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15. The rats were allowed at least 1 week to acclimatize to our laboratory animal facility after delivery from the breeder (Canadian Breeding Laboratories Ltd., Montreal, Quebec). A 12-hour light, 12-hour dark cycle was maintained in the animal housing area. The rats were allowed water but deprived of food for approximately 20 hours prior to the experiment. The experiments were performed from 1000 hours to 1400 hours. The rats were lightly anesthetized with ether and artificially ventilated. A PE 50 catheter was inserted into the femoral artery to record blood pressure. Blood pressure and lead II of the electrocardiogram were recorded continuously on a Gilson multichannel recorder. The heart was exposed by left thoracotomy between the third and fourth ribs. After ligation the thorax was closed and the pneumothorax removed by direct hypodermic aspiration. Animals were ventilated for 10 minutes after ligation. Hemodynamic monitoring was terminated and the rats were allowed to recover spontaneously, undisturbed; they were awake approximately 15 to 20 minutes after ligation.
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Cryoprecipitate Reversal of Opsonic α_2-Surface Binding Glycoprotein Deficiency in Septic Surgical and Trauma Patients

Abstract. *Human opsonic α_2-surface binding glyoprotein (α_2SB-glycoprotein), a molecule having immunologic identity with an amino acid composition similar to cold-insoluble globulin, is concentrated in a cryoprecipitate of plasma. Septic surgical and trauma patients manifesting opsonic α_2SB-glycoprotein deficiency and associated reticuloendothelial system dysfunction were treated by intravenous infusion of cryoprecipitate. This therapy restored circulating bioreactive and immunoreactive opsonin and improved their septicemia, pulmonary insufficiency, and duration of recovery. Cryoprecipitate infusion may offer a new approach to the treatment of septic injured patients in preventing multiple organ failure; measurement of immunoreactive serum opsonic α_2SB-glycoprotein may provide a noninvasive index of reticuloendothelial system function and patient status during severe sepsis that follows trauma.*

Septic complications after multiple trauma, burn injury, and major surgery are a major clinical problem despite advances in surgical techniques, antimicrobial therapy, and patient monitoring (*1, 2*). Resistance to septicemia involves both nonspecific and specific factors; however, recent studies have emphasized the function of the reticuloendothelial system (RES) as a determinant of survival after severe trauma and shock (*3–5*). The RES is depressed after major surgery (*4–7*), blunt trauma (*4, 5, 8*), burn injury (*4, 5*), and hemorrhage (*4, 5*); and therapeutic techniques to reverse systemic RES failure have not been developed.

Previous studies (*4, 9–11*) have implicated opsonic α_2-surface binding glycoprotein (α_2SB-glycoprotein) as a key determinant of RES phagocytic function. The amount of this protein in the serum is decreased after trauma, a decrease which contributes to the observed RES phagocytic depression (*4*). Reticuloendothelial (RE) cells in the liver and spleen remove bacteria, microaggregates of fibrin, injured platelets, denatured protein, and immune complexes from the blood, and thus serve as a selective filter or clearance mechanism to protect the pulmonary and systemic vascular beds from potential microembolization and injury (*3, 4*). Immunologic and biochemical analyses of purified human opsonic α_2-SB-glycoprotein (*12–14*) have revealed that it is identical to cold-insoluble globulin or plasma fibronectin, a major protein fraction recoverable in human plasma cryoprecipitate.

In our study, we intravenously infused fresh plasma cryoprecipitate into severely ill, septic surgical and trauma patients with marked opsonic deficiency and RES failure, and tested for augmented systemic defense against persistent septicemia and associated pulmonary insufficiency. Opsonic replacement was quantified by bioassay (*5, 15*) and immunoassay (*10, 13*), and the clinical course of the patients before and after cryoprecipitate therapy was monitored.

