Postoperative Coagulation Defects

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Uncontrollable generalized bleeding during operation is an alarming complication frequently compounded by uncertainty as to cause and appropriate therapy. The possible causes of defective hemostasis in this situation are numerous, and multiple mechanisms may be simultaneously involved. Similar laboratory findings may be the result of completely distinct insults, each requiring different therapy. The published literature on abnormal bleeding during operation is confusing because most authors have reported on the results of one or a few specialized tests, with emphasis on laboratory abnormalities encountered, rather than mechanisms. In an effort to provide practical guidelines, this review will concern itself primarily with the underlying mechanisms of abnormal hemostasis during surgery and the specific therapies required. This approach, presented in acceptably simple terms, requires a certain amount of dogmatism colored by the author's experiences.

The task of the reviewer has been considerably facilitated by discoveries of recent years, particularly the increasing acceptance of intravascular coagulation as a common denominator by which a number of insults may deleteriously affect the circulation of essential factors, leading to abnormal bleeding.1,2 “Unexplained abnormal bleeding” should become increasingly unacceptable as a diagnostic category. For more details, the reader may consult the proceedings of a recent symposium on “Bleeding in the Surgical Patient.”3 A recently published textbook presents an up-to-date discussion of hemostatic mechanisms, with comments on related clinical situations, in a manner which will be found most useful to those in the surgical professions.4

Pre-existing Defects

Surgical trauma places a stress on the hemostatic mechanism which may uncover mild defects in a patient previously considered normal. It is therefore essential that no patient reach the operating table with an unsuspected and undiagnosed coagulation problem. Once bleeding has manifested itself during operation, insufficient time is available for adequate diagnosis, and the possibility of correct determination of the basic problem is limited by the complicating effects of operation and its related stresses. Prevention of trouble is far easier than cure; this cannot be overemphasized! On the other hand, the routine preoperative bleeding and clotting times have no place in the modern hospital.5 The inadequacies of these tests should make them of little value even in providing protection against legal action. The most important means of determining whether a bleeding tendency is present before operation are the history, physical examination, and routine blood studies (including evaluation of platelet concentration on the blood smear). Exposure to previous trauma or surgery is a better test of hemostasis than any yet devised for the laboratory. Laboratory tests are necessary only if the history is suggestive of a hemostatic defect, if the patient is too young to have had a test of his capacity to control bleeding, or if an acquired disease known to be associated with abnormal bleeding has developed since the previous trauma.

If preoperative screening tests are to be done, they must take into account the fact that normal hemostasis requires (1) normal blood vessels, (2) a normal number of functioning platelets, and (3) a normal plasma coagulation system. An acceptable series of screening tests is outlined in table 1. The bleeding time must be by a standardized technique with an adequate incision. The method of Ivy is preferred to that of Duke because of its greater sensitivity.6 Platelet counts are best

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done by a direct method with phase microscopy, but inspection of a blood smear and of clot retraction is a permissible substitute if accurate counts cannot be obtained. The Quick "prothrombin time" screens deficiencies of clotting factors involved in the later stages of coagulation. Defects in the earlier stages (such as that occurring in hemophilia) are best detected by the partial thromboplastin time. The thromboplastin screening test is also acceptable, but technically more complicated. The whole blood clotting time is insufficiently sensitive to detect milder hemophiliacs, who can be a serious problem at operation, and is not recommended. Finally, observation of the clot takes little extra effort. Clot retraction is an index of platelet function. Further inspection may demonstrate the small clot with excessive red cell fall-out which indicates a low fibrinogen level; clot disappearance may indicate a significant degree of fibrinolysis (see below).

A pre-existing hemostatic defect may be congenital or acquired. Two of the congenital conditions are far more common than all the others combined: hemophilia and von Willebrand's disease. The importance of the latter condition has only recently gained attention, but we find it as common as hemophilia. It is characterized by a prolonged bleeding time (the result of a deficiency of a plasma factor required for platelet adhesiveness and for formation of a platelet plug) and a somewhat low level of Factor VIII (antihemophilic factor). Inheritance is dominant and both sexes are affected. Bleeding occurs predominantly from mucous membranes, especially with trauma. Von Willebrand's disease has been responsible for much of the unexplained bleeding after extraction of teeth, but usually creates far less of a problem for the surgeon than classical hemophilia. The commonest sources of trouble of an acquired nature are hepatic disease and thrombocytopenia.

