renal function in a fourth. Since pyuria is of little value in diagnosing infection in this condition, reliance must be placed solely on regular midstream urine culture. The 14% of positive cultures we have obtained includes "repeats" and is no higher than in some surveys of hospital female patients without known renal disease. Bladder infection, however, is a much greater hazard in these patients with necrotic tissue in the renal pelves than in the general population, and we have treated positive midstream urine cultures on suspicion.

We thank the many family doctors, physicians, and surgeons who have supplied details of the early history of these patients. We are grateful to Professor A. L. Latner, Dr. A. Cassells-Smith, Dr. R. Ashcroft, Professor A. G. Hepplestone, Dr. C. K. Warrick, Dr. T. R. Harlen, and their respective staffs for the biochemical, pathological, and radiological data quoted.

ADDENDUM.—Since submitting this report one patient (Case 2) has died from myocardial infarction and pulmonary oedema. The kidneys showed typical changes of analgesic nephropathy with calcified papillae and a combined weight of only 90 g.

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Prevention of Recurrent Pulmonary Embolism

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British Medical Journal, 1969, **3**, 382–386

Summary: Fifty patients have been studied by bilateral phlebography following their first, or sometimes recurrent, pulmonary embolus. Nineteen were found to have fresh loose peripheral thrombus, and in eight of them the thrombus looked big enough to cause a major pulmonary artery obstruction and death. These 19 patients were treated by vein ligation in addition to anticoagulants.

The incidence of recurrent embolism in the trial group is significantly lower than that found in a retrospective study of 50 patients treated with anticoagulants only. It is suggested that anticoagulants will not prevent all recurrent pulmonary emboli, and that phlebography, and if necessary surgery, should be part of the routine investigation and treatment of all patients after their first pulmonary embolus.

Introduction

Pulmonary embolism kills at least 2,500 people in Great Britain every year (Registrar General Report, 1967). It contributes towards the deaths of many more, and a proportion of these deaths follow the second or third embolus. Barker and Priestly (1942) reviewed the natural history of 1,665 cases of post-operative thromboembolism and found that 30% of patients who survived a pulmonary embolus had a second embolus; this was fatal in 19%.

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It is claimed (Table I) that the use of intravenous heparin will reduce the mortality rate after embolism and also the incidence of second emboli, but the published facts do not entirely support this view. For example, though Barritt and Jordan (1960) had no fatal recurrences in a series of 54 patients treated with heparin and nicoumalone, Ochsner *et al.* (1951) had a second fatal embolus rate of 11.7%. Nevertheless, the figures from almost every publication support the claim that heparin reduces the mortality rate after embolus. The effect of anticoagulants on the non-fatal recurrence rate is not clear. It is obvious from Table I that though the number of recurrences may be reduced they still occur frequently. Those who believe heparin to be the best treatment for pulmonary embolism often suggest that anticoagulation was insufficient in the series with high recurrence rates. This may be true, but it is noteworthy that the clotting-time was not measured in the majority of the papers mentioned in Table I, and there is no correlation between those that measured the effect of heparin and the results.

The alternative to anticoagulants is vein ligation. Blind bilateral superficial femoral vein ligation and vena cava plication and ligation have all been tried (Table I) and have had significant recurrence rates. Vena cava ligation is the most effective surgical measure but is associated with a definite incidence of leg swelling and postphlebotic complications (Dale, 1962). Both Fontaine (1957) and Coon *et al.* (1958) mention the possibility of combining anticoagulants and vein ligation, but no results of this approach have been published.

Our interest in this problem began when we were asked to perform vena cava ligations on a number of patients who had recurrent emboli while being given anticoagulants. We felt this was a blind and often unnecessary procedure and decided to

display the site and nature of any residual thrombus by phlebography so that further treatment to give maximum protection and minimum morbidity could be planned on the basis of a precise diagnosis (Browse *et al.*, 1967). After a short time we considered setting up a controlled clinical trial to compare the value of anticoagulants alone with anticoagulants and surgery based on phlebography, but when the phlebograms revealed some large loose thrombi, at times large enough to be lethal, we decided that such a trial would not be ethical. This paper therefore compares the results of our treatment regimen (Browse *et al.*, 1967) with those obtained in a retrospective series of patients treated with anticoagulants alone. In spite of this disadvantage the difference between the results is significant and shows that the common method of treating pulmonary embolism with anticoagulants can be considerably improved by adding phlebography and, if indicated, surgery.

