was 99·6%. Therefore, chest CT and lung scanning are

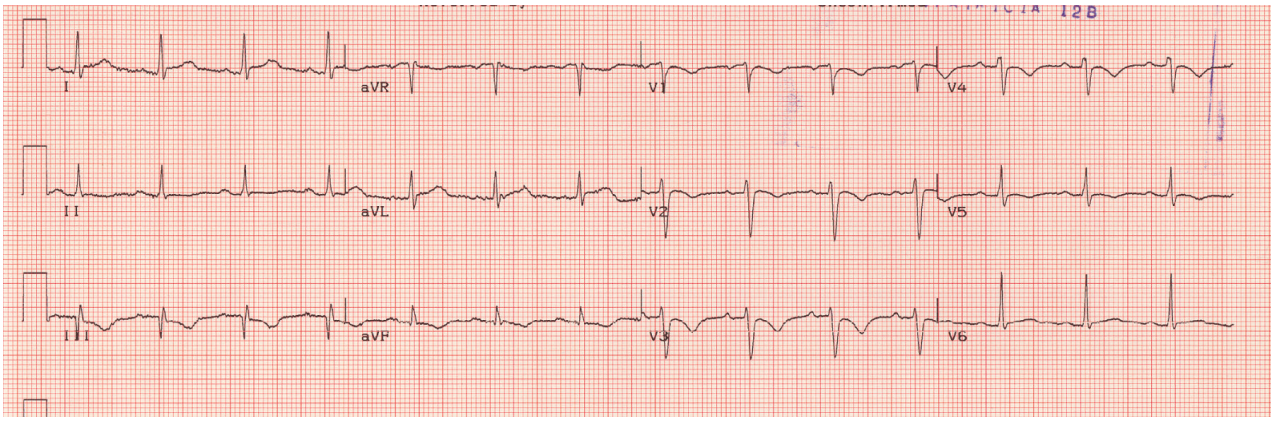


Figure 2: **Electrocardiogram of a haemodynamically stable 63-year-old woman**
The patient presented with acute PE and moderately severe right-ventricular dilatation and dysfunction on echocardiography. The electrocardiogram shows an S wave in lead I, Q wave in lead III, and T-wave inversion in leads III, AVF, and V1–V4 (the McGinn-White pattern), which is typical of right-ventricular strain due to massive PE.

not indicated for most patients with normal D-dimer results. This strategy may improve diagnostic efficiency and reduce costs. However, there is not yet enough evidence to stop the investigation for PE in patients with high clinical probability and normal D-dimer concentrations.[51,52] Such evidence may soon emerge.

Cardiac biomarkers

Cardiac biomarkers are being used with increasing frequency to assess prognosis in patients with newly diagnosed PE. In the Management Strategies and Prognosis of Pulmonary Embolism 2 study,[53] raised troponin concentrations were related to overall mortality and a complicated in-hospital course, presumably because troponin serves as a marker of right-ventricular microinfarction.

Low concentrations of pro-brain natriuretic peptide predict a benign clinical outcome in patients with acute PE.[54] Conversely, high concentrations of brain natriuretic peptide predict an adverse outcome.[55,56]

Imaging studies

The traditional imaging test for suspected PE has been the ventilation/perfusion lung scan. High-probability lung scans and normal lung scans are well validated with paired contrast pulmonary angiograms for diagnosis and exclusion of PE, respectively.[57] The main difficulty with lung scanning is that most scans are of intermediate or indeterminate probability. These non-diagnostic scans can cause consternation among clinicians who have either to undertake additional imaging tests or to decide empirically to diagnose or exclude acute PE.

Because of frustration with lung scanning and the clinical need for definitive diagnosis or exclusion of PE, chest CT is rapidly replacing lung scanning as the main imaging test for suspected acute PE. Lung scanning is becoming a second-line test reserved for patients with a history of allergy to contrast agent or renal insufficiency. Chest CT has two other advantages over lung scanning: thrombus can be directly visualised (figure 3); and alternative diagnoses can be established on lung parenchymal images that are not evident on chest radiography.

