Intravascular coagulation

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BLOOD coagulation is usually an extravascular event, and fibrin is found in relation to damaged vessels as part of the 'haemostatic plug', or in areas of inflammation. However, multiple stimuli which arise in many apparently unrelated diseases may lead to coagulation within the blood vessels. The presence of sufficient intravascular fibrin to be recognizable by light microscopy always indicates a pathological process and one which McKay (1965) has called 'an intermediary mechanism of disease' for it may provoke a great variety of clinical effects.

The process of intravascular coagulation may be acute, subacute or chronic depending on the speed of onset and duration of the initial stimulus. The severity varies from a process so intense that the circulating plasma is virtually converted to serum, due to the utilization of all the available platelets and coagulation factors, to one in which it may be possible to demonstrate circulating products of coagulation in the blood when there is no certain evidence that actual fibrin deposition has occurred anywhere within the blood vessels. The most severe examples, easily recognized by the incoagulable nature of the blood, may be associated with the shock and bleeding of the 'defibrination syndrome' (Schneider, 1959). The recognition of the multiplicity of defects in the severe states prompted the alternative name of 'consumption coagulopathy' (Rodriguez-Erdmann 1965). The generalized nature of the process is emphasized in the terms of 'disseminated intravascular coagulation' (McKay, 1965) or later 'diffuse intravascular coagulation'. Perhaps every prefix should be dropped and intravascular coagulation considered as an entity, though it is one with very variable expression.

Fibrin, in association with platelets, may be deposited anywhere in the vascular system and it has been usual to differentiate the large thrombi in the heart, arteries, and veins, general thrombo-embolic disease, from 'microthrombi' in the small vessels, capillaries, arterioles, and venules. Perhaps both are an expression of generalized hypercoagulability with variable localization of effects depending on the complex interplay between the stimulus to coagulation and the effect of compensating mechanisms.

Clinical manifestations of intravascular coagulation

Bleeding is a manifestation of the severe forms and is due to deficiencies of multiple coagulation factors,

to thrombocytopenia, and to the anticoagulant effects of fibrinogen or fibrin degradation products of the fibrinolytic enzyme system when these are present in excess. However, even with profound changes, and virtually incoagulable blood, bleeding is not particularly common unless there is a local lesion of blood vessels. Surgical wounds, sites of needle puncture, the atonic uterus after childbirth, and benign or malignant ulcers may bleed profusely. More generalized purpura may also occur when vascular endothelium has been damaged, for example by bacterial endotoxin, colonization by virus, local immune reactions, or the formation of thrombi in capillaries, arterioles or venules.

This process of 'microthrombosis' may have damaging effects if it causes obstruction to blood flow. A particular form of intravascular haemolysis, characterized by the presence of irregularly distorted and fragmented red cells (schistocytes) in the blood was recognized by Brain, Dacie & Hourihane (1962) and called 'Microangiopathic haemolytic anaemia'. Some examples of the syndrome are associated with disseminated intravascular coagulation and the typical red cell changes have been produced *in vitro* by passage of blood through a fibrin mesh (Bull *et al.*, 1968). The changes are not, however, specific for disseminated intravascular coagulation and have been observed in patients with other forms of mechanically induced haemolysis especially following the insertion of valve prostheses into the heart (Marsh & Lewis, 1969).

Microthrombosis may cause infarction, often associated with bleeding, in many organs. In the acute phase of florid reactions the main danger is of pulmonary thrombi causing shock due to acute cor pulmonale. If the patient survives these acute manifestations he may do so unscathed or show various manifestations of organ damage ranging from circumscribed focal necrosis to haemorrhagic infarction of whole organs when secondary thrombosis of veins draining the site occurs. In addition subacute and chronic forms are very common in which the florid acute stage is never recognized.

