incidence of between 40 and 70% in series of Caucasian thyrotoxic patients (Roitt and Doniach, 1960; Bastenie *et al.*, 1967).

These studies indicate that the predisposition to form thyroid autoantibodies is weak in the African thyrotoxic patient. In this context it is worth noting that all varieties of autoimmune disease are considered to be uncommon or rare among indigenous African populations (Greenwood, 1968) and autoimmune thyroiditis (spontaneous myxoedema and Hashimoto's thyroiditis) seems to be extremely rare. For example, in Kenya 600 consecutive thyroidectomy specimens from African patients were studied for round-cell infiltration and in one case the histological features of Hashimoto's disease were observed; 520 African patients with a variety of thyroid disorders were reviewed by observers experienced in thyroid disease over a two-year period (with access to P.B.I. estimations and with facilities for the estimation of antithyroglobulin and performing radioiodine tests) and no cases of spontaneous myxoedema or Hashimoto's disease were detected (McGill, unpublished data). Clearly the immunological system of the indigenous African is at present either resistant to or is not exposed to antigenic stimuli which initiate and maintain autoantibody formation. Further study of the apparently unique immunological mechanism of the indigenous African is indicated.

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Comparison of Streptokinase and Heparin in Treatment of Isolated Acute Massive Pulmonary Embolism*

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Summary

Massive pulmonary embolism was confirmed by pulmonary arteriography in 23 patients. All were seen between 2 and 48 hours after the onset of embolism and none had pre-existing cardiorespiratory disease. Fifteen were treated with streptokinase and eight with heparin. Factors which might influence prognosis and rate of resolution were similar in the patients in each group, and there was no significant difference between the groups in terms of pretreatment haemodynamic or arteriographic findings. Haemodynamic and arteriographic findings after treatment for 72 hours provided an objective measurement of resolution, which was significantly greater in the streptokinase-treated patients. There was no mortality in either group, but treatment had to be changed in two heparin-treated patients because of clinical deterioration. The principal complication of treatment, seen more often in the streptokinase-treated patients, was bleeding from cut-down or operation sites.

*This study forms part of an M.D. thesis submitted to the University of Cambridge by one of us (G. C. S.).

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Introduction

This report is concerned with only one aspect of massive pulmonary embolism—namely, the rate of resolution in a selected series of patients after 72 hours' treatment with either heparin or streptokinase. The late results of treatment will be the subject of another report.

In comparing the effects of two different treatments on the natural history of pulmonary embolism certain conditions must be fulfilled. Firstly, patients in each group must be comparable, and, secondly, objective criteria for diagnosis and for assessment must be available. Among factors which may make comparisons difficult are (1) the severity of the embolism, (2) the duration of embolism, and (3) coexisting cardiorespiratory disease. Our 23 patients were similar in that all were shown by pulmonary arteriography to have massive pulmonary embolism of about equal severity, none had a history of more than 48 hours or less than two hours, and none had coexisting cardiorespiratory disease. Additionally, haemodynamic and arteriographic data were available before and after treatment to provide an objective assessment of the response to therapy.

Methods

ASSESSMENT OF PRETREATMENT STATUS (TABLES I AND II)

The 23 patients (8 male, 15 female) studied before and after treatment with either streptokinase or heparin were aged 14 to 69 years. The following factors which might influence prognosis and rate of resolution were also recorded: a history of circulatory arrest occurring as a result of embolism, a history of syncope, or a history of previous premonitory minor pulmonary emboli. When the length of a predisposing illness, period of bed rest, etc., was more than 14 days or when there was no obvious predisposing cause it was assumed that the thrombus could be more than 14 days old.

