Opsonic Glycoprotein (Plasma Fibronectin) Levels after Burn Injury

Relationship to Extent of Burn and Development of Sepsis

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The time course of immunoreactive and bioassayable opsonic α_2-SB glycoprotein (plasma fibronectin), as well as its relationship to both the extent of injury and development of postburn sepsis, was evaluated following burn injury. Immunoreactive opsonic fibronectin was depleted acutely within hours following burn; its maximal depletion occurring 12 hours postburn injury. The magnitude of depletion was correlated with the body surface area burned, and normal levels were restored at 24 hours postinjury. There was a tendency toward rebound hyperopsonemia at two weeks postburn, with a slow return to normal over the ensuing weeks. Bioassayable opsonic protein levels, in general, paralleled those of immunoreactive protein. Following restoration of opsonic protein levels, a secondary phase of opsonic fibronectin deficiency ($p < 0.05$) developed in those burn patients that became septic. Moreover, this opsonic fibronectin deficiency actually became apparent prior to the onset of clinical sepsis, although it was maximal during sepsis. The resolution of the septic episode was associated with the return of plasma opsonic fibronectin levels to normal. The possibility that secondary deficiency in immunoreactive opsonic fibronectin may be a reliable index of impending sepsis following burn warrants further investigation.

THE SUSCEPTIBILITY OF THE BURN patient to sepsis is well documented.[4,20,23] Sepsis is involved in the cause of organ failure, and is the most important cause of complications and death following resuscitation from burn shock.[2,3,20,22,26] Alterations in host defense, both humoral and cellular, are thought to predispose the injured patient to the development of sepsis.[1–7] A major portion of systemic defense is contributed by the reticuloendothelial system (RES), composed principally of sessile macrophages within the liver (Kupffer cells) and spleen. They contribute to systemic defense by removing blood-borne bacteria, tissue debris, and products of disseminated intravascular coagulation (DIC).[18,26,27] Tolerance to experimental burn, trauma, and sepsis has been correlated with the ability of the RES to clear injected test particulates from the blood,[5,16,23,26] and such particle clearance has been used as a test to determine the functional state of the RES. Kupffer cell phagocytosis of these particles is modulated by opsonic α_2-surface binding (SB) glycoprotein, recently discovered to be identical to plasma fibronectin (cold-insoluble globulin).[10,24] This protein has been shown by immunoassay to be depleted following clinical and experimental trauma as well as operation, especially in association with sepsis and multiple organ failure.[24,25,26,31]

Opsonic fibronectin deficiency in septic trauma patients can be reversed by the administration of a cryoprecipitate, which is rich in opsonic protein.[25] Such reversal improves the patient's clinical state, with respect to sepsis and cardiopulmonary function.[31,32] It remains to be determined, however, if the opsonic deficiency in sepsis preceeds or follows the septic state. To evaluate this problem, we investigated the temporal response of plasma opsonic fibronectin, as measured by both immunoassay and bioassay following burn injury, and its relationship to both the extent of injury and postburn sepsis.

Patients and Methods

Fifteen adult patients, ranging in age from 18 to 86 (average: 41 years), who sustained second and third degree burns of between 20 and 90% body surface area

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(BSA) were studied. The average BSA burn was 40% and the average third degree burn was 21%. The studies were designed to evaluate patients during both the acute and long-term postburn period. Patients were studied as soon after injury as possible. Nine patients were studied within 24 hours of injury, while six patients were transferred from other hospitals and therefore were studied later in their postburn course. Blood samples (10 ml heparinized and 3 ml EDTA) for opsonic protein determinations were drawn every six hours for the first 24 hours postburn and then daily thereafter for six weeks, or until discharge or death. Flow sheets were maintained for each patient for daily recording of vital signs, blood counts, bacteriologic culture results, radiographs, antibiotics, and operative interventions. We characterized patients as septic if they had either positive blood cultures or clinical pneumonia correlated with positive sputum smears and cultures. In addition, fever > 38.8 C or WBC count less than 5,000 or greater than 12,000/mm^3 within one day of a positive blood culture was included in the definition of sepsis. Informed consent for blood sampling was obtained in accordance with institutional guidelines.

