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Clinical course and late prognosis of treated subacute massive, acute minor, and chronic pulmonary thromboembolism

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Thirty-eight patients with pulmonary embolic disease, other than acute massive pulmonary embolism, have been assessed clinically and by right heart catheterisation and pulmonary arteriography or pulmonary embolectomy. In addition, complete follow-up information was obtained in 92 per cent (35) of patients 1 to 8 years after their initial illness. On the basis of the history and the pulmonary arteriographic appearances, three subgroups are described—subacute massive, acute minor, and chronic pulmonary embolism. Patients with subacute massive disease rarely had a well-defined predisposing factor to thromboembolism, had pulmonary arteriograms indistinguishable from acute massive embolism, but had long histories mainly of exertional dyspnoea which contrasts with the characteristically short, dramatic histories of patients with acute massive embolism. These patients had higher pulmonary artery pressures than patients with acute massive embolism. Patients with minor embolism usually had a well-defined predisposing cause to thromboembolism and normal haemodynamic findings. Patients with chronic embolism rarely had a well-defined predisposing factor to thromboembolism, had pulmonary arteriograms easily distinguishable from other forms of embolic disease, and had the highest pulmonary artery pressures.

The late prognosis of both acute minor and subacute massive embolism is good, recurrence of embolism is rare, and late pulmonary hypertension is not seen. In contrast, patients with chronic thromboembolic disease follow a progressively worsening course with persistent pulmonary hypertension, increasing right heart failure, and eventual death.

Pulmonary embolic disease has a wide variety of clinical presentations. The definition of subgroups facilitates the understanding of the clinical presentation, the haemodynamic disturbance, the natural history, and the effect of therapeutic interventions. The variables which are important in defining these subgroups are the severity of embolism, which can best be assessed by pulmonary arteriography; the duration of embolism, which can only be assessed from the history; and the presence or absence of additional cardiorespiratory disease other than pulmonary embolism.

We have defined four subgroups in terms of these variables; acute massive, subacute massive, acute minor, and chronic pulmonary embolism. Patients with acute massive pulmonary embolism present with a history of less than 48 hours' duration, have more than 50 per cent obstruction of major pulmonary arteries, and have usually had an acute episode of cardiovascular collapse. The clinical presentation of acute massive pulmonary embolism with and without additional cardiorespiratory disease, and the resultant haemodynamic disturbance, treatment, and long-term follow-up have previously been described (Sutton *et al.*, 1969; Miller and Sutton, 1970; Miller *et al.*, 1971; Miller *et al.*, 1977; Hall *et al.*, 1977).

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This study is concerned with three further subgroups of patients with pulmonary embolic disease.

Subacute massive pulmonary embolism: These patients present with longer histories (more than 2 weeks) with no acute episode of collapse, but they have massive pulmonary embolism (greater than 50% obstruction of major pulmonary arteries) shown at pulmonary arteriography or embolectomy.

Acute minor pulmonary embolism: Patients with less than 50 per cent obstruction of major pulmonary arteries and who usually have short histories (less than 2 weeks).

Chronic pulmonary embolism: Patients who, when first seen, have abnormal pulmonary arteriograms with grossly diminished uneven pulmonary perfusion, not resulting from identifiable recent thrombus, and irregular pulmonary vessels, sometimes with clot adherent to their walls. These

patients usually have long histories (several months, or even years).

