THE PROBLEM OF OOZING DURING SURGERY

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SURGICAL oozing describes a generalized loss of blood from the surfaces of a wound. It is a complication of surgery which is variable in severity. It may be only a slow leaking of blood from innumerable tiny points, a situation which is more annoying than dangerous; or if the wound is large and the hemostatic fault is severe, the oozing may be so rapid and voluminous as to frustrate attempts to control it and prevent the patient's death. It is not a rare accident and yet information concerning it is fragmentary because it is an inconvenient subject to study. When it occurs in the operating room the surgeons and anesthetists are too busy—and rightly so—to be gathering data on the vagaries of the hemostatic mechanisms. Yet if we turn to experimental animals we are confronted with the unassailable fact of life: dogs are different from men. Take, for example, the fibrinolytic reaction which can cause oozing in both species. Hemorrhage severe enough to cause shock will activate the fibrinolytic system in a dog but not in man, while an incompatible blood transfusion reaction activates fibrinolysin in man but not in dogs. In spite of these impediments a few things have been learned about oozing. It may be caused by a number of different things, some of which are avoidable, others correctable and still others completely unknown. The pathogenesis of the reaction can often be deduced from knowledge of hemostatic mechanisms and what happens when they fail. Manipulation of the hemostatic system is difficult and dangerous, and so is the treatment of oozing.

HEMOSTATIC SYSTEM

In order to summarize what is known about the problem of oozing it is important to understand the hemostatic system. First of all a distinction is made between hemostasis and clotting. When blood vessels are opened, hemostasis is the total of all reactions which take place to staunch the flow of blood. One of these reactions is coagulation, which results in the rapid and effective conversion of fibrinogen into a fibrin clot. The clot, which traps blood serum and cells in its web, forms a plug in the leaking blood vessels. But even before the clot has formed the process of hemostasis is under way. As blood flows past the wounded edges of the vessel platelets become stuck there. Rapidly, thousands of them pile up, narrowing the orifice through which the blood is lost. Substances such as serotonin escape from the platelets and their local vasoconstrictor effect squeezes the vessel around the platelet plug. In small blood vessels this platelet plug is enough to accomplish hemostasis. Clotting need not be involved. Thus it is that the bleeding-time test is normal in some people with incoagulable blood. A simple puncture of the skin for the bleeding time cuts only the smaller vessels, and even hemophiliacs or people with a congenital lack of fibrinogen stop bleeding from such a wound after a few minutes. But when larger vessels are cut it is important that the clotting system function adequately. It is a complicated reaction: the fibrin clot is formed by the action of thrombin on fibrinogen. Thrombin is formed from prothrombin by the action of thromboplastin. Thromboplastin is formed by injury of tissues, especially blood platelets but other tissues as well. Thus the process of clotting is a reaction three layers deep which is touched off by an injury such as cutting or damaging a blood vessel. The very complexity of this reaction is a valuable safeguard. It is important for blood to clot to prevent the loss of blood; it is also important that blood refrain from clotting otherwise. The complexity of the coagulation system prevents blood's clotting for trivial reasons. When small amounts of thromboplastin

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form they are carried away by the blood and diluted before the latter reactions can go to completion. If small amounts of thrombin are formed, they are neutralized by natural antithrombins in the plasma. If small amounts of fibrin are formed there is a fibrinolytic enzyme in the plasma which can dissolve them. This is only a partial picture of the complexity of coagulation with its many checks and balances. Other clotting factors are involved: calcium, accelerin, convertin, Stewart and Hageman factors; and there are other inhibitors. Because of its complexity there are many ways in which the system can be upset to cause bleeding and clotting diseases. Sheehy and Ramos have recently prepared a tabular summary of the subject.[1]

One further word on complexity should be said regarding the platelet. The mechanical role of the platelet has already been described: how they pile up in the cut blood vessel to stop the flow of blood or slow it down so clotting can occur. It has been mentioned that the platelet is a source of serotonin which can cause blood vessels to contract, and also that the platelet can form thromboplastin, the first reaction of the clotting system. In addition to these functions the platelet causes clot retraction which squeezes out serum and toughens the clot. It contains an antiheparin factor which would tend to increase the coagulability of blood. And it has still other attributes. Several years ago Seegers enumerated eleven different functions of the platelet, relating them all to hemostasis.[2] With functions so many and so various it is not surprising that the platelet has an important role in hemostasis and is often implicated in the problem of oozing during surgery.

