Disseminated Intravascular Coagulation

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Known variously as disseminated intravascular coagulation, defibrination consumption coagulopathy or, more simply, as defibrination, disseminated intravascular coagulation is a serious epiphenomenon that occurs most often as a complicating factor of an underlying disease process. Although frequently triggered by underlying disease such as infection or tumor, if not recognized and treated appropriately, disseminated intravascular coagulation alone may lead to the patient’s death as a result of hemorrhage or thrombosis, or both, of vital organs. Frequently, it may only manifest itself as an abnormality of coagulation tests, causing no immediate problem for the patient, and potentially normalizing when the inciting cause is appropriately managed.

The central process that marks disseminated intravascular coagulation is the generation of thrombin in the circulating blood by means of the activation of the coagulation mechanism, leading to the conversion of fibrinogen to fibrin, which, in turn, may lead to throm-

As physicians, we are well aware that diseases of the circulation, as manifested by thrombosis of the coronary and cerebral arteries, and pulmonary thromboembolism are major causes of morbidity and mortality. Thus, for cardiologists, the most obvious problem is focal thrombosis within the large arteries and veins of the body. However, fibrin deposition in the microcirculation is also a major mechanism of disease and must be recognized clinically as causing ischemic damage to vital organs, hemorrhage and potentially death. Thus, we must be able to recognize the clinical settings that predispose patients to disseminated intravascular coagulation and understand its pathophysiology so that a rational approach to diagnosis and therapy can be employed.

Coagulation and Inhibitors of Coagulation as the Basis of Diagnostic Laboratory Tests

Normal hemostasis is influenced by 1) platelets, 2) coagulation proteins, 3) inhibitors of coagulation, and 4) fibrinolysis (1). The first two influences are outlined in Figure 1. Although each of these four components is described elsewhere in this symposium (2,3), this brief description is in the context of disseminated intravascular coagulation and its diagnostic laboratory variables.

Platelets. Platelets are cellular elements that serve to plug disrupted areas of the vascular tree and are necessary for the first phase of hemostasis (that is, formation of a primary hemostatic plug after injury) (4). The patient with a defective platelet system, due either to a deficiency in the quantity of platelets or to abnormal platelet function, usually presents with evidence of skin or mucosal bleeding. Platelets are formed from megakaryocytes, the vast majority of which are found in bone marrow and a minority of which are

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present in lung. Each mature megakaryocyte will ultimately release approximately 7,000 platelets into the blood.

**Ultrastructural components of the platelet** include an extracellular coat containing glycoproteins necessary for adherence and aggregation, dense granules containing adenosine diphosphate (ADP), adenosine triphosphate (ATP), serotonin, calcium and nondense or alphagranules containing lysosomal enzymes, platelet factor IV, thromboglobulin, platelet-derived growth factor, von Willebrand factor, fibrinogen, fibronectin and platelet factor XIII. Platelet adhesion at a site of vessel injury depends, among other factors, on a platelet surface glycoprotein (called glycoprotein Iß) and plasma von Willebrand factor. Platelet aggregate formation requires the participation of platelet surface glycoproteins (called glycoproteins Ißb and IIIa), which are specific receptors for fibrinogen and von Willebrand factor, bridging the platelets with each other. Platelet contents released into the blood cause vasoconstriction and recruitment of additional platelets. During this release phase, thromboglobulin, platelet factor IV and thrombospondin can be found in the plasma, and the measurement of these substances has been used as a marker for in vivo platelet activation (5).

