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Diagnosis and Management of Bleeding Disorders

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IT IS GENERALLY ASSUMED that during surgical procedures blood will clot and secure hemostasis, yet this assumption may lead to disaster when clotting does not occur. It is essential that each anesthetist possess a working knowledge of the manifestations of bleeding, a system for evaluation of bleeding, and a rationale for selecting among the alternate means of treatment. This paper presents an approach to evaluating the patient who has a bleeding disorder and selecting treatment. Consultation with a hematologist experienced in the management of coagulopathies seen in surgical patients is strongly recommended.

Bleeding represents a defect in hemostasis, the process by which the body seals off leaks from the circulatory system. Hemostasis is a tripartite function depending on vascular integrity, platelet function, and the coagulation mechanism. No matter how meticulous a surgeon is in securing hemostasis, a patient who has hemophilia will continue to bleed until factor VIII is increased to an acceptable level. Similarly, bleeding will persist in the face of an acceptable level of factor VIII and an adequate number of functioning platelets until vascular integrity is achieved in the case of a slipped ligature on an intercostal artery.

The impact of bleeding on critical care is difficult to assess in terms of absolute numbers. The requirement for blood replacement may be one such measure. Cullen *et al.* recently reported that 21 per cent of total hospitalization charges in 226 consecutive cases of critically ill patients went for blood or blood products. They were able to correlate this requirement for blood with various categories of pathologic processes. Gastrointestinal bleeding, cirrhosis, and portal hypertension were associated with the highest costs for blood, fivefold more than those charged to patients being treated for neurosurgical catastrophes or trauma to the head, who would not be expected to need extensive use of blood products.[1] However, in certain patients who have brain-tissue destruction following trauma to the head, a diffuse coagulopathy, possibly due to exposure of circulating blood to the damaged brain tissue, may be seen.[2]

Vascular Integrity

Of the three components of hemostasis, vascular integrity, defined as a state of unbroken or complete blood vessels, has received the least attention. MacFarlane suggests that while the spontaneous arrest of bleeding from ruptured vessels conveying blood under pressure involves autonomic mechanisms that are extremely complex, the principles are relatively simple.[3] Blood will escape so long as the pressure within the vessel exceeds the pressure at the orifice. Vasoconstriction of the blood vessel at the site of rupture to produce stenosis or the opening of anastomotic shunts to provide alternate pathways for blood flow will reduce the intravascular pressure, as will sufficient blood loss or deliberate hypotension. Anesthesiologists have long made use of the latter technique to reduce blood loss intraoperatively.[4,†]

An increase in extravascular pressure will also reduce the pressure gradient. Thus, the accumulation of blood in surrounding tissues to form a hematoma will reduce the blood supply. Furthermore, tissue damage has the effect of increasing permeability of vessels of the microcirculation, resulting in fluid filtering from the blood stream. This has a twofold effect of further increasing extravascular pressure as edema fluid accumulates in the tissue spaces and producing hemoconcentration due to the diminished plasma volume. The hemoconcentration may further slow circulation and reduce intravascular pressure.

Coagulation Mechanism

Most blood vessels are less than one millimeter in diameter, and in vessels of this caliber platelets and coagulation play the major roles in securing hemostasis.[5] Thus, an efficient coagulation mechanism is essential to prevent bleeding. Figure 1 outlines the currently accepted theory of coagulation, emphasizing the contribution of platelets.

Although the use of common names may be more meaningful, because they describe particular patients or certain functions, a degree of order was brought to the field of coagulation when an international committee assigned Roman numerals to all of the accepted factors.[6] Table 1 lists the coagulation factors with some of their synonyms. The suffix "a" is now used to designate the activated form. Three factors (I, V, and VIII) do not exist in an enzymatically active form.

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† Thompson GE, Miller RD, Stevens WE, et al: Hypotensive anesthesia for total hip arthroplasty: A study of blood loss, heart, kidney, and brain function. Abstracts of Scientific Papers, 1976 Annual Meeting of American Society of Anesthesiologists, pp 153–154.

