EDITORIAL

Defibrination Syndrome or . . . ?

Can the changes detected in patients currently believed to be undergoing disseminated intravascular coagulation (DIC) be due to other processes?

In the past 10 years this clinical syndrome\textsuperscript{1-5} has been frequently considered in differential diagnosis and is even separately listed in \textit{Index Medicus}. It is generally believed that thromboplastic substances released into the blood stream, under a variety of clinical circumstances, trigger thrombin formation. Clotting is initiated inside the blood vessels with “consumption”—or a reduction in the levels—of some of the clotting factors normally disappearing during blood clotting, e.g., platelets, fibrinogen, and Factors V and VIII. Activation of the fibrinolytic system causes lysis of local deposits of fibrin resulting in the accumulation of fibrinogen-fibrin digestion products (FDP) in the circulation.

It is remarkable that this concept is almost universally accepted since there is only indirect evidence of the activation of either thrombin or plasmin in naturally occurring disease states. The intravenous injection of thrombin or thromboplastin, or the induction of the generalized Shwartzman reaction by endotoxin in an animal, can induce similar changes. Defibrination produced by the bite of some poisonous snakes, or following incompatible blood transfusion, as well as amniotic fluid embolism\textsuperscript{6} or endotoxin formation in gram-negative sepsis are the only obvious examples of such a mechanism producing disease in man.

Reduced levels of clotting factors normally consumed during blood coagulation and a reversal of these changes after heparin therapy are certainly compatible with the concept of DIC, yet many patients with apparently similar disease have normal or even elevated levels of these clotting factors. A possible explanation is that, while the levels are in the so-called normal range, they are not normal for the particular disease. For example, a fibrinogen level of 200 mg/100 ml in a patient with abruptio placentae is in the “normal” range, but far below the approximately 440 mg/100 ml level anticipated at term. Patients with cancer frequently have a very high platelet count and Factor VIII level so that, at certain times, a level in the normal range may actually represent a precipitous drop. In some instances, one-stage assays reveal apparently normal or even elevated values (perhaps due to the presence of activated intermediate clotting factors), whereas two-stage assays show reduced values.\textsuperscript{3,7} Accelerated fibrinogen turnover can also be demonstrated in many such patients and this, too, can be corrected by heparin therapy.\textsuperscript{8,9} Curiously, levels of prothrombin, normally consumed during blood coagulation, are often close to normal.

Even in apparently classical examples of this syndrome, it is sometimes difficult (and occasionally impossible) to find thrombi at autopsy despite a quite intensive search.\textsuperscript{10} The usual explanation of this discrepancy is local lysis of previously deposited thrombi. It is also generally assumed that a
similar mechanism is responsible for FDP even though there is little or no
evidence of increased circulating systemic fibrinolytic activity—the euglobulin
lysis time is usually prolonged, and fibrin plate lysis is commonly less than
normal. A reduction in plasminogen level and survival time (also corrected
by heparin therapy)\(^9\) has been interpreted as evidence for fibrinolysis, but
may be due to plasminogen adsorption by fibrin as it forms.\(^11\) Even if due
to plasminogen activation, it does not necessarily indicate intravascular
fibrinolysis since plasminogen consumption might conceivably occur at extra-
vascular sites. However, the sera of patients with defibrination syndrome
often contain fragments which, on immunochemical analysis, resemble those
resulting from in vitro digestion of fibrinogen and/or fibrin by plasmin.

That the plasma of many patients with defibrination syndrome contains
cold-precipitable fibrinogen and “paracoagulation phenomena” can often be
demonstrated by the formation of fibrin strands or gels when protamine
sulfate or alcohol is added.\(^12,13\) The plasma of endotoxin-treated rabbits also
contains cold-precipitable “cryopofibrin,” while thrombin added in vitro in
low concentrations to native fibrinogen of normal rabbits may form a cold-
precipitable complex of fibrinogen and intermediate products of fibrinogen-
fibrin conversion.\(^14,15\) When fibrinogen is mixed with FDP derived from
plasmin-digested fibrinogen and with the fibrinogen-fibrin intermediate prod-
ucts formed by small amounts of thrombin, soluble nonclottable complexes
are formed that precipitate when cooled or when protamine sulfate is added.\(^16\)

There is some indication that these so-called FDP may be complexes of
soluble fibrin monomer with fibrinogen, as well as with proteolytic digestion
products of fibrinogen, fibrin, and fibrinogen-fibrin intermediates. It has there-
fore been suggested that a less specific term than FDP is needed. Fibrinogen-
fibrin related antigen (FR-antigen)\(^17\) has been proposed as an alternative.
Much of the abnormal FR-antigen in human plasma in disease states is
coagulable by thrombin and therefore is lost when serum is used for sampling.
The use of plasma would thus be preferable for assays since the expected
yield levels would more closely approximate those occurring in vivo. Un-
fortunately, the very large amount of normal fibrinogen present makes this
technically difficult, if not impossible, at present. When serum is used for
assay, every effort should be made to prevent an increase in the amount of
antigen due to lysis of the fibrin by thrombin.\(^18\)