Bioassay

The biologic opsonic activity was assessed using a standard liver slice tissue bioassay.[15,16,25] Liver slices weighing 200–250 mg were prepared from normal rat donors with a Stadie-Riggs tissue slicer. The slices were incubated in a medium containing 1 ml of fresh heparinized patient plasma, 2 ml of Krebs-Ringer phosphate (pH 7.4), 100 USP units of heparin, and 2 mg of the gelatinized I 131-labeled "RE test lipid emulsion." This gelatinized RE test lipid emulsion has been previously described and its uptake by phagocytic cells of the RE system has been documented.[16,27] All plasma samples were evaluated three times. Incubation took place in 25 ml Erlenmeyer flasks under a gas phase of 95% O_2 and 5% CO_2 in a Dubnoff metabolic shaker at 37 C for 30 minutes. Following incubation, the liver slices were washed, weighed, and isotopically analyzed for colloid uptake. Opsonic activity was expressed as a percentage of the injected 2000 μg colloid dose (ID) phagocytized per 100 mg of liver slice (%ID/100 mg). Normal value for 13 healthy adults used as controls in the study was 3.24 ± .32 %ID/100 mg.

Immunoassay

Immunoreactive opsonic protein (plasma fibronectin) levels were quantitated by electroimmunoassay, as recently described.[9,11,25] The human opsonic protein was isolated by affinity chromatography[10,14] and monospecific antibody was prepared in rabbits, as documented previously.[9,11] The monospecific antiserum was then mixed with a 1% agarose gel to yield a final antiserum concentration of approximately 0.6% dependent upon the actual antibody titer. Three-millimeter wells were cut in the agarose coated 5 × 10 inch glass plates at intervals of 1 cm, and 10 μl of diluted 10% experimental plasma (EDTA) was added to each well. We used plasma instead of serum in these studies to present better comparison between the immunoassay and bioassay. Samples were electrophoresed toward the anode at a voltage of 7V/cm at 4 C for 22 hours. The plates were then washed and stained as previously described.[11] The human standard for the assay contained 340 μg/ml of immunoreactive human opsonin. Rocket heights were recorded in millimeters and absolute concentration was determined by drawing a standard curve relating rocket height to varying concentrations of the known human standard.

Results

The time course for opsonic fibronectin following burn is illustrated in Figure 1, which demonstrates changes in both immunoreactive and bioassayable protein levels following injury. Maximal depletion of immunoreactive protein occurs at approximately 12 hours after injury, when the level drops to 154 ± 39 μg/ml (normal = 327 ± 23 μg/ml, $p < 0.005$). Immunoreactive opsonic protein levels return to normal at about 24 hours postburn, and remain at or above normal thereafter unless sepsis intervenes (see below). There is a tendency towards "hyperopsonemia" during the time frame of 16–18 days postburn (398 ± 24 μg/ml, $p < 0.05$) with return towards normal thereafter. In general, changes in bioassayable activity parallel those of immunoreactive protein. Because only fresh plasma samples were used for bioassay determination, patients admitted in the middle of the night did not have their acute plasma bioassayable activity consistently measured. The number of bioassay determinations prior to 24 hours were, thus, not sufficient to draw valid statistical conclusions; these points are therefore omitted. In association with the immunoreactive hyperopsonemia, there was a small elevation in the average bioassayable activity (3.70 %ID/100 mg) above control values (3.24 ± 0.32) at about 2 weeks postburn.

The magnitude of the acute depletion was directly correlated with the per cent BSA burned. Figure 2 demonstrates this relationship, which plots the maximal depletion of immunoreactive protein in six patients followed from within six hours of injury versus their per cent BSA burn ($r = 0.90$).

