Progress in Disseminated Intravascular Coagulation

Part II

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Pediatrics

Hyaline Membrane Disease

Hyaline membrane disease (idiopathic respiratory distress syndrome) is still one of the major problems in pediatrics. The demonstration by Hathaway and coworkers[52] that this disease is accompanied by disseminated intravascular coagulation may represent a significant advance toward an ultimate solution of the pathogenesis of this condition. These investigators studied six infants with *severe* respiratory distress syndrome and found thrombocytopenia, prolonged bleeding time, hypocoagulability (as demonstrated by thromboelastography) and a decrease in Factors V and VIII. Fibrin split products were occasionally found in the serum. At autopsy these infants showed hyaline membranes and hemorrhages, and three had pulmonary vascular fibrin thrombi. In a larger group of infants with *mild* respiratory distress, all patients recovered and most had increased amounts of fibrin split products in their blood. This suggests that the clotting episode was proportional to the severity of the respiratory disease.

Although Hathaway was unable to alter the course of the disease with heparin, Parmentier (in Belgium) made an interesting observation.[53] Among 27 newborn infants who had received exsanguination-transfusion for iso-immunization, only one had hyaline membrane disease. In a control group, the incidence was 33.7 percent. Parmentier noted that the infants who had the exchange transfusions were given 0.5 ml of heparin before the transfusion and suggested that this may have prevented or ameliorated the respiratory disease. It may be that the timing of heparin treatment is critical and that the infants reported upon by Parmentier were given heparin early enough to affect the disease.

In a recent report to the Eastern Section of the American Federation for Clinical Research, Huber[54] described the production of pulmonary hyaline membrane in dogs by continuous intravenous infusion of thrombin.

All these studies are in a preliminary stage. There is no doubt that disseminated intravascular coagulation is associated with hyaline membrane disease, but whether it is a cause or an effect of the disease remains to be shown.

Cyanotic Congenital Heart Disease

The occurrence of a hemorrhagic diathesis in certain patients with cyanotic congenital heart disease may constitute a serious complication. Bahnson and Ziegler[55] observed fatal massive bleeding in seven of ninety-nine patients following cardiac operations, and thrombosis in eight others. Hartmann[56] reviewed 31 cases and found significant thrombocytopenia and a decreased concentration of fibrinogen and prothrombin in patients with erythrocytosis. Paul et al[57] reported 200 cases of cyanotic heart disease and found significant thrombocytopenia in patients with hema-

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tocrits greater than 65 percent and oxygen saturation less than 70 percent.

Although surgical operation on the heart seems to be the major challenge to hemostasis in these patients, they may bleed spontaneously or from minor trauma as well. In this disease, the intravascular clotting is predominantly in the pulmonary circulation. Rich[58] described the pulmonary thrombi as extensive and involving small vessels with evidence of recurrent episodes of thrombosis. Occasionally, large vessel thrombosis in the cerebral vessels and aorta have been reported, but the major amount of clotting is in the lungs.

Several recent therapeutic trials with heparin and epsilon aminocaproic acid have brought considerable hope of a solution of this problem.

From the Walter Reed Hospital, Dennis et al[59] reported a patient with cyanotic congenital heart disease who responded to treatment with heparin.

The patient was a 10-month-old boy who was cyanotic and had a heart murmur at birth. He was a well developed infant but had clubbing of the fingers and toes. He was tachypneic, and had a systolic Grade II/VI murmur heard at the upper left sternal border with a split second pulmonic heart sound. X-ray films revealed increased density of the pulmonary vasculature and cardiomegaly. An electrocardiogram demonstrated right axis deviation with evidence of right atrial and biventricular hypertrophy.

On admission, the hematocrit was 85 percent and platelets numbered 17,000 per cu mm. The prothrombin time was 17 percent, and there were severe deficiencies of Factors V and VIII. The thrombin time was prolonged and fibrin split products were present in the plasma.

Heparin therapy was instituted with a dose of 1.0 to 1.5 mg/kg at 6-hour intervals to maintain a clotting time of 25 minutes. Within one week, there was a complete correction of the factors of the hemostatic mechanism.

A Blalock-Hanlon procedure was performed while the child was heparinized, and there were no hemorrhagic complications. Heparin was discontinued after operation, and this was accompanied by a transitory decrease in the levels of Factors V and VIII and an abnormal thrombin time. The patient made an uneventful recovery and was discharged from the hospital 10 days postoperatively.

Dennis et al[60] subsequently observed improvement in thrombocytopenia, prothrombin time, partial thromboplastin time, thrombin time, Factors V and VIII levels, and disappearance of fibrin split products following heparin therapy in five cases of cyanotic congenital heart disease.

The studies of Brodsky et al[61] suggest that in addition to disseminated intravascular coagulation, fibrinolysin activation may play an important role in the alteration of the hemostatic mechanism in these patients. They studied three patients with cyanotic and three with acyanotic congenital heart disease and found evidence of some degree of fibrinolytic activity in all. They treated their patients with epsilon aminocaproic acid, and a partial to complete recovery of the coagulation values ensued within a few days. They observed one patient who did not respond to heparin but did respond to epsilon aminocaproic acid.

This raises the possibility that in cyanotic congenital heart disease, some of the patients may have a so-called "primary" activation of the fibrinolytic enzyme system. If this is true, then it is obviously of great importance to determine whether or not a given patient has primarily intravascular clotting or primary fibrinolysin activation.

