Hereditary Dysfibrinogenemia in a Patient With Thrombotic Disease

By Nadia Carrell, Don A. Gabriel, Philip M. Blatt, Marcus E. Carr, and Jan McDonagh

A new case of congenital dysfibrinogenemia, in which the patient has severe thrombotic disease, is reported. The abnormal fibrinogen molecules are characterized by normal fibrinopeptide release with thrombin and defective polymerization in the formation of fibrin. Clotting times with ancrod and reptilase are significantly prolonged. All other fibrinopeptide release with thrombin and defective polymerization were measured by thromboelastography. Fibrinogen assays varied from 118% to normal, and factor VIII coagulant assays varied from 100% to normal, and factor VIII coagulant assays were determined immunologically. Several other patients with abnormal fibrinogens and varying degrees of associated thrombosis have also been reported (Paris II, Copenhagen, Naples). There has been no obvious explanation for the severe thrombotic disease in these patients with poorly functioning fibrinogen molecules. Another family has recently been reported in which the affected members have severe thrombosis and functionally abnormal fibrinogen. The abnormal fibrinogen is characterized by defective polymerization and decreased binding of plasminogen. In this article, an abnormal fibrinogen is described in which the patient has prolonged ancrod and reptilase clotting times and abnormal fibrin polymerization and yet has severe thrombotic disease. In this case, the apparent paradox of repeated venous thrombosis in conjunction with an inability to form normal fibrin can be explained functionally by the altered mechanical properties of the abnormal fibrin and its altered response to plasmin.

CASE REPORT

The patient is a 16-yr-old white male who has had recurrent episodes of superficial and deep venous thrombosis of the lower extremities and one major episode of pulmonary embolism. He was in good health until age 10, when he suffered a deep cut to his right thigh requiring 25 sutures. Over the ensuing 11 mo the patient intermittently complained of mild to severe pain in his right thigh and groin, for which he was treated with various conservative measures. In July 1977, increasing pain, swelling, and mottling of the right leg led to performance of a right lower extremity venogram, which revealed extensive right iliofemoral thrombosis. Therapy with heparin was instituted and followed with coumadin for 6 mo. During the 6 mo of coumadinization he had no medical problems except for continued thigh swelling despite use of Jobst stockings. In February 1978, the patient was admitted to his local hospital with viral encephalitis manifested by fever, headache, and seizures. During this hospitalization he developed superficial thrombophlebitis of the left upper extremity, which was felt to be secondary to an indwelling intravenous catheter. Coumadin therapy was reinstated because of the phlebotic event and was continued for 6 mo.

Between July 1977 and November 1978 the patient had undergone repeated laboratory testing aimed at determining the cause of the recurrent thrombosis. Normal studies included complete blood count (CBC), sedimentation rate, protein electrophoresis, barium enema, intravenous pyelogram, cryoglobulins, cryofibrinogen, lupus erythematosus prep, Hamtest, sugar water hemolysis test, and rheumatoid factor. Antithrombin III assays done on three occasions were normal, and factor VIII coagulant assays varied from 118% to 95%.

In November 1978, the patient traumatically bruised the right side of his knee. This bruise progressed into the development of red streaking, which was felt to represent superficial thrombophlebitis.

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Supported in part by NIH Grant HL 22505.
Submitted November 16, 1982; accepted March 17, 1983.
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0006-4971/83/6202-0033$01.00/0
Therapy with Persantine, 25 mg twice daily, and aspirin, 0.6 mg at bedtime, was instituted. Shortly thereafter the patient was referred to the University of North Carolina School of Medicine for evaluation of his thrombotic problem.

On this first visit to UNC in February 1979, his past medical history was as noted above and his review of systems unremarkable. His physical exam was normal except for obesity and substantial right thigh and leg swelling. A summary of the results of laboratory tests performed at this time is shown in Table 1. The initial tests indicated no coagulation abnormalities except for an abnormal fibrinogen immunoelectrophoresis, which showed a normally placed arc and also an interlocking arc of faster mobility. A detailed family pedigree was also obtained and indicated that several paternal aunts, the paternal grandmother, and perhaps the paternal great-grandmother historically had episodes of phlebitis (Fig. 1).