Whenever possible, the defect should be corrected prior to operation. Vitamin K will correct the low prothrombin time due to biliary obstruction or malabsorption; polycythemia can be decreased by judicious phlebotomy; uremia may be ameliorated by hemodialysis, and specific clotting factor deficiencies corrected by appropriate transfusion therapy.

### Table 1. Recommended Preoperative Screening Tests of Hemostasis

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<th>Test of Hemostasis</th>
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<tr>
<td>1. Bleeding time</td>
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<td>2. Platelet count</td>
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<td>3. Quick “prothrombin time”</td>
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<td>4. Partial thromboplastin time</td>
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<td>5. Observation of clot</td>
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### Effect of Anesthesia

It appears likely that alterations of vasomotor tone, carbon dioxide tension, and pH induced by anesthesia may increase the amount of oozing of blood from the surface of a wound but there is little reason to believe that they have an important effect on the amount of blood lost.

### Intravascular Coagulation, A Common Mechanism for Hemostatic Defects

Disseminated intravascular coagulation results in two phenomena which, at first glance, appear to be contradictory: thrombosis and hemorrhage. These consequences of the intravascular coagulation are related to the rate at which it occurs. Extensive and severe in vivo clotting will lead to the deposition of fibrin thrombi in the microcirculation and even, at times, in large veins. If coagulation is activated at more moderate rates, fibrin deposits may be removed as fast as they are formed by compensatory activation of the fibrinolytic system, and thrombosis will not be apparent. At the same time, however, coagulation factors may be utilized in the continuing process at a rate faster than they can be replaced. The changes which occur in the circulation with coagulation are the same that occur when blood clots in a glass tube. Platelets, fibrinogen, prothrombin, Factor V, and Factor VIII (antihemophilic factor) disappear. Other clotting factors are more stable in their activated form and will remain in the circulating plasma. Intravascular coagulation may stimulate the fibrinolytic system. In the presence of free circulating plasmin (fibrinolysin), fibrinogen, Factor V, and Factor VIII are even more likely to be lost.

The phenomenon of intravascular coagulation is easily demonstrated at all levels of in-
tensity by appropriate rates of infusion of tissue extracts (thromboplastin) or thrombin into animals. Its spontaneous occurrence in man can be initiated by diverse agents and mechanisms, many of which may be encountered during operation. McKay and Hardaway \(^1\) \(^2\) are primarily responsible for drawing attention to the importance of this phenomenon. In general, it takes one or more of three distinct mechanisms to initiate intravascular coagulation: (1) damage to the wall of blood vessels, especially with associated introduction of thromboplastic tissue juices into the circulation, (2) activation of coagulation by exposure of blood to damaged vessel walls or by liberation of partial thromboplastins from destroyed red blood cells and/or platelets, and (3) stagnant circulation preventing neutralization and reticuloendothelial clearance of clotting intermediates. High levels of plasma clotting factors have not in themselves been shown to initiate intravascular coagulation, but if this should occur, the high levels may increase the likelihood of thrombosis.

From the foregoing, it becomes apparent that prolonged periods of severely inadequate circulation \((shock)\) are likely to be associated with intravascular coagulation. This is particularly true in cardiac arrest. Crowell \(^4\) has demonstrated that thrombosis in small vessels may be one explanation for "irreversible" shock. Although hypotension alone is unlikely to cause abnormal bleeding, it will potenti ate other mechanisms that induce clotting within the circulation. Trauma to tissues, especially those with a high thromboplastic activity such as lung and prostate, may initiate intravascular coagulation. The pancreas is another source of material (possibly trypsin) which promotes clotting. Intravascular coagulation caused by introduction of thromboplastic tissue juices has long been recognized by obstetricians in syndromes such as premature separation of the placenta, amniotic fluid infusion and retained dead fetus. A most dangerous cause of intravascular coagulation is endotoxin released by Gram-negative bacteria. Antigen-antibody reactions have also been shown to induce clotting in circulating blood. For further details, the reader should consult the publications of McKay and Hardaway.\(^1\) \(^2\)

