Bleeding disorders and thromboembolic diseases represent abnormalities of the hemostatic mechanism. As this mechanism is basically a defense device against the loss of blood from the vascular system, any serious breakdown can bring about life-threatening hemorrhages. The author describes the inherent problems involved in these cases; and since many of the recognized congenital and acquired bleeding disorders relate closely to the normal events leading to hemostasis, he reviews the physiology involved.

Hemostasis is accomplished by a harmonious interplay of the blood vessel wall with platelets and the coagulation mechanism. The mechanism becomes triggered by an injury to the blood vessel wall. The exposure of either collagen fibers, microfibril, and/or basement membrane to the blood initiates the adhesion of circulating blood platelets to these vessel wall structures. As these platelets adhere, they undergo a "release reaction" in which certain substances that are normally held within the individual cellular structure are released to the outside. These substances are ADP, serotonin, and phospholipids.

In response to primarily ADP, but also to serotonin and collagen, the platelets begin to accumulate at the site of injury in a process known as platelet aggregation. As the platelets aggregate, they undergo their release reaction, thereby propagating this process—which eventually can lead to the formation of a first hemostatic plug if the vessel is 50µ or less in diameter. This primary hemostatic plug, composed entirely of platelets, brings about primary hemostasis. This event precedes the actual activation of the clotting mechanism and is, thus, a primary function of the blood platelets.

Clinically, this primary hemostasis
can be measured fairly easily by so-called bleeding times. For this reason, abnormal bleeding times in a patient mean either a low number of circulating platelets or an abnormality of the platelets resulting in the failure of either adhesion to the vessel wall or aggregation. This process of primary hemostasis is summarized in Figure 1.

The activation of the coagulation mechanism is initiated by the release of phospholipids from the platelets during their release reaction, which eventually results in the formation of fibrin from fibrinogen. Fibrin then replaces the first hemostatic plug to form the second hemostatic plug. This process of fibrin formation is also referred to as secondary hemostasis.

The coagulation mechanism comprises two systems—a system leading to the formation of fibrin from fibrinogen, referred to as the clotting system; and the system leading to the dissolution of fibrin, referred to as the fibrinolytic system.

The clotting scheme or rather the events leading to the formation of fibrin from fibrinogen by thrombin are summarized in Figure 2. It can be noted that a number of clotting factors participate, and each one of these factors assumes a specific task in this mechanism. As indicated, the last step is the formation of fibrin from fibrinogen by thrombin. Thrombin is a proteolytic enzyme which removes two small fibrinopeptides from a fibrinogen molecule, thereby forming a molecular structure known as a fibrin monomer.

These individual fibrin monomers are the building blocks for the fibrin strands. The monomers polymerize spontaneously side-to-side and end-to-end, thus forming the fibrin strands which are easily visible. Therefore, fibrin represents a large number of individual fibrin monomers which are orderly assembled in a strand-like fashion. Not shown in Figure 2 is the event that follows the initial polymerization of the fibrin monomers, namely, fibrin stabilization.

The process of fibrin stabilization

\[
\begin{align*}
\text{Fibrinogen} & \rightarrow \text{Fibrin} \\
\text{Fibrin} & \rightarrow \text{Large number of fibrin monomers}
\end{align*}
\]
occurs through an enzyme known as activated factor XIII or the fibrin stabilizing factor. This enzyme establishes covalent bonds between the individual fibrin monomers, thus linking them tightly together. Factor XIIIa is activated from its circulating precursor form, factor XIII, by the enzyme thrombin. Thrombin thus assumes two functions in the formation of fibrin from fibrinogen, (1) the conversion of the individual fibrinogen molecules to fibrin monomers, and (2) the activation of factor XIII to factor XIIIa.

Thrombin is formed from its precursor prothrombin by a complex which is composed of phospholipids, calcium ions, activated factor X, and factor V. The phospholipids have to be in micellar form and, thus, present themselves as surfaces to which calcium can bind the clotting factors. It can be seen that the entire process of clotting relies on these complex formations between phospholipids, calcium ions, and certain clotting factors. In this particular prothrombin converting complex, the enzyme function is assumed by activated factor X, whereas factor V assumes the role of a protein which determines the reaction specificity between substrate prothrombin and enzyme factor Xa.