Patients and diagnosis

The present series is made up of 38 consecutive patients with pulmonary embolic disease, other than acute massive embolism, referred for treatment at the Brompton Hospital between 1965 and 1973. None of these patients had other significant cardiorespiratory disease. The diagnosis of embolic disease was confirmed at pulmonary arteriography in 36 patients; in the remaining 2 patients, both of whom had subacute massive pulmonary embolism, the diagnosis was confirmed at embolectomy. Patients were divided into three groups, according to the length of their histories and the pulmonary arteriographic appearances. The main features of these three diagnostic groups are summarised in Table 1. Pulmonary arteriograms were scored (Miller *et al.*, 1971; Hall *et al.*, 1977), taking into account both involvement of major pulmonary arteries by thrombus and reduction of zonal flow. A theoretical score of 34 represents involvement of all major arteries by thrombus and total reduction of flow to all zones, while a score of 0 represents a normal pulmonary arteriogram. An arteriographic score of greater than 17 represents massive embolism. The method of late follow-up was as follows. Patients were recalled and examined by two of the authors. Particular notice was taken of symptoms or signs that might suggest pulmonary hypertension. A chest *x*-ray film, 12-lead electrocardiogram,and perfusion lung scan (^{99m}Technetium labelled albumin macroaggregates) were carried out.

Table 1 *Composition of three diagnostic groups and their treatment and mortality*

	Subacute massive	*Minor*	*Chronic*
Number of patients (female, male)	13 (7F, 6M)	17 (12F, 5M)	8 (6F, 2M)
Age (y)—Mean	45	43	49
Range	24–65	23–66	42–68
Duration of symptoms	2–12 w	1 d–2 w	3 w–5 y
Treatment of initial episode			
Heparin	2	12	0
Streptokinase	7	4	2
Embolectomy	4	0	0
Oral anticoagulants	0	1	6
Early deaths	4	1	0

Results

CLINICAL COURSE BEFORE DIAGNOSIS

The 13 patients with subacute massive pulmonary embolism had symptoms for longer than 2 weeks. The most frequent symptom was progressively increasing dyspnoea, with decreasing effort tolerance (8 patients), often associated with episodes of pleuritic chest pain (7 patients), and haemoptysis (4 patients). No patient had an isolated episode of cardiovascular collapse. These symptoms contrast with those of patients with acute massive pulmonary embolism (Hall *et al.*, 1977), in whom the history was short, with an episode of cardiovascular collapse. The 17 patients with minor embolism had shorter histories (up to 2 weeks), and complained of pleuritic chest pain (15 patients), haemoptysis (4 patients), and dyspnoea (3 patients). In the 8 patients with chronic thromboembolic pulmonary hypertension, the history was usually much longer, and in 6 patients, ranged between 6 months and 5 years. Two patients, however, had shorter histories: one patient had pleuritic pain for 3 weeks, and the other had 6 weeks of progressive dyspnoea. These patients with shorter histories had similar ateriographic findings to the other 6 patients. Of the 6 patients with long histories, 5 had suffered from progressive dyspnoea and decreasing exercise tolerance and only 1 had had recurrent episodes of pleuritic chest pain.

PREDISPOSING FACTORS

The majority of patients (14 of 17=82%) with minor pulmonary embolism had well-defined factors predisposing to the development of thromboembolic disease, for example, recent surgery (8 patients), trauma (4 patients), and oestrogen/progesterone contraceptive preparations (2 patients). In contrast, only 4 of the 13 patients (31%) with subacute massive pulmonary embolism had a well-defined predisposing cause for thromboembolism (oral contraceptives). No patient with chronic thromboembolic disease had a well-defined predisposing factor.

PULMONARY ARTERIOGRAPHY AND EMBOLECTOMY FINDINGS

The mean initial arteriographic scores for each group are shown in Table 2. All patients with minor embolism had fresh thrombus in the pulmonary arteries (Fig. 1). Though the clinical course of patients with subacute massive pulmonary embolism was very different from that of patients with acute massive pulmonary embolism, the pulmonary arteriographic appearances in 8 of the patients with subacute massive pulmonary emboli

and the embolectomy findings in 1, were those of fresh thrombus in the pulmonary arteries, indistinguishable from the appearances seen in patients with acute massive pulmonary embolism (Fig. 2). Three patients in the subacute massive pulmonary embolism group had arteriographic evidence of both old adherent thrombus and new free thrombus, and the remaining patient had mainly new thrombus causing the pulmonary artery obstruction, but also some slight narrowing of a few pulmonary arteries without definite evidence of old thrombus. All patients with chronic thromboembolic pulmonary hypertension had strikingly abnormal pulmonary arteriograms (Fig. 3). None had evidence of new thrombus in the pulmonary arteries, but 2 patients had old adherent thrombus. In all, the most conspicuous abnormality was gross uneven narrowing of major pulmonary arteries; this abnormality did not occur in any patient with subacute or minor pulmonary embolism.