The bioassay for opsonic activity in serum was measured relative to Kupffer cell phagocytosis by liver slice assay (*6, 8, 15*) with the gelatinized ^{131}I-RE test lipid emulsion and heparinized serum (*5, 9, 14, 15*). Immunoreactive opsonic α_2SB-glycoprotein from serum was measured in micrograms per milliliter by electroimmunoassay or rocket immunoelectrophoresis (*10, 13, 16*) with monospecific antiserum (*9, 11, 13*). Isolation of the protein from serum involves a series of steps (*9, 11, 13*), including ammonium sulfate fractionation, high-voltage free-flow electrophoresis, and Sepharose 4B gel filtration. An alternative purification with a gelatin-Sepharose affinity column in the presence of mercaptoethanol is also effective. Immunochemical purity of the protein was tested by electroimmunoassay with unabsorbed, polyspecific antiserum, and homogeneity was ascertained by gradient polyacrylamide gel electrophoresis (*10, 11, 13*).

Cryoprecipitate (*17*) was intravenously infused as a continuous dose throughout a 60-minute interval. Both biologically active and immunoreactive serum opsonic α_2SB-glycoprotein were measured before and at least at 1/2 4, and 24 hours after infusion. Circulating white blood cell levels, body temperature, blood and tissue fluid bacterial cultures, arterial blood gas determinations, and standard cardiopulmonary measurements were recorded.

Patients displayed elevated α_2SB-glycoprotein in their serum during the 1/2- to 4-hour interval after cryoprecipitate infusion. The three patients presented in this study (*18–20*) showed an average increase in immunoreactive opsonic protein of 94 μg/ml above preinfusion levels by 30 minutes after treatment. By 4 hours, the average level of α_2SB-glycoprotein in the serum, determined by electroimmunoassay increased by (on the average) 172 μg/ml. Patient 2 (Fig. 1) experienced a phase of rapid serum depletion

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of α_2SB-glycoprotein; however, later elevation of his serum level was associated with a stabilized clinical course.

We typically observed an increase in immunoreactive opsonin during the early stages after infusion, especially at the 1/2 to 4-hour interval. This period can be followed during the next 48 to 72 hours by a progressive decline of the protein to concentrations typical of those measured before infusion, especially when the patient had a severe focus of injury. Within the 3 days after therapy, particularly in patients with improved clinical conditions, the serum concentration of this protein gradually rose, concurrently with patient stabilization and reversal of the febrile and septic state. The clinical parameters of the three septic patients before and after cryoprecipitate therapy were compared (Table 1). The most consistent response was observed, between 12 and 24 hours, as a rapid reversal of the febrile state and improvement in pulmonary function. In contrast to a deteriorating clinical condition that was severe and unmanageable by routine ventilatory support (two patients) and antimicrobial agents (three patients) before cryoprecipitate infusion, the patients experienced improvement characterized by increased alertness, heightened pulmonary function, stabilized hematological function, lowered body temperature, and survival.

These observations, coupled with our previous demonstration that intravenous therapy with the purified opsonic α_2SB-glycoprotein (*21*) can prevent RES depression in animals after surgery, suggest that the replacement of this protein effectively reversed RES phagocytic depression. Previous attempts to reverse α_2SB-glycoprotein deficiency have been limited by a shortage of the purified human protein (*9, 11, 13*). Although the techniques for isolating pure cold-insoluble globulin (*22*) or plasma fibronectin (*23*) yield a relatively pure protein for characterization studies, the isolated protein appears to lack biological activity (*12, 14*). In contrast, the isolation of the human opsonic α_2SB-glycoprotein either by our methods (*9, 10, 12, 13*) or by affinity chromatography results in a purified protein that retains antigenic and biological activity. Comparison of cold-insoluble globulin and human opsonic α_2SB-glycoprotein has revealed their identity (*12, 14*).

