reached 360 mg./100 ml., heparin therapy was started: the pulsation of the femoral artery returned and the control arteriography showed patency: in this case the

TABLE X.—Some Findings in Case 12

	No. of Blood Sample	Normally Reactive Fibrinogen (mg. 100 ml.)	Fibrinolytic Activity of Plasma on Fibrin Film	
			Unheated (sq. mm.)	Heated (sq. mm.)
Before treatment	2	660	0	0
After injection of 500,000 units S.K.	3	621	256	110
	5	276	10	0
After injection of 500,000 units S.K.	6	145	473	0
	7	136	48	0
	8	318	20	0
	10	330	8	0
	14	474		

results of the streptokinase reactivity test suggest that the plasminogen was markedly depressed (less than 10% of the normal value). If this satisfactory therapeutic result could be reproduced a similar approach would be worth considering, as the fibrinogen level would increase and less bleeding might be expected.

Conclusion

In the first part of this survey the presence and extent of the intra-arterial occlusion were well documented by repeated arteriography. This being established, it was necessary to find a useful parameter for the control of streptokinase administration (rate and amount). No conclusive correlation was found between adequate thrombolysis and fibrinolytic activity of plasma on heated and unheated fibrin film, fibrinogen assay, and streptokinase reactivity tests. However, other factors may interfere, such as the organization of the clot, the reactivity of the vessel wall, the presence of collaterals, and the possible importance of injection of streptokinase close to the occlusion.

Summary

The relation between thrombolysis *in vivo* and changes of fibrinolytic activity on heated or unheated fibrin film, fibrinogen level, and streptokinase reactivity test was investigated.

The blood of the patients undergoing streptokinase infusion showed an increased fibrinolytic activity on heated fibrin film during more than half of the thrombolytic treatment period. It is, however, not possible to state that the thrombolysis was more frequent in this group than in the group of patients in whom a fibrinolytic activity on heated fibrin film was found during less than half of the treated period. The normally reactive fibrinogen was repeatedly assessed during the streptokinase infusion. If the initial fibrinogen level decreased to values under 100 mg./100 ml., effective lysis was obtained in three out of seven arterial occlusions. If the fibrinogen level was decreased but remained above 150 mg./100 ml. of plasma, certain dissolution of 50% of the arterial clots was obtained. This criterion is therefore not a valid one for predicting the adequacy of the thrombolytic trial. The *in vitro* reactivity of the blood to increasing amounts of streptokinase (S.K.R.T. test) was frequently determined in our patients subjected to a thrombolytic trial with streptokinase. These patients are divided according to the results of the S.K.R.T., the first group having a minimum lysis time above 10 minutes in more than half of the S.K.R.T. determinations, and the second group in less than half. Thrombolysis *in vivo* does not seem to be more frequent in either group.

On the basis of our findings we were unable to demonstrate a definite relation between thrombolysis *in vivo* and variations of the parameters used in this study.

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TREATMENT OF PERIPHERAL ARTERIAL OCCLUSION BY STREPTOKINASE PERFUSION

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The purpose of this paper is to describe the biochemical and clinical effects of local perfusion of streptokinase in the treatment of two patients with peripheral arterial occlusion.

Streptokinase owes its fibrinolytic properties to its ability to activate the fibrinolytic enzyme system. Though the detailed enzymatic reactions have not been fully elucidated, streptokinase probably reacts with a proactivator present in plasma to form plasminogen activator. Under the influence of activator the inert enzyme precursor plasminogen, a normal plasma globulin, is converted to plasmin, a proteolytic enzyme. As suggested by Sherry *et al.* (1959) clot lysis *in vivo* probably takes place by diffusion of activator into the thrombus, with conversion of clot plasminogen to plasmin. The plasmin so produced is close to the substrate of choice, fibrin, which is digested.

The object of streptokinase therapy in arterial occlusion is to accelerate this physiological process, and by producing rapid activation of plasminogen in thrombus or embolism restore vascular patency before distal tissue necrosis has taken place. With peripheral arterial occlusion, streptokinase is given by local perfusion in order to reduce dosage and systemic side-effects; angiograms can conveniently be made using the same cannula as serves to introduce the streptokinase.

