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Coagulation and fibrinolysis after injury

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The direct and indirect effects of injury are to stimulate coagulation and fibrinolysis, almost immediately, in direct proportion to the severity of the trauma, and with effects which are both local and remote from the site of damage. A series of blood changes follows in quick succession and may lead to a phase of apparent hypocoagulability and reduced fibrinolysis, although even at this stage there is evidence of continued stimulation of both systems. It is important to examine the mechanism of these changes in order to understand, and to be prepared to counter, the sudden haemostatic failure or thromboembolism which may result.

The accelerated blood clotting after injury is easy to see. William Hewson, describing the killing of sheep in 1772, observed that 'the blood which issued last coagulated first'. Stimulation of fibrinolysis is less readily appreciated but the unusually fluid character of the blood at necropsy in cases of violent death was commented on by Morgagni (1769) and by John Hunter (1794). The frequent succession of a 'positive' phase of hypercoagulability and a 'negative' phase of hypocoagulability was described by Wooldridge in a series of papers beginning in 1886.

To examine the process further it will be necessary to outline current concepts of blood coagulation and fibrinolysis before describing the changes observed, discussing their mechanism, and their possible significance.

Blood Coagulation

In 1964 it was proposed that the conversion of the soluble protein fibrinogen to insoluble fibrin was the culmination of a cascade (Macfarlane, 1964) or waterfall (Davie and Ratnoff, 1964) of proenzyme to enzyme transformations (Fig. 1). The reactions proceed in a stepwise manner. Each enzyme, distinguished for description from its inactive precursor by the suffix *a*, has for its substrate the next proenzyme in the sequence. The original proposals have been modified as additional information has become available based on studies with individual factors purified by chemical and immunological methods and no doubt more changes are to come (Davie, Hougie, and Lundblad, 1969).

Pathways of stimulation which are intrinsic and extrinsic to the blood have been recognized. Contact of blood with a foreign surface initiates the intrinsic pathway by conversion of Hageman factor (XII) to an enzyme (XIIa). In turn factors XI and IX are activated. Activated Christmas factor (IXa) can convert factor X to Xa and this reaction proceeds faster when IXa forms a dissociable complex with antihaemophilic globulin (VIII), phospholipid, and calcium (Hougie,

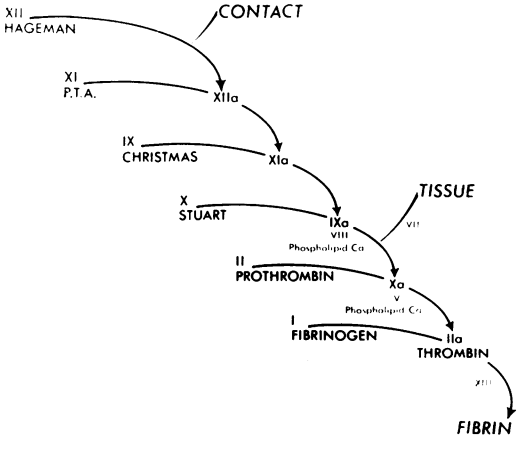

Fig. 1 *A hypothetical scheme of blood coagulation.*

Denson, and Biggs, 1967). Foreign surfaces are known to include silica compounds, ellagic acid, sodium stearate, uric acid, human skin, and collagen but the precise circumstances under which such activation occurs *in vivo* are unknown. The particular physical properties which give coagulant activity to a surface are also undefined, although the importance of water wettability and surface negative charge have been postulated (Nossel, Rubin, Drillings, and Hsieh, 1968).

The extrinsic pathway, independent of factors VIII, IX, XI, and XII, is stimulated when coagulants from tissue microsomes enter the blood to form a complex with factor VII and calcium, also for the activation of factor X.