HAEMODYNAMICS

Pulmonary artery systolic and mean pressure in each group differed significantly from all other groups, and in minor pulmonary embolism were not significantly different from normal (Table 2).

CLINICAL COURSE DURING INITIAL HOSPITAL ADMISSION

The treatment received by each group of patients during their hospital stay is shown in Table 1. The number of patients receiving each treatment is too small to assess the relative merits of the different forms of treatment used. There were no early hospital deaths in the chronic group; treatment with streptokinase infusion was attempted in two of these patients, in whom the pulmonary arteriogram showed old adherent thrombus as well as grossly uneven pulmonary vessels, but this treatment did not alter arteriographic appearances, or lower the pulmonary artery pressure. One patient in the minor group, who had an initial arteriographic index of 15, died from a brain-stem haemorrhage while receiving streptokinase.

Four patients in the subacute massive pulmonary embolism group were treated by pulmonary embolectomy. One patient, seen early in the series, had pulmonary embolectomy as the initial treat-

Table 2 *Results of pretreatment right heart catheterisation and pulmonary arteriography (mean ±SEM)*

	N	*Pulmonary artery systolic pressure (mmHg)*	*Pulmonary artery mean pressure (mmHg)*	*Pulmonary arteriogram severity index*
Minor	17	28·4 ±2·1†	19·0 ±1·5†	9·5 ±1·0†
Acute massive*	42	41·0 ±1·2†	28·0 ±0·75†	24·6 ±0·4
Subacute massive	11	54·0 ±5·0†	35·0 ±3·0†	21·8 ±1·1
Chronic	8	85·2 ±5·7†	48·0 ±2·2†	20·9 ±1·0

*These patients are those with acute massive pulmonary embolism but without cardiorespiratory disease described by Hall *et al.* (1977), and are included for comparison.
†Denotes that this group is significantly different ($P < 0.05$) from each of the three other groups (unpaired t test).

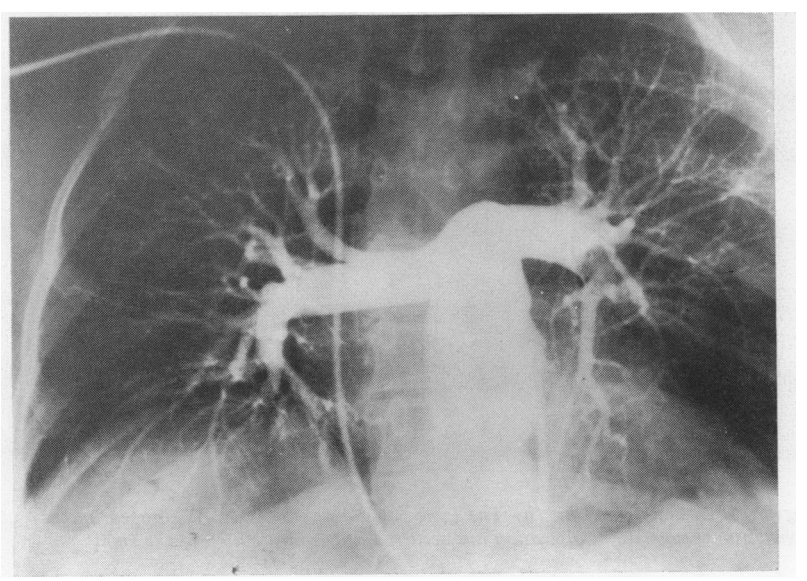

Fig. 1 *The pulmonary arteriogram of minor embolism. The embolism involves less than 50 per cent of the pulmonary arteries.*

