Disseminated intravascular coagulation: a review

P. J. HAMILTON¹, A. L. STALKER, AND A. S. DOUGLAS

From the Departments of Medicine and Pathology, University of Aberdeen, UK

Introduction

Widely differing diseases offering no obvious threat to haemostasis are occasionally associated with inappropriate activation of the coagulation mechanism. When such a reaction is focal and involves a large vessel thrombosis ensues. Sometimes a more diffuse or disseminated intravascular coagulation is encountered. This affects predominantly the microcirculation and causes deposition of derivatives of fibrinogen in arterioles, capillaries, and venules. Disseminated intravascular coagulation is a secondary phenomenon, an intermediary mechanism of disease (McKay, 1965), complicating a variety of primary disorders (Table 1).

Table 1 *Some of the disease processes and clinical conditions associated with DIC*

Disease category	Example
Congenital abnormality	Cavernous haemangioma, hyaline pulmonary disease of newborn
Injury	Trauma, drowning, heat stroke, burns, envenomation
Infection	Bacterial, viral, rickettsial, protozoal (eg, malaria)
Immunological	Incompatible blood transfusion, allograft rejection, anaphylactic drug reactions, immune complex disease
Neoplastic	Leukaemia, solid tumours
Metabolic/endocrine	Diabetic ketoacidosis, acute fatty liver of pregnancy
Circulatory	Shock, pulmonary embolism, dissecting aneurysm, cyanotic heart disease
Obstetric	Amniotic fluid embolism, abruptio placentae, retained dead fetus

Problems of nomenclature

There is a confusing number of synonyms for this pathophysiological process. The term 'generalised Shwartzman reaction' is used when intravascular coagulation is induced in suitably prepared experimental animals by a variety of stimuli, usually endotoxins (Lee and Stetson, 1965); this model has

served a useful purpose in drawing attention to one common mechanism of production of the disease process, but this term should now be confined to the precise experimental situation.

As the process is concerned with the triggering of coagulation and its subsequent evolution, objection can be raised to terms which assign importance to fibrin rather than to fibrinogen, for example, fibrinopathy, fibrination, or defibrination syndrome. Defibrinogenisation is an inelegant term. Hypofibrinogenaemia and consumption coagulopathy (Rodriguez-Erdmann, 1965) are also unsuitable as many examples of the condition have normal, or even elevated, levels of clotting factors. Intravascular coagulation and fibrinolysis (ICF) is the term favoured by Bowie and Owen (1977) and has much to recommend it although the importance of fibrinolysis in the process is disputed. Disseminated intravascular coagulation (DIC) is the most popular term and is used here, although it is necessary to bear in mind that the process can be quite localised. One such example is proliferative glomerulonephritis, an immune-complex disease, where deposition of fibrinogen products occurs within the glomeruli and there is little in the way of systemic abnormality. On the other hand, a good example of a condition in which localised coagulation is associated with systemic effects is the Kasabach-Merritt syndrome, where intravascular coagulation occurs in a large cavernous haemangioma yet consumption of coagulation factors can be identified on examination of peripheral blood (Hillman and Phillips, 1967).

Definition and pathophysiology

DIC begins with the appearance of procoagulant activity in the dynamic (or active) circulation. There is often consumption of clotting factors and platelets, with a resulting haemostatic defect in association with microvascular obstruction by 'fibrin'. Secondary activation of fibrinolysis can follow; this may occur in the microcirculation without detectable changes in the fibrinolytic enzyme system in peripheral blood. The process terminates when the deposited 'fibrin' is totally digested and haemostasis

¹Present address: Haematology Department, Royal Victoria Infirmary, Newcastle-upon-Tyne.

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returns to normal. The intensity and duration of activation of this pathophysiological reaction—what may be called the tempo of the process—is of crucial importance and influences the clinical picture and the laboratory findings. In many instances DIC is of little or no clinical significance and the diagnosis is suspected only after haematological abnormalities have been found. On other occasions the tempo of DIC is such that the features of the primary disease are overtaken by the sudden onset of life-threatening haemorrhage or hypoperfusion of vital organs due to microcirculatory obstruction. Considerable difficulty can occur in making the diagnosis of DIC because of problems in the interpretation of laboratory tests of the haemostatic mechanism and, at necropsy, in the histological demonstration of fibrin and platelets. It is unrealistic to expect a common pattern of laboratory abnormality in both fulminant, severe, and chronic low-grade forms of DIC.

This review deals primarily with clinicopathological problems in DIC, notably its diagnosis and management. No account is given of the complex and incompletely understood mechanisms involved in the activation of the coagulation and fibrinolytic processes.

