

THE MAINTENANCE OF A SUSTAINED THROMBOLYTIC STATE IN MAN.
II. CLINICAL OBSERVATIONS ON PATIENTS WITH MYO-
CARDIAL INFARCTION AND OTHER THROMBO-
EMBOLIC DISORDERS *†

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Acute thromboembolic occlusive vascular disease is an important cause of human illness and the possibility of its treatment by measures designed to produce dissolution of the causative thrombus or embolus by enzymatic means has aroused much interest. Two preceding papers (3, 4) have been concerned with mechanisms of enzymatic clot dissolution and with the establishment of intense and prolonged thrombolytic states in man by the intravenous infusion of streptokinase.

These studies established the feasibility of using an induced thrombolytic state as a therapeutic tool for the treatment of thromboembolic disease in the human. However the effect of the thrombolytic state on infarcted tissue has never been tested and theoretically this effect could be harmful. Consequently the aim of the present clinical trial has been twofold, first to determine whether high levels of plasma thrombolytic activity were locally harmless to infarcted tissue and second to test the therapeutic value of this treatment. The present communication describes our experience with this type of therapy in several classes of human thromboembolic disease including patients suffering from early myocardial infarction.

The results suggest that high levels of plasma thrombolytic activity are harmless to infarcted tissue, including the myocardium, and that at least in a number of patients the clinical evidence was consistent with the view that thrombolysis of the causative thrombus or embolus had occurred.

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METHODS

Assay methods, materials and details of streptokinase¹ dosage were as previously described (3, 4). Biochemical and physiological findings obtained in the present series but pertaining to the induced thrombolytic state have been described elsewhere (4). All 45 patients described in this communication developed and sustained intense thrombolytic states (plasma activities of 100 to 500 μ g. fibrin lysed per ml. plasma per hour) throughout the treatment period.

Myocardial infarction series. This group comprised 22 patients of whom five were female. The average age of the group was 58 years and the age distribution: 30 to 40 years, one patient; 40 to 50 years, five patients; 50 to 60 years, eight patients; 60 to 70 years, two patients; and 70 to 80 years, six patients.

No patient was included in the series unless the clinical history and findings were of diagnostic significance, the electrocardiographic changes were confirmatory and review of serial transaminase (SGO-T) assays sustained the diagnosis. Theoretically greater benefit should follow the early rather than the late use of thrombolytic therapy and consequently patients were treated as soon after the onset of infarction as was practicable. The patients have been divided into two groups, a main one comprising 19 patients in whom thrombolytic treatment was started five to 16 hours (average nine hours) from the time of onset of symptoms and a subsidiary one of three patients in whom treatment was delayed 34 to 65 hours after the onset of the illness. All of the latter patients died and their course is considered in the section on autopsy evidence.

The main group contained five patients known to have been hypertensive for three to 15 years, two of whom had radiologically demonstrable cardiac enlargement. Two patients were known to have had previous attacks of myocardial infarction and this diagnosis had been strongly suspected in a third. Three patients were obese (20 to 40 per cent over ideal weight) and four patients were considered to have suffered from unusually severe and protracted pain following the onset of infarction. Though three patients showed substantially depressed blood pressure, signs of shock were present in only one. Two pa-

¹ Streptokinase was kindly supplied by Dr. J. Rueggesser, Lederle Laboratories, Pearl River, N. Y.

tients showed signs of early congestive failure but these were mild. All patients received streptokinase by intravenous drip for 30 hours in sufficient doses to produce a sustained and intense thrombolytic state and the last eight patients in the series received supplemental intravenous hydrocortisone for the duration of the infusion period (4). The initial organization of the trial involved a "double-blind" design and the decision as to treatment in the first 23 patients was made by the drawing of a lot. However this design was found to impede the collection of physiological data (4) and its use was abandoned, but later reference is made to the 11 control patients in the series.

RESULTS

Pulmonary embolism, thrombophlebitis, thrombotic arterial occlusion, and coronary insufficiency

Case histories 1 through 23 (see Appendix) describe the effects of the induced thrombolytic state in these categories of patients.

