not therefore surprising that in the present study only slight or moderate fibrinolytic activity, less than one-third of that induced in healthy subjects by strenuous exercise, was seen after infusion of 30,000–80,000 units of urokinase. In view of the coagulative activity seen *in vivo* in Subjects 3 and 4, there must be some doubt about the wisdom of administering doses adequate to produce brisk fibrinolytic activity.

It may be, however, that with larger doses of urokinase any fibrin deposited will be so rapidly lysed that no untoward clinical effects will be produced.

Summary

A commercial preparation of human urokinase, the physiological fibrinolytic substance present in normal urine, has recently become available for clinical trial as a fibrinolytic agent in the treatment of intravascular thrombosis. The present paper gives an account of *in-vitro* and *in-vivo* study of this preparation (Leo urokinase). *In vitro* in purified systems the preparation is a potent plasminogen activator, but, because of an inhibitor in plasma, relatively large doses are required to produce fibrinolytic activity *in vivo*. As normal urine has thromboplastic properties the preparation was also examined for coagulative activity, and was found to shorten the recalcification time of fresh normal plasma and of Hageman plasma. On electrophoresis the preparation has at least four components; the fibrinolytic activity is largely located in one specific band. The preparation was infused intravenously in five subjects in an amount which produced only slight fibrinolytic activity in the plasma; in two subjects biochemical but not clinical evidence of coagulative activity *in vivo* was observed. There was no evidence of antigenicity. In view of the coagulative property of the preparation it would seem possible that doses adequate to produce brisk fibrinolytic activity in the circulation may be associated with some hazard; with further purification and elimination of the coagulative component the preparation would be an important agent for clinical trial.

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FIBRINOLYTIC THERAPY OF CORONARY THROMBOSIS CONTROLLED TRIAL OF 75 CASES

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In a pilot study Dewar *et al.* (1961) described the experimental work upon which the use of fibrinolysis in the treatment of coronary thrombosis is based, reviewed the experiences of other workers in this field, and described the methods employed in the present trial. At that time 33 patients, 17 of them treated and 16 controls, had been included and the preliminary results did not disclose any striking difference between the two groups except perhaps in some features of the serum transaminase curves which succeeded the infarction. The preparation used was "thrombolysin," consisting of human plasminogen (fibrinolysin), activated by streptokinase and claimed to be devoid of "free activator." This has been shown to be active in lysis *in vitro*, and free from serious side-effects upon the patients.

In the present account the study has been extended by the addition of a further 42 patients, of whom half were treated and half served as controls. The trial has been terminated because the total of 75 patients has seemed to provide adequate information concerning the safety, potency, and usefulness of the preparation.

It is not proposed to recapitulate in detail the design of the trial and the methods used. In all patients the onset of infarction was abrupt and could be accurately timed as occurring not more than 12 hours prior to the commencement of treatment in hospital. Criteria for acceptance were a strong clinical diagnosis of a fresh

infarct without preceding recent episodes of infarction pain, E.C.G. changes then or later, and abnormal transaminase curves. Only one patient had to be rejected after acceptance into the trial because of unsubstantiated diagnosis. After the pilot series of patients who were allocated alternately to treated and control groups the remainder were allocated by opening consecutive envelopes in a randomized series previously prepared by our statistical adviser. Of the total of 75 patients, 35 men and 3 women were allotted to the treated group and 34 men and 3 women to the controls. The average age of the treated group was 57.2 years (range 35–80) and of the controls 57.1 years (range 38–72). In each group 18 gave a history of angina and 9 had sustained previous myocardial infarction. The average time elapsing from onset of pain to beginning of treatment was 6.2 hours in the treated group (range 3–12) and 6.3 hours in the control group (range 2.25–11.5).

Throughout the study thrombolytic dissolved in 5% glucose in water was infused intravenously in a dosage of 50,000 units per hour for 12 hours, the first 25,000 units being run in rapidly as a "loading dose." The control patients were infused with the same volumes of plain glucose solution. Heparin parenterally and phenindione orally were used after the conclusion of the above infusion, and those who survived to be discharged from hospital were maintained subsequently on long-term anticoagulant therapy, except for one treated patient in whom it was discontinued because of a gastrointestinal contraindication.

