Fibrinogen "New York"—An Abnormal Fibrinogen Associated With Thromboembolism: Functional Evaluation

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A 54-yr-old woman presented with a 23-yr history of repeated life-threatening thromboembolism. The presence of a qualitatively abnormal fibrinogen was suggested by the demonstration of delayed and incomplete coagulation of plasma or partially purified fibrinogen by thrombin or Reptilase. Two brothers showed a similar in vitro defect but were clinically not affected. The plasma fibrinogen concentration was 0.50–1.64 mg/ml when estimated by heat turbidity, clottability, or immunologic techniques. The serum contained 80–820 μg/ml of unclottable fibrinogen-related materials even after 24 hr exposure to thrombin. The fibrinogen-related material in the serum showed faster anodal mobility on immunoelectrophoresis than that of normal plasma. Immunodiffusion studies with rabbit antihuman fibrinogen antiserum showed lines of identity between control plasma and the patient’s plasma and serum. Studies of the kinetics of thrombin action on fibrinogen demonstrated impaired release of fibrinopeptide A and B and defective polymerization of preformed fibrin monomers. The maximum amount of fibrinopeptide A released by exhaustive treatment with thrombin was similar (per milligram protein) for both the patient’s and control fibrinogen. This abnormal fibrinogen variant is tentatively designated fibrinogen "New York"; its possible identity with one of the previously described abnormal fibrinogens has not been excluded.

Qualitative abnormalities of the fibrinogen molecule are now well recognized. In most instances the functional defect was suspected because of delayed coagulation of plasma by thrombin or an abnormal prothrombin time. About half of the reported cases were asymptomatic, and the laboratory abnormalities were incidental findings. Patients with fibrinogen Bethesda I,2 Cleveland II,6 Detroit,7 Giessen,8 Metz,9 Oklahoma,2,10 Vancouver,11 and Wiesbaden12 had abnormal bleeding. Thrombosis was described in association with fibrinogen Paris II,13 while both bleeding and thrombosis occurred in the patient with fibrinogen Baltimore.14,15 The family described by Egeberg in 196716 had a high incidence of thromboembolic disorders associated with abnormally short thrombin time. The author, however, did not designate...
the variant fibrinogen Oslo, as may have been appropriate. Wound dehiscence was the only clinical symptom associated with fibrinogens Cleveland and Paris. The case reported by Imperato and Dettori in 1958 (fibrinogen Parma) was associated with a very low fibrinogen level which in itself could induce abnormal bleeding. The patient with fibrinogen St. Louis also had hemophilia, probably a chance occurrence, and this most likely was responsible for the bleeding diathesis. Family studies, when available, seem to indicate an autosomal dominant mode of inheritance in all reported pedigrees.

Studies were carried out by several investigators to characterize the functional defects in a number of these aberrant fibrinogens. Slow or absent fibrinopeptide release was demonstrated in fibrinogens Baltimore, Bethesda I, Bethesda II, Cleveland, Detroit, Giessen, Metz, and St. Louis. Except for fibrinogens Parma and Vancouver (for which no information is available), and fibrinogen Bethesda I, where it is normal, fibrin monomer aggregation was shown to be impaired in all other patients with dysfibrinogenemia. The exact structural alteration is not known for any of the previously reported abnormal fibrinogens except for fibrinogen Detroit, where an amino acid substitution (arginine for serine in position alpha 19) was demonstrated in the N-terminal portion of the alpha (A)-chain. Similar studies on the N-terminal portions of fibrinogens Baltimore, Paris I, and St. Louis revealed no amino acid abnormalities. It is interesting that no correlation has yet been made between the functional or structural defects of fibrinogen and the clinical findings.

This report describes a patient with a recurrent life-threatening thromboembolic disorder associated with a qualitatively abnormal fibrinogen. With the use of Beck's nomenclature, this abnormal fibrinogen will be designated fibrinogen New York; its possible identity with one of those previously reported is not excluded.

