1982

Traumatic shock: The search for a toxic factor

by F. William Blaisdell, MD, FACS, Sacramento, CA

Any one of a number of forms of shock may follow serious injury, in addition to the shock due to acute hypovolemia following hemorrhage (Table I). Spinal cord injury may produce neurogenic shock, which results from expansion of the vascular bed through loss of vasomotor tone without a corresponding increase in blood volume. Cardiogenic shock can occur as a result of myocardial contusion, coronary air embolism, hypothermia, or valve or septal disruption. Obstruction of venous return by pericardial tamponade, tension pneumothorax, or a ruptured hemidiaphragm also can seriously compromise cardiac output. In addition to these, there is a specific form of shock that is associated with soft-tissue injury which is poorly understood and, as a result, has not been well defined. I would like to refer to this as traumatic shock.

Table I

Types of shock

Hypovolemic	Cardiac Compressive
Neurogenic	Cardiogenic

The source of shock

The principal problem that has confused the recognition and definition of traumatic shock is that most hemorrhagic shock states do not cause this syndrome. The models associated with this entity are primarily those that produce injury to skeletal muscle, whether by compression, crush, gunshot, or ischemia.[2,9,13,18,23] In recent decades, most standard shock models have consisted of hemorrhagic shock,[32] whereas many of the original models used for the study of shock were the trauma models I have just described. The reason for this was that the relationship between hypovolemia and shock originally was not obvious.

Prior to the advent of transfusion in World War II, some patients died without massive overt blood loss, and the source of shock was thought to be some toxic factor related to tissue injury.[1] With transfusion came the ability to resuscitate seriously injured patients, and the relationship of shock to hypovolemia was well established. This obviated the need for a toxic factor to explain the circulatory changes. However, with the Vietnam conflict came rapid transport, definitive volume resuscitation, and survival of patients with massive injuries who never survived before. These patients developed failure of such organs as the lungs, which were never deprived of perfusion; this development confused the problem and once again raised the issue of whether or not there is a toxic factor in shock.[20] This issue relates to how damage to one area of the body can produce critical secondary changes in tissues and organs remote from the site of injury—the toxic factor of traumatic shock.

Clinical models

The easiest way to establish traumatic shock as a distinct clinical entity is to study two clinical models: the crush syndrome, which leads to renal failure, and the fat-embolism syndrome, which leads to respiratory failure. The crush-injury/renal-failure syndrome was noted in World War I,[19] and was clearly documented as a clinical problem by Bywaters during the London bombings in World War II.[10] It typically followed a crush injury of the extremities, which led to renal failure and the patient's death a day or two later.

Recognition of this acute renal-failure syndrome did much to stimulate the development of the artificial kidney, for in the early 1950s, especially during the Korean War, renal failure was a frequent accompaniment of major trauma. The development of better concepts of fluid therapy, including the importance of monitoring perfusion rather than pressure, resulted in a marked decrease in the incidence of this problem. The subsequent advent of the Swan-Ganz catheter has shown that renal failure after trauma is almost entirely due to hypovolemia, as manifested by low, left-sided cardiac filling pressures.[8] With restoration of blood volume, this problem has essentially disappeared as a clinical problem.

The fat-embolism syndrome was thought to be well understood in the 1940s and 50s. It was a syn-

Dr. Blaisdell is professor of surgery and chairman of the department at the University of California, Davis. He delivered this Scudder Oration on Trauma at the 1982 Clinical Congress in Chicago.

drome that followed long-bone fractures, the fractured femur being the classic model.[23] One to three days after the injury, the patient became restless, agitated, confused, and then comatose. Petechial hemorrhages developed in the conjunctivae and skin, especially in the trunk (Figure 1). Death uniformly followed. When various organs were sectioned, including the lung and the brain, fat droplets and marrow fragments could be found in the microcirculation. These appeared to explain the central nervous system symptoms, so that the entity was thought to be due to cerebral fat embolism.