Occurrence of DIC in hospital patients

The literature, predominantly in the form of single case reports, documents DIC as a complication of many diseases; in a recent review (Sharp, 1977), over 50 were listed. There is, however, little information as to the frequency with which it may occur in routine hospital practice. In a consecutive necropsy series 3% of patients were found to have histological evidence of DIC, but this had seldom been suspected clinically (Kim *et al.*, 1976). In a retrospective series from a large Israeli general medical centre (Siegal *et al.*, 1978), the approximate observed frequency of DIC (diagnosed on the basis of abnormalities of haemostatic function) was 1 per 1000 general admissions; in about one-fifth of these cases DIC was clinically silent, only laboratory abnormalities being detected.

Rather more information is available as to the underlying disorders associated with established DIC. At present there is little or no information on the incidence of DIC as a complication of any one disease process.

CLINICAL MANIFESTATIONS OF DIC

These patients are often seriously ill as a consequence of the primary disease process, the microcirculatory embarrassment, and haemorrhage. The clinical features will depend on the initiating disease and the organs affected by the circulatory disturbance. When

the DIC is not acute there may be no symptoms or signs related to this mechanism.

An important presentation of DIC is the laboratory observation (often fortuitous) of distorted and fragmented red cells (schistocytes) and a diminished number of platelets in the peripheral blood film of a patient. The mechanism of production of these cells was clarified by the elegant observations of Brain *et al.* (1962), who demonstrated the production of the fragmentation as a consequence of physical damage to the erythrocytes by the intravascular strands of fibrin, thus producing a microangiopathic haemolytic anaemia (MAHA). Such blood films are often found when the microvascular disease involves the kidneys and may be unaccompanied by any other detectable clinical or coagulation abnormality. In middle-aged or elderly patients without evidence of hypertension, diabetes, or renal failure the finding of MAHA may have sinister connotations as it can be a manifestation of adenocarcinoma, often of gastrointestinal origin (Brain *et al.*, 1970). DIC is often associated with a deterioration in renal function, and two-thirds of microthrombi detectable at necropsy in one series of patients who had died of DIC were found in the kidney (Robboy *et al.*, 1972). In some patients with the haemolytic uraemic syndrome, immune complexes appear to damage vascular endothelium (Barré *et al.*, 1977) and, as a consequence of such damage, activation of the coagulation system occurs, leading to intracapillary and arteriolar thrombus formation and subendothelial accumulations of fibrin polymers (Vitsky *et al.*, 1969).

Renal failure with fever and neurological symptoms and signs characterises Moschowitz's syndrome (thrombotic-thrombohaemolytic thrombocytopenic purpura) in which extensive small-vessel thrombosis and MAHA are demonstrable. DIC provides a final common pathway for the development of this rare syndrome, which can be seen as an expression of diverse conditions, for example, infection, vasculitis, immune haemolytic anaemia, and glomerulonephritis (Umlas and Kaiser, 1970).

Bleeding may be seen as petechiae, purpura which may be elevated, haemorrhagic bullae, and acral cyanosis; the latter appears as a gun-metal grey to purple discoloration of the skin with sharp but irregular demarcation from normal areas (Robboy *et al.*, 1973). The clinician should be alerted to the presence of DIC by such lesions appearing on the fingers, toes, ears, and nose in the presence of arterial pulsation. Occasionally, purpura fulminans dominates the whole clinical syndrome, presenting as a confluent purpura of sudden onset associated with the development of haemorrhagic bullae and focal gangrene. Bleeding can be interstitial or from

the mucosal surfaces, involving the gastrointestinal or genitourinary tracts, or commonly from venepuncture sites.

Involvement of the pulmonary circulation with dyspnoea, haemoptysis, râles, and a diffuse infiltrate on chest x-ray were found as a preterminal complication of DIC by Colman *et al.* (1972). Less dramatically, a progressive and debilitating loss of lung function can develop, particularly after multiple injury. Saldeen (1976) has suggested that the severity of such pulmonary dysfunction correlates better with the number of pulmonary vessels found plugged with fibrin microthrombi than with fat emboli.

The clinical expression of DIC is a consequence of microcirculatory occlusion. Thrombosis of larger vessels is a relatively uncommon presenting sign of DIC; but it complicated the course of approximately one-fifth of patients in one series, usually in relation to the insertion of intravenous catheters (Minna *et al.*, 1974).

Cancer is believed to be associated with an increased incidence of clinical thrombotic events. In cancer predominantly of the pancreas, lung, and stomach (Sack *et al.*, 1977), chronic DIC may be the mechanism causing recurrent episodes of thrombophlebitis, haemorrhage, non-bacterial thrombotic endocarditis, and arterial embolisation. Patients with cancer and DIC may also have confusion, coma, convulsions, and focal signs of brain damage.