A complex of Xa, V, phospholipid, and calcium converts prothrombin to thrombin, an enzyme which splits specific fibrinopeptides from fibrinogen to convert it to fibrin (Laki and Gladner, 1964). Thrombin has other important roles in haemostasis. Trace amounts activate fibrin-stabilizing factor (XIII) (Laki and Gladner, 1964), provoke the platelet aggregation, and release reactions which provide phospholipid catalysts for coagulation and other biologically active materials (Hellem and Stormorken, 1969), and convert factor VIII (Rapaport, Schiffman, Patch, and Ames, 1963) and factor V (Ware and Seegers, 1948) to more reactive forms. Thus factor VIII previously exposed to thrombin will increase the rate of action of IXa on factor X some 20 times. Large amounts of thrombin destroy factor VIII and factor V which are usually almost completely removed during coagulation of human blood in the test tube.

The relative importance of the intrinsic and extrinsic systems is an area of considerable doubt. Defects of either system alone may result in an increased tendency to haemorrhage while neither clearly protects against thrombosis. The patient in whom factor XII was discovered, John Hageman, recently died of pulmonary embolism after a fracture. It is difficult to envisage circumstances where damage to tissues could stimulate one pathway without affecting the other, and the distinction loses some of its importance now that similar intrinsic and extrinsic stimuli have been recognized for fibrinolysis.

Blood Fibrinolysis

Fibrinolytic activity depends on plasmin, a protease of broad specificity, which can be generated from plasminogen, a globulin with a distribution in the body similar to that of fibrinogen. A variety of activators (Fig. 2) achieve the conversion by opening a specific argininyl-valyl bond in the plasminogen molecule (Summaria, Hsieh, and Robbins, 1967).

Insoluble activators of plasminogen are found in most body tissues (Albrechtsen, 1957) associated with the lysosomes (Lack and Ali, 1964), and their entry into the blood in states of tissue damage provides an analogy for the extrinsic pathway of blood coagulation. A soluble activator of plasminogen may be derived directly from vascular endothelial cells (Warren, 1964) or generated in the blood. Activator is formed when human plasma at acid *p*H and reduced ionic strength is incubated with kaolin, an effect which is strikingly reduced in the absence of Hageman factor (Niewiarowski and Prou-Wartelle, 1959; Iatridis and Ferguson, 1961). It has also been shown that some Hageman factor-deficient subjects fail to respond to physical exertion or venous occlusion by the normal increase in circulating activator (Iatridis, Iatridis, and Ferguson, 1966). However, Hageman factor does not appear to act directly but to catalyse the formation of a plasminogen activator from a precursor, distinguishable from the other known substrates of Hageman factor (Ogston, Ogston, Ratnoff, and Forbes, 1969). This is analogous to the intrinsic mechanism of blood coagulation.

In purified solution plasmin digests many of the coagulation factors, including fibrinogen, activates certain components of complement, inactivates peptide hormones, hydrolyses immunoglobulins, and digests even collagen. In plasma, however, a great excess of antiplasmins normally prevents the expression of all proteolytic activities other than the digestion of fibrin. It has been suggested that this specificity for fibrin is conferred by the site of action of the activator. Plasmin formed in the presence of fibrin appears to be protected from antiplasmins which would otherwise be completely inhibitory (Sherry, 1968). Alternatively, circulating plasmin-antiplasmin complexes may dissociate in the presence of fibrin (Ambrus and Markus, 1960). In both hypotheses, which are not mutually exclusive, the presence of

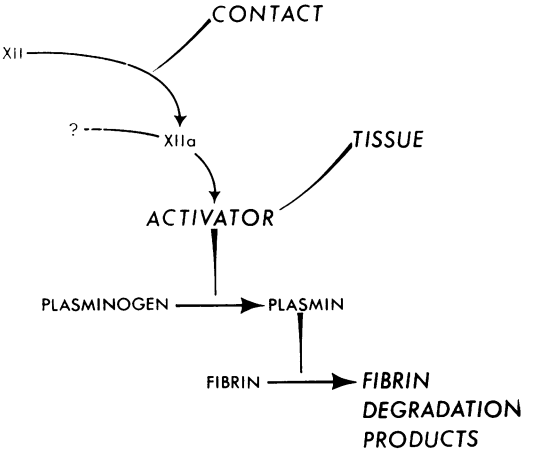

Fig. 2 *A hypothetical scheme of blood fibrinolysis.*

fibrin determines any proteolytic action of plasmin at all in the very inhibitory environment of plasma.