In the 1960s, when arterial blood-gas monitoring was introduced, it became apparent that all patients who manifested cerebral symptoms had a profound fall in the arterial partial pressure of oxygen and that the central nervous symptoms were due to hypoxemia.[29] Since that time, the identity of fat embolism has been obscured by the recognition that many types of trauma, in addition to long-bone fractures, caused this entity, which is now referred to as the acute respiratory distress syndrome (ARDS).[8]

Fat-embolism syndrome ceased to be a problem in such isolated injuries as a fractured femur when it was recognized that the femur fracture was associated with an average thigh-blood loss of one to two liters, and treatment with appropriate fluids was instituted.[14] The paradox presented to the mechanical theory of etiology of fat embolism relates to the fact that good circulatory resuscitation should ensure better perfusion at the fracture and other sites of tissue trauma and should wash more rather than fewer fat droplets and marrow particles into the systemic circulation. Thus, the fat-embolism syndrome was virtually eliminated after good volume resuscitation established its relationship to hypovolemia rather than to particulate embolism of fat per se. Pulmonary, renal, and/or multiple-organ failure may result from soft-tissue injury and inadequate volume replacement, depending upon the rate of development and severity of the shock.[24] When the equivalent injury is well monitored and well treated, the clinical course is benign. Thus I believe that the relative disappearance of acute respiratory distress syndrome in the first few days after trauma, when previously it was epidemic, is the result of careful monitoring of patients and reestablishing and maintaining good cardiovascular hemodynamics.

Damaged tissue

Then what is the mechanism by which hypovolemia and tissue trauma produce the crush-injury/renal-failure syndrome and the fat-embolism/pulmonary-failure syndrome? Is there a toxic factor?

I believe the factor responsible is the damaged tissue itself, and that the damaged tissue constitutes

Figure 1. *Fat embolism: Subconjunctival hemorrhage can be seen on the lower junction with the cornea. This same patient had truncal petechiae as well.*

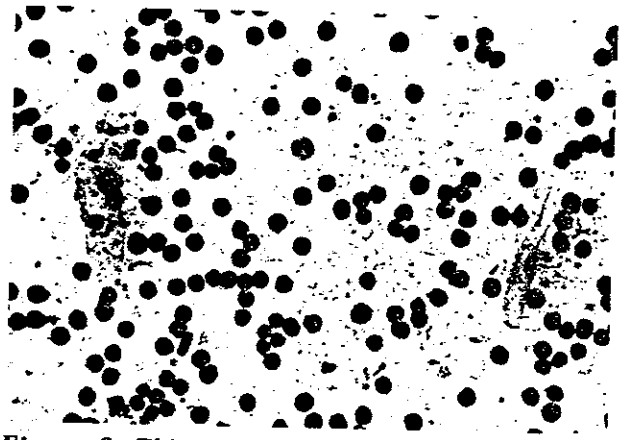

Figure 2. *This specimen of blood from a patient with diffuse intravascular coagulation (DIC) shows two large endothelial cells. Free floating endothelial cells are a consequence of DIC and provide an indirect means of documenting loss of vascular integrity.*

the toxic factor in traumatic shock. Fragments of damaged tissue enter the bloodstream and, through the intermediary mechanism of intravascular coagulation, which is shock augmented, set off intravascular inflammation.[15] This results in endothelial damage and loss of vascular integrity (Figure 2). There is much evidence to support this explanation. First, the forms of acute hypovolemic shock associated with minimal soft-tissue injury are rarely associated with ARDS or failure of other organs. Thus, patients with a simple wound of a major artery and massive hemorrhage—the gastrointestinal bleeder, the stab-wound victim, and the low-velocity gunshot wound victim—rarely now or in the past developed organ-failure syndromes. These injuries lead to simple hemorrhagic shock. Fluid shifts that result from this form of shock seem to be primarily interstitial to intracellular.[28] On the other hand, patients who suffer close-range shotgun wounds, high velocity gunshot wounds, and especially blunt trauma with extensive soft-tissue injury are those at risk for traumatic shock. These injuries appear to cause not only intracellular edema but also diffuse protein-rich interstitial edema, which is a consequence of alterations in vascular permeability.[4,5] The result is a more virulent form of shock than that associated with simple hemorrhage, since fluid may leave the vascular space as fast as it is administered. Proper resuscitation results in severe interstitial edema that is most dramatically manifest in the lung, where interstitial edema is associated with proportional alterations in pulmonary function (Figure 3).