LABORATORY STUDIES IN DIC

When DIC is induced by infusing thromboplastin in rabbits (Slaastad and Jeremic, 1973) or dogs (Cooper *et al.*, 1971; 1973) laboratory tests of coagulation differ according to the intensity and duration of the stimulus triggering the coagulation mechanism and the times of sampling during and after the period of activation. In the clinical situation serial testing may not be possible, and the stage of development of the dynamic process of DIC is thus unknown. The interpretation of an isolated set of findings can therefore be difficult.

Acute DIC

In experiments where large amounts of thromboplastin are infused there is a fall in the number of platelets and the concentrations of fibrinogen and factors V, VII, VIII, XI, XII, and XIII, often to very low levels. Such findings are analogous to those found in the more acute presentations of DIC in man, when activation of coagulation is severe enough to cause consumption and consequential lowered concentration of haemostatic factors. In such circumstances there is little difficulty in establishing the diagnosis of DIC.

However, in inflammatory and neoplastic disease,

fibrinogen and factor VIII levels and the platelet count may in the first instance be elevated, and any consumption of these factors may be masked. In such circumstances the laboratory data may not permit a diagnosis of DIC.

Low-grade DIC

When much smaller amounts of thromboplastin are experimentally infused over periods of days or weeks the platelet count falls, though not always to levels expected from more acute experiments. *Fibrinogen levels* at first fall only to climb to higher than the initial values with continuing infusion. Such a response represents a compensatory increase in synthesis of haemostatic factors induced by chronic DIC. Fibrinogen turnover studies have demonstrated as much as a fivefold increase in hepatic fibrinogen synthesis in dogs (Owen *et al.*, 1973). An apparent paradoxical elevation in *factors V, VIII, XII, and XIII* is also an occasional finding, probably on the same basis. These changes may be accompanied by shortening of *screening tests of the coagulation system*, in particular the activated partial thromboplastin time, a test of the intrinsic clotting system; in the experimental and the clinical settings of subacute or chronic DIC, lengthening commensurate with a consumption coagulopathy seems more appropriate. Such shortening of reaction times in the one-stage coagulation tests and the factor assays based upon them is usually attributed to the presence of activated products of the coagulation cascade. Normally, activated enzymes of the coagulation system complex with antithrombin III and other protease inhibitors and are then cleared by the reticuloendothelial system. In DIC *antithrombin III levels* fall and the *reticuloendothelial system* may become overloaded and work suboptimally.

Similarly, in chronic DIC in man, normal or elevated factor levels may be found at different times in the same patient. However, a low platelet count even in an appropriate clinical context does not, in the absence of other supportive findings, necessarily imply DIC. Thrombocytopenia is not uncommon in septicaemia, and in endotoxaemic rabbits low platelet counts occur despite pretreatment with heparin (Corrigan, 1971).

Fibrinogen derivatives and complexes, and their removal

After the generation of thrombin, fibrinogen is cleaved into fibrin monomer and fibrinopeptides A and B. Fibrin monomer will then polymerise spontaneously, gel, and precipitate to form, under the action of activated factor XIII, cross-linked stable fibrin (Figure). When fibrinogen monomer is found in low concentrations and below a critical level of

Figure Fibrinogen conversion to fibrin

5% of total fibrinogen, polymerisation will not occur spontaneously. Under these conditions fibrin monomer interacts with fibrinogen to form a soluble fibrin complex, fibrinogen dimer. Such a reaction is likely to occur when small amounts of fibrin monomer are generated and fibrinogen levels are high, conditions which can be expected in the more subacute forms of DIC. In addition to fibrinogen dimer, a whole family of soluble fibrin complexes forms in the circulation of patients with DIC because of interactions between fibrinogen, soluble fibrin monomer, and a number of plasmin degradation products of fibrinogen and fibrin (FDP-fibrinogen and/or fibrin degradation products).

The reticuloendothelial system will take up and phagocytose soluble complexes (Lee, 1962; Gans and Lowman, 1967), and leucocytes may have an important role in the removal of microcirculatory deposits of fibrin and fibrin complexes (Lewis *et al.*, 1972; Plow and Edgington, 1975). Plasma also has an intrinsic and potentially powerful fibrinolytic enzyme system (McNicol and Davies, 1973). Activation of this plasminogen-plasmin fibrinolytic enzyme system is demonstrable during cardiopulmonary bypass procedures complicated by DIC (Douglas *et al.*, 1966) and when DIC occurs in connection with the surgical handling of tissues rich in plasminogen activator (McNicol *et al.*, 1966). Furthermore, the FDP that arise after use of the anticoagulant snake venom derivative, anicrod (Arvin), which acts directly on fibrinogen, are indistinguishable from FDP formed from *in vitro* plasmin digests of fibrinogen (Prentice *et al.*, 1974).