After clinical and plain chest *x*-ray examination and a standard 12-lead electrocardiogram, right heart catheterization was performed with an angiographic (closed-tip) catheter in all patients, pressures being referred to the mid-chest level. The following haemodynamic measurements were recorded: pulmonary artery systolic pressure (P.A.S.P.), right ventricular end-diastolic pressure (R.V.E.D.), arteriovenous oxygen difference (A-V O_2), cardiac index (C.I.) (l./min/m^2 body surface area), arterial oxygen saturation (S.A. O_2), and total pulmonary resistance (R.P.) units $\times$ m^2 (mean pulmonary artery pressure/C.I.). Oxygen saturation was measured by reflection oximetry (Zijlstra and Mook, 1962) and cardiac index calculated by the Fick principle. In some cases oxygen consumption was measured by expired air analysis with the micro-Scholander technique (Scholander, 1947), but many patients could not tolerate the mouthpiece and nose clip required for a five-minute expired air collection. In these patients the cardiac index was calculated by using an assumed value for oxygen consumption derived from the data of Robertson and Reid (1952). After these haemodynamic measurement single plane, anteroposterior, serial film pulmonary arteriography was performed with 0·5-1 ml/kg body weight of contrast medium (sodium, calcium, and magnesium metrizoate—Triosil 75%) injected by a pressure injector.

Details of Treatment

The pulmonary artery catheter was left in place and used for the infusion of streptokinase or heparin. The dosage of streptokinase (Kabikinase) used was 600,000 units in the first half hour followed by 100,000 units/hour for a total of 72 hours. In one patient treatment was given for only 40 hours and in two it was curtailed because of bleeding (see below). Estimation of the titrated initial dose (Nilsson and Olow, 1962) indicated that it was adequate to achieve a lytic state in all patients. Hydrocortisone, 100 mg intravenously six-hourly, was given during the infusion. Heparin was given in a dose adequate to prolong the whole-blood clotting time (Lee and White) by a factor of 2 to 3. The dose used ranged from 40,000 to 60,000 units/24 hours. Two patients were given infusions lasting for more than 72 hours (120 and 144 hours), and in two treatment with heparin had to be abandoned (see below).

Selection of Treatment

Initially streptokinase was given to all patients. Later heparin was given to find out whether the response was equally favourable. At no time did the patient's clinical or haemodynamic state determine the drug given, but to avoid any possible bias the last eight patients to be treated were admitted randomly to the heparin or streptokinase group.

Assessment of Response

Within 24 hours after the end of the treatment period all patients had repeat cardiac catheterization and pulmonary arteriography with the indwelling pulmonary artery catheter, which was then removed. All the pulmonary arteriograms were reviewed in random order by a radiologist (I.H.K.), who was ignorant of the treatment used and who was not told whether he was looking at a pretreatment or posttreatment arteriogram. He assessed the severity of embolism by an "index of severity," as described below.

Angiographic Index of Severity (Fig. 1).—The right pulmonary artery was regarded as having nine major segmental branches (three to the upper lobe, two to the middle lobe, and four to the lower lobe). The left pulmonary artery was regarded as having seven major branches (two to the upper lobe, two to the lingula, and three to the lower lobe). The presence of a filling defect or defects (emboli) in any one of these branches scored 1 point, so that involvement by emboli of all the branches of the right pulmonary artery scored a maximum of 9 and of the left pulmonary artery a maximum of 7 points. The presence of a filling defect proximal to segmental branches scored a value equal to the number of segmental branches arising distally; thus

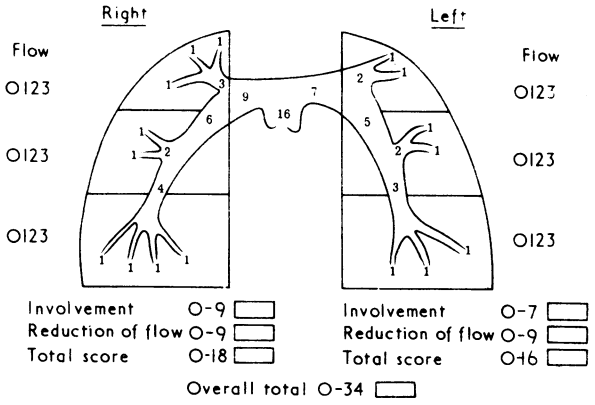

FIG. 1—Form used to grade severity of embolism as judged by the angiographic findings before and after treatment. For explanation see text.

a filling defect in the right lower lobe pulmonary artery scored 4 points and in the main right pulmonary artery 9 points. The maximum possible score for involvement was 16 points. In addition, the effect of embolism on pulmonary artery flow was scored as follows: each lung was divided into three zones (upper, middle, and lower) and flow in each zone was assessed as absent (3 points), severely reduced (2 points), mildly reduced (1 point), or normal (zero). The maximum score for reduction in pulmonary artery flow was therefore 9 points for each lung (total 18), and the maximum possible score for flow reduction and involvement of arteries by embolism was 34 points.