Chest CT takes less than 30 s with a single breath-hold to minimise respiratory motion. Although excellent vascular opacification of the pulmonary arteries with contrast agent can be achieved in most cases, the major limitation of conventional chest CT has been failure to detect PE beyond third-order pulmonary arterial branches.[58] In a prospective study with first-generation CT, the sensitivity of CT compared with angiography was 70%.[58] Other management studies are needed to show the safety of withholding anticoagulant therapy in patients with normal chest CT. With the newer multi-row detector CT scans, four slices can be acquired simultaneously during each rotation of the X-ray source. The total examination time is eight times faster than with conventional single-row detector systems. Fewer motion artifacts occur; resolution increases from 5·00 mm to 1·25 mm; and subsegmental vessels can generally be well visualised. Compared with conventional CT, the

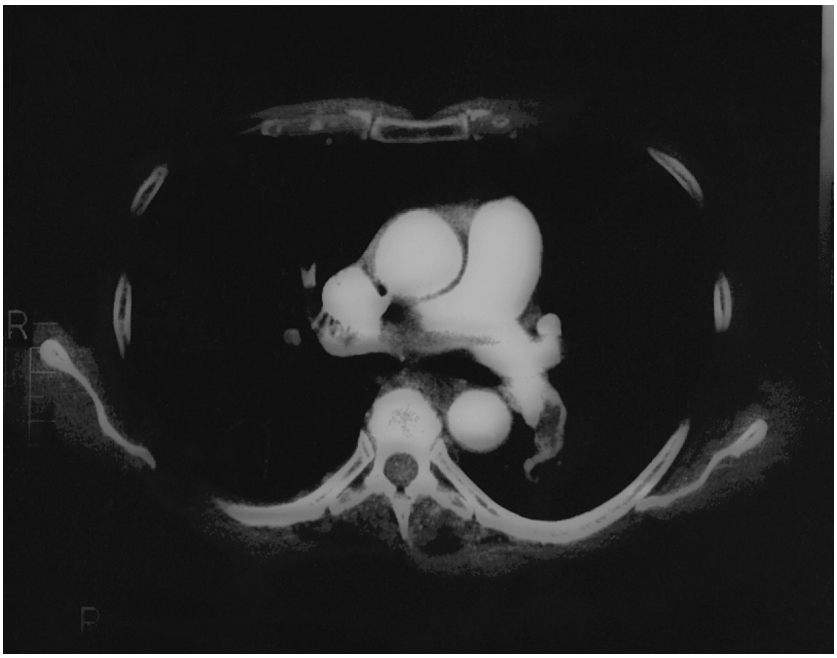


Figure 3: **Chest CT of the patient whose electrocardiogram is shown in figure 2**
The scan shows bilateral central PE, with larger thrombus burden in the left than in the right pulmonary artery.

sensitivity of multi-row detector scanners for acute PE increases from about 70% to more than 90%.[59] Nevertheless, few studies using multi-detector helical CT pulmonary angiography have been published. In future, contrast-enhanced magnetic resonance angiography may supersede chest CT because the contrast agents are safer and no ionising radiation is used.[60]

In the unusual circumstance that high clinical suspicion persists despite a normal or non-diagnostic chest CT, invasive pulmonary angiography or venous ultrasonography should be done. However, this latter strategy is of limited use; at the time of confirmed PE, the clot might have embolised completely from the leg veins and the diagnostic study of the legs will be normal.[61]

Echocardiography is also a disappointing diagnostic test for suspected PE. In a prospective study, echocardiography was normal and failed to identify 50% of patients with angiographically proven PE.[62]

Contrast pulmonary angiography has been the traditional gold standard for the diagnosis of PE, though this invasive test is now rarely done for diagnostic purposes. The complication rate is low when experts carry out this procedure.[63] Contrast pulmonary angiography can be used as the final diagnostic test whenever a diagnostic dilemma persists.[64]

The second trial by the Prospective Investigation of Pulmonary Embolism Diagnosis investigators, now under way, will assess suspected PE prospectively with lung scanning, venous ultrasonography of the legs, digital subtraction pulmonary angiography, contrast venography, and chest CT. The study will provide a thorough analysis of the efficacy of chest CT.[65]

The synthesis of history, physical examination, clinical setting, electrocardiography, chest radiography, D-dimer testing, and chest CT will in most cases lead to a definitive diagnosis or exclusion of PE. When clinical suspicion of PE is high and the necessary diagnostic tests are not immediately available, empirical treatment for PE should begin with anticoagulation in the absence of major contraindications, such as recent neurosurgery, while arrangements are made for further investigation.