Assessment of the fibrinolytic enzyme system in DIC
In routine diagnostic practice there is little to be gained from a search for secondarily increased fibrinolytic activity of the blood; the features of this are raised plasminogen activator levels, measured by euglobulin clot lysis times, lowered levels of plasminogen, or evidence of hyperplasminaemia, but

these changes are surprisingly infrequent in most patients with DIC. An important coagulation investigation is simple observation of the clot that forms in the whole blood clotting time test. Fragile wispy clots, which disintegrate within 15-30 minutes, suggest increased fibrinolysis.

The thrombin clotting time is also a simple but very helpful, rapidly performed test, which provides an indirect measure of fibrinolytic activity in that it is prolonged if the fibrinogen is low (< 0.6 g/l) or significant amounts of FDP have been formed.

Biological activities, detection, and measurement of FDP

FDP, however they arise, have important biological activities, which can be expected to worsen any haemorrhagic diathesis. They interact with fibrin monomer and fibrin complexes and interfere with fibrin polymerisation (Hirsch *et al.*, 1965); they also possess antithrombin activity (Niewiarowski and Kowalski, 1968) and may affect platelet function (Larrieu, 1971).

Unfortunately, the tests used to quantify FDP fail to distinguish FDP from the parent molecule fibrinogen; accordingly, serum rather than plasma must be used. For accurate results fibrinogen is removed by clotting blood in the presence of powerful inhibitors of any continuing fibrinolytic activity, for example, epsilon-aminocaproic acid (EACA), tranexamic acid (AMCA), or aprotinin (Trasylol).

Clotting by thrombin in the presence of a fibrinolytic inhibitor will result in the unavoidable removal of some of the early clottable FDP and soluble fibrin complexes. Such losses may, in part, account for the occasional absence of assayable serum FDP in patients with undoubted DIC. In rabbits, endotoxin-induced DIC can be accompanied by inhibition rather than activation of fibrinolysis (Bergstein and Michael, 1973). Certain strains of staphylococci have been found to clump in the presence of fibrinogen and some of its larger breakdown products, and this

reaction has been used to quantify FDP in serum (Allington, 1967). Most of the techniques used to assay FDP are immunological, dependent upon rabbit antisera raised against fibrinogen and the different end products formed in thrombin cleavage of fibrinogen or plasmin digests of fibrinogen. Much of the work that has so far been reported, using techniques which include latex agglutination slide tests, tanned red cell haemagglutination inhibition assays, immunoelectrophoresis, and radioimmunoassay procedures, do not differentiate between the various FDP, fibrin complexes, fibrin monomer, and fibrinogen. As such these tests are best thought of as measures of fibrinogen-fibrin related antigen (FR-antigen) or of molecules immunologically similar to fibrin/fibrinogen (MISFI). As assays of more specific products of the fibrinogen-fibrin reaction and the different degradation products become available, improvements in our understanding of the reactions themselves and their possible use in diagnosis will become clearer (Gaffney, 1977a, b). One step in this direction has been the description of an assay for fibrinopeptide A (Nossel *et al.*, 1974). Also a radio-immune assay is now available for fragment E, formed as a consequence of fibrin/fibrinogenolysis.

The presence of excess FDP cannot be considered diagnostic of intravascular coagulation. Raised FDP levels are found in the serum of patients with various diseases, appearing, for instance, after surgery, in cancer, rheumatoid arthritis, glomerulonephritis, pregnancy, infection, deep venous thrombosis, and pulmonary embolism (Wood *et al.*, 1972; Cooper *et al.*, 1974; Egan *et al.*, 1974). In some instances they reflect lysis of extravascular fibrin deposits or localised intravascular fibrin deposition. In practice, however, a serum FDP level greater than 100 $\mu\text{g/ml}$ is useful support for a diagnosis of DIC. Cash (1977) has suggested that, provided the plasma fibrinogen is greater than 0.6 g/l, prolongation of the thrombin clotting time is usually associated with serum FDPs greater than 150 $\mu\text{g/ml}$.