Secondly, the factors capable of activating clotting occur as complications of trauma and are related to a high incidence of pulmonary and other organ failure. These include hemolytic transfusion reactions, gram-negative sepsis, and amniotic fluid embolism.[8,12,16]

Thirdly, damaged and devitalized tissue associated with other clinical entities are often associated with the respiratory distress syndrome. These include arterial gangrene or extensive surgical procedures,

Figure 3. *Chest x-ray demonstrates the diffuse reticular pattern consistent with ARDS. As opposed to cardiogenic pulmonary edema, these lungs are dry to auscultation.*

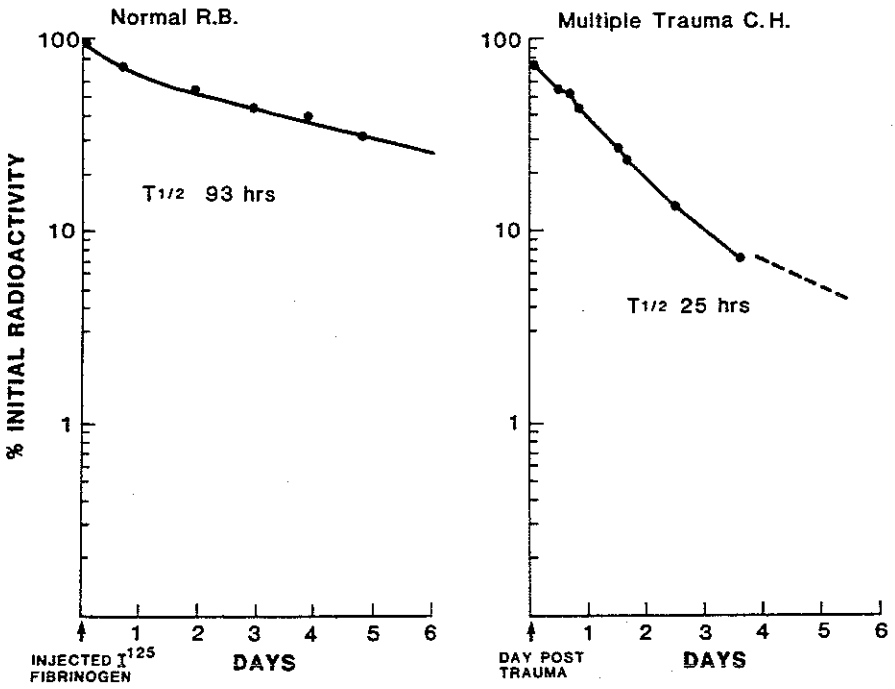

Figure 4. *The normal fibrinogen catabolic curve (left) is compared to that of a victim of massive trauma following a motor vehicle accident (right). The steeper slope of the curve in the trauma victim corresponds to the marked shortening of fibrinogen half-life.*

such as radical cancer surgery or operations requiring cardiopulmonary bypass.[3,11,30]

Clinical studies

Moreover, studies of ours and others have shown that intravascular coagulation follows trauma and correlates best with the simultaneous presence of injuries associated with both tissue damage and hypovolemia.

Our analysis of 12 patients with complicated clinical problems who developed a massive bleeding syndrome after operation showed that this complication was due to a consumption coagulopathy caused by disseminated intravascular coagulation.[11] In these patients, who survived the immediate catastrophic hemorrhage, the incidence of respiratory failure was 75 percent and renal failure 83 percent. Moreover, those patients who survived the initial complications almost uniformly developed septic complications within four to five days.

A subsequent prospective study was carried out in patients with trauma severe enough to require admission to the intensive care unit.[31] Multiple coagulation parameter assessment was carried out, and the appearance of organ-failure syndromes was assessed independently. There was good correlation between the severity of the intravascular coagulation and the subsequent development of the organ-failure syndromes.

All these methods of establishing intravascular coagulation utilized evidence of clotting-factor depletion and fibrinolysis activation and were indirect, making quantitation of the degree of intravascular coagulation difficult. In order to find a more direct means of evaluating the degree of intravascular coagulation, we initiated assessment of fibrinogen catabolism, initially with autologous radioactive-labeled fibrinogen, and subsequently with commercially labeled homologous fibrinogen.[6,7] This established the fact that fibrinogen half-life was markedly altered by trauma and that the correlation between half-life alteration and prognosis was excellent (Figure 4). Morbidity was the rule when half-life was less than 50 percent of the normal 100 hours.