**Coagulation pathway.** The classic coagulation pathway (Fig. 1) is based on the “waterfall” hypothesis of Davie et al. (6,7). Coagulation occurs after a series of enzymes or coagulation factors have been activated. This activation can occur through two main routes designated the extrinsic and intrinsic systems, both converging at the level of factor V into a common pathway. When coagulation is initiated by tissue factor, in the presence of factor VII and calcium, the “extrinsic system” is activated. This system is best evaluated by the prothrombin time test. When coagulation is initiated by contact with a negatively charged or damaged surface in the presence of phospholipids, the coagulation factors comprising the “intrinsic system” are activated. This system is best evaluated by the activated partial thromboplastin time test. Fibrinogen is converted into fibrin in the common pathway of coagulation. The thrombin test monitors this conversion of fibrinogen to fibrin in the presence of thrombin. More specifically, fibrinogen has a dimeric structure, with each half of the molecule containing three pairs of polypeptide chains: alpha (α), beta (β) and gamma (γ). Thrombin removes two pairs of peptides from the fibrinogen molecule during coagulation; these are called fibrinopeptides A and B and correspond to the N terminal portions of the α and β chains (Fig. 2). Thrombin does not remove the terminal peptides of the gamma chain. The activity of thrombin is limited by its major inhibitor, anti-

![Figure 1. Elements of normal hemostasis. (Reprinted with permission from Schafer A. Bleeding Disorders: Finding the Cause. Hosp Pract 1984;19 [11]:88K–88H.)](image)

![Figure 2. Conversion of fibrinogen to fibrin. In the presence of thrombin, the fibrinopeptides (darkened areas) are split off from fibrinogen. This produces two molecules of fibrinopeptide A, two of fibrinopeptide B and one of fibrin monomer. Activated factor (F) XIIIa converts the fibrin monomers into cross-linked fibrin polymer. (Reprinted with permission from Nossel [41].)](image)
thrombin III. The anticoagulant drug heparin markedly increases the activity of antithrombin III and results in marked inhibition of thrombin activity, with decreased formation of fibrin from fibrinogen.

The fibrin clots formed by thrombin's action are hemostatically ineffective until a further reaction (namely, cross-linking) occurs. In this reaction, in the presence of calcium, activated factor XIII converts the fibrin clots into a well linking. In this reaction, in the presence of calcium, the thrombolytic enzyme, may act on fibrinogen or fibrin and produces sequential degradation of these proteins, as will be discussed later.

The thrombin time test is a sensitive indicator of abnormalities of fibrin formation. Prolongation of clotting after the addition of thrombin to plasma is commonly due to 1) the presence of heparin in the patient's blood, 2) the presence of fibrin degradation products interfering with polymerization, 3) hypofibrinogenemia or 4) dysfibrinogenemias. In cases where heparin is the suspected cause of a prolonged thrombin time but clinical confirmation is absent, the reptilase time is useful. Reptilase, venom from the snake Bothrops atrox, cleaves only fibrinopeptide A from the fibrinogen molecule and, unlike thrombin, is not inhibited by heparin. If a prolonged thrombin time is due to the presence of heparin, the reptilase time will be normal. In cases where prolongation is suspected to be due to interference by fibrin degradation products, these products can be measured immunologically for confirmation.

Endogenous inhibitors of coagulation. Substances that act as inhibitors of coagulation are also present in plasma. A number of antithrombins have been described, the most important being antithrombin III. Antithrombin III has activity against not only thrombin, but also other serine proteases generated during blood coagulation (8). Its deficiency in the heterozygous state may result in clinically significant thrombosis, which usually appears after adolescence. The homozygous state may not be compatible with life. The mechanism of action of antithrombin III is to bind to and inactivate thrombin. Heparin's mechanism of action (9) is to bind to antithrombin III, which causes a conformational change of the molecule and markedly increases the affinity of antithrombin III for thrombin.

Protein C is another central protein in the regulatory mechanisms of hemostasis. This system decreases the rate of thrombin formation by controlling factors V and VIIIC. The anticoagulant effect of protein C requires the presence of protein S (10). Protein C also functions as a profibrinolytic enzyme, increasing the rate of fibrin degradation by protecting fibrinolysis from inhibition. Patients with hereditary deficiencies of protein C who have levels of 60% or less than normal can develop thromboembolic syndromes (11,12). Individuals born with homozygous protein C deficiency may develop fatal neonatal purpura fulminans and disseminated intravascular coagulation (13). Protein C deficiency may lead to paradoxical thrombotic complications or skin necrosis when anticoagulation with warfarin (Coumadin) is initiated (14). Protein S deficiency may also cause thrombosis (10).