Results

COMPARISON OF PRETREATMENT STATUS

The pretreatment status of patients treated with streptokinase (group 1) and with heparin (group 2) is shown in Tables I and II. The groups were similar in terms of age of patients and in the duration and severity of embolism, as judged by the history and by any of the haemodynamic variables measured. The factors which might influence the response to treatment were also similar, as was the angiographic index of severity, which averaged 24·3 points for patients in group 1 and 23·9 points for patients in group 2.

RESPONSE TO TREATMENT

No patient treated with streptokinase deteriorated clinically. Two patients receiving heparin (both in the random group) deteriorated so that the clinician responsible, who did not

TABLE I—*Summary of Factors which might Influence Prognosis and Rate of Resolution*

Pretreatment Status	Treatment	
	Streptokinase	Heparin
No. of patients in group	15	8
Males:	6	2
Females:	9	6
Age, average (years)	48·1	55·0
< 20	2	0
20—39	3	0
40—59	6	4
> 60	4	4
History of circulatory arrest	2	2
History of syncope	10	7
Duration of massive embolism before admission, average (hours)	24·5	20·2
2— 6	3	3
7—12	2	1
13—24	5	2
25—48	5	2
Previous minor premonitory emboli	9	4
History suggests thrombus more than 14 days old	9	4

know what was being given, asked to know the treatment and changed it at 3 and 24 hours respectively. The latter patient was subsequently treated successfully with streptokinase, while the former was so critically ill that emergency embolectomy under total cardiopulmonary bypass was successfully carried out. Data from these patients have been omitted from the analysis of post treatment findings. Only two patients treated with streptokinase showed a less than 20% improvement in the angiographic index of severity. No heparin-treated patient improved by as much as 20%.

TABLE II—*Mean Values for Haemodynamic Variables and Angiographic Index of Severity before and after Treatment*

		Treatment		Probability
		Streptokinase	Heparin	
P.A.S.P. (mm Hg)	Before treatment	43·0	43·5	N.S.
	After treatment	27·8	37·2	0·02
R.P. (units × m²)	Before treatment	16·3	15·0	N.S.
	After treatment	7·0	11·2	<0·001
Angiographic index of severity	Before treatment	24·3	23·9	N.S.
	After treatment	9·7	21·8	<0·001
A-V O_2 (ml/100 ml)	Before treatment	7·3	7·5	N.S.
	After treatment	5·5	6·4	N.S.
R.V.E.D. (mm Hg)	Before treatment	12·1	11·6	N.S.
	After treatment	6·9	5·7	N.S.
S.A. O_2 (%)	Before treatment	84·6	81·0	N.S.
	After treatment	93·5	93·8	N.S.
CI (l./min/m²)	Before treatment	2·0	2·1	N.S.
	After treatment	2·9	2·4	N.S.

Posttreatment values for pulmonary artery systolic pressure, total pulmonary resistance, and angiographic index of severity (Table II and Fig. 2) were significantly lower after treatment with streptokinase (group 1) than after treatment with heparin (group 2). Patients treated with streptokinase showed a significant ($P \times 0{\cdot}05$-$0{\cdot}001$) improvement in all the haemodynamic variables measured and in the angiographic index of severity. Patients treated with heparin showed significant improvement in R.V.E.D. and arterial oxygen saturation, but changes in P.A.S.P., R.P., A-V O_2 difference, and cardiac index did not reach significance, though some improvement was, in general, observed. In the heparin-treated patients the average value for the angiographic index of severity fell from 23·9 to 21·8 points. This difference was not significant and contrasts with the highly significant ($P < 0{\cdot}001$) fall from 24·3 to 9·7 points seen in the streptokinase-treated patients. When those patients in whom treatment was selected on a truly random basis are examined as a separate group the pattern of response to streptokinase and heparin was similar to that reported for the group as a whole.