Acute myocardial infarction

The clinical course of the patients during the 30 hour streptokinase treatment period was relatively uneventful and there were no deaths at this time. Eight of the patients, initially considered to be gravely ill, improved considerably as did those others whose conditions appeared to be less serious. Two patients after six hours' treatment experienced a recurrence of moderately severe chest pain of one to two hours' duration; in both instances the blood pressure fell and remained unstable for eight and 12 hours, respectively, though other signs of shock were absent. One patient experienced moderate chest pain after 12 hours' treatment but the blood pressure remained stable and the pain only lasted 30 minutes. Two of the hypertensive patients showed a fall of blood pressure to normotensive levels, a fall that was maintained for the remainder of the hospital course. Two patients, whose blood pressure had been initially depressed, showed a rapid rise while on streptokinase treatment. All patients were started on Dicumarol® therapy prior to the end of the infusion and, except in two instances, were maintained on this drug for the remainder of the hospital course. Nine patients received anticoagulant treatment after discharge from the hospital.

Later course

Following the initial treatment phase, there was one death in a 72 year old male, who died three weeks later from recurrent infarction; the autopsy findings are described later. Three patients, all males, experienced episodes of chest pain that may have been indicative of recurrent infarction three, six and 10 days, respectively, after the onset of the original infarction. The pain in each instance was of less than two hours' duration, but in two of the patients, transient electrocardiographic changes occurred, though in all of them serial transaminase assays remained normal and no other evidence of deterioration was obtained. Four other patients complained intermittently throughout their hospital course of mild precordial aching sensations. However, two were nervous patients and in the case of an obese 74 year old woman abdominal discomfort may have contributed to her difficulty. The convalescence of a 53 year old male was delayed by the development, three weeks after admission, of a severe attack of benign pericarditis, which ultimately resolved without disability. Embolic complications were absent from this series. Following discharge from hospital, two patients, respectively six and 12 weeks later, experienced bouts of chest pain associated with the development of minor electrocardiographic abnormalities; in each instance the pain rapidly disappeared, serial transaminase assays remained in the normal range and the patients are now symptom free.

Followup

Followup was usually conducted six months later but in four instances only the two month followup is available, though the patients are known to be alive and well after five months. In two instances followup was oral but all the other patients were fully investigated. Eleven patients were symptom free and pursuing their normal vocation or activities (though in the case of four elderly patients these were limited); four patients, two of whom were working, complained of dyspnea on unusual exertion though their normal activities were not limited by this disability. The remaining three patients, two of whom were working, experienced occasional very mild chest discomfort on moderate exertion. Physical examination revealed no unsuspected findings and

clinically we gained the impression that the group had made a satisfactory recovery. Radiological examination disclosed no evidence of aneurysm formation and in 13 of the patients the size of the heart shadow was within the limits of normal. Four patients showed mild to moderate cardiac enlargement, in all cases with enlargement of the left ventricle, but in two of them, previous chest films showed that this enlargement had been present prior to the present illness. The other two patients, in whom previous chest films were not available, had both previously suffered from myocardial infarction and in one of the patients, a clinical diagnosis of cardiac enlargement had been made prior to the present illness.

Electrocardiographic evidence

Serial electrocardiograms were recorded several times on the first and second day of therapy and subsequent records were then taken daily until the clinical course of the patient had stabilized. In all cases, the electrocardiograms were considered to be either diagnostic of acute myocardial infarction or consistent with the diagnosis. Weekly or semiweekly records were then obtained until discharge from the hospital. In most instances the electrocardiographic evolution of the infarct was not remarkable. However, in three cases, a subsequent bout of chest pain during the period of convalescence was accompanied by a recurrence of ST segment elevations in the leads previously involved in the original infarct, but in none did the Q waves change and the SGO-T determinations remained within normal limits.

The electrocardiograms were read as showing anterior or anteroapical myocardial infarction in 15 cases, diaphragmatic (posterior) in six cases and left bundle branch block was present in one. Significant Q waves were present initially or developed subsequently in 20 cases. Of the 18 surviving patients, followup records (usually five to six months after the acute infarct) were obtained in 14 instances and in the remaining four patients, the followup was considered to be of insufficient length to permit adequate assessment. Four of the patients showed a normal electrocardiogram on followup examination (one of the four has a slightly prolonged P-R interval which was probably present prior to the infarct). Three of the