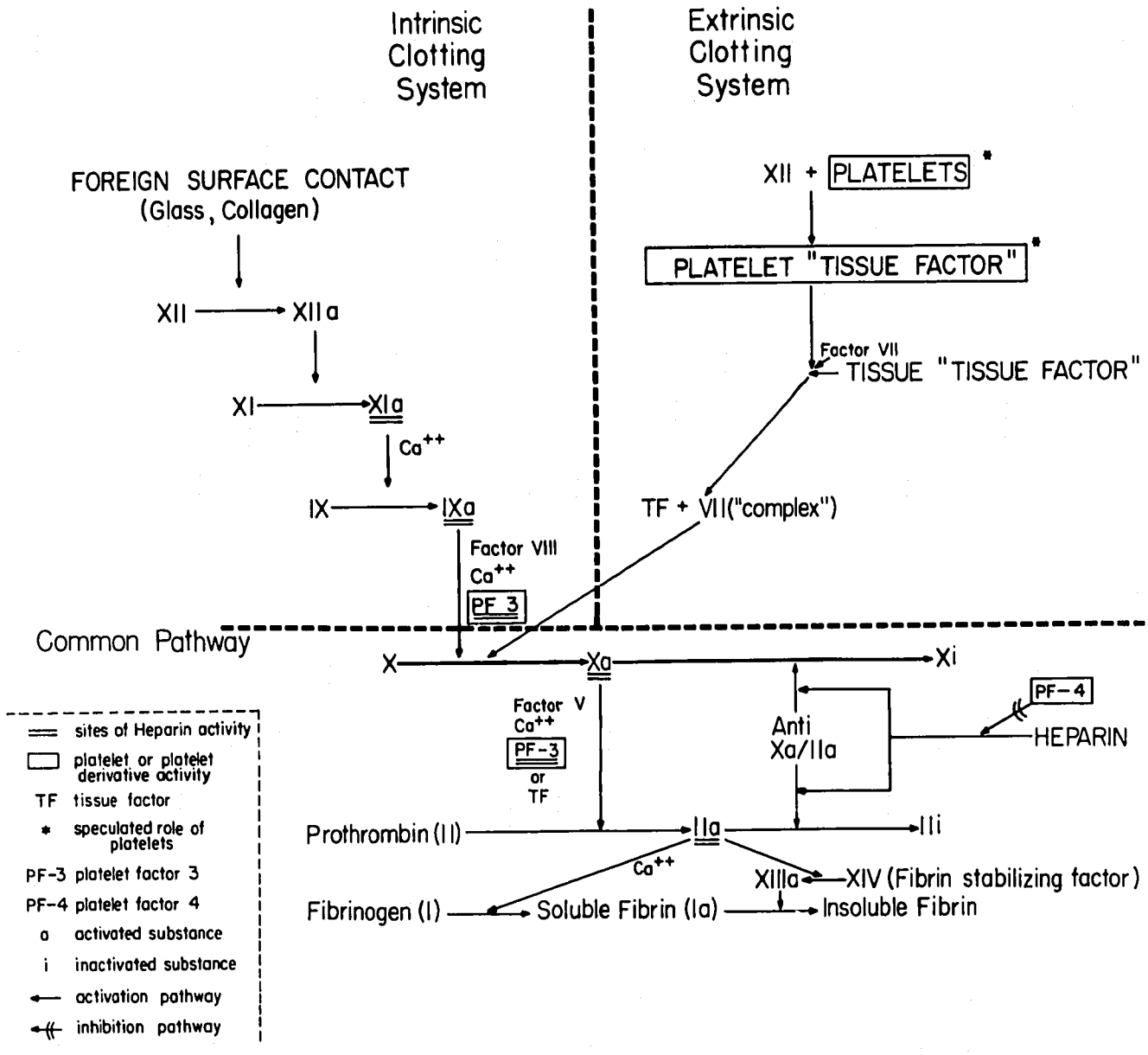

FIG. 1. The generally accepted scheme of the coagulation cascade is modified to emphasize the sites of platelet and heparin activity. Upper left section contains intrinsic clotting system, upper right section contains extrinsic clotting system, and lower section contains the final common pathway. Substances enclosed in boxes represent platelet or platelet derivative activity. Underlined factors illustrate sites of heparin activity. The right portion of the final common pathway illustrates the theoretical interaction of heparin with platelet factor 4 (PF4) and its effect on the inactivation of factors Xa and IIa. Heparin, in combination with circulating substances anti-Xa/IIa, facilitates inactivation of Xa and IIa. PF4 antagonizes this heparin activity. (Reproduced with permission from Barrer MJ, Ellison N: Platelet function. ANESTHESIOLOGY 46:202–211, 1977.)

Platelet Function

The role of platelets has recently been reviewed.[7] In response to vascular injury, platelets accumulate at the site where they come in contact with collagen-containing subendothelial basement membrane that has been exposed by the injury. Platelet aggregation, the affinity of platelets for one another, and platelet adhesion, the affinity of platelets for nonplatelet surfaces, develop simultaneously. In small injuries the resultant platelet plug may be sufficient to seal the defect. Furthermore, platelets contribute to the coagulation mechanism, as detailed in figure 1. The final step in the formation of a clot, clot retraction, is probably due to a contractile mechanism found in platelets.