Fibrinolysis. Fibrinolysis is the mechanism by which fibrin is removed after its role in hemostasis is complete, and results from conversion of an inert plasma proenzyme (plasminogen) into the proteolytic enzyme plasmin. The fibrinolytic system consists of plasminogen and plasmin, together with their activators and inhibitors. Urokinase, isolated from urine, and streptokinase, a bacterial enzyme and tissue-type plasminogen, are plasminogen activators that have been used in thrombotic disease to produce thrombolyis or recanalize occluded blood vessels. Endogenous plasminogen activators are present in varying concentrations in different body organs. Large amounts are found in the uterine wall and fallopian tubes (15), although none is present in the placenta (16). Plasminogen activators are present in other body fluids (for example, milk, tears, saliva and semen) and may play a role in maintaining the patency of excretory ducts.

Plasmin has a broad spectrum of proteolytic activity. It cleaves arginyl-lysine bonds in a large number of different substrates including hormones, complement and coagulation factors, most prominently fibrinogen and fibrin. Fibrinogen and fibrin absorb plasminogen, and when a fibrin clot forms, plasmin is found in both free and fibrin-absorbed forms. Within the microenvironment of a thrombus, the plasmin absorbed is capable of digesting the fibrin mesh. Freely circulating plasmin will normally be destroyed by antiplasmins and would, therefore, be unable to degrade its susceptible substrates. Alpha-2-antiplasmin and alpha-2-macroglobulin are important plasma proteins that neutralize free plasmin. A number of chemical agents have also been shown to inhibit fibrinolysis by inhibiting conversion of plasminogen to plasmin. These include E-aminocaproic acid or EACA (Amicar) (17).

Euglobulin lysis time. A test used for the evaluation of fibrinolysis is the euglobulin lysis time. Euglobulins are those proteins that precipitate when plasma is diluted in water. The plasminogen activators plasminogen, plasmin and fibrinogen are all euglobulins. Antiplasmins and antiplasminogen activators are soluble in water. The euglobulin precipitate is redissolved and thrombin is added to form a fibrin clot. The plasminogen activator activates plasminogen to plasmin. The amount of time required for plasmin to lyse the fibrin clot completely is the euglobulin lysis time. A normal result is longer than 2 hours. Times shorter than this represent increased fibrinolytic activity.

Degradation of fibrin and fibrinogen. The action of plasmin on fibrin or fibrinogen, or both, leads, as mentioned, to the formation of a group of soluble protein fragments called fibrin degradation or split products. The immunologic methods usually used for the assay of these fragments do
Acute disseminated intravascular coagulation is usually a clinically overwhelming problem characterized by depletion of coagulation factors and platelets and with evidence of fibrinolysis. Coagulation factors are depressed because of fibrinolysis. Degradation of fibrinogen by plasmin. See text. (Reprinted with permission from Colman RW, Hirsh J, Marder VJ, Salzman EW. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. Philadelphia: JB Lippincott, 1982.)

**Pathophysiology**

*Acute Disseminated Intravascular Coagulation*

Acute disseminated intravascular coagulation is usually a clinically overwhelming problem characterized by depletion of coagulation factors and platelets and with evidence of fibrinolysis. Coagulation factors are depressed because they are consumed or inactivated during the coagulation process or because activated factors are removed by the reticuloendothelial system; therefore, there is a marked decrease in fibrinogen. Thrombocytopenia is present and is caused by the consumption of platelets at a rate greater than the bone marrow can compensate for the consumption. Active fibrinolysis occurs, as shown by the increase in concentration of split products of fibrin and fibrinogen; blood plasminogen concentrations may decrease (20).