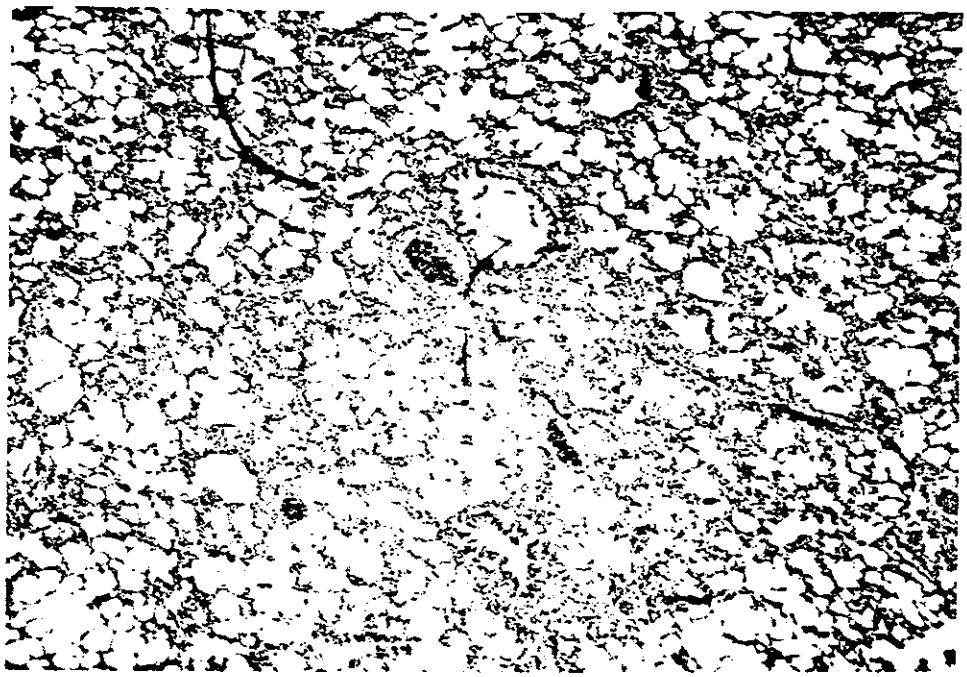

Figure 6. Microscopic changes in the lung. a) Fibrin and platelet aggregates are found in the first 24 hours following injury, b) peri-arterial hemorrhages follow after 12-36 hours, and c) Interstitial and alveolar edema and hemorrhages characterize the lesion at 48-72 hours.

and mortality was extremely high when the half-life was less than 30 percent of normal (Figure 5).

The coroner's office in San Francisco routinely provided us with complete autopsy data on our trauma victims.[5] In those who died within 24 to 48 hours of major injury, fibrin and platelet aggregates were a frequent finding in the lung and correlated well with the alterations in pulmonary function (Figure 6). Models designed to reproduce soft-tissue injury through production of ischemic tissue damage were also associated with embolism of particulate material and respiratory failure.[18]

Intravascular coagulation

It is probably far too simplistic to ascribe all of the circulation changes to particulate embolism alone, since it is known that intravascular coagulation is capable of activating multiple humoral mechanisms: the complement system, kinins, and prostaglandins, to name a few (Table 2). However, it is possible to establish that particulate embolism is associated with vascular disruption and permeability alterations —witness the petechial hemorrhages associated with the fat-embolism syndrome. Subacute bacterial endocarditis with microembolism results in splinter hemorrhages in the skin. Moreover, Seaman, observing the living perfused bovine eye, made the observation that adenosine-diphosphate (ADP)-produced platelet-retinal artery embolism was as-

FIBRINOGEN HALF LIFE vs PROGNOSIS

	Number	Deaths
T 1/2 < 30 hrs	6	4 (67%)
T 1/2 31 - 40 hrs	5	2 (40%)
T 1/2 > 50 hrs	6	0 (-)

