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and performing radioiodine tests) and no cases of spontaneous myxoedema or Hashimoto's disease were detected (McGill, unpublished data).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.

*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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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.

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.

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 After treatment	43.0 27.8	43.5 37.2	N.S. 0.02
R.P. (units $\times$ m ²) ..	{ Before treatment After treatment	16.3 7.0	15.0 11.2	N.S. <0.001
Angiographic index of severity	{ Before treatment After treatment	24.3 9.7	23.9 21.8	N.S. <0.001
A-V O ₂ (ml/100 ml) ..	{ Before treatment After treatment	7.3 5.5	7.5 6.4	N.S. N.S.
R.V.E.D. (mm Hg) ..	{ Before treatment After treatment	12.1 6.9	11.6 5.7	N.S. N.S.
S.A. O ₂ (%) ..	{ Before treatment After treatment	84.6 93.5	81.0 93.8	N.S. N.S.
CI (l./min/m ²) ..	{ Before treatment After treatment	2.0 2.9	2.1 2.4	N.S. 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 ($P \times 0.05-0.001$) 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 O₂ 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 ($P < 0.001$) 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	5	1
Bleeding: other sites	3*	1
Transfusion	2	1
> 10% fall in Hb	0	1
Temperature 38–39°C	3*	2
Treatment curtailed	8	1
Other	4	1
	2	0
	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 Thrombolytin (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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