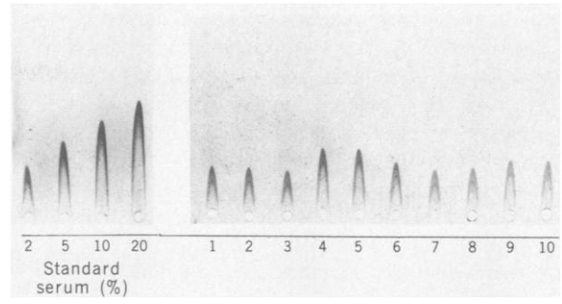

Fig. 1. Typical pattern of immunoreactive opsonic α_2SB-glycoprotein in the serum before and after intravenous cryoprecipitate therapy. The above response was observed in patient 2 (*19*). The standard curve (from 2 to 20 percent serum) was constructed from the four rockets to the left. Immunoreactive levels in patient 2 were measured with a 10 percent test serum concentration. Rockets 1 to 3 represent serum α_2SB-glycoprotein at 7:00 p.m. (6 September 1977), at 9:00 a.m. (7 September 1977), and 12:30 p.m. (7 September 1977) before cryoprecipitate infusion. Rockets 4 to 10 represent serum obtained at 1/2, 4, 24, 48, 72, 96, and 120 hours after therapy.

The correlation between the bioassayable and immunoreactive levels of α_2SB-glycoprotein and in vivo RES phagocytic clearance capacity (*3, 10, 15*), and the correlation between RES function and shock resistance (*4, 5, 8*) suggest that measuring the α_2SB-glycoprotein in serum may provide a noninvasive monitor of RES function and patient response to therapy after shock (*21*). The apparent increase that we observed in immunoreactive opsonic protein levels for several hours after the termination of cryoprecipitate infusion may reflect increased endogenous release or decreased consumptive depletion of the glycoprotein during the early period after therapy. Since data from studies done in tissue culture suggest that cold-insoluble globulin or fibronectin is synthesized by fibroblasts and endothelial cells (*23, 24*), the elevation in the blood of α_2SB-glycoprotein seen late may reflect recovery of cellular integrity after injury and septicemia.

The increase in the bioassayable activity of α_2SB-glycoprotein is typically greater than the relative elevation of immunoreactive protein; this may be due to any one of the multiple factors that can influence liver slice uptake of test particles in the bioassay, such as nonphagocytic adherence of agglutinated particles or Kupffer cell ingestion of the test colloid. However, light and electron microscopic and autoradiographic studies have verified that Kupffer cells do ingest the protein-coated RE test lipid emulsion (*7*) in the liver slice assay, and nonphagocytic adherence of agglutinated particles to Kupffer cells is more apparent with inert particles such as colloidal gold (*7*).

Although extensive biochemical studies of cold-insoluble globulin or fibronectin have been performed (*22, 23*), no prominent physiologic function for the protein has been identified (*12*). The data in this report, coupled with those that link malignant disease, septicemia, and disturbed hemostasis to RES disturbances and alterations in α_2SB-glycoprotein (*2, 3, 5, 12*), support a role for cold-insoluble globulin in macrophage host defense mechanisms. This role may relate to the macrophage's discriminating (*4, 5, 9, 10*) "self" from either "nonself" or "altered self" in removing denatured protein microaggregates and products of cellular injury (*3, 25*).

Table 1. Clinical response of septicemic surgical and trauma patients to intravenous α_2SB-glycoprotein therapy. Values presented for each patient (*18–20*) represent the average of multiple determinations over the 48-hour period before or after therapy. Abbreviations: Pa_{O_2}, partial arterial pressure of O_2; PEEP, positive end-expiratory pressure; and Fi_{O_2}, fraction of inspired O_2.

Patient	Time of measurement	Pulse (beat/min)	Temperature (°F)*	White blood cells (cell/mm³)	Pa_{O_2} (torr)	Fi_{O_2} (%)
1	Before treatment	88–122	101–103	2700–3300		
1	After treatment	88–100	98–99	4200–4700		
2	Before treatment	130–160	103–105	11,600–37,900	88 on 10 cm-H_2O PEEP	50
2	After treatment	88–100	100–102	13,000–16,500	74 on 5 cm-H_2O PEEP	50
3	Before treatment	96–103	103–105	18,500–22,800	53 on 5 cm-H_2O PEEP	40
3	After treatment	88–110	99–100	16,600–17,400	117 on 5 cm-H_2O PEEP	40

*Degrees Fahrenheit equal 9/5 degrees Celsius plus 32.

