A Clinical Study of the Lupus Anticoagulant

By Michael A. Schleider, Ralph L. Nachman, Eric A. Jaffe, and Morton Coleman

Eighty-three patients with circulating anticoagulants were studied at The New York Hospital. The lupus-type anticoagulant, an inhibitor of the prothrombin activator complex, was demonstrated in 58 patients. This inhibitor was identified using the blood and tissue thromboplastin inhibition tests. Inhibition by the lupus anticoagulant was augmented in 67% of these patients by a cofactor present in normal plasma. The lupus inhibitor was detected primarily because of an unsuspected abnormal coagulation test. One-half of the patients with the lupus-type anticoagulant did not have systemic lupus erythematosus.

Spontaneously acquired anticoagulants occur in a number of different clinical states, including systemic lupus erythematosus (SLE). The lupus anticoagulant is a unique inhibitor that acts at the junction of the intrinsic and extrinsic coagulation pathways by interfering with the activation of prothrombin by the prothrombin activator complex (factor Xa, V, calcium, and phospholipid). The specific site on the complex at which the inhibition occurs has not been fully clarified. Much of the evidence suggests that the anticoagulant inhibits the phospholipid portion of the complex. The inhibitor’s activity can be augmented by a normally occurring plasma component. Initially described in patients with SLE, this inhibitor has subsequently been found in other clinical states.

This study reviews the clinical and laboratory data on 83 adult patients with acquired anticoagulants. Fifty-eight of these patients had a lupus-type anticoagulant. The lupus anticoagulant, which inhibited the prothrombin activator complex, was assayed by the blood thromboplastin inhibition (BTI) and tissue thromboplastin inhibition (TTI) tests. One-half of the patients with the lupus anticoagulant did not have SLE.

MATERIALS AND METHODS

Routine Coagulation Studies

Established methods, previously described, were used by the coagulation laboratory in the evaluation of the prothrombin time, activated partial thromboplastin time (PTT), thrombin time, serum prothrombin consumption, plasma prothrombin activity, Lee-White clotting time, bleeding time, platelet count, platelet aggregation, fibrin split products, and individual factor assays.
Circulating Anticoagulant Detection

As defined by Margolius, an acquired circulating anticoagulant is "an abnormal endogenous component of blood which inhibits the coagulation of normal blood." The presence of a circulating anticoagulant was detected by performing PTT's on a mixture of patient and control plasma. The failure of normal plasma to correct the prolonged PTT indicated the presence of an anticoagulant.

Blood Thromboplastin Inhibition Test

Blood thromboplastin was generated by mixing 0.5 ml of Al(OH)₃-absorbed normal plasma (which contains factors VIII, XI, and XII) diluted 1:5 with imidazole-buffered saline (140 mM NaCl, 15 mM imidazole buffer, pH 7.35), 0.5 ml of normal serum (which contains factors IX and X) diluted 1:10 with imidazole-buffered saline, and 0.5 ml of cephalin. After 1 min incubation, 0.5 ml of 25 mM CaCl₂ (in distilled water) was added. The mixture, which generated blood thromboplastin, was further incubated for 6 min at 37°C and iced immediately. The blood thromboplastin mixture (0.3 ml) and the patient's Al(OH)₃-absorbed plasma (0.3 ml) were mixed in 13 x 100-mm disposable glass tubes (Kimble) and the mixture incubated in a water bath at 37°C. After 5 and 10 min incubation, 0.1 ml of normal, unabsorbed plasma (warmed to 37°C for 3 min) and 0.1 ml of 25 mM CaCl₂ were added to 0.1 ml of the previously incubated mixture of blood thromboplastin and patient's Al(OH)₃-absorbed plasma. The clotting time was then measured. At the same time each BTI assay was performed, plasma drawn from a healthy hospital employee on the same day was assayed as a simultaneous control.

Tissue Thromboplastin Inhibition Test

Simplastin (General Diagnostics Division of the Warner Lambert Co., Morris Plains, N.J.) was diluted 1:50 and 1:500 with saline (0.9% NaCl) and incubated at 37°C for 5 min. Simplastin, 0.1 ml of the 1:50 or 1:500 dilution, was added to 0.1 ml of patient plasma (final dilution 1:100 or 1:1000), and the mixture was incubated at 37°C for 5 min. Following this incubation, 0.1 ml of 25 mM CaCl₂ was added, and the clotting time was measured. At the same time each TTI assay was performed, plasma drawn from a healthy hospital employee on the same day was assayed as a simultaneous control.

