Preliminary Communications

Streptokinase and Deep Vein Thrombosis

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[WITH SPECIAL PLATE BETWEEN PAGES 718 AND 719]

Summary: Five patients with deep vein thrombosis were given streptokinase. Five others with similar phlebograms were given anticoagulants, and the results assessed by examining changes in the iliac, femoral, and calf segments of the phlebograms when repeated 7-10 days later. Those of the anticoagulant group were unchanged. Four of the five given streptokinase had a reduction in the size and extent of their thrombosis. Fresh thrombus surrounded by flowing blood was lysed. Thrombus completely blocking a vein was not lysed.

The indications for the use of streptokinase in deep vein thrombosis are reviewed.

INTRODUCTION

The existence of an in-vivo mechanism by which the blood could be made incoagulable was known to Morgagni (1761) and Hunter (1794), but the precise details of the fibrinolytic system were not fully understood until the 1940s. Johnson and McCarty (1959) demonstrated the therapeutic potential of fibrinolysis when they showed that plasmin could lyse a thrombus induced in the superficial arm veins of volunteers. These experiments stimulated a considerable interest in the value of activators of the fibrinolytic system (streptokinase or urokinase) as a method of treating venous and arterial thrombosis and embolism. The result of this interest has been the publication of some excellent studies on arterial thromboembolism—for example, Verstraete *et al.* (1963)—but venous thrombosis has been represented only by a number of short reports, most of which claim clinical improvement without any objective evidence to support the claim that thrombolysis has occurred.

The treatment of venous thrombosis *cannot be assessed on clinical grounds* because the physical signs give little or no indication of the extent or progress of the underlying disease. For example, many cases of venous thrombosis have no physical signs and are discovered only when the patient has a pulmonary embolus (Sevitt, 1967), whereas others show marked improvement of their physical signs during "treatment" without any visible change on the phlebograms (see later Fig. 5 A and B). Therefore we decided to assess the effect of streptokinase (Kabikinase) on deep vein thrombosis by phlebography alone, and this paper describes the results in five pairs of patients, one of each pair having been given streptokinase, the other heparin and warfarin.

METHODS

PATIENT SELECTION

Patients were considered for this study if they had the clinical signs of deep vein thrombosis and if this was confirmed by phlebography; four had had minor pulmonary emboli. Patients with heart failure to whom the administration of extra fluid would be inadvisable were not accepted. Patients with gross ankle and foot swelling which would have made repeated phlebography difficult were also excluded, as were any with possible sites of bleeding—for example, peptic ulcers or recent operation wounds. With such criteria it took over a year to collect this small series of five pairs. The allocation to the streptokinase or anticoagulant group was not entirely a random procedure, for an attempt was made to get matched pairs of phlebograms. The Table gives the main facts about each patient, a description of the extent of the thrombosis, an assessment of the age of the thrombus based on the clinical history and phlebographic appearances, and the results of treatment.

Details of Cases

Case No.	Sex and Age	Site of Thrombus	Age of Thrombus (Days)	Partial or Complete Block	Effect of Treatment. Thrombus Lysed
		Cases Treated with Streptokinase			
1	F 45	I.V.C.	<7	P	100%
		Iliofemoral	<7	C	0
2	M 27	I.V.C.	<7	P	100%
		Iliofemoral	7–10	C	0
		Collaterals (obturator)	<7	P	100%
		Calf	<7	Mixed	5%
3	F 30	Femoral	<7	C	0
		Calf	<7	P	Worse. Complete occlusion
4	M 32	Calf	<7	P	80%
5	F 62	Calf	14–21	Mixed	15%
		Cases Treated with Anticoagulants			
6	F 32	I.V.C.	<7	P	No change
		Iliofemoral	7–14	C	No change
7	M 32	Iliofemoral	7–21	C	No change
8	M 16	Femoral	<7	P	No change
9	M 62	Femoral	<7	P	No change
10	M 75	Calf	7–21	P	No change

PHLEBOGRAPHY

The first phlebogram was performed before treatment was begun in order to confirm the diagnosis and delineate the extent and nature of the thrombosis (Browse *et al.*, 1967).

The patient lay on a tilting-table. A rubber tourniquet (Setoniquet, Seton Products Ltd., Oldham, Lancs) was placed above the ankle to distend the superficial veins of the foot. A 1-in. (2.5-cm.) 20-gauge needle was inserted into a vein on the lateral aspect of the dorsum of the foot. The needle was directed distally (upstream). If percutaneous puncture was not possible a small cut-down was made.

The needle was connected with a polyethylene tube to a 50-ml. syringe containing 40 ml. of the contrast medium, Conray 280 (meglumine iothalamate). The foot was internally rotated to separate (radiographically) the tibia and fibula.

