BLOOD CLOTTING AND HAEMOSTASIS FROM THE STANDPOINT OF THE ANAESTHETIST

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THE DEVELOPMENT of a circulatory system involving a fluid moving under pressure exposes the organism to the mortal danger of losing this fluid. It is, therefore, not surprising that a series of complex mechanisms has been evolved to protect it against such danger. These mechanisms we describe by the term haemostasis, the stopping of bleeding. They include:

- 1 The coagulation of blood or formation of fibrin.
- 2 The clumping of platelets or formation of a plug
3. The reaction and integrity of the blood vessel wall.

Basic to the effectiveness of these mechanisms is blood flow, since on the one hand it brings materials necessary for haemostasis and on the other hand will wash away a partly or poorly formed block, so that we can list it as the fourth factor or mechanism involved.

BLOOD COAGULATION OR FIBRIN FORMATION (Table I)

Present in the plasma in solution is the protein, fibrinogen. Under the influence of the enzyme thrombin fibrinogen is converted to an insoluble protein, fibrin. Thrombin splits off peptide from the protein, thus making available chemical

groups on the fibrinogen molecules which combine to build up a protein fibre. These fibres interlacing form the structure of a gel. The gel has rigidity or tensile strength and as a result the blood becomes solid. For adequate gel strength the fibre formation must be very rapid. In the circulation the flowing blood will interfere with gel formation and therefore fibrin formation must be even more

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rapid. Thrombin is present in the blood only in an inactive form, prothrombin. Prothrombin is converted to thrombin in the presence of calcium ions with the aid of a number of activators. This conversion takes place in several steps involving degradation and marked changes in the prothrombin protein. While blood contains agents which can cause the activation of prothrombin under suitable conditions, the most effective agent and the one which is generally the initiator of clotting is the thromboplastin liberated from damaged tissue. Present in blood and plasma is a fibrinolytic mechanism, due to an enzyme, *plasmin*. Normally this enzyme is present in plasma in an inactive form, plasminogen. Various factors including substances from tissue can cause activation of plasminogen and produce an active enzyme which will very rapidly destroy fibrinogen and fibrin.

PLATELETS OR PLATELET PLUG FORMATION

The platelets constitute the third element of the blood. They are cellular material but contain no nucleus, being formed from the megakaryocytes in the bone marrow. Platelets circulate as discrete objects 1–4 μ in diameter. However, when they come into contact with any foreign material or damaged tissue they stick to it and to each other and in this way build up a plug of material which will effectively seal small breaks in blood vessels—the “clou hémostatique.”

REACTION AND INTEGRITY OF THE VESSEL WALL

The integrity of the vessel wall depends particularly on the cement substance between the cells of the endothelium. This substance is affected by a great many physiological factors, various hormones and vitamins. It is being constantly renewed. As this is the place where leukocytes pass out from the endothelium into the tissue spaces, any defect in the replacement of the cement substances will allow red cells to pass out also and there will be actual bleeding into tissues. Vessels will respond to damage by vaso-constriction. This applies to all vessels down to the capillaries. Any flow of blood through a damaged capillary will be stopped by the constriction of the precapillary sphincter. Various vaso-constrictor agents such as adrenalin and serotonin are an important part of the haemostatic mechanism.

INTERACTION OF MECHANISMS

While it is convenient to examine the three mechanisms separately it must be understood that they interact and reinforce each other. The clotting system, by forming fibrin, ties platelet clumps together and thus makes this mechanism more effective. Fibrin deposition on endothelium probably reinforces the integrity at a point which has been damaged. Platelets adsorb various substances and serve to transport them in the circulation. Amongst these are activators for the blood coagulation system, adrenalin and serotonin, which reinforce the vascular mechanism. The damage of platelets as they adhere or stick to a damaged blood vessel releases these agents to reinforce coagulation and vaso-constriction, the accumulation of platelets concentrating them at the damaged area. Vaso-constriction by impeding blood flow will assist the coagulation and platelet mechanisms in their

haemostatic function. There is probably some difference in the relative significance of these various mechanisms at different levels of the circulation.