Treatment

Risk stratification

Clinically, PE ranges from massive thromboembolism with cardiogenic shock to asymptomatic, anatomically small emboli without haemodynamic, respiratory, or other adverse physiological consequences. The key to appropriate therapy is risk stratification. Low-risk patients have an excellent prognosis with anticoagulation alone. High-risk patients might benefit from thrombolysis or embolectomy in addition to intensive anticoagulation. The Geneva prognostic index identified six factors that predict adverse outcome: cancer, heart failure, previous DVT, hypotension, hypoxaemia, and DVT on ultrasonography.[66] High troponin concentrations at the time of initial hospital admission signify right-ventricular microinfarction and also identify patients at high risk of a complicated hospital course.[53]

Echocardiography, although a poor diagnostic tool for PE, is excellent for rapid and accurate risk assessment.[67] Right-ventricular dysfunction identifies patients who despite initial haemodynamic stability develop cardiogenic shock and are at increased risk of death while in hospital.[68] In a prospective study of 209 consecutive patients with acute PE, 31% presented with echocardiographic evidence of right-ventricular dysfunction. Of those with abnormal echocardiograms, 10% developed PE-related shock, and 5% died while in hospital. Conversely, normotensive patients without right-ventricular dysfunction had an excellent short-term prognosis.[68] Persistent pulmonary hypertension and right-ventricular dysfunction on echocardiography done 6 weeks after the diagnosis of PE identify high-risk patients with an increased likelihood of developing overt right-ventricular failure over the next 5 years.[69]

Anticoagulation

Heparin anticoagulation is the foundation of therapy for acute PE. The traditional approach uses unfractionated heparin in an initial bolus of 5000–10 000 units followed by a continuous intravenous infusion, commonly started at 1250 U/h, to maintain a partial thromboplastin time in the target range of 60–80 s. A potential drawback of this strategy is failure to achieve adequate anticoagulation rapidly.[70] Use of nomograms, mostly weight based, can assist in reaching a therapeutic degree of anticoagulation more quickly than empirical dose adjustments.[71]

More recently, clinicians have used weight-based dosing of subcutaneously administered low-molecular-weight heparins, without dose adjustment, to achieve an immediate anticoagulant effect. The scientific basis of this strategy is that low-molecular-weight heparins provide high and sustained plasma antithrombin activity.[72] In clinical trials of acute PE, reviparin once daily[73] and tinzaparin once daily[74] have proven as effective and safe as unfractionated heparin as a bridge to oral anticoagulation. In a trial of acute DVT in which 32% of patients had confirmed PE, enoxaparin at 1·0 mg/kg twice daily or 1·5 mg/kg once daily was as safe and effective as unfractionated heparin.[75] In another DVT study, reviparin was more effective than unfractionated heparin in reducing the size of the thrombus and in preventing recurrent thromboembolism.[76]

The obvious potential major adverse effect of heparin is haemorrhage. Less apparent, but potentially more serious, is heparin-induced thrombocytopenia with thrombosis, which is more likely with unfractionated heparin than with low-molecular-weight heparins.[77] Patients with heparin-induced thrombocytopenia are at risk of massive PE; heparin must be withdrawn and treatment with a direct thrombin inhibitor, generally hirudin[78] or argatroban,[79] started. Heparin-induced thrombocytopenia is difficult to diagnose but generally develops 4–14 days after initial heparin exposure. However, patients who have received heparin within the previous 100 days can develop heparin-induced thrombocytopenia within a day of further heparin exposure.[80] Conversely, delayed-onset heparin-induced thrombocytopenia, occurring more than 2 weeks after heparin exposure, is being recognised with increasing frequency.[81]

Heparin provides immediate anticoagulation and serves as a bridge until oral anticoagulation with vitamin-K antagonists such as warfarin is fully effective. Oral agents mostly take at least 5 days of administration to achieve full therapeutic efficacy. During this initial period, heparin and oral drugs are given concomitantly.

The vitamin-K antagonists are adjusted to the prothrombin time, which is standardised and expressed as the international normalised ratio. For most patients with PE, the target value of this ratio is between 2·0 and 3·0. However, oral anticoagulants are difficult to manage because many interactions occur between different drugs and between drugs and various foods and alcohol.[82] Warfarin is generally initiated at a dose of 5 mg.[83] Some patients have a genetic mutation that causes very slow metabolism of the *S*-enantiomer of warfarin; most such patients require a lower maintenance dose (1–2 mg).[84]

