A New Life-Long Hemorrhagic Disorder Due to Excess Plasminogen Activator

By N.A. Booth, B. Bennett, G. Wijngaards, and J.H.K. Grieve

A life-long bleeding disorder is described, characterized by hemorrhage occurring after surgery, injury, or dental extraction, and finally by spontaneous intracerebral bleeding. No abnormality of platelet function or plasma coagulation was demonstrable, but grossly enhanced overall fibrinolytic activity was present. The patient had, additionally, a hyperlipidemia with gross arterial atheroma and a family history of myocardial infarction but not of any hemorrhagic disorder. Laboratory studies led to the conclusion that the enhanced fibrinolysis was due to consistently greatly raised levels of a plasma plasminogen activator physically and immunologically related to that in human tissues and blood vessel endothelium. No deficiency of any known inhibitor of fibrinolysis was detected. Free plasmin was not detectable in functional assays but continuous intravascular plasmin generation clearly occurred as evidenced by presence of plasmin-α2-antiplasmin complexes and of fibrin/fibrinogen-related antigens. Excessive production of plasminogen activator appeared to have occurred throughout life and to be independent of the hyperlipidemia. The pathologically increased fibrinolytic activity may have accounted for the complete absence of detectable thrombotic vascular occlusion at autopsy despite extensive arterial disease with severe narrowing of coronary and cerebral arteries.

HEREDITARY OR LIFE-LONG bleeding disorders hitherto described have been due to absolute or functional deficiency of single proteins that normally contribute to coagulation, fibrinolysis, platelet, or connective tissue function. The only such fibrinolytic bleeding syndrome that has been well characterized is due to a deficiency of the principal plasmin inhibitor, α2-antiplasmin, though there have been brief reports of one or two families with enhanced fibrinolysis and low factor VIII activity. In addition, fibrinolytic hyperactivity has been associated with defective factor XIII activity.

We describe a 47-yr-old man with a life-long bleeding disorder due to overactive fibrinolysis. This was not caused by a deficiency of any known inhibitor of fibrinolysis but by an excess of circulating plasminogen activator.

MATERIALS AND METHODS

Thrombin clotting time, one-stage prothrombin times, and partial thromboplastin times were performed by standard techniques. Measurement of factor VIII procoagulant activity, factor-VIII-related antigen level, plasma plasminogen, serum lipid and lipoprotein levels were as described. Presence of factor XIII activity was established by sodium dodecyl sulphate polyacrylamide gel electrophoresis of fibrin. Platelet aggregation was measured after the method of Born as described previously from this unit, with the exceptions that a two-channel aggregometer (AGD Instruments Ltd., Codicote, Herts, U.K.) linked to a Servoscribe potentiometric recorder was used and adenosine diphosphate, collagen, and ristocetin were obtained from Sigma London.

Immunosay of plasma proteins was performed either by radial immunodiffusion or Laurell immunoelectrophoresis. Plasma plasminogen was measured by the former method and the latter was used to quantify factor XIII subunits α and β, α2-antiplasmin, α1-macroglobulin, α1-antitrypsin, CI-inactivator, antithrombin III, histidine-rich glycoprotein, protein C, and the inhibitor of plasminogen activator. Two-dimensional immunoelectrophoresis (2DIEP) against antisera to α2-antiplasmin was performed as described previously. Fast-acting antiplasmin activity was measured essentially by the method of Teger-Nilsson et al. except that a plasma plus plasmin incubation time of 20 sec was used.

Fibrinolytic activity was assessed by measurement of the whole blood or the euglobulin clot lysis time and of lysis by whole plasma of fibrin plates.

Whole blood clot lysis was measured by allowing 1 ml of freshly drawn blood, with no added anticoagulant, to clot at 37°C in a glass tube and by subsequently observing the clot at half-hour intervals until complete lysis occurred.