TABLE I.—Randomly Selected Papers Giving the Incidence of Recurrent Embolism After Various Forms of Treatment

Author	No. of Cases	Anti-coagulant	Follow-up Time	Recurrences (%)		
				Fatal	Non-fatal	Total
Allen <i>et al.</i> (1947) ..	44	O	?	0	2	2
Barker (1947) ..	292	O	?	0.3	1	1.3
Murray (1947) ..	149	H	?	0	2.6	2.6
Cosgriff <i>et al.</i> (1948) ..	107	H & O	?	1	3	4
Jorpes (1950) ..	99	H	?	0	13	13
Jorpes (1950) ..	346*	H	?	0	8.2	8.2
Ochsner <i>et al.</i> (1951) ..	124	H & O	?	11.7	?	11.7+
Crane (1957) ..	124	H	?	1.6	9.6	11.2
Coon <i>et al.</i> (1958) ..	152	H & O	12 weeks	6	8	14
Barritt and Jordan (1960)	54	H & O	4 weeks	0	6	6
Byrne (1960) ..	118*	H & O	?	18.6	?	18.6+
Fuller <i>et al.</i> (1960) ..	416	Varied	?	2.9	8.4	11.3
Thompson and Hamilton (1962) ..	20	H & O	?	0	15	15
Fontaine <i>et al.</i> (1965) ..	241	Varied	?	9.1	10	19.1
Little <i>et al.</i> (1966) ..	67	Varied	?	0	14	14
Kernohan and Todd (1966) ..	26	H	?	0	16	16
Surgery						
Allen <i>et al.</i> (1947) ..	329	F.V.L.	?	0.3	1	1.3
Carlotti <i>et al.</i> (1947) ..	60	F.V.L.	4 weeks	0	21.6	21.6
Ochsner <i>et al.</i> (1951) ..	70	F.V.L.	?	11.4	?	11.4+
Crane (1957) ..	126	F.V.L.	?	7	9	16
Byrne (1960) ..	460	F.V.L.	?	2.8	?	2.8+
Fuller <i>et al.</i> (1960) ..	38	F.V.L.	?	5	5	10
Donaldson <i>et al.</i> (1961)	2,127	F.V.L.	?	0.6	?	0.6+
Fontaine <i>et al.</i> (1965)	140	Varied	?	0.7	2.1	2.8
Spencer <i>et al.</i> (1962) ..	20	I.V.C.P.	1 week-15 mths	0	0	0
Deweese and Hunter (1963) ..	24	I.V.C.P.	1-5 years	0	4	4
Wheeler <i>et al.</i> (1966) ..	11	I.V.C.P.	?	0	18	18
De Meester (1967) ..	55	I.V.C.P.	?	0	16	16
Krause <i>et al.</i> (1963) ..	55	I.V.C.L.	1-8 years	0	0	0
Crane (1964) ..	26	I.V.C.L.	?	4	4	8
Cranley (1965) ..	77	I.V.C.L.	?	0	0	0

H = Heparin. O = Oral anticoagulant. F.V.L. = Femoral vein ligation. I.V.C.P. = Inferior vena cava plication. I.V.C.L. = Inferior vena cava ligation.
* Cases of thrombosis and embolism mixed together.

For convenience the two groups are referred to as the trial and control groups.

Methods and Clinical Data

Criteria for Diagnosis of Pulmonary Embolism.—It is well known that the physical signs of pulmonary embolism are extremely unreliable, but as pulmonary angiography was not used to confirm the diagnosis in any of the patients in this study we have had to accept a clinical diagnosis. The minimum symptoms and signs accepted for a positive diagnosis in either group were a pleuritic pain of sudden onset lasting for at least 12 hours with the exclusion, by clinical examination, E.C.G., and x-ray examination, of chest infection and acute myocardial ischaemia. Most of the patients had other signs to support the diagnosis—for example, haemoptysis, pleural effusion, and x-ray and E.C.G. changes. The diagnosis in the control group was accepted only if there was written evidence in the notes of the physical signs, not just a tentative diagnosis. The administration of anticoagulants to all the patients was in itself an

indication of the certainty of the clinician in charge of the clinical diagnosis.