Patient Selection

All patients studied at the coagulation laboratory of the New York Hospital-Cornell Medical Center from September 1958 to March 1975 who were found to have circulating anticoagulants were evaluated. The following patients were excluded from the analysis: (1) pediatric patients, (2) hemophiliacs who developed circulating anticoagulants during replacement therapy, (3) patients receiving heparin or other anticoagulant drug therapy, and (4) six patients about whom data were insufficient.

Systemic Lupus Erythematosus

Following the guidelines of the American Rheumatism Association Section of the Arthritis Foundation, a patient was considered as having SLE if any four or more of the following 14 manifestations were present, serially or simultaneously, during any interval of observation: (1) butterfly rash, (2) discoid lupus, (3) Raynaud's phenomenon, (4) alopecia, (5) photosensitivity, (6) oral or nasopharyngeal ulceration, (7) arthritis without deformity, (8) positive LE cell preparation, (9) chronic biologic false-positive serologic test for syphilis, (10) proteinuria exceeding 3.5 g/day, (11) urinary cellular casts, (12) either (a) pleuritis or (b) pericarditis, (13) either (a) psychosis or (b) convulsions, (14) either (a) hemolytic anemia, (b) leukopenia (WBC count below 4.0 x 10⁹/liter), or (c) thrombocytopenia (platelet count below 100 x 10⁹/liter).

Statistical Analysis

Tests performed to evaluate statistical significance included calculation of means, standard deviations, variances and correlation coefficients. When sample variances were equal, Student's
Test for the Lupus Anticoagulant

The lupus anticoagulant interferes with activation of prothrombin by the prothrombin activator complex.1,4 The BTI and TTI tests, as modified in our laboratory, were used to detect this inhibitor. The BTI test identified an inhibitory activity directed against the prothrombin activator complex that had been generated through the intrinsic coagulation pathway. An example of the results of a BTI test is shown in Table 1. The patient’s plasma contained an inhibitor of preformed prothrombin activator, which was more apparent with longer incubation times. The TTI test identified an inhibitory activity directed against diluted Simplastin. An example of the results of a TTI test is shown in Table 2. The patient’s plasma contained an inhibitor that was more apparent with the use of more dilute Simplastin. To differentiate normals from abnormals, the BTI and TTI tests were analyzed statistically. For the BTI and TTI tests, a ratio of patient to control clotting times was constructed to eliminate day-to-day variations. When the histogram of the ratios for the TTI test at 1:1000 dilution was constructed, a bimodal distribution was observed (Fig. 1). The two curves interfaced at a value of 1.2. The mean ratios of the two populations separated by this value differed at a p < 0.005. Applying this to the patients, it was concluded that a ratio of 1.3 or greater was abnormal, 1.2 to 1.3 was probably abnormal, 1.1 to 1.2 was probably normal, and 1.1 or less was normal. Similar analyses were performed for the TTI test at 1:100 dilution, for the BTI tests at 5 and 10 min incubation, and for thrombin times. The results were similar.

On the basis of these studies, the lupus anticoagulant was considered present

<table>
<thead>
<tr>
<th>Test</th>
<th>Plasma</th>
<th>Clotting Times (sec)</th>
<th>Clotting Times (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-min Incubation</td>
<td>10-min Incubation</td>
</tr>
<tr>
<td>Patient</td>
<td>36.4</td>
<td>68.4</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25.8</td>
<td>33.5</td>
<td></td>
</tr>
</tbody>
</table>
if the following criteria were met: (1) the PTT was prolonged, (2) mixing of the patient's plasma with small amounts of normal plasma did not correct the prolongation of the PTT, and (3) the blood and/or tissue thromboplastin inhibition test was abnormal.

**Clinical Classification**

Eighty-three patients were found to have circulating anticoagulants and were classified into four groups (Table 3), based upon the presence or absence of SLE and of the lupus anticoagulant. The first group, including all patients with both SLE and the lupus anticoagulant, represented 35% of all the patients and was divided into two subgroups: IA—patients who met the diagnostic criteria of the American Rheumatism Association, and IB—patients who did not meet these criteria, yet were considered by their physicians to have SLE or a lupus-like, "collagen vascular" disease. Four patients in group IB were taking procainamide at the time the lupus anticoagulant was discovered. The female to male ratio in group I was 4:1.

Patients in group II also had the lupus anticoagulant, but did not have a clinical disorder resembling SLE. The various clinical conditions represented by this group are listed in Table 4. The female to male ratio in this group was 1:1.