Plasma euglobulin clot lysis times were performed after the method of Nilsson and Olow. The euglobulin fraction was precipitated from 0.5 ml citrated plasma at 4°C by addition of 9.5 ml 2 mM glacial acetic acid and concentrated by centrifugation at 4°C. The supernatant was discarded and the precipitate redissolved in 0.5 ml 60 mM Tris buffer, pH 7.4: an equal volume of bovine thrombin (Parke Davis, Co., Ltd.) at a connection of 2 U/ml in 0.15 M NaCl was added and the time for complete lysis of the resulting clot at 37°C measured.

Lytic activity of whole plasma on fibrin plates was measured as previously described.

The extrinsic and intrinsic plasminogen activator activities in plasma were distinguished by measurement of lysis of fibrin plates by the plasma euglobulin fraction with or without the addition of CI-inactivator.

Inhibition by the IgG fraction of a monospecific antibody to human tissue plasminogen activator was studied using a clot lysis assay. Clots were prepared from dextran sulphate euglobulin fractions of patient plasma or of a resting pool plasma, with or without the addition of purified plasminogen activator.

CASE REPORT

First seen by us in 1977, the patient was a 43-yr-old white male, referred because of a history since birth of recurrent bleeding after...
trauma. There had been no abnormal bleeding in the immediate postnatal period, but as a child there was prominent bruising on participation in contact sports and frequent episodes of knee swelling occurred after taking part in soccer. As a result the patient had been told that he had "mild hemophilia." As an adolescent he had minor orthopedic surgery for correction of a deformity of the right great toe; this was followed by severe and prolonged bleeding and the patient recalled that his leg was "black from the knee down" due to subcutaneous blood. He had no major surgery thereafter but many dental extractions were followed by prolonged bleeding; bleeding often ceased immediately following extractions and he would be discharged from hospital only to be readmitted when bleeding recurred after a day or two, when it would continue for many days, apparently unmodified by transfusion. One such episode had occurred prior to the studies described here—bleeding continued for over a week and there was no apparent benefit from the use of fresh frozen plasma.

There was no family history of abnormal bleeding; the patient's father and paternal grandfather had died aged 38 and 55 of myocardial infarction. The patient was married, but childless. He had been known since 1974 to have a hyperlipidemia for which he had initially received clofibrate. His mother, paternal grandmother, and two brothers were free of symptoms of bleeding and ischemic heart disease.

The patient was remarkable only for his small stature (5 ft 2 in) and his elfin appearance. He showed trivial bruising of his shins, no petechiae, no hepatosplenomegaly, and no xanthomata; gonadal development was normal and there was no clinical evidence of liver disease. He was normotensive and had no signs or symptoms of ischemic or other cardiac disorder. Blood count and blood film were normal, blood sedimentation rate was 15 mm in the first hour, no paraprotein was detectable in the plasma, and thyroid function was normal. Serum levels of sodium, potassium, calcium, phosphate, iron, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, and gamma glutamyltransferase were all within the normal range. EKG and karyotype were normal.

RESULTS

Hemostatic Studies

Routine investigation of the patient's coagulation mechanism and platelet function is illustrated in Table 1.