**Shwartzman phenomenon (sepsis).** Acute disseminated intravascular coagulation can be associated with sepsis. This phenomenon can be better understood by reconsidering the Shwartzman phenomenon, which consists of disseminated intravascular coagulation, bilateral renal cortical necrosis and death from central nervous system bleeding. The Shwartzman reaction characteristically follows two spaced intravenous injections of bacterial endotoxin into experimental animals and, in part, is believed to be mediated by one or more epidoses of disseminated intravascular coagulation (21). The first “preparatory” injection causes little clinical effect, while the second “provocative” injection can be given 6 to 72 hours after the first to produce dramatic effects. Microscopic examination of the tissues of these animals 1 hour after the “preparatory” injection reveals agglutinated masses of platelets and leukocytes in the lung and liver, soon followed by numerous fibrin thrombi. The second injection causes an increase in the number of thrombi in the liver, lungs and spleen, and new thrombi are found in the kidney. Virtually every glomerular capillary may be filled with fibrin.

By studying the sequence of changes in the blood during the Shwartzman reaction, we can better understand why certain clinical situations such as infection, pregnancy or malignancy may predispose these patients to disseminated intravascular coagulation. Early in these settings, fibrinogen, as an “acute phase reactant,” can be elevated. Likewise, in the Shwartzman reaction, after the first exposure to endotoxin, there is progressive elevation in fibrinogen levels for 48 hours to levels almost as high as control levels. Only with the second injection 24 hours later is there an abrupt decrease in fibrinogen. Other factors that are present after the first injection are an increase in circulating leukocytes and a decrease in platelets. The thrombocytopenia becomes more pronounced with the second injection.

**Role of pregnancy in the Shwartzman reaction.** In humans, pregnancy is a common clinical precursor of disseminated intravascular coagulation. Pregnancy also occupies a unique position relative to the generalized Shwartzman reaction in that only one injection of endotoxin is required to elicit the reaction in pregnant or steroid-treated rabbits (22). Rats do not develop the Schwartzman reaction when exposed to two injections of endotoxin in the classic manner; however, pregnant rats will have the reaction after only a single injection (23). The pregnant state is probably con-
Acute disseminated intravascular coagulation

Obstetrics
- Septic and saline-induced abortion
- Abruptio placenta and placenta previa
- Prolonged retention of a dead fetus
- Amniotic fluid embolism

Infections
- Gram negative sepsis (for example meningococcemia)
- Gram positive sepsis (less common)
- Rickettsial (Rocky Mountain spotted fever)
- Protozoal (malaria)
- Viral (congenital rubella)

Shock
- Hypovolemic
- Hypoperfusion

Tissue injury
- Prolonged surgery
- Trauma
- Burns
- Heat stroke

Anaphylaxis

Chronic disseminated intravascular coagulation
- Malignant neoplasia
  - Solid tumors
  - Leukemia (especially promyelocytic leukemia)
- Vascular disorders
  - Giant hemangioema
  - Aortic aneurysms
  - Valvular heart disease
- Liver disease

Subacute and Chronic Disseminated Intravascular Coagulation

Clinical and laboratory diagnosis. In subacute or chronic disseminated intravascular coagulation, the diagnosis may be less obvious and more difficult to make by both clinical and laboratory observations. The level of the platelets and coagulation factors in the circulating blood is a dynamic balance between the rate of production and the rate of destruction. In the less severe syndromes, the association of multiple coagulation defects, thrombocytopenia, elevated serum fibrin degradation products and low fibrinogen may suggest the disorder. However, compensating mechanisms by the bone marrow, liver and other sites of synthesis of coagulation proteins will have a variable effect so that the absence of one or more of these changes does not exclude the diagnosis. The concentration of some coagulation factors may even be increased if the synthetic processes are fully effective and traces of thrombin produce a striking activation of factor VIII so that one-stage assays of this factor may give unusually high results (27). Simple screening tests such as prothrombin, partial thromboplastin and thrombin times may be normal, prolonged or even shorter than control times if the coagulation factors are activated. A good example of the possible variability is the platelet count. Thrombocytosis associated with malignancy is well recognized, and a "normal" platelet count may reflect significant peripheral destruction of platelets in a clinical setting that may be associated with thrombocytosis. Therefore, a normal platelet count does not rule out disseminated intravascular coagulation, and platelet counts may reach supranormal levels when the disseminated intravascular coagulation is controlled (28).