Unfortunately it is difficult to induce a "thrombolytic" state with streptokinase without also producing a coagulation defect. This is due in part to digestion of circulating fibrinogen and other coagulation factors, in part to accelerated clot lysis, and in part to defective fibrin polymerization; these biochemical consequences of streptokinase infusion are considered in detail elsewhere (McNicol *et al.*, 1962).

A few well-documented single case reports of successful clearing of peripheral arterial occlusion treated with streptokinase have been published—for example, Verstraete and Amery (1962) and Cotton *et al.* (1962). The present communication gives an account of the successful use of streptokinase in two further patients.

Materials and Methods

Streptokinase.—A highly purified preparation, designed for intravascular administration, was kindly provided by Kabi Pharmaceuticals.

Citrated blood was collected by clean venepuncture. Nine volumes of blood were mixed with one volume of 3.8% sodium citrate in a graduated centrifuge tube.

Thrombin.—Parke Davis thrombin topical.

Euglobulin Lysis Times—The method of Nilsson and Olow (1962) was used. Results are expressed in the units of activity described by McNicol *et al.* (1963).

Fibrin plates were made up as described by Nilsson and Olow (1962), with the modifications described by McNicol *et al.* (1963). Thirty- μ l. aliquots of test solution are pipetted on to the surface of the plate, which is incubated for 18–20 hours at 37° C. Lytic activity is recorded in square millimetres as the product of two perpendicular diameters of the area of lysis.

Plasminogen was assayed by the caseinolytic technique of Remmert and Cohen (1949) as modified by Alkjaersig *et al.* (1959).

Fibrinogen was estimated by the method of Ratnoff and Menzie (1951) as modified by Alkjaersig (1960).

Thrombin clotting-times were performed by the method of Fletcher *et al.* (1959a).

Streptokinase sensitivity tests were carried out by the method of Johnson *et al.* (1957). To 0.2 ml. of plasma in each of a series of test-tubes streptokinase (500 units/ml.) was added in volumes ranging from 2 to 80 μ l. as measured in a microburette. Each plasma/streptokinase mixture was immediately clotted by the addition of 0.1 ml. of thrombin (20 N.I.H. units/ml.) and incubated at 37° C.: the times for complete clot lysis were noted. An initial dose of streptokinase was calculated for each patient from the concentration of streptokinase necessary to produce lysis in 20 minutes and an estimated plasma volume based on body weight. The initial dose of streptokinase should therefore neutralize circulating antibody to streptokinase and leave enough free streptokinase to provide a plasma-clot lysis-time of 20 minutes.

Case 1

A 33-year-old woman (in the eighth day of the puerperium after the normal delivery of her second child) was admitted to hospital with a history of sudden onset of pain in her left arm. The pulse was regular and

there was no evidence of heart disease. The pain, which started in the left upper arm and spread within minutes to the left forearm and left hand, was followed by a sensation of "pins-and-needles" and numbness of the left forearm and hand, the fingers of which became cold and fixed in flexion. On examination the left arm was cold and pallid from the elbow distally; there was left wrist-drop and loss of power of all muscles of the left hand, and anaesthesia of glove type was present from the left wrist distally. The features of Volkmann's ischaemic contracture were present. The left axillary pulse was present but not the left brachial, left radial, or left ulnar pulses.

Surgical exploration of the left axillary and brachial artery was carried out to determine whether there was a local occlusion which could be removed. The brachial artery was found to be filled with thrombus, and this extended distally as far as the wound would permit palpation. A "polythene" catheter was inserted into the axillary artery proximal to the block and the first angiogram (Fig. 1) taken. The tip of the catheter was at the junction of the axillary and brachial arteries. This angiogram shows thrombus throughout the brachial artery with coiled thrombus in the vessel extending beyond the elbow-joint. Collateral vessels from the axillary artery were also occluded. It was decided to give streptokinase intra-arterially, and this was started 10 hours after the clinical onset of the occlusion; a Harvard infusion pump was used. Rectal temperature was continuously monitored during perfusion and never rose above 100° F. (37.8° C.).

The sequence of events was as follows:

Day 1.—Start of perfusion; an antibody neutralizing dose of 350,000 units of streptokinase was given over 5½ hours, preceded by 100 mg. of hydrocortisone hemisuccinate intravenously. Passive flexion and extension of fingers and thumb was maintained every 10 minutes. At 5½ hours the streptokinase perfusion rate was reduced to 12,500 units/hour, at which it was maintained for the next 24½ hours. At 7 hours a repeat angiogram showed patency of the brachial artery to the level of the elbow-joint.

