Pathogenesis of Fibrinolysis in Defibrination Syndrome: Effect of Heparin Administration

By CLARENCE MERSKEY, ALAN J. JOHNSON, JAMES H. PERT AND HERBERT WOHL

ACUTE HYPOFIBRINOGENEMIA may result from systemic intravascular coagulation (defibrination), or from spontaneous pathologic fibrinolysis, or both. The pathogenesis of these conditions has been ascribed to the local release of thromboplastic substances,1,2 or fibrinolytic substances3,4 or a combination of these.5,6,7 Since either thromboplastic or fibrinolytic substances may reduce the level of certain plasma components such as Factor V, anti-hemophilic factor (AHF) and fibrinogen, it may be difficult, on occasion, to determine the primary pathogenetic mechanism.

The studies to be reported in this paper were made in a patient with hypofibrinogenemia secondary to disseminated colonic cancer. Evidence will be presented that systemic defibrination occurred and that locally induced fibrinolysis co-existed. The evidence for defibrination consisted of reduced levels of coagulation factors (AHF, Factor V, prothrombin and blood platelets). Fibrinolysis was evidenced by reduced plasminogen levels and streptokinase (SK) and urokinase (UK) inhibitors, together with a prolonged thrombin clotting time. Additional laboratory evidence of fibrinolysis was obtained by the immuno-electrophoretic demonstration of fibrinolytic breakdown products in the plasma and serum. Clinical evidence of fibrinolysis was provided by the rapid disappearance of a large thrombus from a leg vein. Finally, parenteral administration of the anti-coagulant, heparin, sequentially corrected defibrination and secondary fibrinolysis; discontinuation of heparin resulted in the recurrence of intravascular coagulation and reactivation of the fibrinolytic process.

These observations suggested that disseminated local thromboses were associated with both defibrination and fibrinolysis. The data further suggested that thrombosis and defibrination was primary, that fibrinolysis was secondary, and that local thrombosis initiated fibrinolysis.

METHODS

The Lee-White clotting time, one-stage prothrombin, prothrombin consumption, thromboplastin generation, and Factor V assay were performed as described by Biggs and Mac-
Fig. 1.—Immunoelectrophoresis with anti-human fibrinogen serum: (a) normal human serum; (b) normal human plasma; (c) human fibrinogen. (Note similarity of plasma and fibrinogen. No band appears in serum.)

Farlane.8 Other methods utilized were: Prothrombin,9,10 Factor VII-X,10 Factor X,11 AHF,12 Christmas Factor by a partial thromboplastin time method similar to that described for assay of AHF13 except that human Christmas Disease plasma was used as substrate, Plasma Thromboplastin Antecedent,14 platelet count,15 thrombin clotting time,16 with undiluted plasma, and heated and non-heated fibrin plates for plasmin and activator, respectively.17 Blood was drawn in a mixture of citrate and the fibrinolytic inhibitor Trasylol® for the fibrinogen determination. This method and the methods used for euglobulin clot lysis time, SK inhibitor and antibody, UK inhibitor, plasmin inhibitor and plasminogen were performed as previously described.18 The SK inhibitor and antibody, the UK inhibitor and the plasmin inhibitor assays were performed by preincubation of dilutions of sera with a fixed amount of the appropriate enzyme (SK, UK or glycerol-activated plasmin, respectively); and assay of the residual activity was performed on a standard clot system. Total SK inhibition was measured in serum, SK antibody was determined in chelated plasma and SK inhibitor calculated by the difference.

Blood samples obtained during the period of intermittent, deep subcutaneous heparin administration were usually collected immediately prior to the injection of heparin.