Over the ensuing several months following his first visit to UNC the patient did well clinically, and Persantine and aspirin were discontinued. In February 1980 he was admitted to his local hospital with a dry hacking cough, marked shortness of breath, pleuritic chest pain, and left groin pain. Pertinent laboratory data included a lung scan, revealing bilateral multiple perfusion defects consistent with multiple pulmonary emboli, and a left leg venogram, which revealed occlusion of the popliteal and iliofemoral system. The patient was heparinized and discharged on coumadin and referred back to UNC, where further laboratory evaluation was undertaken (Table 1). In April 1980, both the fibrinogen and fibrinogen immunoelectrophoresis were normal. In August 1980, antithrombin III and plasminogen antigen were normal, but the fibrinogen immunoelectrophoresis again revealed both a normally placed arc and an interlocking, faster migrating arc.

Table 2 summarizes many of the tests that have been performed since the patient was seen in April 1980, and Table 3 shows the studies that have been done on the immediate family.

Since February 1980, the patient has been maintained on coumadin. The substantial swelling of his left leg has continued, and he has signs and symptoms of moderate pulmonary hypertension. During this period he has had no acute clinical events suggesting repeated deep venous thrombosis or pulmonary embolism.

**MATERIALS AND METHODS**

Blood was collected in 3.8% citrate or acid citrate dextrose (ACD). Plasma was prepared by double centrifugation and stored at −80°C. Routine coagulation tests were carried out according to standard procedures. Plasma fibrinogen concentration was determined by the methods of Clauss (chronometric) and Ratnoff and Menzie and by radial immunodiffusion on Partigen plates (Calbiochem-Behring). Antithrombin III was measured functionally and immunochemically. Factor XIII activity was determined by dansylcadaverine incorporation and by radioimmun assay for the subunit proteins. Normal values for plasma samples in these assays (±1 SD) are 5.5 ± 1.0 μmole dansylcadaverine incorporation/30 min/0.2 ml for factor XIII activity, 15.6 ± 2.6 μg/ml for a-subunit concentration, and 13.8 ± 2.5 μg/ml for b-subunit concentration.

Thrombin clotting times of plasma were done in a test system containing 0.2 ml plasma, 0.1 ml Tris-saline, pH 7.4, and 0.1 ml thrombin. In most cases, the final thrombin concentration was 5 U/ml. For reptilase times, 0.2 ml plasma and 0.1 ml enzyme diluted 1:20 with buffer were used. For ancrod times, 0.2 ml plasma and 0.1 ml anhind diluted 1:4 with buffer were used. Clotting times were measured at 37°C for ancrod and reptilase and at room temperature for thrombin.

Fibrinogen was purified from patient plasma and normal plasma by ammonium sulfate fractionation and was 88.5%–90% coagulable, with a 55% yield in both cases. This material was used for the specific tests for fibrinogen function described here. (1) Plasmin digestion of fibrinogen and fibrin was carried out at ratios of 0.001–0.02 casein unit plasmin/mg fibrinogen. Digests were made with and without CaCl₂, and both thrombin fibrin and reptilase fibrin digests were analyzed. (2) Release of fibrinopeptides A and B was quantitated by reaction of peptide-bound arginine with phenanthrenequinone. (3) Turbidity measurements were made on a Cary 118C spectrophotometer. Fibrin gels were formed either from a 1:10 dilution of plasma or from purified fibrinogen. Unless stated otherwise, conditions for gelation were 0.1 M NaCl, 0.05 M Tris, pH 7.4, and 5 mM CaCl₂. Bovine thrombin was added at time zero in a final concentration of 1.25 NIH U/ml to initiate clotting. Kinetics of the assembly process were observed by following the change in turbidity, ρ, as a function of time. Turbidity was monitored at the Helium-Neon laser line, 632.8 nm. Mass–length ratios (μ) for each fibrin gel were determined by scanning the gels from 750 nm to 450 nm. Values were calculated as previously described, with turbidity being plotted versus the inverse of the wavelength cubed. The slope of this line is directly related to the mass–length ratio. Aggregation was also followed at 350 nm in a recording spectrophotometer on plasma diluted twofold with Tris-saline, pH 7.5, to which thrombin (0.66 U/ml final concentration) or anhind (0.33 U/ml) was added. The rigidity, or equilibrium shear modulus, of gels formed either from plasma diluted 1:10 or from purified fibrinogen was measured in a modified Zimm-Crothers elastometer. Gels were formed in the elastometer by first introducing thrombin at a final concentration of 1.25 NIH U/ml followed by the solution to be clotted. All gels were formed at 25°C. The equilibrium shear modulus was calculated from the slope of a plot of the shear strain versus the shear stress. Shear stress (in dynes/sq cm) is a measure of the force causing a