Failure of Hemostasis

The failure of hemostasis which results in oozing may be due to difficulty at any stage of the process. (1) There may be a failure of platelet plugs to form; this may be due to abnormal platelets, it may be due to something interfering with platelet function or, rarely, it may be due to an abnormality of the blood vessels. (2) There may be a failure of coagulation due to a lack of one or more coagulation factors or to the action of anticoagulants. (3) There may be a fibrinolytic reaction which dissolves the clots after they have formed.

Lack of platelets results in troublesome oozing which can be promptly stopped by only a few platelets. A platelet count of 20,000 per cubic millimeter is consistent with good hemostasis provided, of course, the platelets are normal and the count is done by the "direct" method.[3] In the days before platelet transfusions, splenectomies for thrombocytopenia were done with platelet counts below 10,000, and it was remarked that almost simultaneously with clamping the splenic pedicle the oozing would stop.[4, 5] The platelet count was already on its way up. Several years ago at Walter Reed a dramatic lesson on the value of a few platelets occurred with one of our first attempts at platelet transfusions. The patient was a child with thrombocytopenia whose spleen was to be removed. Her platelet count was about 1,000. A transfusion of viable platelets was planned to carry her through the operation. The blood was "platelet rich" from a patient whose count was more than a million. Typing and cross-matching were done the day before, and on the morning of surgery the donor was bled and the plastic bag of blood was carried to the operating room still warm. The patient had already been draped and the hematologist working under the drapes had trouble getting the needle in a vein. While he was working the surgeon made his incision. The wound began to ooze rather briskly; wiped dry, it quickly filled with blood again and it was finally packed with a hot towel until the transfusion was started. Then the towel was removed. The oozing immediately recurred, but this time when the wound was wiped dry there was no more oozing.

Abnormal platelets are encountered in a variety of hematologic conditions. The platelet count may be adequate or even greater than normal but the platelets themselves are inadequate for one or another of a variety of reasons.[6] Hemostasis is faulty and there may be oozing during or after surgery. This abnormality of platelet behavior occurs in the purpura associated with a congenital platelet inadequacy but more commonly it is encountered in the myeloproliferative diseases such as chronic granulocytic leukemia, myelofibrosis with myeloid metaplasia, thrombocytosis and

polycythemia vera. An especially difficult situation occurs in the latter diseases where the platelet count may be high. Here the tendency to ooze may be associated with a tendency to thrombosis and surgery carries a high risk. Wasserman has emphasized the importance of establishing control of the hematologic condition if possible before surgery is undertaken.[7] Where the platelet count is normal or low the problem of oozing may be controlled temporarily by transfusions of viable platelets. Osgood, in discussing the management of patients with chronic granulocytic leukemia, strongly advises that surgery be avoided whenever possible.[8] This is sound advice and applies equally to all of this group of diseases.

Alteration of platelets may interfere with their function in such a way as to cause oozing. Dextran, for example, is able to do this in some people. Several years ago a study of this plasma substitute was undertaken at Walter Reed to determine what happened to protein metabolism when dextran was substituted for a portion of the plasma proteins. It was a chronic experiment and involved the injection each day of dextran into a group of volunteer recipients. One of the volunteers developed an infected wen requiring incision and drainage. Following operation the wound bled all afternoon. This led to an investigation of the effects of dextran on hemostasis which demonstrated that the most important alteration involved the platelets.[9, 10] Evidently the thread-like molecules of dextran form a coating on the platelet and prevent its functioning properly to plug the cut end of blood vessels. The bleeding time was prolonged in about 25 per cent of normal volunteers who received a liter of one of the commercially available dextran solutions. About 5 per cent of these volunteers had a prolongation of bleeding time greater than 30 minutes.[11, 12] The clinical significance of this phenomenon is obscured by several factors. Individual susceptibility is one: only a few people are very susceptible. Dose is another: the concentration of dextran in plasma must be about 2 per cent before the bleeding time becomes prolonged. The time interval is important: in many people the bleeding time does not become prolonged for several hours after dextran has been given. The platelet count is of critical significance.[13] Even a moderate depression of the platelet count is enough to increase susceptibility. Consider this in a surgical context. During operation a patient develops unexpected severe bleeding. He is given a transfusion of a large amount of stored blood in which there are no viable platelets. His platelet count is lowered by dilution with this blood. When all the stored blood in the operating room has been used a plasma substitute is called for, and after several units have been infused oozing begins from all portions of the wound. There is a persistant and massive loss of blood. It may be added that this is not a hypothetical construction of a surgical catastrophe.