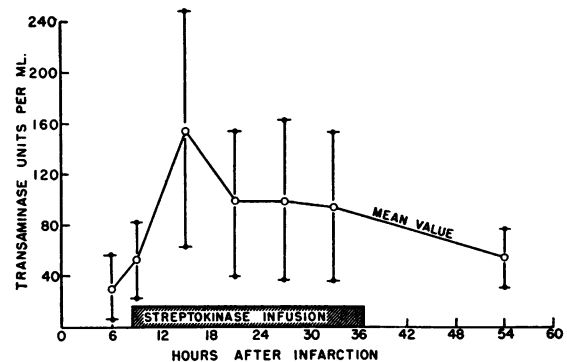


FIG. 1. SERIAL SGO-TRANSAMINASE VALUES IN MYOCARDIAL INFARCTION (SK TREATED)

The average delay between the time of infarction and the start of streptokinase treatment was nine hours (range five to 16 hours). The highest average SGO-T values were recorded in the specimens drawn just after the start of treatment (12 to 18 hour period) and the values thereafter declined.

four patients with normal followup records had developed significant Q waves during the acute infarction. Of the 10 patients with abnormal followup electrocardiograms three were known to have had abnormal records prior to the acute infarction. In the remaining seven patients, previous electrocardiograms were not available.

Arrhythmias or conduction disturbances developed in seven patients. In six of these patients arrhythmias or conduction disturbances were present prior to treatment with streptokinase, although other abnormalities in rhythm or conduction subsequently occurred in several of these patients during or following streptokinase therapy. In one of the seven patients, ventricular premature contractions, auricular fibrillation and prolonged intraventricular conduction occurred after the start of therapy, whereas no arrhythmia or conduction disturbance was previously recorded. The conduction disturbance in this case was thought to be due to quinidine therapy and the patient subsequently made an uneventful recovery. In one of the patients who died, right bundle branch block, ventricular premature contractions and atrial tachycardia with block were present intermittently before death. In another, ventricular premature contractions and intraventricular conduction disturbance were present and this patient also died. In the remaining five cases who survived, ventricular premature contractions were

present in four, atrial fibrillation in three, prolonged P-R interval in one and right bundle branch block in one. These ectopic rhythms were all transient. Right bundle branch block remained in one case and prolonged P-R interval remained in one.

Transaminase determinations (SGO-T)

The induced thrombolytic state does not alter SGO-T values (4) and consequently assay for this enzyme could be used to follow the patient's progress. Figure 1 shows the combined SGO-T determinations in Group 1 patients over a two day period; the time scale corresponds, in the conventional manner, to hours after the onset of infarction. The shape of the curve appears to differ from that usually found in myocardial infarction as peak values were noted as early as 15 hours and the average level had almost returned to normal by the third day. Comparison between the streptokinase treated patients and those in the double-blind control group would at first sight appear to support this hypothesis, for though transaminase values in the two groups were initially similar ($p > 0.1$), the later readings (obtained between 30 to 50 hours) showed the control values to be higher ($p = 0.05$). However, comparatively little weight can be attached to this finding as the control data show evidence of sampling bias.

Urokinase excretion

An interesting and unexplained finding in the myocardial infarction patients concerned their urokinase excretion rates (rates of urinary plasminogen activator excretion). Normally patients suffering from myocardial infarction show a substantial rise in urokinase excretion rates for the month following its onset ($p < 0.001$) (5), but in the streptokinase treated group this rise occurred faster and was of greater magnitude ($0.01 > p > 0.001$) than in the control group. This finding may be of importance (5), but, at present, there is insufficient collateral data for its proper interpretation.

Autopsy evidence from the myocardial infarction series

Four patients died, though in the case of a 74 year old woman, originally in shock and in whom

only three hours' treatment was given, autopsy permission was refused.

A 72 year old male died suddenly three weeks after his initial treatment while receiving Dicumarol®. Autopsy revealed a large normally healing infarct (estimated to be two to four weeks old) and in its center a small very fresh infarct related to a new vessel thrombus. Though the coronary vessels were grossly arteriosclerotic, search revealed no older thrombus to correspond with the original infarct. A 53 year old male, admitted 48 hours after the onset of infarction, showed shock, paroxysmal auricular fibrillation and an SGO-T of over 200. He died 14 hours later, probably from ventricular fibrillation. Though autopsy revealed a huge posterolateral infarct with septal involvement, careful dissection of the coronary vessels revealed only the presence of mild coronary sclerosis and failed to demonstrate the presence of a coronary thrombus. A 49 year old male, admitted to hospital 34 hours after the onset of infarction, was in gross congestive failure and his SGO-T peaked at 340. Though his congestive failure showed an initial response to treatment, he died from this cause, one day after the termination of streptokinase therapy. Autopsy revealed an old large posterior wall infarct and a new extensive anterolateral area of infarction. A small thrombus was found arising from an arteriosclerotic plaque in the left main coronary artery, but since its presence was only demonstrable by microscopy and it appeared to be very fresh, it may have formed after the end of the streptokinase treatment period. Neither in these nor in other patients (4) were myocardial lesions other than those attributable to the primary disease state observed.