Routine Evaluation

The best means of detecting a hemorrhagic diathesis is a properly taken history, and one of the most important items to be checked in the history is the hemostatic response to a prior surgical experience. Abnormal bleeding following dental extraction or tonsillectomy may suggest the need for further evaluation. Especially important in the history is a detailed record of drug ingestion. While patients would probably volunteer that they are taking anticoagulants, they may neglect to mention that they are taking aspirin, which has a coumarin-like effect in high doses and prolongs the bleeding time in low doses. More than 250 preparations contain aspirin, and patients may be unaware that they are taking aspirin unless they are specifically reminded.[8] Many other drugs also may impair platelet function. Drug history should include details about occupation or exposure to toxic agents or ionizing radiation. In patients who have taken platelet-inhibiting drugs such as aspirin, which inhibits release of endogenous ADP in response to an appropriate stimulus, the possibility of defective platelet function should be evaluated by determining bleeding time and platelet aggregation in response to appropriate reagents. In patients who have platelet function deficiencies due to aspirin and are bleeding excessively as a result, transfusion of fresh whole blood or platelet concentrates will provide platelets that do release ADP, to which the patient's platelets will respond and aggregate.

The history should attempt to establish the following pertinent points for any prior or ongoing episode of bleeding: 1) site, duration and severity of bleeding; 2) apparent cause; 3) frequency of such episodes or coexistent bleeding or bruising; 4) family history of bleeding manifestations.[9] Petechiae or prolonged bleeding following superficial trauma are usually due to vascular or platelet abnormalities. Furthermore, the subcutaneous bleeding seen in deficiencies of coagulation factors in usually an ecchymosis, as opposed to discrete petechiae, seen with vascular or platelet abnormalities. Hemarthrosis or deep bleeding into muscles is more likely to be seen with a coagulation factor deficiency. Similarly, the age at onset is an important clue, with onset of bleeding problems in infancy or early childhood suggesting a congenital defect and onset in adulthood, an acquired defect.

When the patient has a history of abnormal bleeding, a coagulation profile, which includes a prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen level, and bleeding time, should be obtained. Recently, we have also frequently measured platelet function by means of a platelet aggregometer. In the operating room a baseline whole-blood coagulation determination or an automated activated coagulation time test is then performed.[10,‡] In the last 1,500 patients who have had open-heart surgery, we have detected one previously undiagnosed very mild factor IX deficiency. While this may seem like a small yield, the advantage of not having to include a pre-existing defect in the differential diagnosis of a bleeding disorder that occurs intraoperatively is obvious.

No one test or pair of tests is sufficient to permit an accurate diagnosis of a bleeding disorder. For that reason, a history of abnormal or excessive bleeding must be given serious consideration, and quantitative assays of at least the three hemophilia factors (VIII, IX, and XI) may be necessary, in addition to the screening tests, to be certain that there is no pre-existing bleeding diathesis.[11]

TABLE 1. Coagulation Factors

Factor	Synonym
I	Fibrinogen
II*‡	Prothrombin, prethrombin
III	Tissue factor, thromboplastin
IV	Calcium
V†	Labile factor, proaccelerin, plasma accelerator globulin (ac-G)
VI	[No factor assigned to this numeral
VII*	Stable factor, proconvertin, autoprothrombin I, serum prothrombin conversion acceleration (SPCA)
VIII†	Antihemophilia globulin (AHG), antihemophilic factor (AHF), thromboplastinogen, platelet cofactor I, antihemophilia factor A
IX*‡	Plasma thromboplastin component (PTC), Christmas factor, autoprothrombin II, antihemophilic factor B, platelet cofactor II
X*‡	Stuart-Prower factor, autoprothrombin C (or III)
XI‡	Plasma thromboplastin antecedent (PTA), Rosenthal syndrome, antihemophilic factor C
XII	Hageman factor, glass factor
XIII	Fibrin-stabilizing factor (FSF), Laki-Lorand factor, fibrinase serum factor, urea-insolubility factor.

* Coumarin-sensitive or vitamin K-dependent factors that are part of the prothrombin complex.
† Found only in fresh blood or plasma or fresh frozen plasma.
‡ Heparin-sensitive factors.

‡ Jobes DR, Bikhazi G, Ellison N: Rapid assessment of heparin anticoagulation and reversal. Abstracts of Scientific Papers, 1976 Annual Meeting of the American Society of Anesthesiologists, pp 437–438.

TABLE 2. Variables Influencing Specific Replacement Therapy of Patients with Coagulation Deficiencies

1. Size of patient
2. Initial level of deficient factor
3. Hemostatic level of deficient factor
4. Potency of preparation
5. Extravascular distribution
6. Half-life
7. Metabolic rate
8. Magnitude of operation

Congenital Deficiencies

The incidences of deficiencies of various coagulation factors vary greatly. For example, there are fewer than 100 cases of familial afibrinogenemia in the world medical literature, and some of these are suspected to have been cases of disseminated intravascular coagulation (DIC) because of associated reductions in platelet counts.[12] In contrast, estimates of the incidence of classic hemophilia A, factor VIII deficiency, run as high as 1/10,000–25,000 live births.

