Fibrinopeptide A in Acute Leukemia: Relationship of Activation of Blood Coagulation to Disease Activity

By Thomas J. Myers, Frederick R. Rickles, Cheryl Barb, and Malcolm Cronlund

Plasma fibrinopeptide A (FPA) levels were determined in 20 unselected adult patients with acute nonlymphocytic and lymphocytic leukemia. The mean FPA level in patients with active disease (15.0 ng/ml) was significantly higher than during clinical remission (2.4 ng/ml, p < 0.01). Elevated FPA levels were observed in patients with all morphological forms of acute leukemia. In the group of patients in clinical remission, 20/47 FPA values remained elevated beyond the normal range, suggesting that low-grade intravascular coagulation was present even when no leukemic cells were observed. Sequential studies revealed reduction of FPA levels to the normal range in five patients who entered clinical remission after chemotherapy and rapid elevation of the levels in eight patients who entered relapse after clinical remission. FPA levels rose significantly in five patients studied during induction chemotherapy. Thus, subclinical activation of blood coagulation, as defined by elevation of plasma FPA level, may occur commonly in acute leukemia. Plasma FPA generation may relate to leukemic disease activity.

PLasma fibrinopeptide A (FPA) levels were determined in 20 unselected adult patients with acute nonlymphocytic and lymphocytic leukemia. The mean FPA level in patients with active disease (15.0 ng/ml) was significantly higher than during clinical remission (2.4 ng/ml, p < 0.01). Elevated FPA levels were observed in patients with all morphological forms of acute leukemia. In the group of patients in clinical remission, 20/47 FPA values remained elevated beyond the normal range, suggesting that low-grade intravascular coagulation was present even when no leukemic cells were observed. Sequential studies revealed reduction of FPA levels to the normal range in five patients who entered clinical remission after chemotherapy and rapid elevation of the levels in eight patients who entered relapse after clinical remission. FPA levels rose significantly in five patients studied during induction chemotherapy. Thus, subclinical activation of blood coagulation, as defined by elevation of plasma FPA level, may occur commonly in acute leukemia. Plasma FPA generation may relate to leukemic disease activity.

OVERT intravascular coagulation occurs commonly in patients with acute promyelocytic leukemia, particularly during induction chemotherapy.1–20 The hypercoagulable state in these patients has been attributed to the release of the thromboplastin material, tissue factor, from the granular fraction of leukemic promyelocytes.1,2,14–18 In contrast, intravascular clotting has been considered to occur infrequently in association with other forms of acute leukemia.4–7,21–26 While the identification of subclinical disseminated intravascular coagulation (DIC) is sometimes difficult with the use of routine tests of blood coagulation, more sensitive assays now permit the diagnosis to be made with greater certainty.

A central step in the process of blood coagulation is the enzymatic conversion of fibrinogen to fibrin by thrombin.27 Thrombin cleaves the amino termini of the A α and B β chains of fibrinogen by limited proteolysis and releases 2 moles each of fibrinopeptide A (FPA) and B (FPB) for each mole of fibrin monomer produced.27 The release of FPA is more rapid than that of FPB, and clotting occurs spontaneously when FPA is cleaved from fibrinogen.28,29 Plasma FPA is cleared rapidly with first-order kinetics and has a circulatory half-life of only 3–5 min.30 The first-order rate constant for this process varies minimally between individuals and over a wide range of plasma concentrations of FPA. Therefore, the plasma concentration of FPA reflects the rate of its production and, thus, the amount of active intravascular blood clotting.30

We have used a radioimmunoassay to measure plasma FPA31 in patients with various forms of acute leukemia. Elevated plasma FPA levels were found in patients with all morphological forms of leukemia at the time of initial diagnosis and during relapse. The FPA levels of patients in clinical remission did not differ significantly from normal control subjects. Induction chemotherapy significantly increased FPA levels. We conclude that subclinical DIC is common in patients with leukemia of various types and may be associated with tumor progression.