The table was tilted 20°, feet downwards, and the contrast medium injected by hand under television control. The tourniquet was adjusted until the deep veins were filled. Deep vein filling was sometimes improved by flexing the foot a few times or placing an additional tourniquet above the knee. Split 14 by 14-in. (35.5 by 35.5-cm.) films were taken of the whole venous system from the calf to the pelvis during injection of the contrast medium under television control. At the end of the injection the table was tilted 20° head downwards to fill the common femoral and pelvic veins. The upper portion of the profunda vein was shown by asking the patient to perform a Valsalva manœuvre when the common femoral vein was full of contrast medium.

After the ascending phlebogram at least 100 ml. of normal saline was injected into each leg and the legs were exercised to clear the contrast medium from the veins. This was checked by television.

This examination caused minimal discomfort to the patient, and required 45 minutes to complete. Reactions to the contrast medium—nausea and vomiting, hot flushes, and an occasional urticarial rash—are uncommon, and none was seen in the patients reported in this study.

This technique of ascending phlebography usually showed the whole of the deep venous system from the ankle to the inferior vena cava, but if the femoral and iliac veins were not visualized percutaneous femoral vein injections were given.

If the ascending phlebogram showed a complete iliac vein block or if the percutaneous femoral puncture was unsuccessful a bilateral simultaneous pertrochanteric intraosseous pelvic phlebogram was performed (Cockett and Lea Thomas, 1965).

Both legs were always examined before treatment, but the follow-up studies were done only on the affected side.

The follow-up phlebograms were performed two to five days after the end of the streptokinase treatment when the patients were stable on oral anticoagulants. All the control group were given anticoagulants, and the follow-up phlebograms were performed on the seventh to tenth day after treatment was started.

Interpretation

Venous thrombus appears on a phlebogram as a filling defect in the veins. It is usually not adherent to the vein wall and so appears as a central filling defect surrounded by a thin stream of more dense contrast material. The semi-opaque appearance over the thrombus has been likened to "ground glass" by Dos Santos.

If the thrombus completely occludes the vein then it cannot be seen on the phlebogram, and in this study we accepted non-filling as indicative of complete thrombotic obstruction only if all the veins above, below, and collateral to the obstructed vein were clearly displayed.

As a thrombus ages it either extends to block the vein completely or retracts and becomes adherent to one side of the vein, its free surface becoming slightly irregular and much more clearly defined. There is no good evidence of when these changes occur, but our experience of over 200 phlebograms has led us to believe that retraction and adherence begin to appear when the thrombus is 7 to 10 days old, and are most marked at about three weeks. A complete block does not alter until recanalization begins, but thrombus that is only partly adherent becomes smaller and smoother as it retracts and the vein remodels its lumen to accommodate flow. We believe, therefore, that it is possible to give an approximate estimate of the age of a thrombus based on the appearance of the phlebogram (Lea Thomas *et al.*, to be published).

Streptokinase Therapy

Verstraete *et al.* (1966) described a regimen for the administration of streptokinase which gave an adequate degree of thrombolysis in 97% of the population living around his hospital in Belgium. Other workers have suggested that the large initial dose he recommends (1.2 mega units) is not necessary (Poliwoda *et al.*, 1966). For this reason and because we have observed a considerable number of minor side-effects with the 1.2 mega units initial dose we have used a smaller loading dose. The treatment was uncontrolled, in that no measurements of plasma thrombolytic activity were made.

The regimen was as follows:

(1) Any anticoagulants, if already being given, were stopped. Streptokinase was not begun until four hours after the last dose of heparin.

(2) Prednisolone 50 mg. was given intramuscularly one hour before starting streptokinase.

(3) (*a*) 600,000 units of streptokinase in 250 ml. of dextrose saline, plus 100 mg. of hydrocortisone, were given in the first hour through a polyethylene catheter inserted into a forearm vein. (*b*) The infusion was then continued for three days, giving 600,000 units of streptokinase in 500 ml. of dextrose saline, plus 100 mg. of hydrocortisone every six hours—that is, a maintenance dose of 100,000 units/hour.

(4) Pulse rate, blood pressure, and temperature were measured every 15 minutes during the first two hours of infusion and then four times a day. The patient was watched for any signs of bleeding and the urine tested for blood each day. Aminocaproic acid (Epsikapron) was kept on the ward in case it became necessary to reverse the effect of streptokinase.

The patients were confined to bed, but no restrictions were placed on movement in bed, on diet, or on fluid intake. The legs were not bandaged; the foot of the bed was raised on 12-in. (30-cm.) blocks.

(5) Conversion to anticoagulation after the streptokinase varied. In Cases 1 and 2 heparin 5,000 units four-hourly was given intravenously, beginning four hours after the streptokinase infusion ceased, together with an oral loading dose of warfarin. The heparin was stopped and the prothrombin time measured 48 hours later. In Cases 3–5 the loading dose of warfarin (45 mg.) was given on the second day of the streptokinase infusion. Then 10 mg. was given the day after the infusion ceased and the prothrombin time measured the following day.