COAGULATION TESTS AND CLINICAL BLEEDING

Various simple coagulation tests illustrate how different mechanisms of haemostasis are deranged in haemorrhagic diseases. The *clotting time*, as its name suggests, is measured by taking a sample of blood, putting it in a test tube, and watching it to see how long it takes to clot (5 min.). The clotting time is quite prolonged or is absent if there is no fibrinogen, and quite prolonged in the haemophilias. The *prothrombin time* is the clotting time speeded up by adding tissue extract for thromboplastin. This is found to be normal (12 sec.) in haemophilia, etc., prolonged with a decrease in prothrombin, Ac-globulin or proconvertin. The *bleeding time* is measured by making a small stab or nick in the skin and determining how long it takes the blood to flow (3 min.) It is normal in haemophiliacs, afibrinogenemia, etc., but is prolonged in the purpuras. This illustrates that there is a difference in the type of bleeding with the different types of defects in the haemostasis. Deficiencies in vascular integrity can be tested for by measurements of *capillary fragility*. suction is applied to the surface of the skin and if there is a defect in the vascular integrity petechiae will appear. Normal functioning of platelets can be checked by the *prothrombin utilization test*. At the time when a sample of blood clots, only 1 per cent of the prothrombin has been converted to thrombin. In the course of 30 minutes, the remainder is utilized. Normal platelets are required for this to occur. Since the addition of thromboplastin reduces the clotting time from 5 minutes to 12 seconds (the prothrombin time), this also represents a test for thromboplastin. The *thromboplastin generation test* is based on the observation that if a sample of blood or plasma at the point of clotting is added to a larger volume of recalcified oxalated plasma, the latter clots in 12 seconds, showing that thromboplastin is produced in plasma during clotting.

The type of clinical bleeding also varies with the mechanism affected. Conditions associated with defects in the coagulation system show the same type of symptoms of bleeding—bleeding from bruises where larger vessels are torn, bleeding into the joints, and intractable bleeding after tooth extraction and similar procedures. Defects in platelet and vascular mechanisms result in purpura. Such bleeding can be not only in the skin but also in internal organs such as the liver. Many of the purpuras are accompanied by a thrombocytopenia and it can be shown that when the platelet count falls below 40,000 per cubic mm., purpura results. More rare are the athrombocytopenic purpuras. In these, while the platelet count is normal, it can be shown that there is some defect in the actual functioning of the platelets or in the blood vessels.

HAEMORRHAGE AND THROMBOSIS

Under-activity of haemostatic mechanisms may result in haemorrhage. This is elicited by trauma. However, serious spontaneous haemorrhage does not occur even though one of the haemostatic mechanisms is absent through inheritance or disease. The other mechanisms will still be sufficient. The haemophilic does not

bleed continually nor do anti-coagulants cause bleeding in the normal individual. A man receiving heparin or dicumarol can shave. A female does not have particular trouble with the menses. It is only if several of the haemostatic mechanisms are interfered with that haemorrhage is very difficult to control. In the rabbit, injection of heparin or cutting the cervical sympathetic nerve to the ear, separately, causes no increase in the bleeding time from the ear. However, if both these procedures are performed together, it is very difficult to stop the bleeding from the ear when the bleeding time is being determined. Stress causes a marked decrease in the effectiveness of the mechanisms for vascular integrity since capillary fragility is greatly increased. When animals receiving anti-coagulants were subjected to stress, 50 per cent died of haemorrhage (3), whereas none died with the anti-coagulant alone. Such stress may be due not only to physical or chemical but also to psychological agents. The control of haemorrhage then requires an understanding of the nature of the defects which have developed, and also of how they may be corrected.

Over-activity of haemostatic mechanisms in the body can lead to intravascular clotting or thrombosis. The factors involved are summarized by Virchow: (1) changes in chemistry of the blood, (2) damage to the vessel wall; (3) stasis. Or, if we divide Virchow's first postulate into the coagulation system and platelets, we have the same four factors we have already seen responsible in haemostasis. Platelets adhering to a damaged portion of the vessel wall will pile up and form a white thrombus. This is followed first down-stream and then up-stream by formation of a solid clot so that the vessel is completely blocked. As anti-coagulants prevent the clotting of blood either directly or indirectly, it was early suggested that they might affect thrombosis. The first demonstration of this with heparin was carried out by Murray, Jaques, Perrett and Best in 1934 and this led to the introduction of anti-coagulant therapy for thrombosis clinically. With the development of dicumarol it was shown that this also could prevent thrombosis and today both groups of anti-coagulants are used. Heparin is used for emergencies and the indirect anti-coagulants for continuous prolonged therapy.