MATERIALS AND METHODS

Patients

Twenty unselected patients with acute leukemia who were followed at the Veterans Administration Medical Center (Newington, Conn.), the University of Connecticut Health Center (Farmington, Conn.), or St. Francis Hospital and Medical Center (Hartford, Conn.) during the 9-mo period from August 1, 1978, to May 1, 1979, were the subject of this study. The initial diagnosis of acute leukemia was determined by standard clinical, morphological, and cytochemical criteria. Relapse was diagnosed when the bone marrow sample revealed more than 10% blast forms or when there was evidence of leukemic infiltration of the nervous system.

A complete profile of the patient population is detailed in Table 1. Eleven patients were classified as having myelocytic or myelomonocytic leukemia, 1 promyelocytic, 4 lymphocytic, 3 blast crisis of chronic granulocytic leukemia, and 1 myelomonocytic leukemia superimposed on a chronic, refractory, nonsideroblastic anemia. At the time of initial patient accrual into the study, the clinical status of their disease was as follows: initial diagnosis, 10; remission, 8; and initial relapse, 2. The patients were followed for 2–9 mo. When the study was terminated, the status of the patients was as follows: 4 died during the initial diagnostic period; 6 were in remission; 7 had relapsed and died; and 3 were in relapse.

Remission induction chemotherapy for patients with acute
nonlymphocytic leukemia consisted of a five drug regimen, including daunomycin, cytosine arabinoside, 6-thioguanine, vincristine sulfate, and prednisone or a three drug regimen utilizing the first three drugs. Consolidation therapy for acute nonlymphocytic leukemia involved monthly courses of accelerating doses of cytosine arabinoside and 6-thioguanine and intrascapular, subcutaneous injections of Corynbacterium parvum (C. Parvum) for a total of 3 mo. Maintenance therapy for these patients consisted of either a combination of monthly cytosine arabinoside, 6-thioguanine, and C. parvum or monthly C. parvum only. The therapy for acute lymphocytic leukemia was the standard St. Jude's protocol. Patients with blast crisis of chronic granulocytic leukemia were given weekly courses of vincristine sulfate and prednisone for 2–3 wk, followed by the above acute nonlymphocytic leukemia protocol, since none of the patients demonstrated a response to vincristine and prednisone.

Sample Collection

Blood samples for fibrinopeptide A (FPA) analysis were collected from the patients at the time of admission to each of the three hospitals for initial diagnosis, or intercurrent illness, or at the routine monthly clinic visit. For patients in clinical remission followed as outpatients, the monthly FPA samples were obtained at least 1 wk following prior consolidation or maintenance therapy on all but three occasions. In most cases samples were drawn by a single trained phlebotomist at each of the three hospitals. Samples not obtained by a clean venipuncture were discarded, since traumatic venipuncture results in a spurious elevation of FPA levels. Whole blood (9 ml) for FPA samples was collected into a polypropylene syringe using a 19–20 gauge needle or siliconized scalp vein needle. The tourniquet was removed prior to obtaining the sample. The blood was transferred immediately into a polypropylene tube and mixed with 1.0 ml of an anticoagulant solution containing 1.0 ml trisodium citrate, 5.0 mg soybean trypsin inhibitor, 50 U heparin, 131 mg epsilon-aminocaproic acid (1 mM), and 3.72 mg disodium ethylenediamine tetraacetate (EDTA) (10 μM). The samples were centrifuged within 2 hr of venipuncture at 4°C for 15 min at 800 g. The plasma was transferred to a new polypropylene tube and extracted immediately or stored at -20°C for no longer than 1 wk prior to extraction. Previous studies in our laboratory revealed that FPA levels remain stable at -20°C if plasma samples are extracted within 1 wk. FPA determinations were performed without prior knowledge of the clinical status of the patients and the clinical records of the patients were analyzed by one of us (T.J.M.) without knowledge of the FPA values.

FPA values were discarded from final analysis if the patient had fever or evidence of an active inflammatory or infectious process on the day of venipuncture, abnormal liver function tests (since these conditions may elevate the FPA level in a nonspecific manner34), or had received induction chemotherapy within the prior 2 wk (see Results section). Although intravenous catheters were in place in several patients, great care was taken to obtain the sample for FPA analysis prior to initiation of intravenous therapy in the majority of patients.