The conversion of factor X into its enzymic form can occur principally by two pathways, an intrinsic one and an extrinsic one. The word intrinsic implies that all of the ingredients essential for this process reside within the blood. The term extrinsic means that substances outside of the bloodstream do participate, in this case, tissue thromboplastin.

The intrinsic factor X activation follows once again through a complex, as can be seen in Figure 2. Also, this complex is composed of phospholipids, calcium ions, an enzyme, and a substance which determines the reaction specificity between enzyme and substrate. The two antihemophilic factors, namely factor VIII and factor IX, participate in this complex.

Furthermore, it can be seen from Figure 2 that the conversion of factor IX to its enzymic form follows through the participation of two clotting factors, that is, factor XII and factor XI. The exact mechanism of how these factors interact is not well known, and the events listed in Figure 2 are at this time speculative. It is known, however, that phospholipids and other surfaces, as well as calcium ions, participate.

The extrinsic pathway of factor X activation requires the availability of tissue thromboplastin. All forms of tissue contain this clot-promoting activity; and biochemically speaking, the tissue thromboplastin seems to be composed of phospholipids and probably enzymes. These two require factor VII, which is present in plasma at all times. The interaction of tissue thromboplastin with calcium ions and factor VII, presumably again through a complex, results in the ultimate conversion of factor X to its enzymic form. Prothrombin can be converted to thrombin via this particular pathway.

It should be mentioned at this point that the first clotting factor to become activated in this sequence is factor XII, or the Hageman factor. This protein is easily activated by adsorption onto surfaces other than the vessel intima. Under physiological conditions, collagen fibers, as well as phospholipid micellar surfaces, are probably the most important structures which lead to the activation of this clotting factor.

All of the clotting factors, except factor VIII, are produced by the liver, which explains why patients with impaired liver parenchymal cell function have coagulation defects. Factor VIII seems to be synthesized in plasma cells, as well as in the intima cells of the vasculature.

Clinically, this complex clotting system can be easily screened by two tests: the partial thromboplastin time and the prothrombin time. The partial thromboplastin time screens the intrinsic activation mechanism, while the prothrombin time assesses the extrinsic pathway. This means that the partial thromboplastin time measures the activities of factors...
XII, XI, IX, VIII, X, and V, and prothrombin, assuming that the fibrinogen level is normal. Conversely, the prothrombin time measures not only the activities of factor VII, but also factors X, V, and prothrombin. Normal partial thromboplastin times and normal prothrombin times in a bleeding patient thus exclude, with a fair degree of certainty, a major abnormality in the clotting event.

Fibrin formation is followed by clot retraction. During clot retraction the fibrin fibers shorten. This shortening is due to a protein derived from the platelets, known as thrombosthenin. Thrombosthenin has striking similarities to actin and myosin and their interaction to actomyosin. The actual mechanism of shortening of thrombosthenin is identical to the shortening of muscle fibers; calcium ions and ATP have to be present. The ATP is required as the source of energy for clot retraction. It also is derived from the blood platelets.

Clot retraction is followed by fibrinolysis which, under physiological conditions, presumably serves to remove fibrin so that the fibroblast can facilitate the repair of the injury. Fibrinolysis is accomplished by a proteolytic enzyme called plasmin or fibrinolysin. This enzyme is derived from a precursor, known as plasminogen or profibrinolysin. Plasminogen, like most of the clotting factors, is produced in the liver but is also carried and possibly even produced in the eosinophilic granulocytes.

Under physiological conditions, the activation of plasminogen to plasmin occurs by either an intrinsic or an extrinsic pathway. The intrinsic is provided by activated factor XII (Hageman factor) which converts a proactivator to an activator, which in turn converts plasminogen to plasmin (Figure 3). Therefore, activated Hageman factor (factor XIIa) activates not only the clotting system but also the fibrinolytic system intrinsically.

The extrinsic plasminogen activation occurs through tissue activators whose biochemical identity is not known at this time. Anatomically, this tissue activator resides in the intima of the blood vessels. It is not known with certainty whether the tissue activators act via the proactivator-activator mechanism or whether they directly affect plasminogen. In addition to these intrinsic and extrinsic activator mechanisms, the erythrocytes contain a plasminogen activator known as erythroklinase. The physiological significance of erythroklinase is not known.