At the present time all new plasma substitutes are studied for their effects on hemostasis. Gelatin, serum albumin and polyvinylpyrrolidone (PVP) of those commercially available, did not cause an important prolongation of bleeding time when tested in volunteers.[11]

Rarely an abnormality of the blood vessels may be responsible for a tendency to bleed.[14]

At the beginning of this discussion it was noted that oozing may be mild and a self-limited phenomenon, or it may be massive and catastrophic. In general these two degrees of oozing may be divided on a pathogenic basis. Recall that small vessel hemostasis is a platelet function and blood coagulation need not be involved. The milder variety of oozing is usually related to an inadequacy of platelet function. Hemostasis in larger vessels requires a functionally adequate clotting mechanism and when this fails the resulting oozing may be difficult to control. The failure of hemostasis consequent to the action of fibrinolysins in dissolving the clots already formed is a comparable problem.

Failure of coagulation may be due to a lack of clotting factors or to the action of coagulation inhibitors. Because the coumarin drugs are extensively used in the treatment of thromboembolic disease "dicoumaralization" is not an uncommon problem in the preoperative management of patients with such diseases. These drugs reduce prothrombin activity by inhibiting formation of prothrombin and proconvertin by the liver. Actually, in the manner in which they are generally employed they seem to have little effect on normal hemostasis. This is exemplified by the experience of one

of the physicians in our laboratory who had taken dicumarol to study its effects. One day, while his prothrombin activity was quite low he accidently cut his hand, a severe laceration that severed several vessels and tendons. Before he arrived at the hospital the bleeding had stopped spontaneously. The effects of the coumarin drugs can be antagonized quickly by injection of vitamin K, but if this substance is used it should be with care.[15] Patients are given coumarin drugs because they have thromboembolic disease, and a release from the effects of the drug may be followed quickly by another thrombotic episode. This is especially prone to happen after operation when even normal peoples' blood is likely to be hypercoagulable. It is advisable not to attempt to restore prothrombin activity to the 100 per cent level.

The normal deficiency of coagulation factors, such as encountered in the various kinds of hemophilia, is a more serious problem. Unless these people are adequately prepared they bleed during operation and continue to bleed afterward. The surgeon is usually alerted by a history of excessive bleeding. Then a diagnosis can be made and the required plasma factor can be transfused into the patient, either as blood if whole blood is needed, or as plasma. In preparing patients with classical hemophilia it is essential that the blood or plasma be fresh or the plasma freshly frozen and that the replacement be adequate both in amount and duration. Antihemophilic globulin has a short life span in the circulation so it is necessary to repeat the transfusion at least daily, well into the postoperative period, until healing is adequate to preclude bleeding.[16] Rarely a patient with hemophilia is encountered who not only lacks the essential clotting factor but also has developed an inhibitor which prevents the transfused material from helping him. In one such patient we were unable, even by what amounted to exchange transfusions, to establish adequate hemostasis. Operation in this case had been undertaken to evacuate a hematoma which threatened loss of the patient's leg. In this instance the patient had concealed his hemophilic background from the surgeon.