Fibrinopeptide A Radioimmunoassay

Plasma FPA was measured by a modification of the radioimmunoassay described previously. Plasma proteins and immunologically cross-reacting substances of high molecular weight (fibrinogen and fibrinogen degradation products) were precipitated from plasma (2 ml) by addition of an equal volume of ice cold 20% trichloroacetic acid, as previously described. After centrifugation to remove all particulate material, the supernatants were extracted 3 times with 3 ml of ice-cold diethyl ether in a disposable 16 x 100 mm screw-capped culture tube. After thorough mixing of the ether-aqueous extract for 15–30 sec with a vortex mixer, the phases were separated by centrifugation. A three-phase system usually formed after the first and second extractions, and care was taken to remove only the uppermost (ether) phase, leaving the bottom and middle phases. There was virtually no middle phase following the third extraction, and what little remained was carefully removed by gentle aspiration. The ether-extracted plasma fractions were then neutralized by addition of 10 N NaOH (20–30 μl); neutrality was

### Table 1. Patient Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)/Sex</th>
<th>Diagnosis</th>
<th>Status Upon Entry</th>
<th>Time in Study (mo)</th>
<th>Status at End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/M</td>
<td>AML</td>
<td>Remission</td>
<td>8</td>
<td>Relapse*</td>
</tr>
<tr>
<td>2</td>
<td>60/M</td>
<td>AML</td>
<td>Remission</td>
<td>5</td>
<td>Relapse*</td>
</tr>
<tr>
<td>3</td>
<td>59/M</td>
<td>AML</td>
<td>Initial Dx</td>
<td>8</td>
<td>Relapse</td>
</tr>
<tr>
<td>4</td>
<td>62/F</td>
<td>AML</td>
<td>Remission</td>
<td>5</td>
<td>Relapse*</td>
</tr>
<tr>
<td>5</td>
<td>22/F</td>
<td>AML</td>
<td>Initial Dx</td>
<td>9</td>
<td>Relapse</td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>AML</td>
<td>Remission</td>
<td>9</td>
<td>Relapse</td>
</tr>
<tr>
<td>7</td>
<td>36/M</td>
<td>AML</td>
<td>Remission</td>
<td>3</td>
<td>Remission</td>
</tr>
<tr>
<td>8</td>
<td>76/F</td>
<td>AML</td>
<td>Remission</td>
<td>9</td>
<td>Remission</td>
</tr>
<tr>
<td>9</td>
<td>33/F</td>
<td>AML</td>
<td>Remission</td>
<td>8</td>
<td>Relapse*</td>
</tr>
<tr>
<td>10</td>
<td>32/M</td>
<td>AML</td>
<td>Relapse</td>
<td>2</td>
<td>Relapse*</td>
</tr>
<tr>
<td>11</td>
<td>62/F</td>
<td>AML</td>
<td>Initial Dx</td>
<td>2</td>
<td>Remission</td>
</tr>
<tr>
<td>12</td>
<td>81/M</td>
<td>AML</td>
<td>Initial Dx</td>
<td>2</td>
<td>Initial Dx*</td>
</tr>
<tr>
<td>13</td>
<td>31/M</td>
<td>APL</td>
<td>Initial Dx</td>
<td>7</td>
<td>Remission</td>
</tr>
<tr>
<td>14</td>
<td>19/F</td>
<td>ALL</td>
<td>Remission</td>
<td>8</td>
<td>Remission</td>
</tr>
<tr>
<td>15</td>
<td>17/F</td>
<td>ALL</td>
<td>Initial Dx</td>
<td>4</td>
<td>Remission</td>
</tr>
<tr>
<td>16</td>
<td>28/F</td>
<td>ALL</td>
<td>Relapse</td>
<td>5</td>
<td>Relapse*</td>
</tr>
<tr>
<td>17</td>
<td>67/M</td>
<td>BC-CGL</td>
<td>Initial Dx</td>
<td>2</td>
<td>Initial Dx</td>
</tr>
<tr>
<td>18</td>
<td>58/M</td>
<td>BC-CGL</td>
<td>Initial Dx</td>
<td>2</td>
<td>Initial Dx*</td>
</tr>
<tr>
<td>19</td>
<td>61/M</td>
<td>BC-CGL</td>
<td>Initial Dx</td>
<td>6</td>
<td>Initial Dx*</td>
</tr>
<tr>
<td>20</td>
<td>68/M</td>
<td>BC-CGL</td>
<td>Initial Dx</td>
<td>2</td>
<td>Initial Dx*</td>
</tr>
</tbody>
</table>

AML, acute myelomonocytic leukemia; APL, acute progranulocytic leukemia; ALL, acute lymphocytic leukemia; BC-CGL, blast crisis of chronic granulocytic leukemia; Dx, diagnosis.