Anticoagulant Therapy

The majority of the patients in this study were under the care of other physicians or surgeons and consequently those allocated to the control group were anticoagulated in the manner prescribed by the consultant in charge. This was usually four- or six-hourly doses of 5,000 units of heparin for 48 hours followed by warfarin. The dose of warfarin was controlled by the coagulation laboratory. A prothrombin index of 1.8–2 was considered ideal—that is, twice the normal. These patients were kept in bed for the first three days of treatment so that they matched the test group, but we decided not to give them a three-day intravenous infusion of dextrose saline as we felt that the extra restriction of mobility was small and that the infusion would add to the morbidity by causing some cases of superficial thrombophlebitis.

Results

We have assessed the results by examining the changes in the three main segments of the venous system (iliac, femoral, and calf veins), rather than compare pairs of patients. This makes the results easier to understand and has allowed us to form some tentative conclusion.

Partial Thrombosis of Inferior Vena Cava

Three patients (Cases 1, 2, and 6) had irregular fresh thrombus jutting from the mouth of the left common iliac vein into the beginning of the inferior vena cava which partly obstructed the vena cava and the end of the right common iliac vein and extended up the left-hand side of the cava for 2–6 cm.

Cases 1 and 2 were given streptokinase, the follow-up venograms showing complete clearing of the inferior vena caval thrombus (Special Plate, Figs. 1 A and B, and 2 A and B). Neither of these patients developed signs of an embolus during treatment.

Case 6 was given anticoagulants, and the phlebogram at 20 days showed a smoothing-out of the surface of the thrombus in the cava, but there was little or no reduction in its size, and the cava was still partly occluded (Special Plate, Fig. 3 A and B).

Comment.—There was definite lysis of the fresh thrombus jutting into the main stream of caval blood flow.

Iliac Vein Thrombosis

Four patients (Cases 1, 2, 6, and 7) had thrombosis of the common and external iliac veins; all had oedema of the thigh up to the groin. Cases 1 and 7 presented with phlegmasia cerulea dolens. Streptokinase was given to Cases 1 and 2.

Case 1.—A woman aged 45 had a history of massive swelling of the left leg and a probable pulmonary embolus eight years ago. The leg returned to normal but suddenly became swollen, blue, and painful eight days after a hysterectomy. Her phlebogram showed a complete block of the left iliac veins, with many collateral vessels diagnostic of long-standing thrombosis, but there was fresh thrombus in the inferior vena cava (see above). It is most likely that the massive swelling was due to a fresh thrombosis in a previously blocked but recanalized iliac vein. Streptokinase was begun five days after the onset of the recent episode of swelling.

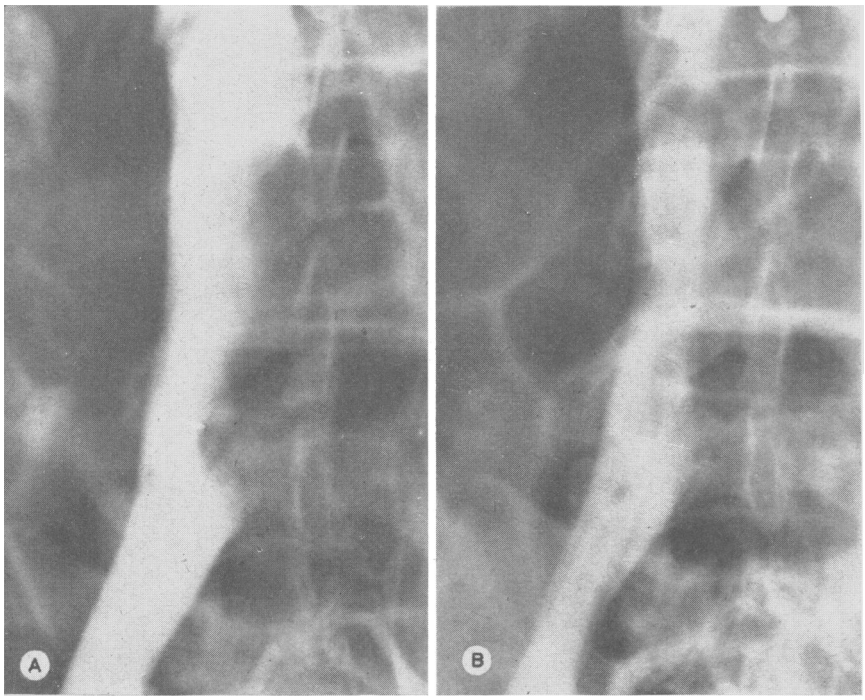

FIG. 1.—A, The inferior vena cava of Case 1. Note the fresh thrombus jutting into the cava and extending up its left-hand side. B, This print is less magnified than A. There is complete lysis of the caval thrombus after streptokinase. The complete iliac vein block was not changed.