Unfortunately, anticoagulated patients with similar international normalised ratios show significant variability in their tissue-factor coagulation response, leading to widely differing risks of bleeding or clotting with subtherapeutic or supratherapeutic international normalised ratio.[85] For patients with excessively high ratios, withholding of warfarin and administration of a 1 mg dose of oral vitamin K normally suffices to lower the ratio to the therapeutic range.[86] Strategies to improve the safety of oral anticoagulation dosing include management by a central anticoagulation clinic[87] or training patients to undertake point-of-care fingerstick testing of their own international normalised ratios followed by self-adjustment of the anticoagulant dose.[88]

Optimum duration and intensity of anticoagulation

For most patients with an initial PE after trauma, surgery, or immobilisation, 6 months of anticoagulation suffices. Three recent trials[89–91] have shown that after 6 months of standard anticoagulation for an idiopathic PE, patients benefit from indefinite-duration anticoagulation.

In the Prevention of Recurrent Venous Thromboembolism study,[89] recurrence rates with low-intensity warfarin (target international normalised ratio 1·5–2·0) were 67% lower than with placebo. There was no increase in major bleeding in the warfarin group. The Extended Low-intensity Anticoagulation for Idiopathic Thromboembolism study[90] compared standard-intensity (target international normalised ratio 2·0–3·0) with low-intensity warfarin. The rate of recurrent VTE in the standard-intensity group was 67% lower than that for the low-intensity group. However, the major bleeding rate did not differ between the groups. Another anticoagulation strategy to prevent recurrent VTE uses ximelagatran, an oral direct thrombin inhibitor.[91] Ximelagatran is currently investigational but holds promise because it can be given twice daily in a fixed dose without adjustment for between-drug or food-drug interactions. No routine coagulation monitoring is needed. In the Thrombin Inhibitor in Venous Thromboembolism III study,[91] ximelagatran reduced the rate of recurrent VTE by 84%.

Thrombolysis, embolectomy, and caval filters

Patients with PE in cardiogenic shock should undergo thrombolysis or embolectomy. More controversial is the management of patients with normal blood pressure who have indicators of poor outcome such as right-ventricular dysfunction. The Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism Trial 3, the largest randomised trial of thrombolysis plus heparin versus heparin alone, showed that alteplase (100 mg over 2 h) strikingly reduced the need to escalate therapy in hospital with measures such as mechanical ventilation, pressor agents, or thrombolysis.[92] Although critics might say that escalation of therapy is a soft endpoint, no one has launched a trial of similar or larger scope. I believe that on the basis of these findings, we should consider expanding the indications for thrombolysis to include this group of patients.[93] Nevertheless, because no mortality benefit has yet been demonstrated,[94] others believe that for the time being, thrombolysis should be limited to patients with massive PE.[95]

Patients with PE have a very high risk of intracranial haemorrhage after thrombolysis.[96] Therefore, they must be screened carefully for haemorrhagic risk. For those in whom aggressive intervention is warranted but haemorrhagic risk is high, the options of catheter[97] or surgical embolectomy are possibilities.[98]

Panel 2: **Specific prevention strategies**

Hospital inpatients with medical illness

Enoxaparin 40 mg daily[112] or dalteparin 5000 U daily

Unfractionated heparin 5000 U twice or three times daily[113]

Graduated compression stockings or intermittent pneumatic compression devices for patients with contraindications to anticoagulation

Combined low-molecular-weight heparin or unfractionated heparin plus graduated compression stockings or intermittent pneumatic compression devices for patients at very high risk

Consider surveillance venous ultrasonography for patients in medical intensive-care units[110]

General surgery

Unfractionated heparin 5000 U every 8 h, first dose 2 h before surgery, continued for 7 days (International Multicentre Trial) or low-molecular-weight heparin once daily

Cancer surgery

Enoxaparin 40 mg daily, first dose 10–14 h before surgery, continued for 28 days[114]

Total hip replacement

Enoxaparin 40 mg daily, beginning the evening before surgery, continuing out of hospital for 21–28 days[115,116]

Enoxaparin 30 mg twice daily, first dose 12–24 h after surgery, until hospital discharge[117]

Dalteparin 2500 U at least 4 h after surgery, then 5000 U daily until hospital discharge[118] or for 35 days[119]

Fondaparinux 2·5 mg 4–8 h after surgery, then at least 12 h after first dose, then daily for 5–9 days[120,121]

Warfarin daily, first dose 7·5 mg 24–48 h before surgery, adjusted to target international normalised ratio of 2·0–3·0[117]

Warfarin daily, first dose 5 mg the evening before surgery, adjusted to target international normalised ratio of 2·0–3·0 and continued for 4–6 weeks