Breakdown products of fibrinogen in serum and plasma were studied by immunoelectrophoresis.19 A microelectrophoresis chamber1 was used (6 v/cm., 3–4 ma./slide for 45 min.) with 7.5 Gm. per cent glycine added to the agar buffer, pH 8.2, in a discontinuous veronal buffer system.20 Rabbit antihuman fibrinogen serum1 was used in the immuno-dif-

*Bovine parotid gland extract, Bayer A 128, Farbenfabriken Bayer A. G., Leverkusen, Germany.
†Buchler Instrument Co., N. Y.
‡Hyland #RP 4760; Behringwerke #171, F.
FIBRINOLOGY IN DEFIBRINATION SYNDROME

Fig. 2.—Immunoelectrophoresis with anti-human fibrinogen serum. (a, b, c) Plasmin digests of plasminogen-deficient, human fibrinogen: (a) 5 minute digest; (b) 15 minute digest; (c) 45 minute digest; (d) patient serum 29 hours after cessation of heparin therapy; (e) mixture of (b) and (d) prior to immunoelectrophoresis. Note resemblance of band #III in (a) to normal plasma or fibrinogen (figs. 1b, 1c). As digestion proceeds band #III disappears even as lateral bands #I and #II appear. (b) As digestion proceeds to completion bands #I and #II migrate further from the point of origin (c). In (d) note presence of bands #III, #I and other bands. In (e) note superposition and identity of bands #III and #I when the 15 minute plasmin digest of purified fibrinogen is mixed with serum from the patient prior to immunoelectrophoresis.

The antisera used gave no precipitin bands when tested against normal serum (fig. 1a). A single, similar band, was obtained when tested against normal human plasma (fig. 1b) or purified human fibrinogen (fig. 1c). Slides were photographed moist and again after staining with Amido Schwartz 10B. Sequential samples of a plasmin digest of highly purified plasminogen-deficient fibrinogen showed consecutive changes on immunoelectrophoresis, characterized by precipitin bands similar to bands #III, #I, #II as previously described by Nussenzweig and Seligmann and of similar nomenclature. The lateral bands #I and #II appeared as the central band #III was digested and disappeared (fig. 2a, b). As digestion proceeded to completion, bands #I and #II migrated further from the point of origin (fig. 2c).

The major precipitin bands observed on immunoelectrophoresis of serum and plasma from the patient were shown to be immunologically identical with fibrinogen and fibrinogen digestion products (Bands #III and #I). Thus, precipitin bands were superposed when patient serum (fig. 2d) was mixed with fibrinogen digestion products (fig. 2b) prior to immunoelectrophoresis (fig. 2e).

CLINICAL OBSERVATIONS

The studies to be presented were performed on a patient with inoperable cancer of the ascending colon and severe hypofibrinogenemia. The course of
the illness may be conveniently divided into A. Initial Phase of Defibrination and Fibrinolysis, B. First Heparin Phase, C. Heparin Withdrawal Phases, and D. Subsequent Heparin Phases.

A. Initial Phase of Defibrination and Fibrinolysis

A 59-year-old white male presented with superficial and deep phlebitis and pulmonary emboli. Therapy withbishydroxycoumarin* had proved to be impracticable because of rectal bleeding, so that inferior vena caval ligation was performed. The next day he was noted to be more anemic. The prothrombin time was over 60 seconds on this and the subsequent day, samples of blood formed very small, soft clots in vitro and the fibrinogen level was 40 mg. per cent. Six Gm. of fibrinogen infused intravenously had a temporary effect only, and the fibrinogen level remained low (fig. 4).

B. First Heparin Phase

Fifty mg. of heparin were given intravenously every 4 hours. Within 12 hours, substantial clots formed in vitro. Abnormalities of coagulation and fibrinolysis were substantially corrected to normal or near normal and these values persisted during subsequent deep subcutaneous administration of 100 mg. of heparin every 8 hours.

C. Heparin Withdrawal Phase

Heparin was omitted for at least 23 hours, for various clinical reasons, on three occasions; defibrination occurred on each occasion. On the first occasion, the patient also had melena, blood streaked sputum, a new shadow on lung x-ray and transient hemiparesis. Heparin therapy was immediately reinstituted. The second occasion occurred 5 days after local resection of the colonic carcinoma. Heparin was discontinued in the hope that the local resection might abolish the defibrination syndrome. On the third occasion, the patient had been treated with warfarin sodium† (30 mg. followed by 20 mg. on the following day) for 48 hours prior to withdrawal of heparin. Defibrination was not prevented.

