Fibrinolysis and Afibrinogenemia

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On occasion, patients develop a severe hemorrhagic diathesis in which the blood clots poorly, if at all, and the laboratory reports a striking reduction (hypofibrinogenemia) or a total absence of plasma fibrinogen (afibrinogenemia). Such states tend to appear with dramatic suddenness, are often catastrophic and frequently complicate other problems (shock, obstetrical accidents, malignancies, transfusion reactions, extensive cardiopulmonary surgery or postoperative states). Under these circumstances, the need for therapy is urgent and often empirical since it is difficult to work out the mechanism and to decide upon the best course of action.

The presence of hypofibrinogenemic disorders (afibrinogenemia is simply a more severe form) usually can be suspected at the bedside; blood specimens taken from these patients either do not clot at all or the clot forms abnormally; further, the latter, when incubated, may dissolve in a matter of minutes to several hours (fibrinolysis is also present) or rapidly shrivel into a persisting small ball (hypofibrinogenemia without fibrinolysis). The clinical suspicion may be fortified further by the use of the Page technique, wherein 1 ml. of blood is added to a test tube containing 0.1 ml. (1,000 units/ml.) topical thrombin. If no clot forms, afibrinogenemia is suspected; the findings with hypofibrinogenemia, with and without associated fibrinolysis, are as previously described. An even more useful bedside test, so as to exclude the influence of heparin or other circulating anticoagulants, is the FITEST. In this procedure, plasma, in several dilutions, is added to a glass slide containing polystyrene particles coated with antifibrinogen serum (FI reagent).* If no agglutination occurs, afibrinogenemia is present; in the hypofibrinogenemic states, agglutination occurs only when the plasma is undiluted or present in low dilutions. The instructions for this technique, when properly followed, can give a semi-quantitative estimation of the fibrinogen level; the test, in our hands, has rarely given misleading information. Final confirmation of hypofibrinogenemia is provided by the laboratory where quantitative estimation of the fibrinogen concentration is carried out by a specific chemical technique.

To better understand the problem under discussion, this presentation will focus initially on the factors regulating the normal plasma fibrinogen level; then consider the hypofibrinogenic disorders; and finally concentrate on the participation of fibrinolysis in these disorders. It should be emphasized, however, that fibrinolysis represents only one mechanism by which hypofibrinogenemia is produced.

Factors Regulating Plasma Fibrinogen

Normally fibrinogen represents about 4 per cent of the plasma proteins; of the 20 g. estimated as being in the body fluids, more than half circulates in the vascular compartment and the remainder is present in the interstitial space. Fibrinogen plays a unique role as the key component of a most important biologic defense mechanism; it represents the readily available and mobilizable form of fibrin, the insoluble fibrous protein which participates in hemostasis in areas of vascular injury or as an important constituent of the inflammatory reaction. Therefore it is not surprising that sensitive, yet poorly understood, homeostatic mechanisms exist for regulating the plasma fibrinogen level; in the healthy male this concentration is maintained at approximately 270 mg./100 ml. and slightly higher in the female, 300 mg./100 ml. When one considers that the normal turnover of fibrinogen is rapid (the half life of about 4 days is

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considerably shorter than for albumin and gamma globulin), maintenance of the plasma fibrinogen level requires a constant high rate of synthesis by the liver, as well as active mechanisms for continuous disposal.

The factors regulating the hepatic synthesis of fibrinogen are poorly understood. Though we recognize that the liver is capable of rapidly increasing the rate of synthesis in response to hypo- or a fibrinogenemic episodes (implying that a feedback mechanism may be operative), observations suggest that other factors (hormones, acute inflammatory reactions, etc.) may also influence the rate of fibrinogen production.

The pathways for the normal disposal of fibrinogen are even more obscure. Three hypotheses have been entertained: (1) fibrinogen is constantly being converted to fibrin (continuous intravascular coagulation) and the latter is degraded by naturally occurring fibrinolytic mechanisms or cleared by the reticulo-endothelial system; (2) fibrinogen is continuously hydrolyzed directly by plasmin, the fibrinolytic enzyme; (3) the body has other specific mechanisms for the clearance of fibrinogen. Only the first two of these considerations have been investigated to any extent and, there is, as yet, little evidence to support either of them.