Total knee replacement

Enoxaparin 30 mg twice daily, beginning 12–24 h after surgery, continued for an average of 9 days[122]

Fondaparinux 2·5 mg, first dose 4–8 h after surgery, second dose at least 12 h later, then daily for 5–9 days[123]

Hip fracture surgery

Fondaparinux 2·5 mg, first dose 4–8 h after surgery, second dose at least 12 h later, then daily for 5–9 days; if surgery is delayed longer than 24–48 h after admission, first dose should be given 10–14 h before surgery[124]

Aspirin 160 mg daily for 35 days as adjunctive prophylaxis[125]

Neurosurgery

Enoxaparin 40 mg daily, first dose 24 h or less after surgery, continued until hospital discharge, plus graduated compression stockings[126]

Craniotomy for brain tumour

Enoxaparin 40 mg daily or unfractionated heparin 5000 U twice daily, first dose on the morning after surgery, continued until hospital discharge, plus graduated compression stockings or intermittent pneumatic compression devices, plus predischarge venous ultrasonography[127]

For patients at high bleeding risk from anticoagulants and for those in whom PE has recurred despite intensive anticoagulation, insertion of a filter in the inferior vena cava is indicated. Although filters prevent most recurrent PE, patients with filters inserted are more likely than those

without to develop DVT during the next few years.[99,100] The introduction of retrievable vena-caval filters has provided the option of a temporary filter in patients who have transient contraindications to anticoagulation for conditions such as trauma, recent major surgery, or temporary major bleeding. These filters must be retrieved within 2 weeks or they endothelialise and become permanent.[101]

Prophylaxis

Long-term recurrent PE

After an initial VTE, patients are at risk of recurrence for at least 10 years.[102] Patients who develop PE after an operation have the lowest recurrence rates.[103] After withdrawal of anticoagulants, a normal D-dimer concentration has a high negative predictive value for recurrent thromboembolism.[104]

In-hospital primary prevention

Vigilant general physicians can improve outcomes by prescribing intensive and effective prophylaxis described in comprehensive consensus guidelines.[105,106] Computer-generated prompts can remind physicians to consider ordering prophylactic measures.[107,108] However, even when implemented, prophylaxis can be ineffective.[109] Therefore, patients at high risk may need surveillance by venous ultrasonography for detection of break-through venous thrombi in high-risk settings.[110,111]

High-risk patients benefit from combined mechanical and pharmacological prophylaxis (panel 2).[110–126] Mechanical measures consist of graduated compression stockings and intermittent pneumatic compression devices, which improve endogenous fibrinolysis[127] and increase venous blood flow. Pharmacological prophylaxis includes unfractionated heparin,[128,129] low-molecular-weight heparin,[130,131] fondaparinux,[119,120,132,133] and warfarin.[134] Aspirin confers incremental benefit.[125,135]

Postoperative PE commonly occurs several weeks after surgery.[136–138] There is convincing evidence to support 3–4 weeks of out-of-hospital prophylaxis after surgery for cancer[114] or high-risk orthopaedic surgery.[139–144]

Conflict of interest statement

I am an investigator in a current study supported by Aventis (manufacturer of enoxaparin). I am a consultant for Pfizer (manufacturer of dalteparin) and for Paion, which is testing an experimental thrombolytic agent for treatment of PE.

Source of funding

I received no funding to write this seminar other than a small payment from *The Lancet*.