Inhibitors of coagulation such as heparin probably have multiple effects upon the clotting system, but their main activity is antithrombic.[17] Once again it is important to distinguish between interference with coagulation and hemostasis. A patient's coagulation time may be greatly prolonged by heparin without impairing hemostasis. It is this fortunate dicotomy which permits the use of heparin to prevent coagulation when extracorporeal circulation is used as an adjuvant to open-heart surgery. More of this later. The antienzyme effects of heparin depend upon the strong negative charge which the molecule carries and thereby it is possible to antagonize heparin by substances such as protamine and toluidine blue which have a strong positive charge. Naturally occurring anticoagulants which cause a tendency to bleed are rarely encountered.[6]

Fibrinolysin (plasmin) is an enzyme of the plasma which is capable of proteolytic digestion of fibrin and fibrin clots.[18] It is normally present in the plasma as an inert proenzyme, profibrinolysin, which can be activated by certain tissue factors ("fibrinokinase") and by bacterial extracts (streptokinase) or by treatment of plasma in vitro with chloroform or even by dilution with water. There are also natural inhibitors of fibrinolysin. Thus we have a system which seems to approach in complexity the clotting mechanism. Like the clotting mechanism this fibrinolytic system is a valuable protection to the organism but it is also dangerous. One suspects that this powerful enzyme is confined by a complex system of activators and inhibitors to prevent its being too easily provoked.

Fibrinolysis may be responsible for a tendency to persistant bleeding not only when the normal proenzyme has been activated, but also when, as in certain malignant diseases, there develops an abnormal proteolytic enzyme.[19] Even spontaneous bleeding and a purpuric state may occur in patients with carcinoma of the pancreas or prostate. The danger of active fibrinolysin during operation lies in the destruction of fibrin clots. When clots dissolve the loss of blood is unimpeded. Since this is apt to be a generalized reaction, all vessels in the wound bleed at once. There is probably an attempt to form new clots, but if the active enzyme persists the fibrin dissolves

as fast as it forms. The fibrinogen concentration falls as fibrinogen is consumed and it is often reduced to levels which are critically low. Normal fibrinolysin is activated by a variety of agents but in surgical situations the precipitating factor often follows embolism. The coagulation mechanism is provoked intravascularly by escape of thromboplastic material such as amniotic fluid [20] or by the "hemoclastic reaction" which is associated, for example, with incompatible blood transfusion.[21] The treatment of this catastrophic condition is transfusion of fibrinogen.[22] It is best to use the fibrinogen fraction rather than plasma itself because it is necessary to inject about 5 Gm. of the active material, and this would require the administration of about 2 liters of plasma. It has been suggested that the albumin fraction of human plasma may be of value in these crises because the fraction may contain a natural inhibitor of fibrinolysin.[23] Other inhibitors of proteolytic enzymes—such as soy bean trypsin inhibitor—have been proposed and even tried, but without notable benefit; the complex which these materials form with the enzyme is easily broken.

Multiple defects of hemostasis may exist simultaneously in certain diseases. Cirrhosis of the liver is one of these: [24] the platelet count may be low and the platelets somewhat abnormal, prothrombin activity may be diminished and only partly correctable by vitamin K, the fibrinogen concentration may be lower than normal and fibrinolytic activity may be present. Operative and postoperative bleeding may be a serious problem in some of these patients who undergo operations for porta caval shunt. Since it is a complicated problem which may require several kinds of therapy—vitamin K, platelets, fibrinogen, whole blood—it is recommended that each patient be given a complete hematologic survey prior to operation.