In our experience, fibrinolysin activation is usually a consequence of disseminated intravascular coagulation. There are few diseases in which, if a consumption coagulopathy is demonstrated clinically, fibrin thrombi cannot be found in the tissues. However, in some patients, the activation of fibrinolysin is concomitant with a triggering of the clotting mechanism and may become the major factor in altering the hemostatic mechanism. Looking to the future, it is clear that a careful evaluation of the hemostatic mechanism is a necessary part of the work-up of a patient with congenital cyanotic heart disease, with appropriate correction of the defect before surgical operation. Whether or not heparin or epsilon aminocaproic acid (or both) will prove to be the most beneficial therapy will await further clinical trials.

Hemolytic-uremic syndrome

In 1955 Gasser et al[62] described a complex of clinical symptoms consisting of acquired hemolytic anemia, acute renal failure, hemorrhagic diathesis and cerebral symptoms which they called the hemolytic-uremic syndrome. This entity seems to be very similar to thrombohemolytic thrombocytopenic purpura. In the hemolytic-uremic syndrome, which occurs more frequently in infants than older children, the thrombi are predominantly

located in the renal glomerular capillaries, whereas in thrombohemolytic thrombocytopenic purpura the thrombi are ubiquitous.

In 152 cases of hemolytic-uremic syndrome recently reviewed by Piel and Phibbs[63] 61 deaths occurred. In 39 of 49 cases which came to autopsy, bilateral renal cortical necrosis (17 cases), thrombi of the glomerular capillaries, or both, were demonstrated. Five cases showed widespread microthrombosis of the vessels in many organs of the body. These observers also reviewed 23 cases of thrombohemolytic thrombocytopenic purpura in childhood. In 8 of 22 autopsy cases, thrombi were found only in the kidney.

Reports of Treated Cases. Various therapeutic agents have been applied, including exchange transfusions, dialysis, steroids and anticoagulants. Treatment with heparin was used in several cases to halt the process of subacute intravascular coagulation.

Piel and Phibbs reported two cases treated with heparin for 9 to 11 days, respectively, early in the disease. In both cases the platelets rose 48 hours after onset of heparinization. Additional therapy consisted of peritoneal dialysis because of the extended period of anuria (6 to 9 days). The patients recovered and were discharged in good health.

Hitzig[64] reported three patients with the hemolytic-uremic syndrome treated with heparin over a longer period. The first patient, a 7-week-old boy, was treated with 2,500 to 5,000 units of heparin per day over a 12-day period, with fibrinogen (0.5 gram per day for the first three days), whole blood and a single dose of prednisolone. Diuresis occurred, hemolysis ceased and the platelets increased from 20,000 to 630,000 per cu mm three weeks after the treatment began. The second patient, a 4-year-old boy, was treated with heparin alone (no corticosteroid, no fibrinogen, or blood transfusion). In this patient, untreated for the first three days after onset of the disease, complete anuria, uremia and hemolytic anemia developed. Heparin therapy (2,500 units per day for 12 days) completely halted the progress of the illness. Laboratory measurements became normal after several weeks. In the third case, that of an 8-month-old boy, heparin was given for about four weeks (5,000 units a day). Additional therapy consisted of one blood transfusion and prednisolone (30 mg a day for about four weeks). In spite of the initial improvement of diuresis the patient died about four weeks after the beginning of therapy.

Corticosteroids are reported to be of no benefit in the hemolytic-uremic syndrome.[65] On the contrary, they predispose animals to disseminated intravascular coagulation.

In 1964, Künzer and Aalam[66] described a case in which two episodes of the disease occurred in a period of two years. During the first episode an exchange transfusion was performed to overcome the anuria. The patient was free of symptoms for two years. In the second occurrence of the syndrome, heparin (40,000 units daily for eight days) was given after there was no clinical or hematologic response to prednisone. The patient recovered rapidly. The platelets rose in 15 hours from 8,000 to 260,000 per cu mm. No further bleeding occurred.

The cause of the hemolytic-uremic syndrome is as yet unknown, but there is some suggestion that viral infections may be the cause of the disease (Gianantonio et al,[65] Glasgow and Balduzzi[67]). About 60 percent of 160 reported patients survived with treatment by conservative management, exchange transfusion, hemodialysis or steroids. The already reviewed cases in which patients were successfully treated with heparin were impressive for the good hematologic response to the anticoagulant. Because the *fatal* course of the hemolytic-uremic syndrome is caused by systemic intravascular coagulation with thrombotic occlusion of the renal glomerular capillaries, therapy with complete heparinization early in the disease has been used with apparent success.

Surgery

Somatic trauma is undoubtedly one of the most frequent causes of disseminated intravascular coagulation. Although no statistics are available, the frequency of traffic accidents and deaths by themselves are indicative of a high incidence. The clotting episode may be caused directly by the trauma or may be indirectly caused by secondary complications or even by therapeutic agents used in the management of emergency cases. In any specific case, or in any specific disease process, the occurrence of disseminated intravascular coagulation may play little or no role in morbidity or mortality, but in other disease processes it may be the major pathogenetic mechanism leading to serious secondary disease problems or to death.