References

1 Pineda LA, Hathwar VS, Grant BJ. Clinical suspicion of fatal pulmonary embolism. *Chest* 2001; **120:** 791–795.
2 Goldacre MJ, Roberts S, Yeates D, Griffith M. Hospital admission and mortality rates for venous thromboembolism in Oxford region, UK, 1975–98. *Lancet* 2000; **355:** 1968–69.
3 Oger E. Incidence of venous thromboembolism: a community-based study in Western France. *Thromb Haemost* 2000; **83:** 657–60.
4 Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; **158:** 585–93.
5 Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002; **162:** 1182–89.
6 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; **159:** 445–53.
7 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; **353:** 1386–89.
8 Nakamura M, Fujioka H, Yamada N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. *Clin Cardiol* 2001; **24:** 132–38.
9 van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. *Arch Intern Med* 1997; **157:** 2593–98.
10 Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. *N Engl J Med* 1992; **326:** 1240–45.
11 Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998; **279:** 458–62.
12 Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000; **160:** 3415–20.
13 Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; **107:** I9–I16.
14 Lapostolle F, Surget V, Borron SW, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med* 2001; **345:** 779–83.
15 Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; **277:** 642–45.
16 Rosing J, Middeldorp S, Curvers J, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet* 1999; **354:** 2036–40.
17 Vandenbroucke JP, Rosing J, Bloemenkamp KW, et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344:** 1527–35.
18 Parkin L, Skegg DC, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000; **355:** 2133–34.
19 Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet* 1999; **353:** 1258–65.
20 Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999; **340:** 9–13.
21 Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. *Thromb Haemost* 2002; **87:** 791–95.
22 Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
23 Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002; **288:** 872–81.
24 Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189–97.
25 Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet* 2002; **360:** 817–24.
26 Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100:** 3484–88.
27 Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349:** 146–53.
28 Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism: Duration of Anticoagulation Trial. *N Engl J Med* 2000; **342:** 1953–58.
29 Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000; **343:** 1846–50.
30 Prandoni P, Lensing AW, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992; **327:** 1128–33.
31 Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. *N Engl J Med* 2001; **344:** 1222–31.
32 Ariens RA, de Lange M, Snieder H, Boothby M, Spector TD, Grant PJ. Activation markers of coagulation and fibrinolysis in twins: heritability of the prethrombotic state. *Lancet* 2002; **359:** 667–71.
33 Price DT, Ridker PM. Factor V Leiden mutation and the risks for thromboembolic disease: a clinical perspective. *Ann Intern Med* 1997; **127:** 895–903.
34 Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic

distribution of factor V Leiden in 4047 men and women: implications for venous thromboembolism screening. *JAMA* 1997; **277:** 1305–07.
35 Simioni P, Prandoni P, Lensing AW, et al. The risk of recurrent venous thromboembolism in patients with an Arg506→Gln mutation in the gene for factor V (factor V Leiden). *N Engl J Med* 1997; **336:** 399–403.
36 De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med* 1999; **341:** 801–06.
37 Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996; **88:** 3698–703.
38 Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. *Circulation* 1999; **99:** 999–1004.
39 Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet* 1999; **354:** 407–13.
40 Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002; **346:** 752–63.
41 Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. *Ann Intern Med* 1998; **128:** 15–20.
42 Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. *Circulation* 2002; **106:** 1874–80.
43 Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest* 2002; **121:** 877–905.
44 Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; **83:** 416–20.
45 Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonary embolism with 12-lead ECG. *Chest* 2001; **120:** 474–81.
46 Pistolesi M, Miniati M. Imaging techniques in treatment algorithms of pulmonary embolism. *Eur Respir J* 2002; **19:** 28s–39s.
47 Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest* 1996; **109:** 78–81.
48 Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Chest* 1995; **107:** 139–43.
49 Kelly J, Hunt BJ. Role of D-dimers in diagnosis of venous thromboembolism. *Lancet* 2002; **359:** 456–58.
50 Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL, Goldhaber SZ. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. *J Am Coll Cardiol* 2002; **40:** 1475–78.
51 Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001; **135:** 98–107.
52 Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; **353:** 190–95.
53 Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation* 2002; **106:** 1263–68.
54 Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation* 2003; **107:** 1576–78.
55 ten Wolde M, Tulevski II, Mulder JW, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation* 2003; **107:** 2082–84.
56 Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. *Circulation* 2003; **107:** 2545–56.
57 PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990; **263:** 2753–59.
58 Perrier A, Howarth N, Didier D, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med* 2001; **135:** 88–97.
59 Qanadli SD, Hajjam ME, Mesurolle B, et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. *Radiology* 2000; **217:** 447–55.
60 Oudkerk M, van Beek EJ, Wielopolski P, et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. *Lancet* 2002; **359:** 1643–47.
61 Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997; **126:** 775–81.
62 Miniati M, Monti S, Pratali L, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. *Am J Med* 2001; **110:** 528–35.
63 Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992; **85:** 462–68.
64 van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism: a critical review. *Clin Radiol* 2001; **56:** 838–42.
65 Gottschalk A, Stein PD, Goodman LR, Sostman HD. Overview of prospective investigation of pulmonary embolism diagnosis II. *Semin Nucl Med* 2002; **32:** 173–82.
66 Wicki J, Perrier A, Perneger TV, Bounameaux H, Junod AF. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost* 2000; **84:** 548–52.
67 Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 2002; **136:** 691–700.
68 Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000; **101:** 2817–22.
69 Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. *Circulation* 1999; **99:** 1325–30.
70 Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy—heparin: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; **103:** 2994–3018.
71 Bernardi E, Piccioli A, Oliboni G, Zuin R, Girolami A, Prandoni P. Nomograms for the administration of unfractionated heparin in the initial treatment of acute thromboembolism: an overview. *Thromb Haemost* 2000; **84:** 22–26.
72 Agnelli G, Iorio A, Renga C, et al. Prolonged antithrombin activity of low-molecular-weight heparins: clinical implications for the treatment of thromboembolic diseases. *Circulation* 1995; **92:** 2819–24.
73 Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997; **337:** 657–62.
74 Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997; **337:** 663–69.
75 Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001; **134:** 191–202.
76 Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 2001; **344:** 626–31.
77 Warkentin TE. Heparin-induced thrombocytopenia: yet another treatment paradox? *Thromb Haemost* 2001; **85:** 947–49.
78 Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation* 1999; **99:** 73–80.
79 Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 2001; **103:** 1838–43.
80 Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; **344:** 1286–92.
81 Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; **136:** 210–15.
82 Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; **279:** 657–62.
83 Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; **159:** 46–48.
84 Higashi MK, Veenstra DL, Kondo LM, et al. Association between *CYP2C9* genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA* 2002; **287:** 1690–98.