Sepsis was associated with a significant depletion of immunoreactive opsonic protein which returned to normal following resolution of the septic episode

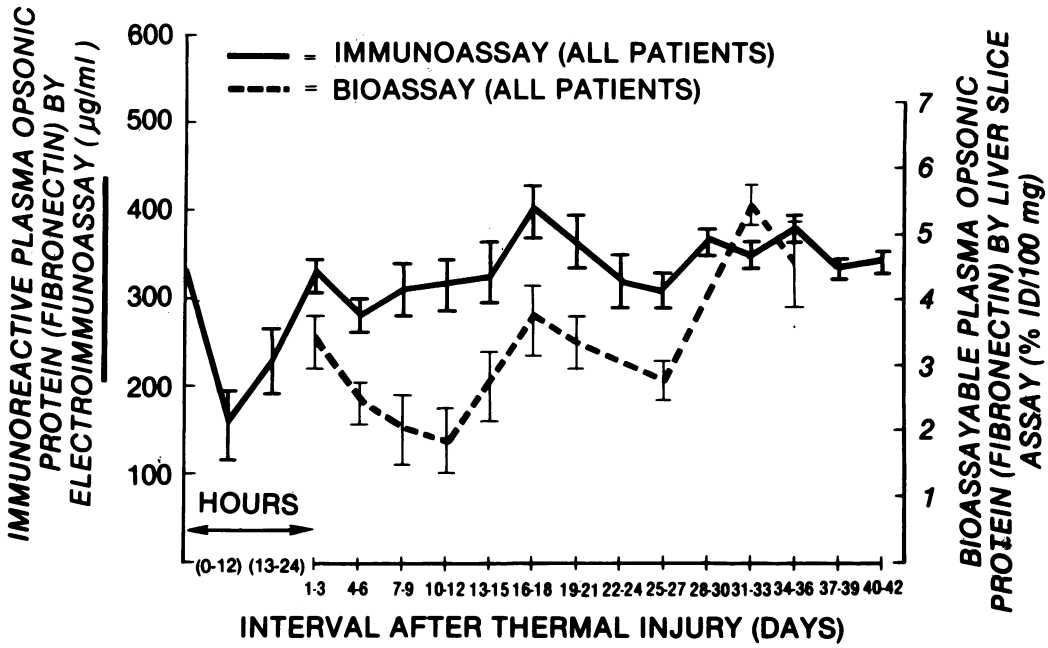

FIG. 1. Immunoreactive and bioassayable opsonic protein following burn. Each point represents the mean ± SEM for 6–18 determinations. Normal values are 327 ± 23 μg/ml for immunoreactive protein (solid line) and 3.24 ± 32%ID per 100 mg liver tissue for bioassayable protein (broken line). The depression of immunoreactive protein at 12 hours is significant ($p < 0.05$). Bioassayable activity parallels immunoreactive protein levels with respect to the temporal pattern.

(Fig. 3). Patients destined to become septic underwent the same acute depletion and recovery as the nonseptic patients. Two or three days prior to the onset of clinical sepsis, however, there was a second phase of opsonic fibronectin deficiency in those patients that became septic which was in contrast to the nonseptic patients (Table 1, Fig. 3). The relative depletion of both immunoreactive and bioassayable fibronectin during sepsis is shown in Figure 4, in which the mean value during sepsis is compared to nonseptic patients over the same post-injury interval with the same per cent BSA burn. Immunoreactive levels fell to 207 ± 14 μg/ml as compared with 358 ± 18 μg/ml in the nonseptic group ($p < 0.01$), while bioassayable opsonic activity decreased to 1.64 ± 0.49 %ID/100 mg as compared with 5.20 ± 0.3 %ID/100 mg in the nonseptic group ($p < .005$).