<table>
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<tr>
<th>Table 1. Initial Coagulation Tests on the Patient</th>
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<tr>
<td><strong>Date</strong></td>
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<td>February 1979</td>
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<td>April 1980</td>
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<tr>
<td>August 1980</td>
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*Method of Claus.
displacement, in this case, of the fibrin gel; and shear strain (in radians) is a measure of the displacement or movement induced by a tangential force (shear stress) on the gel.

Gel electrophoresis was done on 5% and 7.5% polyacrylamide gels in sodium dodecyl sulfate under reducing and nonreducing conditions.\(^2\) Fibrin crosslinking of plasma clots was monitored on reduced SDS gels and also by solubility in 1% monochloroacetic acid. Immunoelectrophoresis was carried out in barbital buffer, pH 8.6.\(^3\)

RESULTS

The significant initial laboratory findings for the patient are shown in Tables 1 and 2. Fibrinogen concentration, measured in clotting assays, was normal on all occasions, ranging from 203 to 281 mg/dl (mean 248 mg/dl). Immunochemically detectable fibrinogen was 34% higher (332 mg/dl), but was still within the normal range. The thrombin time was only slightly long, but the reptilase and ancrd times on patient's plasma were markedly prolonged. The thrombin time of the patient's purified fibrinogen was also significantly abnormal (73.0 sec versus 42.4 sec for the control in this test system). Release of fibrinopeptides A and B with thrombin was normal, both with respect to initial rate and total amount. Maximum peptide cleavage from patient fibrinogen was 3.46 mole/mole fibrinogen compared to 3.70 mole/mole for the control sample. However, fibrin monomer aggregation was found to be markedly abnormal, since no increase in optical density at 350 nm was observed when patient plasma or fibrinogen was clotted with thrombin or ancrd. Fibrinogen immunoelectrophoresis was variable. At times, patient fibrinogen had a second, more anodally migrating arc in addition to the normal arc (Fig. 2); at other times, only the normal arc was observed. The second arc was found not to be due to fibrinogen degradation fragments D or E. Also, there was no evidence for fibrinogen degradation products in the patient's serum. On SDS polyacrylamide gels, patient fibrinogen and fibrin appeared normal. Patient fibrin crosslinked normally, as demonstrated by gel electrophoresis of reduced fibrin and also by clot solubility in 1% monochloroacetic acid. However, factor XIII activity and a-subunit were significantly decreased. The patient's parents and brother were also screened for fibrinogen function (Table 3). Both the brother and father had prolonged ancrd times, decreased factor XIII activity, and abnormal clot formation as monitored by turbidity at 350 nm. These observations, together with the patient's history, led to a diagnosis of congenital dysfibrinogenemia.