Trauma and Disseminated Intravascular Coagulation

The occurrence of disseminated intravascular coagulation following trauma has been well documented. Bergentz and Nilsson[68] studied the blood coagulation system after bilateral fractures of the femoral diaphyses of dogs. The animals were observed over a 30-hour period. A slight shortening of the coagulation time occurred during the first eight hours of the experiment. The platelet count decreased progressively after the trauma to reach a level of about 50 percent of the initial value at the end of the experiment. No significant changes in the levels of prothrombin and Factor VII were observed during the first 12 hours, but, after 24 and 30 hours, the values showed a decrease to about 50 percent of the original. Factor V decreased throughout the experimental period, but particularly during the first few hours after trauma. Factor VIII (antihemophilic globulin) decreased slightly during the first eight hours. Plasma fibrinogen decreased during the first eight hours in all dogs, and the decrease was most pronounced two hours after the fracture. The fibrinogen decreased from an average of 0.36 to 0.33 gm per 100 ml. A variety of tests revealed increased fibrinolytic activity during the first few hours after the trauma. The euglobulin clot lysis time decreased from a mean value of 225 minutes to 85 minutes within two hours. It then increased and at the end of 30 hours was much longer than before the experiment. The activity of the resuspended plasma euglobulin precipitate on unheated bovine fibrin plates also increased during the first few hours. After 12 hours their activity also decreased to less than that found in the blood prior to trauma. The serum inhibitors of plasminogen activation by urokinase had a tendency to decrease during the first four hours, only to be followed by a marked increase at the end of the period, when the inhibitory activity was 179 percent of the pre-experimental value.

Another type of trauma was used in the experiments of Borgstrom et al[69] on rabbits. Contusion of the muscles of one thigh was used as standard trauma. The animals were anesthetized with pentobarbital (Nembutal®), both femoral veins were ligated and the muscles were contused by light blows with a padded hammer, the severity of the trauma being graded by variation of the number of blows. The ligated veins were examined for thrombi 6 to 7 days after trauma.

In the control group with mere ligation of the femoral veins, only 1 out of 20 revealed a thrombus. In the groups with contusion of one hind limb by 50, 100, 150, and 200 blows, there were found 5, 14, 17, and 19 thrombi, respectively. The same number of thrombi was found on non-contused as on contused sides. The thrombi varied in length from a few millimeters to 1 to 2 centimeters and were always located below the ligature. Thrombi always formed first on the contused side, but later the same number was formed on the non-contused side.

The generalized nature of the effect of trauma was demonstrated by observations on the capillary vessels of the bulbar conjunctiva. Red blood cell aggregates appeared 1 to 3 hours after contusion, and aggregates were seen in arterioles, capillaries and venules. The flow became slower, and aggregates occluded parts of the capillary bed.

Following tissue injury, a reduction of the suspension-stability of the blood always occurs and leads to changes in the flow of blood with intravascular aggregation and erythrostasis in capillary vessels. A reduction in the suspension stability of the blood can be caused by changes in the plasma proteins with increase of large and viscidizing molecules as noted by Fahraeus.[70] Cuthbertson[71] showed that such changes occur after trauma, with decrease of albumin, and with increase of globulins, especially fibrinogen. Knisely et al[72] found that the erythrocyte aggregation first appeared locally in a traumatized region and then became generalized if injury was severe enough. The administration of heparin during the early phase prevented both intravascular aggregation and thrombus formation. Erythrocyte aggregation and thrombus formation are parallel phenomena.

In man, Blaisdell, Aggeler et al[73] demonstrated that disseminated intravascular coagulation follows trauma. They found a consistent post-traumatic decrease in Factors II, V, VII, VIII, X and in platelets and plasminogen. Fibrinogen varied greatly and was increased, decreased or unchanged. Fibrin degradation products were often elevated but not consistently. Those patients who manifested severe intravascular coagulation of the type that was easily documented by changes in the clotting factors, rarely survived.

Causes of Intravascular Coagulation in Trauma

Although they are closely related, these mechanisms can be divided into *local,* and *systemic* for purposes of discussion.

Local

Severance of vessels of the microcirculation. Whenever small vessels, arterioles, capillaries or venules are cut across, thrombi composed of platelets and fibrin are quickly formed to seal off the end of the vessel. This is due in large part to the exposure of the blood to collagen or vascular basement membrane, which leads to platelet aggregation and eventual fibrin formation. The extent to which clotting occurs and to which coagulation factors are lowered in the circulating blood will obviously depend upon the extent of trauma, that is, the number of vessels cut across.

Release of tissue thromboplastin into the circulation. All tissues contain a phospholipid substance which is capable of triggering the clotting mechanism rapidly. The relative concentration of this material in cells varies from tissue to tissue. Tissue thromboplastin can be considered to have a beneficial effect in the occurrence of trauma because it hastens the clotting of shed blood and may aid in closing off vessels by thrombosis. If, however, the circumstance occurs that fragments of tissue or extracts of tissue gain entrance to the circulating blood, the effect may be deleterious, even lethal. These effects have been amply demonstrated experimentally by intravenous injection of tissue thromboplastin (Schneider[74] and Vassalli et al[12]).

That tissue or tissue extracts do get into the circulating blood in some traumatized patients is best illustrated by the observation of bone marrow embolism to the lung in patients with fractures. I have observed this phenomenon in older patients subjected to external cardiac massage in whom the fracture of sternum or manubrium was the source of bone marrow. Undoubtedly, it occurs in more extensive damage to bone or may occur in traumatic accidents.

Another clear evidence that tissue may gain access to the circulating blood in traumatized patients is the occurrence of fat embolism. Large fat droplets or fat cells are found in the pulmonary circulation at autopsy. The fact that these patients often exhibit evidence of disseminated intravascular coagulation has been largely overlooked. However, microthrombi composed of fibrin and platelets are found in the lungs of these patients. It seems quite likely that the tissue thromboplastin which gains access to the blood stream at the same time as the fat is more likely to be the lethal factor in these cases than the fat itself. Nevertheless, the presence of fat in the circulation is clear evidence that tissue and tissue extracts do get into the circulation following trauma.