Plasmin is a proteolytic enzyme capable of digesting a variety of plasma proteins, most notably fibrin and fibrinogen. Circulating plasmin thus induces a state of fibrinolysis and fibrinogenolysis. The resulting fragments of fibrin, respectively fibrinogen digestion, are termed fibrin, respectively fibrinogen degradation products (FDP). Initially large molecular weight split products, so-called fragments X and Y, are formed; these are also termed early split products (Figure 4).

These early degradation products are further degraded into smaller fragments, known as fragments D and E. The fragments X and Y possess a strong

![Figure 3](Image)

Intrinsic mechanism of plasminogen conversion by Factor XIIa (Hageman Factor).

- Factor XIIa
- Proactivator
- Activator
- Plasminogen
- Plasmin

![Figure 4](Image)

Fibrinogenolysis by plasmin results initially in the formation of fragments X and Y which are later degraded to fragments D and E.

- Fibrinogen
- Small Fragments
- Fragment X
- Fragment D
- Fragment E
- Fragment Y
- Plasmin
- Plasmin
anticoagulant action, in that they inhibit not only the polymerization phase of fibrin formation but also inhibit thrombin itself. Furthermore, they coat the surface of the platelets and thereby render them unaggregable. For this reason, in the presence of these split products, primary and secondary hemostasis are impaired.

Clinically, an activation of the fibrinolytic system in a patient can be easily assessed by quantitative fibrinogen determinations and by performing thrombin times. The levels of fibrinogen must be expected to be decreased due to the proteolysis by plasmin, whereas the split products inhibit thrombin activity, thereby prolonging the plasma thrombin times.

**Summary of the physiology of hemostasis**

As a response to a vessel wall lesion, platelets initially adhere to the site of injury, releasing ADP and serotonin which, in turn, brings about platelet aggregation. Platelet aggregation results in the formation of a first hemostatic plug or platelet plug, facilitating the arrest of bleedings from the small blood vessels. Due to the release of phospholipids from platelets, the clotting system is activated. During this process, a variety of blood clotting factors interact with these phospholipids and calcium ions, eventually leading to the formation of fibrin from fibrinogen. As fibrin is formed, it becomes stabilized due to the action of the activated factor XIII.

After stabilization, the fibrin clot retracts, a phenomenon in which platelets, once again, play a major role. They not only release the actomyosin-like protein, thrombosthenin, but also the necessary ATP, and thereby the source of energy. Following clot retraction and in preparation for the repair of the tissue, the formed fibrin is lysed by the enzyme plasmin which, in turn, is released from plasminogen upon activation of the fibrinolytic system. The enzyme plasmin not only lyse fibrin but also fibrinogen, leading to the formation of fibrin, respectively fibrinogen degradation products. The early fibrinogen split products known as fragments X and Y have a strong anticoagulant action of the primary and secondary hemostatic processes.

**Bleeding disorders**

Bleeding disorders represent a defect in any one of the various mechanisms previously described. Principally, they can be divided into two major categories: (1) inherited bleeding disorders, and (2) acquired bleeding disorders.

Since hemostasis is accomplished by the interplay of the vessel wall, platelets, and coagulation, the inherited bleeding disorders can be divided into three major subgroups. These are: (1) so-called coagulopathies, if the abnormality resides in the coagulation system; (2) so-called thrombocytopenias, if the platelets are involved; and (3) telangiopathies, if the blood vessels are affected. As a general rule, the congenital coagulopathies are characterized by the lack of the activity of one of the known coagulation factors. This lack of activity is

| Table 1 |
| Congenital coagulopathies |
|--------------|----------|
| Hypofibrinogenemia | Fibrinogen |
| Dysfibrinogenemia | Factor XIII |
| Fibrin Stabilizing Factor "Deficiency" | Factor II |
| Hypoprothrombinemia | Factor V |
| Dysprothrombinemia | Factor VII |
| Parahemophilia | Factor X |
| Factor VII "Deficiency" | Factor VIII |
| Factor X "Deficiency" | Factor IX |
| Abnormal Factor X | Factor XI |
| Hemophilia A- | Hageman Trait |
| Hemophilia A+ | Williams Trait |
| von Willebrand's Disease | Fitzgerald Trait |
| Hemophilia B- | Factor XII |
| Hemophilia B+ | Fletcher Trait |
often referred to as a deficiency. However, this term does not necessarily imply the complete absence, that is the lack of synthesis, of the factor in question; but rather, it may reflect a functional abnormality of the coagulation factor. For each one of the coagulation factors known to participate in the coagulation mechanism, we recognize a congenital abnormality (Table 1).