The specific defect in the aggregation of fibrin monomers was examined further. Kinetics of the

Table 2. Tests for Fibrinogen Function*  

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Control</th>
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<tr>
<td>Thrombin time (sec)</td>
<td>12.6</td>
<td>11.5</td>
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<tr>
<td>Reptilase time (sec)</td>
<td>31.0</td>
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<td>Ancrod time (sec)</td>
<td>43.0</td>
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<td>Fibrinogen concentration (mg/dl)</td>
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<td>Method of:</td>
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<tr>
<td>Clauss</td>
<td>258</td>
<td>216</td>
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<tr>
<td>Ratnoff and Menzie</td>
<td>249</td>
<td>256</td>
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<tr>
<td>Radial immunodiffusion</td>
<td>332</td>
<td>235</td>
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<tr>
<td>Clot solubility in monochloro-</td>
<td>Insoluble</td>
<td>Insoluble</td>
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<td>acetic acid</td>
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<tr>
<td>Fibrin crosslinking</td>
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<td>Normal</td>
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<tr>
<td>Total fibrinopeptide release</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Polymerization at 350 nm</td>
<td>No increase in turbidity</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor XIII activity (% of normal)</td>
<td>39</td>
<td>100%</td>
</tr>
<tr>
<td>a-antigen</td>
<td>45</td>
<td>100%</td>
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<tr>
<td>b-antigen</td>
<td>100</td>
<td>100%</td>
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*All assays except fibrinopeptide release were performed on plasma samples.
assembly of fibrin monomers into a gel for both normal and abnormal plasma are shown in Fig. 3. The gel point, which indicates the first appearance of the three-dimensional network, was delayed in the abnormal plasma; and there was a striking difference in the turbidity of the two plasmas. Turbidity measured in this way is correlated with the diameter of the fibrin fibers in the gel network. Therefore, the lower turbidity seen in the patient sample suggested that fibrin fibers in these gels should be very thin compared to the normal control. Mass–length ratios, calculated from scans of turbidity versus wavelength for completely assembled gels, showed the fibrin fiber mass–length ratios from the abnormal plasma to be approximately half that of normal plasma (1.87 × 10^{12} versus 2.85 × 10^{12} daltons/cm), confirming that the patient’s fibrinogen formed significantly thinner fibers than normal.

Mechanical properties of the fibrin gel formed by the patient’s fibrinogen were investigated by means of elasticity measurements on both plasma gels and with purified fibrinogen. From the initial slopes of shear stress versus shear strain plots for fibrin formed both in plasma and in a purified system from patient and normal, the equilibrium shear modulus for each sample was obtained. For the patient’s plasma fibrin clot this value was 20 dynes/sq cm, compared to 5 dynes/sq cm for the control plasma fibrin. Since the equilibrium shear modulus is a measure of rigidity or deformability of the fibrin gel, these results indicate that the fibrin fibers in the patient’s gel were significantly stiffer than normal.

Previous work has shown that Dextran 70 is effective in reducing the rigidity of gels formed in normal plasma but not in purified systems. Although the reason for this phenomenon is uncertain and probably involves some additional component(s) in plasma, the observation is clear and reproducible. Therefore, similar experiments with Dextran 70 were performed on gels prepared from the patient’s plasma and fibrinogen. These experiments were carried out in the expectation that if Dextran could be shown to reduce the rigidity of the patient’s clots, then Dextran might be useful for effective treatment of a thrombotic event in the patient. The top panel of Fig. 4 shows that the rigidity of fibrin gels formed from the abnormal plasma increased from 21 to 30 dynes/sq cm as the Dextran 70 concentration increased from 0 to 2 mg/ml. In contrast, the rigidity of gels formed from normal plasma decreased sharply in the expected manner, from 6 dynes/sq cm with no Dextran 70 to 1 dyne/sq cm with 0.1 mg/ml of Dextran 70. The lower panel of Fig. 4 shows the effect of Dextran 70 on gels formed from purified fibrinogen obtained from the patient and from normal plasma. As previously described, Dextran 70 has no effect on the rigidity of these gels in the concentration range studied. Except for the higher initial modulus, the effect of Dextran 70 on the patient’s fibrin gel is similar to its effect on fibrin gels formed from normal fibrinogen. More scatter in the data points was always observed with the abnormal fibrinogen, but this was still within experimental error.