Thrombi in the brain may produce coma or convulsions; thrombosis of the sigmoid sinus is a possible sequel. Oliguria follows tubular necrosis and anuria the more severe bilateral renal cortical necrosis; thrombosis of the renal veins may follow. Focal hepatic necrosis may proceed to hepatic vein throm-

bosis. Ulcers in the gastro-intestinal system may be circumscribed or infarction of the intestinal epithelium may be widespread producing pseudomembranous enterocolitis. Haemorrhagic pancreatitis has been described. In the skin the necrotic lesions or more extensive gangrene of purpura fulminans may be visible. Haemorrhagic infarction of the pituitary may later produce panhypopituitarism, a complication which arises more frequently during pregnancy. Haemorrhagic necrosis of the adrenal gland may cause the profound shock of the Waterhouse-Friedrichsen syndrome. Since all the clinical manifestations reviewed by McKay (1965), are often produced by mechanisms which are independent of coagulation it is difficult to define the exact role of thrombosis in the disease process. The importance of doing so lies in the possibility of influencing the mortality or morbidity of the disease by the appropriate use of an anticoagulant.

Pathogenesis of intravascular coagulation

Both coagulation and fibrinolysis may respond to the same original stimulus, either entry of foreign material into the blood or contact between normal blood constituents and the 'foreign' surface provided by damaged tissue. Stimulant materials which may enter the blood include normally intracellular enzymes (thromboplastins) released from inflamed tissue cells, neoplastic cells, or by haemolysis of blood cells; particulate or colloidal matter, for example in amniotic fluid embolism; bacterial endotoxin; antigen-antibody complexes; or the toxins of venomous animals. Blood may perfuse vessels in which the endothelium has been damaged by physical agents, for example burns or heat stroke, bacterial products, virus, immune reaction, or ischaemia in hypovolaemic shock. Intravascular coagulation may thus have many causes and clinical associations which extend to almost the whole spectrum of human disease (Müller-Berghaus, 1969).

Opposed to the stimulus, tending to prevent intravascular coagulation, are a number of exceptionally potent mechanisms. Active coagulation enzymes in the circulation are exposed to the action of powerful and specific natural inhibitors, often in considerable excess. Active coagulation factors of all types are cleared from the blood more rapidly than their inactive precursors, into cells of the reticulo-endothelial system (Wessler *et al.*, 1967). Stimulation of fibrinolysis produces the enzyme plasmin which has a special affinity for fibrin, splitting it into soluble fibrin degradation products (FDP). In addition to this direct removal of fibrin, the action of plasmin provides a supply of these FDP which will complex with fibrin monomer and hold it in solution for ultimate clearance by reticulo-endothelial cells (Kowalski, 1968). It is obvious that the functioning

of these mechanisms is fundamentally dependent on blood-flow, and, therefore, the state of the vascular bed at the site of a stimulus.

Thus, the final effect of a stimulus to coagulation may be limited to the formation of soluble fibrin monomer complexes with FDP, proceed to transient fibrin deposits which are rapidly dissolved by fibrinolysis, or give persistent microthrombus formation. The result will depend on the quantity, quality, portal of entry, and persistence of the stimulus, balanced against the efficiency of the plasma inhibitors, the degree of stimulation of the fibrinolytic system, the activity of the reticulo-endothelial system, and the amount of blood-flow in a particular organ.

The Shwartzman phenomenon

A particular example of intravascular coagulation which illustrates many of these points is given by the experimental Shwartzman phenomenon. This symptom complex of shock, widespread parenchymatous haemorrhage, and bilateral renal cortical necrosis, characteristically follows two spaced intravenous injections of bacterial endotoxin into experimental animals. The first 'preparatory' injection is without clinical effect while the second 'provocative' injection, which may be of a quite different endotoxin or even particulate matter such as kaolin or agar, has only to be spaced 6-72 hr after the first injection to produce the dramatic effects. If the second injection is intramuscular local necrosis is produced at the site of injection. McKay & Shapiro (1958) showed that it is disseminated intravascular coagulation, precipitated by each of the two injections, which causes the signs and symptoms of the phenomenon. The clinical effects of the provocative dose may be prevented by prior treatment with heparin, anticoagulants related to dicoumarol, or by stimulation of fibrinolysis. Leucocytes must also be present for the fully developed reaction which can be ameliorated by treatment with nitrogen mustard to reduce the leucocyte count.