MATERIALS AND METHODS

Venous blood was obtained from the patient and a normal subject and was anticoagulated with 0.1 volume 3.8% trisodium citrate. For the immunoelectrophoresis and immunodiffusion studies, trasylol (10,000 U/ml, FAB pharmaceutical, New York, N.Y.), 100 U per ml blood, was added to neutralize plasmin in vitro. Plasma was separated by centrifugation at 1200 g for 15 min at room temperature and was either used immediately or frozen at -60°C. Serum was obtained by clotting blood with trasylol in 4 x 1/2-inch glass tubes for 2 hr at 37°C, then separating the supernate by centrifugation. An additional control plasma sample was obtained from a young woman who was taking 7.5 mg warfarin daily because of a history of deep vein thrombosis 1 mo earlier. Her prothrombin time was 26/12; she was otherwise healthy and had no previous history or family history suggestive of abnormal hemostasis.

Fibrinogen was isolated from plasma by precipitation with ammonium sulfate. A saturated solution of ammonium sulfate was added by drops at room temperature to an equal volume of citrated plasma. The precipitated material was washed three times with a 25% saturated solution of ammonium sulfate and then dissolved in a small volume of Tris-buffered saline (0.1 M NaCl, 0.05 M Tris), pH 7.4. The clottability of normal fibrinogen isolated by this procedure is 95%-98%.

Bovine thrombin (Parke, Davis & Co., Detroit, Mich.), 1000 U/ml, was dissolved in phosphate buffer, pH 7.4, stored at -60°C, thawed immediately before use, and diluted to the desired concentration with buffer. The activity of the diluted thrombin was tested using normal plasma during the course of each experiment. Unless otherwise stated, the desired concentration of thrombin was used in 0.1-ml aliquots. Human thrombin was prepared by Dr. K. Miller and donated by Dr. D. L.
Aronson, Division of Biologic Standards, Bethesda, Md. It was diluted in Tris-buffered saline, pH 7.4. Reptilase (Abbott Scientific Products Division, South Pasadena, Calif.) was dissolved in distilled water to the desired concentration and used immediately. Coagulation studies included repeated determination of prothrombin time, partial thromboplastin time, one-stage factor V, VIII, XI, and XIII assays, englobulin lysis time, and plasma antithrombin III activity. Plasma fibrinogen was measured by four separate procedures: (1) turbidometrically, after heat precipitation, (2) immunologically, using the tanned red cell hemagglutination inhibition technique, (3) as a clottable protein, using the method described by Ratnoff and Menzie, and (4) as a clottable protein, as described by Blomback and Blomback, using either thrombin or Reptilase to clot plasma, with or without excess calcium. Fibrinogen-related material in the serum was measured either immunologically or by the staphylococcal clumping technique.

The rate and the degree of clottability of the patient's plasma or purified fibrinogen was studied as follows: (1) Thrombin time was measured with different concentrations of thrombin added to an equal volume of plasma, with or without excess calcium (0.1 ml 0.025 M CaCl₂), and with or without protamine sulfate (Eli Lilly, Indianapolis, In.). (2) Reptilase time, with or without added calcium was measured. (3) Changes in turbidity during coagulation of purified fibrinogen after addition of thrombin were measured at room temperature in a Beckman-DU spectrophotometer at 350 nm, as described by Beck et al. (4) Purified fibrinogen was labeled with carrier free ¹²⁵I according to the method of McFarlane, as previously described. The percentage of clottability was determined by measuring radioactivity in the clot and supernate after adding thrombin, at different concentrations, and after incubation for periods of 1 or 5 min at 37°C.

The effect of the patient's plasma on the clottability of normal plasma was assessed by incubating mixtures of the two specimens at different relative concentrations for 5–30 min and then measuring the thrombin time of 0.1-ml aliquots of the mixtures.

The effect of pH on the rate of clotting of plasma was studied by adding acetate barbital buffer (0.2 ml), at various pHs to 0.1 ml of plasma to obtain the final pH values indicated. Clotting times were measured after adding 10 U of thrombin to the mixture.

Polymerization of Fibrin Monomers
Aggregation of preformed dissolved fibrin monomers was achieved by a shift of pH from 5.20 to neutrality, as previously described. In these studies, 0.3 ml of plasma was acidified with 0.6 ml Michaelis' buffer to obtain a final pH of 5.20. Thrombin, 10 U in 0.1 ml buffer, was added, and the mixture was incubated at 37°C for the intervals indicated. Portions (0.1 ml each) of the mixture were then added to equal volumes of buffered hirudin (pH 9.60) to inhibit the enzymatic reaction of thrombin and neutralize the pH, and the clotting time was measured.