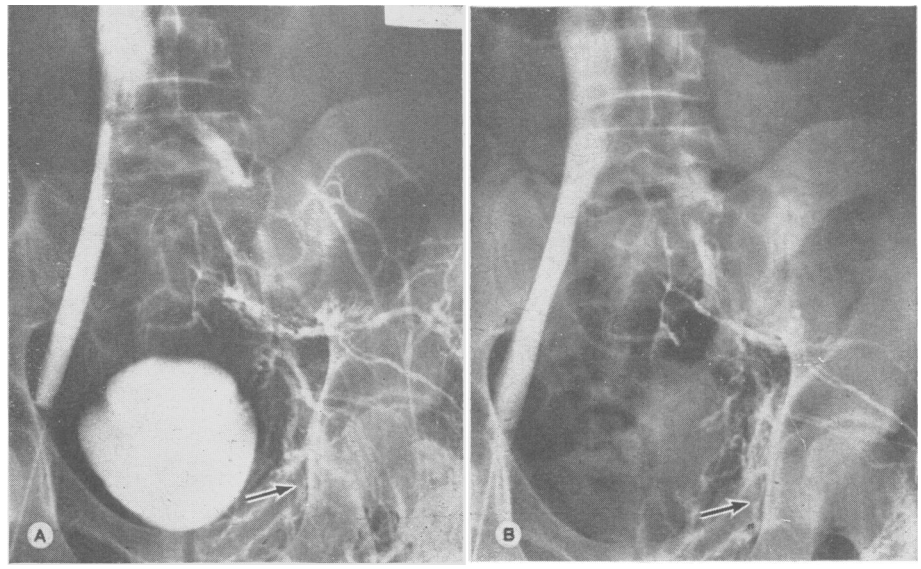

FIG. 2.—A, The phlebogram of Case 2. There is fresh thrombus in the inferior vena cava spreading up the left-hand wall and down into the mouth of the right common iliac vein, a complete block of the left iliac veins, and fresh thrombus in the obturator vein (arrowed). B, After streptokinase. Lysis of the caval and obturator thrombus (arrowed). No change in the external iliac vein, progression to complete occlusion in the left common iliac vein.

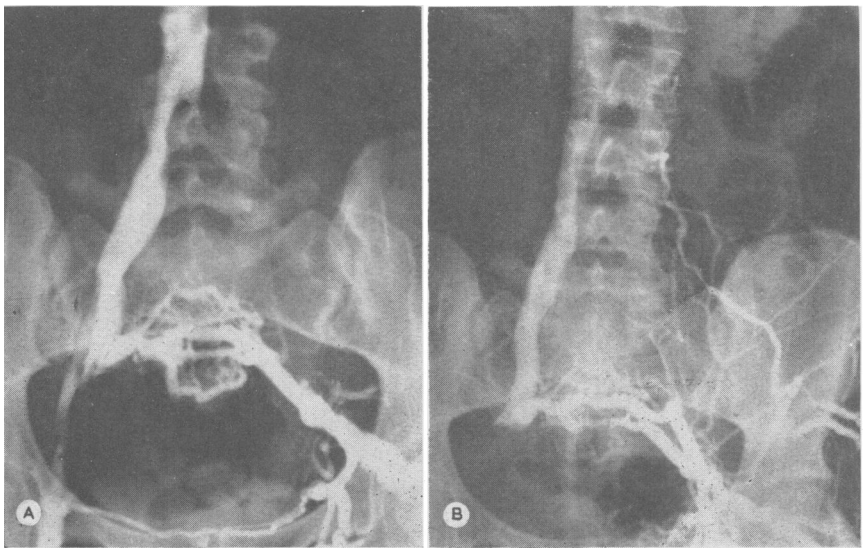

FIG. 3.—A, Control phlebogram of Case 6 shows a complete iliac occlusion with thrombus jutting into the cava. B, Phlebogram after 20 days of anticoagulants shows a smoothing out of the thrombus and extension upwards. There is some retraction of the thrombus without significantly reducing its size. This print is only two-thirds the magnification of A.

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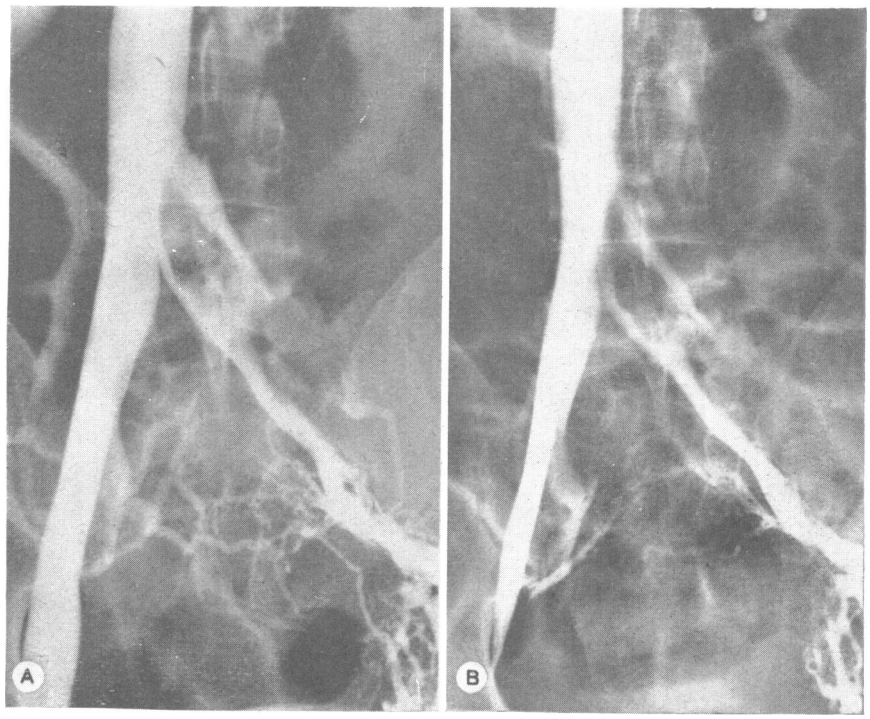