Blood for transaminase estimations (S.G.O.-T.) was withdrawn every four hours for three days, then once daily for 10 days. That for fibrinogen was withdrawn every four hours for 16 hours, then daily for 12 days. After the pilot study, fibrinolytic activity in the blood was estimated before infusion and four-hourly during it. In 16 patients prothrombin activity and clotting-times were also measured. Twelve-lead electrocardiograms were taken daily for seven days and thereafter weekly for two more weeks.

Methods

Serum transaminase was estimated throughout by the method of Reitman and Frankel (1957).

Fibrinolytic activity was estimated by the method of Fearnley *et al.* (1957), modified as previously described, but after the pilot study deep-freezing was omitted and the complete disappearance of clot was taken as the end-point. This enabled a camera to be used as described by Lackner and Goosen (1959), and in a new series of 10 normals the range of normal lysis time was 240–450 minutes with a mean of 330 minutes, almost identical with the figures, obtained by the pilot study, of 240–540 minutes with a mean of 340 minutes in nine subjects.

Clotting-time was estimated by the method of Lee and White (1913) and prothrombin by the one-stage Quick (1935) method.

Plasma fibrinogen was estimated in the pilot study by the methods of Hiller *et al.* (1927) and Harrison (1947). Since it was feared that the readings obtained might have been artificially low owing to uninhibited fibrinogenolysis in the blood after withdrawal, in the last 36 of the patients the estimations were made by the same method upon 5 ml. of blood, drawn into a tube containing the solid content of 0.3 ml. of tenth molar E-amino caproic acid (E.A.C.A.), in addition to the oxalate (Alkjaersig *et al.*, 1959).

Results

Fibrinolytic Activity

Among the 38 patients to whom thrombolytic was administered the fibrinolytic activity was estimated in 22 (58%). Among the 37 controls it was estimated in 13 (35%). The figures for the geometric means of this activity in the two groups are shown in the Chart and Table I, the result being expressed as the reciprocal of the lysis time in minutes multiplied by 10,000, so that in the Chart activity is displayed positively as units in the ordinate. In such units the normal mean is 30 (range 19–42). It will be seen that before infusion the activity was closely similar in the two groups, but during infusion became significantly greater in the treated cases. During the infusion of the thrombolytic, in fact, the level rose to three times the basic reading in 19 (86%) of the subjects tested and in 12 attained "infinity"—that is, either no clot would form or dissolution was immediate. During the control infusion in no subject did the level of activity reach "infinity," and in only 4 (31%) did it rise above three times the basic reading. Since in 12 of the treated cases fibrinolytic activity became so very intense these cases, in this and subsequent analyses of results, have been treated as a "special group."

Fibrinolytic activity of treated and control groups.

TABLE I.—Fibrinolytic Activity. Comparison of 22 Treated Cases (Including 12 of "Special Group") with 13 Controls

	Control Mean	Treated Mean	Special Group	t ₃₃	P
Initial level—geometric mean (of units)	55.3	43.3	52.2	0.48	60% (N.S.)
Lowest during infusion—geometric mean	30.4	82.2	94.6	2.57	<2% (<2%)
Highest during infusion—average*	135	2,090	∞	—	<0.1% (<0.1%)

* Average calculated by a log-reciprocal transformation. Figures in parentheses refer to treated patients of the "special group."

Fibrinogen

Table II shows that when specimens for estimation of fibrinogen were collected in oxalate a significant fall in the level of this substance occurred during the period of infusion, and to a less extent during subsequent days. The figures in parentheses show that in six of the "special group" estimated by this method this reduction was still greater. In two of the treated patients the level during infusion fell to zero but there was no clinical ill effect.

TABLE II.—Fibrinogen

	Control Mean	Treated Mean	t	P
<i>Oxalate Method. Comparison of 18 Control Cases with 17 Treated Cases</i>				
Initial level (mg./100 ml.) ..	399	381 (340)	—	N.S. (N.S.)
Mean during infusion ..	414	294 (226)	3.74 (4.93)	<0.1% ($<0.1\%$)
Lowest figure during infusion and next 3 hours	394	243 (177)	4.42 (5.63)	<0.1% ($<0.1\%$)
Mean during days 2-7 ..	584	443 (409)	3.19 (2.44)	<1% ($<5\%$)
<i>E.A.C.A. Method. Comparison of 15 Control Cases with 18 Treated Cases</i>				
Initial level (mg./100 ml.) ..	339	365 (395)	—	N.S. (N.S.)
Mean during infusion ..	327	295 (311)	1.27 (0.46)	20% (60%)
Lowest figure during infusion and next 3 hours	295	248 (274)	1.50 (0.52)	20% (60%)
Mean during days 2-7 ..	528	450 (446)	1.82 (1.36)	10% (20%)

Figures for comparison with 6 treated cases of the "special group" are given in parentheses.