ment. This patient suffered a cardiac arrest at the induction of anaesthesia, and we now recognise this to be an avoidable complication (Miller *et al.*, 1977). It is unlikely that we would now recommend surgery for such a patient, but would give either streptokinase or heparin infusion. Two patients who showed little arteriographic improvement after 6 and 8 days of heparin treatment were subjected to embolectomy. Both survived the operation, but one died of a fatal recurrent embolism a week after the operation. We would not now recommend pulmonary embolectomy for either of these patients. The fourth patient was treated by embolectomy because of severe gastrointestinal bleeding during heparin therapy. This patient, unfortunately, died during the operation, but we

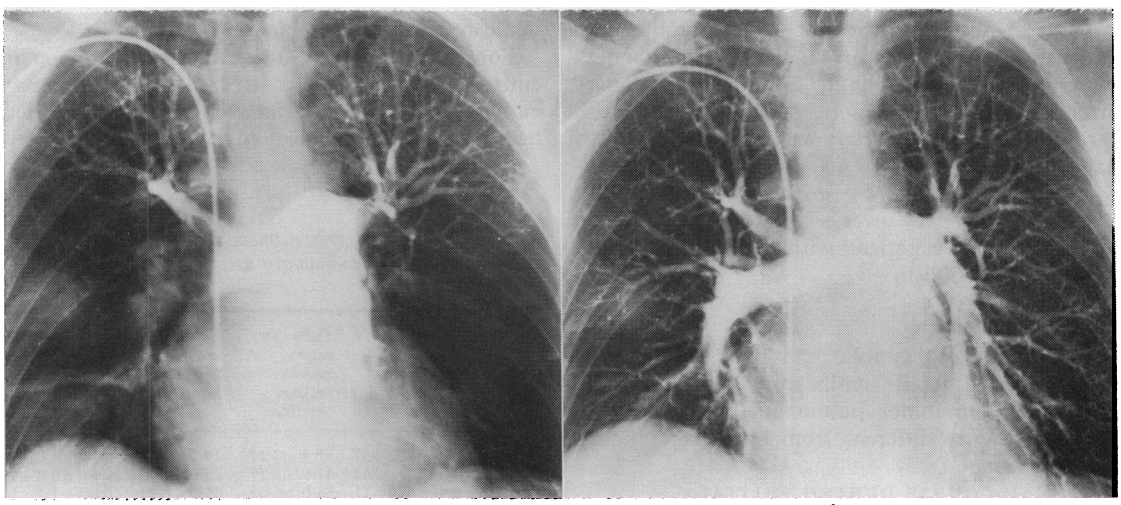

Fig. 2 *(a) The pulmonary arteriogram of subacute massive embolism. The embolism involves more than 50 per cent of the pulmonary arteries. (b) The same patient 3 days later, after treatment with streptokinase. The response is similar to acute massive pulmonary embolism.*