Day 2.—At 13½ hours there was no improvement in the features of ischaemia of the left hand and grave doubt on clinical assessment as to viability. At 16 hours hydrocortisone hemisuccinate 100 mg. intravenously; and started oral prednisone. At 17 hours good radial pulse restored—at this stage the hand was painful, cold, and dark purple. There was no sensation and no function, and clinically it did not appear viable. At 20 hours repeat angiogram showed patency of ulnar, radial, and posterior interosseous arteries to the level of the wrist-joint. At 24 hours the limb was warm to the finger-tips; radial pulse improved. At 26 hours started on warfarin sodium. At 27 hours repeat angiogram

FIG. 1.—Angiograms from Case 1.

revealed patency of the palmar arch. At 30 hours angiogram repeated and there was now clearing of the digital arteries. Streptokinase discontinued, and continuous intravenous heparin infusion started.

Day 3.—Heparin infusion continued. Marked oedema of forearm and hand.

Day 4.—Heparin infusion discontinued. Coumarin drug effect established; maintained on warfarin sodium at the 15% thrombotest level.

Day 13.—Clot removed from wound site.

Day 44.—By this stage the clinical picture was reasonably static and the features consequent on the ischaemia were: (a) complete loss of all forms of sensation in distribution of ulnar and median nerves and in distal distribution of superficial radial nerve from level of wrist; (b) paralysis of all interosseous muscles of the hand and also of extensor pollicis longus and extensor pollicis brevis; lumbricals functioning; and (c) slight contractures of long flexor muscles of the fingers and flexor pollicis longus; severe contracture of first dorsal interosseous muscle.

Case 2

A 64-year-old man, with no previous history of cardiovascular disease, complained of severe pain in the left leg of sudden onset, associated with pallor, coldness, and numbness of the leg below the knee. The heart was in sinus rhythm. He was first seen by us 18 hours later. At that time he was unable to move his ankle or toes, and his leg was insensitive to touch below the knee. It was apparent that he had occlusion of the superficial femoral artery at the adductor hiatus; this was confirmed by angiography. The foot did not appear to be viable and the alternatives in management were amputation, attempted surgical disobliteration, or treatment with streptokinase.

Intra-arterial infusion of streptokinase was begun 24 hours after the block occurred, and was continued for 60 hours. Streptokinase was administered, using a Harvard infusion pump, through a fine catheter introduced into the common femoral artery by the Seldinger technique and advanced until its tip lay just proximal to the block.

The progression of clot lysis was assessed by angiography performed through the catheter (Fig. 2) and by monitoring the skin temperature at mid-calf (Fig. 3). The rate of return of sensation is shown in Fig. 4. After 36 hours the pedal pulses in the left leg were readily palpable and the foot was obviously viable; movement of the ankle and toes had returned. The local infusion of streptokinase caused little upset to the patient. The rectal temperature, which was monitored throughout, ranged between 98 and 100° F. (36.7 and 37.8° C.). Prednisone (5 mg. six-hourly) and antibiotic cover were given prophylactically. Hydrocortisone hemisuccinate 100 mg. was given intravenously at the beginning of treatment.

Fig. 2.—Angiograms from Case 2.

As blood flow was restored progressive woody swelling of the calf and foot with pitting oedema was noted. The swelling was measured and reached a maximum on the third day. The leg was then elevated and the oedema regressed

Fig. 3.—Showing rise in mid-calf skin temperature during streptokinase therapy in Case 2.

Fig. 4.—Showing steady return of skin sensation during streptokinase therapy in Case 2.

during the subsequent three weeks. A cystic swelling remained, however, in the anterior fascial compartment of the leg. This was drained and found to contain thick pus (*Escherichia coli* on culture). Subsequently it healed uneventfully. Five weeks after the occurrence of the block the leg was of normal size; there was no sensory loss; voluntary dorsiflexion of the foot remained absent, but other movements were normal and there was a small area of epidermal loss at the tip of the fourth toe.

Biochemical Data

Case 1.—Results are shown in Fig. 5. After an initial dose of 350,000 units, intra-arterial perfusion was maintained with 12,500 units of streptokinase/hour. Fibrinolytic activity in the plasma, as demonstrated in the euglobulin lysis time and the fibrin plate test, was induced by the initial dose and was maintained for the duration of the perfusion. The maximum elevation of the thrombin clotting-time was to 15 seconds. Plasma plasminogen was depressed to zero, and fibrinogen fell to 110 mg./100 ml. Assays had all returned to normal values 10 hours after the end of the 30 hours' infusion.