Usually the existence of a given factor is first suspected on the basis of the clinical picture presented by a given patient. Factor VIII deficiency, classic hemophilia A, is the factor for which the kinetics of replacement therapy have best been worked out. The eight variables that will influence specific replacement of any factor are listed in table 2. When a deficient factor is infused into a patient, the volume required depends on patient size, desired increment in level of deficient factor, and preparation potency. Survival of the transfused factor *in vivo* shows a characteristic double exponential curve in which the early rapid disappearance represents equilibration with the extravascular space and the later slower disappearance, natural degradation, which is accelerated in febrile patients or in the presence of infection.[13] Higher levels are required for longer periods of time, for example, following a major orthopedic procedure, than for dental extractions. The volume of deficient factor infused must take into consideration these eight variables to insure that the level remains above the minimal hemostatic level at all times. To accomplish this, the initial level commonly is considerably in excess of the minimal level sufficient to permit partial saturation of the extravascular stores and to allow for intravascular decay with a reasonable booster schedule. Table 3 lists the therapeutic agents and commonly accepted schedules of administration for the various coagulation factor deficiencies.

The effects of these eight variables may best be illustrated by the schedule of factor VIII administration in a patient with hemophilia A. A 10 per cent factor VIII level will prevent spontaneous bleeding; 20 per cent is necessary to insure hemostasis in response to trauma; more than 30 per cent is necessary to secure hemostasis following major operations. To insure that factor VIII levels do not drop below 30 per cent, it is common to infuse sufficient factor VIII to raise the level to 80–100 per cent and then give booster doses *q*. 12 *h*. To calculate the dose of factor VIII needed, the following equation is used:

$$\text{Dose (units of factor VIII)} = (0.01)\,(\%\text{ factor VIII increment})\,(\text{plasma vol in ml})$$

After the initial infusion, when measurement of factor VIII has established that a satisfactory response was achieved, the patient should have a normal activated partial thromboplastin time (aPTT), which is a measure of the intrinsic system of coagulation. The aPTT may be then measured serially following subsequent factor VIII infusions to be sure that the response remains satisfactory.

One congenital bleeding disorder, von Willebrand's disease, merits special comment. When von Willebrand originally reported in 1926 a familial bleeding disorder, he attributed the disorder to an abnormality of platelets and blood vessels. Subsequent investigation of the same patients 30 years later established that there was a reduction in factor VIII levels also. Today it is agreed that a triad of prolonged bleeding time, reduced factor VIII level, and altered platelet retention characterize the typical patient. Unfortunately, all three characteristics are not always present in each patient, or even in the same patient all the time! This cyclic variability has resulted in confusion as to diagnosis. One pathognomonic test for von Willebrand's disease is the response to the infusion of plasma. In contrast to the patient with hemophilia, whose factor VIII level is maximal immediately after plasma or cryoprecipitate infusion, patients who have von Willebrand's disease show the same immediate increase in factor VIII levels, but then the level continues to increase for as long as 48 hours more, indicating that the patient is producing factor VIII. In other words, these patients seem to lack a factor that controls factor VIII production, as opposed to lacking the ability to produce factor VIII *per se*. Plasma infusion will produce an increase in factor VIII levels that is sustained for 20–30 hours. While the bleeding time will be corrected for only a few hours after infusion, clinical bleeding does not seem to be correlated with this.[11]

Acquired Deficiencies

In contrast to congenital deficiencies, which are usually limited to one factor, acquired deficiencies are usually multifactoral. Six common acquired deficiencies of hemostasis are caused by massive blood trans-

TABLE 3. Minimal Levels of Coagulation Factors and Platelets Necessary for Effective Hemostasis; Distribution and Fate of Clotting Factors after Transfusion Therapy, and Schedules

Factor	Minimal Level for Surgical Hemostasis (Per Cent of Normal)	Apparent Volume of Distribution (X Plasma Volume)	*In-vivo* Half-life (Hours)	Therapeutic Agent	Dose (per kg Body Weight)	
					Initial	Maintenance
I	50–100	2–5	72–144	Cryoprecipitate	ppt from 100 ml	ppt from 14–20 ml, *q.d.*
II	20–40	1½–2	72–120	Plasma	10–15 ml	5–10 ml, *q.d.*
V	5–20	?	12–36	Fresh or fresh frozen plasma	10–15 ml	10 ml, *q.d.*
VII	10–20	2–4	4–6	Plasma	5–10 ml	5 ml, *q.d.*
VIII	30	1–1½	10–18	Cryoprecipitate	ppt from 70 ml	ppt from 35 ml, *b.l.d.*
von Willebrand's	30	—	—	Plasma	10 ml	10 ml, *q.* 2–3 *d.*
IX	20–25	2–5	k18–36	Plasma or II, VII, IX, X conc.	60 ml Variable	7 ml, *q.d.*
X	10–20	1–2	24–60	Plasma	15 ml	10 ml, *q.d.*
XI	20–30	1–1⅓	40–80	Plasma	10 ml	5 ml, *q.d.*
XII	0	?	?50–70	Plasma	5 ml	5 ml, *q.d.*
XIII	1–3	?	?72–120	Plasma	2–3 ml	None
Platelets	50,000–100,000/mm³			Platelet concentrate	1–2 units per desired 10,000 increment in count	