Clinical toxicity

Neither pyrexia nor hypotension was noted after streptokinase administration. The sole serious or potentially serious toxic effects of the treatment have lain in the development of a hemorrhagic diathesis, secondary to the induced thrombolytic state (4). This complication can, at least in part, be prevented by steroid administration (4). One patient developed, 24 hours after the termination of the infusion, a 5×4 cm. erythematous area around the infusion site: This lesion,

thought to represent a sensitization reaction, disappeared three days later. Though streptokinase solution occasionally has become infiltrated at the infusion site, reactions have not resulted except in one patient in whom massive infiltration of the leg was produced and in this case the reaction was slight. Minor thrombophlebitis subsequently developed at the site of the indwelling needle in four patients.

DISCUSSION

The evaluation of a new therapeutic procedure in disease states that exhibit variable morbidity and mortality patterns is fraught with the possibility of error. Evaluation must necessarily rest on a quasistatistical basis involving the observation of a number of favorable results where the contrary would normally be expected. Obviously, whatever the outcome in an individual case, chance can never be excluded. Accordingly the total case material has been presented, individually described where the usual outcome would be customarily judged on the severity of the presenting disease state (see Appendix), but grouped together, as in the myocardial infarction patients, where the initial findings constituted a less certain guide to the eventual outcome.

The case histories 1 through 23 (described in Appendix), comprising patients suffering from disease states other than myocardial infarction, are consistent with the view that, at least in a number of patients, *in vivo* thrombolysis was produced as a result of the treatment. The series of events that occurred in Patients 1 through 6, suffering from pulmonary embolism, in Patients 7 through 10 suffering from thrombophlebitis of the large veins, in Patients 18 and 19 suffering from arterial obstruction and Patient 23 with a fibrinous exudate in the anterior chamber of the eye, though perhaps individually explainable as a series of chance findings, are, taken as a whole, difficult to reconcile with such a view. A corollary to these findings would indicate that restoration of blood flow to an infarcted area is not only of over-all benefit but also without deleterious effect. Where failure was met with Patients 11 through 14 suffering from thrombophlebitis and Patients 15 through 17 suffering from arterial disease, there appeared to be an adequate reason for this result, either on the grounds of the unsuitable nature of

the disease condition or on the basis of the irreparable structural damage that had already occurred.

Theoretically there is a danger that the use of thrombolytic therapy in venous thrombosis might increase the likelihood of pulmonary embolism. Though Cases 2, 8 and 10 experienced transient symptomatic episodes that could have been indicative of pulmonary embolism, it is emphasized that confirmation of this diagnosis was not obtained; the patients were suffering from disease conditions where spontaneous pulmonary embolism is common and unusual attention was being given to the patient's symptomatic complaints. We do not regard the danger of pulmonary embolism as a contraindication to the treatment, since even if it were to occur, rapid lysis of the embolus would be expected to take place (see Patients 1 through 6).

It is our present view, based solely on theoretical conjecture, that thrombolytic treatment should be followed by anticoagulant treatment. However, not all our patients have been given anticoagulant treatment and so far we have seen no ill effects from its omission.

Myocardial infarction presents a difficult therapeutic problem, because of the numerous etiological factors involved in its causation. The rapid dissolution of a coronary thrombus by enzymatic means could result in reduction of the final area of muscle infarction, reduction of the degree of electrical instability present during the early critical phase of infarction and in the prevention or removal of mural thrombi. However, the thrombolytic state could conceivably cause deleterious changes within the infarcted area and perhaps increase the tendency to or the degree of subintimal hemorrhage. Moreover in those instances of infarction, unrelated to thrombosis, benefit could only occur by the prevention of or by the lysis of mural thrombi. These problems were similar in substance but more acute in nature than those involving the therapeutic use of anticoagulants in this condition. In contrast, while the aim of anticoagulant treatment is to limit myocardial damage and prevent further spread of infarction, the aim with thrombolytic therapy is to restore the circulation and permit the restoration of function to still viable, but otherwise doomed, tissue. Clearly the timing of thrombolytic therapy is criti-

cal and, theoretically at least, it should be started as soon as possible after the onset of infarction. This therapeutic indication is fortunate since by far the greatest mortality occurs in the first 24 hours of the disease and conventional therapy is largely unavailing. Furthermore, thrombolytic therapy if used late in the disease, after the formation of mural thrombi, might carry a serious risk of causing arterial embolism.