FIG. 4.—A, Phlebogram of Case 7 showing a complete block of the external iliac vein and a partial block of the common iliac vein. B, The phlebogram seven days later, patient receiving anticoagulants, was unchanged.

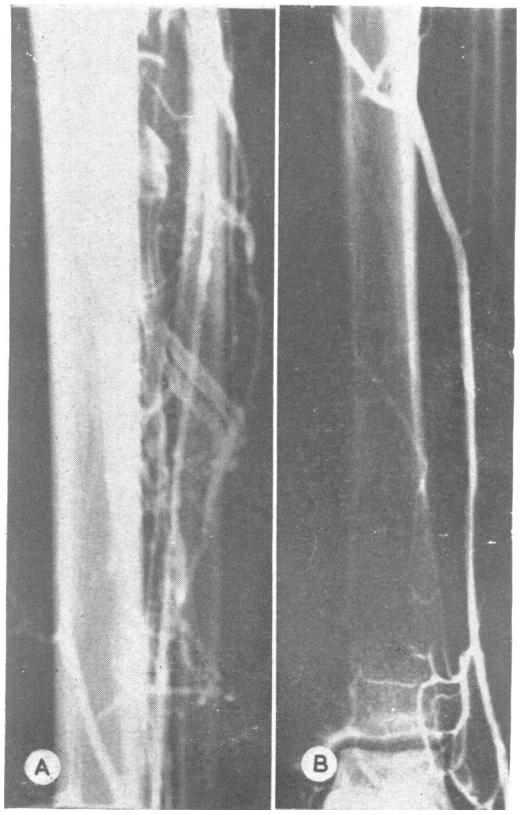


FIG. 5.—A, Phlebogram of Case 3 shows extensive fresh thrombus in the calf veins; other films showed a complete femoral block. B, Os calcis interosseous phlebogram after streptokinase. All the thrombus has become adherent, completely blocking the deep calf veins. An interosseous injection was given to confirm the complete block, first demonstrated by the routine intravenous phlebogram. In spite of this phlebographic deterioration the patient's symptoms of pain and swelling had improved.

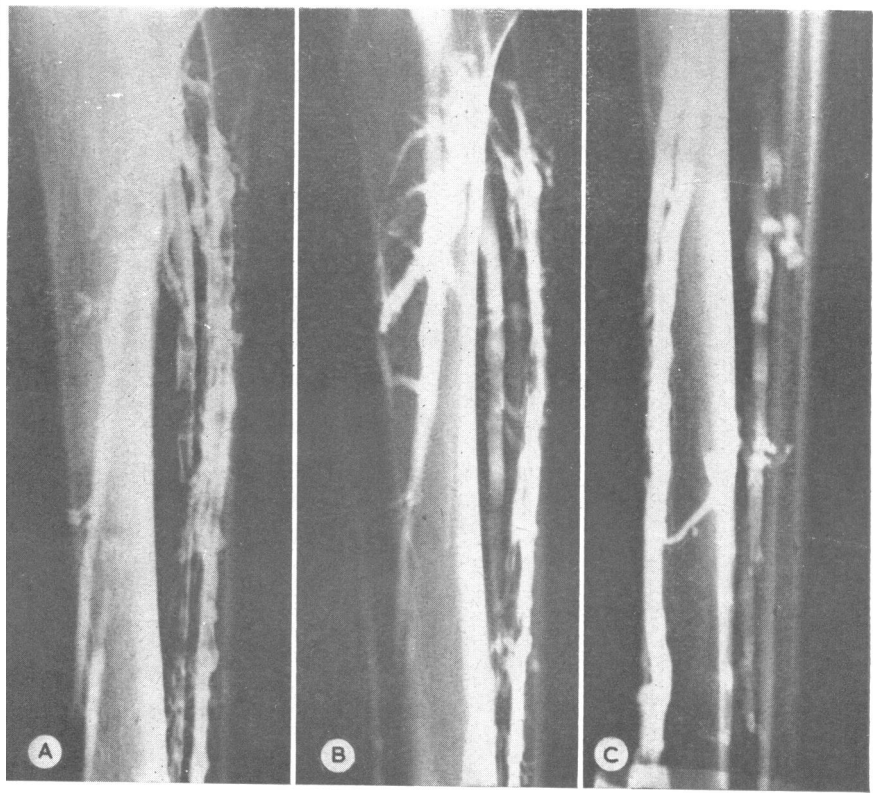


FIG. 6.—A, Phlebogram of Case 4 shows extensive fresh thrombus in the deep veins of the calf. The popliteal and femoral veins were normal. B, Almost complete clearing of the veins after streptokinase. Note that the valves are present and appear competent. C, Phlebogram obtained nine months later. Veins still patent and valves competent.