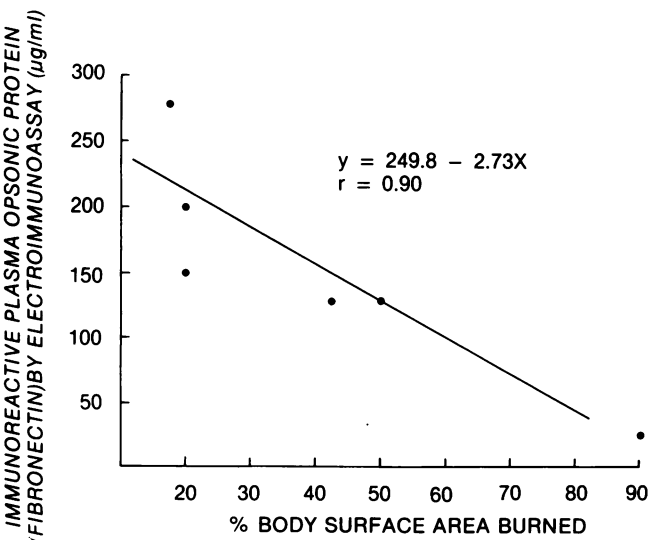

FIG. 2. Correlation between per cent body surface area burn and maximal depletion of immunoreactive opsonic protein measured within the first 12 hours postburn in six patients ($r = 0.90$, $p < 0.05$).

The time course of opsonic fibronectin following burn injury and its relationship to the degree of injury and development of postburn sepsis is exemplified in the following typical case history chosen from the 15 patients studied.

Case History

Patient E.P., a 25-year-old man, sustained a 50% total, 20% third degree burn when his heater exploded in his mobile home. He was admitted to the Albany Burn Unit within six hours of injury, at which time his immunoreactive opsonic protein level was 200 μg/ml (Fig. 5). At 12 hours, there was a further decrease in his opsonic protein level (165 μg/ml) which increased to 225 μg/ml 24 hours postburn and to 375 μg/ml on the second postburn day. Thereafter, his osonic fibronectin decreased daily, reaching 150 μg/ml on day 6. For example, immunoreactive opsonic protein levels fell to 235, 244, 213 μg/ml on days 3, 4, and 5, respectively. The patient had a fever of 39.2 C on day 5 following surgical debridement and on day 7 had a positive blood culture for *Staphylococcus aureus*. The patient was started with Gentamycin and underwent further debridement and skin grafting on day 10. He continued to have intermittently positive blood cultures for *S. aureus* until day 12, during which time his opsonic protein level averaged 150 μg/ml. This episode was followed by gradual clinical improvement and slowly increasing fibronectin levels which reached normal values 25 days postburn. Thereafter, his hospital course was uncomplicated and he was discharged seven weeks postburn.

Discussion

Burn injury results in complex alterations in host defense which are thought to predispose the injured patient to the development of sepsis. These include