When in the latter part of the trial the collection was made into tubes which also contained E.A.C.A. the fibrinogen levels thus estimated, although lower in the treated series, did not differ significantly in the two groups. This also applied to the remaining six of the "special group." This would tend to support the contention expressed above that the apparent fall in the fibrinogen levels produced by thrombolysis is due to uninhibited fibrinogenolysis after withdrawal of the blood. It should be noted, however, that the addition of E.A.C.A. affects the actual method of estimation, and the figures for the two parts of the trial should not be compared with each other.

Prothrombin Levels as Percentage Activity

Treated Group.—Before infusion in 11 subjects the prothrombin activity was 100% in all except one, in whom it was 85%. During infusion it fell in nine to a mean lowest of 63% (range 46-95%). In two subjects it remained 100%.

Control Group.—Before infusion in 11 subjects the prothrombin activity was 100% in all except one, in whom it was 59%. During infusion in nine of these it remained 100% in seven, rose from 59 to 87% in one, and in the other fell to 66%.

Clotting-times in Minutes (Normal in Venous Blood, 3-8 Mins.)

Treated Group.—Before infusion in eight subjects the clotting-time was normal in five and up to 10 minutes in three. During infusion in 10 subjects it exceeded 10 minutes in seven (range 11-20 minutes except for one patient whose blood would not clot).

Control Group.—Examination before infusion in five subjects and during infusion in six showed that the clotting-time was normal in all.

The times when the prothrombin activity of the treated group was low and the clotting-time prolonged did correspond with the times when the fibrinolytic activity of these patients was shown to be intense.

Clinical Effects

In general, thrombolysis has been very well tolerated but has not had any obvious clinical effect. The use of morphine prevented accurate assessment of pain, but thrombolysis did not seem to have any influence upon this symptom.

Fever.—Thrombolysis did not cause a rigor in any subject. The statistical analysis of the pyrexial reaction in all 75 patients showed that it developed significantly earlier in the treated group—namely, at 16.3 hours after onset, as compared with 25.4 hours in the controls ($t=2.42$, $P<5\%$) (Table III). This was presumably due to the pyrogenic effect of thrombolysis, but since the mean peak reached in the treated group was 100.3°F . (37.9°C .) and in the control group 100.1°F . (37.8°C .) and the mean total duration of fever 7.3 and 6.4 days respectively, this effect is unimportant.

TABLE III.—Fever and Systolic Blood-pressures

	Control	Treated	t	P
<i>Fever ($^{\circ}\text{F}$). Comparison of 37 Control Cases with 38 Treated Cases</i>				
No. with no fever ..	3	3	—	5%
Time from onset to fever in hours—mean	25.4	16.3 (17.9)	2.42 (1.22)	(N.S.)
Peak during infusion and next 3 hours—mean	98.8°	99.4° (99.8°)	—	(N.S.)
Subsequent peak—mean ..	100.1°	100.3° (100.2°)	—	(N.S.)
Duration of fever in days—mean	6.4	7.3 (8.1)	—	(N.S.)
<i>Systolic Blood-pressure (mm. Hg). Comparison of 37 Control Cases with 38 Treated Cases</i>				
Before treatment—mean ..	128	130 (128)	—	(N.S.)
Lowest during infusion and next 3 hours—mean	109	107 (100)	—	(N.S.)
Subsequent lowest—mean	98	97 (92)	—	(N.S.)
At 14 days—mean ..	115	120 (118)	1.36	(N.S.)

Figures for comparison with 12 "special" treated cases are given in parentheses.

Blood-pressure.—A similar analysis of the systolic blood-pressure is given in Table III, the figures for the 12 "special cases" being shown in parentheses. It will be seen that in these 12 "special cases" the fall in systolic blood-pressure exceeded the fall in the control cases by 9 mm. Hg. The difference is not of statistical significance. Eleven of the control cases and eight of the treated were given pressor drugs.