Figure 5. Abnormalities of fibrinogen half-life in victims of trauma is compared to the incidence of complications. The latter often precedes the overt appearance of complications.

sociated with eye-ground hemorrhages, but only when the emboli lysed and moved on (Figure 7).27

This phenomenon explains the delay in the manifestation of systemic vascular permeability alteration following shock and trauma. That is, permeability alterations occur following particulate embolism when there is delay in lysis of the clot long enough for local vascular damage to occur. The presumption is that an active dynamic circulation brings lytic factors to the site of particle lodgement with rapid lysis preventing vascular damage. Also, the dynamic circulation would wash pro-coagulants, tissue fragments, and clotting particles through the reticulo-endothelial system and facilitate rapid removal.

The stagnant circulation, on the other hand, promotes intravascular clotting, as Virchow noted 100 years ago. Acidosis and catecholamines, resulting from shock, promote platelet aggregation and coagulation, as do many of the other factors associated with shock and trauma (Table 3). Moreover, shock paralyzes fibrinolysis and reticulo-endothelial cell function and thus the ability of the circulatory system to clear particulate matter and clot.25,26

Table II

Humoral factors

Complement	Kinins
Fibrinopeptides	Prostaglandins
Histamine	Serotonin
Leukotreines	Thromboxane

Thus, the evidence suggests that extensive soft-tissue trauma is associated with intravascular coagulation and activation of multiple secondary humoral factors. It results from a combination of two factors: hypovolemia and tissue trauma. These factors produce diffuse microcirculatory damage manifested clinically by alterations in integrity of the vascular system. The most critical organ affected is the lung, where initially microvascular obstruction and humorally-induced bronchial spasm and subsequently leaking blood vessels with resulting interstitial edema and hemorrhage are associated with clinical evidence of dysfunction. If treatment of

Figure 7. *Taken from Seaman AJ (Ref. 27), who observed that following retinal artery embolism produced by ARDS in the living perfused bovine eye (left), eye-ground hemorrhages occurred when the embolus broke up and moved on (right).*

hypovolemia is inadequate because the volume deficiency is not recognized, or because of fear of aggravating the lung lesion, other organs, such as the kidney and liver, may be affected. Hypoperfusion of the kidney and liver from inadequately treated hypovolemia results in dysfunction of these organs and ultimately renal tubular necrosis and hepatic central lobular necrosis.[17,21] It is also probable that stress ulcer with gastrointestinal hemorrhage results from gastric mucosal hypoperfusion due to thrombosis of gastric microvessels (Figure 8).[33] Moreover, it can be speculated that particulate embolism overwhelms the reticuloendothelial system, producing an immune blockade and vulnerability to infection.[25]

Table III

Factors activating DIC

Tissue Fragments	Acidosis
Red Cell Membranes	ADP
Exposed Collagen	Catecholamines

Treatment

The significance of untreated traumatic shock is profound, as documented by historical assessment of the fat-embolism syndrome and by its disappearance with adequate treatment. Thus, the key factor in eliminating morbidity from traumatic shock is prompt, definitive resuscitation to the endpoint of a dynamic circulation. Vascular permeability alterations that have already developed must be accepted and treatment continued nonetheless. Attempts to protect the lung by limiting fluids to prevent higher pulmonary pressures, thus decreasing fluid leak into the lung, is ill-advised. Allowing hypovolemia to persist only serves ultimately to increase vascular damage and compromise function of other organs. Correcting hypovolemia and monitoring vascular volume result in prompt vascular repair, ultimately lessening the impact of the vascular injury. Moreover, the kidney is the key; a good urine output is the guide to adequate resuscitation. In the past, attempts to protect the lung by allowing renal shutdown on the basis that it could be treated effectively by dialysis was ill-advised. The mortality from renal failure in the trauma victim is several times that of respiratory failure.[17]

The addition of PEEP (positive end-expiratory pressure) to mechanical ventilation has provided a method of preventing progressive alveolar collapse after traumatic shock. As a result, we rarely have a death from acute respiratory failure, and this only in patients whose treatment is delayed for many hours after injury.