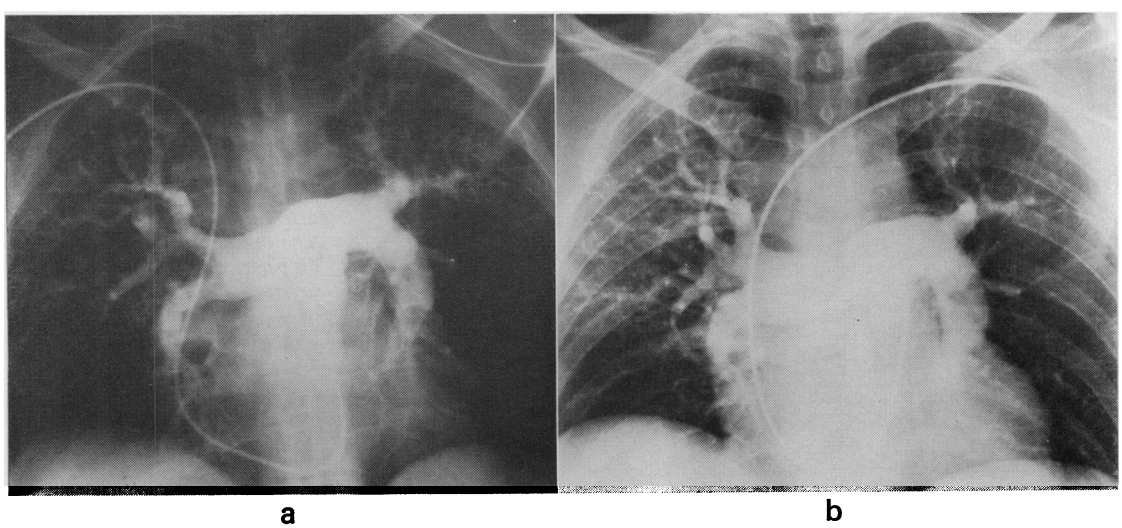

Fig. 3 *(a) The pulmonary arteriogram of chronic embolism. (b) The same patient 3 years later. The appearances remain those of chronic pulmonary embolism though slight alteration has occurred at the bifurcation of the right pulmonary artery.*

would recommend embolectomy if faced with such a patient again. Therefore, of the 3 deaths in patients who had pulmonary embolectomy, 2 were directly related to the operation, and 1 of these 2 was probably avoidable in the light of our current knowledge.

LATE FOLLOW-UP

Complete follow-up was obtained for 35 of the original 38 patients (92%). Details and duration of follow-up in the 33 patients who survived initial treatment are summarised in Table 3. The clinical course of the patients originally diagnosed as having chronic thromboembolic pulmonary hypertension was very different from that of the other two groups. Four (50%) of these patients died during the follow-up period, and 3 of these deaths resulted from progressive right ventricular failure. The fourth patient died elsewhere during an attempted surgical clearance of the pulmonary arteries. No patient in this group, surviving or dead, had clinically identifiable recurrent pulmonary embolism or infarction during the follow-up period. Of the 4 patients who survived to follow-up, 3 had severe dyspnoea and fatigue on exertion, and the same 3 patients had physical signs of pulmonary hypertension and electrocardiographic evidence of right ventricular hypertrophy. The fourth survivor (case 7 in Table 5) was totally asymptomatic and had a normal electrocardiogram. All 4 survivors in this group had grossly abnormal perfusion lung scans with multiple perfusion defects (Fig. 4). Similar findings have been shown in perfusion scans in patients with chronic thromboembolic disease by Wilson *et al.* (1973). The chest *x*-ray films of all patients in the chronic group showed enlarged main and right pulmonary arteries and cardiomegaly (Table 4). Late pulmonary arteriograms and right heart catheterisations in 2 patients, including case 7 who was asymptomatic (Table 5), showed that the arteriographic index of severity had fallen while pulmonary hypertension remained unaltered. The significance of the changes in the severity index are uncertain, since it is extremely difficult to assess this index accurately in this group of patients.

The clinical course of patients with minor and subacute massive pulmonary embolism during the follow-up period was strikingly different from that seen in patients with chronic disease. There were no late deaths in either group resulting from thromboembolic disease. There was one late death in each group from malignant disease; in neither case was this evident at the time of the initial illness. Three patients, all in the minor group, had episodes of pleuritic chest pain, one associated with haemoptysis, possibly caused by a recurrent embolism. These occurred 1, 2, and 5 years after the initial episode. At follow-up, 2 of these patients had normal lung scans and chest *x*-rays, and the third, case 3 (Table 5), had a normal pulmonary arterio-

Table 3 *Details of late deaths and follow-up (follow-up was 92 per cent)*

	Subacute massive	*Minor*	*Chronic*
Survivors of initial episode	9	16	8
Late death	1	1	4
Lost to follow-up	1	2	0
Seen at follow-up	7	13	4
Duration of follow-up (y)			
Median	3	5	3, 4, 5 and 7
Range	1–6	1–8	