Clinical Factors Tending to Precipitate Haemorrhage or Thrombosis

Factors of interest to the anaesthetist which tend to precipitate either haemorrhage or thrombosis are listed in Table II. Omitted are the congenital haemorrhagic diatheses discussed briefly above, since these should be detected and dealt with prior to operation. The first group listed are those which affect the formation of fibrin. Fibrin formation may be affected directly through an effect on the concentration of fibrinogen in the blood and the latter is a sensitive indicator of liver function. Hepatotoxins and hepatic anoxia will cause a decrease, while acute infections and tissue damage generally cause an increase, in the plasma fibrinogen level. Plasma fibrinogen can be decreased to a very low level by fibrinogenolysis and by defibrination. The former is due to the activation of the plasminogen system, which can occur in stress and in anaphylactic reactions. When large amounts of thromboplastin enter the circulation, the blood frequently becomes incoagulable. This paradoxical result is due to the fact that, as the fibrin forms in the flowing blood, instead of creating an intravascular clot, it is

TABLE II
FACTORS TENDING TO PRECIPITATE HAEMORRHAGE OR THROMBOSIS

Haemostatic mechanism affected	Haemorrhage		Thrombosis	
	Factor changed	Causes	Factor changed	Causes
Fibrin formation	(1) Hypofibrinogenemia—depression of liver	Hepatotoxins Hepatic anoxia	(1) Hyperfibrinogenemia—over-activity of liver	Acute infections
	(2) Fibrinogenolysis—activation of plasminogen	Stress Tissue damage	—	—
	(3) Defibrination—entry of large amounts of thromboplastin	Anaphylaxis Tissue damage Abruptio placentae Eclampsia	(2) Fibrin embolism—thromboplastin entering circulation	Eclampsia
Thrombin formation	(1) Decrease due to liver depression	Laparotomy	(1) Increase in Ac-globulin, etc	Postoperative xanthines
Prothrombin	(2) Vitamin K lack	Drugs		
Ac-globulin	(3) Prothrombogenic drugs	Obstructive jaundice Dicumarol, etc		
Proconvertin				
Thromboplastin			(1) Increased circulating thromboplastin	Shifts in blood volume—digitalis and diuretics Operative trauma Postoperative
Anti-coagulants	Heparinemia Antibodies	Anaphylaxis		
Platelets	Thrombocytopenia	Toxic Allergic-platelet Agglutinins and lysins from transfusions Drugs	Thrombocytosis	Postoperative peak reached on 10th day
	Thrombasthenias	Dextran Athrombocytopenic purpuras	Thrombophilias	Postoperative peak on 10th day Thrombotic thrombocytopenia
Blood vessels	Loss of vascular resistance	Stress antibodies (sensitivity reactions) Anaphylaxis Histamine Deficiency of vitamins C & P	Endothelial damage	Trauma infection (e.g., bacterial endocarditis)
				Capillary anoxia
Flow	Increased pressure head	Hypertension	Stasis	Bed-rest Local interference with circulation

deposited on the vessel walls as fibrin threads, leaving the circulating blood incoagulable. Such entry of thromboplastin occurs particularly in abruptio placentae, from the intervillous lake. It is possible for the fibrin as formed to provide emboli and this is a significant factor in eclampsia.

The rate of thrombin formation in haemostasis is significantly affected by surgery and drugs through alterations in the plasma level of the components of the prothrombin complex (prothrombin, Ac-globulin, proconvertin), of thromboplastin, and of anti-coagulants. The level of Ac-globulin and proconvertin in the blood is the most sensitive indicator of hepatic function, simple operative manipulation of the liver causing it to fall. More specific effects are produced by obstructive jaundice owing to the interference with absorption of the K-vitamins, and by the prothrombopenic drugs (dicumarol, danilone, etc.). An increase in concentration of the complex appears to occur postoperatively and also with the xanthine group of drugs. Normally, there are only traces, if any at all, of thromboplastin and heparin in the blood. However, shifts in body fluids from tissues to blood do increase the amount of circulating thromboplastin and resulting circulating thrombin. This is the explanation for the action of digitalis in the cardiac patient increasing the thrombotic tendency. Heparin enters the blood in anaphylaxis. Other anti-coagulants can also appear, particularly antibodies to specific coagulation activators such as the anti-haemophilic factor of the haemophilic. These may develop following repeated transfusions.

Changes in platelets are among the most common responses to the various procedures of the anaesthetist. It is not appreciated that a transient thrombocytopenia, lasting thirty or forty minutes, is a frequent result of introducing materials intravenously. This is due to the temporary agglutination of platelets and the sieving out of the clumps in capillary beds, particularly in the pulmonary circulation. The occurrence of actual agglutinins and lysins of platelets can now be detected, using the newer techniques of Harrington and Stefanini (4) and are probably on the increase with the great rise in the number of blood transfusions in the past decade which have not allowed for platelet blood groups. In any patient who has received more than twenty transfusions of whole blood there is a significant possibility of platelet agglutinins being present. Such a patient should not be used as a donor and if a recipient, this hazard must be kept in mind. Allergic thrombocytopenic purpura can occur when various drugs such as sedormid or quinidine are given. While defective platelets occur in rare idiopathic conditions, they are not a common phenomenon. However, an increased platelet stickiness or increased activity does accompany the postoperative thrombocytosis and is a reflection of the relatively greater numbers of young platelets in the circulation at that time.