D. Subsequent Heparin Phases

When heparin therapy was reinstituted, abnormalities of coagulation and fibrinolysis were sequentially corrected to normal or near normal.

At necropsy, 13 days postoperatively, widespread, diffuse carcinomatosis was found. Also noted were: a recent pulmonary infarct, multiple thrombi involving the veins of the extremities, a thrombus in the inferior mesenteric artery (without local infarction), non-bacterial thrombotic endocarditis of the aortic and mitral valves, a recent posterior-wall myocardial infarct, and numerous infarcts in the kidneys and spleen.

*Dicumarol,R Abbott Laboratories, North Chicago, Ill.
†Coumadin,R Endo Laboratories, Inc., Richmond Hill, N. Y.


Table 1.—Blood Coagulation—Initial Observations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time, mins. (Lee White)</td>
<td>10 (Tiny clot)</td>
<td>4–8</td>
</tr>
<tr>
<td>One-stage prothrombin time (secs.)</td>
<td>&gt;60</td>
<td>12</td>
</tr>
<tr>
<td>Prothrombin consumption index %</td>
<td>100</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Thromboplastin generation test (secs.)</td>
<td>30</td>
<td>8–10</td>
</tr>
<tr>
<td>Fibrinogen (mg. per 100 ml.)</td>
<td>40</td>
<td>200–500</td>
</tr>
<tr>
<td>Prothrombin (2 stage) units</td>
<td>109</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Prothrombin (one stage) %</td>
<td>74</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Factor V %</td>
<td>27</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Factor VII–X %</td>
<td>78</td>
<td>&gt;75</td>
</tr>
<tr>
<td>AHF %</td>
<td>27</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Christmas factor %</td>
<td>100</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Factor X %</td>
<td>50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>PTA %</td>
<td>130</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Platelets per cu. mm.</td>
<td>115,000</td>
<td>200,000–400,000</td>
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Table 2.—Fibrinolysis—Initial Observations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase inhibitor (units)</td>
<td>12</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Streptokinase antibody (units)</td>
<td>25</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Urokinase inhibitor (units)</td>
<td>28</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Plasmin inhibitor (units)</td>
<td>145</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Plasminogen (units)</td>
<td>2500</td>
<td>&gt;4000</td>
</tr>
<tr>
<td>Thrombin clotting time (secs.)</td>
<td>33.2</td>
<td>10</td>
</tr>
</tbody>
</table>

**Results**

**A. Initial Phase of Defibrination and Fibrinolysis**

Laboratory findings typical of defibrination syndrome were seen in the initial blood samples taken from the patient (table 1). There was gross impairment of prothrombin consumption and of thromboplastin generation, a marked decrease in circulating fibrinogen, AHF and Factor V, and a slight decrease in prothrombin and blood platelets. When fibrinogen was infused, it persisted for at least 2 hours but had disappeared after 19 hours (table 3). The marked increase in the thrombin clotting time, marked decrease in SK inhibitor and circulating plasminogen, and moderate decrease in UK inhibitor suggested active fibrinolysis (table 2). Fibrin plate assays and euglobulin clot lysis times with or without epsilon aminocaproic acid (EACA) to distinguish activator from plasmin showed minimal evidence of fibrinolysis (table 3).

Immunoelectrophoresis of serum before fibrinogen infusion is shown in fig. 3a. Lateral band #1 is present as in an intermediate phase of in vitro digestion of fibrinogen by plasmin (fig. 2c); a faint central band #III is also seen. In the immunoelectrophoretic pattern 19 hours after the fibrinogen infusion (fig. 3b), band #I is still evident and a very prominent band #III is also seen. Since the coagulable protein was only 30 mg. per 100 ml. at
this time (table 3), the mixed pattern of early and intermediate digestion products was interpreted as being due to the superposition of bands resulting from the rapid fibrinolysis of the newly infused fibrinogen on the pre-existing pattern.