85 Brummel KE, Paradis SG, Branda RF, Mann KG. Oral anticoagulation thresholds. *Circulation* 2001; **104:** 2311–17.

86 Crowther MA, Douketis JD, Schnurr T, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy: a randomized, controlled trial. *Ann Intern Med* 2002; **137:** 251–54.

87 Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding: a multicenter inception cohort study. *Thromb Haemost* 2001; **85:** 418–22.

88 Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet* 2000; **356:** 97–102.

89 Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **348:** 1425–34.

90 Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **349:** 631–39.

91 Schulman S, Wåhlander K, Lundström T, Clason SB, Eriksson H, for the THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; **349:** 1713–21.

92 Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, for the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002; **347:** 1143–50.

93 Goldhaber SZ. Thrombolysis for pulmonary embolism. *N Engl J Med* 2002; **347:** 1131–32.

94 Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. *J Am Coll Cardiol* 2002; **40:** 1660–67.

95 Dalen JE. Thrombolysis in submassive pulmonary embolism? No. *J Thromb Haemost* 2003; **1:** 1130–32.

96 Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. *Chest* 2001; **120:** 120–25.

97 Meyer G, Koning R, Sors H. Transvenous catheter embolectomy. *Semin Vasc Med* 2001; **1:** 247–52.

98 Aklog L, Williams CS, Byrne JG, Goldhaber SZ. Acute pulmonary embolectomy: a contemporary approach. *Circulation* 2002; **105:** 1416–19.

99 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med* 1998; **338:** 409–15.

100 White RH, Zhou H, Kim J, Romano PS. A population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. *Arch Intern Med* 2000; **160:** 2033–41.

101 Millward SF, Oliva VL, Bell SD, et al. Gunther Tulip retrievable vena cava filter: results from the Registry of the Canadian Interventional Radiology Association. *J Vasc Interv Radiol* 2001; **12:** 1053–58.

102 Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; **160:** 761–68.

103 Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med* 2000; **160:** 769–74.

104 Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost* 2002; **87:** 7–12.

105 Prevention of venous thromboembolism: International Consensus Statement Guidelines compiled in accordance with the scientific evidence. *Int Angiol* 2001; **20:** 1–37.

106 Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; **119** (1 suppl)**:** 132S–75S.

107 Durieux P, Nizard R, Ravaud P, Mounier N, Lepage E. A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. *JAMA* 2000; **283:** 2816–21.

108 Dexter PR, Perkins S, Overhage JM, Maharry K, Kohler RB, McDonald CJ. A computerized reminder system to increase the use of preventive care for hospitalized patients. *N Engl J Med* 2001; **345:** 965–70.

109 Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest* 2000; **118:** 1680–84.

110 Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA* 1995; **274:** 335–37.

111 Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest* 2003; **22:** 1933–37.

112 Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; **341:** 793–800.

113 Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; **83:** 14–19.

114 Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; **346:** 975–80.

115 Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996; **335:** 696–700.

116 Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996; **348:** 224–28.

117 Colwell CW Jr, Collis DK, Paulson R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty: evaluation during hospitalization and three months after discharge. *J Bone Joint Surg Am* 1999; **81:** 932–40.

118 Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double- blind, randomized comparison. *Arch Intern Med* 2000; **160:** 2199–207.