The use of simple qualitative tests for the presence of *soluble fibrin complexes* as an indicator of intravascular coagulation has advocates. These so-called paracoagulation or gel tests are based on the principle of fibrin monomer being less soluble in plasma than fibrinogen. By simple physicochemical manipulation fibrin complexes can be dissociated and the fibrin monomer component induced to polymerise and gel out of solution. Cooling to demonstrate cryofibrinogen was the first test developed (Shainoff and Page, 1962), but more recently ethanol (Breen and Tullis, 1969) and protamine (Gurewich and Hutchinson, 1971) have been used. The specificity of these tests has been questioned (Godal and Kierulf, 1971) as fibrinogen and other plasma proteins may be

precipitated out on occasion.

The presence of circulating soluble fibrin monomer may also result in prolongation of thrombin clotting times, which shorten towards control values if performed with the addition of calcium. Furthermore, soluble fibrin monomer is associated with considerable delay in the Reptilase test when the venom of *Bothrops atrox* is used instead of thrombin to clot fibrinogen. Such observations are diagnostically useful.

Antithrombin III and thrombocytopenia

An important advance in our understanding of haemostasis has been an appreciation of the key role of antithrombin III. In the promotion of blood coagulation there is generation of the serine proteases, activated Fletcher factor, factors XIIa, XIa, IXa, Xa, and thrombin. Antithrombin III combines irreversibly with these activated factors to neutralise them (Rosenberg, 1976). In DIC, consumption of antithrombin III would be expected to occur, and preliminary investigations have demonstrated that this is so (Bick *et al.*, 1977). The usefulness of measuring antithrombin III in clinical practice remains to be determined.

Thrombocytopenia is a common accompaniment of DIC, and methods have been developed aimed at detecting substances released from platelets into plasma during intravascular coagulation. A radio-immune assay for platelet factor IV has been described (Bolton *et al.*, 1976); Ludlam *et al.* (1975) have introduced a technique for detecting β -thromboglobulin, a platelet specific release protein. These tests are at present at the developmental stage.

LABORATORY DIAGNOSIS OF DIC IN PRACTICE
Particular clinical situations will suggest the possibility of DIC; laboratory assistance will be required to provide support. Every test of haemostatic function has limitations, and no single technique can be used to confirm or exclude a diagnosis of DIC. A battery of tests can do no more than provide support for confirmation or denial of the diagnosis and can never replace the overall assessment of all the evidence by the clinician. The patient may be seen because of serious bleeding. On other occasions no unusual bleeding or thrombosis may be present, and microcirculatory blockage may not be apparent. A biopsy may be inappropriate or fail to show the pathological lesion. Even the most sophisticated laboratory facilities may not provide a precise definition, and the clinician may be forced to make a working diagnosis. He should seek assistance from his laboratory but appreciate that the findings may be unhelpful.

The laboratory findings have been studied by several investigators (Colman *et al.*, 1972; Minna *et al.*, 1974; Al-Mondhiry, 1975; Lewis *et al.*, 1977; Siegal *et al.*, 1978). The tests used have been blood film, platelet count, thrombin time, prothrombin time, partial thromboplastin time, the fibrinogen-related (FR) antigen, staphylococcal clumping, protamine gel, ethanol gel, assays of antithrombin III, fibrinogen, prothrombin, factor V, factor X, factor VII, factor VIII, factor IX, and euglobulin lysis time. The findings of these authors have been collected together in Table 2.

Table 2 *Percentage of laboratory abnormalities found in patients with DIC*

Tests performed	Series				
	A n = 215	B n = 118	C n = 89	D n = 48	Total n = 470
Blood smear	71	—	27	—	
Platelet count	96	88	100	93	94
Thrombin time	71	85	84	59	76
Prothrombin time	72	98	87	90	83
Partial thrombo- plastin time	65	93	62	—	72
Fibrinogen	55	23	66	71	51
FR-antigen	79	67	67	92	74
Staphylococcal clumping	82	—	—	—	
Protamine gelation	59	—	—	—	
Ethanol gelation	78	—	—	—	
Euglobulin lysis time	—	—	7	42	
Anti-thrombin III	76	—	—	—	
Factor II	65	—	—	—	
Factor V	52	—	61	—	
Factor VIII	13	—	18	—	
Factor VII	71	—	—	—	
Factor X	54	—	—	—	
Factor IX	24	—	—	—	

Series A Lewis *et al.* (1977)
 B Siegal *et al.* (1978)
 C Al-Mondhiry (1975)
 D Colman *et al.* (1972)

The most useful and consistently abnormal findings were thrombocytopenia and prolonged thrombin and prothrombin times. Fibrinogen level was low in approximately half the patients; infection causes a rise in fibrinogen level, and as this is the commonest primary cause of DIC it is not surprising that a fibrinogen level below normal is then unusual.