Table 4 *Results of perfusion lung scans and chest* x-*rays at follow-up*

	Subacute massive	*Minor*	*Chronic*
Lung scans (no.)	6	12	4
Normal	2	8	0
Single perfusion defect	2	2	0
Multiple perfusion defects	2 (33%)	2 (17%)	4 (100%)
Chest x-rays (no.)	7	13	4
Enlarged main or right pulmonary artery (17 mm)	0	0	4 (100%)

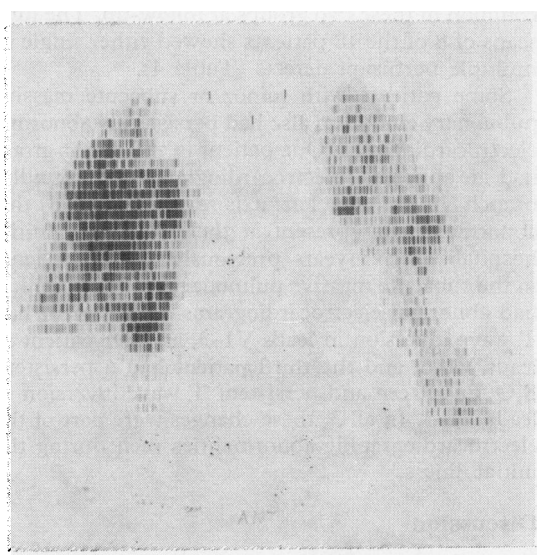

Fig. 4 *The perfusion lung scan of the same patient as Fig. 3, with chronic pulmonary embolism.*

Table 5 *Results of late cardiac catheterisation and pulmonary arteriography*

	Pulmonary artery systolic pressure (mmHg)			*Pulmonary arteriogram severity index*			*Interval between early and late studies (mth)*	*Lung scan follow-up*
	1	*2*	*3*	*1*	*2*	*3*		
Subacute massive								
Case 1	55	38	30	25	23	5	4	M
Case 2	75	44	35	28	19	0	5	N
Minor								
Case 3	55	34	23	16	10	0	5	—
Case 4	31	24	22	14	16	1	2	N
Case 5	30	21	23	4	9	0	11	N
Chronic								
Case 6	66	—	65	21	—	12	24	M
Case 7	70	—	70	23	—	15	84	M

The pulmonary artery pressures and arteriographic scores in the 7 patients in whom late cardiac catheterisation and pulmonary arteriography were performed.
Investigation 1, pretreatment; 2, immediately after initial treatment; 3, late study.
Lung scans were performed at follow-up (N, normal; M, multiple perfusion defects).

gram with normal right heart pressures and a normal chest *x*-ray film. No patient developed pulmonary hypertension during the period of follow-up, as assessed by physical signs, chest *x*-ray films, or electrocardiograms, or had developed significant cardiorespiratory symptoms. Late right heart catheterisation and pulmonary arteriography were performed mainly in patients who had shown a poor response to initial therapy. Despite this, pulmonary hypertension resolved and pulmonary arteries cleared in these patients (Table 5). One patient in the subacute massive group had a slightly raised pulmonary artery pressure, and the other, minor residual pulmonary arteriographic abnormalities. Persistent lung scan abnormalities were common in these two groups at follow-up. The lung scans of 8 of the 18 patients showed either single or multiple perfusion defects (Table 4).

Some patients with minor or subacute massive pulmonary embolism also had persistently abnormal electrocardiograms. One patient in the minor group had an abnormal electrocardiogram (right bundle-branch block and left axis deviation) and this abnormality was present at the time of his initial hospitalisation 3 years previously. Three patients in the subacute massive pulmonary embolism group had abnormal electrocardiograms. One patient had T wave inversion in leads V1–3, another patient in leads V1–6, and the third patient had a persistent $S_1Q_3T_3$ pattern and persistent T wave inversion in leads V1–3. In all 3, these changes were part of the electrocardiographic abnormalities seen during the initial illness.