Hypofibrinogenemia

Despite uncertainties concerning the normal regulatory pathways governing plasma fibrinogen levels, hypofibrinogenemic states must in the last analysis result from either a decreased rate of synthesis or increased rate of removal, or a combination of both. The following classification of hypofibrinogenemic states is designed to include the mechanisms most commonly encountered clinically:

Deficient Synthesis:

- Genetic deficiency, e.g., congenital a fibrinogenemia.
- Severe liver disease, e.g., massive hepatic necrosis, far advanced hepatic cirrhosis, etc.
- Other causes of deficient hepatic synthesis.

Increased Loss:

- Loss by extensive hemorrhage or into areas of extravascular fibrin deposition, e.g., premature separation of placenta (other clotting mechanism usually operate as well).
- Intravascular defibrination or disseminated intra-
- vascular clotting, e.g., amniotic fluid embolism, snake bite, etc.
- Increased fibrinogen proteolysis, e.g., pathological fibrinolytic states.
- Combined intravascular clotting and fibrinolysis.

Deficient Synthesis

Genetic Deficiency. Congenital a fibrinogenemia is a rare, genetically determined disorder. Though such patients are completely lacking in fibrinogen, they usually exhibit only a mild hemorrhagic diathesis except after severe trauma; thus a lack of fibrinogen by itself is not a sufficient cause for bleeding unless there is an underlying wound or vascular injury.

Excluding this rare congenital disorder, patients with acquired hypofibrinogenemic states, particularly those in whom fibrinogen levels are less than 100 mg./100 ml., commonly exhibit a serious hemorrhagic diathesis. This stems from the fact that the mechanisms responsible for the hypofibrinogenemia also produce other important coagulation abnormalities; under these circumstances, the low fibrinogen level represents only one significant contributing factor to the bleeding problem. It is emphasized, therefore, that the real significance of hypofibrinogenemia lies not in the reduction of fibrinogen itself but in its occurrence in association with a number of complex and frequently severe coagulation disorders; since the hypofibrinogenemia is easily demonstrated, it serves to call attention to the total hemorrhagic problem under consideration.

Severe Liver Disease. The most common type of acquired hypofibrinogenemia resulting from impaired synthesis is that seen in association with severe hepatic disease. Patients with massive hepatic necrosis (“acute yellow atrophy”) due to toxic (e.g., phosphorus poisoning) or other causes will usually have a rapidly falling fibrinogen level and, if they live long enough, will exhibit extensive cutaneous hemorrhage and bleeding at other sites. The striking hypofibrinogenemia in this state is incidental, for all other coagulation factors are similarly depressed, and the bleeding problem, though severe, is of relatively minor importance in comparison to the total hepatic problem. Patients with far advanced hepatic cirrhosis, no longer able to maintain the normal hepatic
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synthetic capacity, also suffer from multiple deficiencies of coagulation factors, including fibrinogen, and exhibit a hemorrhagic tendency; in addition, they have increased blood fibrinolytic activity which contributes to the hemostatic problem. Exclusive of the problem of gastrointestinal bleeding associated with portal hypertension, these patients may well bleed excessively after operation, particularly following shunting procedures. In these patients, it has been demonstrated that the use of epsilon aminocaproic acid (Amicar), a potent inhibitor of fibrinolytic activity, will ameliorate the bleeding state. The use of newly developed human prothrombin complex preparations, containing prothrombin and Factors VII, IX and X, should likewise ultimately prove useful under these circumstances.

Other Causes for Deficient Hepatic Synthesis. Severe central liver cell necrosis and hepatic dysfunction accompany protracted episodes of shock, but the extent to which these may impair synthesis of fibrinogen and contribute to the development of hypofibrinogenemia has not been determined; eventually, however, they may be shown to contribute significantly to the pathogenesis of some of the hypofibrinogenemic disorders.

