Thrombotic Complications of Heparin Therapy

Including Six Cases of Heparin–Induced Skin Necrosis

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Thrombotic complications of heparin administration were observed in eight patients during a two year period. At sites of subcutaneous heparin injection, six patients developed areas of the skin and subcutaneous necrosis. Systemic thrombotic events and thrombocytopenia were observed in two of these patients when they received intravenous heparin and in two other patients who did not have primary skin necrosis. The complications included peripheral ischemia in three patients (two requiring amputation), myocardial infarction in two, and a cerebral infarction in one. All patients were receiving heparin for at least six days before complications occurred. Seven patients received heparin of bovine origin. Heparin-induced *in vitro* platelet aggregation was present in all six of the eight patients tested. (It was marked in four of these patients). It is theorized that skin necrosis and the other thrombotic complications observed are the result of heparin-induced *in vivo* platelet aggregation followed by intravascular thrombosis. Heparin-induced skin necrosis is a rare but serious hazard encountered with prophylactic heparin regimens. If heparin-induced thrombosis is present, the further use of heparin is contraindicated in most instances.

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HEPARIN IS A NATURALLY occurring, strongly acidic sulfated mucopolysaccharide. Many types with varying actions have been isolated from different animals and different tissues. It is not a single compound but a collection of compounds of different chain lengths and molecular weights which possess similar repeating saccharide units and functional groups.[28]

The anticoagulant function of heparin is a result of its ability to accelerate the action of the enzyme inhibitor antithrombin III. Thrombin, as well as the coagulation factors IX, X, and XI, are slowly inactivated in the presence of this substance. When heparin is added to the solution inactivation is almost instantaneous.[48] Factor X is quite sensitive to low concentrations of the heparin-antithrombin complex. Minidose heparin probably inhibits the coagulation cascade at this point.[21] Once thrombin has been generated, much larger doses of heparin are required to interrupt the clotting process.

In recent years, heparin has become a popular agent for the prevention of deep venous thrombosis (DVT) in postoperative or immobilized patients. Prophylactic measures seem warranted because pulmonary embolism is a major cause of death in patients undergoing elective operations. Many studies have shown that minidose heparin reduces the incidence of DVT and two studies have recorded a decrease in fatal pulmonary emboli.[27,50] More recent papers have stressed the complications seen with heparin in general and minidose prophylactic heparin in particular.

The most common problem following the use of heparin is hemorrhage. In the minidose therapeutic trials reviewed by Pachter and Riles[41] the incidence of hemorrhagic complications varied from 0 to 14%. In their own series, it was 27%. They therefore raise the question of whether the morbidity of the cure outweighs the morbidity of the primary disease. The occurrence of other nonhemorrhagic complications with heparin use lend further strength to this statement. Heparin, in rare instances, has been associated with thrombocytopenia and in the potentiation of arterial embolization. These complications have been associated with prophylactic heparin use in only four patients.[24,45] Anaphylaxis is also reported with heparin[7,11,44] but apparently has not been recognized in recent minidose trials.

Skin necrosis at the site of heparin administration is a rare occurrence. However, six patients with this com-

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plication were treated during a two year period at The Toledo Hospital. All six patients were receiving bovine lung heparin (Upjohn) as prophylaxis against DVT. Two additional patients are presented who developed ischemia of the legs while receiving heparin for suspected venous disease. These two patients represent new cases of heparin-induced thrombocytopenia with thrombotic sequelae. Of these two patients, one received porcine intestinal heparin (Elkin-Sinn) and the other bovine heparin (Upjohn).

Methods

The eight patients described in this paper were all admitted to surgical services for nonhematologic problems. After the development of skin necrosis or thrombotic events associated with thrombocytopenia, six of them were seen in consultation by the authors. Two patients, N.R.M. and S.H., were seen after their discharge from the hospital when all lesions had resolved.

Activated partial thromboplastin times (PTT) were determined on a Sherwood Lancer Coagulyzer which utilizes a photo electric endpoint for clot determination. Normal range in this laboratory is 20–29 seconds.

Platelet estimations were determined from appropriate areas of peripheral blood smears by multiplying the average number of platelets in five high power fields by a factor of 10,000. Actual platelet counts were performed on a Coulter Thrombocounter C—a type of electronic particle counter.