The phagocytic clearance failure of hepatic Kupffer cells is associated with an increased pulmonary localization of blood-borne particulate matter (*4*) that appears to reflect microembolization of the microcirculation; a similar event may occur in peripheral vascular beds. After surgery, or traumatic or thermal injury, especially when sepsis or endotoxemia is present, there is an increased potential for disseminated intravascular coagulation and generation of circulating microaggregates and immune complexes. All these factors contribute to a pulmonary insufficiency after trauma (*4, 26, 27*). Improved pulmonary function in septic surgical and trauma patients after cryoprecipitate infusion may be due to an increase in opsonin-mediated RES clearance of such blood-borne substances. The finding that opsonic α_2SB-glycoprotein deficiency induced RE blockade and exaggerated the degree of pulmonary insufficiency after experimentally induced low-grade intravascular coagulation (*28*) supports the concept that liver RES clearance of blood-borne particulates is closely associated with multiple organ failure after trauma or burn, especially in patients with severe septicemia. An analogous pattern of "consumptive opsoninopathy" has been discussed by Alexander *et al.* (*29*) in their studies on altered leukocyte phagocytosis of bacteria in septic surgical and burn patients.

The reversal of opsonic deficiency and the improvement in patient health observed after infusion of cryoprecipitate suggests an important role for RES function in cardiopulmonary function and survival during septic shock. Cryoprecipitate (*30*) infusion or alternative administration of the purified protein may provide an approach for treating septic injured patients; measuring both immunoreactive (*31*) and bioreactive (*32*) levels of opsonic α_2SB-glycoprotein offers a noninvasive method for indirectly monitoring RE function.