*Patient expired during study.
determined by prior addition of a mixed methyl red indicator as previously described.11 Volatile substances in the ether-extracted plasma fractions have been found to interfere in the immunoassay; therefore, these fractions were lyophilized and subsequently reconstituted with water to their original weight. The coefficient of variation for multiple extractions of the same plasma sample is 26%–28% in the normal range and 15%–17% when the FPA level is elevated to 10–20 ng/ml. The radioimmunoassay procedure has been made more sensitive by dilution of the rabbit anti-human FPA antiserum 1:10,000 in each assay tube. Under these conditions, plasma concentrations of 0.3 ng/ml can be measured reliably. The slope of the least squares fit to the logit transformed binding data obtained from FPA standards (included with every group of samples assayed) is decreased to −0.85 ± 0.03, indicating that at this dilution a more heterogeneous but higher affinity population of antibodies in the antiserum is responsible for FPA binding.

Routine Studies

Peripheral blood and bone marrow aspirates were prepared with a Wright-Giemsa stain. Differential counts of 200 and 400 cells, respectively, were performed on these samples. Routine coagulation studies including prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen level were performed respectively, were performed on these samples. Routine coagulation studies including prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen level were performed by standard laboratory methods. Fibrin(ogen) degradation products were determined using the Thrombo-Wellcotest (Wellcome standard laboratory methods. Fibrin(ogen) degradation products were determined using the Thrombo-Wellcotest (Wellcome Research Laboratories, Beckenham, England).

Statistical Analysis

Values for the plasma FPA in the three groups were compared by chi square (χ²) analysis with Yates' correction, the Mann-Whitney rank order sum test (U test), and a two-sided Student's t test. Regression analysis was performed by the method of least squares and correlation coefficients (r) were determined. These tests were performed using prepared programs for the Olivetti P652 (Olivetti Corporation of America, New York, N.Y.)

RESULTS

Ninety-four plasma FPA levels were determined in 20 patients during the 9 mo of the study (Fig. 1). Forty-seven samples were obtained from 17 patients at the time of initial diagnosis or during relapse of acute leukemia (group I) and 47 samples were obtained from 12 patients during remission (group II). No significant difference was found between the mean FPA level from the group of patients at the time of initial diagnosis compared with the mean value obtained from patients during relapse (10.2 ± 2.4 ng/ml versus 15.6 ± 6.6 ng/ml, mean ± 1 SEM, p > 0.40). Therefore, these values were considered as one group (group I). In addition, no significant difference was present in the mean FPA levels among patients with various forms of acute leukemia in either group I or group II. Therefore, the morphological variants were grouped for analysis.

As shown in Fig. 1, the mean FPA level of patients in group I was 15.0 ± 5.3 ng/ml versus a mean FPA of 2.4 ± 0.5 ng/ml for FPA group II, p < 0.01. All FPA values in group I were elevated with the exception of three values in two patients (Fig. 1). The first patient went into a complete remission but relapsed 6 mo later in association with an elevated FPA level (7.2 ng/ml); the second of these two patients demonstrated an increased FPA level (3.3 ng/ml) in a subsequent sample drawn immediately prior to chemotherapy. Sequential FPA levels from five patients in group I who responded to induction chemotherapy and who entered a clinical remission are illustrated in Fig. 2. FPA levels decreased rapidly to the normal or near normal range in all five patients.

Although there was no difference in the mean FPA level between group II and the normal control group (p = 0.2) (Fig. 1), 20 of 47 FPA values (43%) from patients in group II were clearly above the normal range (>2 SD). While not all patients in group II had increasing FPA values prior to relapse, a trend was
observed when serial FPA determinations were obtained from 8 patients who progressed from clinical remission to leukemic relapse (Fig. 3). All 8 patients demonstrated a rapid elevation of the FPA level coincident with the time of clinical relapse. In addition, in 3 patients the rise in plasma FPA concentration preceded clinical or peripheral blood evidence of leukemic relapse by 1 mo. When these 8 patients were evaluated as a group, however, no statistically significant increase in the mean FPA level was observed prior to relapse.