Blood obtained for platelet aggregation studies was handled in a fashion designed to minimize trauma and inadvertent platelet alterations. Only siliconized glass or plastic materials were used in collection and processing.

Samples for aggregation studies were drawn into plastic syringes and immediately gently mixed with 3.8% Citrate. Platelet rich plasma was obtained after centrifugation at 900 rpm and platelet poor plasma after centrifugation at 2400 rpm. Final platelet rich mixtures were standardized to about 250,000/mm^3 for use in aggregation testing. Studies were performed on a Chrono-log Dual Channel model #340 Aggregometer® with attached dual channel 10 millivolt recorder. All reaction mixtures were constantly agitated and maintained at 37° during the procedure. PH was not recorded during the studies reported in this paper. Subsequent tests done under identical conditions have revealed a pH of 7.6 to 7.7 in the platelet rich plasma during and following aggregation with all the aggregating agents.

The standard aggregating reagents were ADP in final concentrations of 10 μg/ml (50 μM/ml) and 1 μg/ml (5 μM/ml), epinephrine in concentrations of 10 μg/ml (25 μM/ml) and 2 μg/ml (5 μM/ml), and soluble calfskin collagen in a final concentration of 0.2 mg/ml. The final test concentrations for heparin in the aggregating mixture were 0.5 and 0.6 units/ml. Previous studies in this laboratory had revealed that a heparin concentration of 0.5 units/ml resulted in an elevation of the APTT to 40 to 60 seconds.

Normal control specimens were always tested at the same time as patients' specimens. A second control group consisted of 25 patients who had recently undergone cardiac surgery. These patients had been heparinized during surgery, but were free of any manifestations of heparin-induced thrombosis.

Case Reports

Patient H.D. When admitted for a total hip arthroplasty, this 49-year-old woman suffered from severe degenerative arthritis, hypertension and diabetes mellitus. She had lost 20 kg in preparation for surgery, but was still obese. On the first postoperative day, subcutaneous heparin injections were begun. The PTT was monitored daily and remained normal. Ambulation progressed on a normal schedule. On the sixth postoperative day, a purple discoloration appeared on the right flank. Heparin was injected in the left flank later in the day and then discontinued. Within 12 hours the right flank contained a large band of skin necrosis (Fig. 1). An identical lesion later appeared on the left side. Hemorrhagic bullae developed in 24 hours. The patient complained of severe burning pain for four days, but as the cuff of erythema surrounding the necrosis resolved, pain diminished.

Excision with primary closure was performed 19 days later. Ischemic necrosis extended through the subcutaneous tissue and into the muscle. Microscopic examination revealed necrosis juxtaposed to normal tissue. Six months later an arthroplasty was performed on the opposite hip. Heparin was again administered for six days but was given intravenously. Platelet counts were not obtained. There were no complications.

Patient N.L. (Fig. 5A). This 55-year-old woman was admitted for a right knee arthroplasty. She was obese, hypothyroid, and had insulin dependent diabetes mellitus. The platelet count on admission was grossly normal. Mild T-wave abnormalities were present on the electrocardiogram. Subcutaneous heparin injections were started two hours before the operation and continued postoperatively. Daily PTT's were normal. She initially did well, ambulating with a walker on the third day. On the eighth postoperative day she complained of pain in the left chest and in the left lower abdomen at the site of heparin injections. Within 36 hours a necrotic eschar surrounded by an erythematous cuff had formed in the left lower abdomen. Two days later a second lesion appeared on the right side. Subcutaneous injections were stopped on the following day, but the same dose was given intravenously. The chest pain resolved but pain in the area of necrosis became severe. A spiking fever to 39° developed. The fever was thought to be secondary to the necrotic lesions and they were excised. The entire layer of subcutaneous adipose tissue was necrotic, but no hematomas or abscesses were present.