Table 1. Routine Hemostatic Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Mean Normal Value or Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Platelet function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding time</td>
<td>4.0 min</td>
<td>4.5 ± 1.3 min</td>
</tr>
<tr>
<td>Platelet count</td>
<td>70–130 × 10⁹/liter</td>
<td>&gt;100 × 10⁹/liter</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADP</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Ristocetin</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>(2) Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin time</td>
<td>10.8 sec</td>
<td>9–11 sec</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>15.5 sec</td>
<td>11–14 sec</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>39.0 sec</td>
<td>38–45 sec</td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td>210 mg/dl</td>
<td>300 ± 70 mg/dl</td>
</tr>
<tr>
<td>Factor VIII activity</td>
<td>104%</td>
<td>100%</td>
</tr>
<tr>
<td>Factor-VIII-related antigen</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>Factor XII (immunoassay)*</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Factor Xllla (immunoassay)*</td>
<td>33%</td>
<td>100%</td>
</tr>
<tr>
<td>Factor Xlllb (immunoassay)*</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td>Ethanol gelation test</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>(3) Fibrinolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood clot lysis time</td>
<td>&lt;6 hr</td>
<td>&gt;48 hr</td>
</tr>
<tr>
<td>Plasma euglobulin lysis time</td>
<td>&lt;50 min</td>
<td>80–240 min</td>
</tr>
<tr>
<td>Plasma lysis of fibrin plate containing plasminogen</td>
<td>15 mm</td>
<td>0 mm</td>
</tr>
<tr>
<td>Plasma lysis of plasminogen-free fibrin plate</td>
<td>0 mm</td>
<td>0 mm</td>
</tr>
<tr>
<td>Euglobulin lysis of fibrin plate containing plasminogen†</td>
<td>19.7 mm</td>
<td>6.2–16.5 mm</td>
</tr>
<tr>
<td>Euglobulin plus Cl-inactivator lysis of fibrin plate containing plasminogen†</td>
<td>13.0 mm</td>
<td>0–8.8 mm</td>
</tr>
<tr>
<td>Plasminogen (caseinolysis)</td>
<td>4.5 CU/ml</td>
<td>4.1 CU/ml</td>
</tr>
<tr>
<td>Plasminogen (immunoassay)</td>
<td>130%</td>
<td>100%</td>
</tr>
<tr>
<td>Serum fibrin/fibrinogen-related antigens (FDP)</td>
<td>&gt;40 µg/ml</td>
<td>&lt;5 µg/ml</td>
</tr>
<tr>
<td>Protein C*</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Values expressed as percent refer to those observed in a plasma pool that was prepared from 25 normal healthy male subjects between 20 and 40 yr old and that was stored at –70°C.

*These data were kindly supplied by Dr. U. Hedner who performed the assays.
†These data were kindly supplied by Dr. C. Kluft who performed the assays. 

BOOTH ET AL.
Platelet function was normal apart from a minor reduction in platelet count, clearly insufficient to account for his bleeding symptoms, as witnessed by a repeatedly normal bleeding time. Plasma coagulation pathways were intact. Clot solubility in monochloroacetic acid and in urea was not increased, suggesting that adequate levels of factor XIII were present, but factor XIII levels measured immunologically were reduced at 33% and 30% of normal pooled plasma for the α and β subunits, respectively (Table 1). The possible effect of these reduced levels was examined by SDS-polyacrylamide gel electrophoresis of fibrin produced from the patient’s plasma. As seen in Fig. 1, the pattern in patient and normal plasma samples was virtually identical and is in contrast to that in plasma from a patient congenitally deficient in factor XIII, where the α and γ chains are still present and only a faint band of γ–γ dimer is apparent. These data suggest normal fibrin crosslinking, compatible with evidence that between 1% and 5% of normal plasma factor XIII concentrations is sufficient for normal hemostasis.

Screening of the fibrinolytic pathway revealed grossly abnormal indices of overall fibrinolytic activity (rapid whole blood and euglobulin clot lysis and extensive lysis of a plasminogen-containing fibrin plate by resting plasma), evidence of breakdown of fibrin and/or fibrinogen, but no depletion of plasma plasminogen (Table 1). This excessive fibrinolytic activity, invariably present on repeated study over 3 yr, was not due to deficiency of a known inhibitor. Table 2 shows that functional assay of fast-acting antiplasmin, measuring α2-antiplasmin, with minor contributions from α2-macroglobulin and Cl-inactivator, was normal. Levels of these and all other known inhibitors of plasmin were normal or high when assayed immunologically.

Histidine-rich glycoprotein, also known to interfere with the fibrinolytic process, was present in normal concentration. Similarly, the patient was not deficient in the inhibitor isolated by Hedner, originally described as an inhibitor of plasminogen activator (urokinase), which is also a potent inhibitor of factor XIIa.