INCREASED LOSS

Loss by Extensive Hemorrhage or into Areas of Extravascular Fibrin Deposition. Hemorrhage in itself may serve as a mechanism for fibrinogen depletion. Calculations reveal that a loss of a liter of blood will reduce the circulating fibrinogen pool by approximately 1.8 g. and with spontaneous restoration of blood volume, the plasma fibrinogen level will be reduced by 50 mg./100 ml. until the deficit is made up by fibrinogen synthesis or mobilization from other sources. For this reason it has been suggested that severe hemorrhage may be responsible for some of the hypofibrinogenemic disorders. For example, Pritchard and Wright have claimed that the hypofibrinogenemia which accompanies premature separation of the placenta can be accounted for by the fibrinogen sequestered as fibrin in the retroplacental clot. Though it is likely that blood loss contributes to a fibrinogen deficit, it is difficult to explain such a deficit as the sole mechanism for severe hypofibrinogenemic states.

Disseminated Intravascular Coagulation. Acute Form: Present evidence indicates that most of the acutely acquired hypogenemic disorders encountered clinically are due to disseminated intravascular coagulation. Interest in this phenomenon was first aroused by observations that slow infusions of thromboplastin or thrombin into animals caused intravascular defibrination with progressive consumption of blood coagulation factors and, eventually, a severe hemorrhagic diathesis. This mechanism is now generally accepted as being operative in the obstetrical catastrophies following abruptio placentae, amniotic fluid embolism and retained dead fetus. Thromboplastic substances, derived from the placenta or amniotic fluid, are suspected of being liberated into the maternal circulation and producing extensive intravascular defibrination followed by a hemorrhagic diathesis. The same mechanism has been shown to operate in the severe bleeding following incompatible blood transfusions; here the intravascular lysis of red cells presumably liberates corpuscular stromal thromboplastin and triggers the defibrination.

The characteristic clotting profile which occurs in these patients is one of severe hypofibrinogenemia and sharply reduced levels of prothrombin, platelets and many other coagulation factors, most notably Factors V and VIII (labile substances known to be consumed in the process of clotting). On occasion, acceleration of thromboplastin generation can be demonstrated in the laboratory, and this serves as suggestive evidence of a thrombosing state. In addition, the body counters with a secondary fibrinolytic response, and the blood frequently exhibits increased fibrinolytic activity and all its consequences. Because of the virtual disappearance of fibrinogen, platelets and other clotting factors, the fully developed stage of this syndrome is not too difficult to recognize, and the severe hemorrhagic diathesis can be attributed readily to the thrombopenia, consumption of blood clotting factors, striking hypofibrinogenemia and the consequences of the fibrinolytic state.

From a practical standpoint, the sudden appearance of severe hypofibrinogenemia
in a patient should immediately raise the question of disseminated intravascular coagulation (also referred to as a "consumption coagulopathy"). This will almost invariably prove to be cause if afibrinogenemia is present (i.e., complete defibrination) or if the findings are typical of a consumption coagulopathy, i.e., hypofibrinogenemia in association with severe thrombopenia and striking reductions in prothrombin, and Factors V and VIII. When the findings are not typical, yet intravascular clotting is suspected on clinical grounds, heparin may be administered judiciously as a diagnostic test (provided the patient is not bleeding actively) to determine whether it will reverse the coagulation disorder.

Fortunately, afibrinogenemic episodes are usually short-lived and by the time the patient is seen, the acute defibrination is usually over; thus if the patient can be supported adequately by the commonly used measures for treatment of hemorrhage and shock, the coagulation disturbance will disappear spontaneously over the next 24-48 hours. The use of fibrinogen intravenously (4-6 g. and repeated as necessary), though obviously of value, should be restricted to those instances where there is excessive or uncontrolled bleeding or where surgery is contemplated; otherwise the patient may be unnecessarily exposed to a 20 per cent risk of hepatitis and, occasionally, to further intravascular clotting. Similar therapeutic principles pertain when, under the same clinical situations (obstetrical catastrophes, transfusion reactions, etc.), hypofibrinogenemia rather than afibrinogenemia is observed.