Studies of platelet and fibrinogen kinetics. These studies have helped clarify some of these apparent anomalies. The use of chromium-51-labeled platelets and iodine-125-fibrinogen has assisted in distinguishing between changes in levels caused by altered production, destruction or distribution. By using these techniques, Slichter and Harker (29) showed that malignancy may be associated with increased consumption of both platelets and fibrinogen, the turnover rate being related to the type and extent of the disease. These techniques can also be used to assess the value of various approaches to therapy. However, such techniques are not widely available, and the more conventional, static coagulation studies remain the basis of evaluation in the majority of patients.
**Focal and migratory venous thrombosis and thrombotic endocarditis.** There may be a delay in recognition of chronic disseminated intravascular coagulation because of the complexities already noted. Clinically, obvious bleeding may not be present unless the coagulation factors and platelets are severely decreased, or the patient may present with a focal thrombotic tendency due to the activation of the clotting system. Thus, in a group of patients with malignancy and various manifestations of thrombosis, as reported by Sack et al. (30), isolated venous thrombosis occurred in 113 of 182 patients, and “migratory” venous thrombosis in 96 of the patients (Troussseau’s syndrome). An unusual feature of these chronically ill patients is nonbacterial thrombotic endocarditis, which may be a reflection of chronic disseminated intravascular coagulation.

**Etiology and Clinical Settings**

Table 1 outlines the clinical situations where disseminated intravascular coagulation is encountered. A short description follows:

**Acute disseminated intravascular coagulation.** Pregnancy. Acute disseminated intravascular coagulation may be caused during complications of pregnancy. These include abruptio placenta, placenta previa, amniotic fluid embolism, prolonged retention of dead fetus, retained placenta and septic abortions or deliveries and eclampsia (31,32).

**Infections.** Disseminated intravascular coagulation has been described with almost all infective agents. The meningococcus is a classic culprit, disseminated intravascular coagulation being particularly common in patients with gram negative bacteremias. It is also seen in staphylococcal, pneumococcal and clostridial infections and has been reported in viral, rickettsial and malarial infections (33). Purpura fulminans is a virulent form of disseminated intravascular coagulation related to infections, although in some cases no infective agent can be isolated.

**Tissue injury.** Prolonged surgical procedures or procedures utilizing extracorporeal circulation may activate the coagulation or fibrinolytic systems. Massive trauma, especially involving brain tissue, may release thromboplastic material and initiate intravascular coagulation. Disseminated intravascular coagulation can also be seen in association with severe burns or heat stroke.

**Shock.** Any cause of shock may result in acute disseminated intravascular coagulation. The initiating event is unclear, but it may be the result of acidosis produced by stasis in the microcirculation. In the experimental animal, hypovolemic shock may cause blood to become hypocoagulable.

**Immunologic.** When bleeding occurs after blood transfusion, the possibility of an incompatible blood transfusion should always be considered. Severe allergic reactions and anaphylaxis after injection of contrast medium for radiologic studies may cause defibrination.

**Chronic disseminated intravascular coagulation.** **Malignancy.** Neoplasia is a common cause of chronic disseminated intravascular coagulation and may be seen in association with a variety of tumors including those of the lung, prostate, pancreas, breast, colon and stomach (30,34). Hematologic malignancy, especially acute promyelocytic leukemia, can cause disseminated intravascular coagulation, especially after chemotherapy that causes cell death and liberation of cellular contents into the circulation (35).

**Vascular and circulatory disorders.** Congenital heart disease, especially of the cyanotic type, can be associated with a hemorrhagic diathesis due to consumption (36). Patients with abnormal or prosthetic heart valves may also have a shortening of platelet and fibrinogen life spans and elevated plasma B thromboglobulin and platelet factor IV levels. Although these patients are known to have a higher incidence of clinical thromboembolic disease (37), disseminated intravascular coagulation is less common, except in cases associated with infective endocarditis, shock or nonbacterial thrombotic endocarditis, as previously mentioned.