In the absence of demonstrable deficiency of any known fibrinolytic inhibitor, the patient’s plasma was examined to determine whether the excessive fibrinolytic activity was due to free plasmin. His plasma produced no lysis on plasminogen-free fibrin plates and did not split the plasmin-sensitive chromogenic substrate S2251. Thus, no free plasmin activity was demonstrable. Fibrinolytic activity was evident only on fibrin plates containing plasminogen, indicating that plasminogen activator was the agent responsible for the fibrinolytic state. The high activity of an euglobulin fraction prepared from the patient’s plasma in a fibrin plate assay was largely resistant to Cl-inactivator (Table 1). Cl-inactivator inhibits the generation of

Table 2. Fibrinolytic Inhibitor Concentrations

<table>
<thead>
<tr>
<th>Inhibitor of Plasminogen Activator (%)</th>
<th>Percent Normal Pooled Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-acting antiplasmin</td>
<td>103</td>
</tr>
<tr>
<td>α2-Antiplasmin</td>
<td>109</td>
</tr>
<tr>
<td>α2-Macroglobulin</td>
<td>140</td>
</tr>
<tr>
<td>α2-Antitrypsin</td>
<td>227</td>
</tr>
<tr>
<td>Cl-inactivator</td>
<td>105</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>114</td>
</tr>
<tr>
<td>Inhibitor of plasminogen activator</td>
<td>175</td>
</tr>
<tr>
<td>Histidine-rich glycoprotein</td>
<td>98</td>
</tr>
</tbody>
</table>

*Data kindly supplied by Dr. U. Hedner, who performed the assays.
plasminogen activator by the pathway involving factor XII/prekallikrein activation; Cl-inactivator-resistant activity has been equated with the plasminogen activator released into the blood in response to stress and sometimes referred to as “extrinsic.” The behavior of the patient’s plasma activator was compared with characterized normal human activators in three ways, namely, by examining their behavior on chromatography in buffers of varying ionic strength, their binding to lysine-Sepharose, and their reactions with an antibody specific for plasminogen activator purified from human uterus.

Chromatography of Activator on Sephadex G-200

The elution characteristics of plasminogen activator on gel filtration depends on the ionic strength of the buffers employed. This is true of the activator detectable in plasma after exercise or prolonged venous occlusion and of activator eluted from the vascular endothelium of cadavers. Both of these activators elute from Sephadex G-200 with proteins of large molecular size in 0.15 M NaCl, but much later, close to albumin, in 0.5-1.0 M NaCl. Gel filtration of this patient’s resting plasma in 0.15 M NaCl (Fig. 2) separated a peak of activity in a position identical to that of activator present in the blood of normal subjects after venous occlusion. Plasminogen, identified immunologically, eluted in a position different from that of the fibrinolytic activity (Fig. 2). When gel filtration was repeated in buffers containing high salt concentration, activity eluted later as described, indicating its similarity to other human plasminogen activators provoked by exercise and venous occlusion. Activity in fractions eluted from these columns was, like that in whole plasma, demonstrable only on fibrin plates containing plasminogen.

Binding of Activator to Lysine-Sepharose

Plasminogen activator from normal postexercise plasma and from limbs of human cadavers is bound to lysine-Sepharose and can be eluted using 1.5 M NaCl while plasminogen remains bound. Very little recovery of activator is possible from resting plasma of normal individuals by this method. This patient’s resting plasma behaved identically to normal postexercise and postocclusion plasma in this system, fractions eluted from lysine-Sepharose columns again showing activity only on plasminogen-containing fibrin plates. These preparations were free of detectable lipids and lipoproteins, which were not bound to the columns.