B. Heparin Therapy Phase

Heparin rapidly corrected abnormalities of coagulation (fig. 4) and fibrinolysis. Abnormal precipitin bands on immunoelectrophoresis of serum disappeared (fig. 3c) and the plasma showed a normal fibrinogen band (fig. 3d).

C. Heparin Withdrawal Phases

Abnormalities of coagulation and fibrinolysis rapidly recurred (fig. 5, 6) and serum immunoelectrophoresis 29 hours later showed precipitin bands (fig. 3e) which resembled an intermediate phase of in vitro digestion of fibrinogen by plasmin.26

D. Subsequent Heparin Phases

All abnormalities were corrected to normal or near normal during treatment with heparin. One of these is illustrated in figures 5 and 6. The somewhat lengthened thrombin clotting time shown during the first 35 hours in figure 6 was probably related to the direct antithrombic effect of heparin, this effect disappearing during the early hours of heparin withdrawal. As fibrinolysis recurred and before heparin therapy was reinstituted, the thrombin clotting time became markedly prolonged. Heparin therapy reduced this to near normal levels.

DISCUSSION

A low fibrinogen and prolongation of the one-stage prothrombin time and thrombin clotting time were the most striking laboratory findings in this patient. In addition, the demonstration of markedly reduced levels of AHF and Factor V with some reduction in prothrombin and platelets indicated intra-

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Table 3.—Plasma Fibrinogen and Fibrinolytic Activity before and after the Infusion of Fibrinogen Intravenously

<table>
<thead>
<tr>
<th>Time in Hours</th>
<th>Plasma Fibrinogen mg./100 ml.</th>
<th>Whole Blood</th>
<th>Plasma</th>
<th>Lysis of Fibrin Plates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>without EACA</td>
<td>with EACA</td>
<td>without EACA</td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>no clot</td>
<td>no clot</td>
<td>no clot</td>
</tr>
<tr>
<td>0.5</td>
<td>232</td>
<td>6.0</td>
<td>16.0</td>
<td>4.8</td>
</tr>
<tr>
<td>1.0</td>
<td>278</td>
<td>4.0</td>
<td>21.0</td>
<td>4.8</td>
</tr>
<tr>
<td>2.0</td>
<td>288</td>
<td>3.0</td>
<td>10.0</td>
<td>3.8</td>
</tr>
<tr>
<td>19.0</td>
<td>30</td>
<td>no clot</td>
<td>no clot</td>
<td>4.0</td>
</tr>
</tbody>
</table>

normal values 200-500 >1.5 >3.5 >2.0 >12.0 1-3 mm.
vascular coagulation. The effect of the anticoagulant, heparin, in reversing these changes provided additional strong evidence for diffuse coagulation. Autopsy findings subsequently showed widespread thrombosis.

As noted earlier, pathologic fibrinolysis can also produce hypofibrinogenemia. Activation of fibrinolysis with the formation of fibrinolytic digestion products was suggested by the marked reduction in SK and UK inhibitors,
Fig. 4.—Blood coagulation findings during the patient's illness. Heparin therapy was omitted on 6 occasions, the first two of these being inadvertent. Detailed observations were made on the 3rd, 5th and 6th occasions. The 4th period coincided with the resection of the primary tumor (day 27).

the fall in plasma plasminogen,\textsuperscript{27} and the prolonged thrombin clotting time.\textsuperscript{28,29} Abnormally increased fibrinolysis was confirmed by the immunoelectrophoretic demonstration of fibrinolytic breakdown products in the patient's serum. Clinical evidence included the disappearance, overnight, of a 4-inch thrombus in a leg vein. It was remarkable that the fibrin plate assays and whole blood and euglobulin lysis times showed minimal activity in spite of abundant indirect evidence of fibrinolysis.