Blood Coagulation after Injury

Although the natural stimulus for coagulation and for fibrinolysis is not known with any precision it is clear that both systems respond to similar intrinsic and extrinsic stimuli *in vitro* and the same is likely to be true *in vivo*. There are many examples of human disease where tissue damage can be shown to stimulate both systems. After injury direct tissue damage, damage to the cellular elements of the blood, shock and haemorrhage, hypoxia, infection, and fat embolism provide ample reason to expect exposure of the blood to foreign surfaces and the entry of tissue materials into the circulation.

The resulting changes have been well described in experimental animals (Bergentz and Nilsson, 1961; Penick, Roberts, and Dejanov, 1965; Hardaway, 1967; Leandoer, 1968), in injured patients (Innes and Sevitt, 1964; Hardaway, 1966, 1967, and 1968), and after surgery (Phillips, Malm, and Deterling, 1963; Sharp and Eggleton, 1963; Barkhan, 1969).

For purposes of description the reactions may be grouped into three phases: (1) circulation of active coagulation intermediates; (2) increased consumption of coagulation factors and platelets, leading to their decreased concentration in the blood; (3) increased synthesis of coagulation factors and release of platelets, leading to their increased concentration in the blood. It should be emphasized that this is a purely artificial separation; the phases will overlap, increased consumption may not be detected after minor injuries, and little is known of their relative duration. The intensity of the changes will be directly related to the degree of injury.

Circulation of Active Intermediates

Immediately after injury the clotting time is shortened and the clotting time of blood in siliconed tubes approaches that found in uncoated glass tubes. This apparent loss of the surface-activating effect of glass suggests that the contact factors are circulating in an activated form. At the same time there may be an increase in factor VIII levels as measured by one-stage assay, for which a possible reason would be the release of thrombin already described (Penick *et al*, 1965). However, a similar increase of factor VIII follows the injection of adrenaline (Ingram, 1961) and the precise mechanism is unknown.

The importance of this stage is shown by the experiments of Wessler and his associates (Wessler and Yin, 1968a). The intravenous infusion of normal human serum, but not of plasma protected from surface contact, induces in rabbits a transient hypercoagulable state during which massive thrombosis develops in large vascular segments containing stagnant blood. The phenomenon is still observed when the static blood is far removed from the site of infusion and the production of thrombi has been shown to depend on the presence in an area of stasis of activated factors, namely, XIIa, XIa, and IXa. Thrombosis is not produced by stasis alone, or by activated factors alone, but by the combination of the two. In addition suggestive evidence has been obtained in animals that increases in factor VIII may predispose to, though not initiate, thrombosis (Penick, Dejanov, Reddick, and Roberts, 1966).

It is important that the factors are present in the activated form. Factor Xa equivalent to the activity that can be derived from 10 ml of plasma was thrombogenic in rabbits while the injection of non-activated factor X equivalent to that which could be derived from 1 litre of plasma was not (Wessler and Yin, 1968b). The hypercoagulability produced by the activated form persisted for only 10 seconds after injection unless factor Xa was combined with a suitable phospholipid, which prolonged its duration of action to 200 seconds. The rapid disappearance of factor Xa may represent the action of plasma inhibitors or its clearance, like that of other activated coagulation factors, into the reticuloendothelial cells of the liver (Spaet, 1962; Wessler, Yin, Gaston, and Nicol, 1967; Deykin, Cochios, DeCamp, and Lopez, 1968). Only the activated clotting factors are rapidly cleared by the liver which appears to discriminate between them and their non-activated forms. Though there is evidence that the clearance of factors XIIa and XIa may be slower than that of factor Xa, this dangerous phase, when thrombosis is likely in areas of stasis, probably ends rapidly once the stimulus to coagulation is removed.