In the postoperative period, intermittent intravenous heparin was resumed. An electrocardiogram performed following surgery suggested anterior wall ischemia. Chest pain occurred on the following day and ischemic changes were more pronounced. The serum sodium was 118 and the hematocrit had fallen over two days from 32 to 26. Three days after the excision frank changes of an inferolateral

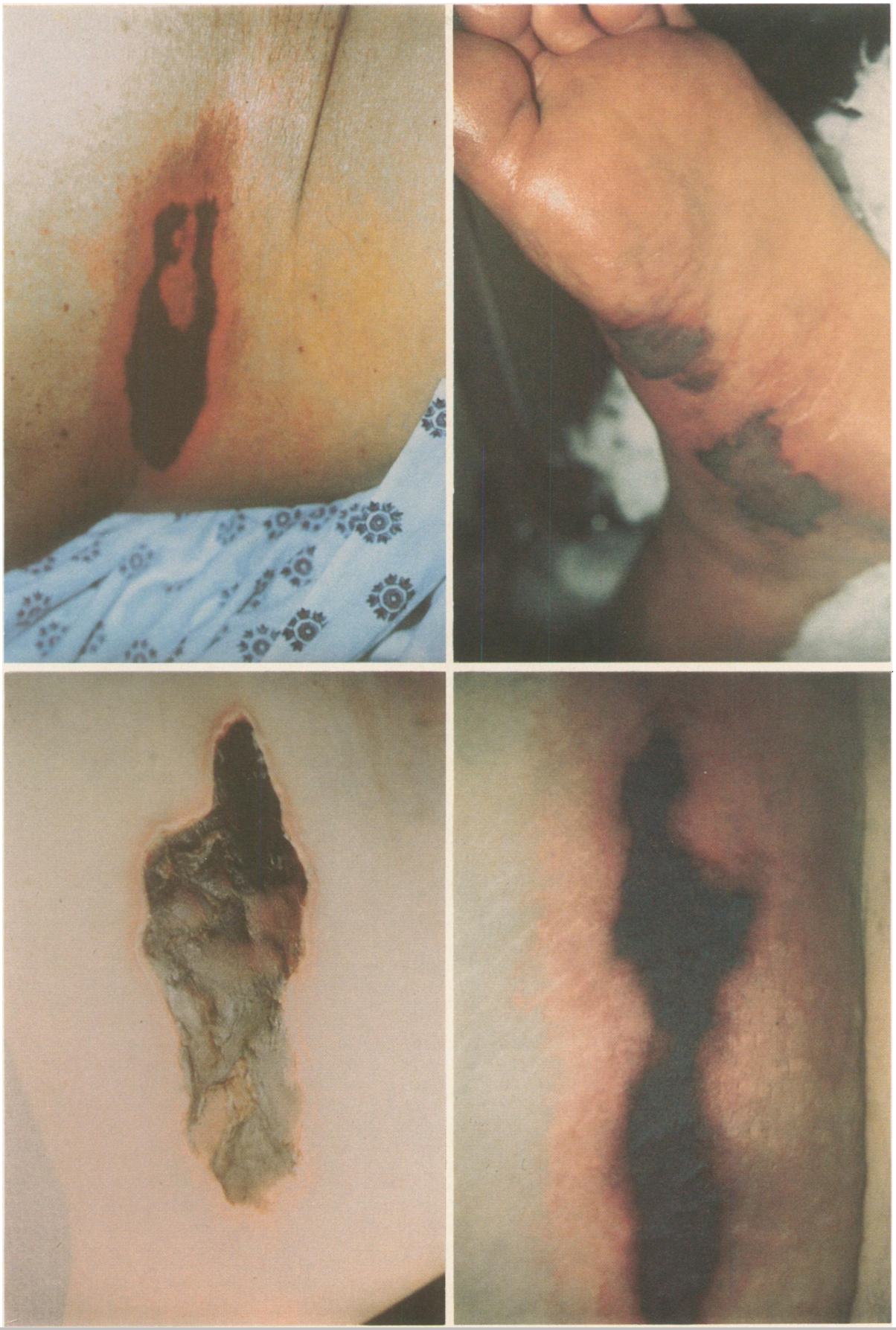

FIG. 1. Patient H.D.: lesion of the abdominal wall with hemorrhagic bullae. FIG. 2. Patient N.M.: lesion of the abdominal wall. FIG. 3. Patient M.O.: lesion of the abdominal wall. FIG. 4. Patient M.O.: lesion of the left foot.

infarct were present. Her serum sodium had risen to 124 meg/l, but her level of consciousness deteriorated and she became decerebrate. Her temperature rose to 40.3° but there was no apparent origin for the fever. On all blood counts performed during this period, platelets were noted to be decreased. Heparin was discontinued and by the following day the platelet count was normal.