SUBACUTE FORM: A similar clinical state through less dramatic and frequently more protracted and slower in evolution, so as to mimic ultimately a more acute form of disseminated intravascular coagulation, is now being described in an ever increasing number of situations. Unfortunately there is a considerable variation in the laboratory findings, nor are these as striking as in the acute, more devastating syndrome; as a result the diagnosis is more difficult to establish. Nevertheless well-documented pathological reports of the occurrence of disseminated intravascular clotting have appeared in purpura fulminans, Waterhouse-Friderichen syndrome, carcino-

matosis, lymphoma, acute promyelocytic leukemia, thrombotic thrombocytopenic purpura, the Kasabach-Merritt syndrome, viper snake bites and overwhelming infections (e.g., Rocky Mountain spotted fever and Pseudomonas septicemia). The syndrome has also been observed as a complication of extra-corporeal circulation, and has appeared following extensive surgery, particularly on the lung or following protracted hemodynamic shock of various types. Obviously these represent a heterogeneous group of cases and it is quite likely that the mechanisms responsible for disseminated intravascular coagulation may be somewhat different in each; but they have provided clinical counter-parts for a variety of observations in animals made in recent years. Included among the latter are:

1. The defibrination syndromes produced by the systemic administration of various thrombolytic materials or other activators of the coagulation mechanism (e.g., snake venom).

2. The demonstration of the occurrence of intravascular clotting in severe forms of hemodynamic shock; in antigen-antibody reactions; and following injection of a variety of bacterial toxins.

3. The importance of intravascular coagulopathy in the pathogenesis of the Schwartzman phenomenon, both of the local and generalized type.

4. The striking effects of endotoxin on platelets and the coagulation mechanism, and prevention of some of the pathological changes by anticoagulants.

5. The presence of readily mobilizable and dynamic systems for the rapid clearance of fibrin from the vascular bed: reference here is to fibrinolysis and the phagocytic activity of the reticuloendothelial system.

The experimental observations made relative to the factors that may precipitate intravascular fibrin deposition are so striking and intriguing that one is tempted to conclude that intravascular clotting is probably one of the more frequent events in human pathology and that intravascular fibrin deposition, as a response to injury or a variety of other stimuli, is a frequent occurrence. One may postulate that under ordinary circumstances, minor deposits
are readily cope with by the phagocytic activity of the reticuloendothelial system and/or the body's fibrinolytic mechanisms; however, when the amount of fibrin formed is greater than the total available potential of these clearing systems, or when these systems are overwhelmed then clinically significant pathological sequelae may follow.

Despite the expanding interest in disseminated intravascular coagulation and increasing evidence for its significance at the clinical level, there is a need to guard against the tendency to over-interpret its incidence or importance as well as the too liberal transfer of data from models. Nevertheless this is a fascinating area for clinical investigation and one likely to provide a significant contribution to medicine.

Various therapeutic principles govern the management of the protracted forms of disseminated intravascular coagulation; however, heparin is an agent of choice. Experience with the use of rapid anticoagulation in this disorder is still quite limited, for not only must one recognize the syndrome of intravascular coagulation but the decision to infuse heparin in the face of a hemorrhagic diathesis is not an easy one. The first report of the use of heparin for this problem was by Little in 1959, who successfully used this agent in the management of a case of purpura fulminans. Since then, there have been several reports of its use in a number of hypofibrinogenemic states associated with a hemorrhagic diathesis occurring in a variety of diseases and fulfilling the criteria for a disseminated intravascular coagulation syndrome. This literature has been reviewed recently by Rodriguez-Erdmann and by Verstraete and his associates, who reported several cases of their own. The latter authors indicate that heparin has proven so useful in the protracted form of disseminated intravascular coagulation that they routinely employ this agent as a diagnostic test to determine whether or not a hypofibrinogenemic state is due to an intravascular consumption coagulopathy. Despite the established value of heparin therapy in the treatment of purpura fulminans and in the management of the hypofibrinogenemic disorder seen with malignant diseases and other forms of protracted disseminated intravascular coagulation, the value of heparin in the management of the more acute episodes (e.g., those seen in overwhelming infections, the Waterhouse-Friderichsen syndrome and as a complication of shock, surgery, etc.,) remains to be established, particularly in the face of the hazards involved. Certainly in shock and the postoperative state, it would be most important to establish first that excessive bleeding is not due to a more direct cause (i.e., unligated blood vessel); at present, it would seem wise to await the further development of specific diagnostic tests before recommending the widespread use of heparin.