Increased Consumption of Coagulation Factors

While active intermediates continue to circulate the obvious stimulation of coagulation may be replaced within a few hours, or even earlier in severe injuries, by a phase of apparent hypocoagulability due to a loss of blood coagulation factors, which in fact represents even more intense stimulation.

Clotting time, prothrombin time, and partial thromboplastin time are prolonged by the multiple deficiencies, which also coincide with a fall in the blood platelet count. Any factor may be decreased; reductions of factor VIII and V are most frequently observed. Fibrinogen is only greatly reduced in the most severe examples.

The losses could be accounted for in part by

bleeding or by leakage of intravascular contents into the tissues. They would be accentuated by dilution of the remaining plasma with extravascular fluid poor in protein as transcapillary refilling occurs and by the various fluids given by transfusion. The changes occur too rapidly for impaired synthesis to be responsible. These processes have been studied in man following burn injuries (Davies, Ricketts, and Bull, 1966) and in dogs subjected to severe haemorrhage (Leandoer, 1968) using preparations of fibrinogen labelled with radioactive iodine, and it has been clearly shown that often the preceding explanations do not suffice. With even moderately severe injuries the widespread activation of the coagulation and fibrinolytic systems uses up the factors more rapidly than they can be replaced.

The importance of intravascular coagulation is shown by the fall of the platelets, which would not be affected by fibrinolysis alone, and by the frequency with which cryoprofibrin can be demonstrated. Plasma collected at this time, particularly heparinized plasma, forms a precipitate when cooled to 4°C (cryoprofibrin), exposedt o acid *p*H, or treated with protamine or similar basic materials (Shainoff and Page, 1962; Kowalski, 1968; Lipinski and Worowski, 1968). The precipitate contains fibrin, the phenomenon has been called paracoagulation, and is thought to represent the precipitation of fibrin monomer previously held in a soluble complex with fibrinogen. Similar complexes, also soluble but incoagulable with thrombin and therefore found in the serum, are formed between fibrin monomer and the degradation products of fibrinolysis.

Further evidence of the importance of intravascular coagulation comes from the frequency with which widespread thrombosis of the microcirculation of different organs may be demonstrated at this stage. It will be necessary to return to the question of the relative importance of coagulation and fibrinolysis when the changes in the latter have been discussed.

Increased Production

A compensatory increase in output is the usual biological response of the intact organism to a decrease in the blood concentration of a particular constituent, however caused. This increase in output is also frequently excessive, as it appears to be in the case of platelets and coagulation factors whose production is increased following the phase of increased consumption, sometimes leading to blood levels of 800% or more. The increase in fibrinogen synthesis occurs very rapidly and can be demonstrated by radioactive fibrinogen studies within two hours of a major haemorrhage (Leandoer, 1968). An increased plasma fibrinogen level is usually already evident on the day after injury or surgical operation, rising progressively to a peak between seven and 10 days, and often persisting for several weeks. Increase of the platelet count is often relatively delayed so that thrombocytopenia may persist for several days before it is succeeded by a thrombocytosis. Increases of many of the blood coagulation factors, including factor VIII, may still be evident 10 to 20 days after fracture of a long bone (Davidson and Tomlin, 1963).

Although it might be reasonably argued that such an increase of clotting factors could predispose to thrombosis no such evidence of a causal effect has been presented. The experiments of Wessler, already quoted, show that the capacity to produce thrombi resides in the presence of the factors in the activated form. Presumably the circulation of active intermediates would continue during the phase of increased consumption, limited only by the availability of their precursors, but it remains uncertain whether this stimulus continues into the phase of increased production, or if so for how long. Certainly the effects of overproduction, taking into account the normal survival of the various constituents, could persist for some time after active intermediates are no longer being produced. It is, therefore, of considerable importance to determine whether the increased levels of factor VIII found at this stage are apparent, representing continuing activation by thrombin, or real due to increased synthesis of non-activated factor VIII. Some preliminary evidence (Penick *et al*, 1965 and 1966) suggests that the total quantity of factor VIII is increased.