Fifteen FPA samples were obtained from 5 patients during induction chemotherapy (Fig. 4). The mean FPA level rose significantly in this group of patients in temporal association with chemotherapy \( (p < 0.01) \). The effect of chemotherapy could be demonstrated more precisely when samples were obtained from these same 5 patients prior to and on day 2 of chemotherapy (for comparison of single points before and after chemotherapy in the same patients) (Fig. 5). The mean FPA levels still remained significantly different \( (p < 0.01) \). Although the duration of the FPA elevation following induction chemotherapy could not be accurately determined in this study, preliminary data from sequential studies in patients 4 and 5 suggested that FPA levels measured within 1 wk following induction chemotherapy remained elevated (Fig. 6). Because of our uncertainty as to whether these elevated FPA values were related to drug effect (either on the vasculature or the tumor itself) or disease activity, we discarded values obtained within 2 wk of chemotherapy from analysis. Although we cannot exclude the potential long-term effect of chemotherapy on the circulating FPA level, most of the samples in this study were obtained 2–4 wk following cessation of drugs when the immediate effects of drugs on the vasculature might be expected to have dissipated.

The relationship between the percentage of bone marrow blast forms and plasma FPA levels was evaluated in 18 patients. Twenty-four samples from patients in group I and 13 samples from patients in group II were included. FPA assays were performed within 24 hr of obtaining the marrow samples. Although an association between the percentage of bone marrow blast forms and the FPA level was
DISCUSSION

The present study demonstrates that fibrinopeptide A (FPA) levels are elevated in patients with all morphological forms of acute leukemia at the time of initial diagnosis and during relapse. The plasma FPA level in leukemic patients at the time of initial diagnosis or during relapse was usually elevated to at least 3.0 ng/ml (normal < 1.8 ng/ml). In addition, the FPA level decreased to the normal or near normal range when clinical remission of the leukemia was achieved with chemotherapy. Sequential sampling revealed that when patients in remission later relapsed, the plasma FPA values again rose to elevated levels. Plasma FPA levels also increased significantly during induction chemotherapy, suggesting that cell death may generate procoagulant substances or proteases capable of fibrinogen cleavage during the early treatment phase of leukemia.

Disseminated intravascular coagulation (DIC) occurs commonly in association with the lysis of tumor cells in acute promyelocytic leukemia \(^1,3,11,19,20\) and has observed for all patients \((r = 0.61)\), these results were not statistically significant \((p = 0.23)\). Similarly, the relationship between the FPA level and the number of blast cells in the peripheral blood \((r = 0.60)\) was not statistically significant \((p = 0.25)\).

The results of routine coagulation tests, performed on blood samples from 17 patients in group I, showed no correlation with plasma FPA levels (Table 2). Nine elevated FPA values were associated with normal coagulation test profiles. Abnormal coagulation studies consistent with DIC were found on only three occasions, and in each of these patients the plasma FPA level was elevated. A shortened activated partial thromboplastin time (APTT) \((<5 \text{ sec below normal})\) was observed in two patients with elevated FPA level. As previously reported, a shortened APTT is usually associated with an increased FPA level, suggesting subclinical activation of blood coagulation.
led to the prophylactic use of heparin anticoagulation prior to or in association with the initiation of chemotherapy for that disease.\textsuperscript{3,8,13,14} In contrast, DIC, defined by standard laboratory tests, rarely occurs during the treatment of acute myelomonocytic leukemia\textsuperscript{24} and acute lymphocytic leukemia.\textsuperscript{25,36}

Although we have no direct evidence in this study for activation of blood coagulation by the leukemic cells themselves, the strong association of an increased FPA level with the proliferative phase of the disease and with presumed tumor cell death during induction chemotherapy is suggestive of this possibility. It is uncertain whether the FPA in these patients is generated by activation of a conventional coagulation pathway (e.g., secondary to release of tissue factor from either leukemic cells\textsuperscript{1,2,14–18} or from sensitized mononuclear cells\textsuperscript{37}) or in response to release of a tumor-specific protease (analogous to the alternative pathway for fibrinogen cleavage described in leukocytes\textsuperscript{38,39}). Regardless of the mechanism by which subclinical or clinical intravascular blood coagulation is initiated, this study demonstrates that FPA generation, a presumed marker for subclinical activation of blood coagulation, is common in acute leukemia. Routine coagulation studies appear rather insensitive to this event in patients with acute leukemia, as has been reported previously in patients with solid tumors.\textsuperscript{40} Moreover, FPA generation is not limited to patients with the progranulocyte form of leukemia.