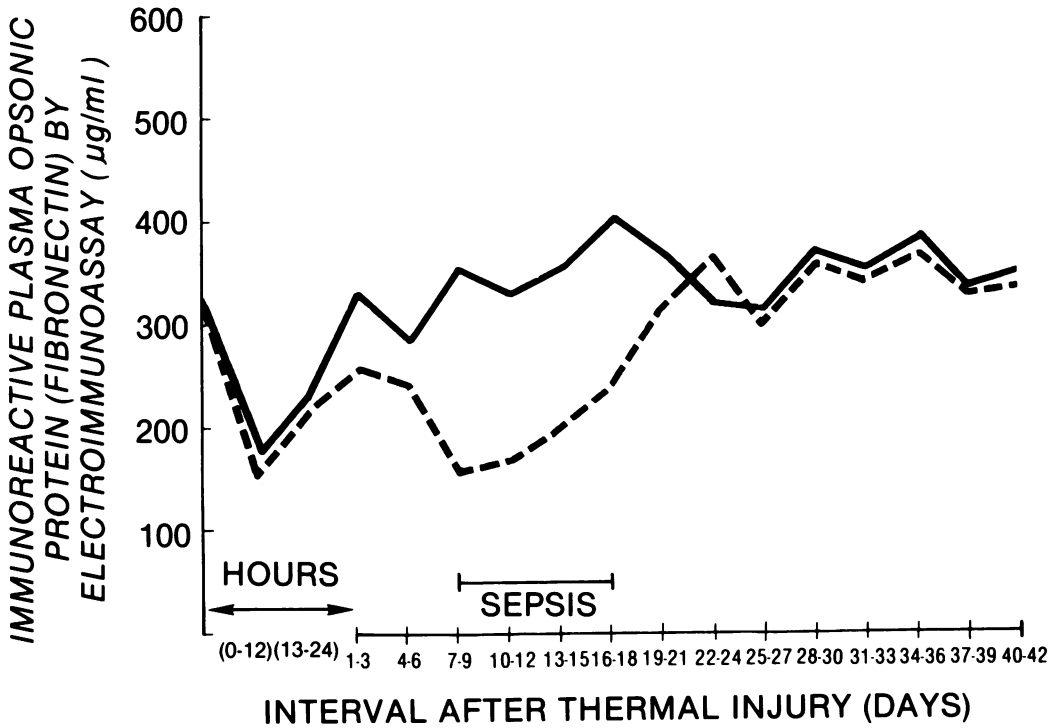

FIG. 3. Immunoreactive opsonic protein patterns following burn in three septic (broken line) and 12 nonseptic (solid line) patients. Sepsis occurred between days 7–17 in all three patients. Patients destined to become septic deviate from the nonseptic pattern two to three days prior to the onset of clinical sepsis, attaining the lowest levels during the septic period. Recovery of immunoreactive protein levels is complete following the resolution of the septic episode. Specific comparisons are: days seven to nine (154 ± 9 vs 392 ± 29; $p < 0.05$); days 10–12 (166 ± 14 vs 334 ± 23, $p < 0.05$); days 13–15 (196 ± 88 vs 378 ± 36, $p < 0.05$) and days 16–18 (249 ± 30 vs 408 ± 43, $p < 0.05$).

deficits in neutrophil and lymphocyte function,[1–4] depletion of immunoglobulins,[13] alterations of the complement cascade,[7] anergy to delayed hypersensitivity tests[3,12] and functional depression of the RES.[15,23,25,32] The phagocytic functional state of the RES following burn has been evaluated experimentally by measuring the rate of clearance of inert particles,[23,28,33] or by determining the ability of burn plasma to support phagocytosis by normal rat liver Kupffer cells *in vitro*.[15,29] Plasma opsonic fibronectin is now known to modulate the above RES function, and its deficiency following experimental blockade, trauma or surgery has been well documented.[11,24,25,26]

Warner and Dobson,[33] using chromic phosphate P32, Rittenbury and Hanback[23] using a colloidal fat emulsion (Lipomul) and Schildt[28,29] using human chromic chloride Cr 51-labelled red blood cells all demonstrated decreased clearance of these particles following experimental burn with a tendency towards a supranormal rate of clearance at approximately 14

TABLE 1. *Immunoreactive Plasma Opsonic Fibronectin (FN) in Burn Patients Prior to and During Sepsis As Compared with Nonseptic Patients with Comparable Injury*

Patient (age)	Per Cent Burn	Day of* Sepsis	FN During† Sepsis (μg/ml)	FN Preceeding‡ Sepsis (μg/ml)	Organism
Septic patients					
CW (34 years)	65	7–19	165 ± 20	222	*S. pneumoniae*
AM (56 years)	30	6–11	278 ± 18	338	Enterobacter
EP (25 years)	50	6–16	198 ± 30	232	*S. aureus*
Average (38 years)	48		207 ± 14§	255 ± 23	
Nonseptic patients‖					
CS (61 years)	35	7–17	357 ± 14	287	
KF (22 years)	35	7–17	444 ± 18	324	
MC (18 years)	50	7–17	431 ± 32	ND	
MF (41 years)	40	7–17	422 ± 17	344	
Average (41 years)	40		358 ± 18§	292 ± 8	

* Sepsis was defined as positive blood cultures or clinically documented pneumonia. Fever > 38.8C or WBC count less than 5,000 or greater than 12,000 within one day of positive blood cultures were also included in the diagnosis of sepsis.