As shown for the fibrinogen molecule, we differentiate a congenital hypo-or afibrinogenemia from a congenital dysfibrinogenemia. In the former, we have the complete absence of the protein from the plasma, that is, the liver fails to synthesize the protein; whereas in the latter, we deal with the presence of the protein but in a functionally abnormal form. This dual form of abnormality is now also known for certain other clotting factors. In analogy to the abnormal hemoglobins, it has become customary to name the abnormal clotting factors by the city of their discovery. In the case of hemophilia A and hemophilia B, the terminology A, respectively B, implies the absence of factor VIII or factor IX, whereas the designation A+ and B+ reflects the physical presence of the protein in plasma but apparently in a functionally altered form.

With the exception of hemophilia A, hemophilia B, and von Willebrand's disease, the congenital coagulopathies are rare, and in most instances, are known and have been properly diagnosed since early childhood. The management of these patients occurs with the aid of factor concentrates, and for most of the individual clotting factors, the pharmaceutical industry has manufactured respective concentrates.

By viewing Figure 2, the exact nature of the defect can be established. We can also recognize which of the two tests, partial thromboplastin time or prothrombin time, might be abnormal in any one of the congenital coagulation factor deficiencies.

The congenital abnormalities related to the blood platelets, the so-called thrombocytopathies, can manifest themselves as quantitative or qualitative abnormalities. The hereditary thrombocytopenia is a rather rare disease that is marked by a low platelet count. The qualitative platelet abnormalities can affect each one of the platelet functions known, so that we can recognize congenital abnormalities related to platelet adhesion, related to platelet aggregation, related to the proper release of phospholipids for coagulation, and related to clot retraction. Table 2 lists some of these congenital platelet abnormalities. Again, these congenital forms of platelet abnormality are relatively rare and usually are diagnosed in early childhood. Their management occurs with the administration of platelet concentrates.

The congenital disorders affecting primarily the blood vessels are termed telangiopathies. In these patients, hemostasis is normal, but the bleeding is due to a vascular abnormality. The two most commonly encountered disorders are hereditary hemorrhagic telangiectasia (Morbus Osler) and hereditary familial purpura simplex (Morbus Davis). In contrast to the congenital bleeding disorders which generally affect one clotting factor function or one platelet function only, the acquired bleeding disorders are not only much more frequent but also much more complex in nature. As a general rule, and again in contrast to the congenital bleeding disorders, usually more than one factor is involved. Frequently, in addition, the platelets are affected. Nevertheless, the acquired co-

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td><strong>Congenital thrombocytopathies</strong></td>
</tr>
<tr>
<td><strong>Quantitative</strong></td>
</tr>
<tr>
<td>Congenital thrombocytopenia</td>
</tr>
<tr>
<td><strong>Qualitative</strong></td>
</tr>
<tr>
<td>von Willebrand's disease (Adhesion)</td>
</tr>
<tr>
<td>Storage pool disease (Aggregation)</td>
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<tr>
<td>Thrombocytopathy A (Phospholipids)</td>
</tr>
<tr>
<td>Thrombasthenia glanzmann (Clot Retraction)</td>
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</table>
agulopathies can be categorized in several groups as is demonstrated in Table 3.

### Table 3

**Acquired bleeding disorders**

<table>
<thead>
<tr>
<th>Consumption coagulopathy, DIC</th>
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<tbody>
<tr>
<td>Impaired procoagulant production</td>
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<tr>
<td>Circulating anticoagulants</td>
</tr>
<tr>
<td>Dysproteinemias</td>
</tr>
<tr>
<td>Massive blood replacement</td>
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<tr>
<td>Thrombocytopenias</td>
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<tr>
<td>Telangiopathies</td>
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**Consumption coagulopathy syndrome**

One of the most complex acquired coagulopathies is *consumption coagulopathy* or disseminated intravascular coagulation (DIC). This syndrome is characterized by a generalized activation of the coagulation system in vivo, leading to the conversion of plasma to serum. In this process, fibrinogen is converted to fibrin, prothrombin is converted to thrombin; in the latter process, platelets, factor V, and factor VIII are consumed. The resulting hypofibrinogenemia, hypoprothrombinemia, thrombocytopenia, factor V, and factor VIII deficiency leads to a complete breakdown of the hemostatic mechanism, causing a serious diffuse bleeding problem. The bleedings are thus due to the consumption of certain coagulation constituents. For this reason the terminology used is *consumption coagulopathy*.