There was no change of this patient's iliac block, though her caval thrombus was lysed (Special Plate, Fig. 1 A and B).

Case 2.—A man aged 27 gave a history of swelling of the left leg for three days before treatment began, but he had also had a febrile illness two months previously that caused him to spend seven days in bed. The phlebogram (Special Plate, Fig. 2 A) showed a completely blocked left common and external iliac vein except for a thin strip of the last 3 cm. of the common iliac vein. The age of the thrombus could not be definitely ascertained. It was probably at least seven days old, but parts may have begun two months previously during his febrile illness. There was no improvement after streptokinase (Special Plate, Fig. 2 B); in fact, the segment of common iliac vein that was patent had occluded, but thrombus in the inferior vena cava and in the left obturator vein, which was developing into a collateral, was completely lysed (Special Plate, Fig. 2 A and B, arrowed).

Case 6.—A woman aged 32 gave a history of swelling of the leg for five days and an episode of pleuritic chest pain and haemoptysis two weeks previously. The phlebogram showed that the iliac veins were completely blocked. The thrombus may therefore have been anything from 5 days to 2 weeks old. A phlebogram performed after three weeks of anticoagulants was no different from the control film (Special Plate, Fig. 3 A and B).

Case 7.—This man aged 32, had swelling of the left leg and thigh for one week before admission but an episode of pleurisy (? pulmonary embolus) three weeks earlier. The phlebogram showed an iliac thrombosis involving the whole of the external iliac vein and part of the common iliac vein (Special Plate, Fig. 4 A). On clinical grounds the thrombus could have been from 1 to 3 weeks old, but the radiological appearance of the thrombus in the common iliac vein was more suggestive of a 3-week-old thrombus. There was no change in the phlebogram after one week of anticoagulants (Special Plate, Fig. 4 B).

Comment.—No thrombolysis by streptokinase of two complete iliac vein blocks due to thrombus which was probably at least 1 week old. Both patients showed evidence of thrombolysis at other sites.

Femoral Vein Thrombosis

Case 2.—The history of this patient has been discussed. His iliac thrombosis extended down the femoral vein to its attachment in the upper popliteal vein. A very thin strip of contrast medium could be seen in the phlebogram around the thrombus along the whole of the superficial femoral vein so that the vein was almost totally occluded. The thrombus in the upper popliteal vein showed signs of retraction. There was no feature in the history to help with the assessment of the age of this thrombus; our estimate was that it was probably 7 to 10 days old. Streptokinase did not affect this thrombus. In the second phlebogram the popliteal thrombus was unchanged but the superficial femoral vein thrombus had progressed to block the vein completely.

Case 3.—A woman aged 30 developed swelling of her left leg and thigh five weeks after chidlbirth. Her phlebogram showed a completely blocked superficial femoral vein, and streptokinase was begun six days after the onset of swelling. The thrombosis was not changed by streptokinase.

Case 8.—A boy of 16 developed a femoral vein thrombosis after a blunt injury to the left iliac fossa and a fractured pelvis. The first phlebogram showed a fresh thrombus extending along the whole of the left superficial femoral vein. He was given anticoagulants. The follow-up phlebogram showed the beginning of retraction and adherence of the thrombus but no thrombolysis.

Case 9.—A man aged 62 was seen two days after a pulmonary embolus, seven days after multiple ligations of varicose veins. He had a slight aching pain in the left groin but no swelling of the legs. The phlebogram showed a fresh thrombus adherent to one side of the femoral vein. This was unchanged after one week of anticoagulants.

Comment.—Relatively fresh thrombus (7 to 14 days) that was completely occluding the femoral vein was unaffected by streptokinase. The natural progression to complete adherence by thrombus which was almost blocking the vein was not prevented, but there was no longitudinal extension of the thrombosis in either group of patients.

Calf Vein Thrombosis

Case 2.—This case has already been described. The phlebogram of his calf failed to fill two of the main channels. In the repeat phlebogram these channels had become patent but they still contained some thrombus. As there were no technical difficulties with either phlebogram we think that this change was due to a minor degree of thrombolysis.

Case 3.—This woman had a history of tenderness in the calf and swelling of the whole leg for five days before phlebography. The phlebogram showed all the main venae comitantes of the calf to be patent but full of fresh thrombus. This patient also had a complete femoral vein block (see above). The phlebogram after streptokinase showed the calf veins to be completely occluded even though the symptoms of pain, tenderness, and swelling had improved (Special Plate, Fig. 5 A and B).