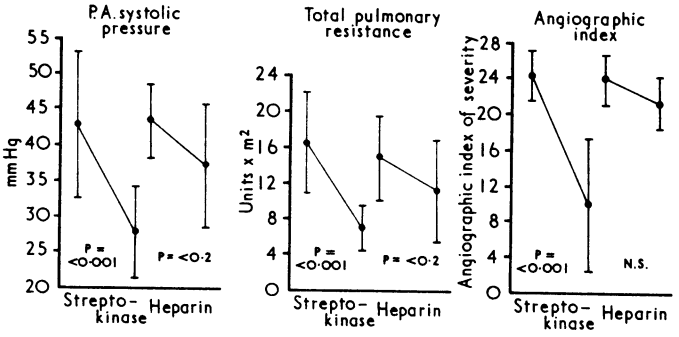

FIG. 2—Mean values and standard deviations before and after treatment for groups 1 (streptokinase) and 2 (heparin) in respect of pulmonary artery systolic pressure (left-hand panel), total pulmonary resistance (middle panel), and angiographic index of severity (right-hand panel).

COMPLICATIONS AND SIDE EFFECTS

Bleeding from cut-down or operation sites was seen in eight of the patients receiving streptokinase and in two of those receiving heparin (Table III). The bleeding was severe in three of the streptokinase-treated patients (one of whom had an undiagnosed coagulation defect and should probably not have been treated with streptokinase) and in only one of the heparin-treated patients. Bleeding led to treatment being curtailed (by five and nine hours respectively) in two streptokinase-treated patients. Bleeding from other sites occurred in two patients in the streptokinase-treated group and also in two in the heparin-treated group, and severe bleeding (gastrointestinal haemorrhage) occurred in one heparin-treated patient.

A fall in haemoglobin was almost invariable in the streptokinase-treated patients and exceeded 10% (range 2-25%) in eight patients, while only one patient treated with heparin had a fall in haemoglobin of more than 10% (after a gastrointestinal haemorrhage).

TABLE III—*Complications and Side Effects of Treatment*

	Streptokinase (15)	Heparin (8)
Bleeding: cut-down or operation sites: Slight	5	1
Severe	3*	1
Bleeding: other sites: Slight	2	1
Severe	0	1
Transfusion	3*	2
> 10% fall in Hb	8	1
Temperature 38-39°C	4	1
Treatment curtailed	2	0
Other	Nil	Nil

*Includes one patient with coagulation defect.

If a fall in haemoglobin of more than 10%, pyrexia to 38-39°C, severe bleeding, and a need for blood transfusion are all regarded as complications of treatment, one or more of these occurred in 10 of the 15 streptokinase-treated patients and in three of the six patients in whom heparin treatment was continued.

Discussion

This study shows significantly greater resolution of pulmonary embolism at 72 hours after streptokinase than after heparin therapy. Though arteriography may be unreliable in estimating accurately the changes in quality of embolic material in only minor degrees of lysis (Wolf and Genton, 1970), this applies equally to post-heparin and post-streptokinase arteriograms. Indeed our angiographic index of severity almost certainly underestimated improvement, since it made no allowance for reduction in size of filling defects if their location was unchanged. Subjective impressions determined the outcome in only those two patients whose treatment was changed because of clinical

deterioration; in both the clinician was in ignorance of the treatment being given.

Reports of comparisons between thrombolytic and anticoagulant therapy in pulmonary embolism are few. Hirsh *et al.* (1968) contrasted the pronounced arteriographic improvement seen at 24 hours in 12 out of 16 streptokinase-treated patients with the absence of such improvement in three heparin-treated patients. Subsequently these authors (Hirsh *et al.*, 1970) reported a series of 10 heparin-treated patients with only slight arteriographic improvement in two contrasted with 14 streptokinase-treated patients of whom eight showed "great" and six "moderate" arteriographic improvement. Wilcox *et al.* (1970) reported a strikingly lower mortality in patients with acute massive pulmonary embolism treated with Thrombolysin (streptokinase-activated plasma) than in those treated with heparin.

Others have reported slow early resolution with heparin therapy as judged by arteriography or by scintillation scanning. Thus Tow and Wagner (1967) found that only 18% of patients with "severe" pulmonary embolism had resolved at one month, and Dalen *et al.* (1969) found only minimal arteriographic improvement in seven patients studied at one to seven days. However, these authors also noted that moderate or complete resolution occurred at 10 to 21 days after anticoagulant therapy in 7 out of 10 patients. Scintillation scans and pulmonary arteriograms after pulmonary embolism have also shown that resolution is slower in patients with coexisting cardiopulmonary disease (Hirsh *et al.*, 1968), in those with severe embolism (Tow and Wagner, 1967), and in those who have recurrent embolism (Murphy and Bulloch, 1967)—emphasizing the importance of considering these factors in any comparison of different therapeutic regimens.