Consumption coagulopathy can be precipitated by either a massive invasion of the circulation with tissue thromboplastin (extrinsic activation), or by a massive intravascular release of phospholipids from platelets (intrinsic activation). Since erythrocyte stroma contains the same phospholipids as platelets, a massive hemolytic episode can equally well trigger consumption coagulopathy. Consumption coagulopathy is never a disease per se, but a complication of another underlying disease which also triggers it.

Functionally speaking, consumption coagulopathy can present itself in three forms: (1) an activation of the clotting and the fibrinolytic system, (2) an activation of primarily the clotting system, and (3) an activation of primarily the fibrinolytic system.

### Table 4

**Examples of disease entities that can be associated with the three functional forms of consumption coagulopathy**

1. *Clotting plus lysis (Secondary lysis)*
   - Abruptio placentae
   - Dead fetus syndrome
   - Amniotic fluid embolism

2. *Clotting without lysis*
   - Generalized Shwartzman equivalents
   - Thrombotic thrombocytopenic purpura
   - Purpura fulminans
   - Hemolytic uremic syndrome
   - Shock

3. *Lysis without clotting (Primary lysis)*
   - Post-surgery hemorrhages
   - Prostatic surgery (carcinoma)
   - Extracorporeal hemocirculation
   - Liver cirrhosis

Table 4 illustrates a few examples of disease entities that are most commonly found with one or the other of the three functional forms of consumption coagulopathy. In patients with abruptio placentae, consumption coagulopathy is triggered by the invasion of the maternal circulation with tissue thromboplastin from the partially or totally separated placenta. This initiates the activation of the clotting system extrinsically; but as the first traces of thrombin are formed, the platelets aggregate and the intrinsic system becomes activated as well. This, in turn, leads to a massive consumption of fibrinogen, prothrombin, platelets, factor V, and factor VIII; the result is a breakdown of the hemostatic mechanism with the ensuing bleedings.

Due to the fact that placental tissue also contains activators of the fibrinolytic system, plasminogen is simultaneously converted to plasmin, which then dis-
solves the fibrin as it forms. Plasmin, however, as previously pointed out, not only breaks down fibrin but also fibrinogen, causing the formation of the fibrin(ogen) degradation products with their anticoagulant action on the clotting system. Inasmuch as the fibrinolysis further compounds the bleeding problem, it basically provides the patient with an opportunity to dissolve the fibrin and, therefore, prevent its deposit in the vasculature. For this reason, the prognosis of abruptio placentae is basically good if the acute bleeding episode can be handled promptly.

The activation of the clotting and lytic systems in dead fetus syndrome and in amniotic fluid embolism basically follows the same pathophysiological mechanism that was just described for abruptio placentae. The fibrinolysis associated with clotting is termed secondary fibrinolysis.

It is important to recognize that, in this particular group of disease entities, consumption coagulopathy is initiated by means of tissue thromboplastin coming into contact with the blood. What this means is that there is a variety of other disease entities in which tissue thromboplastin can potentially come into contact with the circulating blood. All of these disease entities also are then potential disorders which can trigger consumption coagulopathy.

Generally speaking, the second functional form (namely, the form where only the clotting system is activated without the participation of the fibrinolytic system) is characterized by the deposition of fibrin in the microcirculation in the form of microthromboses or microemboli. These events, in turn, lead to organ necrosis, especially bilateral renal cortical necrosis, which then leads to uremia if the patients survive the acute consumption coagulopathy. Due to the intravascular fibrin deposition, the prognosis of these patients is generally very poor. Table 4 lists a few disease entities associated with this form of consumption coagulopathy.

The generalized Shwartzman reaction is usually produced in rabbits by the infusion of endotoxin. This leads to consumption coagulopathy associated with bilateral renal cortical necrosis and other micronecroses. This same reaction can be observed in humans with an identical pathology when endotoxin, especially in association with pregnancy, comes into contact with the organism. In these instances, the endotoxin itself triggers the clotting system intrinsically by virtue of bringing about a massive intravascular platelet aggregation, followed by the massive release of phospholipids. Patients with infected abortions, chorioamnionitis, missed abortions, but also meningococcal sepsis and other forms of sepsis can encounter this type of consumption coagulopathy.