There are individual reports throughout the literature on DIC suggesting lowered levels of factors V and VIII; in the most systematic studies involving series of patients this has not been confirmed, although two-stage tests, which avoid the problems caused by the presence of activated factors in the assays, may not always have been used. Of some interest is the report by Lewis *et al.* (1977) that lowered factor VII concentration is not uncommon. Endotoxin activation of the extrinsic clotting system through an action on leucocytes and factor VII in

the absence of platelets has been suggested (Muller-Berghaus and Bohn, 1976). In the future, comparisons of assays (immunological and coagulant) of factor VIII may prove a sensitive indicator of DIC. This has already proved of value in pre-eclampsia (Thornton and Bonnar, 1977).

Clearance of activated coagulation factors by the liver may be defective in hepatic disease; this could lead to DIC. The *diagnosis of DIC in liver disease* presents particular problems. Increased fibrinolytic activity after reduced clearance of plasminogen activator and impaired synthesis of fibrinolytic inhibitors has long been associated with liver disease. Such activity will, in combination with disordered synthesis of fibrinogen, result in hypofibrinogen-aemia in the absence of DIC. Reduction in vitamin K-dependent clotting factors is not unusual. Thrombocytopenia is often attributable to concomitant hypersplenism. Bloom (1975), in reviewing this difficult subject, was forced to conclude that the presence of significant intravascular coagulation in patients with hepatocellular disease has not been unequivocally established.

HISTOPATHOLOGY OF DIC

It is important to establish a tissue diagnosis of any pathophysiological process, and DIC is no exception to this principle. There are, however, difficulties. Identification of platelet aggregation and fibrin deposition in the microcirculation would be the best evidence of triggering of the coagulation mechanism. However, studies by the optical microscope are unrewarding in the case of platelets; these require ultrastructural studies for proper demonstration and evaluation, and all too often necropsy material is unsatisfactory for this.

Problems also exist with the histological identification of fibrin. 'There are few satisfactory staining methods for fibrin; there are even fewer clear definitions of the material for which these stains are commended' (Lendrum *et al.*, 1962). This is still true today. Variables such as the degree of agitation of fibrin clot, other substances incorporated within the clot (such as albumin, high molecular weight globulins, and lipoproteins) and concomitant fibrinolysis all affect staining (Stalker, 1976). Most laboratories have their preferred methods of staining, and the studies of Gitlin and Craig (1957), Moe and Abildgaard (1969), and Lendrum *et al.* (1962) may be consulted for techniques. We favour the Martius Scarlet Blue (MSB) technique of the latter authors but recognise that its specificity is still imprecise. Use of immunofluorescence techniques gives a more specific demonstration of fibrinogen, fibrin, and some of their split products although immunological overlap still clouds the picture. The characteristic

ultrastructural appearance of fibrin (fibril cross-striations with a 24 nm periodicity) is also dependent on variable factors, especially agitation and fibrinolysis, so that it is infrequently seen in examining pathological material. Not only are the available methods for identification of fibrin imperfect but also the occurrence of postmortem fibrinolysis (Mole, 1948) must be recognised. This can reduce very substantially the amounts of fibrin found at necropsy.

There are thus major limitations to the uncritical use of histopathological techniques in assessing microvascular fibrin deposition and the severity of DIC in necropsy material. Fresh biopsy material affords a better chance but this will not often be available. At the moment it is all too common to encounter negative findings at necropsy in cases diagnosed as DIC in life by haematological findings (Robboy *et al.*, 1972; Kim *et al.*, 1976). There is, therefore, an urgent need for more extensive investigation of the ultrastructural changes in the microvasculature in biopsy material, especially from organs in experimental DIC in animals. In one such model it has been shown (Brown *et al.*, 1969) that fibrin deposition in the microvessels is associated with extrusion of endothelial cell nuclei, which become intensely haematoxylinophilic on staining in contrast to the eosinophilia of the deposited fibrin. These 'haematoxylinophil bodies' circulate, and can be numerous, and occasionally aggregated and compacted, in pulmonary capillaries. Their association with fibrin-like material in microvessels has been suggested as presumptive evidence of DIC (Simpson *et al.*, 1971); experimental (Donald, 1972) and clinicopathological (Goodall, 1973) support exists for this view, although it has not yet been fully tested. Goodall has also pointed to the value of examining the buffy coat of the blood for irregular nuclear masses as a ready way of drawing attention to the diagnosis of DIC in the living.

In summary, the histopathology of DIC is straightforward in theory but difficult to demonstrate in practice. Careful search for even tiny microthrombi or strands of fibrin in the microcirculation is well worth while. With increasing use of ultrastructural and immunopathological methods and better knowledge of the structure of fibrinogen and its products we can look forward to improvement in our diagnostic facilities.