Changes in the blood vessels are produced by many factors of fairly common clinical occurrence. Loss of vascular resistance can be produced by many agents. Recent studies (5) have shown that stress is a very effective agent in lowering vascular resistance. The production of antibodies to endothelial elements can result in serious vascular reactions, for example, the Arthus reaction. Anaphylaxis, histamine and deficiency of vitamins C and P cause a marked decrease in vascular resistance. On the other hand, damage to endothelium promotes thrombosis. While trauma and blood-borne infections can produce this, it is probable that capillary anoxia is the most common factor. Finally, changes in blood flow can promote either haemorrhage or thrombosis. Hypertension increases susceptibility to haemorrhage while stasis from any cause encourages thrombosis.

CONCLUSIONS

It is obvious that the various procedures used in modern anaesthesia have multiple effects on haemostatic mechanisms. In general, the liver damage produced by anoxia, etc., tends to increase the danger of haemorrhage and this is further increased by the effects of stress from the preoperative preparation and the operative procedure. The possibilities of transfusion reactions and allergic reactions to drugs increase the possibilities of haemorrhage. On the other hand, shifts of blood volume, tissue damage, prolonged depression of the cardiovascular system, and stasis all tend to favour thrombosis. Postoperatively, the thrombocytosis and accompanying thrombophilia increase the thrombotic tendency. Keeping in mind the fact observed experimentally that derangement of several factors simultaneously is required to cause either haemorrhage or thrombosis, it is not surprising that it has been difficult to demonstrate clinically individual factors as important causative agents. It also makes difficult the development of any single test which will evaluate the possible prognosis of either haemorrhage or thrombosis in the individual patient. However, neither of these deleterious developments occurs without some warning in many patients. If all involved in the care of patients are alert to the importance of traces of bleeding, unexplained rise in body temperature, examination of superficial vessels for thrombi, and general evaluation and support of adequate blood flow to the extremities, pelvis, abdominal and thoracic regions, it can be confidently expected that the incidence of severe complications from both haemorrhage and thrombosis will be reduced. In particular, with the extensive use of anti-coagulant therapy today, it is useful to remember that haemorrhage is not simply the natural result of the use of anti-coagulants but is a warning sign of a change from the normal, requiring evaluation of the new pathological factor.

RÉSUMÉ

L'hémostase dépend des mécanismes de la coagulation du sang, de la formation de la fibrine, de la formation du "clou hémostatique" par les plaquettes, de la réaction et de l'intégrité de la paroi vasculaire et enfin, du courant sanguin. Ces mécanismes s'influencent réciproquement et peuvent additionner leurs pouvoirs. Les modifications dans les simples tests cliniques du temps de coagulation, de temps de saignement, de la fragilité capillaire, etc., dénotent, tout comme le fait le site de l'hémorragie, que le mécanisme hémostatique peut être défectueux. Une hémorragie spontanée sérieuse ne survient habituellement pas si un seul mécanisme hémostatique est en cause mais elle suppose un dérangement simultané de plusieurs mécanismes. Ainsi en est-il de la thrombose qui suppose leur empiètement simultané. En anesthésie moderne, les procédés employés ont des effets multiples sur les mécanismes hémostatiques. Les dommages hépatiques, les stress, les transfusions, les réactions allergiques aux médicaments augmentent les possibilités d'hémorragie qui peuvent être dues soit à la diminution des facteurs responsables de la coagulation, soit à des variations de la résistance vasculaire ou des plaquettes sanguines. L'extravasation sanguine, les dommages tissulaires, la dépression prolongée du système cardiovasculaire et la thrombo-

cytose post-opératoire augmentent les possibilités de thromboses dues à l'entrée dans la circulation de thromboplastine, favorisées par la stase et par la thrombocytose. Il n'y a pas un seul test qui puisse laisser prévoir la possibilité soit d'hémorragie, soit de thrombose chez un malade, mais une attention particulière à leurs signes cliniques peut réduire leur incidence. Une hémorragie n'est pas une conséquence naturelle de l'emploi d'anticoagulants, mais elle indique la présence d'un facteur pathologique.

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