**Table 3. Clinical Classification of Patients With Circulating Anticoagulants**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Clinical Diagnosis</th>
<th>Type of Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>29</td>
<td>SLE</td>
<td>Lupus</td>
</tr>
<tr>
<td>A</td>
<td>16</td>
<td>Definite*</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>13</td>
<td>Probable†</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29</td>
<td>Other</td>
<td>Lupus</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>SLE</td>
<td>Other</td>
</tr>
<tr>
<td>IV</td>
<td>17</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

*Patients in this category satisfied criteria for diagnosis of SLE as determined by the American Rheumatism Association.
†Patients in this category did not satisfy the aforementioned criteria, but were considered by their physicians to have SLE or a lupus-like "collagen-vascular" disease.
Table 4. Clinical Diagnoses in Patients With the Lupus Anticoagulant but Without Clinical SLE

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologic</td>
<td>Multiple myeloma, Cervical carcinoma, four abortions</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s disease, Cecal carcinoma, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Prostatic carcinoma, Metastatic adenocarcinoma, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Myelofibrosis, Lymphosarcoma, diabetes mellitus</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>Meno, metrorrhagia, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Eclampsia</td>
</tr>
<tr>
<td></td>
<td>Elective abortion</td>
</tr>
<tr>
<td></td>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td>Urologic</td>
<td>Benign prostatic hypertrophy (3)</td>
</tr>
<tr>
<td></td>
<td>Benign prostatic hypertrophy, diabetes mellitus</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vasculitis</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Acute Guillain Barré syndrome, acute myelogenous leukemia</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Acromegaly, diabetes mellitus, dementia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>ASCVD, HCVD</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease, s/p thyroidectomy</td>
</tr>
<tr>
<td></td>
<td>ASCVD, s/p spontaneous abortion and secondary hypoadrenalism</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Congenital lymphedema</td>
</tr>
<tr>
<td></td>
<td>Chondromalacia</td>
</tr>
<tr>
<td></td>
<td>von Willebrand’s disease</td>
</tr>
</tbody>
</table>

The patients in group III had classical SLE with an anticoagulant other than the lupus anticoagulant, as defined above. The anticoagulants in this group of patients included two inhibitors of factor VIII and six which were not well defined.

The 17 patients in group IV with anticoagulants of a type different than the lupus anticoagulant did not have SLE. Nine of these anticoagulants (53%) were inhibitors of factor VIII, three of factor XI, one of thrombin, and four were not specified.

Hemostatic Profile

A profile of the major coagulation studies is shown in Table 5. The mean PTT was substantially prolonged in all four groups; this defect was not corrected by the addition of normal plasma.

The addition of small amounts of normal plasma to plasma of patients with the lupus anticoagulant may lead to a paradoxical prolongation of the PTT. An example of this phenomenon is shown in Table 6. This phenomenon was observed in 20 of 30 (67%) of our patients with the lupus anticoagulant.
Table 5. Coagulation Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean PT (sec)</th>
<th>Mean PIT (sec)</th>
<th>Mean Thrombin Time*</th>
<th>Mean Thrombin Time With Mixing*</th>
<th>Mean BTI*</th>
<th>Mean TTI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12.0</td>
<td>&lt;40</td>
<td>1.0</td>
<td>1.0</td>
<td>&lt;1.2</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>I (SLE-L)</td>
<td>14.0</td>
<td>61.4</td>
<td>1.3</td>
<td>1.2</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>II (OD-OA)</td>
<td>13.7</td>
<td>54.5</td>
<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>III (SLE-OA)</td>
<td>12.6</td>
<td>65.0</td>
<td>2.2</td>
<td>2.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IV (OD-OA)</td>
<td>12.5</td>
<td>68.1</td>
<td>1.8</td>
<td>2.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Reported as ratio of patient/control clotting times.

1L, lupus anticoagulant; OD, diagnosis other than SLE; OA, anticoagulant other than the lupus anticoagulant.

The mean BTI and TTI times in patients with the lupus anticoagulant (groups I and II) were significantly prolonged compared to normal controls. These tests were not performed on patients with other anticoagulants (groups III and IV). No significant correlation was found between a positive BTI or TTI and any other laboratory test of hemostasis. The mean thrombin times were elevated in all four groups (p < 0.001). This elevation was particularly evident in patient groups III and IV (Table 5). In none of the groups was the thrombin time corrected to normal by the addition of normal plasma. The reason for this lack of correction, particularly in the patients with the lupus anticoagulant, was not clear.

Reasons for the Detection of the Anticoagulants

The factors leading to the detection of a circulating anticoagulant were analyzed (Table 7). Three possibilities were considered: (1) the finding of an abnormal screening coagulation study (such as the PTT or prothrombin time) which was clinically unsuspected, (2) the presence of an overt clinical hemorrhage, and (3) a clinical concern for potential bleeding. The lupus anticoagulant was detected predominantly because of an abnormal screening coagulation test, whereas other anticoagulants were detected more frequently because of an overt hemorrhagic state or a high index of suspicion.