Selection of Cases.—(a) *Trial group*: This consists of the first 50 patients referred to us during 1965–8 after a pulmonary embolus. (b) *Control group*: The records of St. Thomas's Hospital were examined (going backwards in time), beginning in August 1968, until we had collected 50 patients with a definite clinical diagnosis of pulmonary embolism who had survived at least seven days (to eliminate those who might have been too ill to have been investigated), and who were treated with anticoagulants alone. No patient was treated before 1965 and none had phlebograms.

Comparability of the Two Groups.—The age distribution (Table II) is similar (χ^2 test, two-tailed probability, $P=0.1$). Particularly noticeable is the relatively high incidence of pulmonary embolism in patients under 50 years of age. The males and females in each group are almost identical in number: trial group, 29 males and 21 females; control group, 28 males and 22 females.

TABLE II.—Age Distribution

Age (years):	10–20	21–30	31–40	41–50	51–60	61–70	71–80
Trial group	1	2	8	10	13	12	4
Control group	0	2	2	12	12	17	5

There is no overall difference between the two groups, nor is the difference between 10–30 and 61–80 significant.

Underlying Illness (Table III).—The underlying disease was classified as (1) postoperation, (2) medical illness not requiring surgery and excluding spontaneous deep vein thrombosis, and (3) spontaneous unexplained deep vein thrombosis. There is no difference between the groups in this respect. There are more “medical” than “surgical” patients in both groups. Thirteen of the medical patients in the control group had co-existent heart disease; only three of the trial group had heart disease.

TABLE III.—Predisposing Illness

	Trial Group	Control Group
Medical illness ..	9	12
Post-operation ..	21	20
Idiopathic venous thrombosis ..	20	18

Number of Emboli Suffered before Treatment Began.—Twenty-four of the trial group and 28 of the control group had clinical evidence of a single embolus; 11 and 12 respectively had two emboli and 15 and 10 had more than two emboli before treatment was begun. There is no statistical significant difference between these figures.

Incidence of Clinically Detectable Deep Vein Thrombosis.—thirty-one of the trial group and 36 of the control group had some physical signs in the legs to support the diagnosis of deep vein thrombosis. This is a higher incidence than commonly reported (Gibbs, 1957).

Clinician in Charge.—The patients were distributed among all the medical and surgical wards of the hospital. During the years 1964–8 there was no change in the consultant staff, so that both series of patients were treated by the same group of clinicians under similar ward conditions. Anticoagulation by oral agents was under the control of a common coagulation laboratory.

Initial Treatment of Both Groups

Anticoagulants

Trial Group.—All patients were given intravenous heparin and oral warfarin as soon as the diagnosis was made. The heparin was continued until the oral anticoagulants were effec-

tive. The dose of heparin was controlled by the clinician in charge and was either 5,000 units four-hourly or 10,000 units six-hourly. The coagulation time was not measured. The maintenance dose of warfarin was controlled by the coagulation laboratory, whose aim was to maintain the prothrombin index between 1.8 and 2.0, the optimum level on our standards that gives maximum anticoagulation with the lowest risk of haemorrhage. The oral anticoagulants were continued for as long as the physician in charge desired, usually three months.

Control Group.—These patients were treated in exactly the same way as the trial group except that those treated before 1965 were given phenindione. The duration of anticoagulation was not as long as in the trial group; the majority being anticoagulated for only one month.

Ancillary Treatments

Raising of the legs, degree of ambulation, compression bandages, and all other forms of non-specific treatment were not recorded and varied from patient to patient in both groups.

Further Treatment of Trial Group

Phlebography

Our techniques of ascending peripheral, percutaneous femoral, and intraosseous iliac phlebography have been described in detail elsewhere (Browse et al., 1967; Lea Thomas and Fletcher, 1967). Peripheral phlebograms under local anaesthesia gave an adequate demonstration of the major veins from ankle to vena cava in 37 cases, percutaneous femoral punctures were also needed in nine and intraosseous trochanteric injections in four. The only complication of these investigations was discomfort, sometimes with minor wound infection if an incision was made on the foot. All phlebograms were performed within 36 hours of one of us being asked to see the patient—that is, usually within 48 hours of the most recent embolus.