Adapted from Ratnoff OD (editor): Treatment of Hemorrhagic Disorders. New York, Harper and Row, 1968; Biggs R (editor): Human Blood Coagulation, Haemostasis and Thrombosis, London, Blackwell Scientific Publications, 1972.

fusion, anticoagulants, hepatic disease, disseminated intravascular coagulation, thrombocytopenia, and inadequate surgical hemostasis.

MASSIVE TRANSFUSION

Factors V and VIII and platelets may be deficient in stored blood. The factors decrease after 21 days of storage to 20–50 per cent, which would still be in excess of the minimal hemostatic level, and thus deficiencies of factors V and VIII are rarely a primary cause of bleeding. In contrast, the hemostatic effectiveness of platelets rapidly decays over 48–72 hours. Miller *et al.* infused 500–1,000 ml volumes of fresh frozen plasma, which contains factors V and VIII but no platelets, into combat casualties who were bleeding after receiving more than 20 units of blood, and demonstrated return to normal of the activated partial thromboplastin and prothrombin times without correction of the bleeding disorders. Subsequent administration of fresh blood resulted in correction of these bleeding disorders.[14] When dilutional thrombocytopenia is the cause of a bleeding disorder, deficiencies of factor V and VIII, which are insufficient to produce bleeding on their own, may aggravate the situation. Fresh frozen plasma or fresh whole blood will correct deficiencies of factors V and VIII. Platelet concentrates or fresh whole blood, both of which contain viable platelets, will correct bleeding due to dilutional thrombocytopenia.

ANTICOAGULANTS

There are two types of anticoagulants, both of which produce various hemostatic defects. Coumarin-like drugs inhibit production of factors II, VII, IX, and X, which together are known as the prothrombin complex or vitamin K-dependent factors, while heparin inhibits factors IXa, Xa, and XIa. Small doses of coumarin inhibit factor VII, resulting in prolongation of the prothrombin time (PT) while the activated partial thromboplastin time (aPTT) remains normal. Larger doses of coumarin produce depression of factors X and II also, and then both PT and aPTT are prolonged. Small doses of heparin inhibit factor IXa initially, resulting in a prolonged aPTT and a normal PT. Larger doses affect factors Xa and IIa, and then both PT and aPTT are prolonged. The presence of heparin in the patient's blood can be confirmed by adding protamine to the patient's citrated plasma and seeing whether this improves the aPTT.[10] Coumarin can also be measured in the patient's plasma, a technique especially valuable in suspected cases of surreptitious ingestion or "coumarin malingers."[11,15]

The advisability of surgical treatment of patients receiving anticoagulants remains controversial. We believe that except for operations on the eye, central nervous system, or large raw surfaces such as the liver bed, major surgical procedures can be carried out on such patients.[16]

In the event that reversal of the anticoagulant is elected, only one agent, protamine, is available to reverse heparin. Its effect is immediate. The dose of protamine administered may be calculated on the basis of the heparin previously given or, preferably, on the basis of a protamine titration in which the micrograms of protamine needed to neutralize the heparin in 1.0 ml of blood are measured. After protamine administration, a repeat titration or aPTT should be performed to insure that the action of heparin has been adequately reversed. The possibility of excess protamine's producing a hemorrhagic diathesis suggests that care should be taken to see that excessive doses of protamine are not administered.[17]

Transfusion of blood or plasma and administration of vitamin K are the two methods available to reverse coumarin. While transfusion produces immediate results, there is no formula available to predict the volume of blood or plasma needed, since the extent of depression of the patient's coagulation factors for a given prothrombin time and the levels of coagulation factors present in individual units of blood or plasma are extremely variable. Since the four vitamin K-dependent factors are all present in banked blood, fresh whole blood or fresh frozen plasma is not necessary. Vitamin K is the specific antidote for coumarin, but takes at least three and sometimes six, hours to achieve an effect. Vitamin K_1 in doses of 2.5 to 50.0 mg should be given orally or parenterally, depending on severity. Response to therapy should be monitored with serial prothrombin times to insure a satisfactory response. Since the action of coumarin may last four or five days, it is advisable to follow the prothrombin time daily for that period. Concentrates of the prothrombin complex are no longer recommended as an antidote for coumarin since, as a pooled product, their use is associated with a high risk of hepatitis.[18] Furthermore, recent reports of concentrates containing thrombogenic material or activated clotting factors have prompted the recommendation that these products be covered with small doses of heparin and that they not be given to patients with hepatic disease, who would be less likely to inactivate any procoagulant activity contained in the concentrate.[19,20]

