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Blood Coagulation in Burn Injury (38460)

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Do the laboratory changes which occur following tissue trauma relate to the susceptibility or magnitude of thromboembolic disorders or intravascular coagulation in the burn patient? Clotting and bleeding disorders have been reported to occur after many forms of stress and trauma (1–5), and have been specifically noted following burn injury (6–15). To be able to predict the occurrence of such disorders by the identification of changes *in vitro* clotting, and to prevent or modify their occurrence and sequelae (16–19) requires an appreciation of coagulation changes in the uncomplicated postburn period and correlation of these laboratory phenomena with *in vivo* hemostasis.

In this study, we prospectively evaluated the *in vitro* coagulation dynamics both in a human burn population and in an experimental animal model.

Materials and Methods. Thirty-five consecutive burn patients with greater than 35% total body surface burns admitted to the U.S. Army Institute of Surgical Research within 5 days of injury were studied. Blood was collected three times weekly for a period of 3 weeks postburn and weekly thereafter. These 35 patients consisted of 17 surviving patients with a mean total body surface burn of 42%, 18 nonsurviving patients with a mean total body surface burn of 55%. Three patients with documented disseminated intravascular coagulation were excluded from this study as they have been previously reported (16).

Male Sprague–Dawley rats, weighing 150–200 g were shaved on the dorsal surface, anesthetized with pentobarbital (1 mg/25 g intraperitoneally) and given a 30% full thickness scald burn. The burn was applied through a plaster mold by immersion of the dorsal surface in water at 100° for 10 sec. All animals were housed in separate cages on standard feed and water *ad lib*. Rats injured in this manner have a normal life span if they survive the initial insult (95% survival). Growth rate returns to normal by 48 hr and invasive or systemic infection does not occur.

Blood was collected by venipuncture from patients and by cardiac aspiration from rats and was anticoagulated with either 3.2% trisodium citrate, or 3.2% trisodium citrate–50 mg EACA (epsilon amino caproic acid) for standard coagulation and plasminogen assays, respectively, or was coagulated with thrombin–soybean trypsin inhibitor for assessment of fibrin–fibrinogen split products.

Fibrinogen concentrations were determined by the ammonium sulfate precipitation method of Parfentjev (20), and checked frequently by the thrombin clottable assay of Ratnoff (21).

Platelet counts were determined by phase microscopy from whole blood diluted 1:200 with 1% ammonium oxalate.

Titration of fibrin–fibrinogen degradation products was performed on thrombin treated sera with a well dilution staphylococcal clumping technique (22), and expressed as concentration in micrograms per milliliter.

Plasminogen concentrations were determined with standard caseinolytic technique (23). For rat plasminogen studies, 0.1 vol of pooled human plasma was used to initiate the reaction (24).

Measurements of prothrombin, activated partial thromboplastin and thrombin times were performed in a 37° water bath using the tube "tilt" method. All data are expressed as 95% confidence limits of the mean (95% CL_m). Fibrinogen, platelet, and plasminogen concentrations

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were corrected for changes in blood volume as outlined in an earlier publication (12). Data for humans are grouped into 0–3, 4–6, 7–10, 11–15, 16–25, 26–40, and 41–60 day intervals. Fifteen normal human volunteers and 25 normal rats served as controls in these studies.

Results. Fibrinogen concentrations in human plasma rose in the first few days after burn injury, peaked at the end of the first week, and then slowly fell toward the accepted normal range (Fig. 1). This response was identical for survivors and nonsurvivors. A similar response was observed in the scald burned rats, but occurred earlier, during the first 24 hr after injury. In both groups of patients and rats, thrombocytopenia occurred initially and was followed by thrombocytosis in surviving patients and in rats. Rebound thrombocytosis did not occur in nonsurviving patients.

Titers of fibrin–fibrinogen split products rose both in patients and in rats, and paralleled the respective fibrinogen responses (Fig. 2). Unlike the disparity in platelet response between surviving and nonsurviving patients, fibrinogen and FSP titers were identical in these two groups. In addition to this, rats displayed an additional transient but significant peak immediately after injury, which had disappeared by 6 hr postburn. The secondary elevation persisted throughout the study. A precipitous fall in plasminogen concentration in the human burn patients which was consistent with either fibrinolysis or fibrinogenolysis, was not observed in the burned rats.

While prothrombin and activated partial thromboplastin times rose in the human burn population, this elevation was significant only in nonsurviving patients (Fig. 3). In the rat studies, we observed an early significant prolongation in clotting times, which returned to normal or supernormal activity.

Discussion. Hyperfibrinogenemia was consistently observed in burn patients and in the animal burn model, was identical in surviving and nonsurviving patients, and appeared to have no prognostic value.