Results of Phlebography.—Thrombus was visible in the phlebograms of 39 of the 50 patients studied. The absence of evidence of peripheral thrombus was not accepted as indicating no peripheral clot. If the physical signs of the pulmonary embolus were definite it was assumed that there was thrombus in those veins, such as the calf muscle sinusoids, which cannot be displayed by phlebography. This assumption has since been justified, for in five out of six recent cases with negative phlebograms the presence of thrombus in the calf has been confirmed by the ¹²⁵I-fibrinogen test (Negus et al., 1968). Thrombus was found below the level of the knee joint in 17 patients, in the superficial femoral vein in 15, in the common femoral and iliac veins in six, and in the vena cava in one. The thrombus was fresh and non-adherent and adjudged to be a potential embolus (Browse et al., 1968) in 19 patients. In eight patients it looked big enough to obstruct the whole pulmonary artery or one of its main branches.

Surgery

Non-adherent fresh thrombus was “locked-in” by ligating the vein above the proximal limit of the clot. Large veins such as the iliac vein and vena cava were usually plicated rather than ligated, the choice depending on an estimate of the size and number of the previous emboli. Ligation is obviously safer and was preferred for patients who had frequent small emboli or who appeared to have little pulmonary circulatory reserve. A simplified scheme of the surgical techniques is given in the Diagram.

Table IV shows the surgical procedures performed on the 19 patients with residual loose thrombus. In the majority (11)

TABLE IV.—Operations Performed on 19 Patients. (Some Patients had Different Operations on Each Leg)

Unilateral superficial femoral vein ligation	..	6
Bilateral superficial femoral vein ligation	..	5
Unilateral common femoral vein ligation	..	3
Bilateral common iliac vein ligation	..	1
Unilateral common iliac vein plication	..	1
Vena cava plication	..	4
Vena cava ligation	..	1

a superficial femoral vein ligation was all that was required. Four vena cava plications and one ligation were performed. Three of these patients had bilateral common iliac thrombus, one had vena cava thrombus, and the remaining one was having multiple small emboli whose source, which could not be shown by phlebography, was thought to be the pelvic veins. A thrombectomy was performed on eight of these patients in the hope of reducing late morbidity. In some cases it was possible to remove thrombus from the common femoral vein and ligate only the superficial vein.

Simplified plan of treatment given to prevent recurrent embolism.

Follow-up Methods

With a few exceptions all the trial group have been seen regularly in the outpatient department since their discharge from hospital. Most of the control group have also been seen regularly by their physician. All patients were sent a letter in which they were asked to state: (a) whether they had experienced any episode of chest pain since their discharge from hospital; (b) whether they had been admitted to any other hospital, and why; and (c) whether they had any leg symptoms such as pain, swelling, or varicose veins.

All who gave a positive reply to any question were asked to come to a special follow-up clinic. Eight in the control group and none of the trial group were lost to late follow-up by December 1968; their period of follow-up was taken to the last examination recorded in the outpatient notes. There is a longer follow-up for the control group (Table V), but, as is shown below, this has not affected the significance of the results, since most recurrent emboli occurred within three months of treatment.

TABLE V.—Duration of Follow-up. The Control Group Has Been Followed for a Statistically Significant Longer Period of Time than the Trial Group. The 10 Short Follow-ups in the Control Group are 10 Patients Who Died

Time:	3 months	3-6 months	6-12 months	1-2 years	> 2 years
Trial group ..	..	11	14	19	6
Control group ..	10	2	5	9	24

The diagnosis of a recurrent embolus was based on the minimum signs of an episode of pleuritic chest pain. In the

first two weeks after the first embolus the pain had to be in a *different* site from that of the first attack lest a haemorrhage into the old infarct be confused with a new embolus. By using these very wide criteria we have erred on the side of over-diagnosis.

At the special follow-up clinic the legs were examined for swelling, varicose veins, eczema, and ulcers. Oedema of cardiac origin and symptoms due to pre-existing varicose veins were carefully excluded.

Results

Recurrent Emboli

Control Group.—Table VI shows that 20 of the 50 patients in the control group had clinical evidence of second emboli. Seven patients died in a manner typical of massive embolism ;

TABLE VI.—*Recurrent Embolism*

	Control Group	Trial Group
Fatal emboli	7	0
Non-fatal emboli	13	6

These differences are significant ($P=0.05$).

the cause of death was confirmed in the five who were examined after death. All the patients who died did so within one month of the first embolus and five had coexistent heart disease. Table VII shows that over half the recurrent emboli occurred within