Blood Fibrinolysis after Injury

As with coagulation the immediate effect is an apparent stimulation of fibrinolysis, with increased circulating activator of plasminogen giving a decrease in blood clot and euglobulin clot lysis times. A similar increase is found after exercise, emotion, or the injection of adrenaline (Iatridis and Ferguson, 1963; Cash and Allan, 1967a and b). This is followed by a phase of apparent reduction in circulating activator with prolonged lysis times, a finding which may persist for several weeks (Franz, Kark, and Hathorn, 1961; Davidson and Tomlin, 1963; Innes and Sevitt, 1964; Borowiecki and Sharp, 1969). However, this coincides with a rapid fall in blood plasminogen which suggests increased consumption of this protein and an increase in fibrin degradation products in the serum. Together these show that fibrinolysis remains very active. Fibrin degradation products retain the antigenic properties of fibrinogen and can be recognized in the serum as material, incoagulable with thrombin, which inhibits the reaction of an antifibrinogen serum in a variety of sensitive assay systems (Merskey, Kleino, and Johnson, 1966; Allington, 1967; Merskey, Lalezari, and Johnson, 1969).

Proof of the activity of fibrinolysis under these circumstances is provided by studies with radioactive fibrinogen in dogs following experimental haemorrhage (Leandoer, 1968) and similar experiments with the infusion of coagulants, either thrombin (Nordström, Blomback, Olsson, and Zetterquist, 1967), tissue thromboplastins (Nordström and Zetterqvist, 1969), or active material derived from postpartum human serum (Zetterqvist, 1969), which reproduce the blood changes of injury. The initial fall in circulating radioactivity, accompanied by the formation of capillary microthrombi, is followed shortly afterwards by a reappearance of circulating radioactivity, which is protein bound but incoagulable with thrombin. This has been shown to represent the presence of fibrin degradation products bearing the radioactive label. This rebound of radioactivity can be blocked with fibrinolytic inhibitors and is accompanied by a fall in circulating plasminogen. Circulating plasminogen activator may be slightly increased but is often normal, or even reduced, perhaps because of adsorption to the fibrin deposits.

There is no need to assume that *in vivo* fibrinolysis is necessarily a simple function of the amount of plasminogen activator detectable in cubital vein blood. Indeed, there is good evidence to the contrary. Activator is cleared rapidly from the blood by lungs and liver (Menon, Weightman, and Dewar, 1969). Experiments with animals (Tsapogas and Flute, 1964) and clinical experience with infusions of streptokinase and urokinase show that a very high level of activator can be present in a local area of the circulation and yet give little direct evidence of its presence in venous blood taken from a remote site. A high concentration of natural activator in uterine venous blood with little change in cubital vein blood has also been demonstrated during Caesarian section (Basu, 1969; Prentice, McNicol, and Douglas, 1969). Local activity can be recognized indirectly only if it is sufficiently intense and prolonged to produce a reduction in circulating plasminogen and an increase in fibrin degradation products (Flute, 1964 and 1965). The validity of single measurements of activator as an indicator of overall thrombolysis has also been questioned by Cash (1968) who has investigated differences between individuals in their capacity to respond to recognized stimuli.

A similar phenomenon suggestive of local fibrinolysis, with reduced activator, reduced plasminogen, and increased fibrin degradation products, is produced by the intravenous administration of Arvin, a purified fraction of the venom of the Malayan pit viper (Regoeczi, Gergely, and McFarlane, 1966; Kakkar, Flanc, Howe, O'Shea, and Flute, 1969; Pitney, Bell, and Bolton, 1969). This digests fibrinogen to form microclots but does so independently of the coagulation enzymes. It may be that the appearance of fibrin is the trigger for plasminogen depletion, increase in fibrin degradation products, and local activator release.