A cerebral infarct was diagnosed by computerized axial tomography. For three days the patient had continuous focal motor seizures. Thereafter, she slowly improved but was left with an expressive aphasia and right hemiparesis.

Patient R.U. This 50-year-old woman suffered from recurrent superficial bladder tumors over a three year period. Two transurethral resections, a segmental bladder resection and intravesical thiotepa were employed in treatment but hematuria again developed. She was therefore admitted for a radical cystectomy. She also suffered from ischemic heart disease with angina pectoris. The platelet count on admission was normal.

A spiking fever developed postoperatively. At re-exploration a necrotic ileal segment was removed, and a new conduit constructed. Venous thrombosis was noted in the resected specimen. In order to prevent thrombosis in the reconstructed conduit, heparin was administered. Initially, the heparin was injected into the abdominal wall or given intravenously. Daily PTT's were within two to 11 seconds of control. On the sixth postoperative day the buttocks became the site of injections. Two days later, a circular region of skin necrosis appeared. The next injection of heparin was placed just below this area and a second lesion developed. Heparin was discontinued and dipyridamole and aspirin were started. The erythematous borders resolved rapidly and excision was not necessary.

Patient N.M. This 77-year-old man complained of epigastric pain and weight loss. On admission, the hematocrit was 41, but fell to 33 prior to surgery; the platelet count was normal. At laparotomy, an unresectable gastric carcinoma was uncovered. A gastrostomy tube was placed and the abdomen was closed. Subcutaneous heparin was started two hours prior to the operation and continued postoperatively. Three days later the tube was found to be lying free in the peritoneal cavity. It was replaced under anesthesia. Abdominal distension became severe and he was unable to eat.

A horizontal band of skin necrosis appeared in the right lower quadrant of the abdomen on the eighth postoperative day (Fig. 2). Hemorrhagic bullae were present but there was no tenderness. Heparin was discontinued and a skin biopsy was obtained. Several estimations of the platelet count were done prior to the onset of necrosis and all were normal. A numerical count on the ninth postoperative day was 125,000/mm^3. On the following day, he became acutely dyspneic and a respiratory arrest followed an episode of vomiting. An autopsy was refused.

Patient M.O. (Fig. 5B) This 64-year-old woman sustained a fracture of the midshaft of the right femur. She had been in good health except for chronic asthma and mild arterial hypertension. She was obese with mild dyspnea on admission. Her hematocrit was 41% and the platelet count was normal. Arterial blood gases on room air were Po_2-57, Pco_2-37. After being placed in traction, her wheezing transiently worsened but improved with theophylline. Since she was at risk of developing DVT, subcutaneous heparin was started three days after admission. Eight days later, a purple discoloration appeared in the left lower abdomen. Within 24 hours bilateral narrow bands of skin necrosis were present (Fig. 3). The patient complained of severe burning pain and acute tenderness in the area of erythema surrounding the necrosis. Subcutaneous heparin was stopped, but the same dose was given intravenously for seven days. When venous access became difficult, heparin was discontinued and warfarin was started. Wheezing worsened and prednisone was started.

Calf tenderness appeared the day after heparin was stopped and the left foot appeared mildly cyanotic. Even though she was adequately anticoagulated with warfarin, a continuous infusion of heparin was started three days later as treatment for suspected DVT. Warfarin was discontinued. She rapidly became confused and restless and her respiratory status worsened. On 2 l of oxygen per minute, she had a Po_2 of 53 and a Pco_2 of 54. Both feet became deeply cyanotic and symmetric areas of skin necrosis appeared on the medial aspects (Fig. 4). Nevertheless, pedal pulses remained strong. Heparin was stopped after 48 hours. Within 24 hours she was alert and breathing comfortably. Four days after the heparin was stopped, a long leg cast was applied. The remainder of her hospitalization was uneventful. All skin lesions resolved without excision.