Coagulation *in vivo*

The dynamic system of coagulation cannot be well understood by observing its behavior only in the test tube. Blood in a tube is either clotting or the coagulation system is held static by an anticoagulant. However, the clotting system *in vivo* exists in a state of dynamic equilibrium.[25] All of the components are continually changing. Consider the platelets for example: their life span is probably about 12 days and thus about 8 per cent are normally destroyed each day. Or prothrombin: some of the fast-acting coumarin drugs cause the prothrombin level to fall within 24 hours. They do this, not by destroying prothrombin, but entirely by inhibiting its production. This rate of fall indicates how quickly that particular globulin is replenished in the plasma. During this normal replacement of clotting constituents there may be a certain amount of interaction between them. The destruction of platelets is associated with the release of some thromboplastin. Perhaps most of it is prevented from acting by dilution and inhibition by antithromboplastin, but there is some activation of prothrombin to form thrombin. Even in normal blood there is to be found some thrombin present in an inactive form combined with antithrombin. In hypercoagulable states such as those associated with postoperative thromboembolic accidents the amount of this thrombin-antithrombin complex is increased.[26] This strongly suggests that the hypercoagulable states are associated with an increased rate of replacement of the clotting factors. There is an increased tendency to intravascular coagulation which is held in check by the natural inhibitors and other safeguards against intravascular clotting such as autogenous heparin and activation of fibrinolysin. This concept of the dynamic equilibrium of the coagulation system is an important one for our discussion, because some of the outstanding examples of oozing during operation occur when the dynamic equilibrium is disturbed.

Hemoclastic Reaction

"*Hemoclastic reaction*" is the name that Widal gave to the acute syndrome which he observed when he induced a hemolytic crisis in patients with paroxysmal cold hemoglobinuria.[27] It has since been discovered that the syndrome is not confined to the crises of a single rare disease. It may be induced by a wide variety of physiological insults to the circulating blood, and with only a few of them—such as hemolytic transfusion reaction—is hemoglobinuria a part of the picture. The reaction has been studied both in man and in ani-

mals.[21, 28–31] The severity of the hemoclastic reaction may vary tremendously depending upon the gravity of the injury and to some extent upon individual susceptibility of the patient. In a reaction of moderate severity the pattern may be described in two parts: the systemic and the hematologic. In the systemic part there is a chill followed by fever, the blood pressure rises shortly and then falls even to shock levels. There may be pain such as headache, backache, chest pain with coughing, abdominal pain with borborygmy and diarrhea, even bloody diarrhea. The hematologic picture shows a temporary leukopenia and in some cases hemolysis, but the fascinating and dangerous reactions take place in the coagulation system. The platelet count is reduced abruptly, the prothrombin activity is decreased and so is fibrinogen concentration. Yet, while all of these coagulation factors are decreasing, the clotting time of the whole blood becomes shortened. At first glance this appears paradoxical: that *increased* coagulability occurs with a *lack* of clotting factors. Actually the overall picture is the reflection of an attempt at intravascular coagulation. The platelets are injured and they form clumps which become small thrombi and emboli. The platelet count falls while the damaged platelets form thromboplastin. The consequent activation of prothrombin not only reduces residual prothrombin activity but it also shortens the clotting time: the process of coagulation has already begun as an intravascular phenomenon. When we withdraw a sample of blood and measure its clotting time in the tube we witness only the end of the process and, naturally, only a short time is required. Formation of fibrin also takes place *in vivo* and the fibrinogen level falls. There is probably embolism of fibrin shreds as well as platelet clumps. The manifold symptoms—pain, cough, diarrhea—are probably a consequence of the shower of emboli. Very severe reactions provoked in experimental animals produced fatal thromboembolic damage in the lungs and intestine.[32]

This is not the end of the hemoclastic reaction. The forces tending to cause intravascular coagulation are opposed by others which prevent it. Shortly after the onset of hemoclasia the fibrinolytic system becomes activated, and it may become intensely active. The clotting time, which was shortened, gradually returns to normal and then becomes prolonged, probably the result of a release of autogenous heparin. At this point, imagine such a patient on the operating table. His platelets have been destroyed or sequestered, the fibrinolytic system is intensely active and his blood is relatively incoagulable because of the heparin. Under these conditions bleeding is likely to be severe if not uncontrollable.