Interaction of Activator With Antibody to Human Uterine Activator

The γ-globulin fraction of an antiserum to plasminogen activator purified from human uterus quenches the activity of such tissue activator and of activator released by perfusion of cadaveric blood vessels; it also inhibits the activator in normal blood, which is present after exercise or venous occlusion. These studies show immunologic similarity between the agents variously known as “tissue,” “vascular,” and “postocclusion or extrinsic” activators and their nonidentity.
with urokinase.\textsuperscript{25,40} The fibrinolytic activity of a dextran sulphate euglobulin fraction\textsuperscript{27} prepared from the patient's plasma was quenched by this \( \gamma \)-globulin preparation to a much greater extent than that of normal plasma (Fig. 3). This indicates an increased plasma concentration of a plasminogen activator that is immunologically related to plasminogen activators in normal human tissues and endothelium. Thus, the active agent in the patient's plasma behaves similarly to normal vascular plasminogen activator on gel filtration, has the same lysine-binding properties, and is immunologically related to this activator.

No plasmin activity was identifiable in the patient's plasma, which was not unexpected in view of the avidity of \( \alpha_2 \)-antiplasmin, the major antiplasmin, for free plasmin. In spite of this, evidence that some plasmin had been generated was obtained by two-dimensional immunoelectrophoresis, using an antiserum to \( \alpha_2 \)-antiplasmin. Figure 4 shows that while normal plasma produces a single peak, the plasma of this patient produced an additional slow-moving peak. This pattern is similar to that seen in plasma of patients receiving the bacterial plasminogen activator streptokinase\textsuperscript{41} or in normal plasma after in vitro plasminogen activation by urokinase\textsuperscript{42} and presumably reflects complex formation between \( \alpha_2 \)-antiplasmin and plasmin formed in the circulation. The slow-moving peak in the patient's plasma could be removed by second dimension electrophoresis through a gel containing antiserum to plasminogen before the gel containing antiserum to \( \alpha_2 \)-antiplasmin was reached (Fig. 5), confirming that this peak represented \( \alpha_2 \)-antiplasmin complexed with molecules antigenically related to plasminogen or plasmin.

**Lipid Analyses**

The patient's lipid profile was highly abnormal.\textsuperscript{43} He had grossly increased levels of very low density lipoproteins (VLDL) and raised intermediate density lipoproteins (IDL), while high density lipoproteins (HDL) levels were markedly reduced. Apoproteins \( C_{\text{III}}, C_{\text{IV}}, \) and \( E \) showed no apparent abnormality on isoelectric focusing of the VLDL fraction.

**Family Studies**

The patient's mother and one of his brothers have attended for study. Neither has shown evidence of abnormal fibrinolysis and their lipid profiles were unremarkable. His second brother has declined to be studied.

**Evolution of the Disorder**

The patient remained well and free of troublesome bleeding for 3 yr, during which he sustained no trauma.
and underwent no surgery or dental extractions. On each occasion on which he was studied results were as described above. We reasoned that his gross lipid abnormalities had been shared by his father and grandfather, both of whom had died young of myocardial infarction, that the patient himself probably had arterial disease as well, and further that his hyperactive fibrinolytic system might well be protecting him from the thrombotic complications of such vascular abnormalities. Therefore, as his bleeding episodes had been restricted to episodes of trauma, we decided to refrain from normalizing his fibrinolytic activity, as to do so might simply expose him to the vascular occlusions sustained by his relatives. No specific treatment was therefore given continuously. However, in 1980 he was admitted to our ward after 7 days’ malaise, nausea, and vomiting and one day’s severe headache. He was afebrile, showed signs of severe meningeal irritation, had a quadrantic hemianopia but no other neurologic abnormalities. CAT scan showed a hematoma in the right parieto-occipital region. Treatment with epsilon-amino-caproic acid (EACA) was started at once, followed by tranexamic acid. Over the following 5 days, plasma fibrinogen rose to a high level (690 mg/dl) and the euglobulin clot lysis time and whole plasma activity on fibrin plates returned to normal; serum fibrin/fibrinogen-related antigens fell to levels just above normal while levels of factor XIII subunit a rose from 27% to 70% and those of subunit b from 25% to 50% of normal values. On admission on this occasion, his $\alpha_2$-antiplasmin level measured in functional and immunologic assays was approximately 60% of normal and gradually rose during treatment with fibrinolytic inhibitors as shown in Table 3. Concurrent with this rise, the slow-moving peak seen on 2DIEP against $\alpha_2$-antiplasmin antiserum diminished but did not completely disappear (Fig. 4). Plasminogen levels showed little change. His clinical condition stabilized for several days and the hematoma did not enlarge. However, on the sixth day, signs of raised intracranial pressure with papilledema and features of early brain stem compression arose; craniotomy with evacuation of the clot was undertaken without bleeding but the patient died within 24 hr of surgery.