119 Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out- of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med* 2000; **160:** 2208–15.

120 Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002; **359:** 1715–20.

121 Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002; **359:** 1721–26.

122 Leclerc JR, Gent M, Hirsh J, Geerts WH, Ginsberg JS. The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: a multi-institutional cohort study of patients who underwent hip or knee arthroplasty. *Arch Intern Med* 1998; **158:** 873–78.

123 Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001; **345:** 1305–10.

124 Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001; **345:** 1298–304.

125 Pulmonary Embolism Prevention (PEP) Investigators. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin. *Lancet* 2000; **355:** 1295–302.

126 Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med* 1998; **339:** 80–85.

127 Comerota AJ, Chouhan V, Harada RN, et al. The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg* 1997; **226:** 306–13.

128 International Trial Investigators. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. *Lancet* 1975; **2:** 45–51.

129 Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; **318:** 1162–73.

130 Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2001; **161:** 1952–60.

131 Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002; **347:** 726–30.

132 Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the

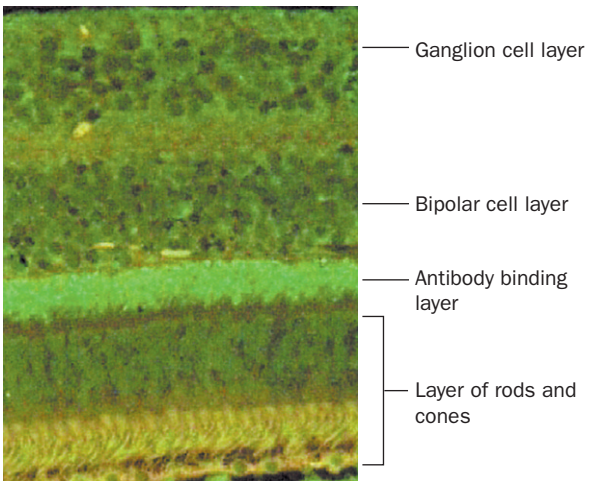
prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 2001; **344:** 619–25.
133 Bounameaux H, Perneger T. Fondaparinux: a new synthetic pentasaccharide for thrombosis prevention. *Lancet* 2002; **359:** 1710–11.
134 Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002; **162:** 1966–71.
135 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.
136 Bergqvist D, Lindblad B. A 30-year survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. *Br J Surg* 1985; **72:** 105–08.
137 White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998; **158:** 1525–31.
138 White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med* 2000; **343:** 1758–64.
139 Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; **358:** 9–15.
140 Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; **135:** 858–69.
141 Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty: a meta-analysis. *Thromb Haemost* 2001; **85:** 940–41.
142 Douketis JD, Eikelboom JW, Quinlan DJ, Willan AR, Crowther MA. Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Intern Med* 2002; **162:** 1465–71.
143 Sarasin FP, Bounameaux H. Out of hospital antithrombotic prophylaxis after total hip replacement: low-molecular-weight heparin, warfarin, aspirin or nothing? A cost-effectiveness analysis. *Thromb Haemost* 2002; **87:** 586–92.
144 White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998; **158:** 1525–31.

Clinical picture

Cachexia and poor night vision

A C Browning, W M Amoaku, S A Vernon, J Morgan, C E Thirkill

A 68-year-old woman with longstanding anorexia nervosa, malnutrition, and a past history of breast cancer, collapsed and was admitted to hospital. On examination she was cachectic, weighing 36·3 kg (BMI 11·1) with a blood glucose of 1·0 mmol/L. She gave a 2-week history of blurred vision, particularly in dim light, and complained of seeing flashing lights and having sore eyes. Ocular examination was unremarkable except for dry eyes. Electroretinography showed reduced rod function. We thought that she had vitamin A deficiency and so we gave her 25 000 U per day. After 2 weeks there was no improvement in her symptoms. Unfortunately, the patient's condition deteriorated and she died of metastatic breast cancer. Subsequent western blotting and indirect immunohistochemistry with the patient's serum on sectioned retina, showed a focus of antibody activity against selected retinal cells (figure), confirming that her ocular symptoms were due to cancer-associated retinopathy.



Department of Ophthalmology and Visual Sciences, Eye, Ear, Nose and Throat Centre, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK (A C Browning FRCOphth, W M Amoaku PhD, S A Vernon MD, J Morgan FRCOphth)**; University of California, Ophthalmology Research, Sacramento, CA, USA** (C E Thirkill PhD)