Hepatic Disease

Hepatic disease may produce bleeding because of defects in coagulation factors, thrombocytopenia on the basis of hypersplenism, or excessive fibrinolysis, or on a mechanical basis, as with esophageal varices. In addition to depression of the four vitamin K-dependent factors in the prothrombin complex, hepatic disease results in decreased production of factors V and XI. Therefore, vitamin K therapy alone, even in massive doses, will not correct the deficiency. Slight improvement may be seen following parenteral administration of vitamin K because of malabsorption of vitamin K due to lack of bile salts. This amount of improvement can be achieved with usual doses. Any improvement seen during vitamin K therapy results from alleviation of the underlying hepatic disease rather than from the administration of the vitamin *per se*.[11]

To distinguish between a bleeding disorder due to vitamin K deficiency only and a bleeding disorder that is the result of advanced hepatic disease, a comparison of the prothrombin times of the patient's plasma mixed with fresh normal plasma (containing factor V) and with aged normal plasma (factor V-deficient) is performed. Correction of a prolonged PT with the fresh normal plasma only indicates that the prolongation of the PT is due to more than just a deficiency of the vitamin K-dependent factors. Alternatively, a therapeutic trial with vitamin K and measuring the prothrombin time response is performed. Improvement would suggest that the patient has mild hepatic disease, since the four vitamin K-dependent factors are the first affected in hepatic disease or a deficiency of vitamin K due to malabsorption, inadequate diet, or coumarin administration.[12]

One iatrogenic cause of bleeding that may be seen in patients receiving critical care is the intestinal sterilization syndrome. The intestinal flora are a major source of vitamin K in man. Patients who have their gastrointestinal tracts sterilized with large doses of antibiotic preoperatively lose this source of vitamin K. When they are maintained on intravenous fluids or receive restricted diets without vitamin K-containing foods, their vitamin K stores will be depleted in approximately a week. This syndrome is easily diagnosed on the basis of history, the finding of an isolated prolonged PT, and the prompt response to vitamin K administration.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a pathologic syndrome in which formation of fibrin thrombi, consumption of factors V and VIII, loss of platelets, and activation of the fibrinolytic system suggest the presence of thrombin in the systemic circulation.[21] Although coagulopathies associated with specific clinical entities such as dead fetus or hemolytic

transfusion reaction have long been recognized, appreciation of a common denominator and the term "disseminated intravascular coagulation" are relatively recent developments. In 1972, DIC first appeared as a separate heading in *Index Medicus*, earlier references being listed under disorders of blood coagulation. In the late 1950's and early 1960's, researchers at several centers began to focus on DIC as a final common pathway for several disease states.[22,23] While DIC may be looked on as a "disease of medical progress" which is now being diagnosed more frequently because larger numbers of critically ill patients are surviving for longer periods, a more likely explanation is that the entity is now well accepted and thus just being recognized more readily.

The clinical findings of DIC may vary, with patients manifesting thrombotic, hemorrhagic, or mixed signs and symptoms. Furthermore, some patients who have no clinical manifestations may have classic laboratory findings of DIC. Mehta *et al.* studied a group of patients following cardiac arrest through the recovery phase or to autopsy and clearly demonstrated laboratory evidence of DIC without concomitant hemorrhage or thrombosis.[24]

The hemorrhagic component of the DIC spectrum is readily appreciated, and has been characterized as a paradox, in that bleeding and thrombosis are occurring simultaneously and are further complicated by another paradox in that one of the recommended forms of treatment of the hemorrhage is the administration of an anticoagulant, heparin![25] The thrombotic component of the DIC spectrum, though obviously a necessary precursor to the hemorrhagic component, is less readily appreciated. McKay commented, "When thrombosis becomes the cause of death, one finds at autopsy that the process involves not only the original site of the thrombus formation but many other organs as well."[22] Minna *et al.* suggest that the assignment of DIC-induced thrombosis as a major cause of death is rarely straightforward.[26] The presence of intravascular catheters, endocarditis, or fungal infection in such cases is often credited with being the thrombogenic agent responsible for the thrombosis.