Coagulation versus Fibrinolysis

The phase of increased consumption is sometimes associated with abnormal bleeding, particularly from areas of tissue damage where the characteristic appearance is the paradoxical association of haemorrhage and thrombosis. This kind of bleeding is uncommon and is found primarily in those with massive injury or severe haemorrhage from other causes. In such cases, both coagulation and fibrinolysis are increased and the question arises as to which is mainly responsible for the bleeding. The question is far from academic as it is often necessary to decide in a particular case of sudden haemostatic failure whether to rely on transfusion of blood and blood products alone, to give anticoagulants, or to inhibit fibrinolysis.

Platelet and coagulation factor concentrations in the blood could be reduced below the critical levels for haemostasis if they are used up in the process of coagulation. Similar reductions in coagulation factors, though not of platelets, could be produced by fibrinolysis sufficient to cause the uncontrolled action of plasmin. The increase in fibrin degradation products may contribute to the haemorrhagic state, for these products of fibrinolysis, when not complexed with fibrin monomer, inhibit the action of thrombin and other coagulation enzymes, cause defective polymerization of fibrin monomer, and block platelet adhesion, aggregation, and release reactions (Kowalski, 1968).

Final judgment of the relative importance of the two systems must await more definite identification of specific intermediates in individual cases, not possible at present. Perhaps the fibrin formation of coagulation could be measured from the amount of circulating fibrinopeptides, the specific fragments released from fibrinogen by thrombin. Fibrinolysis, which is desirable, and fibrinogenolysis, which may indicate the uncontrolled action of plasmin, could be separated if it were possible to distinguish between the degradation products of the two reactions. However, there is good evidence from experimental and clinical studies that reversal of coagulation is the more important and that inhibition of fibrinolysis alone may be dangerous. In experimental studies with labelled fibrinogen the decrease of platelets, fibrinogen, and plasminogen and all the changes in plasma radioactivity, that is to say, both coagulation and fibrinolysis reactions, are blocked by the administration of heparin before bleeding or the infusion of coagulants (Zetterqvist, 1969). It should be emphasized that heparin, in the doses given, would have no direct inhibitory effect on fibrinolysis; this is a biological effect in the intact organism,

preventing the formation of fibrin appears to prevent fibrinolysis. In the experimental studies heparin has usually been given before the stimulus to coagulation but there is good evidence that heparin will also correct the changes in fibrinolysis in human patients already suffering from the effects of disseminated intravascular coagulation (Merskey, Johnson, Pert, and Wohl, 1964; Straub, Riedler, and Frick, 1967; Robboy, 1969). An example observed by the author is illustrated in Figure 3. In these and other patients heparin has been given with success even while the patient is actually bleeding (von Francken, Johansson, Olsson, and Zetterqvist, 1963; Verstraete, Amery, Vermylen, and Robyn, 1963; Merskey, 1968).

The administration of specific fibrinolytic inhibitors, epsilon-aminocaproic acid, tranexamic acid, or Trasylol, blocks only the fall of plasminogen and secondary release of fibrin degradation products in the experimental situation while allowing the fall in platelets, fibrinogen, and coagulation factors, and therefore the tendency to microthrombosis, to proceed unchecked. The inhibition of fibrinolysis increases fibrin deposition in the organs which could contribute to further tissue damage (Ratnoff, 1969). It has been shown (Wessler, Freiman, Suyemoto, and Reimer, 1961) that it is not possible to produce thrombi in areas of stasis within the small vessels of the hamster cheek pouch by injections of serum, which are sufficient to cause massive thrombosis in an isolated segment of the jugular vein of the same animal, unless the animals are pretreated with fibrinolytic inhibitors. Fibrinolysis therefore seems to be more active in the microcirculation. Whether this implies a qualitative difference in fibrinolytic potential in vessels of differing size or merely reflects a greater surface-to-volume ratio in the small vessels is unknown.