Evidence concerning the effect of the thrombolytic state on the myocardial lesion was of a dual nature, that derived from the living and that obtained by postmortem examination. The three patients treated late in the illness, 34 to 65 hours after its onset, died during the acute phase of the disease. These patients were not included in the main group as the delay placed them outside the scope of the study and their treatment was only reluctantly undertaken as a measure of last resort. Postmortem examination was also made on the one patient in the main series who died three weeks after his initial treatment. Pathological study was consistent with the belief that *in vivo* thrombolysis had been produced and also with the view that the thrombolytic state had exerted no harmful effect upon the evolution of the infarcts. Of collateral interest are two reports (6, 7) offering suggestive evidence that the relief, by enzymatic means, of acute coronary obstruction in the dog lessens the final degree of myocardial damage.

Patients treated early in the course of the disease all survived the acute phase of the illness, though one of the 19 patients died three weeks later from recurrent infarction. It is probable that these patients suffered from myocardial lesions of greater than average severity since the incidence of features indicative of a poor prognosis was high and the referring physicians naturally tended to favor the use of this treatment in patients whose prognostic outlook, under conventional treatment, was deemed to be relatively unfavorable. The hospital course and the followup period have been devoid of unusual incident and it is our impression that the survivors have made good recoveries. Radiological examination has failed to reveal aneurysm formation and the incidence of cardiac enlargement has been very low. The fact that four of 14 patients showed normal electrocardiographic findings six months after the

attack is unusual, especially when three of these 14 patients were known to have shown abnormal ECG findings prior to the attack. Though the mortality rate of the group appeared to be unusually low testing of its statistical significance against the mortality rate in patients treated as double-blind controls (four out of 11 died) and also against the hospital mortality during the time of the trial (19.5 per cent) gave in each instance $p = 0.2$ (χ^2 with Yates correction). Thus though our findings may suggest that the patients derived clinical benefit from the treatment, on the crucial question of mortality we would have seen as favorable a series, by chance alone, one trial in five. Clearly, while the number of patients treated has been insufficient to arrive at a decision that benefit occurred, it does appear to be sufficient to give considerable assurance that certain theoretical objections that could be raised to this form of treatment are without practical basis.

Though clinically we have been gratified by the results of this treatment we would emphasize that these observations are of a preliminary nature and serve only to establish that the present therapeutic approach is feasible. Clinical, pathological and biochemical evidence all indicate that plasma thrombolytic states are harmless to the infarcted myocardium and that the development of thrombolytic therapy for the treatment of myocardial infarction will not be impeded by deleterious consequences, secondary to its primary effect.

APPENDIX

Case histories 1 through 23. The effect of the induced thrombolytic state upon the clinical course of patients suffering from pulmonary embolism, thrombophlebitis, thrombotic arterial occlusion and coronary insufficiency.

Pulmonary embolism

Six patients, all gravely ill, have been treated. However, absolute proof of the diagnosis was lacking in *Case 1*, a 32 year old male. Though there was adequate clinical evidence to support the diagnosis, his poor general condition precluded the obtaining of radiological confirmation. He died two days after streptokinase treatment from congestive cardiac failure of rheumatic etiology and, at autopsy, dissection of the pulmonary vascular tree disclosed no abnormality.

Case 2. The successful treatment of a 53 year old farmer, suffering from acute cor pulmonale, secondary to repeated pulmonary emboli has been previously reported (1).

Case 3. A 38 year old female gave a history suggestive of four episodes of pulmonary embolization in two days; physical signs and chest film confirmed the diagnosis. Her last episode of pulmonary infarction, which occurred two hours before the start of treatment, was massive and had caused brisk hemoptysis. Rapid clinical improvement followed streptokinase therapy, no further emboli occurred and signs of phlebothrombosis present in the calf rapidly regressed. Radiological examination showed almost complete clearing of the chest in a two day period. This patient was awaiting operation for uterine myomata and it was noteworthy that successful treatment was impeded neither by the presence of vaginal bleeding nor by the hemoptysis. The extent of bleeding was not increased from either site by the establishment of a thrombolytic state.