Studies of the Rate of Fibrinopeptides A and B Release
Simultaneous experiments were performed using normal fibrinogen and the patient's fibrinogen; each were at a protein concentration of 0.5 mg/ml as determined by the Lowry technique. One-milliliter aliquots of fibrinogen in Tris-buffered saline, pH 7.4, were incubated at room temperature with human thrombin at a final concentration of 0.02 U/ml. The reaction was stopped in each sample after a specified time interval by the addition of hirudin, 0.11 U in 0.1 ml. The samples were processed by the addition of an equal volume of ethanol to each, followed by centrifugation at 4800 g for 10 min at 4°C. The top 1 ml of supernatant solution was removed and recentrifuged in the same way. The top 0.5 ml was diluted 1:5 with Tris-buffered saline, pH 8.6, with 0.1% ovalbumin and tested by radioimmunoassay for fibrinopeptides A and B. In order to achieve maximum fibrinopeptide A release, normal fibrinogen and the patient's fibrinogen were treated with higher concentrations of thrombin. 0.5 mg of each fibrinogen sample was incubated at 37°C with 1 U of human thrombin for 2 hr, and the samples were processed and assayed for fibrinopeptide A as described above.

Immunologic Studies
Ouchterlony double-diffusion immunoprecipitation and immunoelectrophoresis of the patient's plasma and serum were performed using rabbit antihuman fibrinogen antiserum (Hyland Laboratories, Costa Mesa, Calif.).
Platelet Function Studies

Platelet aggregation was estimated by a modification of the optical density method described by Born and Cross. Platelet-rich plasma (PRP) (platelet count, 220,000/cu mm) was prepared from citrated venous blood centrifuged at 300 g for 15 min. The aggregating agents were epinephrine (Eastman Organic Chemical Co., Rochester, N.Y.), $1 \times 10^{-7} M$, $5 \times 10^{-6} M$, adenosine diphosphate (Sigma Chemical Co., St. Louis, Mo.), $1 \times 10^{-7} M$, $5 \times 10^{-6} M$, or dilute collagen. $^{14}C$-serotonin (Amersham-Searle, Arlington Heights, Ill.; specific activity, 48 mCi/mM) release from platelet was studied by the method described by Zucker and Peterson.

CASE HISTORY

The patient is a white woman born in 1919. While working in a hospital in 1947, she was told that her prothrombin time was abnormally long by 3-4 sec and that her fibrinogen was "10% of normal." She was asymptomatic. Between 1951 and 1972 she suffered at least six documented episodes of venous thrombosis involving both legs, the right upper extremity, the left external jugular and subclavian veins, and the right foot. In 1967, she sustained a major episode of pulmonary embolism and was treated with heparin followed by warfarin which she has continued to take. A right radical mastectomy in 1959, then left simple mastectomy in 1968, both for carcinoma, were complicated by venous thrombosis in the legs and arms. She had no abnormal bleeding. Repeated diagnostic studies, including liver function tests, calcium, phosphorus, BUN, uric acid, skeletal x-rays, and pyelograms, since 1968, have shown no evidence of cancer.

The patient has four sisters and seven brothers (Fig. 1). Fourteen of her relatives, including all of her living siblings, were available for study. Two of her brothers, ages 54 and 56, showed similar coagulation defects, with markedly prolonged thrombin time (> 180 sec), prolonged Reptilase time (34-37 sec; control, 18 sec), abnormal prothrombin time (24-26 sec; control, 12 sec), and very low fibrinogen (10-45 mg/100 ml). Both, however, are healthy and have no history of abnormal bleeding or thrombosis. Another brother died at the age of 57 with suspected pulmonary embolism 6 wk following cholecystectomy. The patient's only child died at the age of 6 mo with congenital heart disease. Her parents died of unrelated diseases and had no history to suggest abnormal hemostasis.
FIBRINOGEN "NEW YORK"

Table 1. Plasma Fibrinogen- and Serum Fibrinogen-related (Unclottable) Material (FRM)