Case 2.—Results are shown in Fig. 6. After an initial dose of 250,000 units (which induced fibrinolytic activity in the circulation) intra-arterial perfusion was maintained with 10,000 units/hour,

later increased to 20,000 units/hour; fibrinolytic activity in venous blood was elevated for the 60 hours of perfusion. Plasma plasminogen was depressed to zero at one point, and fibrinogen fell from 520 to 290 mg./100 ml. There was no change in the thrombin clotting-time.

FIG. 5.—Biochemical effects of streptokinase perfusion in Case 1.

FIG. 6.—Biochemical effects of streptokinase perfusion in Case 2.

Discussion

Because of its tendency to cause fever, the risk of a grave coagulation defect, and difficulties in laboratory control, streptokinase is not the ideal thrombolytic agent. It is, however, the only reasonably satisfactory fibrinolytic substance at present available (McNicol *et al.*, 1962). In both patients presented in this communication, intra-arterial streptokinase perfusion, for 30 to 60 hours respectively, was effective in clearing extensive arterial thrombosis; but the angiograms were more gratifying than the clinical outcome, as both patients were left with residual disability. However, both might have required amputation if streptokinase had not been available, and the therapy can be regarded as a qualified success. If treatment had been initiated more quickly after occlusion, the outcome might have been better; in particular, the woody oedema of the muscles noted in both our patients, which was possibly due to restoration of flow through capillaries rendered unduly permeable by prolonged anoxia or to muscle infarction, might not have occurred. Only larger arteries can be mechanically cleared by the surgeon; a particular merit of thrombolytic therapy is its ability to clear small vessels beyond the reach of the surgeon, as, for example,

in the present patients, where the small digital arteries became patent during treatment.

Clinical Considerations

The evidence suggests that streptokinase therapy should be restricted to patients in whom vascular occlusion is recent; and because of the toxicity of streptokinase (McNicol *et al.*, 1962) it should not be given to seriously ill, debilitated, or old patients. Peptic ulcer or other lesions liable to bleed, and recent cerebral vascular accidents, are contraindications, as is also recent extensive surgery. As suggested by Cotton *et al.* (1962), streptokinase may well be most useful in obtaining clearing of distal vessels after surgical removal of proximal thrombus or embolism. For intra-arterial perfusion a constant-rate pump is necessary.

Therapy should be controlled by angiography, so that it can be stopped as soon as vascular clearing has been obtained; our experience and the experiments of Johnson and McCarty (1959) suggest that treatment for 30 hours or more may often be needed. We believe, with Fletcher *et al.* (1959b), that to prevent re-thrombosis anticoagulants should be given at the end of streptokinase therapy, but that anticoagulants should not be given concurrently with streptokinase because of the haemorrhagic risk. To reduce the incidence of pyrexial reaction (Nilsson and Olow, 1962) and the severity of the streptokinase-induced coagulation defect (Fletcher *et al.*, 1959a) steroids should be given with streptokinase.

Laboratory Considerations

Streptokinase is a streptococcal antigen, and antibodies to streptokinase are distributed through the population, varying in concentration over at least a fiftyfold range. Until enough streptokinase has been given to neutralize circulating antibody, the specific biochemical effect on the fibrinolytic system is not seen. For this reason with systemic streptokinase therapy, administration of an initial antibody neutralizing dose is essential. We have also given such an initial dose to the present patients treated by regional perfusion; and while further experience may show that this is not necessary, in the meantime, to be certain of inducing a thrombolytic state locally, administration of an initial antibody-neutralizing dose over one to two hours is recommended.

As regards the further infusion rate, this can be controlled with the euglobulin-lysis time and the thrombin clotting-time: infusion rate can be gradually increased until acceleration of euglobulin lysis is produced, provided only a slight prolongation of the thrombin clotting-time is observed. In our experience (McNicol *et al.*, 1962) the thrombin clotting-time has been the best indicator of the streptokinase-induced coagulation defect. A dosage rate which produces significant fibrinolytic activity in the circulation will almost certainly produce intense activity in the perfused limb.