Case 4.—A man aged 32 presented with a history of recurrent attacks of pleuritic pain for two weeks. Two days before admission he developed pain and tenderness in the left calf. Phlebography showed fresh thrombus in the deep veins of the calf (Special Plate, Fig. 6 A). The combination of clinical and *x*-ray evidence suggested that this thrombus was less than a week old. Streptokinase lysed all of this thrombus (Special Plate, Fig. 6 B). Two very small pieces of older thrombus and one short completely blocked segment were unchanged. The valves in the veins that had been cleared of thrombus were competent and were normal in a late follow-up phlebogram performed nine months later (Special Plate, Fig. 6 C).

Case 5.—A woman aged 62 had episodes of pleuritic pain for three weeks before admission, but the valves were tender for only five days. Phlebography showed a complete occlusion of the venae comitantes of the anterior tibial artery with a small amount of non-adherent thrombus above and below the complete block. Streptokinase lysed the very small pieces of non-adherent thrombus but did not alter the complete block.

Case 10.—A man aged 75 had a history of pain in the chest three days before admission and pain in the right calf and swelling of the ankle for two to three weeks. Phlebography showed small thrombi in the deep calf veins—some fresh, some old and adherent. After one week of anticoagulants the appearances were unchanged except for some retraction of the more recent thrombi.

Comment.—Fresh thrombus was lysed by streptokinase in three of the four patients. The fourth patient had an extensive block of the veins proximal to the calf veins and her thrombosis progressed in spite of the streptokinase and a prothrombin time of 30 seconds. Completely blocked veins were not altered.

Discussion

The studies of Verstraete *et al.* (1966) on the antistreptokinase titre of the population living around his hospital in Louvain showed that an initial loading dose of 1.2 mega units of streptokinase would produce adequate fibrinolysis in 97% of the population. We found that this large dose, given rapidly, occasionally caused side-effects such as pyrexia, rigors, loin pain, and even mild bronchospasm, in spite of adequate steroid cover, and so we decided to give only 600,000 units in the first hour followed by 100,000 units hourly. This meant that complete fibrinolysis may not have been achieved in some patients until the sixth or seventh hour of treatment but after this time all would have had a therapeutic level of fibrinolytic activity.

Others have suggested that a loading dose of the size we have used is more than adequate, and the general opinion is that a dose of 600,000 or 750,000 units followed by 80,000–100,000 units hourly will give effective therapeutic fibrinolysis in all but a few of the population (Poliwoda *et al.*, 1966).

Verstraete had two other reasons for recommending the massive initial dose. He was using streptokinase for the treatment of arterial occlusions where time was important, and in such circumstances, particularly when treating pulmonary emboli, we too would favour the massive dose (1.2 mega units) given in 30 minutes.

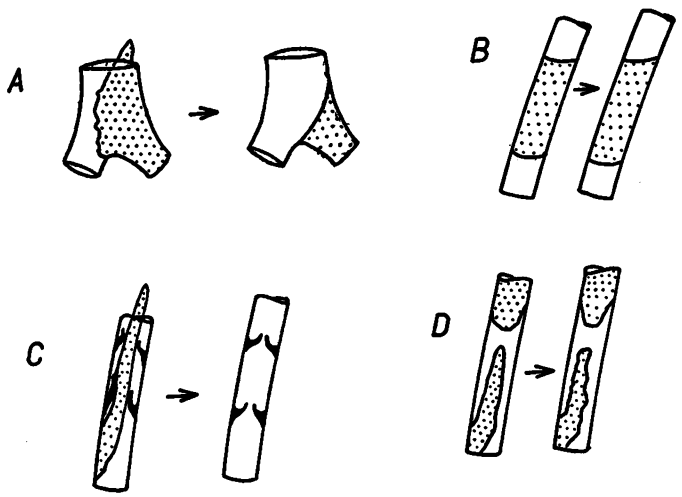
The other advantage of the massive dose is that the other circulating coagulation factors are not destroyed to the same extent as when streptokinase is given slowly. However, though some of our patients had prothrombin times of 40–50 seconds, only one had any bleeding. This patient (Case 5) had bruises over her pressure areas and moderate haematuria but it was not necessary to reverse the streptokinase. She had been on warfarin before beginning streptokinase, and it is probable that the combined effect of the two drugs was the cause of her bleeding.

Whatever the changes in the blood, four of the five patients given streptokinase in this manner showed some reduction in the size of their thrombus, and so we believe that our dose regimen did produce therapeutic levels of fibrinolysis. It would, of course, be better to measure the antistreptokinase titre so that the occasional person who needed a large initial dose could be picked up, but this study was performed with the object of testing an uncontrolled regimen that could be used safely by anyone in any hospital.

The clinical signs in the leg—swelling, discomfort, discoloration—have not been presented, for all improved during either form of treatment, some dramatically, whether there was any change in the phlebogram or not. This improvement was due to the development of collaterals and had nothing to do with the existing thrombosis, for none of the patients had a major vein unblocked by either form of treatment. This fact was particularly demonstrated by one patient (Case 3) who had a considerable extension of her calf vein thrombosis but her physical signs continued to improve because the new thrombus did not involve collateral channels.