Thrombocytosis, seen in human burn patients and in the laboratory burn model, was preceded by a thrombocytopenia, which persisted in nonsurviving patients as previously reported by Gerhke (10). Postburn thrombocytopenia in the rat is related to burn wound platelet sequestration

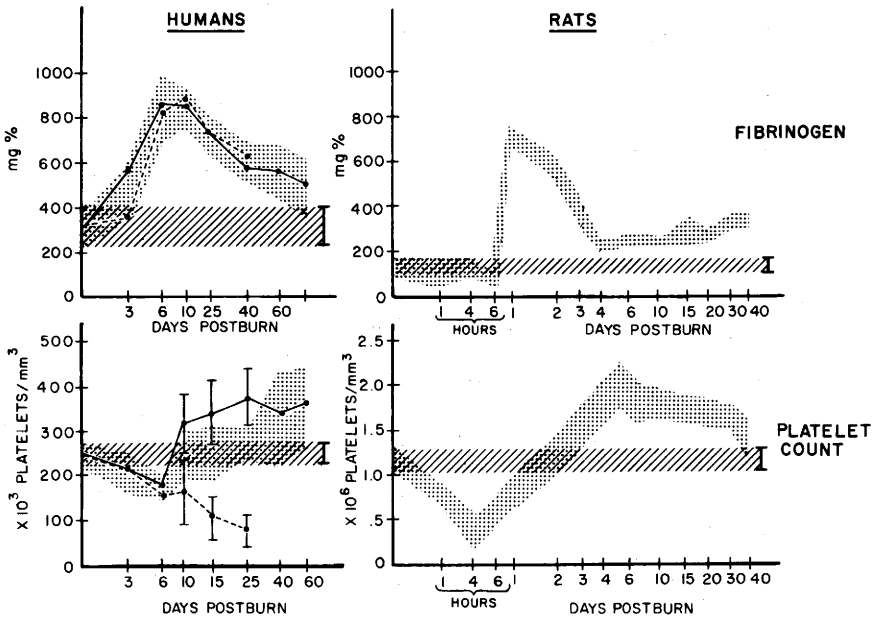

FIG. 1. Fibrinogen (per 100 ml) and platelet (cells/mm³) concentrations in 35 consecutive burn patients (left) and 30% third-degree scald burned rats (right), measured as a function of time postburn. All data are expressed as 95% CL_m, with controls described by the lined areas, burns by the dotted areas. Solid lines describe human burn survivors while dotted lines describe nonsurvivors. In animal experiments, at least 15 rats were examined at each designated time.

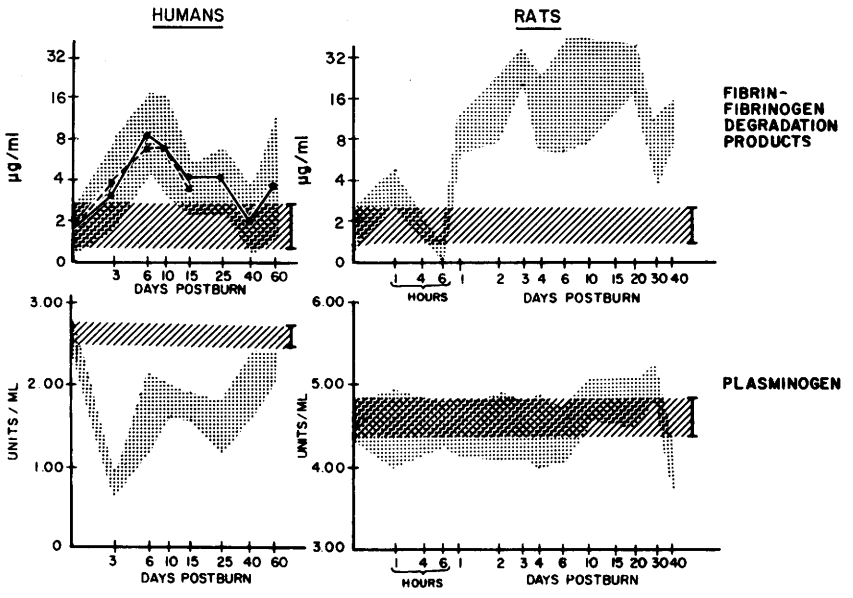

FIG. 2. Fibrin split product (FSP) titers (µg/ml) and plasminogen concentrations (casein units/ml) in 35 consecutive burn patients (left) and in 30% third-degree scald burned rats (right), measured as a function of time postburn. All data are expressed as 95% CL_m, controls by lined areas, burns by dotted areas. Solid lines describe human burn survivors while dotted lines describe nonsurvivors. At least 15 animals were examined at each time period.

