patients treated with streptokinase, one of seven treated with Arvin, and two of seven given heparin.

Streptokinase was shown to cause extensive dissolution of thrombi in all but two of the 12 patients studied, sometimes within 12 hours but in one patient not until after six days of continuous infusion.

Methods and aims of laboratory control were discussed (Kakkar *et al.*, 1969) and the side effects of each treatment described. Two fatal cases of retroperitoneal haemorrhage occurred in the heparin-treated group. There was only one other case of severe bleeding, an increased menstrual flow in a patient receiving streptokinase, and this was easily controlled. Most of the patients given streptokinase, but not those in the other groups, developed a pyrexia sometimes with rigors. One patient suffered a serious allergic reaction after a small part of the loading dose of streptokinase had been given; this responded to an antihistamine and hydrocortisone and the infusion was continued with ultimately complete dissolution of the thrombus.

Full results of the trial will be reported elsewhere.

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Two further papers relating to 10 patients each were read by Drs Browse and Olow.

HAEMODYNAMIC AND ANGIOGRAPHIC FINDINGS IN PATIENTS WITH PULMONARY EMBOLISM TREATED WITH STREPTOKINASE

G. A. H. MILLER (*Cardiac Department, Brompton Hospital, London*) Nine patients with arteriographically proven pulmonary emboli have been treated by a 36-hour infusion of streptokinase (Kabikinase^(R), AB Kabi, Stockholm) into the pulmonary artery (eight patients) or right atrium (one patient). In all patients single-plane (anteroposterior) serial pulmonary arteriograms were obtained before treatment and repeated, sometimes on two occasions, at times varying from 24 hours to a month after starting treatment. In all but one patient an indwelling pulmonary artery catheter permitted repeated haemodynamic measurements during treatment and was used for the infusion of streptokinase, generally a dose of 600,000 IU for the first half hour followed by 100,000 IU/hour thereafter. The results were as follows:

1 *Acute massive pulmonary embolism.* Four patients studied within 48 hours of the acute episode were shown arteriographically to have emboli involving at least half of the major pulmonary artery branches. All exhibited the characteristic haemodynamic disturbance of massive pulmonary embolism with moderate elevation of pulmonary artery pressure, wide arteriovenous oxygen difference and (in three of the four patients) mild arterial oxygen desaturation. Haemodynamic improvement was evident in all at 12 to 15 hours after starting streptokinase and, in three of the cases without preexisting cardio-respiratory disease, was complete at the final study

48 hours, six days, and 28 days later respectively. The fourth patient had evidence of preexisting thrombo-embolic disease and had mild residual pulmonary hypertension (33 mm Hg systolic) at the final study 34 days after starting treatment. Arteriographic improvement was seen as early as 24 hours and was complete in two patients when studied at 48 hours and six days respectively. In the remaining two patients considerable arteriographic improvement was present at 48 and 65 hours respectively. One of the patients, who was not critically ill, was initially treated with heparin alone for six days. No haemodynamic or angiographic improvement had taken place by this time but was complete 48 hours after starting a 36-hour infusion of streptokinase.

2 *Chronic pulmonary thromboembolism.* Three patients with a history of longer duration were treated with streptokinase. In one, embolism had occurred six weeks previously, in another repeated emboli had probably occurred over weeks or months, and the third patient had a left pulmonary artery thrombosis at the site of an attempted delayed embolectomy for massive embolism occurring three months previously. In none was there any haemodynamic improvement when studied shortly after completing treatment and angiographic improvement was at the most slight in two and absent in the third patient.

3 *Minor recent pulmonary embol.* In two such patients streptokinase infusion was followed by complete disappearance of the filling defects seen on the pulmonary arteriograms when these were repeated at two and three days respectively.

Complications of treatment included bleeding from skin incisions, haematoma formation, haematuria, and vaginal bleeding.

The indications for streptokinase in treating pulmonary embolism are not yet clear. Encouraging results were obtained in acute massive pulmonary embolism and these patients were spared embolectomy. Nonetheless there will be patients in whom the delay in response associated with streptokinase therapy is unacceptable and in whom embolectomy may be life-saving. Little benefit was obtained in three patients with thromboembolism of longer duration but resolution of minor recent emboli was demonstrated within three days in two patients. There is an urgent need for a controlled trial of streptokinase and of heparin therapy in such patients.

