useful if practicable because this is invariably raised in acute myocardial infarction but is normal in pulmonary embolism.

A "paradoxical" arterial pulse, which falls at the onset of inspiration and rises on expiration by more than 15 mm. Hg—so that the change is detectable by the finger palpating the femoral pulse—is almost invariably present in acute cardiac tamponade from pericardial effusion. Unfortunately, it is also present sometimes in acute cardiac dilatation from any cause and is not infrequent in acute pulmonary embolism. Electrical alternans on the E.C.G. is a frequent sign of cardiac tamponade and is virtually a diagnostic finding.

Sudden internal haemorrhage as from a ruptured ectopic

pregnancy may cause collapse with air hunger and restlessness, tachycardia, and gallop rhythm. The arterial blood gases are usually normal but there may be hypoxaemia and the site of bleeding usually very rapidly becomes obvious.

To sum up, the mainstays of diagnosis of acute pulmonary embolism are alertness to the possibility, the observation of tachypnoea and hyperpnoea in an acutely ill patient, measurement of the arterial blood gases, and pulmonary angiography. The clinical findings, aided only by electrocardiography and chest radiography allow the diagnosis to be made with confidence in most patients, but angiography should still be carried out for confirmation and for establishment of severity.

Massive Pulmonary Embolism—Medical Management

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Acute pulmonary embolism may be minor or massive; the distinction is important not only in terms of the differing symptomatology but also because the prognosis and treatment of the two conditions are very different. *Minor* pulmonary embolism, presenting with the symptoms and signs of pulmonary infarction, carries a good prognosis. Treatment is primarily directed at the deep venous thrombosis with the aim of preventing either subsequent massive embolism or recurrent minor pulmonary embolism, which can lead to chronic thrombo-embolic pulmonary hypertension. No specific therapy is needed for the pulmonary infarct itself except in those rare cases which progress to cavitation.

Massive pulmonary embolism may be defined as embolism involving at least half of the major pulmonary arterial branches; the condition may be suspected clinically, but definition of severity requires special investigations (e.g., pulmonary arteriography). In general, such special investigations are probably rarely performed, and massive embolism tends to be diagnosed most often at necropsy. Thus we lack figures for both the incidence and the mortality of massive embolism against which treatment can be assessed and the stage is set for controversy. In many cases massive pulmonary embolism is rapidly fatal; of 100 patients dying from pulmonary embolism studied by Gorham¹³ 41 were dead within 10 minutes and 66 within 2 hours. While this high initial mortality may be reduced by resuscitative measures (external cardiac massage, vasopressor drugs, oxygen therapy, and, possibly, D/C countershock) it is unlikely that any specific medical treatment will be effective in this group, for whom emergency embolectomy by the Trendelenburg technique may still be the treatment of choice.¹⁴ There remain those patients who, having survived for 2 hours, will still die over the next few hours or days (29% in Gorham's series¹³) and in whom there is time for specific medical therapy.

Assessment of Treatment

Any series of patients seen 2 hours or more after proved massive pulmonary embolism will also include an unknown proportion who would survive *without* any specific treatment. Assessment of treatment in this group of patients thus requires either a method for assessing prognosis in any individual at the time of study, or admission of all such patients to a randomized trial of treatment. While attempts have been made to assess prognosis,^{15 16} these have not found wide accep-

tance, and probably a properly controlled trial will be required to show the advantages of any particular form of therapy. Such a controlled trial of heparin and a thrombolytic agent, urokinase, is in progress in the U.S.A.¹⁷ and a similar trial of heparin and another thrombolytic agent, streptokinase, is presently being planned in Britain. In neither trial is it regarded as ethical to include an untreated control group since D. W. Barritt and S. C. Jordan¹⁸ in a controlled trial, showed a significant reduction in the mortality from pulmonary embolism when anticoagulants (heparin and Nicoumalone) were given.