It is recognized now, however, that not only endotoxin, but also microorganisms as well as viruses, can initiate a massive intravascular platelet aggregation with a massive release of phospholipids. In the cases of thrombotic thrombocytopenic purpura, purpura fulminans, and in the hemolytic uremic syndrome, possibly antibody-antigen reactions trigger the clotting system intrinsically. All forms of shock may also lead to consumption coagulopathy, whereby metabolic acidosis may play an important role in triggering the clotting system.

From this, one can clearly infer that all disease entities which are associated with a massive intravascular platelet breakdown, respectively with a massive intravascular erythrocyte breakdown (hemolysis), are disease entities which can precipitate consumption coagulopathy.

As indicated earlier, the extremely poor prognosis of these patients is due to the lack of the fibrinolytic system being activated simultaneously. The reason for this is unknown, but it is conceivable that the mechanism for failure resides in the activation mechanism of the clotting system, namely the platelets. Platelets do not contain activators of plasminogen, and for this reason only, the clotting system is activated.
The functional forms of consumption coagulopathy where only the fibrinolytic system is activated (the so-called primary fibrinolytic states) are basically rare; and quite often, it is difficult to establish the proper differential diagnosis between primary and secondary fibrinolysis. In these forms of consumption coagulatory plasmin is generated from plasminogen which, in turn, brings about the consumption of fibrinogen with the formation of fibrinogen degradation products.

In addition to fibrinogen, plasmin may also digest factors V and VIII, thus impairing the hemostatic mechanism further. There may be a variety of stimuli which can become operative in these instances, but only hypoxia and anxiety shall be mentioned here. As can be seen from Table 4, many post-surgery hemorrhages, bleedings associated with prostatic surgery and prostatic carcinoma, as well as patients after extracorporal hemocirculation and patients with liver cirrhosis may have primary fibrinolysis.

Before attempting to manage these forms of consumption coagulopathy, it is imperative that the proper diagnosis be established—one which not only entails the diagnosis of consumption coagulopathy, but also identifies the proper functional form of consumption coagulopathy. In treating these patients for consumption coagulopathy, it should always be kept in mind that the underlying disease entity also has to be treated, since it is responsible for triggering the actual consumption coagulopathy.

**Further causes of acquired coagulopathies**

Another complex group of acquired coagulopathies results from impaired procoagulant production. These are bleeding problems associated with liver disorders, vitamin K malabsorption, and bleedings associated with oral anticoagulant therapy. It was pointed out previously that virtually all clotting factors, except for factor VIII, are synthesized in the liver. For this reason, liver disorders which affect the function of the liver parenchymal cell will result in impaired production of virtually all clotting factors. The factors most sensitive to disturbed liver function are the so-called vitamin K-dependent factors, that is, prothrombin, factors VII, IX, and X.

In severe forms of liver cirrhosis, however, one will find also the other clotting factors decreased. Due to the low level of these clotting factors, hemostasis may be impaired, resulting in a hemorrhagic diathesis. In addition, liver cirrhosis is frequently associated with a thrombocytopenia which is due to the associated splenomegaly. Furthermore, and as indicated earlier, primary fibrinolysis may be seen in patients with liver cirrhosis. In these instances, the fibrinolytic system is possibly activated by activators released from the diseased liver. Last, but not least, patients with severe cirrhosis (especially when approaching hepatic coma) may also develop intravascular clotting in the form of disseminated intravascular coagulation with secondary fibrinolysis.

The vitamin K malabsorption syndrome basically affects only the vitamin K-dependent factors, that is, prothrombin, factors VII, IX, and X. These forms of coagulation disturbance may be encountered in patients with long-lasting biliary obstruction, as well as in patients with some form of sprue, causing severe diarrhea. The parenteral administration of vitamin K will usually correct this type of clotting defect.

Oral anticoagulant therapy is usually conducted with derivatives of coumarin or indandione. These drugs replace the vitamin K in the synthesis of the clotting factors, prothrombin, factors VII, IX, and X at the liver parenchymal cell level. If the therapy is not adequately monitored, bleedings can be encountered due to the low level of these four clotting constituents.