MANAGEMENT OF THE PATIENT WITH DIC

It cannot be overemphasised that DIC is an intermediary (or secondary) mechanism of disease occurring within the context of the primary disease process. As such the most important principle of treatment is the adequate therapy of the underlying disease so that the factors responsible for triggering

DIC are rapidly reduced and ideally abolished. Cash (1977) has drawn attention to the importance of the serial use of coagulation tests in order to monitor the adequacy of treatment of the primary disease process. He has also stressed the need for close and continuing clinicopathological review if the significance of the contribution of DIC to a patient's clinical condition is to be assessed properly and requisite counter-measures promptly set in hand when necessary.

In the confused and conflicting literature on this subject there is a similarity of recorded fatality rates:

Israeli series	(Siegal <i>et al.</i> , 1978)	55%
Pittsburgh series	(Lewis <i>et al.</i> , 1977)	65%
Massachusetts General series	(Minna <i>et al.</i> , 1974)	67%
Sloan Kettering series	(Al-Mondhry, 1975)	49%

In the acutely ill patient the need is to buy time until the underlying disease process can be brought under control. Vital bodily functions must be sustained, if need be by artificial ventilation and renal dialysis. The management of any haemostatic defect is based upon the intensive use of appropriate blood component therapy. The importance of combating shock must be appreciated. Shock is not only a frequent clinical accompaniment of DIC in the critically ill patient but shock itself is a potent factor in initiating and perpetuating DIC (Hardaway, 1967). Steps must be taken to ensure adequate tissue perfusion by maintaining blood volume with the prevention or reversal of anoxia, acidosis, and vasoconstriction if the problems of the patient with DIC are not to be compounded. In this regard it will be remembered that human plasma protein solution is the acute volume expander of choice as dextrans can exacerbate bleeding (Moriau *et al.*, 1974). Alpha-adrenergic blocking drugs may also be useful, for there is evidence that intense sympathetic overactivity is involved in the development of local DIC in experimental animals (McKay *et al.*, 1971). Steroids may potentiate the vasoconstrictor effects of catecholamines (Reis, 1960), and the present vogue for high-dose steroids in the treatment of shock requires reassessment if DIC is present.

The sudden onset of catastrophic life-threatening haemorrhage is mercifully an infrequent presentation of DIC in clinical practice. It is most often seen as an obstetric emergency (Merskey *et al.*, 1967), and treatment in such situations requires prompt intervention to ensure complete evacuation and contraction of the uterus combined with blood replacement. Intense activation of the blood coagulation mechanism turns plasma to serum with the consumption of platelets, factors I (fibrinogen), II (prothrombin), V, VIII, and XIII. Regeneration of these haemostatic factors takes some time, and the patient will continue to be at risk of haemorrhage for an

appreciable period unless suitable replacement therapy is instituted. As Wallace (1973) has pointed out, even in this era of component therapy, there is a place for the transfusion of fresh whole blood, particularly if the defect is of the multifactorial type. But the cornerstone of therapy is likely to remain stored blood or red cell concentrate and plasma protein solution to maintain blood volume complemented by platelet concentrates, fresh frozen plasma, and cryoprecipitate, a rich source of fibrinogen, to maintain haemostatic integrity. At present use of prothrombin complex concentrates containing factors II, VII, IX, and X is not recommended on account of their thrombogenic potential (Kaspar, 1975).

The problem with replacement therapy lies with the patient in whom the basic underlying disease process has not been brought promptly under control and triggering of intravascular coagulation continues. By replenishing the supply of exhaustible coagulation factors there is a risk of further generation of fibrin; this fibrin will then be deposited throughout the microcirculation to the embarrassment of vital organ function. There has been interest in interrupting, or at least modulating, the process of intravascular coagulation by using anticoagulants, usually heparin. There is no doubt that in experimental circumstances the protective effects of heparin and warfarin have been demonstrated for many years (Good and Thomas, 1953; Shapiro and McKay, 1958). The role of heparin in the management of DIC in man is much less certain. The individual clinician is left to take this decision in the face of very incomplete evidence. The emphasis must be on the correction of the triggering mechanism. There are very few clinicians who would be prepared to give heparin in placental abruption.