Of the tests run on plasma, the action of thrombin and the presence of
fibrin might be shown by radioimmunoassay of fibrinopeptide A\(^19\) or indirectly
by the incorporation of \(^{14}\)C glyceryl-ethyl ester into fibrinogen by fibrin stabiliz-
ing factor, which occurs after the A peptide has been hydrolyzed.\(^20\) Further-
more, complexes larger than fibrinogen (? intravascular clotting) are probably
demonstrable by plasma fibrinogen chromatography.\(^21\) These larger com-
plexes occur, inter alia, postoperatively, after myocardial infarction or acute
thrombotic stroke, during normal pregnancy, and after the use of progesta-
tional agents; also, the fibrinogen half-life is reduced in some patients with
malignant disease (especially when disseminated), polycythemia vera, infec-
tions, venous thrombosis, afibrinogenemia, cirrhosis of the liver, hemophilia,
and in postoperative patients.\(^8,9,22,23\) The presence of neoantigen in plasma\(^24\)
suggests the possible action of plasmin.

There seems little doubt of changes in the structure and metabolism of fibrinogen in many clinical situations; we are questioning whether the process is always disseminated, or intravascular, or even always due to coagulation. Defibrination in hemangiomas, in large aneurysmal or other vascular malformations is clearly local in origin. Certain malignant tumors, for instance, have been shown to contain an enzyme (possibly thrombin), which clots fibrinogen, removing peptides A and B. These tumors may also contain a clot-stabilizing enzyme and similar clot-stabilizing enzymes have been isolated from liver and from skeletal and uterine muscle. It seems unreasonable to ignore certain possibilities: (1) that the extravascular pool of fibrinogen could be metabolized more rapidly than normal, (2) that fibrinogen turnover is not entirely dependent on intravascular events, and (3) that destruction does not occur solely through the coagulation pathway.

Could in vivo mechanisms other than DIC explain some of the abnormal laboratory findings? Why should all these disparate clinical groups involve the same enzymes? Thrombin and plasmin are not the only enzymes that can alter fibrinogen. Fibrinogen can be polymerized or precipitated in a number of ways. For instance, it may polymerize when precipitated by dialysis against a neutral buffer of low ionic strength. It polymerizes to some extent after protamine is added, and forms protamine-fibrinogen complexes. Protamine may also transform soluble fibrin monomer complexes and FDP, nonclottable by thrombin, into a clotlike gel with a highly ordered structure and axial periodicity similar to fibrin. While protamine is found almost exclusively in fish sperm, the histones present in mammalian cells can also precipitate soluble fibrin monomer complexes or neutralize heparin’s anticoagulant activity. A lysosomal protein fraction derived from rabbit polymorphonuclear leukocytes also interacts with complexes to form a precipitate. Similarly, the glycoprotein platelet factor-4, staphylococcal clumping factor, and several physicochemical agents can also precipitate the complexes. A proteolytic enzyme (vasculokinase) which clots fibrinogen has been purified from human and bovine aortas. It is conceivable that histones, lysosomal or other enzymes released from cells, or other as-yet-unidentified mechanisms instead of thrombin may so alter fibrinogen that it precipitates or forms fibrin strands, or clots slowly or incompletely with thrombin, inducing or adding to the amount of FR-antigen in plasma and serum. Kinases derived from endothelial cells and cathepsins or other enzymes derived from cells, may participate in these reactions in addition to thrombin.

Mechanisms other than those involving thrombin and plasmin may possibly be responsible for the clinical syndrome of defibrination, as the only essential indication of this syndrome is a quantitative and/or qualitative change in fibrinogen. The latter might be shown in numerous ways, e.g., by a reduced level of fibrinogen, by a prolonged thrombin clotting time, by an abnormal pattern of fibrinogen on immunoelectrophoresis or immunodiffusion against antifibrinogen serum, by plasma fibrinogen chromatography, by an increase in the levels of FR-antigen in serum, or by the protamine paracoagulation or alcohol gelation tests.
Implicit in this concept is the belief that the changes in fibrinogen could result from various mechanisms and the defibrination syndrome might sometimes arise from cellular injury in which released nonenzymic or enzymic substances could alter fibrinogen and its reactivity. Furthermore, thrombin evolution does not necessarily occur, and plasmin or other proteolytic enzymes are not necessarily activated. The extent to which these enzymes are activated would govern the type and amount of change in the clotting or fibrinolytic systems. It would not always be necessary to postulate local lysis of previously deposited fibrin, and heparin’s beneficial effect could be due to its strong negative charge as well as to its anticoagulant and other actions. The diagnosis of DIC has prompted the wide use of heparin. Yet, in some cases, possibly involving enzymes other than thrombin, it may aggravate or even cause severe hemorrhage. In view of these possible differences in the pathogenesis of this disease, the fact that a considerable percentage of patients fail to benefit from this treatment becomes understandable.

The terms DIC and consumption coagulopathy are perhaps too restrictive, as they represent only part of the syndrome. In a sense they also direct attention away from the initiating process. Defibrination syndrome is also inadequate since fibrinogen but not fibrin is primarily affected. Although we prefer it because intravascular clotting is not necessarily implied, a more meaningful term should be sought when the pathogenetic mechanisms are more clearly defined.

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REFERENCES

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