Haemorrhage.—In a few of the treated patients haematomata and ecchymoses occurred on the institution of heparin therapy after the infusion of thrombolysis. This was thought to be due to a summation of the effects of heparin and thrombolysis, and points to the unwisdom of administering these two substances simultaneously, as has previously been reported by Grossi and Clifton (1960).

Post-infarction Myocardial Weakness Among Those Surviving Three Months.—As judged by x-ray evidence of cardiac enlargement and clinical evidence of congestive

TABLE IV.—Post-infarction Angina and Myocardial Insufficiency

Surviving at Three Months	Angina			Dyspnoea			C.H.F.		C.E.		
	Better	Worse	No Change	Better	Worse	No Change	Yes	No	Yes	No	No
Treated (30)	7	3	20	7	8	15	3	27	8	22	
Controls (32)	10	8	14	1	11	20	1	31	11	21	
P ..	N.S.	N.S.	N.S.	>5% N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	

C.H.F. = Congestive heart failure. C.E. = Cardiac enlargement.

failure, there was no difference between the two groups. Judged only by the symptom of dyspnoea, the treated cases had an apparent but not statistically significant advantage ($P>0.05$) (Table IV).

Mortality

Of the 75 patients, 17 died, 4 of them one year or more after the infarct. Of the 17, 9 were treated and 8 were controls. All died of heart disease except one who developed a bronchial carcinoma. Their survival times are shown in Table V.

Necropsies have been obtained on 14 subjects (8 treated, 6 controls). The experimental work of Rueg-

segger *et al.* (1959) had shown that in dogs treated with thrombolytic not only had the artificial clots in the coronary arteries lysed completely or partially, but there were also differences in the histological appearances of the infarcts even when the lysis was incomplete. The treated animals showed less fibrinous deposition, less dilatation of the capillaries, and an absence of microthrombi in them. The necropsy studies were therefore made with these particular features in mind. All the hearts were examined by one observer (P. A. E.), who did not know which specimens were from treated or control patients. Since death took place at intervals after onset ranging from a few hours to 19 months, an attempt has been made to match treated and control patients according to length of survival. The results of these studies are shown in Table VI. The numbers are too small for valid comparison, but they certainly give no grounds for believing that coronary thrombi have been lysed more frequently in the treated patients than in the controls, or that the inflammatory reaction in the infarcts has been modified in a way which might have been expected from Ruegsegger's experimental

TABLE V.—Survival Times in Fatal Cases

Time of Death	Treated	Controls
First 48 hours	3	2
8–14 days	2	1
6–11 weeks	2	3
12–19 months	2	2
Total	9	8

TABLE VI.—Necropsy Findings in Matched Cases

		Sex and Age	Time Onset to Death	Thrombus in Relevant Coronary Artery		Stage of Infarct	Capillary Dilatation		Endocardial Fibrin Deposition		Microthrombi		
				Control	Treated		Control	Treated	Control	Treated	Control	Treated	
Deaths at 8-27 Hours													
Treated	{	M 58	13 hours		+	Cellular infiltration. Minimal muscle change		++		0		+	
		F 78	14 "		0	" "		+		+		0	
		M 80	27 "		+	" "		+		0		+	
Control	{	M 58	8 "	+		No infarct recognized	0		0		0		
		M 50	10 "	0		" " "	0		0		0		
Deaths at 8-14 Days													
Treated	{	M 62	10 days		+	Polymorphs degenerate. Early muscle autolysis		++		0		0	
		M 56	8 "		+	" "		+		0		+	
Control	{	M 60	14 "	0		Polymorphs "disappeared." Muscle autolysis in progress	0		0		0		
Deaths at 6-11 Weeks													
Treated	{	M 49	8 weeks		+	Polymorphs disappeared. Muscle autolysis in progress		++		0		+	
		F 69	6 "		0	Muscle autolysis and early fibrosis		++		++		0	
Control	{	M 57	6 "	+		Fibrosis advanced	+		++		0		
		F 56	11 "	+		Muscle autolysis and early fibrosis	0		0		+		
Deaths at 12-19 Months													
Treated	{	M 64	12 months		+	Fibrous scar		0		0		(+)	
Control	{	M 64	19 "	0		" "	0		0		0		
Total		..		3 6	6 8			1 6	7 8	1 6	2 8	1 6	5 8
				(N.S.)				(P=1.6%)		(N.S.)		(P=12%)	