Other agents like dextran and thrombolytically active substances (streptokinase, etc.) also are being investigated as potential therapeutic measures in the management of widespread intravascular coagulation. Lasch, on the basis of his studies, has expressed the view that such agents may well find a useful place in the management of these disorders.

Increased Fibrinogen Proteolysis (Pathological Fibrinolysis). Excessive plasma proteolysis represents another major mechanism for the development of an acute (occasionally protracted) hemorrhagic diathesis associated with hypofibrinogenemia; such states are referred to as pathological fibrinolysis. Since this is a complex and rapidly evolving subject, and the fibrinolytic disorders may be either primary or complicate the disseminated intravascular coagulation syndromes, the following discussion is designed as a brief review of fibrinolysis and the fibrinolytic disorders.

Fibrinolysis in man is controlled and regulated by the activity of a proteolytic enzyme system termed the plasminogen-plasmin system. This enzyme system embraces a naturally occurring globulin in the form of the inactive precursor, plasminogen, that can be converted by activators or kinases (streptokinase, urokinase, staphylokinase) to plasmin, a proteolytic enzyme, active at neutral pH, and capable of digesting fibrin into a number of soluble fragments.

Plasminogen, a normal constituent of all body fluids and secretions, exhibits its highest concentration in plasma. Plasminogen activators, however, are concentrated in the body
tissues and vascular endothelium; though not well characterized, they appear to be highly specific proteolytic enzymes capable of converting plasminogen into plasmin. Plasmin is a proteolytic enzyme of relatively undifferentiated specificity. It has the capacity to hydrolyze peptide bonds adjacent to arginine and lysine residues and extensively digests fibrinogen in a manner and rate similar to its action on fibrin. Plasmin acts rapidly on a great many other biologically important proteins including antihemophilic (Factors VIII) and accelerator globulin (Factor V) and hydrolyzes many protein substrates commonly used in the laboratory (e.g., casein). In many respects plasmin has characteristics similar to but not identical with trypsin.

**Physiological Fibrinolysis:** For many years, the mechanism by which the organism utilizes plasmin, an enzyme of such undifferentiated specificity, to lyse fibrin selectively without simultaneously destroying other susceptible plasma proteins of biological significance, posed problems of considerable importance, particularly since it was known that over-activity of this system, in disease states, was productive of severe coagulation defects and a sometimes catastrophic hemorrhagic diathesis. Rapid strides were made in understanding how this enzyme system works in vivo when it was recognized that plasminogen was deposited in significant amounts whenever fibrin was laid down. This led to the development of a hypothesis which appears adequate to account for the facts; namely that, in vivo, plasminogen exists as a “two phase” system, as a soluble phase in the body fluids and a gel phase in thrombi and fibrinous deposits. The effect of activators on plasminogen at the two sites are dissimilar. Minor or slow activation of plasminogen in plasma, because of the presence of inhibitors, will not result in detectable signs of plasma proteolysis since the enzyme is effectively inactivated when formed; rapid activation of soluble plasminogen, however, produces excessive plasma proteolytic activity, and fibrinogen, the most abundant available substrate, is the chief target of degradation (fibrinogenolysis). On the other hand, activation of the gel phase or clot plasminogen produces fibrinolysis, even in the presence of low levels of activator, for here the enzyme is activated in close spatial relationship with substrate fibrin, and the reaction appears, initially at least, to be independent of the inhibitors in body fluids.

Under physiological circumstances, fibrinolytic phenomena are regulated by the release of a plasminogen activator, and the latter plays the key role in mediating fibrinolysis. The activator appears transiently in the circulation, following an appropriate stimulus, and directly raises the clot dissolving activity of the plasma without invoking the consequences of increased plasma proteolysis. This fibrinolytic mechanism is particularly effective when significant quantities of activator are present at the time fibrin formation occurs; under these circumstances, the activator is incorporated throughout the clot while the latter is forming, and the subsequent widespread activation of clot plasminogen leads to very rapid fibrinolysis.