When the lungs are normal, central venous pressure (CVP) accurately reflects left-sided cardiac filling pressure, but as the lung lesion develops, the CVP progressively disassociates from left atrial pressure. This concept is easily understood if one accepts the concept that microembolism is responsible for the lung lesion.[22] As embolism and associated humoral activation increases, pulmonary vascular resistance alters, much as one would see with gross pulmonary embolism obstructing larger pulmonary vessels. In order to maintain cardiac output through this progessively increasing pulmonary vascular resistance, higher right-sided pressures are required.

The advent of the Swan-Ganz catheter removed all controversy regarding whether ARDS was caused by over-enthusiastic fluid resuscitation or was related to shock per se. As a result of its adaptation in monitoring the adequacy of resuscitation, it has been possible to document that in the trauma victim with increasing pulmonary failure and a decreasing urinary output, hypovolemia is inevitably present. If volume therapy is pushed, renal function will resume. If doubt exists as regards the etiology of the renal failure, appropriate studies, in addition to Swan-Ganz catheter monitoring, should be obtained to rule out unsuspected mechanical factors, such as bladder rupture, renal avulsion, or ureteral injury. Should wedge pressures be high, and an intact urinary tract verified, then attention is appropriately directed toward improving myocardial function utilizing cardiotonic agents or (more rarely) diuretics. Edema, should it develop in the face of persistently low wedge pressures and low

Figure 8. Microscopic section of gastric mucosa with "stress ulceration." Numerous thrombi can be seen in the underlying blood vessels.

urinary output, should be accepted and the volume therapy maintained. Persistent hypoperfusion only results in promoting further damage to vascular integrity.

A study of traumatic shock also helps explain the pathophysiology of the stress response to surgery. The act of operating is a traumatic event that leads to the same vascular permeability problems, but usually to a lesser degree. Thus, major surgery, especially if associated with simultaneous tissue damage and hypovolemia, activates intravascular coagulation and results in intravascular inflammation from associated humoral factors. Excessive fluid loss from the vascular space activates renal and adrenal mechanisms, producing sodium and water retention. Healing of the vascular lesion several days after an operation results in fluid shifts back into the circulation with subsequent diuresis.

The primary means of modifying intravascular coagulation is by circulatory support. If bleeding should occur during transfusion, that unit of blood should be immediately discontinued and sent back to the blood bank with the presumption that there may be transfusion mismatch. Ill-advised attempts to save badly mangled limbs should be abandoned in favor of amputation. Consideration should be given to reoperation to assess the bowel, liver, or other organs if there is any question regarding their viability. Finally, if the massive bleeding syndrome should have developed and be refractory to the above, a 10,000 u bolus of heparin should be administered intravenously to stop intravascular utilization while platelets and fresh frozen plasma are rapidly administered to build up hemostatic factors.

Conclusions

I have attempted to define traumatic shock and establish its separate identity. Its cause is a combination of shock and soft-tissue injury. Tissue fragments entering the bloodstream are the toxic factors sought for so long. In the presence of shock, the coagulation mechanism is activated. Associated humoral mechanisms that follow intravascular coagulation induce intravascular inflammation. This impairs the integrity of the circulatory system and produces diffuse alterations in vascular permeability. This further increases the tendency for hypovolemia, as fluid extravasates into the interstitium, in some instances, almost as fast as it is administered intravenously.

These alterations in vascular permeability produce secondary organ damage—the most obvious is to the lung—resulting in compromise of oxygenation. The persistent tendency toward hypovolemia decreases perfusion of the kidney and liver, and ultimately results in failure of these organs. Impaired protein synthesis by the damaged liver results in an impaired humoral response. Particulate embolism

overwhelms the reticulo-endothelial system, further compromising immune function and results in a vulnerability to sepsis four to five days following the initial clinical insult.

Treatment involves prompt and definitive fluid and circulatory resuscitation, using Swan-Ganz catheter monitoring as necessary, and elimination of those factors (insofar as possible) that contribute to intravascular coagulation.