TABLE VII.—Electrocardiograms (Figures of Geometric Means)

	Greatest in mm.							No. of Leads						
	Control	Treated	t	P	Special Group of Treated	t	P	Control	Treated	t	P	Special Group of Treated	t	P
<i>Q waves:</i>														
Initial	1.43 (35)	1.55 (38)		N.S.	0.96 (12)	0.70	N.S.	0.99 (35)	0.85 (38)		N.S.	0.67 (12)	0.82	N.S.
At 24 hours ..	2.75 (35)	2.77 (37)		"	1.95 (12)		"	1.42 (35)	1.46 (37)		"	1.06 (12)		"
" 7 days ..	2.87 (34)	2.80 (34)		"	1.84 (11)		"	1.27 (34)	1.43 (34)		"	0.95 (11)		"
" 21 days ..	2.67 (34)	2.69 (33)		"	2.00 (11)		"	1.22 (34)	1.54 (33)		"	1.21 (11)		"
" 3 months or more	2.52 (31)	2.24 (32)		"	1.38 (11)	0.92	"	1.24 (31)	1.14 (32)		"	0.83 (11)		"
<i>ST elevation:</i>														
Initial	1.59 (35)	1.84 (37)		N.S.	1.54 (12)		N.S.	1.81 (35)	2.18 (37)		N.S.	1.21 (12)	2.085	<5%
At 24 hours ..	1.34 (35)	0.93 (37)	2.35	<5%	0.48 (12)	2.47	<5%	1.63 (35)	2.35 (37)		"	1.02 (12)		N.S.
" 7 days ..	0.99 (34)	0.74 (34)	1.42	N.S.	0.35 (12)	1.84	N.S.	1.23 (34)	1.72 (35)	0.95	"	0.59 (12)		"
" 21 days ..	0.57 (34)	0.30 (33)	1.49	"	0.14 (11)		"	0.87 (34)	1.10 (33)		"	0.29 (11)		"
" 3 months or more	0.30 (31)	0.18 (32)		"	0.04 (11)		"	0.37 (31)	0.59 (32)		"	0.06 (11)		"
<i>T inversion:</i>														
Initial	0.31 (35)	0.36 (37)		N.S.	0.35 (12)		N.S.	0.45 (35)	0.50 (37)		N.S.	0.73 (12)		N.S.
At 24 hours ..	1.19 (35)	1.06 (37)	0.38	"	1.00 (12)		"	1.72 (35)	1.53 (37)		"	2.09 (12)		"
" 7 days ..	0.96 (34)	0.82 (35)	0.22	"	0.86 (12)		"	1.72 (34)	1.72 (35)		"	2.24 (12)		"
" 21 days ..	2.97 (32)	2.83 (32)		"	3.20 (11)		"	3.04 (32)	2.66 (32)		"	2.95 (11)		"
" 3 months or more	1.37 (31)	0.95 (32)	0.98	"	0.63 (11)	1.510	"	2.36 (31)	1.73 (32)	1.15	"	1.41 (11)	1.792	"

Figures in parentheses refer to number of patients.

work. Capillary dilatation in particular was much greater among the treated patients and microthrombi were certainly not prevented.

No attempt has been made to compare the size of the infarcts in the two groups, since this depends on too many factors, especially the location of a thrombus and the presence or absence of pre-existing collateral channels. With such small differences in size would be without meaning.

Electrocardiograms

As in the pilot study, electrocardiographic changes have been analysed in each patient from the initial tracings and from those at 24 hours, 7 days, 21 days, and 3 months or more from the onset of pain. Again by using the unipolar limb leads and chest leads V2 to V6, the maximal pathological Q wave, ST elevation, and T-wave inversion were recorded together with the number of leads in which these abnormalities appeared. The results are expressed in Table VII, and it will be seen that the only significant difference between controls and treated is in the ST elevation at 24 hours, which is about 0.5 mm. less in the treated, though not in the "special group" of them. The difference in the T-wave inversion at 24 hours shown in the pilot study is no longer demonstrated.