**Autopsy Findings**

No macroscopic or histologic evidence of disfunction was found anywhere except in the brain and in the arterial tree. In particular, the liver, kidneys, and myocardium were normal. The brain showed signs of the recent craniotomy with drainage of a hematoma cavity. There was no evidence of aneurysm in any cranial artery.

The arterial tree was grossly abnormal for an individual of 47 yr. The aorta and all vessels arising from it showed gross atheromatous deposits that caused severe narrowing of coronary and basilar arteries. Heavy lipid deposits were visible in the intima and were also seen on the outer surface of blood vessels in a curious annular distribution. In spite of the many areas of severe narrowing of these arteries, in no situation was there any evidence whatsoever of any thrombotic occlusion of the vessels (all the major veins were likewise free of thrombus). Many of the arterial lipid deposits showed marked subintimal hemorrhage.

**Table 3. Plasma $\alpha_2$-Antiplasmin Concentrations**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Functional (% Normal Pooled Plasma)</th>
<th>Immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>95-103</td>
<td>91-109</td>
</tr>
<tr>
<td>Admission (8/14/80)</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>8/15/80</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>8/16/80</td>
<td>65</td>
<td>87</td>
</tr>
<tr>
<td>8/18/80</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>8/19/80</td>
<td>98</td>
<td>91</td>
</tr>
</tbody>
</table>
Life-long bleeding due to excessive fibrinolysis has hitherto been defined clearly only in patients with deficiency in α2-antiplasmin,4 the principal inhibitor of plasmin. The patient recorded here has no detectable deficiency of any known inhibitor of fibrinolysis. On no occasion was plasmin activity detectable in his plasma, but there was immunologic evidence that it had been formed and was complexed with α2-antiplasmin in sufficient quantity to allow its detection by 2DIEP. In contrast, he invariably showed grossly raised levels of a plasminogen activator that behaved physicochemically in a manner identical to that released after venous occlusion in normal subjects and behaved immunologically in a manner similar to tissue plasminogen activator in neutralization experiments. The observations appear to represent a genuine excess of extrinsic or vascular activator in the blood. Whether this reflects increased synthesis or decreased clearance of activator from the plasma is unknown.

With the single exception of his final episode of intracerebral hemorrhage, this man did not sustain spontaneous bleeding but bled severely only after trauma. He showed, nonetheless, evidence of continuously enhanced fibrinolytic activity, with consistently very high levels of plasminogen activator, grossly elevated levels of fibrin/fibrinogen-related antigens, and evidence of plasmin–antiplasmin complexes in the blood. It is not clear where fibrin/fibrinogen-related antigens and plasmin–α2-antiplasmin complexes were generated, that is, whether they were generated in the blood or generated as a result of lysis of locally deposited fibrin. All that can be said is that they were continuously present. The fact that there was no deficiency of plasminogen, α2-antiplasmin, and only a very slight reduction of fibrinogen level must indicate that the rate of synthesis of these proteins was equal to their consumption. The rapid rise of fibrinogen levels and the high levels reached after pharmacologic inhibition of the fibrinolytic system indeed suggests that fibrinogen synthetic processes were in high gear. The virtual disappearance of plasmin–α2-antiplasmin complex from the blood during the administration of fibrinolytic inhibitors, which act primarily by preventing plasminogen activation, indicates that plasmin generation was effectively suppressed and the complexes cleared from the circulation. We have evidence in other patients, which will be presented separately, to indicate that complexes generated in a single but transient episode of hyperfibrinolysis are cleared from the blood rapidly and become undetectable within 24 hr. In this man, plasmin generation was clearly not completely suppressed initially, thus accounting for the traces of complex that persisted. The rise in level of α2-antiplasmin observed during treatment presumably reflects reduction of plasmin generation with consequent reduction in the consumption of α2-antiplasmin.