The question of how frequently and how much tissue thromboplastin gets into the blood stream remains to be answered. In view of the variability of tissue thromboplastin concentration from one organ to the next, it will depend to a certain extent upon the organ or organs involved in the trauma. Also to a certain extent it will depend on the accident of cutting across vessels of a size large enough to allow entry of fragments of tissue, and it obviously requires the presence of an established or reestablished circulation in the incised part.

Ischemia. Ischemia implies a cessation of flow through a vascular bed, and it must be acknowledged that such an event is accompanied not only by deprivation of oxygen, but with acidosis, increased carbon dioxide and possibly changes in electrical potential, all of which may play a role in triggering clotting.

An example of this mechanism is found in the "crush syndrome." Crushing injury results in aggregation of platelets in the microcirculation of the crushed area.[75,76]

Ischemia followed by recirculation of blood. If the vascular supply to an organ is cut off, the local thrombosis which follows will result in infarction of the tissue with very little systemic damage. If, however, the circulation is temporarily stopped and then subsequently reestablished, the result may be fatal.

The occurrence of local clotting after temporary ischemia was first demonstrated by Sheehan and Davis.[77] They clamped off the renal artery for a period of two hours and then released the clamp. Immediately after release of the clamp, blood circulated in the kidney but soon the flow stopped completely. They referred to this phenomenon as a "failed reflow." The secondary cessation of the circulation was due to the development of thrombi in the microcirculation.

The occurrence of disseminated clotting after temporary ischemia was first recognized in rela-

tion to intussusception of the intestinal tract.[1] The intussuscepted segment drags in with it portions of mensenteric veins and arteries. The length of the segment determines the extent of vascular involvement. With the slowing or cessation of blood flow in this variable portion of the vascular system, ischemic damage to the coagulation mechanism and the vessel wall occur. When the intussusception is reduced, blood may recirculate through this segment, and clumped platelets and procoagulant substances are swept into the general circulation. This induces intravascular clotting in distant organs.

Recently this phenomenon has been extensively explored by Blaisdell and Lim.[78] They encountered it first in patients undergoing major vascular operations, particularly operations for repair of ruptured aneurysm. In their search for the cause of death in these patients who had had an otherwise successful operation, they found thrombosis of the pulmonary microcirculation.

In attempts to elucidate the course of events, they reproduced the syndrome in dogs.[79,80] This they did by the production of regional ischemia in the lower half of the body by temporary occlusion of the aorta below the renal arteries and simultaneous ligation of the collateral arterial flow. After four hours the aortic clamp was released and blood allowed to recirculate. Although no serious systemic problems were noted during the period of occlusion, shortly after release of the clamps respiratory distress developed and the animals eventually died. At autopsy most of the capillaries contained numerous masses of aggregated platelets and arterioles contained fibrin thrombi. As time progressed the lungs showed increasingly severe damage with atelectasis, edema, vascular congestion, and focal hemorrhage. The degree of morbidity and mortality was related to the duration of ischemia of the lower extremities and was proportional to the number of micro-emboli in the pulmonary circulation.

The etiologic role of the thrombi was clearly demonstrated when they prevented the lethal effect by heparinizing the animals before release of the clamp.

More recent studies[81] have indicated the precise chain of events. They prepared a group of animals with a portocaval shunt which diverted the blood from the extremities through the liver. They subjected these dogs to the aortic clamping experiment and all the animals survived, with the majority of platelet masses in the liver rather than the lung. These experiments suggest that the platelet (and fibrin) thrombi are formed in the ischemic limbs during the period of aortic clamping, and with reestablishment of blood flow are then swept into the pulmonary circulation where they lodge and exert a profoundly deleterious effect on the blood pressure and the normal functioning of the lung, leading to death.

The repair of major vessels, sometimes necessitating temporary occlusion of the vessel, is fraught with this danger, in human patients as well as in experimental animals.

Systemic Factors

Anoxemia, cardiac arrest. The total cessation of the circulation associated with cardiac arrest results in intravascular coagulation. It represents the systemic example of local anoxia. Crowell[82] was the first to demonstrate this when he induced cardiac arrest in dogs for a period of three minutes followed by reestablishment of the circulation. At autopsy, small blood clots were demonstrated in the pulmonary vessels. It was then shown that the survival rate of the dogs could be approximately doubled if the animals were heparinized.

Coon and Hodgson[83] have described the same phenomenon in patients suffering from cardiac arrest.

Shock. One of the most consistent sequelae to trauma is shock. Shock is a trigger to disseminated intravascular coagulation. This was first demonstrated by Crowell[84] in animals subjected to hemorrhagic shock. He produced a controlled steady state of shock (lowering the blood pressure to 50 mm of mercury for 90 minutes and 30 mm for 45 minutes) by bleeding the dogs into a reservoir containing citrate as the anticoagulant. A pronounced shortening of the whole blood coagulation time was found during the period of shock. When the animals' own blood was reinjected into the circulation, the blood pressure tended to rise to normal levels; but subsequently it dropped and after several hours the dogs died. Small blood clots were demonstrated in the pulmonary vessels by washing them out by reverse perfusion. Crowell was able to prevent death in nearly all dogs under the same experimental conditions if heparin was administered before shock developed.