In primary defibrination, as in abruptio placentae, neoplastic disease and following thoracic surgery, the fibrin plate assay and the euglobulin clot lysis time have usually shown minimal fibrinolytic activity. The evidence presented above indicates that occult fibrinolysis occurred in this patient despite normal results of these assays. Immunologic studies by others\textsuperscript{31-33} have also demonstrated fibrinolytic breakdown products in the serum of patients with abruptio placentae, carcinomatosis and other clinical syndromes.

Defibrination, under these circumstances, is considered to result from the
entry of thromboplastic material into the circulation. Fibrinolytic activity, when present, has been ascribed to coincidental entry of activator into the blood stream. In the present case, disseminated peripheral thromboses were associated with defibrination and subsequent fibrinolysis at these local sites perhaps from the release of thrombin. When the anticoagulant heparin was administered, systemic defibrination was inhibited first, then the fibrinolytic process. Following withdrawal of heparin, both defibrination and fibrinolysis recurred. Fibrinolysis, as indicated by the low plasminogen and SK inhibitor levels, also persisted longer than defibrination (as exemplified by the low level of AHF) after heparin administration had been re instituted. This suggests that recovery from defibrination preceded recovery from fibrinolysis, as might be anticipated if the primary effect of heparin was on the coagulation process. For all these reasons fibrinolysis appeared to be secondary to defibrination.

Clinical results in the patient presented above clearly indicate that heparin is a useful adjuvant in the therapy of this disease. The use of heparin in defibrination syndromes has been previously suggested. Since heparin has been reported to affect fibrinolysis, the possibility of a direct effect on fibrin-
olysis in this patient also needs to be considered. Heparin has been variously reported to accelerate fibrinolysis, inhibit fibrinolysis, to have no effect, or to have an effect on fibrinolysis which varied according to the dosage level. Doses of heparin comparable to those given this patient, did not inhibit fibrinolysis when administered to patients receiving urokinase.

When heparin is given to patients in whom fibrinolysis has previously been induced, it further increases the already prolonged thrombin clotting time, and may cause serious hemorrhage. The fact that heparin administration reduced the thrombin clotting time in this patient also indicates clearly that heparin stopped further systemic intravascular coagulation, which in turn prevented fibrinolysis and the formation of antithrombin.

The short-term administration of warfarin, without heparin, appeared to be ineffective; similar results have been reported by others. Since warfarin was only used late in the disease, and since similar drugs have appeared to be beneficial in other instances, the efficacy of oral anticoagulant drugs in this syndrome is still undecided.

A clear distinction should be made between primary spontaneous pathologic fibrinolysis and fibrinolysis which follows defibrination, since the underlying
disease state and treatment are different for each. In pathologic fibrinolytic states, rapid lysis of whole blood clots, euglobulin clots, and/or fibrin plates usually occurs. Preliminary observations suggest that the nature of the fibrinolytic state is determined by the balance of endogenous kinase or activator and the activator and plasmin inhibitors. Therefore, when plasmin is inhibited and activator is in excess, there is a reduction in plasminogen, streptokinase inhibitor, and urokinase inhibitor. However, there is little reduction in fibrinogen and other coagulation factors. When excess circulating plasmin activity is present, there is a marked decrease in both fibrinolytic and coagulation factors. In addition to reduction of plasminogen, SK and UK inhibitors, there is usually also a reduction in plasmin inhibitor, fibrinogen, Factor V, possibly AHF, and an increased thrombin time. While these varieties of fibrinolysis may be separate entities, they usually occur together, with activator predominating. When widespread defibrination occurs, there is a similar but greater reduction in fibrinogen, AHF, Factor V and platelets with some decrease in prothrombin. (Surprisingly, levels of prothrombin were not reduced below 50 per cent in three patients we have studied).

In general, when coagulable fibrinogen is normal, clinically significant intravascular coagulation is unlikely. If fibrinogen or Factor V are low, either defibrination or fibrinolysis may have occurred. On the other hand, low levels of AHF and platelets must be considered as evidence that defibrination is more likely. Replacement therapy with fibrinogen may be needed as a temporary measure in the treatment of defibrination syndrome pending definitive therapy. Should secondary fibrinolysis co-exist (with defibrination) the fibrinolytic system may dissolve thrombi and should not be inhibited by the administration of fibrinolytic inhibitors. The dangerous results associated with the use of EACA under these circumstances have been previously reported.