Intravascular coagulation should be suspected, then, if any of the above situations are present. Though detailed coagulation studies are too time-consuming to be immediately helpful (plasma can be frozen for retrospective analysis), several tests are of value during the acute emergency. The syndrome may result in low platelets, a prolonged Quick prothrombin time and low to absent fibrinogen. The platelet count can be very quickly estimated on a Wright-stained smear. One of the most useful and simple tests is the observation of a tube of blood to see if a clot forms, whether it is firm or quickly shrinks spilling out red cells \((hypofibrinogenemia)\), or whether it dissolves completely \((fibrinolysis)\). A rough quantitation of the fibrinogen level can be quickly obtained by adding thrombin to serial dilutions of anticoagulated whole blood or plasma.\(^1\)

The first step in the control of abnormal bleeding due to intravascular coagulation is to interrupt the cause, if possible. Restoration of the normal blood volume is essential so that adequate circulation will permit neutralization and removal of clotting intermediates. If intravascular coagulation is not interrupted, the transfused donor blood will share the same fate as that of the patient. The second aspect of therapy is restoration of adequate levels of the factors destroyed by the \(in\ viso\) clotting. If fibrinogenopenia is severe, a commercial preparation of Cohn fraction I may be required.\(^1\) If platelets, Factor V or Factor VIII are needed, only fresh blood will contain these in adequate amounts. This is particularly true of platelets. When larger amounts of blood are being rapidly replaced, donor blood collected within the previous six to eight hours will be fresh enough; even 24-hour-old blood is likely to be adequate. If severe persistent thrombocytopenia is a significant abnormality, platelet concentrates may be required. An adult will need platelets derived from at least eight units of blood, and the concentrates must be given within six hours of collection of blood.

Intravascular coagulation in certain situations has been shown to persist for days, either continuously or on a recurrent basis. In such a situation, interruption of \(in\ viso\) clotting by administration of heparin has led to control of
bleeding. The control of abnormal bleeding by administration of an anticoagulant seems paradoxical, but the logic and practical success cannot be denied. Heparin must not be given unless intravascular coagulation is definitely present, since bleeding due to any other cause will be aggravated. Intravascular coagulation during operation is usually of brief duration and frequently complicated by abnormal hemostasis of other origins. Heparin is thus unlikely to be indicated in this acute situation.

**Fibrinolysis**

It is increasingly accepted that fibrinolysis is almost always secondary to intravascular coagulation and is evidence that the latter phenomenon has taken place. Fibrinolysis may be induced, however, by severe emotional stress and other stimulators of adrenal secretion, and sensitive tests frequently show that patients have some activation of fibrinolysis before operation begins. Patients with cirrhosis are particularly prone to fibrinolysis, the result either of deficiency of natural inhibitor or of a reduced rate of clearance of circulating activator. Finally, certain tissues are rich in fibrinolysin activator (prostate, lung, uterus), and trauma to them may release activator into the circulation.

Fibrinolysis is unlikely to be responsible for clinical bleeding by itself unless severe enough to lyse a whole blood clot in an hour or two. This is one reason for the recommended clot observation test. On the other hand, rapid lysis of this degree can be secondary to intravascular coagulation, and the distinction between primary and secondary fibrinolysis is a most difficult one to make. The one rapid test which may be useful is an estimate of the platelet count which should be normal in primary uncomplicated fibrinolysis. Unfortunately, other causes of thrombocytopenia frequently coexist. Specific therapy is available for primary fibrinolysis in the form of an inhibitor of activator, epsilon aminocaproic acid (EACA), and an inhibitor of plasmin, Trasylol; the former has had the more extensive use. It should be strongly emphasized that inhibitors of fibrinolysis must not be used unless the possibility of intravascular coagulation has been eliminated, since interruption of secondary fibrinolysis may result in massive thromboses. When underlying in vivo clotting cannot be ruled out, it may be safer to give heparin (see above) with the fibrinolysin inhibitor.