Many kinds of material introduced into the blood stream can evoke the hemoclastic reaction. Particulate matter such as finely ground quartz, peptone, killed bacteria are some of the things which have been used experimentally. As a complication of human surgery incompatible blood transfusions are probably the commonest cause of hemoclastic reactions. We have also seen it in patients with abdominal wounds where there is massive contamination of the peritoneum.[33] The open-end lymphatics which normally serve to keep the peritoneum clean, pick up and deliver into the blood an overwhelming amount of bacteria and other matter. In obstetrical patients amniotic fluid embolism causes a similar catastrophic disturbance of hemostasis. Presumably, the foreign materials behave as thromboplastin to start the cycle of platelet clumping or blood coagulation, or both. Injury of the lung is capable of initiating the same sort of reaction. The devastating hemorrhage which may complicate pulmonary surgery has been studied by Soulier.[34] During these operations there appears to be some activation of fibrinolysin even when the hemoclastic reaction is not evoked, which suggests that manipulation of the lung may liberate "fibrinokinase," this in addition to thromboplastin.

The appearance of a hemoclastic reaction during operation is usually accompanied by a deterioration of the patient's circulation. The blood pressure falls and at the same time oozing begins. The loss of blood may be serious enough to contribute to the circulatory instability. On the other hand, the fall in pressure may be sufficient to prevent bleeding. The concurrence of oozing and hypotension should suggest the possibility of a hemoclastic reaction and the situation should be surveyed im-

mediately. It is advisable to discontinue all infusions and transfusions until it can be ascertained whether or not they are involved. In case of an incompatible transfusion reaction the oozing blood may demonstrate granularity due to clumping of incompatible red cells. This may be seen better by picking up some of the blood on the flat of a scalpel blade. The bleeding is difficult to control. Mechanical hemostasis by clamping is usually ineffectual, but packing and pressure may partially stop the bleeding. The intravenous injection of fibrinogen solution is the best means we have of counteracting the fibrinolysin.

In addition to controlling the bleeding, treatment of the hemoclastic reaction requires, first of all, stabilization of the circulatory system. Blood transfusion is indicated even though the cause of the reaction was an incompatible transfusion reaction. Also, there are some things to avoid. Dextran should not be used because of its effects on hemostasis.[11] Antihistamines are of no value; they are useful in urticarial transfusion reactions but not in the incompatible reactions. If hemoglobinuria is a part of the reaction do *not* give sodium bicarbonate, sodium lactate or any substance containing sodium; it does not assist the kidney to excrete hemoglobin, and if real insufficiency develops the sodium adds to the patient's physiological embarrassment.

Blood Transfusions

Blood transfusion is related to oozing in ways other than by incompatible reactions. Modern surgical techniques have required several modifications of the ordinary use of blood transfusions and these are likely, for one reason or another, to cause disturbances of hemostasis. *Massive blood transfusions* are sometimes required as an adjuvant to extensive surgery.[33, 35–38] When multiple transfusions are given rapidly the platelet count falls. The patient's blood may be replaced by stored blood in which there are no viable platelets. But this is not the only factor. Even the use of fresh blood with viable platelets is accompanied by some lowering of the platelet count.[39] Only rarely does the count fall enough to permit bleeding, and in cases of serious bleeding one suspects that a hemoclastic reaction has somehow been provoked. In Korea, where massive transfusions of fairly old blood were used, the surgeons encountered a mild or moderate oozing after about twenty pints of blood had been given.[35] At this time the platelet counts were not seriously reduced, and platelet function *in vitro* was satisfactory. The bleeding time was moderately prolonged. The oozing was more a cause of annoyance than of concern. The hemostatic fault—whatever it may have been due to—was promptly self-limited.

The citrate used as the anticoagulant in stored blood is often mentioned as a possible cause of bleeding when large transfusions are given rapidly. Professor Soulier once encountered a patient who during operation was given such a transfusion and developed generalized bleeding. The patient's blood was found to be incoagulable due to lack of ionized calcium—a result of the citrate infused.[39] However, this is a rarety. Other citrate effects such as prolongation of ST interval in the electrocardiogram or hypotension would appear before the calcium level became low enough to prevent coagulation. In some of the Korean wounded a persistant hypotension was corrected by administration of calcium gluconate. It has been calculated that citrated blood must be given a normal adult at a steady rate of 500 to 600 ml. per five minutes in order to approach undesirable levels of citrate in the plasma.[40] There are certain conditions under which citrate-induced hypocalcemia may be a problem: [40, 41] (1) the patient with liver disease who cannot metabolize the citrate rapidly; (2) the young infant whose ability to metabolize citrate is similarly impaired; (3) clamping the aorta in the thorax or high in the abdomen; (4) hypothermia; (5) anuria which prevents excretion of citrate, and (6) use of citrated blood for extracorporeal circulation; when the machine is attached to the circulatory system there may be an abrupt drop of ionized calcium in the patient's blood.[42] The administration of calcium chloride solution has been recommended: a 10 per cent solution given intravenously slowly up to 10 ml.[40]