Conclusions

We believe that for carefully selected relatively fit patients with recent thrombotic or embolic arterial occlusion, local perfusion with streptokinase can play a valuable part. Even in those cases where proximal thrombus has been removed surgically from a major occluded artery streptokinase treatment may be used as a sequel, to open up the still-blocked smaller peripheral

vessels beyond the reach of surgical methods of mechanical removal. Steroids should be given with the streptokinase, which should be followed by anti-coagulant therapy. Local streptokinase therapy, which should be initiated by administration of an antibody-neutralizing dose, can be controlled thereafter by relatively simple laboratory tests.

Summary

Two patients with peripheral arterial occlusion have been treated by local perfusion of streptokinase. The first was a 33-year-old woman with thrombosis in the left brachial artery during the puerperium. The second was a 64-year-old man with thrombosis in the left superficial femoral artery.

Streptokinase was infused through a catheter into the artery above the thrombus and in each case the flow of blood was restored, after 30 hours perfusion in the first patient and 60 hours in the second.

It is concluded that streptokinase can be of benefit to carefully selected relatively fit patients with recent thrombotic or embolic arterial occlusion.

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B.C.G. DISSEMINATION IN CONGENITAL HYPOGAMMAGLOBULINAEMIA

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[WITH SPECIAL PLATE]

The purpose of this paper is to report a case of congenital hypogammaglobulinaemia associated with widespread dissemination of B.C.G. organisms and a terminal *Pneumocystis carinii* pneumonia.

Case Report

The patient was born in February, 1961, the first child of healthy parents. The birth took place in a hospital which serves a part of Liverpool in which tuberculosis is relatively prevalent; all babies born there are vaccinated with B.C.G. unless parental consent is refused. The patient was vaccinated on the fourth day of life.

Six months later he was referred to Alder Hey Children's Hospital because a swelling had appeared in the left axilla five days previously. The lesion at the site of the vaccination over the left deltoid had developed when he was 6 weeks old and was still discharging. He was admitted for incision of the axillary abscess and a lot of thick green pus was evacuated. No organisms were seen in it or cultured from it by routine methods. At this time he weighed 14 lb. (6.4 kg.), although his weight had exceeded 15 lb. (6.8 kg.) a little while previously.

A month later neither the original B.C.G. lesion nor the axillary incision had healed. Hydrocortisone ointment (containing hydrocortisone, neomycin, and bacitracin) was applied locally without effect. The infant was readmitted at the age of 9 months. His weight had dropped to 12½ lb. (5.7 kg.) and there was a history of poor appetite and nocturnal cough for two months. For a fortnight he had been listless.

He was ill and unhappy, with a curious flush to the face. His skin was dry and rough, particularly on the extremities,

and there were a few petechial haemorrhages on the legs. He had clearly lost weight. His muscles were very soft and he could not sit up. His B.C.G. ulcer and axillary sinus were still discharging.

A chest radiograph showed diffuse miliary shadowing throughout both lungs (Fig. A). The total white-cell count was 9,000/c.mm. with only 7% lymphocytes. The total serum protein level was 5.3 g./100 ml., of which just over half was globulin. Paper strip electrophoresis showed a raised α_2 -globulin (1.02 g./100 ml.) and a very low γ -globulin (0.21 g./100 ml.). A swab from the axillary sinus showed large numbers of acid- and alcohol-fast bacilli. The Mantoux reaction was negative up to 1:100 old tuberculin.

On the basis of these findings the provisional diagnosis was felt to be congenital hypogammaglobulinaemia with either disseminated B.C.G. infection or *Pneumocystis carinii* pneumonia. Treatment was started with streptomycin, *p*-aminosalicylic acid, isoniazid, and γ -globulin. However, his condition continued to deteriorate with increasing respiratory distress and cyanosis. A chest radiograph on November 16 showed the shadowing to be more confluent (Fig. B), and he died later the same day.

Further investigations, some of which were not completed until after the infant's death, gave the following results.

Tibial bone-marrow: erythroid and myeloid series show normal maturation; megakaryocytes present; plasma cells not seen.

Serum protein immuno-electrophoresis (Dr. J. F. Soothill): γ -globulin 20 mg./100 ml. γ 1-macroglobulin 6% of standard "normal" serum.

Blood group (Dr. D. Lehane): group A₂ Rh positive; weak anti-B demonstrated at 4.6° C. only.