Clinical Correlations

The lupus anticoagulant correlated with only one of the criteria of SLE established by the American Rheumatism Association, the biologic false-positive serologic test for syphilis (Table 8). Patients with the lupus anticoagulant had a higher than expected incidence of positive Coombs' tests and antinuclear antibody tests. Nevertheless, it was the disease SLE with which these laboratory
abnormalities best correlated. The Farr test, which is highly specific for SLE, was negative in the group of patients with the lupus anticoagulant but without SLE (group II). Complement levels bore no relationship to the presence of the lupus anticoagulant.

It is important to note that one-half of the patients with the lupus anticoagulant did not have clinical SLE, but rather a wide range of disease entities (Table 4).

A past medical history of clinically significant bleeding was found in 31% of patients with classical SLE and the lupus anticoagulant (group IA), but in only 18% of the patients with the lupus anticoagulant and probable SLE (group IB) or some other disease (group II). In the majority of patients, bleeding could be attributed to a hemostatic defect other than the anticoagulant, particularly thrombocytopenia.

DISCUSSION

The incidence of the lupus anticoagulant in patients with SLE is not known. Regan’s study21 of 50 consecutive patients with SLE yielded a 6% incidence and this figure correlates well with the 5%-10% estimate given by others.1,2,22 In our institution, the detection of the lupus anticoagulant has increased dramatically since the introduction of the automated PTT into routine hospital use. It is our experience that the lupus anticoagulant is usually discovered consequent to an abnormal laboratory test. Clinical bleeding is unusual. This experience is similar to that recorded in the literature.23-25 Frick15 was one of the first to recognize that the lupus anticoagulant occurred in conditions other than SLE, and reviews by others1-3 have confirmed this observation. In our series, one-half of the patients with the lupus anticoagulant did not have SLE.

Table 8. Incidence of Abnormal Laboratory Parameters of SLE*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Biologic False-positive Serology (%)</th>
<th>Coombs' Test (%)</th>
<th>ANA (%)</th>
<th>Thrombocytopenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (SLE-L)†</td>
<td>29</td>
<td>71</td>
<td>72</td>
<td>72</td>
<td>32</td>
</tr>
<tr>
<td>II (OD-L)</td>
<td>29</td>
<td>11</td>
<td>38</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>III (SLE-OA)</td>
<td>8</td>
<td>63</td>
<td>43</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>IV (OD-OA)</td>
<td>17</td>
<td>0</td>
<td>11</td>
<td>33</td>
<td>7</td>
</tr>
</tbody>
</table>

*Given in per cent of patients with positive tests.
†L, lupus anticoagulant; OD, diagnosis other than SLE; OA, anticoagulant other than the lupus anticoagulant.
The lupus anticoagulant inhibits the interaction between the prothrombin activator (the factor V, factor Xa, phospholipid, calcium complex) and prothrombin, but the exact molecular substrate against which it is directed is not known. Lechner has recently summarized the evidence favoring the phospholipid component of the prothrombin activator as the substrate of the lupus anticoagulant. Many have reported that the lupus anticoagulant is an immunoglobulin. It has been characterized as an IgG in 11 cases, an IgM in 8 cases, and a mixed IgG–IgM in 12 cases.

Loeliger, in 1959, was the first to demonstrate that a cofactor in normal plasma was necessary for maximal action of the lupus anticoagulant. This cofactor, which potentiates the inhibitory action of the lupus anticoagulant, is responsible for the augmentation effect (Table 6). In 1965, Yin and Gaston demonstrated that the cofactor and the anticoagulant had to be present in correct proportion for the anticoagulant to exert its maximal activity. They postulated that the cofactor was a gamma globulin. A detailed study by Rivard, Schiffman, and Rapaport showed that the cofactor was: (1) unstable at 56°C for 30 min; (2) minimally absorbed by BaSO₄ or Al(OH)₃; (3) of a molecular weight of 200,000 on gel filtration; and (4) precipitable between 50°–75% (NH₄)₂SO₄ saturation. Although these characteristics are similar to those of complement, complement levels in our patients were variable and did not correlate with the anticoagulant’s activity. The augmentation effect of the cofactor was demonstrated in 67% (20 of 30) of our patients. The absence of the augmentation in the remaining ten patients may reflect the heterogeneity of the population of patients with the lupus anticoagulant and/or the crucial requirement of appropriate ratios of cofactor to anticoagulant.