In man, the occurrence of disseminated intravascular coagulation in shock has been amply documented by Hardaway.[85]

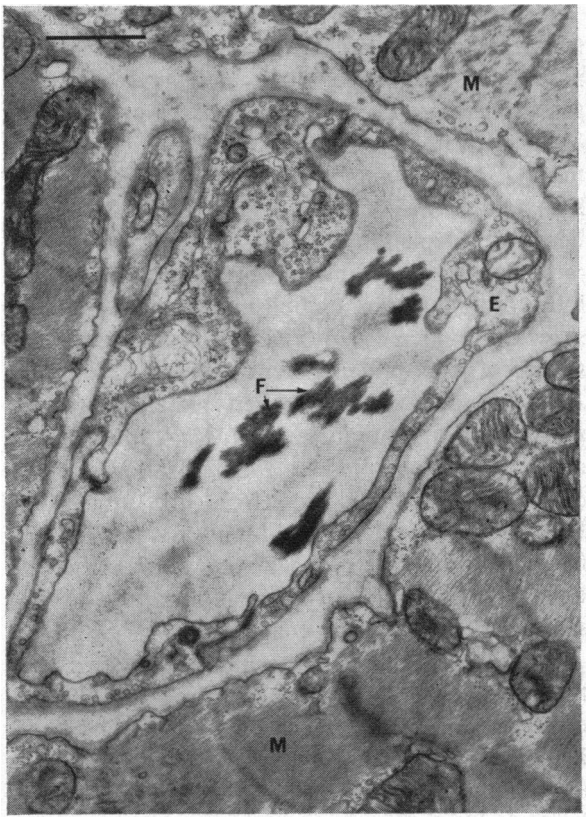

Figure 7.—Catecholamine shock. Monkey heart. Fibrin strands apparently floating free in the plasma of a myocardial capillary. × 21,600. F=Fibrin. E=Endothelium. M=Cardiac muscle cell.

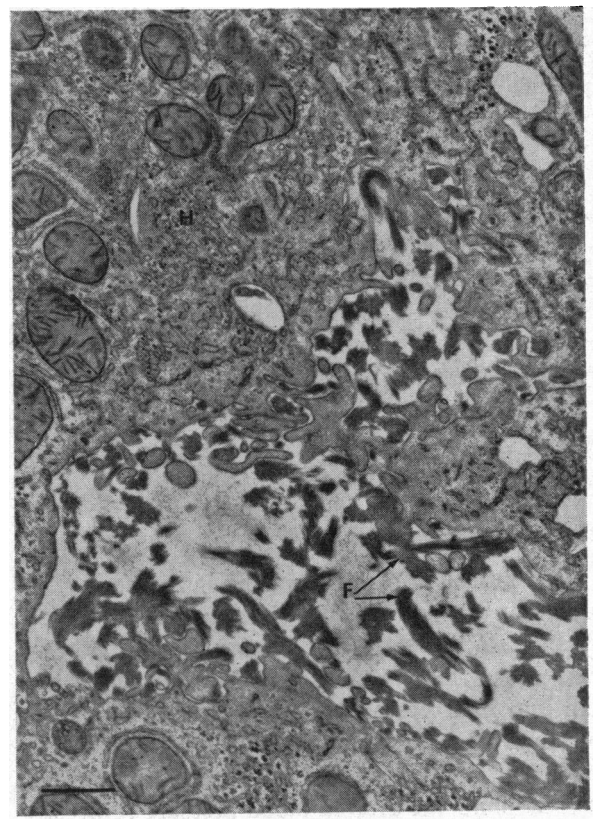

Figure 8.—Catecholamine shock. Monkey liver. Fibrin strands adherent to the microvilli lining the sinusoidal space. × 16,000. F=Fibrin. H=Hepatic cell.

Bacterial endotoxin. Infections such as peritonitis, local abscesses and bronchopneumonia are frequent complications of trauma. They may be the source of a bacteremia which, due to release of bacterial endotoxin into the circulation, triggers intravascular clotting.

Endotoxin shock illustrates an important principle, namely, that considerable intravascular clotting may occur and not be visible by light microscopy. In animal experiments, large doses of bacterial endotoxin are lethal. Pathologic examination by the light microscope reveals congested vessels in many organs but no thrombi. However, electron microscopy in these animals readily reveals platelet clumps in capillaries of the lung and liver and fibrin strands in capillaries of all organs.[86] With the exception of the liver no occlusive thrombi are formed. Rather, the fibrin strands appear to be floating free in the plasma. Hematologic studies simultaneously show a drop in platelets and fibrinogen. This phenomenon is probably ascribable to a rapid massive activation of the fibrinolytic enzyme system which destroys the fibrin as fast as it is formed. This accounts for the frequent occurrence of disseminated intravascular coagulation, demonstrated by hematologic means, but not demonstrated by the routine light microscope examination.

Catecholamine shock. One of the common denominators in shock due to various causes is the release from the adrenal glands of high concentrations of epinephrine and norepinephrine. Whitaker and McKay recently studied the effect of high doses of epinephrine on the microcirculation and the coagulation mechanism.[87] Electron microscopy revealed strands of fibrin, associated with platelets, in capillaries or arterioles of the heart, spleen, liver, adrenal, kidney and placenta (Figures 7 and 8), and by hemostatic studies which showed reductions of platelets, fibrinogen and elevation of cryofibrinogen. Preheparinization prevented the reduction of fibrinogen and elevation of cryofibrinogen caused by epinephrine.

The survival time, when animals were infused continuously with epinephrine, was lengthened by anticoagulation with heparin, and shortened by

the addition of epsilon aminocaproic acid to inhibit fibrinolysis, showing that disseminated intravascular coagulation is a contributory lethal factor when animals are subjected to severe adrenergic stimulation.