**Bleeding Due to Transfusion Therapy**

The administration of large amounts of stored bank blood is one of the most frequent causes of abnormal bleeding at operation. If unexpected blood loss occurs, due either to a surgical accident or to some other cause of defective hemostasis, blood from routine stores will inevitably be required. The harmful effects of this on hemostasis are related to the changes which occur in donor blood on storage (fig. 1). Primarily this relates to loss of viability of blood platelets; viability is appreciably decreased after three hours and almost totally gone after 48 hours of storage. The patient's reserve of platelets approximates only the number in his circulation; therefore, replacement of his blood with donor blood which is essentially platelet-free will sooner or later result in thrombocytopenia. Generally, for an adult, this requires at least 10 to 15 units in rapid succession. The activity of coagulation Factors V and VIII also decreases in bank blood during storage, but the decrease is slow and these usually play little role in the bleeding which occurs after uncomplicated massive transfusion of stored blood. Fibrinogen is stable in bank blood for the entire period of permissible storage.
Correction of the defects induced by stored blood requires replacement with fresh blood. Usually a call for the freshest blood available from that day's procurement is adequate. Blood up to 24 hours old will generally hold the patient's platelet count at an adequate but low level (50,000 to 60,000 per cu. mm.) but will not, in small amounts, correct a more severe thrombocytopenia. In that instance, platelet concentrates may be required (see above).

Massive transfusion of citrated blood of any age may lower the ionized calcium level in the patient's circulation to the point where cardiac standstill occurs. However, except in prolonged severe shock, this is unlikely to occur with any but the most exceptional rates of blood transfusion. If more than 10 units per hour are administered to an adult, 0.25 g. of calcium chloride should be given following each unit. Larger or more frequent amounts of calcium can result in dangerous levels of hypercalcemia. Ionized calcium is also required for blood coagulation, but hypocalcemia is almost never a cause of abnormal bleeding. Although in very unusual instances hypocalcemia appears to have been responsible, the general belief that cardiac standstill will occur before coagulation can be significantly impaired is still true.

A second cause of abnormal bleeding due to blood transfusion is the administration of incompatible red blood cells. The anesthetized patient cannot exhibit the usual warnings of a hemolytic transfusion reaction (chills, fever, backache), and the first sign that the wrong blood has been administered is the appearance of generalized oozing from the wound surfaces and unexplained hypotension. If this appears suddenly without any reason, it is safest to stop that unit of blood and have the hospital transfusion service recheck its compatibility along with examination of a fresh sample of patient blood for free plasma hemoglobin and a direct antiglobulin test. If incompatible blood is inadvertently administered, it may be necessary to continue with transfusion of other units (whose compatibility with the blood of the patient should be positively ascertained). Patients with bleeding due to incompatible blood transfusion demonstrate findings in their blood characteristic of intravascular coagulation. It is believed that the partial thromboplastin activity released into the circulation by the destroyed red blood cells plays a role in initiation of this reaction.

The most infrequent form of abnormal bleeding with blood transfusion follows the infusion of grossly contaminated blood. The effects are those of the bacterial endotoxin contained (see above). Diagnosis of this catastrophe can be made by a Gram stain of the donor blood which should be teeming with organisms. Prevention is aided by inspection of each unit of blood before transfusion, with quarantine of any that present an unusual appearance. Therapy is almost always in vain.

Another form of transfusion therapy which can contribute to abnormal hemostasis is the plasma substitute dextran. Dextran, albumin, and lyophilized aged pooled plasma are all excellent materials for maintenance of blood volume in an emergency while compatible blood is being obtained. The use of as much as 1,000 ml. of standard clinical dextran (6 per cent solution, mean molecular weight 75,000) appears to have no harmful effects. Beyond that point abnormal bleeding is likely to occur. The primary mechanism appears to be coating of the platelets with dextran, impairing their ability to function, and leading to a prolonged bleeding time. High concentrations of dextran will also precipitate fibrinogen and Factor VIII. The effect of the dextran is greater the higher the molecular weight, but even the material of 40,000 mean molecular weight will do the same if sufficient quantity is used.

Inadequate Surgical Hemostasis

Time and again continued postoperative bleeding at the surgical site will be found due not to an hemostatic defect but to inadequate surgical hemostasis. Re-exploration of the wound and ligation of the bleeding vessel(s) should always be done if bleeding is excessive at the operative site but not apparent elsewhere, platelets are adequate and a firm clot is quickly formed. Even in situations were hemostasis has been demonstrably abnormal, re-exploration may be required to control the situation. The cardiac surgeons who use extra-
corporal bypass have long been aware of this. The renewed bleeding after the incision is closed may be due to a rise to normal of the patient's blood pressure or to lysis of small clots which had temporarily sealed vessels. We have had an experience with a severe hemophilia whose bleeding was controlled with difficulty after amputation through an infected fracture site. On each occasion when his bleeding rate increased markedly to a degree not expected in the face of replacement therapy, removal of the dressing demonstrated that the infection had eroded a small blood vessel.