References

1. Bayliss WM and Cannon WB: Traumatic toxemia as a factor in shock. Medical Research Committee Special Report. Series 26, pp 19-23, London, 1919.
2. Berman IR et al: Pulmonary microembolism after soft tissue injury in primates. Surg 70:246, 1971.
3. Blaisdell FW et al: Pulmonary microembolism: A cause of morbidity and death after vascular surgery. Arch Surg 93:776, 1966.
4. Blaisdell FW et al: The mechanism of pulmonary damage following traumatic shock. Surg Gynecol Obstet 130:1, 1970.
5. Blaisdell FW: Pathophysiology of the respiratory distress syndrome. Arch Surg 108:44, 1974.
6. Blaisdell FW, Graziano CJ, and Effeney DJ: *In vivo* assessment of anticoagulation. Surg 82:827, 1977.
7. Blaisdell FW and Graziano CJ: Assessment of clotting by the determination of fibrinogen catabolism. Am J Surg 136:436, 1978.
8. Blaisdell FW and Lewis FR Jr: Respiratory distress syndrome of shock and trauma. W.B. Saunders Co., Philadelphia, PA., 1977.
9. Blalock A: Experimental shock: The cause of low blood pressure produced by muscle injury. Arch Surg 20:959, 1930.
10. Bywaters EGL: Crush injuries with impairment of renal function. Brit Med 1:4185, 1941.
11. Cafferata HT et al: Intravascular coagulation in the surgical patient. Am J Surg 118:281, 1969.
12. Corrigan JJ, Ray WL, and May N: Changes in the blood coagulation system associated with septicemia. New Engl J Med 279:851, 1968.
13. Duncan GW and Blalock A: The production of experimental shock by crush injury. Ann Surg 115:684, 1942.
14. Fuchsig P et al: A new clinical and experimental concept of fat embolism. New Engl J Med 276:1192, 1967.
15. Hardaway RM: Syndrome of Intravascular Coagulation. Charles C Thomas, Publisher, Springfield, 1966.
16. Hardaway RH: Mechanism of traumatic shock. Surg Gynecol Obstet 151:65, 1980.
17. Humphreys MH and Sheldon G: Acute renal failure in trauma patients. West J Med 123:148, 1975.
18. Lim RC Jr et al: Massive pulmonary microembolism in regional shock. Surg Forum 17:13, 1966.
19. Mohardt J: Crush and compression injuries with uremic death. Surg 12:151, 1942.
20. National Academy of Science/National Research Council: Pulmonary effects of non-thoracic trauma. J Trauma, 9/68.
21. Nunes G, Blaisdell FW, and Margaretten W: Mechanism of hepatic dysfunction following shock and trauma. Arch Surg 100:546, 1970.
22. Pinet F et al: Post-traumatic shock lung: Postmortem microangiographic and pathologic correlation. Am J Rad 139:449, 1982.
23. Price PB and Rizzoli HV: That strange dangerous malady—the crush syndrome. West J Surg 57:569, 1949.
24. Regoeczi E and Brain MC: Organ distribution of fibrin in disseminated intravascular coagulation. J Haemat 17:73, 1969.
25. Saba TM: Disturbance in plasma and cell surface fibronectin. Relationship to altered vascular permeability and host defense. J Trauma 21:679, 1981 (Suppl.)
26. Saldeen T: Intravascular coagulation and inhibition of fibrinolysis in fat embolism. Acta Chir Scand 136:87, 1970.
27. Seaman AJ: Induced intravascular thromboembolic phenomena. Arch Int Med 119:600, 1967.
28. Shires CT et al: Distributional changes in extracellular fluid during acute hemorrhagic shock. Surg Forum 11:115, 1960.
29. Sproule BT, Brady TD, and Gilbert TA: Studies on the syndrome of fat embolism. Canad Med Assn J 90:1243, 1964.
30. Stallone RJ, Lim RC Jr, and Blaisdell FW: The pathogenesis of pulmonary changes following ischemia of the lower extremities. Ann Thor Surg 7:539, 1969.
31. String T, Robinson AJ, and Blaisdell FW: Massive trauma: Effect of intravascular coagulation on prognosis. Arch Surg 102:406, 1971.
32. Thal AP and Kinney JM: On the definition and classification of shock. Prog Cardiovasc Dis 9:527, 1967.
33. Wilson S and Blaisdell FW: Superficial gastric erosion. Ann J Surg 126:136, 1973.