Patient N.R.M. This 56-year-old woman had a gastric ulcer which did not heal during treatment with antacids and a bland diet. Because of the possibility of cancer, she underwent a vagotomy and gastric resection. The ulcer was benign. Heparin was started two hours before the operation and continued in the postoperative period. On the sixth postoperative day a fever of 39.2° developed. The chest roentgenogram showed bilateral pleural effusions; the lung scan was negative. Cephalothin was started and the fever resolved in 48 hours.

On the eighth postoperative day, purple tender lesions appeared at heparin injection sites. Within 24 hours three areas of necrosis were present which progressed to formation of hemorrhagic bullae. The black areas were surrounded by a ring of acutely painful erythema. Warm saline soaks were applied and pain resolved over four days. Two lesions resolved after discharge, but the largest lesion required excision and primary closure.

Patient A.L. (Fig. 5C) This 74-year-old woman with severe degenerative disease of her left hip was admitted for an arthroplasty. Her only other medical problem was mild hypertension. The hematocrit on admission was 44 and the platelet count 231,000. Subcutaneous heparin was started two hours before surgery and continued in the postoperative period.

On the ninth postoperative day, the right leg became cold and pulseless. A thrombectomy was performed and a continuous heparin drip instituted. Thereafter, the right leg was viable but two subsequent thrombectomies on the left leg did not restore adequate circulation. All thrombi were composed of aggregates of platelets and fibrinogen. Heparin was stopped 16 days after the initial operation and on the following day, the left leg was amputated above the knee.

Platelets were decreased in number on all estimates done between postoperative day ten and 17, but the count rose rapidly when heparin was discontinued. The PTT never rose above 38 even though she was receiving 24,000 units of heparin daily.

Patient S.H. This 58-year-old man was admitted for an arthroplasty of the left hip. He was otherwise healthy and had a normal hematocrit and platelet count. Prophylactic subcutaneous heparin was started on the third postoperative day. The patient made a rapid uncomplicated recovery and was discharged 9 days after surgery (Fig. 5D).

Two days later he was readmitted with right sided chest pain and fever. A right basilar opacity was seen on the chest roentgenogram. He was treated empirically with antibiotics and improved. A pulmonary embolus was suspected, however, and after a perfusion lung scan showed multiple right basilar defects, a continuous infusion of heparin was instituted. Within hours after the first dose of heparin, the patient sustained an acute inferolateral myocardial infarct. Simultaneously, he became confused and combative. A ventilation scan suggested that the perfusion defects were of inflammatory origin but heparin was continued because a pulmonary embolus rather than pneumonitis was still suspected on clinical grounds. His legs became cyanotic and the pedal pulses were im-