and secondary thrombocytosis reflects selective bone marrow megakaryocyte proliferation (12). Persistent thrombocytopenia occurred when the scald burned rat was infected locally with Pseudomonas organisms at the time of burning (25). Since infection is the major cause of death in burned patients, persistent thrombocytopenia in the nonsurviving patients may reflect a failure to produce the predicted postburn megakaryocyte response. Localized intravascular coagulation may be responsible for early postburn thrombocytopenia, at least in the rat model where early platelet depression is associated with laboratory changes of consumption and fibrinolysis. Early thrombocytopenia in the scald burned rabbit may be reversed with heparin administration (9). Hypofibrinogenemia with "rebound" associated with hypoplasminogenemia and elevated fibrinogen–fibrin split product titers has also been reported in trauma patients (4, 5). The mechanism appears to be nonspecific for burns and may or may not reflect an *in vivo* clotting tendency. It was during this "rebound" period that we observed five patients with well-documented disseminated intravascular coagulation (16), and that String observed coagulation disorders in trauma patients (2). While thrombotic disorders do occur (1, 8, 14, 17) and disseminated intravascular coagulation has been documented after burn injury (16), the true incidence of this complication is unknown.

We observed modestly elevated fibrinogen–fibrin split product titers in burn patients well beyond 10 days postburn. These titers were of no prognostic value and were identical both in surviving and nonsurviving patients. While the early elevation in fibrinogen–fibrin split product titers observed in burned rats is consistent with intravascular coagulation accompanied by a localized platelet consumption, the later elevation in titers seen both in patients and in rats is associated with increasing fibrinogen and platelet concentrations. While fibrinogen–fibrin split product titers have been described by others in trauma patients (4, 5), the role or nature of these products is not clear. Meyers (6) reported modest elevation in fibrin split product titers in 77 burn patients, but was unable to correlate these changes with morbidity or burn size. Titers in his study reached a maximum between the second and sixth day postburn, and returned to normal by 16 days. Other evidence of fibrinolysis or fibrinogenolysis was lacking.

We suggest that burn injury may induce local

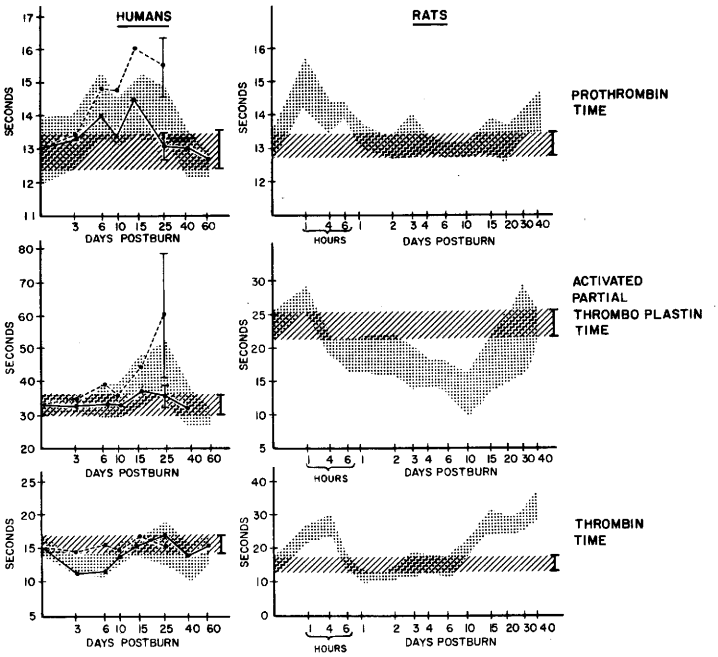

FIG. 3. Prothrombin, activated partial thromboplastin, and thrombin times (sec) in 35 consecutive burn patients (left) and in 30% third-degree scald burned rats (right), measured as a function of time postburn. All data are expressed as 95% CL_m, controls by lined areas, burns by dotted areas. Solid lines describe human burn survivors while dotted lines describe nonsurvivors. At least 15 animals were examined at each time period.

intravascular clotting in the burn wound, which may be the result of local exposure to procoagulant material, followed by a brief period of active fibrinolysis. Then a "rebound" phenomenon, during which consumable products are overproduced through feedback mechanisms, occurs. Disseminated intravascular coagulation might be precipitated by shock or sepsis during this period of high coagulation factor concentration.

Summary. Coagulation studies were performed in 35 consecutive burn patients and in scald burned rats. Between 3 and 10 days after injury, patients exhibited hyperfibrinogenemia, thrombocytosis, and elevated fibrin–fibrinogen split product (FSP) titers. Fibrinogen and (FSP) titers were identical in surviving and nonsurviving patients. A similar response occurred in burned rats, but was preceded in the first hours after injury by evidence of intravascular coagulation. We conclude that elevated FSP titers in the burned patient are not a reflection of classical intravascular coagulation or primary fibrinolysis, but may reflect early local intravascular coagulation in the burn wound, and later a nonspecific or "acute phrase reactant" response.

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