Case 4. A 54 year old male had been treated one year previously for multiple pulmonary embolization secondary to thrombophlebitis. Conservative management led to an excellent functional recovery. Three days prior to admission he experienced pain and tenderness in the left popliteal region and shortly prior to admission, left-sided pleuritic chest pain, cough, sweating and dyspnea. He was acutely ill exhibiting cyanosis, tachycardia, tachypnea and had a cold clammy skin with a blood pressure of 80/60. The electrocardiogram showed a partial right bundle branch block and other signs suggestive of pulmonary embolism. Twelve hours treatment with heparin and oxygen with a continuous norepinephrine drip to maintain the blood pressure produced no improvement. Rapid improvement followed streptokinase treatment and after 10 hours his blood pressure rose to normal values and remained stable without the use of norepinephrine. Cyanosis disappeared and oxygen was dispensed with at the end of streptokinase treatment. His transaminase (S-GOT) rose to over 200 units per ml. and, though this finding was regarded as rather unusual for pulmonary embolism, his electrocardiogram returned to normal after five days. Three days later despite the use of Dicumarol®, the physical signs of acute thrombophlebitis were apparent in the left thigh. In view of his history, left femoral ligation was performed and he was discharged shortly afterwards symptom free except for the residual functional effects of the femoral ligation.

Case 5. A 47 year old male was discharged from hospital 14 days after the performance of a subtotal gastrectomy. Three days later the patient was seized by shaking chills and noted the sudden onset of severe pain in the right chest. He was cyanosed, hypotensive and had physical findings consistent with multiple pulmonary embolism, a diagnosis confirmed radiologically. The patient's condition deteriorated rapidly and he died 16 hours later, but for the last seven hours he received streptokinase therapy. Autopsy revealed the primary cause of death to be generalized peritonitis secondary to a leaking suture line, but though three areas of recently infarcted lung tissue were found, dissection of the pulmonary vascular tree revealed no emboli.

Case 6. A 43 year old female developed, following hysterectomy, pelvic vein thrombosis. Despite adequate

treatment with Dicumarol®, repeated pulmonary embolism occurred over a 35 day period. Following streptokinase therapy, her chest film cleared and no further episodes of embolization occurred.

Thrombophlebitis

Eight patients were treated in this group and though patients suffering from severe clinical manifestations secondary to lesions of large veins responded well to streptokinase treatment, other patients with lesions of small veins and few clinical manifestations, except those of local disease, apparently did little or no better than with conventional therapy. We attribute this somewhat paradoxical response to the fact that whereas with disease of the large veins clinical disability is related primarily to venous obstruction, this fact is of little importance in disease of small veins, inflammation of the vein wall being the predominant clinical lesion.

Case 7. A 44 year old woman, who had had several hospital admissions on account of idiopathic steatorrhea, developed acute iliofemoral thrombophlebitis secondary to an indwelling catheter in the inferior vena cava. Three days' streptokinase therapy produced a rapid resolution of the condition. Her hospital stay was prolonged on account of the intestinal disorder but on discharge there was no evidence of venous insufficiency.

Case 8. A 53 year old male suffered from iliofemoral thrombophlebitis secondary to trauma and responded rapidly to streptokinase therapy. During the course of treatment he developed transient symptoms suggestive of pulmonary embolism but further evidence to support this diagnosis could not be obtained. On discharge from the hospital eight days later there were no signs of venous insufficiency.

Case 9. A 78 year old man with gouty arthritis developed iliofemoral thrombophlebitis. The response to treatment was slower than in the other two cases and he also developed an exacerbation of gout. However his leg was free from edema on discharge though he was wearing an elastic support. Two months later iliofemoral thrombophlebitis recurred, temporary shortage of streptokinase prevented his retreatment and despite the use of anticoagulants he developed a marked post-phlebotic syndrome.

Case 10. A 46 year old male developed calf, popliteal and femoral thrombophlebitis, following injury. Response to streptokinase therapy was very satisfactory and he left the hospital without disability. During the first day of treatment he experienced transient symptoms that could have been due to pulmonary embolism but investigation failed to confirm the diagnosis.