Recent observations have demonstrated that the fibrinolytic mechanism in vivo appears to be continuously active and quite dynamic in response to appropriate stimuli. The plasma of healthy adults normally contains significant but slight degrees of activity of plasminogen activator, and this level rises sharply whenever there is increased circulating fibrinolytic activity (accelerated euglobulin or whole blood clot lysis time). Enhanced fibrinolytic activity is observed frequently in certain diseases, e.g., hematological neoplasia, cirrhosis of the liver and various infections; but more striking changes are produced by a variety of physiological and pharmacological stimuli, e.g., electroshock, pneumoencephalography, hypocglycemia, ischemia, anoxia, intense exercise and parenteral injections of adrenaline, aceylcholine, nicotinic acid and pyrogens. Current evidence indicates that the activator is released from the vascular endothelium into the circulation at sites of ischemia or other acute vascular changes, either of a vasoconstrictive or vasodilatory nature. The lysosomal granules of tissue cells also appear to be rich in plasminogen activator but the factors controlling the release from these sites are less well understood.

**Fibrinolytic Disorders:** Though, physiologically, fibrinolysis is accomplished without a significant increase in plasma proteolysis, certain clinical situations arise where there is excessive digestion of fibrinogen; this state is
associated with an acute or chronic coagulation disorder, and, when the onset is sudden, a serious hemorrhagic state may develop with severe bleeding, usually at the site of underlying disease or previous surgery or trauma. Though the blood of patients suffering from this disorder frequently demonstrates multiple coagulation defects, the most striking finding is poor and slow blood clotting, even upon the addition of thrombin, and the clot which forms is loose and friable. Subsequently the clot undergoes rapid spontaneous dissolution and, because of the latter phenomenon, the syndrome is referred to as pathological fibrinolysis or fibrinolytic bleeding. The severity of this disorder readily can be attributed to the particularly ineffective form of hemostasis present; clotting occurs slowly with the formation of an inadequate clot which subsequently dissolves.

The understanding of this hemorrhagic diathesis has come from studies which demonstrate that the products of the proteolytic digestion of fibrinogen and fibrin interfere with blood clotting, and that the addition of such products of proteolysis to normal blood reproduces, in vitro, the abnormal blood clotting seen in the fibrinolytic disorders. Further study of this problem has revealed that during the early phases of fibrinogen and fibrin proteolysis, large fragments are released which are capable of interfering both with the action of thrombin and the ability of platelets to aggregate. Ultimately, however, several fragments are formed which are incapable of being digested further by the action of plasmin. One of these fragments (sedimentation constant 5.27 S, molecular weight approximately 88,000), as well as its precursors, inhibits the interconversion of fibrinogen to fibrin; this inhibition does not appear to occur on the thrombin reaction per se; rather, the effect is to inhibit the subsequent steps, i.e., the spontaneous polymerization of fibrin monomer (the subunit of the long insoluble fibrin polymers of the normal clot). For this reason, these fragments are referred to as polymerization inhibitors, and, when present in large amounts, they delay normal polymerization and cause the formation of abnormal polymers which weaken and distort the final clot. This anomaly of polymerization has been termed defective fibrin polymerization and its significance dem-

strated, as a major factor in the coagulation defect underlying the hemorrhagic diathesis seen in clinically encountered fibrinolytic disorders. Under clinical circumstances this anomaly can be assessed by measuring the thrombin clotting time (providing there are adequate amounts of fibrinogen present, i.e., greater than 100 mg./100 ml.). In the presence of excess thrombin, the thrombin clotting time is virtually a measure of the polymerization time; as a result, the thrombin clotting time, though lacking in specificity, has proved to be a useful screening test. The delay in clotting is also reflected in a prolongation of the one-stage prothrombin time, and the latter, though less specific, also correlates well with the polymerization anomaly.

Pathogenetically, two major types of fibrinolytic disorder exist, i.e., the primary and secondary forms. In the primary fibrinolytic disorders, the condition is induced by a sustained increase in plasma proteolytic activity (hypoplasminemia) sufficient to digest large amounts of circulating fibrinogen (fibrinogenolysis). Whereas, in the secondary form (see section below, on combined Intravascular Coagulation and Fibrinolysis), the condition appears either as a response to or in association (simultaneous release of tissue thromboplastin and tissue activator) with intravascular clotting or defibrination. In latter type, the coexistence of clotting and fibrinolysis in large areas of the vascular bed results in the release of excessive amounts of breakdown products of fibrin into the circulation.