The PTT is invariably prolonged in patients with the lupus anticoagulant and is considered the most sensitive screening test. Mixing experiments, in which the addition of normal plasma fails to correct the defect, indicate the presence of a circulating anticoagulant, rather than a factor deficiency. Because of the sensitivity of the PTT to the effects of an anticoagulant, one-stage assays for factors VIII, IX, XI, and XII may appear to show deficiency of a factor actually present in normal amounts, when measured by specific two-stage assays.

The BTI and TTI were valuable in identifying a circulating anticoagulant as a lupus-type inhibitor. The inhibitory effect of the patient’s plasma, as monitored in the BTI (Table 1), was time-dependent. This observation differed from that previously reported in the literature. Results of the TTI test (Tables 2 and 5) confirmed the observation that the lupus anticoagulant’s inhibitory effect was more apparent when a more dilute suspension of thromboplastin was used. The ratio of patient to control clotting times differentiated normals from abnormals. Patients with the lupus anticoagulant demonstrated blood and/or tissue thromboplastin inhibition. This suggested an intrinsic heterogeneity of this group of patients.

The prothrombin time in patients with the lupus anticoagulant is often normal or only slightly prolonged. As demonstrated by Yin and Gaston, this prolongation is due to the influence of the inhibitor. They showed that ad-
ditions of prothrombin activator to a mixture containing purified prothrombin, the lupus anticoagulant, and the lupus cofactor resulted in the generation of additional thrombin. True prothrombin deficiency may occur in patients with the lupus anticoagulant, but is probably exceedingly rare.

Thrombin times are usually normal in patients with the lupus anticoagulant. When abnormally prolonged, they have been explained by a decreased prothrombin content or by an antithrombin activity in the face of a normal amount of prothrombin. Evidence has been presented against the anticoagulant's role as an antithrombin. Ramot and Singer demonstrated that the thrombin time remained prolonged at a time when the anticoagulant was no longer detectable. Thrombin times were prolonged in 38% (20 of 53) of our patients with the lupus anticoagulant. Circulating fibrin split products were demonstrable in 4 of the 20, absent in 7, and not evaluated in 9. Only 1 of the remaining 33 patients with normal thrombin times had demonstrable fibrin split products. Prolonged thrombin times in the absence of elevated fibrin split products have been observed in patients with SLE without anticoagulants. Thus, the exact significance of a prolonged thrombin time in patients with the lupus anticoagulant remains to be determined.

Drugs have been implicated as an etiologic factor in cases of circulating anticoagulants to factors V, VIII, and XIII. It is of interest that 4 of 13 of the patients with the lupus anticoagulant and probable SLE (group IB) were receiving procainamide, a drug known to induce a lupus-like illness.

Bleeding is generally considered a rare manifestation of the lupus anticoagulant. When present, bleeding has been ascribed to a second hemostatic defect, e.g., thrombocytopenia. The lupus anticoagulant was discovered more frequently because of an abnormal coagulation test (Table 7) than because of overt bleeding or suspicion of a hemorrhagic disorder. A past medical history of clinically significant bleeding was noted in 31% of those patients with the lupus anticoagulant and definite SLE (group IA), but in only 18% of those patients with the lupus anticoagulant and probable SLE (group IB) or some other diagnosis (group II). Patients with the lupus anticoagulant have undergone major surgery without excessive postoperative bleeding. Paradoxically, patients with the lupus anticoagulant may manifest thrombotic clinical events. A similar situation has been observed with other inhibitors.

Our experience (Table 8) confirms the increased incidence of biologic false positive serologic tests for syphilis observed in patients with the lupus anticoagulant. Lechner noted that 47% of 64 patients with the lupus anticoagulant had a positive serology. In contrast, the incidence was only 10.9% in 520 patients with SLE but without the lupus anticoagulant.

Without therapy, the lupus anticoagulant usually persists, although spontaneous disappearance has been observed both with and without remission of the disease. Steroid administration in the treatment of the primary disease may result in the reduction or disappearance of the anticoagulant activity if the disease remits. Specific therapy is usually not indicated since bleeding is rarely a problem. Despite the fact that the lupus anticoagulant does not produce significant clinical manifestations, the exploration of its biologic
significance should be enhanced by the ability to detect it easily with the blood and tissue thromboplastin inhibition tests and by the knowledge that it occurs in a heterogeneous group of patients.

ACKNOWLEDGMENT

We wish to express our thanks to the many individuals whose efforts contributed to this work, including members of the Coagulation Laboratory staff, Dr. John Weber, Dr. Grace Hucko, Karen Fox, J. Chris Lincoln, and Vivian Weinberg.

REFERENCES

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