Another possible cause of serious acquired bleedings can be circulating anticoagulants. They can be present in the form of either immunoantibodies or in the form of heparin. Immunoantibodies can be found against many coag-
ulation factors including the platelets. The presence of such an immune antibody usually results in a complete neutralization of the biological activity of the factor. For reasons unknown, most of the immune antibodies are directed against factor VIII. In most instances, these antibodies develop as a consequence of a blood transfusion or blood component infusion, but they can also occur in otherwise healthy persons without the prior stimulation by blood or blood components. Some patients have developed immune antibodies in association with pregnancy, while others may have systemic lupus.

Heparin is a powerful anticoagulant that produces a very effective block of the activation of the clotting system. The primary action of heparin is on thrombin itself. In the presence of heparin, therefore, no fibrinogen can be converted to fibrin. If patients are treated with heparin and not properly monitored, bleedings can occur. The management of these patients consists of the immediate neutralization of heparin with protamine sulfate.

Another form of acquired coagulopathy can be encountered in patients with abnormal proteins, that is dysproteinemias. Dysproteinemias such as macroglobulinemia Waldenstrøem, cryoglobulinemia, and multiple myeloma may produce a bleeding problem. This can be caused by one of two mechanisms: either the interference of polymerization of the fibrin monomers by the circulating abnormal proteins, or the coating of the blood platelets by these abnormal proteins, creating an inability of the platelets to adhere and aggregate.

Bleeding problems also arise in conjunction with massive blood transfusions. Massive blood transfusion is, in this case, defined as 8 or more units of blood per 24 hours. The bleeding problems relate intimately to the storage changes that occur in the ACD blood. One of the most frequently encountered problems is a loss of aggregability within the first 48 hours. The massive replacement of a patient's blood with this type of blood then creates a major thrombocytopenia-type bleeding problem.

In addition, certain clotting factors (factors V and VIII) lose their activity while the blood is stored. Furthermore, one can encounter increased fibrinolytic activity in these units of blood which may be brought about by the release of proteolytic enzymes from the slowly decaying leukocytes. For these reasons, patients with massive blood replacement may have not only low clotting factor profiles and slightly increased fibrinolytic activity but, most importantly, a thrombocytopenia.

Acquired thrombocytopenias may present as quantitative or qualitative defects. The quantitative platelet defects are either thrombocytopenias or thrombocythemia. Acquired thrombocytopenias are probably the most commonly acquired bleeding problems. They can be divided into those that are due to impaired platelet production or those that are due to increased platelet utilization. The thrombocytopenias caused by impaired platelet production are usually characterized by the absence of megakaryocytes in the bone marrow. Certain drugs and chemicals, as well as the growth of malignancies in the bone marrow, can create this form of thrombocytopenia.

Those thrombocytopenias that are caused by increased peripheral platelet utilization are either due to immune antibodies against platelets or are the result of certain drugs, infectious diseases, splenomegaly, autoimmune disease, or occasionally are a manifestation of consumption coagulopathy.

The thrombocythemia are characterized by an excessive number of platelets in the peripheral blood. They can be found in association with polycythemia vera or chronic myeloid leukemia.

Acquired thrombocytopenias in the sense of a qualitative platelet defect are found in association with a variety of disease entities, most frequently uremia. Retained metabolites are responsible for...
impairing platelet function which most often affects platelet aggregation. However, thrombocytopathies are also found in conjunction with myeloproliferative diseases, pernicious anemia, liver cirrhosis, systemic lupus, sepsis, and with stress ulcers. In many instances, the exact pathophysiological mechanism by which these acquired platelet functions arise is not known.

In addition to the thrombocytopathies associated with disease entities, a number of abnormal platelet functions can be noted in conjunction with drugs. Papaverin, low molecular weight dextran, acetylsalicylic acid-containing drugs, penicillin, and nitrofurantoin are just a few examples of drugs that can produce these thrombocytopathies.

Parallel to the congenital telangio-pathies, there are also acquired telangio-pathies. The most common ones are scurvy, purpura senilis, and anaphylactoid purpura (Schoenlein-Henoch). In these cases, the hemostatic mechanism is functioning properly but the abnormality resides in the blood vessel itself.

Summary

The bleeding disorders basically present as congenital or acquired bleeding diseases. Whereas the congenital bleeding disorders are usually single clotting factor abnormalities or single platelet function abnormalities, the acquired bleeding disorders are much more complex in nature. With rare exceptions, however, all of the bleeding disorders can be explained on the basis of abnormalities associated with the basic physiological mechanism of hemostasis.

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