† Values represent the mean ± SEM for all determinations during sepsis. The values in nonseptic patients are those determined during the 7–17 day postburn period.

‡ The mean of all determinations made during the three days immediately preceeding the diagnosis of sepsis. In nonseptic patients the determinations made during four to six days postburn are used.

§ The difference between the groups is highly significant ($p < 0.001$).

‖ Four nonseptic patients of comparable age, burn size and period postburn were used as a control group.

ND = not done.

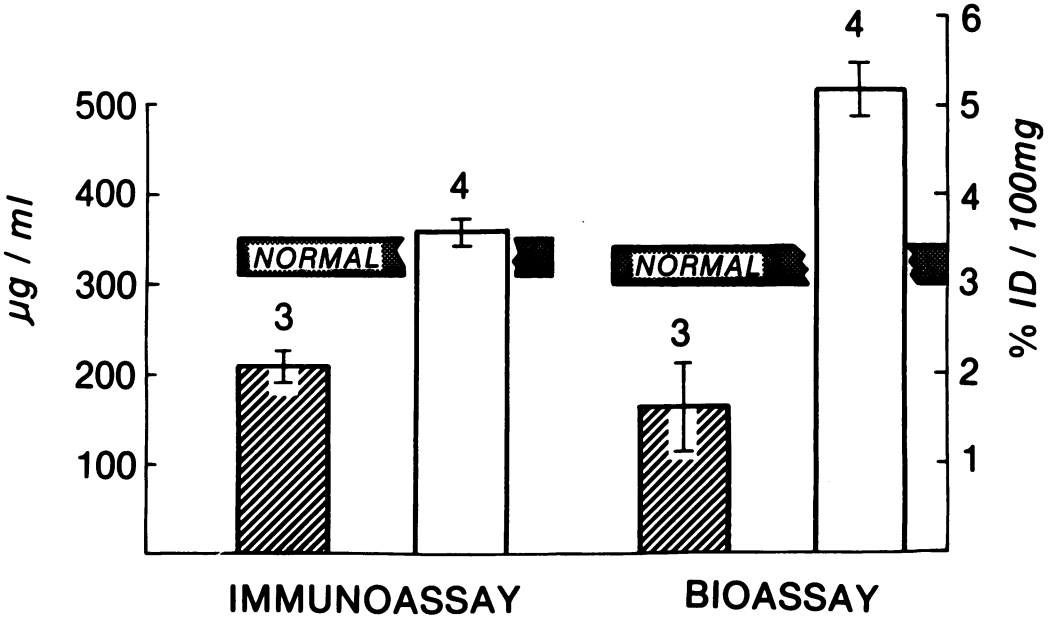

FIG. 4. Immunoreactive and bioassayable plasma opsonic protein (fibronectin) in sepsis. The mean values ± SEM during documented sepsis (striped bars) are compared with nonseptic patients (solid bars) during the same period postburn with the same per cent body surface area burn. Immunoreactive protein fell to 207 ± 14 μg/ml compared to 358 ± 18 μg/ml in the nonseptic group ($p < 0.01$) and bioassayable activity decreased to 1.64 ± 0.49 %ID/100 mg compared to 5.20 ± 0.3 %ID/100 mg ($p < 0.005$). Details for the above patients (septic n = 3; nonseptic n = 4) with respect to degree of burn and individual fibronectin levels are presented in Table 1.