It is not entirely clear why two spaced injections are necessary. Under certain circumstances the response follows a single injection. This can be demonstrated after reticulo-endothelial blockade, inhibition of fibrinolysis, treatment with cortisone and, in some species at least, during pregnancy. The continuous infusion of endotoxin for a period of 8-14 hr will also produce typical lesions in rabbit glomeruli (Beller & Graeff, 1967). It seems that the first injection initiates clotting, either by stimulating the intrinsic plasma system, by a direct effect on platelets or vascular endothelium, or by the damaging effects of antigen-antibody complexes and the activation of complement. At the time of the second injection the animal is particularly vulnerable to any further stimulus to coagulation because the already extended

compensating mechanisms for the removal of the activated products may be overwhelmed. The state of the circulation is also clearly important in determining the localization of the fibrin deposits. Unilateral sympathectomy prevents fibrin deposition in the glomeruli on the denervated side (Palmerio *et al.*, 1962). It is possible that vasoconstriction of the afferent arteriole, produced by release of catecholamines from damaged platelets, provides the area of congestion and stasis which conditions the deposition of fibrin in the glomeruli. This would perhaps explain the participation of white cells whose breakdown may liberate vasoactive materials. There is evidence that the release of bradykinin and serotonin forms part of the mechanism.

Diagnosis of intravascular coagulation

Evidence for the occurrence of intravascular coagulation comes from two sources, histological demonstration of fibrin deposition in tissues and from a series of secondary changes in the blood. Fibrin in tissues may be recognized only by electron microscopy or immunofluorescence. In more advanced lesions the fibrin is visible by light microscopy, but early lesions may not stain specifically for fibrin. Secondary blood changes depend on the severity of the process. In the most severe type a decrease occurs in the blood concentration of platelets and of many of the coagulation factors, particularly fibrinogen, factor V, factor VIII and factor XIII, (Merskey *et al.*, 1967). In less severe forms as production increases in an attempt to offset the increased consumption there may be normal or even increased numbers of platelets, normal fibrinogen, and an increase of factor VIII. One-stage assays of factor VIII may give exceptionally high results, perhaps due to activation by traces of thrombin (Penick, Roberts & Dejanov, 1965). In all grades of severity it is possible to demonstrate soluble fibrin monomer complexes in the blood and an associated increase of fibrinolysis. The former may be precipitated from solution in plasma at a low temperature, acid pH, with ethanol, or with protamine sulphate. A very sensitive test with protamine has been described recently (Niewiarowski & Gurevitch, 1971). Stimulation of fibrinolysis is shown by an increase in fibrin degradation products, recognizable by direct immuno-assay in the serum (Merskey, Lalezari & Johnson, 1969) or by their ability to prolong the thrombin clotting time of plasma. Blood plasminogen concentration falls probably due to increased consumption following adsorption to fibrin and local activation to plasmin (Flute, 1964). However, it is unusual to show an increase in circulating activators of plasminogen, again probably because they are adsorbed to the fibrin and rapidly cleared from the circulation. Additional evidence for intravascular coagulation

can sometimes be obtained by showing an increased catabolism of one or more of the coagulation factors, especially fibrinogen (Regeoczi, 1971).

Acute hepatic necrosis

Many of these points can be illustrated by reference to the specific example of acute hepatic necrosis. Here the stimulus to intravascular coagulation probably arises from the necrotic cells, for there is evidence for intravascular coagulation when the necrosis follows a variety of aetiological agents, infective hepatitis, paracetamol overdose, halothane hepatitis (Rake *et al.*, 1970), transplantation of the liver (Flute *et al.*, 1969), and yellow fever (Dennis *et al.*, 1969). In these patients the coagulation defects are due both to decreased synthesis and increased consumption. In a series of thirty-one patients admitted to King's College Hospital in hepatic coma all showed prolongation of prothrombin and partial thromboplastin times, mainly reflecting decreased synthesis. This could not, however, account for the additional finding of thrombocytopenia, prolonged thrombin clotting time, increased FDP by immunological assay of the serum, low blood plasminogen, and in the later cases soluble fibrin monomer in the plasma easily demonstrated by protamine precipitation. Daily transfusion of 2 l of fresh frozen plasma consistently failed to replace the missing coagulation factors, giving certain evidence of an increased loss of coagulation factors. This can be confirmed by measuring the disappearance of ¹²⁵I-labelled fibrinogen from the circulation. The increased rate of loss is not a specific sign of intravascular coagulation, but heparin decreased the rate of loss and this is good evidence that it is responsible at least in part. Plasminogen activator is not increased and there is no evidence of fibrinogenolysis.