Changes in the phlebographic appearance of a thrombus might have been due to fragmentation with embolism, autogenous fibrinolysis, contraction and retraction of the thrombus, or thrombolysis due to streptokinase. None of the patients treated with streptokinase had any physical signs or symptoms during treatment to suggest that they had had a pulmonary embolus and the thrombi in the control patients did not alter. Consequently we have interpreted any reduction of the size of the thrombus in the streptokinase-treated group as evidence of thrombolysis.

Only some of the thrombus was lysed by streptokinase, and our tentative explanation of why this should occur is summarized in the Diagram. These explanations are based on the phlebographic changes, but they agree with the theoretical considerations of the mode of action of streptokinase. Fresh (up to 7 to 10 days) thrombus jutting into a flowing stream of blood was lysed. Thrombus causing complete obstruction of a vein was not lysed even though it was quite fresh. Fresh thrombus not completely occluding a vein but below a complete block was not lysed.



Schematic representation of the effect of streptokinase. A and C, Fresh thrombus surrounded by flowing blood is lysed. Valves may be left competent. B, Thrombus completely blocking a vein is not lysed. D, Thrombus surrounded by blood but below a complete block, when presumably there is little blood flow around it, is not lysed.

There are two possible mechanisms of clot lysis. Firstly, the thrombolytic enzymes in the blood around the thrombus will gradually reduce its size by dissolving its outer layers. Secondly, the activator can diffuse into the thrombus and activate the entrapped plasminogen to plasmin and so cause simultaneous lysis throughout the whole thrombus. Both ways need an adequate meeting of blood and thrombus. It is logical to expect thrombus lying in a flowing stream to be lysed, as most of its surface is in contact with fresh activated blood and there is also mechanical action of the blood on the thrombus, tending to break off small particles from its surface. However, thrombus that is completely occluding a vein is less likely to be lysed, as it will be in contact with the blood stream only at its ends, so that the "washing off" action is absent and the area over which activator can diffuse into the thrombus is small. Such occlusive thrombi will also be more resistant to lysis as complete occlusion and adherence are a sign of advancing age, which means a greater degree of fibrin polymerization and organization. Our findings suggest that the first mechanism, lysis by slowly dissolving the surface of the thrombus, is the most important.

If our interpretation of the mode of action of streptokinase on venous thrombi is correct what is the place of streptokinase in the treatment of deep vein thrombosis? It would be wrong to make definite statements on studies from five patients, but we are at present using the following criteria to guide future studies.

(1) A phlebogram must be performed to assess the nature and extent of the thrombosis.

(2) Streptokinase is given in the dose regimen detailed above if: (*a*) There is fresh thrombus lying in a good flowing stream—that is, early propagated thrombus. (Unfortunately this type of thrombus is quite often symptomless. In the present study we have seen it in the calf veins, in collateral veins, and jutting from the iliac vein into the vena cava. We have felt obliged to perform thrombectomy on patients with large loose thrombi because of the danger of embolism, but it may be that the extensive early iliofemoral thrombus would be suitable for streptokinase treatment.) (*b*) If there is a danger of the thrombus progressing rapidly and making the symptoms worse, in particular, by clearing partial caval obstruction one may prevent the other leg becoming involved. (*c*) To reduce the incidence of late sequelae such as post-thrombotic venous valve incompetence, for if a thrombus can be lysed before it becomes adherent the valves are left competent.

(3) Streptokinase is not given if the veins are totally occluded.

These studies need to be continued and expanded, and be followed up over a period of 5 to 10 years, by phlebography, to assess the long-term value of the drug. As a total occlusion cannot be cleared one must rely on recanalization and the development of collaterals for permanent improvement, or, in the early case, surgical thrombectomy, though the long-term results of this operation are not very encouraging (Mavor and Galloway, 1967).

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REFERENCES

Browse, N. L., Lea Thomas, M., and Solan, M. J. (1967). *Brit. med. J.*, 4, 596.
Cockett, F. B., and Lea Thomas, M. (1965). *Brit. J. Surg.*, 52, 816.
Hunter, J. (1794). *A Treatise on the Blood, Inflammation, and Gunshot Wounds*, p. 26. London.
Johnson, A. J., and McCarty, W. R. (1959). *J. clin. Invest.*, 38, 1627.
Mavor, G. E., and Galloway, J. M. D. (1967). *Brit. J. Surg.*, 54, 1019.
Morgagni, G. B. (1761). *De sedibus, et causis morborum per anatomen indagatis libri quinque*. Venice.
Poliwoda, H., *et al.* (1966). "Thrombolytische Therapie," Symposium of the German Society of Angiology. Stuttgart.
Sevitt, S. (1967). *Brit. J. Surg.*, 54, 886.
Verstraete, M., Amery, A., and Vermylen, J. (1963). *Brit. med. J.*, 1, 1499.
Verstraete, M., Vermylen, J., Amery, A., and Vermylen, C. (1966). *Brit. med. J.*, 1, 454.