Disseminated intravascular coagulation can cause multiple organ failure including adult respiratory distress syndrome by obstruction of visceral microcirculation by microclots. It was reasoned that if a clot causes vascular obstruction, lysing the clot by a plasminogen activator would be of value.

Plasminogen activator was given to pigs in both traumatic and septic shock with significant protection by a plasminogen activator and without affecting the coagulation mechanism. Eighteen human patients suffering from either traumatic or septic shock with severe adult respiratory distress syndrome (ARDS) were treated by plasminogen activator, and excellent results were reported.

These studies examined the theory that traumatic and septic shock are caused by disseminated intravascular coagulation (DIC) and the production of microclots of the viscera. Although DIC has undoubtedly always been present, the first recognized case occurred on April 3, 1952. A 21-year-old soldier was wounded in Korea, sustaining a severe compound comminuted fracture of the left femur and left side of the pelvis. Shell fragments also penetrated the bladder, rectum, and colon. A colostomy and cystostomy were performed, but the wound became infected with Eschericia coli and other organisms. The patient was given 11 units of blood and was treated with debridement and antibiotics but developed acute renal failure. His wound bled relentlessly and he was given 22 more units of blood. Wound culture further showed hemolytic Staphylococcus aureus and prothrombin was 40% normal. He continued to bleed copiously and formed a pool in the bed in spite of pressure dressings, with the blood clotting in the bed, but liquefying within a period of a few minutes. Urine output rose to 800 ml a day by July 15. However, his non-protein nitrogen had steadily risen to 245 mg%. The patient died on July 17, 1952, by renal failure and with continuing hemorrhage of his wound. Autopsy showed necrosis of tubular cells of the kidneys and focal necrosis of the liver. It was concluded that the bleeding was due to the consumption of clotting factors by an episode of intravascular coagulation most evident in the microcirculation where it caused
acute renal failure by cutting off circulation to the microvasculature of the kidney, although clotting factor assays were not available at that time. The blood contained enough clotting factors to clot in a long period of time; however, liquefying of the clotted blood indicated the activation of the body's own fibrinolytic mechanism in an attempt to lyse the clot in the microcirculation.

The following are the stated conclusions in the report: "Hemorrhage was a major problem; all clotting elements were affected; there was fibrinolytic activity; depletion of all blood clotting elements is probably indicative of disseminated intravascular clotting with resultant using up of clotting elements; activation of fibrinolysin may occur in the body's attempt to stop this process; it is conceivable that the intravascular clotting is more responsible for necrosis of the tubules in lower nephron nephrosis than vascular spasm."

The mechanism of production of DIC is believed to be the thrombogenic effect of the inner surface of all cell walls which are exposed to blood when a cell is broken. The inner layer of all cell membranes (mammal or bacterial) is composed of thrombogenic aminophospholipids. The outer layer does not contain aminophospholipids (Fig. 1). When hemolysis of red cells takes place as a result of a transfusion reaction or trauma, DIC may result.

A theory of traumatic and septic shock is presented. It is perceived that both traumatic and septic shock are accompanied by DIC, which temporarily occludes the microcirculation of any or all organs, temporarily cutting off the circulation to those organs and causing multiple organ failure (MOF). DIC may be brought on by rupture of red cell walls, tissue cells, bacteria, or all 3. Red cells and tissue cells may be damaged by trauma, cold or heat, anoxia, viruses, or plasmodia. Bacterial cell walls may be damaged by antibiotics, heat, or antibodies. The inner layer of all cell walls consists of thrombogenic aminophospholipids. Thrombogenic phospholipids may initiate DIC, acting as an autotoxin when cells are broken. DIC may block the microcirculation of any or all organs, causing ARDS and MOF. It is presumed that polysaccharide endotoxin is not the main initiator of septic shock, but rather, that thrombogenic phospholipids are. Microclots of DIC in an organ's microcirculation may be lysed by a plasminogen activator.

**MATERIALS, METHODS, AND RESULTS**

**Traumatic Shock.** Nine pigs were anesthetized for 48 hours. Trauma was initiated by 60 standard blows to each thigh, resulting in a bruise of muscle but no injury to skin, bone, or major vessels. Nutrition, blood volume, and respiration were maintained at normal levels. The trauma caused hemolysis of red cells, which was first evident 8 hours after trauma and reaching a maximum at about 24 hours after trauma. All 9 pigs died with severe lung pathology and low pAO₂. Ten other traumatized pigs were treated with tissue plasminogen activator (diluted in 20 mL saline and injected at a 20-min period starting 20 min after trauma), 5 with tPA (Genentech, South San Francisco, Calif) and 5 with urokinase (Abbokinase, Abbot Laboratories, Chicago, Ill). All pigs treated survived for a period of 48 hours and maintained a normal pAO₂ (Figs. 2 & 3), and autopsy showed minimal lung pathology. The 9 control pigs showed significant kidney and liver failure, whereas the 10 treated pigs had significantly less kidney and liver failure. Coagulation parameters remained relatively normal in all pigs and no bleeding was documented.

**Endotoxin Shock.** A different study examined the ability of a plasminogen activator to prevent death from an injection of killed *E. coli* organisms. Killed *E. coli* organisms administered intravenously caused death within 24 hours with a low arterial and venous pH, high cardiac output, increased core temperature, elevated white cell count, and other metabolic changes. Death and acidosis were significantly prevented by plasminogen activator (Fig. 4). There was no bleeding and no notable change in the coagulation profile.

**Clinical Study.** A Phase I clinical study is under way regarding the ability of plasminogen activator to treat ARDS. Eighteen patients suffering from severe ARDS were studied. ARDS was secondary to trauma or sepsis or both. To be included in the...