THROMBOLYTIC THERAPY IN CORONARY THROMBOSIS

H. A. DEWAR AND I. S. MENON (*Royal Victoria Infirmary, Newcastle-upon-Tyne*) The use of thrombolytic agents in coronary thrombosis has been based on the experimental work of Rueggsegger, Nydick, Hutter, Freiman, Bang, Clifton, and LaDue (1959). They described the lysis by streptokinase of thrombi artificially produced in the coronary arteries of dogs and showed that this lytic agent also substantially modified the histological appearances of the infarcts which followed the thrombosis. The lytic treatment had, however, to be given within three hours. A few controlled clinical trials have been

reported since then. The first, reported by Dewar, Horler, and Cassells-Smith, in 1961, where the treatment was always given within 12 hours and on average in about six, gave wholly negative results. Two more in 1963 (Dewar, Stephenson, Horler, Cassells-Smith, and Ellis) and in 1966 (Menon and Dewar) in which treatment was begun later also gave negative results. Details are now given of another trial, organized internationally by Professor Verstraete and his colleagues, in which we took part, where treatment was begun up to 72 hours after onset and was controlled very carefully for both potency and safety. The two groups of carefully randomized patients comprising 84 treated and 83 controls proved to be fully comparable in all important respects. The treated group unfortunately developed significant side effects from the drug, notably fever, back pain, and bleeding, and the mortality figures were no better than in the controls. The only trials which have given convincing evidence of beneficial effect from a streptokinase preparation have been those of Poliwoda, Diederich, Schneider, Rodenburg, Heckner, Körtge, van de Loo, Pezold, Praetorins, Schmutzler, and Zekorn (1966). They can be accused of unsatisfactory randomization, but do nevertheless suggest that where treatment can be so organized as to begin within three and a half hours a definite beneficial effect can be expected, but not during the first 24 hours of treatment.

Evidence was presented as to why it is difficult to institute treatment early and of how large is the initial and hitherto unavoidable mortality. It is suggested therefore that the thrombolytic approach to coronary thrombosis may prove to be more successful when based on the prophylactic enhancement of the fibrinolytic activity of the blood of susceptible persons.

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EXPERIENCES WITH INTRAARTERIAL STREPTOKINASE PERFUSSION IN THE TREATMENT OF ACUTE ARTERIAL THROMBOSIS

A. BOSE, S. S. BROSE, AND G. HARTLEY (*Departments of Surgery and Radiology, Withington Hospital, Manchester*) This paper describes our experiences over the past 18 months with streptokinase in the treatment of the severely ischaemic limb.

Initially, we used thrombolytic therapy in 11 cases of poor risk advanced atherosclerotics who presented with severe pain at rest and incipient gangrene. Many had been treated unsuccessfully or successfully for a time with direct arterial surgery, lumbar sympathectomy *etc.*, and were presenting with the end result of a long battle to

preserve their peripheral circulation. Four were given intravenous streptokinase, 1.2 million units over a 24-hour period; the other seven were given a continuous intraarterial perfusion for 48 hours during which they received a total dose of streptokinase of between 0.25 to 0.75 million units. In this first series of 11 cases, our results were uniformly disappointing: we had two deaths, five major amputations, and the remaining four cases initially showed slight improvement but relapsed within six weeks.

The twelfth patient was a 47-year-old obese woman who had undergone a pelvic operation and had post-operatively developed a massive collapse of the left lung with peripheral circulatory collapse. She was hypotensive and lay on her side for a considerable period of time. Twelve hours after operation she was found to have an ischaemic painful left hand with ascending oedema of the arm and absent radial and brachial pulses. A stellate ganglion block and anticoagulants did not improve her condition over the next eight hours. A long Teflon catheter was threaded in retrograde fashion via the right femoral artery into the aortic arch and its tip engaged in the origin of the left subclavian artery. Two million units of Kabikinase in 2 litres of normal saline to which 2,400 mg of lincomycin was added was infused over 18 hours. Ten hours later a faint radial pulse appeared and by 15 hours the colour of her hand improved considerably, the acute pain was diminished, and the radial pulse was full and bounding. Her subsequent recovery was uneventful and with physiotherapy she regained the full use of her hand by the end of three weeks.

Thereafter we tried to standardize our regimen of thrombolytic therapy in arterial thrombosis. First we restricted streptokinase perfusion to the cases of acute or acute-on-chronic thrombotic episodes. Secondly, in the acute cases, we gave a continuous intraarterial perfusion over 24 to 48 hours of a litre of normal saline containing 1.2 million units of Kabikinase and 1,200 mg of lincomycin every 12 hours. Thirdly, in the less urgent acute-on-chronic episodes, we gave a continuous intraarterial perfusion for 48 to 72 hours during which thrombolytic therapy was given intermittently by alternating, each 12 hours, a litre of normal saline containing streptokinase and lincomycin with a litre of Lomodox (low molecular weight dextran 40,000) containing thymoxamine (Opilon) 160 mg and lincomycin 1,200 mg.

Initially we used hydrocortisone systemically before and during perfusion but subsequently found this was not necessary. We did not use any laboratory control.

Of the last 36 cases, 11 showed side reactions of variable degree but none warranted discontinuation of perfusion. The complications broadly fell into two main groups. Firstly, bleeding at the site of arterial puncture (six cases) ranging from ecchymosis (two cases), persistent ooze (two cases), subcutaneous extravasation (one case), to haematoma (one case). Secondly, pyrexia over 100°F in five cases which persisted during perfusion only; this was not troublesome except in one patient who had rigors, arthralgia, and pain in the back which lasted during perfusion.