Discussion

Although most clinicians are familiar with patients who present with subacute massive pulmonary embolism, the haemodynamic consequences and arteriographic appearances of this group have not been described previously, or contrasted with those of other forms of pulmonary embolic disease. These patients had pulmonary artery, systolic, and mean, pressures which were significantly higher than those in a group of patients with acute massive pulmonary embolism, in whom the extent of pulmonary artery obstruction was essentially the same. The mean systolic and pulmonary artery pressures of subacute massive pulmonary embolism were significantly lower than those of a group of patients with chronic thromboembolic pulmonary hypertension, in whom the extent of pulmonary artery obstruction was similar (Table 2). These findings suggest that the subacute course of pulmonary artery obstruction allows the right ventricle time to adapt to the increased load and to generate a higher pressure than it can achieve when acutely stressed. In chronic thromboembolic disease with long-standing obstruction to right ventricular ejection, the right ventricle generates even higher systolic pressures.

The main object of this and our previous study (Hall *et al.*, 1977) was to assess the incidence of serious long-term sequelae in patients with documented pulmonary embolic disease. We were particularly interested to know if recurrence and non-resolution were common and how often chronic thromboembolic pulmonary hypertension developed. In our previous study, which concerned the patients with acute massive pulmonary embolism, we found that recurrence and non-resolution were rare, and did not find evidence of chronic thromboembolic pulmonary hypertension in any of the 56 survivors, despite a follow-up period ranging from 1 to 9 years (median 5 years). These patients with acute massive embolism and those with minor embolism described here usually had

well-defined predisposing factors to the development of thromboembolic disease, which were later eliminated, and short histories. They received energetic treatment early in their illness. Therefore, it is perhaps not surprising that they should have a good prognosis if they survive the initial embolism. This was not true of the patients with subacute massive embolism, since many of these patients had no identifiable predisposing cause, long histories, and started treatment relatively later in the course of their disease. These patients were, therefore, of great interest, since they might be expected to be at particular risk of non-resolution and late pulmonary hypertension. Yet, in spite of these adverse factors, we found no evidence that the late prognosis was any worse in these patients than in those with acute massive or minor embolism.

Our finding of a poor prognisis in chronic thromboembolic disease is in agreement with several previous reports (Fowler *et al.*, 1966; Goodwin *et al.*, 1963; Fleischner, 1967). Our finding of a good long-term prognosis in all other groups of pulmonary embolism is in agreement with Paraskos *et al.* (1973) who also studied the late prognosis of arteriographically documented pulmonary embolism. These authors noted only one late death from pulmonary hypertension, and this patient in their series undoubtedly had chronic embolic disease when first seen. In contrast with these favourable results, Phear (1960) found that serious symptoms, often related to chronic thromboembolic disease, were frequently found after acute embolism of all types, while deSoyza and Murphy (1972) reported that mild pulmonary hypertension was often found at late follow-up in patients who had suffered acute pulmonary embolism. Though these findings seem contradictory, it must be remembered that Phear studied patients in whom the diagnosis was established without the aid of cardiac catheterisation or pulmonary arteriography, and many of the patients subsequently developing symptoms may well have had chronic thromboembolic disease when first seen. In contrast, the diagnosis was confirmed in all our patients with minor, subacute massive, and acute massive pulmonary embolism by pulmonary arteriography or at pulmonary embolectomy, and consequently, patients who had chronic thromboembolic disease were not included in these diagnostic categories. Our patients with chronic embolism, who have been shown to have a poor prognosis, were often referred with a diagnosis of acute embolism, and the true diagnosis was established only by careful history taking and pulmonary arteriography. These patients with chronic disease might have been grouped with the others had not the diagnosis of chronic embolism been established by this process. If this separation had not been made, our results might have been similar to those of Phear. The findings of deSoyza and Murphy (1972) are more difficult to compare, since, though they state that pulmonary embolism was arteriographically documented, the arteriographic findings were not described. Their patients also showed frequent recurrence of embolism.