Transaminase Curves

From the specimens taken four-hourly for three days and thereafter daily, curves have been plotted in respect of each patient. In several instances for various technical reasons, such as haemolysis of samples, these curves were incomplete, and when the deficiency involved the peak of the curve the results have not been included in the analysis. Complete curves were available in 28 treated and 29 controls, and the former included 10 out of the 12 in the "special group" showing intense fibrinolytic activity. These curves have been analysed in respect of a number of parameters, and the mean figures for these groups are compared in Table VIII. In no respect was there any significant difference.

TABLE VIII.—*Analysis of Transaminase Curves. Comparison of 28 Treated Cases (Including 10 of Special Group) with 29 Controls*

	Control Mean	Treated Mean	(Special Group)	$t_{55}df.$	(t_{37})	P
Hours from onset to peak	25.3	25.6	(26.0)	0.13	(0.22)	90% (80%)
Days from peak to resting level	7.3	7.2	(7.6)	0.15 (56 df.)	(0.33)	90% (70%)
Rate of rise*	9.1	12.1	(12.1)	1.08	(0.74)	30% (50%)
Peak*	226	274	(305)	1.00	(0.96)	30% (30%)
Rate of fall from peak to half-way*	6.3	8.4	(6.3)	0.89	(0.54)	40% (60%)
Area*	350	401	(475)	0.58	(0.87)	55% (40%)
Hours before treatment	6.4	6.2	(5.5)	0.23 (60 df.)	(1.11)	80% (30%)
Rate of rise/peak	0.045	0.050	(0.042)	0.77	(0.38)	45% (70%)
Rate of rise/area*	0.026	0.031	(0.029)	1.04	(0.40)	30% (70%)
Peak area*	0.657	0.713	(0.723)	0.95	(0.92)	35% (40%)
Rate of fall/peak*	0.026	0.031	(0.027)	1.10	(0.20)	30% (80%)
Rate of fall/area*	0.017	0.022	(0.019)	1.17	(0.48)	30% (60%)

N.B. In order to be significant at the 5% level t_{55} must exceed 2.0, at the 1% level t_{55} must exceed 2.7.

* Geometric mean. Analysis was carried out on the logarithms of these data. Accordingly the means are geometric means.

Columns of figures in parentheses refer to treated patients of the "special group."

Discussion

It has been pointed out in the pilot study that the conditions under which thrombolysin was administered

to the patients in this series differed in important respects from those obtaining in Rueggsegger's experiments on dogs upon which the trial was based. In those experiments a mixed fibrin and platelet clot was rapidly produced by thromboplastin-containing serum in stenosed segments of healthy coronary arteries, and the thrombolysin was given intravenously in a dosage of 4,000 units/kg. for one to seven hours, so as to keep the lysis time of a standard fibrin clot at 15–60 minutes. In this clinical trial the drug was being administered to human subjects whose coronary arteries were presumed to be already extensively damaged by atheroma, and the final occlusive thrombus when present would be expected to have a predominantly platelet structure which might well be more resistant to lysis.

Owing to the difficulty of estimating the hour-by-hour requirement of fibrinolysin for each patient, an arbitrary dosage, as agreed with the manufacturers, was selected. This was certainly less than that used by Rueggsegger in his animal work, but the estimations of fibrinolytic activity which had been made on the patients indicate that it did enhance such activity in the venous blood in a significantly large proportion of those to whom it was given. In 12 of the subjects this activity was particularly intense, and to these special attention has been paid. With this intense activity went a reduction in fibrinogen content of the blood, a prolongation of the clotting-time, and a reduction of prothrombin activity, but in this series there has been no ill effect.

Regarding the safety of thrombolysin, the study has shown clearly that, in contrast with some other fibrinolytic preparations, its use has not been attended by any serious side-effects. A mild pyrexia, antedating but no more intense than the fever caused by the infarct, has been observed. A preliminary impression that the drug caused hypotension has not been confirmed by further experience. But it is clearly wise, when using it, to check dosage needs by clotting-times and prothrombin estimations. The special risk of anaphylaxis during re-treatment has not been tested in this study, but is well documented in the literature (Ambrus *et al.*, 1960).