The severity of the hemostatic response to epinephrine infusion paralleled the vascular response, and did not occur when the alpha-adrenergic receptor sites were blockaded by phenoxybenzamine (Dibenzyline®). The action of epinephrine is indirect and is mediated by the effect on the vascular system.

It seems quite likely that the release of vasomotor active substances in shock in man may play a role in triggering the clotting.

Shock Due to Intravascular Clotting

The induction of disseminated intravascular coagulation by shock may become a two-edged sword, since disseminated intravascular clotting also causes hypotension. The infusion of thrombin into monkeys and rabbits causes an immediate but transient drop in blood pressure, which is prevented by heparinization beforehand.[88] Within certain limits the drop in blood pressure is directly proportional to the amount of thrombin given, and there is a direct relationship between the decrease in blood pressure and the decrease in circulating platelets and fibrinogen.

The superimposition of a clotting episode in an animal with shock due to another cause increases the lethality. In normal rabbits the LD_{50} dose of thrombin was 24 units per kilogram. In animals subjected to catecholamine shock, the LD_{50} was 11 units per kilogram. This suggests that hypotension due to other causes increases the hypotensive and lethal effect of disseminated intravascular coagulation.

Thromboembolic Disease

Thromboembolism remains a major complication of patients subjected to trauma. The experiments of Bergentz[68] demonstrated that trauma at distant sites may result in large vein thrombi under the conditions of local distortion of the vein, as in ligature. In a sense the trauma initiates an increased coagulability of the blood which then results in a thrombus at a distant site where circulatory dynamics are altered. Disseminated intravascular coagulation may thus lead to local large vein thrombosis.

Conversely, the release of a venous thrombus to the pulmonary circulation may lead to disseminated intravascular clotting. We have observed two patients with large pulmonary emboli with clear-cut histologic evidence of disseminated clotting.[89] Merskey and Johnson[90] have provided the hematologic evidence. They observed three patients with depletion of the circulating clotting factors, thrombocytopenia and fibrinolysin activation following pulmonary embolism. Schoenfeld et al[91] showed an increase in acid phosphatase in the serum of two patients with pulmonary emboli. Acid phosphatase rises when platelets are destroyed in large numbers *in vivo*. A more direct demonstration of platelet damage following pulmonary embolism comes from the studies of Hirsh and McBride,[92] who found increased platelet adhesiveness in patients with pulmonary embolism. Platelet adhesiveness is increased in disseminated intravascular coagulation.

The clinical use of heparin has provided further evidence. Thomas[93] pointed out that the use of heparin greatly diminishes the mortality following pulmonary embolism. This observation also indicates that the clotting episode in some patients is the lethal factor.

The major question remaining is the mechanism by which pulmonary embolism triggers the clotting mechanism. It may be that it is initiated by release of thrombin absorbed onto the fibrin of the thrombus, or contained within pockets of serum within the clot, at the time of impaction of the embolus against the walls of the pulmonary artery. Anoxia, endothelial damage, and release of serotonin and histamine from damaged platelets may be contributory factors.

Iatrogenic Factors

A number of accidents may occur in the therapy of a traumatized patient which in themselves may lead to intravascular coagulation. Hemolytic transfusion reactions, multiple transfusions, and blood contaminated with Gram-negative bacteria have been shown to cause disseminated intravascular clotting.[1] The injection of therapeutic agents intravenously, particularly colloidal substances, may occasionally be responsible. Intravascular coagulation may develop in an occasional patient subjected to extracorporeal circulation.

In the analysis of any patient who presents pathologic, hematologic or clinical evidence of disseminated intravascular coagulation all these

possibilities must be kept in mind in order to determine the precise cause or causes of the clotting episode.

Kidney Transplants

Every group with experience in clinical renal transplantation has experienced a number of catastrophic failures, commonly referred to as "hyperacute" rejections, during the first minutes to hours after transplantation. In some cases, the homograft was irreparably injured in this way even while the patient was still on the operating table.

Starzl[94] reported such hyperacute rejection five times in three human recipients. The kidneys, removed 1 to 54 days later, had cortical necrosis. The major vessels were patent, but the arterioles and glomeruli were the site of fibrin deposition. The findings were characteristic of the generalized Shwartzman reaction.

In a search for the cause of intravascular clotting in these kidneys, efforts were made to determine whether or not the patients had had a Gram-negative endotoxemia. Cultures of the dialysate baths were reviewed for the period during which three patients were treated on the artificial kidney. Growth of Gram-negative organisms was invariably present, the most common bacteria being *Aerobacter aerogenes, Pseudomonas aeruginosa, Escherichia coli* and paracolon strains. Nevertheless, no bacteria were found in available blood specimens and a search for endotoxin in the blood yielded negative results.

Hemolysis, increased coagulability of the blood caused by the artificial kidney, and the blockade of the reticuloendothelial system by immunosuppressive drugs, were considered as possible causal factors.

While any or all of these factors may have contributed to the clotting episode, the studies of Williams et al[95] point to a more likely mechanism. These investigators described studies in severe cases of "hyperacute" rejection. They observed a significant accumulation of "hyperacute" rejections in recipients of multiple grafts and inferred that immunologic mechanisms operated in these rejections. The almost immediate occurrence of the reaction, as well as the absence of mononuclear-cell infiltration in the grafts, argued against the involvement of cell-mediated immunity in these rejections. They suggested that the rejection may be related to humoral antibodies. This relation was suggested by one of their patients who was demonstrated to have an ABO incompatibility. The patient was a Group O recipient who received a graft from a Group B donor and the anti-B humoral antibodies were implicated. Other observers have also reported acute anuria of grafts mismatched for ABO groups.