TABLE VII.—*Time of Recurrence of Embolism*

Time:	Weeks		Months			
	2	2-4	1-2	2-3	3-6	6+
Control group (20) ..	7	5	3	2	2	1
Trial group (6) ..	1	0	0	1	0	4

one month of the first embolus and that only one occurred after more than six months. Twelve of the 20 recurrences occurred while the patients were adequately anticoagulated with phenindione (Table VIII). The time of the second embolus of

TABLE VIII.—*Relation Between Recurrences and Administration of Anticoagulants*

	Control Group	Trial Group
On anticoagulants	12	1
Off anticoagulants	8	5

the 12 still receiving anticoagulants was: six fatal emboli—9 days (two), 11 days, 13 days, 26 days, and 10 weeks ; six non-fatal emboli—4 days, 7 days (two), 31 days, 4 months, and 6 months. Eight patients had recurrent emboli after being taken off anticoagulants ; one was fatal at 19 days, seven were not fatal—at 3 weeks (two), 5 weeks (two), 8 weeks, 10 weeks, and two years. The time between stopping anticoagulants and the recurrence in the seven non-fatal recurrences was less than one month in three, between one and three months in three, and longer than three months in one.

Trial Group.—Table VI shows that six of the trial group had second emboli. None was fatal. The recurrences occurred at 14 days, and 2, 6, 8, 12, and 16 months. None of these patients was anticoagulated at the time of the recurrence. One was taking warfarin but on the occasion of the second embolus his prothrombin time had risen to within normal limits, two failed to take their tablets, one had her drugs stopped because of menorrhagia, and the remaining two had finished their prescribed course.

There is no correlation between the incidence of recurrent emboli and the age of the patient in either group.

Though five of the seven patients in the control group who died from recurrent emboli had coexistent heart disease, there is no correlation between non-fatal recurrences and heart disease in either group.

All patients in the trial group who suffered a recurrence and the seven fatal cases in the control group had more than one embolus before being treated. The chance of having a further embolus after either treatment is significantly greater if the patient has had more than one embolus before beginning treatment (Table IX).

TABLE IX.—*Relation Between Recurrence and Number of Emboli Before Treatment*

No. of Emboli before Treatment	No. of Patients with Recurrences	
	Control Group	Trial Group
One	6	0
2 or more	14	6

$P=0.01$.

Complications of Treatment

Haemorrhage.—Two of the trial group bled heavily (haematuria and menorrhagia) ; none died from haemorrhage. Five of the control group had their anticoagulants stopped because of bleeding ; two of these died from cerebral haemorrhage.

Sequelae in the Legs.—There is no difference in the incidence of late sequelae between trial and control groups (Table X). Eighteen patients in the control group had symptoms in the legs compared with 29 in the trial group ; nevertheless, 14 of the control group were dead—seven from pulmonary emboli and seven from other causes. Thus of the surviving patients the incidence in the trial group of leg symptoms is 58% compared with 50% in the control group (or 56% of the 32 available for late follow-up). In no patient were the symptoms severe or incapacitating. None had venous ulceration and only four (trial) and five (control) had varicose veins. Within the trial group there is a significant difference in the incidence of leg symptoms between those treated with anticoagulants plus surgery (73%) and those treated with anticoagulants alone (48%) (Table X).

TABLE X.—*Incidence of Symptoms in Legs*

	Control Group (32)	Trial Group (50)		
		All	No Surgery	Surgery
Aching	8	13	7	6
Swelling	12	26	12	14
Varicose veins	5	4	1	3
Total with symptoms ..	18	29	15	14
Total without symptoms	14	21	16	5

No information was available for 18 of the control group; this was due to the death of 14. Four were lost to follow-up and had no record of leg symptoms in their notes.

Discussion

The treatment of pulmonary thromboembolism is not clearly defined. Many of the problems arise from the difficulties of diagnosis. This paper compares the results of treating two similar groups of patients—the one by administering anticoagulants, the other by administering anticoagulants, performing a phlebogram, and then, if indicated, “locking-in” potential recurrent emboli by vein ligation or plication.

The diagnosis of pulmonary embolism was based on clinical evidence, and, with the exception of the surgery, the anticoagulants and ancillary treatments were administered and supervised by many different physicians. This study therefore can only show whether the addition of surgery based on phlebography has improved the results of the treatment of pulmonary embolism in our hospital.