Plasmin digestion of the patient’s purified fibrinogen was found to be somewhat delayed, but degreda-
tion of his fibrin was markedly inhibited. Figure 5 shows several electropherograms of fibrinogen degradation products that formed at various times. In each case, patient and control samples were treated identically. It can be seen in the nonreduced gels that the formation of fragment X from fibrinogen was moderately delayed, with a significant amount of high molecular weight material remaining at 30 min (gel 5) in contrast to the control sample (gel 2). The reduced gel patterns (gels 11 and 12) show a persistence of all three polypeptide chains. Throughout the digestion, the fragments that formed were of normal size, but their appearance was retarded. More striking results were observed in the degradation of patient fibrin, in which plasmin cleavage essentially did not occur (Fig. 6). Very little fragment X formed, and only trace amounts of Y and D could be observed, even after 180 min (gel 6). Under the same conditions, the control gave rise to the expected degradation products. The reduced gel patterns show the marked persistence of all three polypeptide chains of noncroslinked fibrin. Even at the 3-hr point, the patient’s α, β, and γ chains appear to be essentially intact. The gel patterns in Fig. 6 were made from fibrin prepared by clotting fibrinogen with thrombin. Essentially the same pattern was observed when patient fibrinogen was treated with reptilase. This fibrin also failed to lyse with plasmin.

The functional properties of this abnormal fibrinogen appear to be unique, and it has been designated fibrinogen Chapel Hill III.

DISCUSSION

The polymerization of fibrin monomers to form a three-dimensional gel is a complex, multistep process that is both orderly and kinetically determined.25 Once thrombin has cleaved fibrinopeptide A, monomer units associate to form protofibrils that are two molecules in diameter. Protofibrils may then associate laterally in solution to form fibrils. The formation of fibers and the gel network is dependent on the number of contact points that result from lateral association and branch-point formation. Any condition, such as pH or ionic strength, which alters the reaction rate of any of the individual steps in the process can have a marked effect on the type of fibrin fibers that ultimately form.26 Alterations may occur in the length of protofibrils, in the degree of lateral association, and in the number of branchpoints.

The type of fibrin fibers that form determines the
Fig. 5. SDS polyacrylamide electrophoresis of patient and control fibrinogen samples treated with plasmin. Concentrations in the incubation mixture were 3 mg/mL fibrinogen and 0.07 casein unit (CU)/ml plasmin. At various time intervals, 50-μl aliquots were removed and mixed with an equal volume of SDS buffer, with and without DTT, and run on gels.

The clotting defect is particularly evident in the patient when snake venom proteases, which cleave fibrinopeptide A but not fibrinopeptide B, are used to measure the clotting time. With either ancrod or reptilase, the patient’s clotting time was markedly prolonged, even though peptide release was normal. The reasons for the different specificity of the patient fibrinogen to snake venom proteases probably relates to the fact that there are other sensitive bonds in fibrinogen that are cleaved by venom proteases in addition to the fibrinopeptide A cleavage. Such differential specificities toward thrombin, ancrod, and reptilase have also been observed with other abnormal fibrinogens. Because it is possible for a variant fibrinogen to clot abnormally with one, two, or all three enzymes, we have found it very helpful to perform reptilase and ancrod times on all patient plasmas that seem to form thrombin clots that are in any way abnormal.

An abnormal ancrod time was also observed in the brother and father of the proband, and both also had
DYSFIBRINOGENEMIA AND THROMBOSIS

Defective fibrin monomer aggregation. All three family members also had decreased levels of factor XIII activity, which was again most pronounced in the patient. However, the partial deficiency of factor XIII was not sufficient to prevent fibrin crosslinking. There is no obvious explanation for the decreased factor XIII, since factor XIII activity is not correlated with fibrinogen function or concentration. Abnormal fibrin crosslinking has been found in some abnormal fibrinogens, but it is normal in most cases.

We also do not fully understand the variable fibrinogen immunoelectrophoresis that was observed for this patient, with a second more anodally migrating arc sometimes apparent. All other defects in this fibrinogen were consistently abnormal and were not correlated in any way with the electrophoretic pattern. However, the variable electrophoretic mobility appears to be a real phenomenon, which could be related to altered fibrinogen biosynthesis associated with undetected liver dysfunction. Abnormal electrophoretic patterns have been reported in a few cases of dysfibrinogenemia, and differences in sialic acid content have been observed in liver disease.