In other cases reported by Williams and coworkers, antibodies to tissue isoantigens were demonstrated by means of mixed agglutination and lymphocytotoxicity tests in pre-transplantation sera. The lymphocytotoxicity test provided evidence for the presence of antibodies specifically combining with the donor antigens in two of six cases. However, the mixed agglutination tests provided such evidence in all but one case, either by directly demonstrating antibodies acting upon the donor's cell culture or by demonstrating that antibodies were bound to the grafted tissue. Moreover, in two patients, the disappearance of antibodies from the circulation was observed after the renal graft, and this could clearly be related to the removal of antibodies by the graft.

The findings imply that this form of rejection may result from the effect of humoral antibodies on the graft.

Our own interpretation would be that the deposition of circulating antibody on the endothelium of arteries and capillaries of the donor kidney would result in a layer of antigen-antibody complex on the endothelial surface. The ability of antigen-antibody complex to trigger the clotting mechanism has been well documented.[1] This would explain also the localization of thrombi in the renal circulation and the lack of evidence of clotting in other organs of the body in these cases.

It is possible that anticoagulant therapy might be useful in these cases, if given in time, but a better solution would be to attempt to avoid the immunologic incompatibility through appropriate antibody tests.

Obstetrics

Postpartum Hemolytic-Uremic Syndrome. This condition is fortunately a rare one, but it is a serious problem that occasionally must be faced by both obstetrician and internist. It has been described under a variety of labels, including *postpartum malignant nephrosclerosis, postpartum renal failure,* and *postpartum malignant hypertension.* It has been included in series of patients with the diagnosis of thrombotic thrombocytopenic purpura and undoubtedly many of these

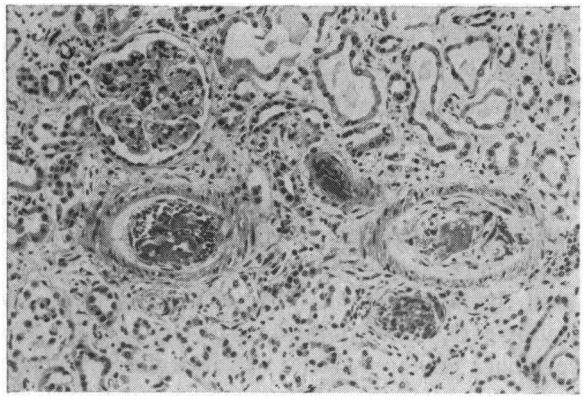

Figure 9.—Postpartum hemolytic-uremic syndrome. Kidney. Old and recent thrombi obstruct the lumen of a small artery. Hematoxylin and eosin stain. × 160.

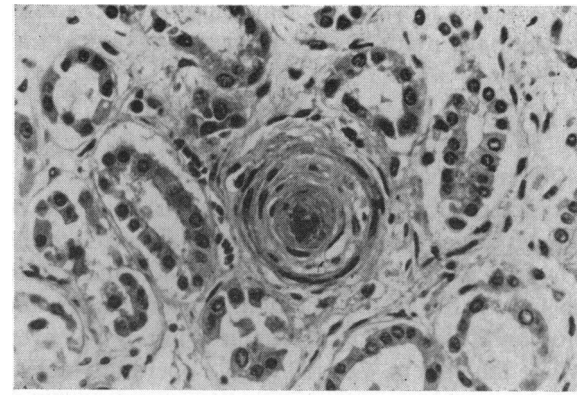

Figure 10. — Postpartum hemolytic-uremic syndrome. Kidney. Hyperplastic thickening of arteriolar wall. Hematoxylin and eosin stain. × 400.

patients in the past have been included in series of patients categorized as postpartum toxemia of pregnancy.

We agree with Clarkson[96] that until the cause of the disease is found, the best name for it is *postpartum hemolytic-uremic syndrome.* The name carries with it the implication of a fundamental component of the disease—that is, disseminated intravascular coagulation—and it is descriptive of two of the major clinical manifestations of the disease. Also, to a large extent, it is quite similar to the hemolytic-uremic syndrome of infants.

Clinically, the disease is characterized by a normal prepartum and intrapartum course without evidence of hypertension, renal disease or toxemia. Soon after delivery (three days to ten weeks) a prodrome of mild gastrointestinal disturbance, fever and upper respiratory symptoms appears. Some patients present initially with anemia, edema, and a hemorrhagic diathesis with purpura, bleeding or bruising and ecchymoses without preceding minor complaints. Acute renal failure always develops. Although none of the patients thus far observed were hypertensive before the illness, the blood pressure became elevated during the disease in half of the cases. The anemia is characterized by a negative Coombs test and the appearance in the smear of "burr" cells, fragmented cells, microspherocytes and "helmet" cells, which is characteristic of "micro-angiopathic hemolysis."

Tissue examination has proved that these patients have undergone an episode, or perhaps repeated episodes, of disseminated intravascular coagulation. Although the kidneys bear the brunt of the clotting process, fibrin deposits have been found in many organs. Three cases have exhibited verrucous (non-bacterial thrombotic) endocarditis which we have shown to be a complication of disseminated intravascular coagulation. Focal hepatic necrosis, pulmonary thrombi and focal hemorrhage, microscopic infarction and hemorrhage in the brain are indicative of the disseminated nature of the clotting.

But the kidneys demonstrate it best. In my experience these cases are unique, from the standpoint of the pathologic changes, and present certain differences that may serve to distinguish the process from either the hemolytic-uremic syndrome of infants or thrombotic thrombocytopenic purpura.