The intravascular coagulation may contribute to the bleeding diathesis and it is possible that damage to the liver, kidney, and gastro-intestinal mucosa may be caused by microthrombosis. With a disease of such high mortality a trial of heparin therapy seemed justified. However, the administration of anticoagulants always carries a risk of bleeding, particularly where vessels are damaged, and this risk is increased in liver disease by the associated lack of synthesis of coagulation factors. Initial results suggest that heparin treatment is worthy of further study (Rake *et al.*, 1971). Very close laboratory control of the dose is essential and repeated transfusions of fresh plasma are needed if this type of approach is contemplated.

The treatment of intravascular coagulation

In acute states associated with bleeding the first priority is to maintain the blood volume by suitable transfusions, preferably of fresh blood, while

attempts are made to remove the original stimulus, where this can be identified. Laboratory tests may indicate the need for transfusions of fibrinogen and, less commonly, of platelets. It is uncertain whether the anticoagulant action of heparin is beneficial in the acute states. Inhibitors of fibrinolysis should be avoided if there is evidence of intravascular coagulation (Merskey *et al.*, 1967).

There have been many reports of the use of heparin in the less severe type of disease, though no controlled trials in human disease. These reports include the use of heparin for purpura fulminans (Hjort, Rapaport & Jorgensen, 1964), the haemolytic-uraemic syndrome (Moncrieff & Glasgow, 1970), *Clostridium perfringens* septicaemia (Rubenberg *et al.*, 1967), and virus infections (McKay & Margaretten, 1967) as well as the studies already referred to in acute hepatic necrosis. McGehee, Rapaport & Hjort (1967) carefully investigated nineteen patients with acute meningococcal infection. Heparin was given to some and in the opinion of the authors saved at least one life. A study by Dennis *et al.* (1967) of thirty-one patients with malaria due to drug-resistant strains of *Plasmodium falciparum* showed many with signs of intravascular coagulation due to haemolysis. Heparin combined with antimalarials gave a more rapid control of the infection than antimalarial drugs used alone. In contrast, rhesus monkeys experimentally infected with yellow fever were given heparin which reversed the coagulation effects but did not prolong the life of the animals (Dennis *et al.*, 1969). Similar results were obtained in another animal model using fowl plague in chickens (Gagel *et al.*, 1970).

It seems logical to advocate careful individual assessment of each patient and to use heparin in one who is suffering from bleeding, micro-angiopathic haemolysis, or damage to a vital organ and when there are reasonable grounds for assuming that any of these is due to continuing intravascular coagulation. There should be clear laboratory evidence that at least a moderately severe process is involved, with for example thrombocytopenia, low fibrinogen, and prolonged thrombin clotting time. There is evidence from animal experiments that better results are obtained if heparin is given early and in a dose large enough to prolong the clotting time or thrombin time. However, the coagulation is always likely to be a secondary phenomenon and every effort is necessary to remove the initial stimulus to coagulation by other means. For example, heparin may occasionally be of value to prevent coagulation while awaiting the specific effect of antibiotics in acute infections associated with haemorrhagic phenomena.

Conclusion

The phenomenon of intravascular coagulation has many names, many causes, and many possible

results. The mere presence of intravascular coagulation is no longer enough to indicate the need for anticoagulant treatment. It is the few individuals in whom the normal compensatory mechanisms fail and allow intravascular coagulation to produce clinical effects that we must learn to recognize so that they can be offered temporary support by anticoagulants.

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