Extracorporeal Circulation and Hypothermia

Extracorporeal circulation, involving dialysis machines or pump-oxygenators, requires the use of supplemental blood to fill the equipment, it requires the use of heparin to prevent coagulation and it subjects the circulating blood to a severe and unnatural trauma.[43] The platelet count is depressed by dilution and physical damage. All of these factors would seem to summate to the detriment of the hemostatic system, yet oozing is not a problem unless the situation is further complicated. Patients with severe uremia, for example, have a predisposition to bleeding which is not well understood.[44] Hemostasis in surgical patients with uremia is often difficult,[48] yet heparinization and the insult incident to hemodialysis does not appear to make the bleeding worse. On the other hand, establishment of diuresis does not immediately correct the bleeding tendency. The pathogenesis of this inclination to ooze and measures to correct it are unknown. Congenital malformation of the heart with coincident polycythemia is another symptom complex in which a bleeding tendency may complicate operation and the use of extracorporeal circulation.[46, 47] These patients exhibit a combination of thrombocytopenia and fibrinogenopenia in the presence of a high hematocrit, so there is a faulty clot retraction; some have a diminished prothrombin activity as well. When these abnormalities are complicated at operation by the use of heparin, hypothermia and large transfusions, a tendency to ooze may be encountered. The problem is more serious in adolescent and adult patients than in children. It is recommended that these patients be transfused at operation with fresh blood containing viable platelets. After hypothermia their wounds should not be closed until the blood pressure and body temperature have been restored in order to observe and correct bleeding which may have been masked by the hypotension.

Hypothermia is another adjuvant of surgery which is capable of disturbing the hemostatic system. Deep hypothermia (20 C.) in dogs is accompanied by a lowered platelet count and oozing during operation.[48] The oozing is not copious because blood circulates very slowly at that temperature. Upon rewarming the animal the platelets, which have been sequestered in the liver and spleen, reappear in the blood.[49] These changes have not been observed in human surgical patients when the body temperature is reduced to 28–30 C.,[50] but certain faults of the clotting mechanism have been observed in hypothermic children. These changes reverted to normal after the body temperature was raised. When the techniques for hypothermia are improved lower body temperatures will become feasible and the "platelet problem" in the hypothermic human will require further study.

Prevention and Treatment of Oozing

Preparation for operation is important to prevent operative and postoperative oozing in patients in whom it is possible to anticipate such complication. Where there is a lack of a clotting factor, as there is in hemophilia and similar diseases, arrangements must be made for adequate replacement therapy during and after operation.[16] With thrombocytopenia, platelet transfusions or transfusions of fresh, platelet-rich blood should be available.[51–54] It is important to realize that at the present time there are no platelet substitutes of value and stored or dried platelets may be slightly worse than nothing at all.[55] There are certain diseases which are often associated with multiple faults of the hemostatic mechanism; polycythemic heart disease and cirrhosis of the liver, both discussed earlier, are examples. Trouble should be anticipated and prepared for by a thorough preoperative evaluation of the patient's hemotologic status and correction of such deficiencies as can be corrected. Where the possibility of a fibrinolytic reaction exists—as in pulmonary surgery, abruptio placenta with amniotic fluid embolism, cancer of the pancreas—adequate amounts of fibrinogen should be on hand, stored in a refrigerator in the operating room or the delivery room. Fibrinogen for intravenous injection is potentially infectious so that 20 to 25 per cent of patients who receive it develop clinical hepatitis. Therefore, such fibrinogen preparations should not be used without due regard for the risk involved. Prophylactic administration is

unjustified. Serious, unexpected or accidental compromising of the hemostatic mechanism is almost always associated with deterioration of the patient's general condition. The reaction is usually a shocking one, and depending upon the depth of anesthesia there may be other evidence of distress: shivering, incontinence, or opisthotonus. While appropriate measures are taken to stop the bleeding and stabilize the circulation, as discussed earlier, one must also obtain and preserve materials to document the reaction and the diagnosis: samples of infusions which were administered to the patient, specimens of blood for cross-matching, coagulation studies, blood counts and plasma hemoglobin. The urine should also be saved.