The clinical effect of thrombolysin in the dosage used in this study is quite clearly negative. During the first month there were five deaths among the treated group as compared with three in the controls, but by the end of three months the proportions were seven and six. The necropsy studies, conducted "blind" by the pathologist, failed to demonstrate any difference in the proportion of infarcts for which coronary thrombi were shown, and the histology entirely failed to confirm the findings that should have been expected from the experimental work. The elaborate transaminase studies likewise did not show any difference between treated and controls, and the tentative finding in the pilot study that peak/area ratio differed significantly has not been confirmed in the larger series. Differences in the electrocardiograms between the groups were confined to a small but "statistically significant" decrease of the ST elevation in the treated group at 24 hours. The "special group" with the most intense fibrinolytic activity did not, however, show this change, so that its clinical significance is very doubtful. The decreased T-wave inversion at the same stage noted in the pilot study was present but not significant in the full series.

There are a number of possible reasons for the negative results of this trial. It is debatable how important thrombi are in the aetiology of human

myocardial infarction (Ravin and Geever, 1946). At necropsy they are often not found, but how frequently this is because they have lysed spontaneously or never been formed is not really known. The possible importance of their predominantly platelet structure has already been discussed. It is also possible that the 6.2 hours which on average in the present study elapsed between the onset of pain and the administration of thrombolytic was too long, but it is difficult to see how it could readily be shortened. The method of application of the substance may also have been at fault, and Boucek and Murphy's (1960) technique of injecting it at the root of the aorta is at least logical. It is possible that the dosage may have been inadequate, and in some of the patients it almost certainly was; but the poor results in those patients of the "special group," who almost certainly did have enough, hardly suggest that a mere increase of dosage would produce better results.

An alternative explanation of failure is the nature of the fibrinolytic preparation itself. Thrombolytic is designed to exert its action by virtue of its content of preformed plasmin, and Alkjaersig (1961) has stated that rapid formation of plasmin in the circulating bloodstream usually results in lysis of the fibrinogen in it and not of thrombi. She claims indeed that thrombolysis can be achieved *in vivo* only by activation of plasminogen already absorbed on to the fibrin in such thrombi and that streptokinase alone, therefore, should have a much better chance of success. The work of Ambrus *et al.* (1961) is, however, in conflict with these views, for they have shown that in dogs better thrombolysis stems from the use of streptokinase-activated plasmin than of streptokinase alone. Moreover, Rueggsegger's experimental work, upon which the present study was based, was done using thrombolytic itself. The question of whether in their work it was the preformed plasmin or, after all, some streptokinase activator contaminant which was effective is therefore perhaps rather academic.

A final possibility in the present study is that the thrombi were lysed but that the observations made failed to demonstrate it. The omission of coronary angiography was deliberate, since it has its own hazards and problems, but if lysis can be demonstrated only by that technique then it can have very little value to patients.

Summary

Seventy-five patients suffering from acute coronary thrombosis have been included in a clinical trial of a fibrinolytic agent, thrombolytic, which is designed to exert its action predominantly by its content of preformed plasmin.

The 38 treated patients were given the drug by intravenous infusion in a dosage of 50,000 units an hour over a 12-hour period, and the 37 controls were given comparable infusions of 5% glucose in water. Both groups were then given routine anticoagulant therapy.

Examination of the venous blood has shown that a high level of fibrinolytic activity was attained in a large proportion of the treated group, and side-effects were confined to slight pyrexia.

A comparison of the clinical progress, the electrocardiograms, and the transaminase curves did not demonstrate any differences between the treated and control groups. A separate analysis of 12 cases that

showed particularly intense fibrinolytic activity was likewise negative.

At three months after the infarct seven of the treated and six of the controls had died. Necropsies in 14 patients who died under observation did show some histological differences of doubtful significance, but there was no evidence that thrombi had been lysed.

It is concluded that this scheme of treatment has been ineffective, and the reasons for this are discussed.

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Twenty-eight students have started the first year of the six-year medical degree course at the University College of Rhodesia and Nyasaland in Salisbury. They have been selected from over 110 applicants, and include five women, 13 European, and 10 non-European male students. After they have completed their pre-medical training in the various sciences at the existing University College accommodation, they will go forward to the various stages of their clinical training in the Medical School. The foundation stone of the Teaching Hospital and Medical School will be laid by the Marquess of Salisbury on April 5. The University of Birmingham is to grant its own degrees to the students of the multi-racial medical school. The University College of Rhodesia and Nyasaland is a college in special relationship with the University of London and it is the degrees of this University that are awarded in the present faculties of the University College in Salisbury. (Rhodesia House, March 15.)