There is no one pathognomonic laboratory test to diagnose DIC. Colman and Robboy have established the following criteria: In the absence of hepatic disease or blood transfusion, they use a screening triad of prothrombin time greater than 15 seconds, fibrinogen level less than 160 mg/100 ml, and platelet count less than 150,000. Abnormalities of all three indicate DIC. If results of two of three tests are abnormal, than either the thrombin time (more than 5 seconds longer than control in the absence of heparin therapy) or fibrin split products must be abnormal to confirm the laboratory diagnosis of DIC.[21]

Disseminated intravascular coagulation is never a primary disease state, nor will it develop in every patient who receives, for example, an incompatible blood transfusion. The body has several defense mechanisms that will eliminate any thrombin within the vascular tree. These include: 1) rapid blood flow, producing dilution of activated coagulation factors to below clotting threshold levels; 2) hepatic and reticuloendothelial-system clearance of activated coagulation factors; 3) inhibition of thrombin produced by naturally-occurring plasma proteins such as antithrombin III. Thus, in most cases of incompatible blood transfusion the combination of rapid blood flow–dilution, hepatic–RES clearance, and naturally-occurring inhibitors will prevent DIC. However, when blood flow is stagnant, as in shock, or there is hepatic–RES impairment, as in hypoxemia, or where the insult is overwhelming, as when 3,000 ml of ABO-incompatible blood have been transfused,[27] DIC may develop.

The body will then respond to the intravascular deposition of fibrin with yet another defense mechanism, fibrinolysis, in which plasminogen is activated to plasmin, which will destroy fibrinogen and factors V and VIII. The consumption of platelets and coagulation factors results in the hemorrhagic diathesis because available platelets or coagulation factors are insufficient to form clots in wounds or venipuncture sites. Furthermore, the fibrin split products, which result from the plasmin degradation of fibrin or fibrinogen, possess anticoagulant properties that will further aggravate the bleeding disorder.

This type of fibrinolysis, which is a secondary defense mechanism, must be differentiated from primary fibrinolysis, an extremely rare disorder, in which the fibrinolytic system is activated without preexisting DIC.[21] In primary fibrinolysis excessive plasminogen activator or plasmin is present and lyses clot or fibrin pathologically. Differentiation of primary from secondary fibrinolysis is vital, since the treatments differ radically. Epsilon-aminocaproic acid (EACA) blocks plasminogen activation to plasmin, resulting in inhibition of fibrinolysis. In cases of primary fibrinolysis this treatment is specific. However, the administration of EACA to a patient whose fibrinolytic activity is secondary to DIC may result in a thromboembolic catastrophe. Since primary fibrinolysis does not result in platelet consumption, a normal platelet count would suggest primary fibrinolysis. However, in some cases the fibrin split products resulting from fibrinolysis will produce platelet clumping and thrombocytopenia.[12] Thus, a reduction

in platelets does not necessarily rule out primary fibrinolysis. In most clinical situations where the bleeding is acute, the diagnosis and therapeutic decision must be made rapidly. Since the existence of a primary fibrinolytic state in man rarely produces a hemorrhagic state and the entity is far less common than DIC,[28] beginning therapy based on the assumption that DIC is present is both logical and conservative.

The initial treatment of DIC is not administration of heparin! Since DIC is never a primary disorder, the first goal of treatment should be correction of the primary disorder. This may be all that is necessary, and DIC will be self-limited. However, in some patients who have primary disorders such as septic shock or neoplasia, correction of the primary disorder cannot be readily accomplished. While the administration of blood products sufficient to support oxygen-carrying capacity and to maintain intravascular volume is necessary in cases of continued bleeding, the infusion of fresh frozen plasma or platelet concentrates while the coagulopathy is ongoing may contribute to the bleeding by "adding fuel to the fire."[23,25]

Heparin therapy in such cases is designed to stop clot formation and to inhibit the continued consumption of coagulation factors and platelets so that they can reach normal levels. Heparin doses of 40–80 units/kg are administered *q*. 4–6 *h*., the object being to prolong the whole-blood coagulation time (WBCT) to two to three times normal. Ideally, this should produce sufficient anticoagulation to prevent clot formation but not produce bleeding. Monitoring heparin therapy with the WBCT instead of the aPTT is recommended, since the latter is more sensitive to depleted coagulation factors and the anticoagulant effects of fibrin degradation products and cannot distinguish between them and the effect of heparin.[21]

Heparin therapy is by no means universally accepted for the treatment of DIC, and the decision to employ heparin is not to be taken lightly. Straub argues that heparin therapy at best merely replaces one cause of bleeding with another, and that theoretical grounds are not sufficient to justify use of such a dangerous drug.[29] Alleviation of the coagulation defects by heparin therapy without improvement in the mortality rate has also been reported.[30] Marcus suggests reserving heparin therapy for symptomatic cases while observing the patients and managing the primary disorders. Laboratory evidence of DIC in the absence of bleeding or thrombosis is an example of "balanced consumption" and does not necessitate heparin therapy.[24,31] We have been extremely reluctant to administer heparin therapy to surgical patients, following the guidelines of Green *et al.* who caution against the use of heparin in cases with associated severe hypofibrinogenemia (fibrinogen less than 50 mg/100 ml), vasculitis, or local defects in the vasculature.[32]

A recent addition to the therapeutic regimen for DIC is cryoprecipitate. While this blood product was originally developed for treatment of hemophilia, a unit of cryoprecipitate contains a third of the fibrinogen in the plasma from which it is derived. There is less risk of hepatitis with cryoprecipitate than with fibrinogen, which is a pooled product that contains no factor VIII. The use of cryoprecipitate will raise levels of fibrinogen and factor VIII, both of which are depressed in DIC.[33]

Thrombocytopenia

Although disorders of platelet function are more readily appreciated and diagnosed today than ever before, the most common cause of bleeding attributable to platelets is a reduction in platelet count.[7] Reductions in platelet counts may be due to decreased production, as in patients receiving cancer chemotherapy; increased utilization, as in DIC; or increased destruction, as in idiopathic thrombocytopenic purpura or hypersplenism, or secondary to massive transfusion with bank blood which contains no viable platelets.