Cases 11 and 12. Both suffered from long standing thrombophlebitis of the calf and though both were improved following streptokinase therapy, the improvement could well have been a chance finding and was unimpressive.

Cases 13 and 14. These two patients had thrombophlebitis of superficial veins and though clinical symptoms abated rapidly following treatment, venous cords remained palpable.

Peripheral arterial occlusions

Six patients have been treated.

Cases 15, 16 and 17. All were elderly patients suffering from acute obstruction to the femoral artery. The patients were treated with streptokinase after extensive and wholly unsuccessful surgical intervention had been undertaken in each patient. Though in one instance a previously absent popliteal pulse returned after treatment, lasting benefit was not obtained. Two patients died, one from myocardial infarction six weeks later, the other from acute renal tubular necrosis following surgery. Probably the condition of the artery wall after unsuccessful surgical intervention is such as to preclude other treatment.

Case 18. One year previously an arterial homograft had been inserted to bridge the left iliac and femoral arteries in this 61 year old female. The limb circulation failed suddenly and, on examination, signs of acute arterial insufficiency were apparent midway up the thigh. The graft, which was easily palpable throughout the greater part of its course, was hard and pulseless. Eight hours after the start of streptokinase therapy the superior one-third of the graft was pulsatile. However, by next morning when treatment was restarted, the whole graft was again hard and pulseless and further treatment failed to change its condition. Nevertheless, perhaps because the graft thrombosis was an incidental finding, the circulation of the leg improved during therapy. Gangrene did not develop and the patient's ambulatory ability on discharge from hospital was similar to that present before her current admission.

Case 19. A 66 year old female, bedridden as the result of a previous vascular accident, was admitted suffering from pneumonia of great severity. Despite the exhibition of antibiotics her condition remained serious. Blood pressure could only be maintained by the administration of intravenous norepinephrine over the first three days. On the fourth day, two localized patches of gangrene were apparent on the left limb in the distribution of the anterior tibial artery. On the fifth day she developed signs of acute arterial insufficiency in the limb with the border of temperature change 5 cm. above the knee. During streptokinase therapy oscillometric pulsations were again recorded in the lower limb, muscle power returned to the foot and the temperature differential between the legs diminished to an insignificant difference. However the original patches of gangrene were unaltered by the treatment and since owing to her previous bedfast state mobilization was impossible, below the knee amputation was performed.

Miscellaneous

This group consisted of three patients with coronary insufficiency and one patient with an intraocular fibrinous exudate.

Case 20. A 61 year old male suffering from mild coronary insufficiency received therapy; his course thereafter was uneventful.

Case 21. A 44 year old male experienced an attack of severe and prolonged chest pain with electrocardiographic abnormalities and a slightly raised SGO-T assay; however Q waves did not subsequently develop. Following 30 hours' streptokinase treatment his course was satisfactory and he is now, five months later, symptom free.

Case 22. A 64 year old emaciated female was admitted with gross congestive cardiac failure, an enlarged heart and severe chest pain. After an initial response to therapy she suddenly died three weeks later. Autopsy revealed severe coronary artery disease, several areas of old healed infarcted tissue and one fresh infarct estimated to be no more than two days old.

Case 23 (1). A 71 year old male developed an intraocular infection following a cataract operation. Despite intensive antibiotic therapy a dense fibrinous exudate developed and completely filled the anterior chamber. Four days of streptokinase treatment was given and serial slit lamp examination revealed progressive resolution until, at the end of treatment, the anterior chamber was free of exudate. It is known that spontaneous resolution of such exudate seldom if ever occurs and this patient was thought to provide a rather unique demonstration of *in vivo* fibrinolysis.

SUMMARY

Fifty patients suffering from several varieties of acute occlusive thromboembolic disease, including 22 patients suffering from early acute myocardial infarction, were treated by the intravenous infusion of streptokinase in massive doses and for prolonged periods. Intense plasma thrombolytic activity (100 to 500 μ g. fibrin lysed per hour per ml. plasma) developed and was maintained for 30 or more hours.

The thrombolytic state produced no important deleterious consequence and there was evidence, at least in a number of patients, to suggest that *in vivo* thrombolysis had been produced. The low mortality rate and the relative absence of complications experienced by the myocardial infarction patients suggested that the induced thrombolytic state was harmless to the infarcted myocardium.

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