Paraskos *et al.* (1973) attributed the satisfactory prognosis to long-term anticoagulation and inferior vena caval ligation, both of which were frequently employed in their series. We cannot comment on the role of anticoagulation for several months after the acute event, since we do not have a control group in which this treatment was not employed. The results in our patients do, however, show that inferior vena caval ligation is not necessary to prevent either the recurrence of embolism or the development of chronic thromboembolic pulmonary hypertension.

Although the prognosis of all our patients other than those with chronic thromboembolism was good, patients with both minor and subacute massive pulmonary embolism, as well as patients with acute massive embolism (Hall *et al.*, 1977), frequently had abnormal perfusion lung scans at follow-up. This suggests that permanent obstruction to small vessels in the lungs has occurred, though the large pulmonary vessels have cleared: the arteriographic appearances at follow-up confirm normal large pulmonary vessels. The absence of serious symptoms or pulmonary hypertension suggests that small vessel damage is not of poor prognostic significance, at least over the first 5 to 10 years. The fact that lung scan and electrocardiographic abnormalities may persist must be remembered when attempting to make a diagnosis of recurrent pulmonary embolism, particularly if previous records are not available.

Although we have not observed chronic thromboembolic pulmonary hypertension develop in any of our patients, we need to ask whether this disease occurs as a result of unresolved pulmonary emboli. Clinical evidence and experience suggest that it can (Goodwin *et al.*, 1963; Fowler *et al.*, 1966; Fleischner, 1967); however, its development as a result of embolism proven at angiography in an initially normal pulmonary vasculature has not been documented. The possible reasons for this and why we have not observed it are numerous. Chronic thromboembolic pulmonary hypertension is a rare disease (Owen *et al.*, 1953) whereas acute pulmonary embolism is common, and, therefore, chronic embolism can only occur in an extremely small number of patients who have had acute embolism.

Chronic thromboembolic pulmonary hypertension is nearly always diagnosed late in its course, when pulmonary vascular obstruction is severe, as in our 8 patients, and the preceding embolic episodes are often so minor that they did not attract attention, or are wrongly diagnosed as other chest disease (Fleischner, 1967). Therefore, its development is not documented because symptoms warranting investigation did not occur until the disease was well advanced. Though this may be the sequence of events in some cases of chronic thromboembolic pulmonary hypertension, there has been a tendency to ascribe these cases of pulmonary hypertension to embolism (Blount, 1967) and other possible mechanisms have been ignored. A considerable number of patients in every series with this disease (Goodwin *et al.*, 1963; Fowler *et al.*, 1966), as well as in the present group, have not shown any clinical evidence at any time of the presumed causative emboli. In view of our failure to find this complication at follow-up of proven embolic disease, the possibility exists that at least some cases of chronic thromboembolic pulmonary hypertension result from thrombosis in abnormal pulmonary arteries rather than from embolism.

Whatever may be the aetiology of chronic thromboembolic pulmonary hypertension, occasional patients have been noted to improve on long-term anticoagulant therapy (Goodwin *et al.*, 1963; Wilhelmsen *et al.*, 1972). Though we did not see clinical improvement in our chronic patients, it is essential that the diagnosis of chronic thromboembolic pulmonary hypertension be confirmed by arteriography and anticoagulant treatment initiated since this is the only available treatment which may occasionally help to prevent the progression of this disease.

The division of patients with pulmonary embolic disease into the subgroups described helps in the understanding of the wide range of clinical presentations and haemodynamic disturbances that may occur as a result of pulmonary embolism. The long-term prognosis of patients surviving treated minor or subacute massive embolism is good, in contrast to the poor prognosis of patients with chronic thromboembolic pulmonary hypertension.

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