**Hemangiomas (Kasabach-Merritt syndrome)** are vascular benign tumors that may sequester and consume fibrinogen and platelets from the blood (38). Although rare, this phenomenon may also be seen in enlarging aortic aneurysms.

**Liver disease.** Disseminated intravascular coagulation can occur in patients with liver disease (39). However, it may be difficult to differentiate from decreased synthetic ability of the liver in the setting of portal hypertension and hypersplenism.

**Laboratory Evaluation**

**Screening tests of coagulation.** The diagnosis of disseminated intravascular coagulation depends on suspecting its association with one of the conditions that have been mentioned and outlined in Table 1. The laboratory can be used to confirm the clinical suspicion; however, the interpretation of laboratory tests poses a number of difficulties unless the pathophysiology of consumption is well understood. The presence of thrombin in the circulating blood would be diagnostic evidence of intravascular coagulation; however, because of its rapid inactivation by antithrombin III, it cannot be identified directly. Therefore, to assess the presence of thrombin in the circulating blood, it may be necessary to measure the products of thrombin activity, as will be discussed.

**The levels of coagulation factors and platelets** may be decreased, normal or rarely even increased because their functional and numerical levels depend on their rate of production, activation and destruction. Therefore, screening tests of coagulation (prothrombin time, partial thromboplastin time, fibrinogen and platelet count) may reflect this variability when evaluating a patient with disseminated in-
travascular coagulation. The bone marrow, for example, can release 10 times the usual number of platelets, and the liver can increase the synthesis of fibrinogen by fivefold. Thus, in mild cases of disseminated intravascular coagulation, there is ample reserve capacity to keep up with the slow consumption of coagulation factors and platelets; therefore, the static levels of these elements may be normal. The finding of an elevated level of fibrin degradation products is a helpful laboratory finding to confirm the presence of disseminated intravascular coagulation because fibrinolysis is nearly always secondary to intravascular coagulation.

**Immunoaosays of thrombin activity.** The diagnosis of disseminated intravascular coagulation is frequently a clinical one. Because of the difficulty in directly demonstrating the presence of thrombin in the blood, when screening laboratory variables for disseminated intravascular coagulation are not confirmatory, the indirect effect of thrombin activity in the circulation may have to be evaluated to help make the diagnosis. Thrombin binds to platelets and causes platelet aggregation and release of the contents of their alpha and dense granules. Thus, platelet factor IV and B thromboglobulin can be measured by radioimmunoassays and are elevated in disseminated intravascular coagulation (40), but are not specific. Thrombin cleaves fibrinopeptides A and B from fibrinogen. Accelerated fibrinopeptide A generation in blood directly indicates an increased concentration of thrombin in the circulating blood and implies systemic activation of the coagulation mechanism. A radioimmunoassay has been described by Nossel (41) for measuring the level of this 16 amino acid peptide. Initial application of the fibrinopeptide A assay showed elevated levels in all patients with disseminated intravascular coagulation diagnosed by other criteria. However, patients with a variety of medical conditions including infections, lupus erythematosus and thrombosis can also have elevated levels and, therefore, the test by itself is not diagnostic.

**Antithrombin III assay.** From a theoretical point of view, with the pathologic generation of thrombin, one would also expect to see consumption of antithrombin III. Using both an immunologic and functional antithrombin III assay system, it has been shown that antithrombin III is usually decreased in disseminated intravascular coagulation and it, thus, may be used as a confirmatory test. Anithrombin III levels can also be used to follow the response of disseminated intravascular coagulation to appropriate therapeutic manipulation (42). Protein C antigen and the protein C inhibitor have also been reported to be decreased in disseminated intravascular coagulation and to decrease progressively during the initial stages of disseminated intravascular coagulation before returning toward normal in nonfatal cases (43).

**In summary,** the laboratory may be useful in confirming the clinical suspicion of disseminated intravascular coagulation. Although a battery of sophisticated tests is available in a modern coagulation laboratory, the results can be quite variable and are rarely diagnostic.