A prominent feature of the fibrin gels formed by this abnormal fibrinogen is the marked rigidity of the gels (Fig. 4). This is especially striking since turbidity measurements indicated that lateral association in the fibrin assembly process was greatly diminished, as evidenced by the decreased fiber diameter (low mass-length ratio) of patient fibrin compared to the control (Fig. 3). In light of this, the remarkable rigidity of these gels could be related both to the rigidity of the individual fibrin fibers between their contact points and to an increase in the branchpoint density between the fibrin fibers. Increased rigidity of the fibers seems unlikely vis-à-vis the decreased mass-length ratio and the thin fibers formed by the abnormal fibrinogen. As a consequence, an increased branchpoint density seems the most probable explanation for the increased rigidity. This abnormality in the polymerization process could result from a biochemical alteration at or near a contact site, which affects the rate of lateral association.

A remarkable resistance to plasmin degradation is also an important feature of this abnormal fibrinogen (Figs. 5 and 6). Plasmin degradation of fibrinogen and
fibrin is an orderly, sequential process, which results in the production of characteristic core fragments.\textsuperscript{13,14} If cleavage is inhibited at any point in the process, all subsequent steps are delayed. The rate at which plasmin cleaves fibrin is a function both of the biochemical and physical properties of the fibrin gel. Defective plasmin degradation, also in association with a polymerization defect, has been observed in other congenital variants of fibrinogen.\textsuperscript{29,35} In the present case, the fibrinolytic defect appears to result from the primary biochemical defect, since cleavage of fibrinogen is inhibited. In addition, the type of rigid fibrin that this fibrinogen forms results in a further increase in resistance of the fibrin gel to plasmin degradation. Thus, the effect on fibrin is greatly magnified. This is somewhat analogous to the effect of covalent cross-linking by factor XIII\textsubscript{a} in increasing rigidity and resistance to plasmin.\textsuperscript{36,37} In that case, an increased branchpoint density produces an increase in rigidity and a concomitant increase in plasmin resistance. In this patient it is the combination of abnormally high rigidity of the fibrin and its imperviousness to plasmin that can explain the tendency for thrombotic disease.

The influence of Dextran 70 on the rigidity of gels formed from patient plasma was unexpected. In view of Dextran's effect on reducing the rigidity of gels formed from normal plasma,\textsuperscript{24} it was hoped that Dextran would provide a means of reducing this patient's thrombotic tendency. However, on the basis of these studies, Dextran 70 would be a poor treatment modality. In addition, the plasmin studies presented here indicate that streptokinase or urokinase therapy would not be helpful.

Laboratory evaluation for the diagnosis and treatment of patients with defects similar to those described in this case must be pursued beyond the usual coagulation screening tests. As seen in Table 1, the usual coagulation tests were normal in this patient. Only the fibrinogen immunoelectrophoresis pattern appeared to be abnormal. Definitive diagnosis of the abnormal fibrinogen required further clotting studies, purification of the fibrinogen, and detailed characterization of the mechanical properties of the fibrin and its fibrinolytic susceptibility. Although some of these studies are beyond the purview of most diagnostic laboratories, there are several rather straightforward procedures that can be employed whenever abnormal fibrinogen function is suspected. These include: (1) measurement of the plasma clotting time with dilutions of both anecrod and reptilase, and (2) measurement of the increase in turbidity during fibrin formation in a spectrophotometer at 350 nm. It is likely that many cases of abnormal fibrinogen go undetected because routine tests are insensitive to the abnormality. Many patients with poorly understood hemorrhagic or thrombotic problems, particularly idiopathic thrombosis, may well have a dysfibrinogenemia.

ACKNOWLEDGMENT

We wish to thank the patient, Roy Nabors, and his family for their great interest and cooperation in this study. We also wish to thank Dr. Helen Vodopick, Oak Ridge, Tenn., for referring this patient to us.

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