The low plasma level of factor XIII is unexplained. It is unlikely to have had any causal relationship to the high fibrinolytic activity, as qualitatively normal fibrin crosslinking was demonstrated. It seems possible that the low factor XIII level was secondary to high fibrinolytic activity, though it is not generally accepted that this factor is degraded during fibrinolysis.44 Other proteolytic agents, particularly leukocyte enzymes, are known to act on factor XIII45 but also act on factors VIII and XII, which were at normal concentrations in this patient. The rise in factor XIII levels noted during the period of therapeutic inhibition of fibrinolysis does support the suggestion that factor XIII changes were secondary events.

It was tempting to postulate initially that the patient’s lipid disorder may have played a role in altering his fibrinolytic activity. Hyperlipidemias, however, when they have been studied in the past, have been associated with depressed rather than enhanced fibrinolysis.46,47 Additionally, this man’s plasminogen activator had physical properties similar to that present in normal postocclusion plasma and preparations of his activator were free of lipid so that no abnormal association of activator with any lipid fraction was evident. Finally, the patient’s father and grandfather both died young of myocardial infarctions, suggesting that they shared this man’s lipid disorder; from historical evidence it is clear that they did not share his bleeding tendency. These observations suggest that the lipid disorder was not responsible for the hemorrhagic one. At present, the conclusion must be that this patient’s life-long bleeding disorder was not due to deficiency of any known plasma agent but to a true excess of a normal protein–vascular endothelial plasminogen activator. He may thus be the first patient reported with a life-long bleeding disorder due to excess of rather than to deficiency of a plasma protein.

The coincidence of overactive fibrinolysis with a severe lipid disorder predisposing to gross atheroma is of interest from another viewpoint. For over a century the concept that fibrin deposits, incorporated into arterial intima, might play a role in the development of atheromatous disease has had proponents. It is clear that grossly enhanced fibrinolysis failed to prevent the development of severe atheroma. Fibrin incorporation into the intima can have played little part in the development of arterial disease in this hyperlipidemic man. The complete absence of any evidence of occlud-
disease and severe narrowing of many arteries might failure. Quantitation of antigens by single radial immunodiffusion. Immuno-
sensible and the bizarre experiment of nature repre-
ses in this patient, its risks would appear consid-
tect a patient with atheromatous disease from occlu-
indicate, however, that enhanced fibrinolysis
izes episodes. If, to provide such protection effectively,
its fibrinolytic disorder clearly proved a
Homozymous a2-antiplas-
deficiency. Lancet 2:206, 1979
R: Plasma activator of plasminogen: Cause of a familial bleeding
Hampton JW, Weidenbach A, Skye GE, Rubenstein C, Taylor
Haemophilia: Modified by a post-exercise plasminogen activa-
tor. Thromb Diath Haemorrh 34:612, 1975 (abstr)
Baggett RT, Hampton JW, Bird RM: Fibrinolytic bleeding
Self J, Matthews C: Inherited fibrinolytic hyperactivity. Arch
Intern Med 122:357, 1968
Bennett B, Ratnoff OD: Studies on the response of patients
with classic hemophilia to transfusion with concentrates of anthea-
Ratnoff OD, Bennett B: Clues to the pathogenesis of bleeding in
Alkaersig N, Fletcher AP, Sherry S: L-Aminocaproic acid: An
Robertson FW, Cumming AM: Genetic and environmental
variation in serum lipoproteins in relation to coronary heart dis-
J Med Genet 16:85, 1979
weights by electrophoresis on SDS-acrylamide gel. Meth Enzymol,
26:3, 1972
Pisano JJ, Finlayson JS, Peyton MP, Nagai Y: y-(γ-Glutamyl)
lysine in fibrin: Lack of crosslink formation in factor XIII deficien-
cy. Proc Natl Acad Sci USA 68:770, 1971
Born GVR: Aggregation of blood platelets by ADP and its
Warlow C, Ogston D, Douglas AS: Platelet function after the
administration of chlorpromazine in human subjects. Haemostasis
5:21, 1976
Mancini G, Carbonara AD, Heremans JF: Immunochemical
quantitation of antigens by single radial immunodiffusion. Immuno-
chemistry 2:235, 1965
Laurell C-B: Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Analit Biochem 15:45,
1966