**Theraoy**

Many of the therapeutic options available in managing patients with disseminated intravascular coagulation are controversial. This may be due to the heterogeneity of the underlying disorders causing disseminated intravascular coagulation and the clinical variability of the manifestations of the condition.

**Treatment of the underlying cause.** This is the cornerstone of management and the most universally accepted principle in the treatment of patients with disseminated intravascular coagulation. In association with infection, specific antimicrobial therapy along with intensive supportive treatment to maintain intravascular volume and organ perfusion are essential. For acutely bleeding patients and those in shock, the maintenance of blood volume is crucial. Evacuation of the uterus in obstetric patients with complications, cytotoxics in malignant disease and removal of necrotic tissue at surgery are important principles of management. These are recognized as accepted approaches to therapy. Other aspects of intervention are considered to be more controversial.

**Heparin and other agents.** Because the intravascular generation of thrombin is considered the essential pathogenic factor of consumption coagulopathy, it is a logical therapeutic option to attempt to interfere with thrombin’s activity. Heparin should function in this manner to prevent further consumption of the hemostatic proteins and platelets. However, the use of heparin in the management of disseminated intravascular coagulation remains controversial, and widely differing practices exist. Some investigators (44,45) found that the careful use of heparin is beneficial; others (46,47) failed to observe improvement in clinical hemostasis or influence on survival.

**Our approach to the use of heparin in disseminated intravascular coagulation** is to recognize it as a potentially hazardous drug, but one whose benefit may outweigh its risk in selected patients. If a patient is bleeding or requires a surgical or invasive procedure in the setting of a low fibrinogen level and a low platelet count, it is important to attempt to improve the level of these factors with transfusion of cryoprecipitate (a source of factor VIII and fibrinogen), fresh frozen plasma (a source of other coagulation proteins) and platelet concentrates. In the setting of active disseminated intravascular coagulation, until the underlying cause can be removed or controlled, it may be very difficult to increase the level of these circulating hemostatic factors with transfusion therapy alone. Therefore, replacement therapy may be given along with a continuous heparin infusion to interfere with thrombin’s action and prolong the half-life of the circulating factors. Sufficient data support low dose hep-
arin therapy as equivalent to higher dose therapy in the management of disseminated intravascular coagulation (48). We recommend heparin at 500 units/h and the dosage is monitored by following up the clinical disappearance of fibrin degradation products and the increase in the fibrinogen concentration and platelet count.

**Most obstetric cases of disseminated intravascular coagulation resolve on evacuation of the uterus.** Occasionally, the disseminated intravascular coagulation continues and can only be reversed by heparin (49). Heparin therapy has been reported to be effective in improving clinical hemostasis and the coagulation profile in excessive bleeding associated with a giant hemangioma (50) and neoplastic disease, particularly promyelocytic leukemia (51).

Another indication for heparin therapy, we believe, is evidence of organ ischemia in the setting of disseminated intravascular coagulation. When intravascular volume has been optimized and progressive ischemia to major organs such as the brain or kidney continues, active inhibition of thrombin by heparin to interfere with continued formation of fibrin is probably indicated. The documentation of episodes of thrombosis is considered to be a strong indication for heparin.

**Antithrombin III.** Because heparin’s anticoagulant activity depends on the presence of antithrombin III in the blood, heparin may be less effective when antithrombin III is deficient. In patients with disseminated intravascular coagulation, because antithrombin III levels are frequently low, antithrombin III concentrates have been given along with heparin therapy (52,53). These studies suggest that supplementation of antithrombin III in cases of disseminated intravascular coagulation is a valuable addition to the therapeutic strategies currently employed.

**E-aminocaproic acid.** The use of agents such as E-aminocaproic acid (EACA) to block the fibrinolytic component of the syndrome is controversial, and in our opinion is generally contraindicated. In most discussions of treatment, it is stated that E-aminocaproic acid should be administered only in cases of primary fibrinolysis. This condition is very rare, and it is feared that use of this agent in conditions associated with disseminated intravascular coagulation may precipitate thrombosis (54) and should, thus, be avoided.

**References**