In chronic DIC in association with disseminated malignancy the fibrinogen level will rise and bleeding will cease with heparin; where haemorrhage in these patients is troublesome, for example, persistent epistaxis, heparin can be used. In missed abortion, heparin will raise the fibrinogen level; once this has been attained heparin should be stopped and the uterus emptied forthwith. The present authors would be reluctant to use heparin in other circumstances. The reports of heparin-induced thrombocytopenia (Bell *et al.*, 1976) provide further discouragement to the use of heparin in DIC. Spontaneous correction of DIC in the absence of heparin therapy has been reported in children with septic shock after the institution of aggressive supportive and antibiotic therapy (Corrigan *et al.*, 1973), and the onset of fulminant DIC during heparin therapy for pulmonary embolisation (Klein and Bell, 1974) can be cited in support of the need for more critical evalua-

tion of the use of heparin in DIC.

We recognise that others use heparin more widely and believe in its therapeutic efficacy (eg, Colman *et al.*, 1972; Minna *et al.*, 1974), reporting that therapy may have to be continued for several days to obtain benefit. Others have found antithrombotic regimens (heparin and dipyridamole) to correct the haemostatic factor deficiencies in pre-eclampsia without clinical benefit (Bonnar, 1977). There are numerous other accounts of the place of heparin in the therapy of DIC (Straub, 1974; Merskey, 1976; Bick *et al.*, 1977; Cash, 1977).

On the evidence currently available most believe that drugs capable of inhibiting the secondary fibrinolytic response accompanying DIC should not be used. Powerful inhibitors of the plasminogen-plasmin fibrinolytic enzyme system, such as epsilon-aminocaproic acid (EACA), have been associated with the development of extensive thrombosis when used in attempts to stop bleeding attributed wrongly in DIC to fibrinolytic activity (McKay and Muller-Berhaus, 1967; Gralnick and Griep, 1971). A possible line of future management might depend upon enhancing natural inhibition of the coagulation cascade, perhaps even by infusing antithrombin III if suitable concentrates could be prepared. Antiplatelet agents, such as aspirin, dipyridamole, and sulphinpyrazone, are exciting interest in the management of syndromes associated with microthrombi in the arterioles and capillaries of the brain and kidney in thrombotic thrombocytopenic purpura (Amorosi and Karparkin, 1977). Certainly where it is suspected that primary intravascular aggregation of platelets is involved in the initiation of DIC, as may be the case in immune complex disease and endotoxin-induced vascular endothelial damage, these drugs would seem logical alternatives worthy of evaluation in controlled clinical trials. Dipyridamole has been claimed to inhibit the non-thrombin mediated precipitation of fibrin monomer complexes in endotoxin-induced DIC in rabbits (Gurewich *et al.*, 1975). However, advances in the treatment of DIC are more likely to come from more rapid and effective methods of dealing with the initiating pathological process.

Conclusions

The body's defence against infection and injury involves complex reactions which are responsible for mediating inflammation, immunity, and haemostasis. The homeostatic mechanisms involved are controlled by numerous checks and balances. Where inappropriate overstimulation of these physiological processes occurs the checks and balances can be overwhelmed. Secondary disorders such as DIC will be the consequence. DIC is a clinicopathological

syndrome of variable expression, resulting from unchecked activation of haemostasis.

DIC can be triggered in many different ways, and there is much still to be learnt from the various animal models available—infusions of tissue thromboplastins, injections of agents that activate Hageman factor, immune complex activation of the coagulation mechanism (Simpson, 1975), pro-coagulant snake envenomation, and the generalised Schwartzman reaction. The significance of reticulo-endothelial blockade is inadequately appreciated. Little is known about the factors that inhibit the clearance of fibrinogen/fibrin degradation products in pregnancy, for instance, and that may contribute to eclamptic toxæmia, a syndrome undoubtedly complicated by DIC (Bonnar, 1973). If we are to understand the factors predisposing to DIC, more studies are needed to determine the importance of vascular endothelial damage, haemodynamic changes, and the role of naturally occurring inhibitors of haemostasis. By increasing our understanding of the mechanisms involved in triggering haemostasis it is hoped that patient management will improve after the use of more rational therapeutic measures than can be applied at present.

Improvements in diagnostic techniques are also necessary. In addition to its obvious intravascular role in maintaining vascular integrity, the coagulation system has an important function in extravascular repair processes, providing a scaffold for the mounting of the cellular response to injury. Some of the laboratory tests used in making the diagnosis of DIC, for example, FR-antigen, are positive whether fibrin be generated intra- or extravascularly. Furthermore, many of the laboratory tests of haemostasis measure concentrations of substances, be they substrates or end-products, when what is needed are measures of activity. As yet direct studies of fibrinogen/fibrin turnover and degradation studies are fraught with difficulties in interpretation (Reeve and Franks, 1974). However, such approaches to more direct kinetic measurements of the activity of the coagulation system and its inhibition should provide us with an improved understanding of DIC.

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- Requests for reprints to: Professor A. S. Douglas, Department of Medicine, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD, UK.