PRIMARY FIBRINOLYTIC DISORDERS: Three mechanisms exist for the production of the primary disorders (excessive plasma proteolytic activity with fibrinogenolysis). First, inordinate amounts of plasminogen activator (thrombolytic agents) may be administered for therapeutic purposes, or released endogenously from activator-rich neoplastic tissue (e.g., in metastatic prostatic carcinoma) or in response to profound stimuli, such as severe anoxia, shock or following extensive surgical procedures, particularly on the lung; this temporally overwhelms normal plasma inhibitory mechanisms, sustaining free levels of plasmin in the circulation for significant periods of time. Second, deficiencies in inhibitory mechanisms may exist in patients with disease, such as cir-
rhosis of the liver where the ability to clear activator from the circulation is deficient. Under these circumstances, the body cannot cope adequately with the release of plasminogen activator, in amounts that would ordinarily not produce significant hyperplasminemia. Finally, proteolytic enzymes other than plasmin, but also capable of degrading fibrinogen, may appear in the circulation and produce a similar state; such events have been described in the late stages of certain leukemias.

Examination of the blood of patients with sustained increases in circulating plasmin frequently demonstrates the following: delayed clotting and abnormal appearance of the blood clot; prolonged thrombin clotting time; prolonged prothrombin time (two-stage prothrombin time usually normal); delayed thromboplastin generation; reduced fibrinogen level (usually only moderate); large amounts of immunologically identifiable fibrinogen breakdown products; moderate reductions of Factors V and VIII; reduced plasminogen level; and increased fibrinolytic activity. Of these, the first six abnormalities can be traced to the effects of fibrinogen proteolysis; the other changes represent the proteolytic effects on other susceptible clotting components (Factors V and VIII) and evidence for increased activity of the fibrinolytic enzyme system (plasminogen activation and increased fibrinolytic activity).

Fortunately the polymerization inhibitors formed during fibrinogen or fibrin proteolysis are spontaneously cleared from the circulation; their half-life is approximately nine hours. Thus control of the underlying mechanism responsible for the fibrinolytic disorder is followed by spontaneous recovery; such recovery is usually rapid since the severity of the disorder is critically dependent upon the concentration of the breakdown products in the circulation.

Control of the primary fibrinolytic disorders can be accomplished rapidly by the administration of the synthetic amino acid, epsilon aminocaproic acid, a potent inhibitor of plasminogen activators. Shortly after the oral or intravenous administration of this agent in appropriate dosage (priming dose of 5 g. followed by 20–30 g. per day), plasma plasminogen activation ceases and the hemorrhagic diathesis usually subsides, frequently in dramatic fashion. Such therapy need be carried out only as long as the underlying pathogenetic mechanisms are operative. In most instances, 2–3 days of treatment are sufficient; however, in the fibrinolytic disorder occasionally encountered in metastatic carcinoma of the prostate, much longer periods of treatment are desirable. Epsilon aminocaproic acid also has proved useful in the management of severe post-prostatectomy bleeding; here the agent, which is excreted rapidly in the urine following oral or systemic administration, inhibits the action of urokinase, the naturally occurring urinary plasminogen activator which, by virtue of its ability to lyse clots, impairs hemostasis in the traumatized urinary tract. Trasylol, a plasmin and plasminogen activator inhibitor derived from ox lung, also has been claimed to be effective in the management of primary fibrinolytic disorders.