In this study 35 patients with a clinical diagnosis of pulmonary embolism and no contraindication to anticoagulant therapy were admitted to the trial. By random selection 19 patients were admitted to the control group, of whom 5 died and 5 others had non-fatal recurrences of embolism. In the treated group there was only one death, which was due, in part, to anticoagulant therapy. No further patients were admitted to the control group but 38 more patients were admitted to the treatment group, with one further death from anticoagulant therapy. Of the 5 deaths occurring in the control group one was due to recurrent embolism, one to cerebral infarction and two were from progressive necrosis of infarcted lung. Only one patient died from the uncomplicated effects of the initial massive embolism.

This trial thus highlights the effect of anticoagulants in reducing the risk of further embolism but leaves unclear the mechanism whereby anticoagulants prevented death from occurring as a result of the initial embolus. Nonetheless the absence of mortality from embolism per se in the treated group is in striking contrast to the 33% mortality for untreated pulmonary embolism reported by H. Zilliacus.¹⁹ The optimal dosage of heparin to be employed remains uncertain, while the minimum dose required to prevent clot formation or propagation appears to be that which doubles or trebles the clotting time,²⁰ the dose needed to achieve this effect may vary considerably and may be much higher in patients with thrombo-embolism. Recently C. Crane and his colleagues²¹ have advocated massive dosages of about 100,000 U.S.P. units/day given not only to achieve anticoagulation but also to abolish the bronchoconstriction which occurs in pulmonary embolism and is abolished by intravenous heparin²²—possibly by preventing serotonin release from platelets.²³ This action of heparin may explain the rapid clinical improvement observed by some authors after the first intravenous dose of heparin.^{21 24 25} At present it seems reasonable to give an initial intravenous dose of 10-15,000 units of heparin as part of the resuscitative measures for massive pulmonary embolism;²⁶ continued high-dose treatment must carry risks from bleeding which may be no less than those from thrombolytic therapy.

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Thrombolytic Treatment

Unlike anticoagulant therapy, treatment with thrombolytic drugs is aimed at accelerating lysis of existing emboli. Streptokinase was first used for pulmonary embolism by N. L. Browse and D. C. O. James²⁷ in four patients diagnosed as having pulmonary embolism, rapid clinical improvement being obtained in all. In 1968 J. Hirsh and his colleagues²⁸ reported 18 patients treated with streptokinase in whom there was angiographic assessment of severity of embolism before and after a 24-28 hour period of treatment. These authors made several very important observations. Firstly, angiographic and haemodynamic improvement were most marked in the four patients who had a 24-hour infusion of streptokinase and who had recent embolism uncomplicated by previous cardiorespiratory disease. Improvement was less apparent in the 12 patients who had either associated cardiorespiratory disease or clinical evidence of recurrent embolism. Secondly, the definite angiographic improvement seen after streptokinase contrasted with the lack of such improvement seen in patients after treatment with heparin; one such patient was then given streptokinase, with obvious clinical and angiographic improvement. Similar findings were reported by G. A. H. Miller *et al.*,²⁹ who obtained considerable haemodynamic and angiographic improvement following streptokinase in four patients with acute massive and two with acute minor pulmonary embolism, but little improvement in three patients with recurrent embolism. In one patient with acute massive pulmonary embolism there was no angiographic improvement after six days of heparin, but complete resolution occurred 48 hours after starting streptokinase.

Though spontaneous resolution of massive pulmonary embolism treated with heparin is known to occur,^{12,30} the rate of such resolution would appear to be significantly slower than can be obtained with streptokinase. Thus Tow and Wagner found complete resolution, as judged by lung scans, occurred in only 1 of 11 patients with severe or massive embolism (at the 60th day), the earliest partial resolution being observed at the eighth day.³¹ Recently J. E. Dalen and his co-workers used pulmonary arteriograms to assess resolution rate in 15 patients treated with heparin or venous ligation, or both, and found only minimal resolution at seven days.³² Similar findings have also been reported,³³ and our own experience indicates that, over a period of 3-7 days, little angiographic (though some haemodynamic) improvement occurred in a heparin-treated group but that resolution was almost complete in a group investigated after a 72-hour streptokinase infusion.³⁴