Contrasting with reports of slow resolution of pulmonary emboli with anticoagulant therapy are reports of rapid lysis after streptokinase (Hirsh *et al.*, 1968; Miller *et al.*, 1969) or urokinase (Dickie *et al.*, 1967; Sautter *et al.*, 1967; Sasahara *et al.*, 1967; Tow *et al.*, 1967; Genton and Wolf, 1968). The evidence is thus strong that thrombolytic therapy accelerates lysis of pulmonary emboli. In accepting this conclusion it is important to question how far heparin was correctly administered. Under experimental conditions the optimum dose of heparin seems to be that which keeps the clotting time in excess of twice the control value at all times (Wessler and Morris, 1955), and that was our policy. The dose required to achieve this varies considerably. Clinicians claiming the greatest success for heparin therapy have used dosages of at least 40,000 units/24 hours (Jorpes, 1947; Barritt and Jordan, 1961). The doses we used ranged from 40,000 to 60,000 units/24 hours. Recently, however, several workers (Bauer, 1964; Morris and Balk, 1965; Crane *et al.*, 1969) have adopted doses in the region of 100,000 units/24 hours to combat the bronchoconstriction which is occasionally observed (Gurewich *et al.*, 1965) and Crane *et al.* (1969) reported no deaths among 11 patients with undoubted massive embolism treated in this way.

That heparin administration reduces mortality from pulmonary embolism has been established by Barritt and Jordan (1961). However, since heparin has no thrombolytic action it must affect mortality in some other way. Analysis of Barritt and Jordan's data shows that the major effect of heparin was to prevent further episodes of pulmonary embolism. Thus it is the anticoagulant effect of heparin that is important. The effect of streptokinase on thrombus formation is uncertain, but it has the additional advantage of causing lysis of the remaining deep venous thrombosis (Chesterman *et al.*, 1969).

It has yet to be shown that accelerated lysis of pulmonary emboli is a desirable objective. Some patients undoubtedly die between two hours and several days after embolism (Gorham, 1961). Since none of our patients died our study has not shown a reduction in mortality with the use of streptokinase. It is of interest, though, that the only two patients who deteriorated on treatment and in whom treatment had to be changed were receiving heparin. There was no clinical evidence of further emboli in either case, and it is our impression that deterioration was a result of a prolonged and severe haemodynamic disturbance. In either situation rapid lysis, by reversing the haemodynamic disturbance and by clearing the vascular bed so that further emboli would have a less serious effect, would seem to be a desirable aim.

Many questions about the use of streptokinase in pulmonary embolism remain to be answered. The response to therapy is not invariably excellent and the duration of embolism which may with profit be treated by streptokinase has yet to be defined. Also it has yet to be determined whether thrombolytic therapy will reduce the late sequelae of pulmonary embolism.

It is our present policy to use streptokinase for the treatment of isolated acute massive pulmonary embolism and to reserve embolectomy for (1) those patients who are so ill that delay in achieving a haemodynamic response is unacceptable, indeed such patients may be too ill for arteriography to be performed; (2) those patients who have deteriorated on medical treatment, a situation which we have not so far met when streptokinase has been used; and (3) those patients in whom a contraindication to streptokinase therapy exists.

With streptokinase therapy some clinical improvement is usually seen in two to four hours, but measurable haemodynamic change is not seen for six to eight hours. Deterioration is best defined as continuing severe arterial hypotension with evidence of poor tissue perfusion (impaired cerebration, low or absent urine flow, peripheral vasoconstriction, etc.). Contraindications to streptokinase therapy are necessarily ill defined but include recent surgery where bleeding might constitute a risk. Such contraindications are probably equally applicable to high-dose heparin therapy. In our experience the complications of streptokinase therapy were virtually limited to bleeding from cut-down or operation sites and were not of serious importance.

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Requests for reprints should be sent to Dr. G. A. H. Miller.

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