days postburn in surviving animals. The acutely diminished clearance capacity was related to the severity of burn, and nonsurviving animals demonstrated a persistently depressed clearance ability. Colloid injections have been used for assessment of RE function in patients with the same results,[30] but its application is limited due to the blockading effect on the RES of the test substance itself[27] and the known heightened susceptibility to injury, sepsis and trauma following RES blockade due to a depletion of opsonic fibronectin.[11,16,26] The ability of plasma to support phagocytosis of test particles *in vitro*, therefore, has been used as a useful noninvasive index of RES function, as the *in vitro* liver slice assay correlates well with the ability of the RES to clear the blood of particulates *in vivo*.[16,26,27] Following the isolation, purification and characterization of opsonic α_2-SB glycoprotein[9,10] it has been demonstrated to be the plasma constituent responsible for opsonization of test particles, and its depletion following experimental surgery and trauma correlates well with the above *in vivo* and *in vitro* assays.[10,24] To our knowledge, this is the first clinical study documenting the temporal changes in immunoreactive opsonic protein (fibronectin) following burn

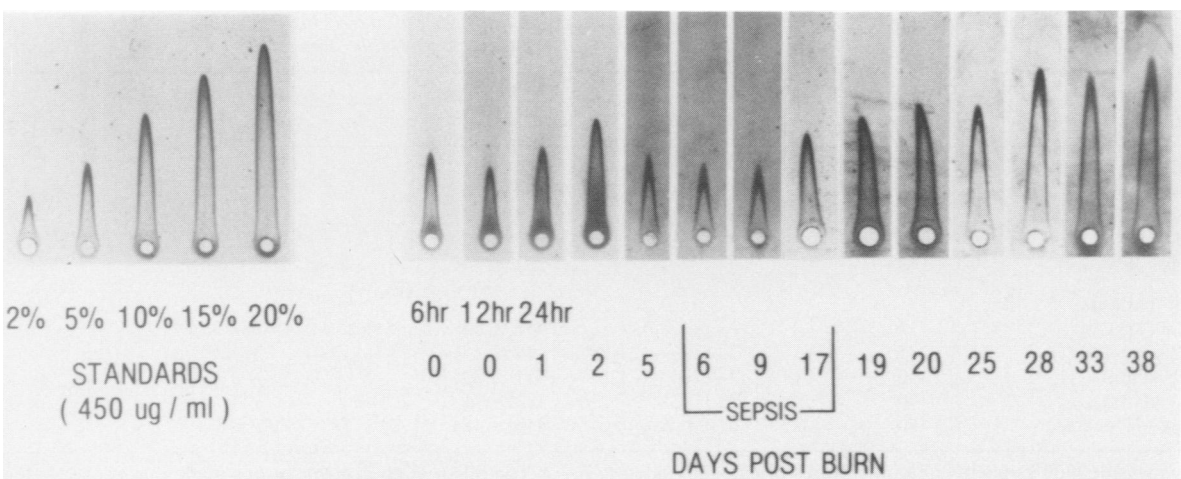

FIG. 5. Patient E.P.: immunoreactive opsonic protein as measured by rocket immunoelectrophoresis. A standard curve was constructed from the five rockets on the left containing 2–20% plasma of known opsonic protein concentration. A 10% dilution of the patients plasma on the days indicated were placed in the wells to the right. A normal plasma concentration would correspond to a rocket height equal to the 10% standard dilution. Documented sepsis was present between day 7 and 13 postburn. Immunoreactive opsonic protein levels fell from 375 on day 2 to 235, 244, 213 and 150 μg/ml on days 3, 4, 5, and 6 respectively. A positive blood culture for *S aureus* first recorded on day 7.

injury and as such, suggests that this parameter may be a noninvasive measurement of RES function following burn and have prognostic value during the course of burn therapy.

Goldman et al.,[15] in studying biologic opsonic activity in plasma of burned children found a prolonged depression lasting 49 days following burns of greater than 40%, and found an even greater depression associated with septic complications. Our findings of normal biologic activity, except in the cases of sepsis, is not at variance with their results as the average burn size was 41% BSA in our study, and the patients with larger burns did, in fact, have a prolonged opsonic deficiency when evaluated individually.