An initial dose of 600,000 units of streptokinase is infused over the first half hour followed by 100,000 units/hour for 72 hours. Although some patients, by reason of a high antistreptokinase titre, will require a higher dose, this standard dosage will provide effective fibrinolysis and with few side-effects in all but a few of the population.³⁵ In our experience 72 hours of this treatment is adequate for almost complete lysis of emboli and is probably accompanied by a lower incidence of complica-

tions than would follow a more prolonged period of treatment. Patients who at any time deteriorate while on such treatment or who, having been resuscitated from the initial event, fail to maintain an adequate circulation would be candidates for pulmonary embolectomy. Such clinical deterioration, "as evidenced by intolerably low levels of mean arterial pressure despite pressor support," is probably today the major indication for pulmonary embolectomy on cardiopulmonary bypass.²¹

The use of urokinase in pulmonary embolism has, at present, been confined to the U.S.A., where several reports of its efficacy in lysing pulmonary emboli have appeared.³⁶⁻³⁹ Again, these reports have indicated that urokinase results in more rapid lysis than does heparin treatment^{37,38} and that lysis is most rapid when there is no complicating cardiorespiratory disease.³⁹ Many of the patients successfully treated with urokinase would previously have been considered candidates for embolectomy.

Indications for Embolectomy

While it may be accepted that thrombolytic therapy hastens resolution of emboli it has yet to be shown that this reduces the mortality. Certainly a low or zero^{34,37} mortality has been reported for such treatment, and probably some critically ill patients will die unless there is rapid lysis and haemodynamic improvement; however, patients being treated in this way presumably represent those who, having survived long enough for investigation and treatment have a better prognosis than that overall for patients with massive pulmonary embolism. Even a controlled trial of treatment may not show a reduced mortality, since probably patients who deteriorate on medical treatment will be submitted to pulmonary embolectomy. While such deterioration is the main indication for embolectomy there is one other group for whom embolectomy may be indicated—namely, patients in whom there are contraindications to thrombolytic therapy. Such contraindications may apply equally to thrombolytic or anticoagulant therapy and are necessarily ill defined. They include a known bleeding diathesis, actively bleeding gastro-intestinal and genito-urinary lesions, severe renal or hepatic disease, severe systemic hypertension, pregnancy and recent surgery where bleeding would constitute a serious risk. Complications are almost solely due to bleeding from surgical wounds, venepuncture sites, etc., though febrile reactions can occur unless steroid cover is given.

The incidence of incomplete resolution with pulmonary hypertension as a late result of a single massive embolus is thought to be low but is unknown. Equally unknown is whether thrombolytic therapy, at the time of the initial embolus, will reduce the incidence of this serious complication. D. Phear found that 19 of 68 patients surviving pulmonary embolism had moderate to severe exertional dyspnoea and three of these patients died.⁴⁰ However, many of his patients may have had recurrent emboli—a condition recognized as predisposing to pulmonary hypertension. It is to prevent this serious complication of deep venous thrombosis that patients should be maintained on oral anticoagulants unless the factors predisposing to venous thrombosis no longer exist.

Surgical Management of Massive Pulmonary Embolism

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The operative removal of massive pulmonary emboli was first advocated by F. Trendelenburg in 1908,⁴¹ who showed experimentally that the principles underlying his operation were correct. He never himself, however, had a successful case to report, and it was his pupil M. Kirschner who recorded the first successful case treated by this technique in 1924.⁴² The

operative mortality remained exceedingly high, and it was only the development of cardiopulmonary bypass and the availability of pre-packed, sterile, disposable oxygenators that altered the picture of the treatment of this frequently lethal condition. Up to 1961 there were only sporadic reports of successful interventions, but then E. H. Sharpe performed the first operation involving the use of cardiopulmonary bypass.⁴³ Since then there have been numerous reports of

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