<table>
<thead>
<tr>
<th>Method</th>
<th>Plasma Fibrinogen* (μg/ml)</th>
<th>Serum FRMt (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat turbidity</td>
<td>500-1220</td>
<td>620f</td>
</tr>
<tr>
<td>Clottable protein (Blomback and Blomback32) using thrombin</td>
<td>650</td>
<td>620f</td>
</tr>
<tr>
<td>using thrombin with Ca2+</td>
<td>1300</td>
<td>820f</td>
</tr>
<tr>
<td>using Reptilase with Ca2+</td>
<td>1120</td>
<td>820f</td>
</tr>
<tr>
<td>Clottable protein (Ratnoff and Menzie31)</td>
<td>640</td>
<td>820f</td>
</tr>
<tr>
<td>Immunologic (tanned red cell hemoagglutination inhibition30)</td>
<td>1480-1640</td>
<td>80f</td>
</tr>
</tbody>
</table>

*Normal, 2000-4500 μg/ml.
†Normal, <4 μg/ml.
‡Plasma was clotted for 2 hr, FRM assayed by staphylococcal clumping.34,35
§Plasma was clotted for 24 hr, FRM assayed by tanned red cell hemoagglutination inhibition.

RESULTS

Table 1 shows that the patient's plasma fibrinogen, estimated by heat turbidity or as clottable protein, is low and that significant amounts of unclottable material remain in the serum. When calcium was added to the clotting mixture, the quantity of clottable protein was substantially increased. The fibrinogen concentration was higher when determined immunologically by the tanned red cell hemoagglutination-inhibition technique.32 The serum contained a significant titer of unclottable, fibrinogen-related material even after clotting for 24 hr.

Table 2 shows that the patient's thrombin time is markedly prolonged unless a very high concentration of thrombin is used. Figure 2 shows that calcium shortens the thrombin time of both the patient's and normal plasma; this effect is more pronounced with a low concentration of thrombin. Protamine sulfate also partially corrects the patient's prolonged thrombin time. Clotting of the patient's plasma with Reptilase is also prolonged, and the prolongation is partially corrected by calcium. Coagulation factors other than those affected by warfarin were normal; so also was platelet aggregation with adenosine

Table 2. Coagulation Studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin time (Sec)</td>
<td></td>
</tr>
<tr>
<td>1 U</td>
<td>&gt;300</td>
</tr>
<tr>
<td>10 U</td>
<td>70–74</td>
</tr>
<tr>
<td>100 U</td>
<td>12–14</td>
</tr>
<tr>
<td>Thrombin 1 U + 0.1 mg protamine sulfate</td>
<td>59–62</td>
</tr>
<tr>
<td>Human thrombin, 1 U</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Reptilase time (1 mg)</td>
<td>72–75</td>
</tr>
<tr>
<td>Euglobulin lysis time</td>
<td>&gt;120 min</td>
</tr>
<tr>
<td>Factor V, VIII, XI, and XIII</td>
<td>Normal or</td>
</tr>
<tr>
<td>Platelet count per cu mm</td>
<td>285–325,000</td>
</tr>
<tr>
<td>Platelet aggregation, platelet and serotonin release</td>
<td>Normal</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>110%</td>
</tr>
</tbody>
</table>
Fig. 2. Effect of calcium on the rate of clotting of plasma. 0.1 ml of 0.25 M calcium chloride or 0.1 ml phosphate buffer was added to an equal volume of plasma. Thrombin in the concentration indicated was added and the clotting time measured.

Fig. 3. The rate of coagulation of partially purified fibrinogen by thrombin. Increase in absorbance was recorded after addition of 0.1 ml thrombin (10 or 100 U) to 1.0 mg of control (C) or patient's (P) fibrinogen in 0.9 ml of Tris-buffered saline.

Fig. 4. Per cent clottability of 125I-labeled fibrinogen. Control (C), or patient's (P) fibrinogen in buffer were labeled with carrier free 125I. Percentage clottability was determined after adding 5, 10, or 100 U of thrombin and allowing the mixture to incubate for 1-5 min at 37°C.
diphosphate, epinephrine, and collagen. Platelet ¹⁴C-serotonin release was also normal. Plasma antithrombin III activity was 110%.

The abnormal coagulability of the patient's fibrinogen was further demonstrated by the following studies: Figure 3 shows that, after addition of 10 or 100 U of thrombin to the patient's fibrinogen dissolved in buffer, the rate of coagulation as reflected by change in turbidity is abnormally slow. Figure 4 shows that the percentage clottability of the patient's ¹²⁵I-labeled fibrinogen with various concentrations of thrombin was much lower than that of the control specimen, especially when low concentrations of thrombin were used.