In cases of decreased production or massive transfusion, the use of platelet concentrates will increase the platelet count and correct the hemostatic defect. While it is impossible to fix an absolute minimum platelet count below which the risk of hemorrhage dictates transfusion, a range of 50,000–75,000/mm^3 is generally accepted for surgical hemostasis, while 10,000–25,000 is acceptable in patients receiving cancer chemotherapeutic agents.[7,18] It is also difficult to predict what increment in platelet count will result from a platelet transfusion. A reasonable estimate is that in an adult patient who has not previously received a blood transfusion, an increase of 5,000–10,000 platelets/mm^3 for each unit of platelet concentrate infused will result. When stored at 22 C, meticulously handled, and transfused within 24 hours, the platelets will survive as long as eight days, in contrast to a normal life span of nine to 11 days.

While storage at 4 C reduces survival to two to three days, platelets stored at 4 C are reportedly more capable of shortening the bleeding time in thrombocytopenic patients, whereas platelets stored at 22 C develop a "storage lesion" that prevents effective hemostasis during the first 8–24 hours following infusion. Therefore, it would seem that platelets stored at 4 C should be used to treat active bleeding secondary to thrombocytopenia and platelets stored at 22 C

should be used for prophylaxis in the thrombocytopenic patient at risk for hemorrhage.[34] However, this is a decision that must be arrived at in conjunction with the blood bank staff in any particular institution, since the issue has not been completely resolved.

When the patient is thrombocytopenic due to increased utilization in DIC, administration of platelet concentrates as well as fresh plasma may be indicated to increase the speed with which normal levels of the hemostatic components are achieved. This is usually reserved for severe cases in which heparin therapy is indicated and platelet transfusion should be delayed until heparin therapy is instituted.

Platelet transfusion is not indicated in cases of patients who have increased destruction of platelets on an autoimmune basis. Steroid therapy is much more effective than platelet transfusion in these cases. When hypersplenism warrants it, splenectomy is the treatment of choice.

An Approach to the Bleeding Patient

When unexpected bleeding occurs in a critically ill patient, the following tests will facilitate a rapid evaluation and guide to therapy:

Test	*Comment*
1. Whole-blood coagulation time (WBCT)	Can be done in OR; observe for clot retraction and lysis
2. Fibrinogen level	Depressed in DIC
3. Prothrombin time (PT)	Prolonged in hepatic disease, vitamin K deficiency, coumarin anticoagulation, DIC
4. Activated partial thromboplastin time (aPPT)	Prolonged in factor V, VIII deficiencies (massive transfusion), the hemophilias, or in the presence of heparin
5. Platelet count	

These tests can be all performed quickly and reliably. The WBCT can be readily performed in the operating room or ICU while blood is being transported to the laboratory for the other tests. No elaborate equipment or special reagents are necessary for the WBCT, which can yield meaningful results if properly performed.[10] The clot can then be observed for retraction, a rough measure of platelet function, or lysis. Care must be taken not to confuse the dissolution after vigorous shaking of a weak, friable clot due to hypofibrinogenemia from true fibrinolysis. A fibrinogen level will obviously assist in making this distinction, as well as forming part of the triad of screening tests for DIC along with the prothrombin time and platelet count. Abnormalities of all three tests would suggest a diffuse, multifactoral coagulopathy, *i.e.*, DIC.

In addition to its value in screening for DIC, the prothrombin time is of value in diagnosing hepatic disease, vitamin K deficiency, or small doses of coumarin. As previously mentioned, the aPTT and PT will both be abnormal with higher doses of coumarin. Similarly, the aPTT will be prolonged with small doses of heparin, and both the PT and aPTT will be prolonged with higher doses of heparin.

As with any laboratory determination, serial tests are of value in making a diagnosis and in assessing the response to therapy. This is especially true when initial screening test results were obtained in the preoperative or precritically-ill state and can serve as baseline values.

When the patient is bleeding postoperatively or during a critical illness, and results of these five tests are normal, the likelihood of a bleeding disorder is extremely small. Re-exploration in anticipation of finding inadequate surgical hemostasis in the postoperative patient or looking for other causes of bleeding such as a peptic ulcer should be pursued in such cases.[28]

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