Precipitin band #111, on immunoelectrophoresis, is due to fibrinogen or early fibrinolytic products. Thus band #111 was present in the serum collected shortly after the infusion of fibrinogen (fig. 3b), or after the recurrence of defibrination when heparin therapy was discontinued (fig. 3e). Although coagulable fibrinogen was not measured in these sera, it is improbable that reduced levels of clotting factors retarded coagulation to the point where residual fibrinogen remained in the serum. In addition, serum collected on admission, when hypofibrinogenemia and fibrinolysis had been present for a considerable period of time, showed minimal evidence of this band (fig. 3a). In these sera, band #1 was prominent representing an intermediate stage of fibrinogen digestion. Additional, as yet unidentified bands, are also present. These are currently under investigation.

**Summary**

1. Spontaneous local fibrinolysis occurred with, and was probably a consequence of thrombosis, with defibrination in vivo.
2. The efficacy of heparin in the prevention of defibrination was clearly demonstrated; warfarin therapy seemed to be ineffective.
3. The efficacy of heparin in the prevention of the associated fibrinolysis was clearly inferred.

4. Serum immunoelectrophoresis against anti-fibrinogen sera demonstrated abnormal precipitin bands, during defibrination and fibrinolysis, which disappeared during heparin administration.

5. The serum bands showed immunologic identity with in vitro plasmin digests of fibrinogen and the intensity and position of these precipitin bands appeared to depend on the amount of fibrinogen and the duration of the in vivo digestion period.

6. In this hypofibrinogenemic state, defibrination was indicated by markedly reduced levels of anti-hemophilic factor and Factor V and a fall in blood platelets. The presence of fibrinolysis was shown by the lowered levels of plasminogen, streptokinase and urokinase inhibitors, prolonged thrombin clotting times and fibrinolytic breakdown products in the serum even though little or no lysis occurred on fibrin plates and the euglobulin lysis times were within normal limits.

7. The administration of fibrinolytic inhibitors is strongly contraindicated under these circumstances.

SUMMARIO IN INTERLINGUA

1. In disfibrination in vivo, ii occurreva spontanee fibrinolyse local in association con thrombosis que esseva probablemente su causa.

2. Le efficacia de heparina in le prevention de disfibrination esseva demonstrate clarmente. Therapia a warfarina pareva esser inefficace.

3. Le efficacia de heparina in prevenir le associate fibrinolyse esseva clarmente inferibile.

4. Immunoelectrophorese de sero contra seros anti fibrinogeno demonstrava anormal bandas de precipitina durante disfibrination e durante fibrinolyse. Le bandas dispareva durante le administration de heparina.

5. Le bandas del sero revelava identitate immunologic con digestos a plasmina de fibrinogeno in vitro. Le intensitate e le position de iste bandas de precipitina pareva depender del quantitate de fibrinogeno e del duration del periodo de digestion in vivo.

6. In iste stato hypofibrinogenemic, disfibrination esseva indicate per marcatemente reducite nivellos de factor anti-hemophilic e de factor V e per un declino in le numeration del plachettas sanguinne. Le presentia de fibrinolyse esseva monstrate per le reduce niveles de plasminogeno e de inhibitores de streptocinase e urocinase, le prolongate tempores de coagulation thrombinic, e le presentia de productos de disintegration fibrinolytic in le sero, ben que pauc o nulle lyse occurreva in placas a fibrina e ben le tempores de lyse a euglobulina esseva intra le limites del norma.

7. Le administration de inhibitores fibrinolytic es fortemente contraindicate sub iste circumstantias.

ACKNOWLEDGMENT

Dr. Graham A. Jamieson’s assistance in the preparation of the fibrinogen digests is gratefully acknowledged.
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