There is a very high recurrence rate in the control group. The figures are almost identical with those of Barker and Priestly (1942) for the untreated disease, and suggest either that anticoagulants are of no value at all, which is contrary to all the previous published work on this subject, or that the doses given were not adequate. The latter suggestion can apply only to heparin, as the oral anticoagulants were controlled by laboratory tests. It is possible that the heparin dose was inadequate, as the clotting-time was not measured during treatment and it was given intermittently. Against the suggestion of inadequate heparinization must be set the phlebographic findings in the 50 trial group patients. Nineteen had fresh thrombus, which appeared sufficiently loose to be able to break free and embolize. Nineteen with potential emboli is very similar to the control group's 20 patients with recurrent emboli, and Barker and Priestly's 30%. If this was true residual thrombus—that is to say, it was present at the time of the first embolus—then it is probable that a similar proportion of the control group had fresh residual thrombus which broke free while on anticoagulants.

Another, in our opinion unlikely, possibility is that the thrombus seen on the phlebograms developed after the first embolus because of the inadequate heparinization. All x-ray films were taken within 24 to 48 hours of the embolus and some that showed residual thrombus were obtained within six hours. It is our experience that thrombus can remain for some days without showing any gross phlebographic changes, and propagation is measured in days rather than hours, so we believe that the figure of 38% is a true indication of the incidence of residual thrombus. There is no reason to believe that heparin can prevent recurrent embolism by preventing loose thrombus breaking free. Heparin is not thrombolytic, it is administered to stop further thrombosis, and we believe (in the light of our phlebograms, the recurrences in the control group, and the figures quoted in Table I) that heparin is not as effective in preventing recurrent embolism as many claim.

The difference between the recurrence rates of the two groups shows that the addition of phlebography and surgery has definitely improved the results of treating pulmonary embolism in our hospital. Even if the most sceptical view is taken of the anticoagulant regimen—namely, that this study is a comparison between no treatment at all and phlebography with surgery—the results show that fatal recurrent embolism can be abolished by the latter and the overall recurrence rate reduced to a level equal to that of any other form of treatment. The recurrence rates during the first month after treatment are 24% for the control group and only 2% for the trial group, a result equal to the best of the studies in Table I.

The majority of studies of pulmonary embolism are concerned with recurrences during the first few weeks or months. Our long-term follow-up has shown that a considerable proportion of patients have further emboli three to six months after the first. In the trial group this was confined to those who had stopped anticoagulants, but this was not the case in the control group. This suggests that long-term anticoagulants are valuable. Patients should probably be anticoagulated for at least six months and those who have more than one embolus before treatment begins should perhaps be anticoagulated for longer.

The phlebography had no associated morbidity, nor in the overall figures did the surgery. It is most likely that the amount of swelling that follows deep vein thrombosis is directly related to the extent of the underlying thrombosis. As most of those in the trial group who required surgery had extensive thrombosis it is not surprising that they had a higher incidence of swelling than those given only anticoagulants. The equal incidence of sequelae between the two groups as a whole suggests that those who developed swelling after surgery would still have done so if they had not been operated on.

Not only is the study of pulmonary embolism difficult because of inadequate diagnostic techniques but many of the published papers on the subject are sadly lacking in objective data. Lest this paper should add to the confusion we feel we should clearly state its limitations. This is not a prospective controlled clinical trial and the groups are not exactly comparable. The paper does not study the effect of anticoagulating the patients' blood on the incidence of recurrent emboli. Throughout the paper we have referred to the "administration of anticoagulants." As no measurements of clotting-time were made during heparinization it is possible that none of the patients was adequately anticoagulated during the 48 to 72 hours after their embolus; however, after 48 hours the patients were properly anticoagulated. The data concerning the thrombus in the peripheral veins of the trial group are completely objective but all other data are based on clinical examination. We have therefore studied the incidence of *clinically detectable* recurrent emboli, and in view of all the problems surrounding the diagnosis of pulmonary embolism this may bear no relation to the true recurrence rate. This disadvantage must be accepted until a simple and certain means of diagnosis is developed.

These limitations do not invalidate the main conclusions that can be drawn from this study—namely, (1) more than one-third of patients who have a pulmonary embolus have other potential emboli in the legs, (2) the only way to be sure of preventing early recurrent embolism is to perform bilateral phlebography to display any loose thrombus in the peripheral veins and then lock it in by suitable surgery in addition to the administration of anticoagulants, and (3) the anticoagulants should be given for at least six months.

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