REFERENCES
1. Ratnoff OD, Bennett B: The genetics of hereditary disorders of
blood coagulation. Science 179:1291, 1973
2. Hardisty RM, Caen JP: Disorders of platelet function, in
Bloom AL, Thomas DP (eds): Haemostasis and Thrombosis. Edi-
burgh, Churchill Livingstone, 1981, p 301
3. Bloom AL: Inherited disorders of blood coagulation, in Bloom
AL, Thomas DP (eds): Haemostasis and Thrombosis. Edinburgh,
4. Aoki N, Saito H, Kamiya T, Koie K, Sakata Y, Kabakura M:
Congenital deficiency of α2-plasmin inhibitor associated with severe
5. Kluijt C, Vellenga E, Brommer EJP: Homozygous α2-antiplas-
min deficiency. Lancet 2:206, 1979
6. Hampton JW, Oldham FB, Banneree D, Kalmaz E, Delaney
R: Plasma activator of plasminogen: Cause of a familial bleeding
FB: Haemophilia: Modified by a post-exercise plasminogen activa-
tor. Thromb Diath Haemorrh 34:612, 1975 (abstr)
8. Baggett RT, Hampton JW, Bird RM: Fibrinolytic bleeding
Intern Med 122:357, 1968
with classic hemophilia to transfusion with concentrates of antithe-
11. Ratnoff OD, Bennett B: Clues to the pathogenesis of bleeding in
12. Alkaersig N, Fletcher AP, Sherry S: L-Aminocaproic acid: An
13. Robertson FW, Cumming AM: Genetic and environmental
variation in serum lipoproteins in relation to coronary heart disease.
J Med Genet 16:85, 1979
weights by electrophoresis on SDS-acrylamide gel. Meth Enzymol,
26:3, 1972
15. Pisano JJ, Finlayson JS, Peyton MP, Nagai Y: y-(γ-Glutamyl)
lysine in fibrin: Lack of crosslink formation in factor XIII deficien-
cy. Proc Natl Acad Sci USA 68:770, 1971
16. Born GVR: Aggregation of blood platelets by ADP and its
17. Warlow C, Ogston D, Douglas AS: Platelet function after the
administration of chlorpromazine in human subjects. Haemostasis
5:21, 1976
quantitation of antigens by single radial immunodiffusion. Immuno-
chemistry 2:235, 1965
19. Laurell C-B: Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Analit Biochem 15:45,
1966

ACKNOWLEDGMENT
We are grateful to Dr. D. Collen for gifts of antisera to α2-
antiplasmin and histidine-rich glycoprotein and to Dr. U. Hedner
and Dr. C. Kluijt who provided data and helpful advice. Y. Ligert-
wood provided expert technical assistance and S. Short and
L. Walde tirelessly typed and retyped the manuscript.
A new life-long hemorrhagic disorder due to excess plasminogen activator

NA Booth, B Bennett, G Wijngaards and JH Grieve