Immunodiffusion studies (Fig. 5) of the patient's plasma and serum using antihuman fibrinogen antiserum showed precipitation lines identical to those of control plasma. Similar results were obtained when purified fibrinogen derived from the patient and normal control were used. On immunoelectrophoresis (Fig. 6), the arc seen in the patient's plasma appears to have a slightly
faster anodal mobility than the arc seen in normal plasma. The patient's serum shows fibrinogen-related material which also appears to move faster towards the anode than normal plasma fibrinogen. Control serum showed no immunoreactive material, and no precipitation line was seen in the panels. When immunoelectrophoresis was repeated using purified fibrinogen in buffer, no gross difference was noted between the patient's fibrinogen and control fibrinogen.

Figure 7 shows that the patient's plasma has no inhibitory effect on the clotting of normal plasma.

Optimal coagulation of the patient's plasma occurred over a narrow range of pH, around 5.90–6.10 (Fig. 8). No clot was noted in the patient's plasma when the pH was over 7.85, whereas normal plasma clotted optimally when the pH was between 5.50 and 8.65.

Abnormality of polymerization of preformed fibrin monomers derived from the patient's fibrinogen was demonstrated by the method used by Forman et al., and is shown in Table 3. Normal plasma, acidified to pH 5.20, which was preincubated with thrombin for 5, 10, 15, or 20 min, clotted within 25–18 sec when the pH of the mixture was shifted to 7.20. No visible clot formed
Table 3. The Polymerization of Fibrin: Clotting Time (sec) Upon Neutralization
(Time of Incubation of Plasma and Thrombin)

<table>
<thead>
<tr>
<th>Plasma</th>
<th>10 sec</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>&gt;300</td>
<td>25</td>
<td>23</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Patient</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

*0.3 ml of plasma, 0.6 ml Michael's buffer (pH 2.62), and 0.1 ml thrombin (100 U/ml) incubated at 37°C. The pH of the mixture was 5.20-5.24. At the interval noted, 0.1 ml of the mixture was added to 0.1 ml hirudin (10 U/ml) in buffer, pH 9.6, and the clotting time was measured. The pH of the mixture after adding hirudin was 7.48.

when the patient’s plasma was similarly treated. The absence of clotting in the control plasma at 10 sec indicated that the amount of hirudin used was sufficient to inactivate the thrombin present in the mixture.

Figure 9 shows that the release of fibrinopeptides A and B by human thrombin from the patient’s fibrinogen is grossly retarded. After 60 min incubation with thrombin, the patient’s fibrinogen released about one-half as much fibrinopeptide A and only one-third the amount of fibrinopeptide B released by the control specimen. The patient’s fibrinogen and control fibrinogen, treated exhaustively with thrombin for 2 hr, released equal amounts of fibrinopeptide A, about 4350 ng per 0.5 mg fibrinogen.

**DISCUSSION**

The studies reported here have demonstrated that the rate of clotting of the patient’s plasma or partially purified fibrinogen by thrombin or Reptilase is abnormal in all systems employed, especially when the concentrations of thrombin are low. When quantitated as a clottable protein, the patient’s plasma fibrinogen was markedly reduced (Table 1); the amount of clottable protein doubled when excess calcium was added to the clotting mixture. The fibrinogen concentration was higher when estimated by immunologic techniques.

Immunoelectrophoresis (Fig. 6) using antihuman fibrinogen antiserum showed that the patient’s fibrinogen in its native plasma has a slightly faster anodal mobility than control fibrinogen. No gross difference was observed when purified fibrinogens in buffer were tested. This may be due to the loss of some negatively charged components during purification. The presence in the
serum of high titers of poorly coagulable material, immunologically related to fibrinogen (Figs. 5 and 6), indicates that components of this patient’s fibrinogen remain unclottable even after prolonged exposure to thrombin. Immunoelectrophoresis shows that the incoagulable component in the serum has a faster anodal mobility than normal fibrinogen, suggesting an increased negative charge. Two possible inferences may be drawn from this observation. One possibility is that this patient’s fibrinogen has two components, a normal component which clots as expected and an abnormal, negatively charged component which clots very slowly or not at all in response to thrombin action. Another possibility is that the unclottable, anodally moving component in the serum is a partially clotted and altered protein whose surface charge was changed by exposure to thrombin. Using column chromatography, Mosesson and Beck separated two components of fibrinogen Baltimore. The defective component gave no clot when treated with thrombin, while the normal component clotted in the expected way. The presence of two components, one normal and the second abnormal, would be anticipated in the heterozygote state of a condition inherited as autosomal dominant, which seems to be the mode of inheritance in all previously reported dysfibrinogenemias.\(^4\) Family studies in our patient are in agreement with this concept.