Changes in Coagulation Factors During and After Operation (Figure 2)

Since many of the mechanisms described above operate to a certain extent during major surgery, it is not surprising that following an operation the patient may have a somewhat lower platelet count, lower Factor V, and lower prothrombin than before operation. These changes may persist for several days. Fibrinogen and antihemophilic factor (Factor VIII) tend to rise with stress and tissue trauma. Their postoperative levels will be greater than the control value if no complications have occurred. Low levels are an indication that intravascular coagulation has taken place. The levels of these two clotting factors rise steadily above the normal in the following one to two weeks, then decrease slowly. Factor V and prothrombin recover after the first few days. The platelets increase to a supranormal level with a peak about 10 days after operation.

Anticoagulants and Open Heart Surgery

Increasing numbers of patients are being maintained on anticoagulants of the coumarin type for prolonged periods, and some require surgery. If the indication for the anticoagulant has been appropriate, there may be a risk of inducing thrombosis if the anticoagulant effect is completely reversed prior to operation. Increasing experience suggests that it may be desirable to perform surgery on these patients while the anticoagulant effect is maintained (except in operations on the eye, the central nervous system, or where large, raw surfaces remain). Although some surgeons prefer to let the anticoagulation wear off to some extent, others have shown that surgery can be safely performed with the prothrombin time at the upper limit of the therapeutic range. It is essential to be certain that the prothrombin time is not excessively depressed. If restoration of normal levels of coagulation factors is urgently required before operation, 5 to 10 mg. of vitamin K₁ oxide may be administered. During operation, blood replacement will tend to correct the coumarin effect to some extent because the clotting factors depressed by such therapy (prothrombin, and Factors VII, IX and X) are all stable in stored bank blood. Thus, it may be desirable to heparinize the patient for a few days starting 24 hours after operation until the prothrombin time is brought into the desired range. Unless the possibility of thrombosis is great, resumption of coumarin therapy after surgery may be sufficient. The blood of postoperative patients is relatively resistant to anticoagulants in the first two to three days after surgery, but the greatest risk of postoperative thrombosis comes seven to ten days after operation when platelets and other clotting factors are at their highest levels.

Open heart surgery provides a situation where operative trauma and incision into high pressure blood vessels are necessary in the face of completely incoagulable blood (heparin). Since such surgery is being carried out on a very large scale with success, it is obvious that normal hemostasis during surgery is not an absolute essential. However, blood loss is greater with these procedures than with other operations, and occasionally cardiac surgical patients evince massive bleeding, per-
TABLE 2. Causes of Abnormal Bleeding after Open Heart Surgery

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| 1. | The large volume of donor blood  
ad. Priming solution for the extracorporeal circuit  
b. Replacement of the large amount of blood lost |
| 2. | Intravascular coagulation  
a. Trauma to tissues  
b. Liberation of thromboplastic materials from red cells and platelets destroyed in the extracorporeal circuit |
| 3. | Fibrinolysis  
a. Secondary to intravascular coagulation  
b. Primary (?) |
| 4. | Failure to neutralize heparin completely after the bypass |
| 5. | Excessive dose of protamine (heparin antagonist) |
| 6. | Incompatible blood transfusion |
| 7. | Unclean extracorporeal circuit (thrombocytopenia)  
a. Bacterial endotoxin (stable in autoclave)  
b. Particulate matter |
| 8. | Protein denaturation (?) |

sisting after the procedure. Possible causes of such abnormal bleeding are indicated in Table 2.

Many of these mechanisms have already been discussed since they occur (usually to a lesser degree) in other forms of major surgery. Adequate levels of heparin must be maintained throughout the period of extracorporeal bypass to overcome the tendency to intravascular coagulation. On the other hand, minute traces of heparin will have a disproportionate effect on patients who are thrombocytopenic and deficient in certain plasma coagulation factors. Complete neutralization is necessary once the threat of in vivo clotting is past, to ensure minimal postoperative blood loss. A safe but effective dose of protamine presents a wide range, but a gross excess will aggravate bleeding. Protamine in large amounts injected rapidly will cause a drop in the platelet count, exerts a weak anticoagulant effect of its own, and can induce a temporary depression of Factor VIII. This is a rare and generally inexcusable source of trouble, since protamine should not be administered in considerably more than the usual dose unless it can be shown, in the test tube, that it will shorten the patient’s clotting time. The problem of unclean extracorporeal circuits was a major one during early experimental work in the dog laboratory; it is largely avoided by using as much disposable equipment as possible. Protein denaturation occurs at the large air-blood interphases of bubble or even filming oxygenators, but there is no direct proof as yet that coagulation factors can be significantly depressed by this mechanism. Salzman has demonstrated that the moderate thrombocytopenia which is an inevitable occurrence in extracorporeal circulation is accompanied by an almost complete loss of adhesive platelets, which may aggravate the effect of the thrombocytopenia. He suggests that an inhibitor of platelet adhesiveness is elaborated during heart-lung bypass, but proof of this is incomplete; it seems equally probable that the adhesive platelets would be the ones primarily lost, since these would adhere to the large surface of the external circuit. In any case, normal adhesiveness is quickly restored after bypass.