The mean plasma FPA level from the group of patients with leukemia in clinical remission showed no

### Table 2. Plasma Fibrinopeptide A Levels and Routine Coagulation studies in Acute Leukemia*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>FPA (ng/ml)</th>
<th>PT (sec)</th>
<th>APTT (sec)</th>
<th>Fibrinogen (mg/dl)</th>
<th>FSP (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AML</td>
<td>9.1</td>
<td>12</td>
<td>30</td>
<td>300</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2</td>
<td>AML</td>
<td>6.0</td>
<td>13</td>
<td>30</td>
<td>280</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3</td>
<td>AML</td>
<td>1.8</td>
<td>12</td>
<td>43</td>
<td>420</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>AML</td>
<td>2.8</td>
<td>12</td>
<td>40</td>
<td>400</td>
<td>10–20</td>
</tr>
<tr>
<td>5</td>
<td>AML</td>
<td>2.9</td>
<td>13</td>
<td>30</td>
<td>360</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>AML</td>
<td>3.1</td>
<td>12</td>
<td>30</td>
<td>350</td>
<td>&lt;10</td>
</tr>
<tr>
<td>13</td>
<td>APL</td>
<td>4.1</td>
<td>12</td>
<td>30</td>
<td>380</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9</td>
<td>12</td>
<td>30</td>
<td>300</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4</td>
<td>12</td>
<td>23</td>
<td>350</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7(R)</td>
<td>12</td>
<td>23</td>
<td>330</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>12</td>
<td>24</td>
<td>175</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3‡</td>
<td>13</td>
<td>40</td>
<td>110</td>
<td>20–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.6‡</td>
<td>12</td>
<td>59</td>
<td>136</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal range</td>
<td>1.8</td>
<td>11–13</td>
<td>20–37</td>
<td>170–410</td>
</tr>
</tbody>
</table>

*FPA, fibrinopeptide A; PT, prothrombin time; APTT, activated partial thromboplastin time; FSP, fibrinogen-fibrin split (degradation) products; AML, acute myeloid(myelo)cytic leukemia; APL, acute promyelocytic leukemia. All values were obtained from patients at the time of initial diagnosis or during relapse of the acute leukemia except one sample from patient 6 at the time of remission (R).

‡During infection.

‡During heparin therapy.
significant difference from the mean of the normal control group. Nevertheless, 20 of 47 FPA determinations (43%) were still elevated above the normal range. Thus, low-grade intravascular blood coagulation may be occurring even in leukemic patients in clinical remission with no apparent tumor. Since patients with leukemia in clinical remission may have a residual tumor burden of $10^5$–$10^{10}$ cells, intermittent elevations of FPA values in these patients may reflect the release of low levels of procoagulant material into the circulation. It is conceivable that as additional patients are followed for longer periods of time, a subgroup of patients may be selected out of the "remission group" for more intensive chemotherapy by virtue of persisting or recurrent elevation of the FPA level. Indeed, moderately elevated FPA levels appeared to predict a leukemic relapse in three patients who were in complete clinical remission with normal peripheral blood smears. FPA determinations in a larger number of patients will be required to determine if FPA is an early nonmorphological marker of relapse of acute leukemia.

ACKNOWLEDGMENT

The authors wish to thank Drs. Norma B. Granville, Barbara A. Wister, Gerald Roth, and Leon Hoyer for allowing us to study their patients. The secretarial assistance of Jane Pultinas is gratefully acknowledged.

REFERENCES


Fibrinopeptide A in acute leukemia: relationship of activation of blood coagulation to disease activity

TJ Myers, FR Rickles, C Barb and M Cronlund