The most striking abnormality is the presence of organized recanalized thrombi in the arcuate and straight arteries to the cortex. The walls of these vessels are perfectly normal with no damage to the smooth muscle cells, but the lumina are practically obliterated by a fibrous proliferation with a tiny recanalized lumen that can only be explained as an organized thrombus. Occasional fresh fibrin thrombi are found in these vessels, sometimes associated with focal infarction, indicating that this is a recurrent process, but for the most part the thrombi are old (Figure 9). In addition, the precapillary arterioles show the concentric laminated proliferation of smooth muscle cells that we ordinarily associate with malignant hypertension (Figure 10). This in spite of the fact that the hypertension is usually mild or may even be absent.

The glomeruli are involved in a variety of ways. A few show recent glomerular capillary thrombi, with hemorrhage into the capsular space. Many are atrophic and shrunken, leaving a very dis-

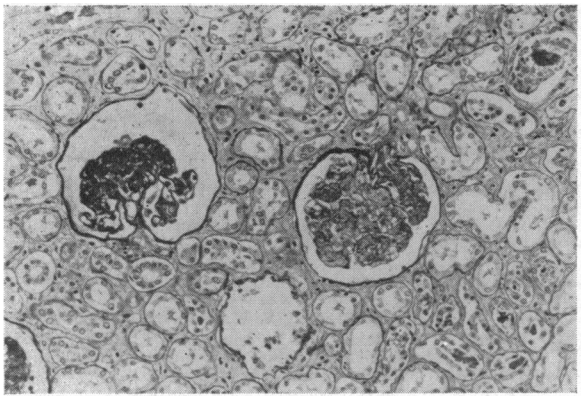

Figure 11. — Postpartum hemolytic-uremic syndrome. Kidney. Atrophic glomeruli. Periodic Acid Schiff reaction. × 160.

tended, almost cystic, capsular space (Figure 11). These latter imply long-standing ischemia to these glomeruli. Still other glomeruli show a complete hyalinization and obliteration of the capillary tuft with a covering of enlarged epithelial cells of the visceral layer of Bowman's capsule.

This combination of changes seems to me unique, but the greatest overlap occurs with the hemolytic-uremic syndrome of infants. The renal lesions of thrombotic thrombocytopenic purpura are characterized by platelet and fibrin thrombi in the hilar region of the glomerulus or by organized recanalized thrombi in the efferent arteriole. As a corollary, thrombotic thrombocytopenic purpura is seldom associated with renal insufficiency.

Thus far, anticoagulant therapy with heparin, which has been tried in a few of these patients, has not been of any benefit.[96] Most have died of renal failure. However, these patients have usually been treated long after the initial clotting episode, and it is unlikely that anticoagulants will be of any help unless the disease is diagnosed in its early stages.

Conclusions

Disseminated intravascular coagulation is an important intermediary mechanism of disease. It is a dynamic biologic response involving many inextricably interrelated chemical substances and physiological responses. It is triggered by eight basic etiologic agents including: (1) intravascular hemolysis, (2) tissue thromboplastin, (3) bacterial endotoxin, (4) proteolytic enzymes, (5) particulate or colloidal matter, (6) anoxia and anoxemia, (7) endothelial damage, and (8) ingestion of certain lipid substances.

Disseminated intravascular clotting often presents a characteristic constellation of clinical signs and symptoms. These include hypotension (shock), a bleeding tendency, oliguria or anuria, convulsions and coma, nausea and vomiting, diarrhea, abdominal pain, back pain, dyspnea, and cyanosis. Not all are present in every case.

A clinical test for disseminated intravascular coagulation has been proposed, consisting of a therapeutic trial of heparin with an evaluation of the response (or lack of it) of the hemostatic mechanism.

In a few specific disease entities, heparin therapy has proved effective. These include acute renal failure in glomerulonephritis, cyanotic congenital heart disease, infantile hemolytic-uremic syndrome, a few selected cases of cirrhosis of the liver and a strong suggestion of benefit in hyaline membrane disease (respiratory distress syndrome).

Some specific diseases have not responded to heparin — for example, postpartum hemolytic-uremic syndrome. It is possible that heparinization was begun too late and might be useful if given early in the disease.

It is not to be expected that heparin will prove to be a panacea. Further trials with anticoagulants are indicated in order to determine the actual usefulness of heparin in many disease states.

For the future, it is possible that agents not ordinarily considered anticoagulant may prove extremely useful. The indirect antithrombotic effect of alpha-adrenergic blockade by phenoxybenzamine is one of these. The inhibition of platelet aggregation by anti-inflammatory drugs such as sodium salicylate, sulfinpyrazone and phenylbutazone must be tried in these diseases.

Disseminated intravascular coagulation is the major pathogenetic mechanism of "microangiopathic hemolytic anemia." It has recently been shown that disseminated intravascular coagulation may be a factor of significance in the pathogenesis of acute renal failure in glomerulonephritis, certain patients with cirrhosis of the liver, vascular surgical operation causing regional ischemia with recirculation of blood, hyperacute rejection of renal homografts, hyaline membrane disease, fat embolism, malignant hypertension, and the postpartum hemolytic-uremic syndrome.

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GIVE CASTOR OIL FOR "ATHLETE'S FOOT"

"I advise patients who have fungus infections on their feet . . . to soak their feet twice weekly for 15 minutes in a warm foot bath containing two tablespoons of household chlorine solution, such as Chlorox, and to put castor oil between their toes after each bath. The castor oil works simply by penetrating the dead or the chorionic layer of the skin, and the fungus cannot grow on it."

—MARK M. MARKS, M.D., Kansas City

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