The first step in the action of thrombin on fibrinogen is the cleavage of fibrinopeptides A and B and the formation of fibrin monomers followed by aggregation of the monomers and the formation of polymers. Qualitative changes in fibrinogen can theoretically result in abnormalities in one or both steps. Studies on this patient’s fibrinogen indicate that both the cleavage of peptides and the polymerization of fibrin monomers are impaired. After 1 hr exposure to thrombin, the patient’s fibrinogen released about one-half as much fibrinopeptide A and only one-third as much fibrinopeptide B as the control specimen. After exhaustive treatment with thrombin, both fibrinogens released equal quantities of fibrinopeptide A, about 4350 ng per 0.50 mg fibrinogen, or 1.94 moles of peptide per mole of fibrinogen. This indicates that the patient’s fibrinogen has a normal total content of fibrinopeptide A.

The two-stage method used by Forman et al.\(^18\) to assess fibrin monomer aggregation provided evidence for abnormal fibrin polymerization in our patient. Incubation of plasma with thrombin at acid pH (5.2) allows the cleavage of peptides, but polymerization does not occur until the pH is neutralized.\(^18,39\) No clot formed in the patient’s plasma after neutralization with hirudin, whereas the control plasma clotted in 18–25 sec. Since peptide cleavage is also impaired in our patient’s fibrinogen, a high concentration of thrombin was used in the incubation mixture (10 U/ml) to ensure the cleavage of the peptides and the formation of free fibrin monomers.

The effect of calcium provided further evidence for defective fibrin monomer polymerization. It has previously been shown that the calcium ion accelerates the aggregation of preformed fibrin but has little effect on peptide cleavage.\(^50\) The shortening of the thrombin time of the patient’s plasma (Fig. 2) and the near doubling of the amount of clottable protein upon the addition of excess calcium (Table 1) suggest that added calcium might have partially corrected abnormal fibrin monomer aggregation. Another possible explanation for the
enhancing effect of calcium is that the positively charged ion might have partially neutralized an abnormal negative charge on the fibrinogen molecule. This would also explain the partial correction of the prolonged thrombin time by protamine sulfate, another positively charged substance.

Ferry and Morrison51 have previously suggested that coarse clots, usually correlated with heterogeneous distribution of fibers due to lateral interfibrillar aggregation, form when normal fibrinogen clots at an acid pH. On the other hand, the formation of fine, translucent clots, predominantly correlated with end-to-end aggregation, occurs with a low concentration of thrombin, when only fibrinopeptide A is released,52 and with an alkaline pH. The abnormal coagulability of the patient’s plasma under these circumstances (no clot forming above pH 7.6 (Fig. 8) and the markedly prolonged Reptilase time (Table 2)) provides further evidence for abnormal fibrin monomer aggregation.

The relationship of the in vitro observation of the functional properties of abnormal fibrinogens, including the one reported in this study, to the clinical symptoms, remains unknown. It is interesting that the patient’s two brothers who showed similar coagulation defects have no hemostatic symptoms. So far, no correlation has been made between the functional defects of abnormal fibrinogens and the clinical presentation of the patients. It is possible that procedures used for preparation of purified fibrinogen for in vitro studies involve removal of cold insoluble fibrinogen or other forms of altered fibrinogen which may have biologic activity.15 Another possibility is that the functionally altered protein interacts differently with the blood vessel wall or the blood-formed elements in the circulation in such a way as to result in thrombosis and/or bleeding.

Clinical and laboratory studies of patients with dysfibrinogenemia, and characterization of the biochemical and physiologic defects, should provide a better understanding of the role of fibrinogen in normal and abnormal hemostasis. Compared to other abnormal fibrinogens described in the literature, the functional defect of fibrinogen “New York” appears similar to that of fibrinogen Baltimore; most interestingly, both patients were afflicted with excessive thrombosis.

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