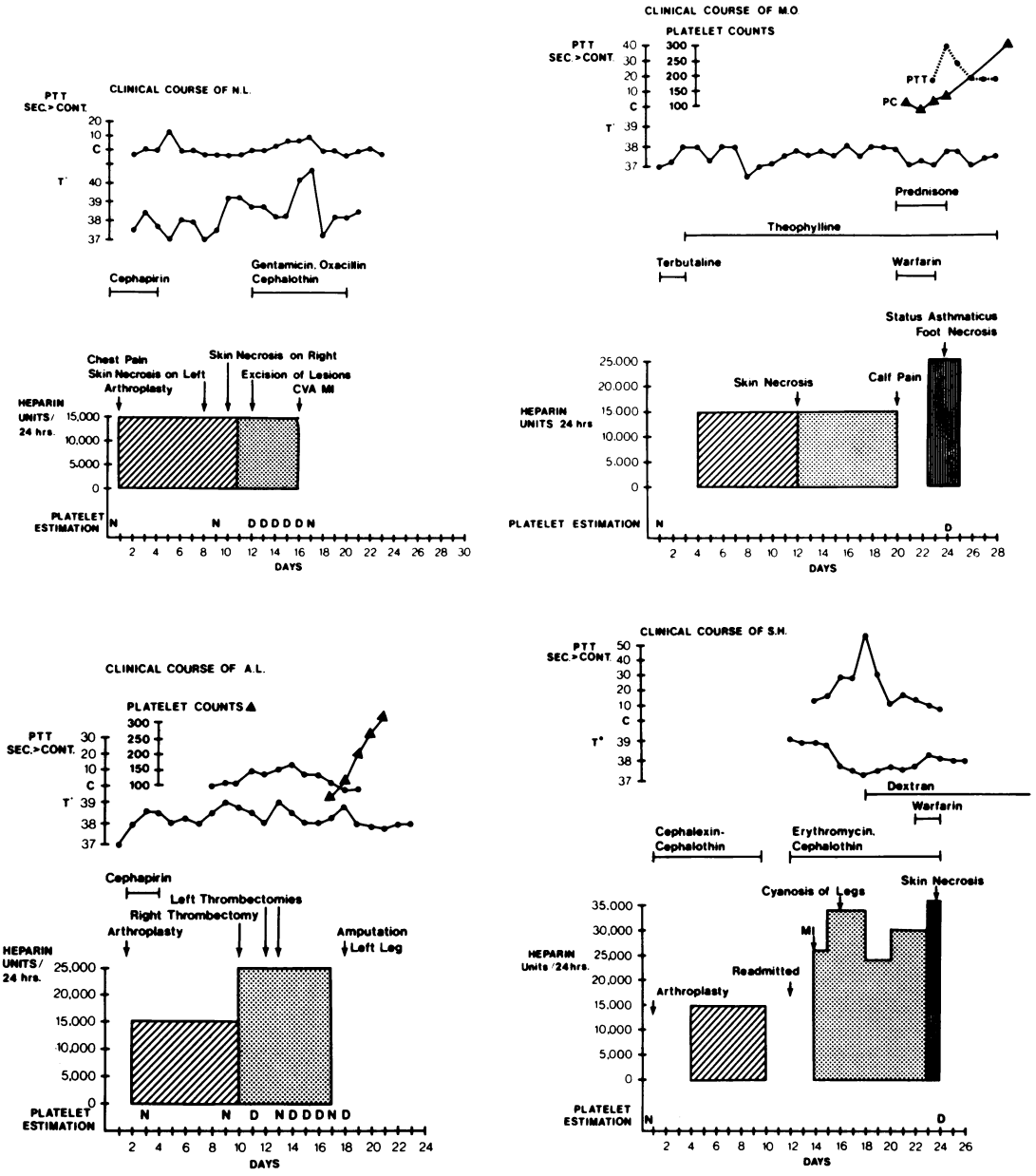

FIG. 5. Graphic demonstration of the hospital courses of selected patients. (a, top left) Patient N.L. (b, top right) Patient M.O. (c, bottom left) Patient A.L. (d, bottom right) S.H. Diagonal lines: subcutaneous injection. Dotted area:continuous infusion. Vertical lines: intermittent intravenous.

palpable. Nevertheless, arteriography demonstrated patent vessels. A diagnosis of "phlebitis with associated vasospasm" was made. As general deterioration continued, he had vivid hallucinations and severe leg pain. Warfarin and dextran were employed. The popliteal pulses disappeared and areas of skin necrosis appeared on both feet as well as large areas on the right thigh and left flank. Since the latter areas of necrosis were considered to be subcutaneous hemorrhage, all anticoagulants were stopped. Platelets were estimated only on the last day of treatment. They were noted to be markedly decreased.

Within four days the patient's pain resolved and he was mentally alert. The left flank lesion was debrided and covered with multiple skin grafts. The right leg was amputated below the knee. Pathologic examination revealed skin and subcutaneous necrosis, but very mild ischemic changes in the calf muscles. Severe atherosclerosis affected the tibial arteries but they were patent. Recent thrombi filled the veins.

Ten weeks after admission the patient suffered a second myocardial infarct. Heparin was continuously infused for 6 days without complications. The patient was discharged three weeks later.

Results

Table 1 summarizes the characteristics and admitting diagnoses of the six patients who developed skin necrosis at injection sites. All six patients were receiving subcutaneous bovine heparin as a prophylactic measure against DVT. Five were recovering from a surgical procedure and one was immobilized following a femoral fracture. The patients ranged in age from 49 to 77. All were Caucasian and five were women. All five women had two or more separate necrotic lesions,

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