Management of Abnormal Bleeding During Operation

Sophisticated evaluation of the hemostatic system is best left for retrospective analysis. The most useful and simplest procedures are an estimation of the platelet count, Quick prothrombin time, and observation of the clot. If thrombocytopenia, loss of labile clotting factors, hypofibrinogenemia, or fibrinolysis are discovered, the cause should be apparent in terms of the mechanisms outlined above. Whatever the cause, the patient will generally require replacement of blood at a rapid rate to restore normal circulation. If blood collected on the day of surgery (or at least on the prior day) can be used for this replacement, the deficiencies will in most instances be corrected. Rarely, fibrinogen (Cohn Fraction I) or platelet concentrates may also be required. Adrenal corticosteroids appear to assist in the control of bleeding due to thrombocytopenia and certain vascular defects.

Conclusions

The causes of abnormal bleeding during operation are many, and multiple complica-
tions can confuse the situation, leading to an impression that the bleeding is completely unexplainable. The most common situation is one in which bleeding commences due to a surgical accident, intravascular coagulation, or undiagnosed previous defect, and the situation is compounded by administration of excessive amounts of stored bank blood, perhaps with large amounts of dextran. The most useful single therapeutic measure is replacement with fresh blood of the blood lost. When bleeding from the wound continues after operation, but defective hemostasis does not appear to be an explanation, the wound should be re-explored with the expectation of finding one or more bleeding vessels that require ligation.

References


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35. Salzman, E. W.: Blood platelets and extracorpo-

INTRATHORACIC PHEOCHROMOCYTOMA The differential diagnosis of tumors of the posterior mediastinum must include those of nervous origin, lipomas, enterogenous and bronchogenic cysts and pheochromocytoma. The 17th reported case of intrathoracic pheochromocytoma demonstrated no prior symptoms or signs. Hormonal activity was demonstrated only upon palpation of the tumor and hydroxyzine hydrochloride proved to be of great value in partially controlling the effects of epinephrine and norepinephrine on cardiac rate, rhythm and blood pressure. (Cueto, J. C., McFee, A. S., and Bernstein, E. F.: Intrathoracic Pheochromocytoma, Dis. Chest 48: 539 (Nov.) 1965.)

HEPATITIS Fibrinogen is useful in the treatment of secondary afibrinogenemia and hypoafibrinogenemia. Fibrinogen deficiency is usually associated with pregnancy (i.e., abruptio placenta, threatened abortion, postpartum hemorrhage, amniotic-fluid embolism or long-standing fetal death) but may also occur with thoracic surgery, generalized body trauma or extensive burns. Unlike albumin and γ-globulin, fibrinogen cannot, at present, be prepared free of the hepatitis virus. The incidence of hepatitis following the use of whole blood or derivatives varies considerably among different series but the rate following fibrinogen is significantly higher than that following whole blood transfusion. Although the prophylactic use of γ-globulin with fibrinogen has been suggested, no clear-cut evidence exists that γ-globulin is effective in preventing post-transfusion hepatitis. A unit of fresh whole blood contains about 1.25 g. of fibrinogen but patients with severe hemorrhage may require, in order to raise the fibrinogen level to normal, an amount of whole blood which would overload the vascular system. The use of fibrinogen alone eliminates this problem if the blood volume has been restored. However, fibrinogen should be used only in life-threatening conditions and then with the realization of the considerable risk of transmitting hepatitis by its use. (Mainwaring, R. L., and Brueckner, G. G.: Fibrinogen-Transmitted Hepatitis, J.A.M.A., 195: 437 (Feb.) 1966.)