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18. Patient 1 (K.H.) was a 66-year-old woman who developed oral mucosal ulcers, diarrhea, and fever. Soon after the onset of this illness, she developed lower abdominal pain and was admitted to a regional hospital. Septicemia due to Gram-negative bacteria was discovered, and an exploratory laparotomy revealed a large pelvic abscess with, as was suspected, perforated appendicitis. After appendectomy and drainage of pelvic abscess, the patient developed upper gastrointestinal bleeding and required transfusion. Subsequently, an enterocutaneous fistula was identified, and 4 weeks after her first operation, she was transferred to the Albany Medical Center. The cutaneous fistula, identified by sinogram, originated from the sigmoid colon. At this time, the patient showed signs of sepsis with tachycardia, intermittent high fever, and leukopenia. At operation, a pelvic abscess was drained and a diverting colostomy was created with closure of the sigmoid fistula. In view of her progressive septic state and deteriorating clinical course, we transfused cryoprecipitate intraoperatively to reverse her opsonic α_2SB-glycoprotein deficiency. Her bioassayable opsonic activity, in percentage injected dose per 100 mg of liver tissue, was 1.66 before therapy. After therapy, her bioassayable opsonic activity was 3.64 at $^1/_2$ hour, 4.81 at 4.0 hours, and 2.72 at 24 hours; after cryoprecipitate infusion and associated drainage of her abscess, her fever and white count immediately returned to almost normal ranges. Although multiple antibiotics had been used before her transfer and operation, no further antibiotic therapy was needed.
19. Patient 2 (R.S.) was a formerly healthy 20-year-old man who suffered a vehicular accident resulting in mild cerebral contusion and extensive injuries to his right lower extremity, consisting of fractures in both lower bones of the extremity and a very extensive soft tissue injury with lengthy devitalized skin flaps. Hematuria was present with a normal intravenous pyelogram. Although extensive debridement of the lower extremity was performed at a regional hospital, he developed septicrosis and marked deterioration in the appearance of the soft tissue injuries of his leg during the first 36 hours after his injury. He was transferred to Albany Medical Center where smears of the wound demonstrated pleomorphic rods, Gram-positive rods, and Gram-positive cocci. He manifested a high fever, marked tachycardia, tachypnea, and severe hypoxia. He was intubated and placed on a volume cycle ventilator. Operative debridement of his wounds revealed myonecrosis, and an above-the-knee amputation was performed. Before his operation, he received high doses of penicillin and tobramycin, and this treatment was continued after the operation. On day 1 after operation, his febrile course and severe respiratory insufficiency persisted with subcutaneous emphysema and etythema noted over the anterior chest wall. In view of his severe septic condition and associated persistent pulmonary insufficiency, we initiated cryoprecipitate therapy on day 2 after operation to reverse his opsonic α_2SB-glycoprotein deficiency. His bioassayable opsonic activity (in percent of injected dose per 100 mg of liver tissue) was 2.40 before therapy. After therapy, his bioassayable opsonic activity was 6.85 at $^1/_2$ hour, 4.05 at 4 hours, and 1.13 at 24 hours. Within 24 hours, the patient's pulmonary function and hyperpyrexia markedly improved and he became more alert and responsive. A steady modest temperature elevation persisted until eventual closure of the amputation stump.
20. Patient 3 (J.J.) was a 58-year-old man who was an accident victim and sustained a fracture dislocation of his left hip, fractured left ulna and left tibia, and multiple fractured ribs resulting in a flail chest and bilateral pneumothorax. There was evidence of lung contusion on x-ray within the first 24 hours of injury. Exploratory laparotomy was performed at a regional hospital, revealing a stellate laceration in the right lobe of his liver and in the region of the duodenum and pancreas. During the first 24 hours after surgery, there was a rapid deterioration of his pulmonary function, and he was transferred to the Albany Medical Center. Severe respiratory insufficiency persisted for the first several weeks after injury, complicated by a large intrapleural air leak. Mild renal failure developed with creatine clearance as low as 25 ml/min with oliguria. Four weeks after injury, a left pleural emphysema was identified and drained. *Serratia marcescens* was cultured from the left pleural space, urine, and sputum. The patient developed tachycardia, fever, leukocytosis, and persistent respiratory insufficiency. As a result of his deteriorating and severe septic course, he was treated with cryoprecipitate. His bioassayable opsonic activity (in the percent of injected dose per 100 mg of liver tissue) was 2.11 before therapy. After therapy, his bioassayable opsonic activity was 9.41 at $^1/_2$ hour, 8.76 at 4 hours, and 8.12 at 24 hours. During a 2-day period after treatment, the febrile course and sensorium all improved with relief of the persistent pulmonary insufficiency. By day 4 after therapy with cryoprecipitate, the ventilator was discontinued; at this time his white blood cell count was 6600 per cubic millimeter.
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30. Cryoprecipitate was prepared from fresh acid-citrate dextrose anticoagulated plasma from the American Red Cross by quick freezing at −30°C and thawing at 2°C. The resulting precipitate was isolated by centrifugation with approximately 25 ml of the supernatant plasma. The precipitate was stored at −20°C until use. The dose of cryoprecipitate given to patients was the equivalent fraction obtained from 10 units of fresh plasma suspended in a volume of 250 ml.
31. Serum immunoreactive opsonic α_2SB-glycoprotein was measured by electroimmunoassay. A 10 percent dilution of serum (10 μl) was added to each well and subjected to electrophoresis with an LKB multiphore system at 82 volts for 22 hours at approximately 15° to 17°C. After staining, rocket heights were measured in millimeters, and a double reciprocal standard plot [$(ml)^{-1}$ versus $(\mu g)^{-1}$ opsonin] was defined with a human serum standard (400 μg/ml). The normal serum level of α_2SB-glycoprotein is approximately 300 to 350 μg/ml.
32. Bioassayable data was expressed as the percentage of added colloid that was phagocytized in 100 mg of liver with a rat liver slice (200 to 300 mg) and the gelatinized ^{131}I-RE test lipid emulsion. In each flask, 2000 μg of emulsion, 100 USP units of heparin, and 1 ml of test serum were added. All flasks were supplemented with 2 ml of Krebs-Ringer phosphate solution (*p*H 7.4) and incubated with rotation (60 cycle/min) in an atmosphere of 95 percent O_2 and 5 percent CO_2 for 30 minutes at 37°C. After incubation, the slices were washed, weighed, and analyzed for radioactivity.
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