Significance of the Changes

Injury, therefore, stimulates blood coagulation and fibrinolysis concurrently. This would be the expected and desirable response, providing a mobilization of resources for haemostasis and tissue repair. The stimulation would be held in check and localized, so far as possible, to areas of damage by a variety of highly efficient compensation mechanisms equally significant to the coagulation and fibrinolytic systems (Fig. 4). Circulating enzyme inhibitors are supplemented by the rapid and selective clearance of the activated factors into cells of the reticuloendothelial system of the liver and elsewhere. This requires the continuation of blood flow which, as seen already in this symposium, may itself be affected by injury. Arterial hypotension, arteriolar constriction, the opening of fresh capillaries, and arteriovenous shunts contribute to reductions in tissue perfusion (Hardaway, James, Anderson, Bredenberg, and West, 1967; Hardaway, 1968). Changes in the rheological properties of the blood itself must also be mentioned, particularly the increase of fibrinogen and haemoconcentration (Replogle, 1969). In addition, flow may be affected by platelet adhesion and aggregation, which will also have modifying effects on coagulation and fibrinolysis (Hellem and Stormorken, 1969).

Fibrinolysis is the only recognized compensation for fibrin in static blood. It serves the dual function of dissolving fibrin deposits and providing a supply of fibrin degradation products which will hold additional fibrin monomer in

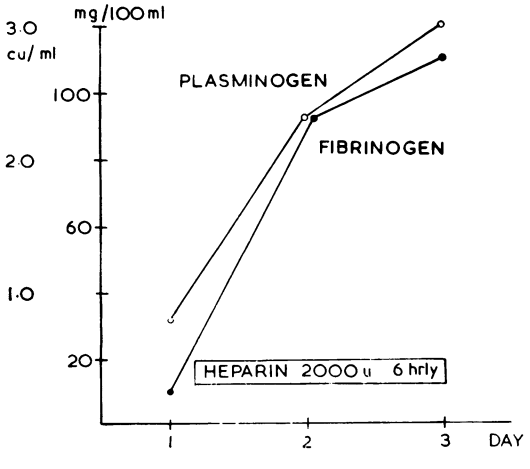

Fig. 3 *Effect of heparin treatment on plasma plasminogen and fibrinogen in a patient with disseminated intravascular coagulation and secondary fibrinolysis.*

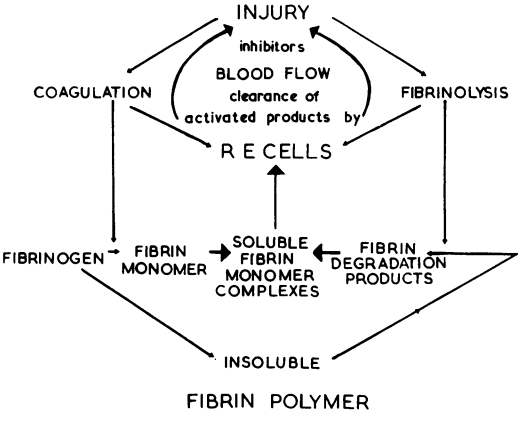

Fig. 4 *Compensating processes following stimulation of coagulation and fibrinolysis.*

solution, and thereby allow its carriage to fixed cells of the reticuloendothelial system for final disposal.

When these compensating mechanisms fail 'disseminated' intravascular coagulation may cause widespread thrombosis of the microcirculation with the possibility of the shock, bleeding, and tissue necrosis of the defibrination syndrome. For longer periods the presence of circulating active intermediates of coagulation implies a risk of 'localized' intravascular coagulation, thrombosis of major vessels in areas of stasis. Perhaps this tendency continues, in some measure, until all the injuries are finally healed and the stimulation of cellular damage to coagulation and fibrinolysis is at an end.

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