Liedberg[19] demonstrated decreased phagocytosis of Pseudomonas by peritoneal macrophages and polymorphonuclear leukocytes (PMN) when the bacteria were injected intraperitoneally (IP) 24 hours after burning. McRipley and Garrison[21] found that susceptibility to IP injection of *Pseudomonas aeruginosa* increased markedly within minutes after burns of greater than 30%, much before any drop in immunoglobulins or complement could occur.[1,7,13] Three days following burn, however, susceptibility was equal to control. Alexander[1] confirmed these observations, but in addition found that animals innoculated with Pseudomonas IP two or seven days postburn had a decreased susceptibility when compared to controls. He also examined peritoneal exudates following IP injection of Pseudomonas one hour and 72 hours following burn. Phagocytes were more numerous and clearance of bacteria was greater in control animals than animals burned 1 hour prior to IP innoculation, but the situation was reversed 72 hours after burning, when the number of phagocytes were greater and clearance more effective in burned animals. It was not possible to separate intracellular killing from phagocytosis in these studies. Recently, Bjornson[7] demonstrated that opsonins other than IgG and complement might be deficient in acute burn sera, and postulated that alterations in the alternative pathway could account for the deficiency. Though documenting functional depression in the alternative pathway and depressed classical activity in patients destined to become septic, they could not consistently demonstrate an opsonic defect toward the offending organism, nor correlate complement deficiency to opsonic deficiency when found. They concluded that other as yet unidentified opsonic factors could account for the observed results.

This acute depression of RES activity and antibacterial host resistance followed by hyperactivity and increased resistance corresponds to the time course of immunoreactive opsonic fibronectin following experimental burn, trauma, and operation.[16,26,28,31] The recent finding in our laboratory that fibronectin is involved in bacterial phagocytosis,[17] as well as clearance of test colloids, may partly explain the above alterations in host defense seen experimentally and clinically following burn.

Alexander and Moncrief[3] demonstrated a depressed primary immune response to particulate antigen given four days postburn. Antigens given prior to burn injury elicited an effective primary immune response. They hypothesized that a defect existed in the afferent limb of the immune response, specifically in macrophage phagocytosis of the particulate antigen prior to immunologic processing. Because of the documented role of fibronectin in opsonization of particulates by macrophages, it is possible that the above defect is explainable on the basis of the acute hypoopsonemia following burn. The role of fibronectin in the afferent limb of the immune response warrants investigation.

Decreased resistance to experimental trauma after RES blockade is postulated to be due to inadequate removal of generated particulates because of the associated fibronectin deficiency. Injury alone is capable of producing an acute opsonic fibronectin deficiency due to both the high affinity of FN for exposed collagen as well as its consumption during particle clearance (24). Products of DIC, platelet aggregates, and microthrombi, known to be produced by the septic process[8] are cleared by the RES and opsonization by plasma fibronectin appear to modulate their clearance.[16,24,26] Clearance of these particulates is thought to ensure integrity of organ function by preventing microembolization of these particulates in organ vascular beds with subsequent organ failure.[24] The finding that a second depression in circulating opsonic fibronectin seemed to precede the onset of clinical sepsis, is both interesting and unexpected. Fibronectin deficiency associated with sepsis and injury has heretofore been understood to be the result of, rather than a predisposing condition for, the development of sepsis.[16,25,31] In light of new evidence that fibronectin is necessary for maximal neutrophil phagocytosis of bacteria in a serum medium,[17] acute postburn deficiency could well be a contributing cause to the development of subsequent sepsis. Indeed, this potential physiologic role of opsonic α_2SB glycoprotein (plasma fibronectin) may, in part, explain the marked improvement seen in septic surgical, trauma and burn patients with coexistent organ failure following reversal of opsonic fibronectin deficiency by infusion of plasma cryoprecipitate.[24,25,31,32]

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