One should be careful about the fluids and electrolytes administered at this time. Anuria due to lower nephron nephrosis is a common sequel in the patients who survive this serious reaction. Indiscriminate infusion of water and sodium is to be avoided. Alkalinizing the urine is of no value in hemoglobinuria, and large volumes of water will not induce a diuresis in such damaged kidneys.

The Future

Future studies on the problem of oozing during surgery will involve more investigation of hemostasis actually conducted during operations where oozing is likely to develop.[56] They will include careful evaluation of new procedures such as deep hypothermia, mentioned above, which may injure the hemostatic system. New therapeutic agents used in surgical patients should be investigated before they are assumed to be free of harmful effects on hemostasis. A good example of this is the investigation of intravenous lipids which has demonstrated that these materials may cause profound changes both in men [57] and in dogs.[58] Even those materials which we use with more assurance occasionally produce a tremendous reaction in apparently normal people, as de Nicola [59] found when he used an American dextran. His object had been to study prolongation of the bleeding time, but the infusion precipitated a profound fibrinolytic reaction. Improved means of treating the crises of bleeding will become available to the surgeon and the anesthetist. One of the most valuable will be prolongation of the storage life of blood platelets so that large amounts could be transfused as needed. There is as yet no indication that freezing platelets may prove a feasible means of storage. The paradoxical reaction of a bleeding state which results from hypercoagulability has been discussed above. Treatment of these conditions by means of anticoagulants seems a further paradox, but there is evidence to suggest that such therapy may prevent severe damage.[31, 60]

With regard to any studies of hemostasis which may be proposed or any claims which may be advanced one is well advised to maintain a position of conservatism regarding two points: (1) The extrapolation of animal studies into the human situation. While the structure of the hemostatic systems is fundamentally the same, the behavior is likely to vary. (2) The use of "clotting agents" to treat bleeding-states. Over the past 30 years dozens of substances have come and gone. Tissue juices, vegetable extracts, platelet powder, chemicals, dyes, hormones and marrow, all at one time or another have been suggested as the treatment for bleeding, but none has lived up to its billing. Some day we may find a good, all-purpose hemostatic agent, but when we do a healthy scepticism will not interfere with its usefulness.

Summary

Oozing at operation reflects an inadequacy of the hemostatic system which may be due to many causes. Where it occurs accidently—not as a specific deficiency as in hemophilia or with a metabolic disease such as uremia—it is usually self-limited. It is not always a serious or life-threatening event, so it is best to determine the severity of the reaction before attempting heroic measures for treatment of the patient.

When it is known that the patient has a lack of some coagulation factor such as platelets or antihemophilic globulin, adequate replacement should be accomplished prior to surgery. Patients who have diseases such as cirrhosis or polycythemia should be evaluated carefully so that the magnitude of the risk is understood and the patients prepared as well as possible. Well-controlled anticoagulation, as with dicu-

marol, is not of itself a serious threat to adequate hemostasis, and one should consider the risk of thromboembolic disease before hastening to correct the prothrombin activity in surgical patients.

Certain operative and auxiliary procedures (extracorporeal circulation, deep hypothermia) frequently involve enough alteration of hemostatic elements to cause oozing. This usually does not represent a serious fault of hemostasis.

Dangerous, massive oozing is almost uniformly attended by abrupt deterioration of the patient's general condition with development of shock or instability of the circulatory system. Corrective measures must be prompt and appropriate. At the same time provision should be made for diagnostic procedures and baseline studies in order to support the patient better during the period of recovery.

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