**Combined Intravascular Clotting and Fibrinolysis.** The secondary fibrinolytic disorders are seen in association with the disseminated intravascular coagulation syndromes when a simultaneous release of tissue thromboplastin and tissue activator occurs, or the disseminated clotting provokes a rapid release of endogenous plasminogen activator; under these circumstances, the activator, along with plasminogen, is rapidly incorporated into the fibrin deposits and followed by rapid fibrin dissolution. Thus, the coagulation consumption coagulopathies exhibit a hemorrhagic diathesis which is frequently further complicated by evidence of secondary fibrinolysis, as demonstrated by the presence in the blood of immunologically identifiable breakdown products (presumably fibrin); however the contribution of the latter both to the hemorrhagic diathesis and to the laboratory findings varies greatly from case to case. In such instances, the problem of intravascular coagulation is the more serious, but, on occasion, the presence of excessive evidence of fibrinolysis may mask the underlying thrombosing state. The latter instance may be difficult to unravel pathogenetically, a considera-

† Frequently it can be demonstrated that the serum from such patients will agglutinate the F1 reagent.
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tion of particular importance since the therapeutic indications depend upon the nature of the primary insult. Noteworthy is the observation that the blood of patients with the secondary fibrinolytic disorders is much less likely to demonstrate an increase in circulating fibrinolytic activity, since the extensive dissolution of fibrin is consequent to localized fibrinolytic phenomena rather than a generalized state of heightened fibrinolytic activity.

At present, antifibrinolytic agents are not recommended for use in the secondary fibrinolytic disorders. Here therapy is directed at controlling the intravascular coagulation; the use of antifibrinolytic agents in the absence of appropriate anticoagulation may prove hazardous by aggravating the underlying thrombosing tendency. In problem cases, where the differentiation between intravascular clotting complicated by secondary fibrinolysis and a primary fibrinolytic disorder may be extremely difficult, it has been suggested that the patient be treated with heparin and epsilon aminocaproic acid in combination. It is unfortunate that the guidelines for differentiating the primary from the secondary fibrinolytic disorders are still hazy, for there is a fair overlapping of findings; nevertheless recognition of the problem should result in the development of appropriate laboratory methods designed to make the therapeutic approach more scientifically grounded and effective. At present reliance on good clinical judgment (nature of disease state, etc.) and careful laboratory study (the amount of increased fibrinolytic activity and the severity and nature of the coagulation deficiencies, etc.) will usually help resolve this difficulty.

Conclusion

In recent years it has become apparent that an ever increasing number of medical, surgical and obstetrical states may be further complicated by the development of hypofibrinogenemia and a serious hemorrhagic diathesis which may profoundly affect the outcome for the patient. Since this is an area of active investigation, information concerning the pathogenesis, diagnosis and management of these disorders is rapidly accumulating, and new concepts continue to emerge.

The circumstances under which these events occur are most commonly those capable of precipitating disseminated intravascular clotting and/or abnormal states of fibrinolysis. These two phenomena, either singly or in combination, are responsible for most of the disorders.

Effective agents for the treatment of such problems are already available and newer ones are under development, but the scientific basis of this subject must be further elaborated before the therapeutic approach can be entirely rational.

References


RINGER'S LACTATE Persistent intraoperative hypotension, in which blood loss and the effect of drugs or anesthetics have been ruled out, may be due to the sequestration of large amounts of extracellular fluid into the operative area. The sequestered fluid is a transudate: electrolytes and water cross the cellular membrane in the same concentration that they are in blood plasma. Formerly, the main objection to the intraoperative use of replacement electrolyte solutions was that hypermetraemia and pulmonary edema could readily occur because of the depressed renal function caused by deep anesthesia. However, under modern conditions of light general anesthesia, with normal kidney function, the technique of operative hydration with electrolyte solutions is beneficial. Alexis Hartmann in 1929 developed such a solution for use as a vehicle for sodium r-lactate. Known as "Ringer's lactate" or "Hartmann's solution," it consists of modified Ringer's solution to which sodium r-lactate has been added. The use of this solution effectively aids the maintenance of blood pressure and fewer blood transfusions are required. With moderate blood loss, blood pressure can be maintained by giving this solution at the rate of 500 to 1,000 ml./hour as a supplement to minimal necessary blood transfusions. If blood loss is greater than 700 ml., much less blood replacement is necessary if Ringer's lactate is infused at rates greater than 1 liter/hour, i.e., the use of large amounts of this solution is more effective in reducing the number of required blood transfusions than is the use of moderate amounts. (Trudnowski, R. J.: Hydration with Ringer's Lactate Solution, J.A.M.A. 195: 545 (Feb.) 1966.)