Rearrangements of Chromosome 3 Involving Bands 3q21 and 3q26 Are Associated With Normal or Elevated Platelet Counts in Acute Nonlymphocytic Leukemia

By Mitchell A. Bitter, Mary E. Neilly, Michelle M. Le Beau, Marilyn G. Pearson, and Janet D. Rowley

Fourteen patients with acute nonlymphocytic leukemia (ANLL) or dysmyelopoietic syndromes were found to have abnormalities involving the long arm of chromosome 3. In eight patients, the structural rearrangements involved both bands 3q21 and 3q26 and included t(3;3) (four patients), inv(3) (three patients), and ins(5;31) (one patient). Before treatment, seven of these eight patients had platelet counts above 100,000 per microliter, five had normal or elevated platelet counts, and four had significantly elevated platelet counts (600,000 to 1,731,000 per microliter). In each of the eight cases, normal or elevated platelet counts were associated with marked abnormalities of megakaryocytosis, including increased numbers of megakaryocytes and numerous micromegakaryocytes. Classification within the French-American-British system (CML),\textsuperscript{8,10,12} accompanied by thrombocythemia or abnormal megakaryocyte morphology. Some investigators, however, advise caution in accepting this association.\textsuperscript{8}

The existence of other cytogenetic-clinopathologic correlations in ANLL are now well recognized. These include the t(15;17) in acute promyelocytic leukemia,\textsuperscript{13-18} t(8;21) in acute myelocytic leukemia with maturation,\textsuperscript{19-25} inv(16) in acute myelomonocytic leukemia with abnormal eosinophilia,\textsuperscript{26,27} and abnormalities of the long arm of chromosome 11 in acute monoblastic leukemia.\textsuperscript{28,29} Our purpose in this study was to define further the relationship between various abnormalities of 3q and disorders of thrombopoiesis in ANLL and DMPS. We have reviewed the karyotypes, bone marrow morphology, and initial platelet counts in patients who had ANLL or DMPS together with abnormalities involving 3q and who were studied at our institution over a 14-year period. We included the three patients referred to above. Our new data provide additional support for our original proposal that structural rearrangements of chromosome 3, involving both bands 3q21 and 3q26, are associated with much higher platelet counts than are typically seen in patients with ANLL. However, upon careful analysis of the banding pattern of cells from more recent patients with longer chromosomes that show more sharply defined bands, we have modified our interpretation of the rearrangement that affected both chromosomes 3. At present, we believe that cells from these patients have a balanced reciprocal translocation [t(3;3)(q21;q26.2)] rather than an insertion.

MATERIALS AND METHODS

Patient selection. Of 490 patients with ANLL on whom cytogenetic analyses were performed at the University of Chicago (references 3, 5, 30, and 31; J.D.R., unpublished observations, February 1970 through January 1985) (277 were treated at our institution, 213 were treated elsewhere), 21 patients (12 with ANLL de novo, nine with secondary ANLL) were found to have abnormalities involving the long arm of chromosome 3 (3q). Abnormalities of 3q were present in an additional eight patients with DMPS. Twelve of these 29 patients received their treatment at the University of Chicago. The remaining patients had specimens referred for cytogenetic studies, but they were evaluated and treated elsewhere. This study focuses on the 12 patients treated at the University of Chicago...
and two additional patients treated at other hospitals, from whom adequate material was available for morphological review.

Cytogenetic studies. Cytogenetic analysis with trypsin-Giemsa or quinacrine fluorescence banding techniques was performed on bone marrow and/or peripheral blood cells in 13 patients and on bone marrow biopsy material alone in one patient (No. 12). All patients except one were studied at the time of diagnosis; patient No. 12 had received two courses of chemotherapy without response before being referred to the University of Chicago. Metaphase cells were examined from direct preparations, from 24-hour unstimulated cultures, or from methotrexate-synchronized cells cultured for 48 hours with phytohemagglutinin-stimulated leukocyte-conditioned medium. Chromosome abnormalities were described according to the International System for Human Cytogenetic Nomenclature. The criteria proposed by Rowley and Potter, and adopted at the First International Workshop on Chromosomes in Leukemia, were used for the identification of abnormal clones, defined as two or more cells with the same structural rearrangement.

Morphological and cytochemical studies. The diagnosis and classification of leukemias and DMPS according to the criteria of the French–American–British (FAB) cooperative group were based on examination of peripheral blood films and bone marrow biopsy specimens and aspirates obtained prior to therapy. At least 400 bone marrow cells were counted in all cases in which adequate marrow aspirates were available for review. In many cases, the results of cytochemical reactions were available, including the myeloperoxidase (MPX), naphthol ASD chloroacetate esterase, acid phosphatase, periodic acid-Schiff, and nonspecific esterase reactions, the last with alpha naphthyl acetate (ANA) (with and without sodium fluoride) and alpha naphthyl butyrate (ANB) used as substrates. The platelet peroxidase reaction was performed on peripheral blood from two patients according to the method described by Breton-Gorius and associates.

RESULTS

Clinical features. Clinical features and blood counts for the 14 patients included in this report are listed in Table 1. There were seven male and seven female patients, with ages ranging from 25 to 76 years (median, 54) at the time of diagnosis of a hematologic malignancy. Platelet counts at the time of the initial diagnosis of ANLL or DMPS ranged from 20,000 to 1,731,000 per microliter (median, 104,000 per microliter). Counts were normal (150,000 to 400,000 per microliter) in two patients and elevated in three others. In an additional patient (No. 2), the platelet count was 61,000 per microliter. Counts were increased to more than 1 million per microliter over a four-month period, during which the patient was supported with red cell transfusions, but received no cytoreductive therapy.

FIVE of the patients had received chemotherapy (including at least one alkylating agent) and/or pelvic radiotherapy for previously diagnosed malignant diseases, including ovarian, lung, and cervical cancers. Hodgkin's disease, and multiple myeloma. An additional two patients (No. 5 and 6) had histories of significant occupational exposure to potentially mutagenic chemicals or pesticides.

Cytogenetic findings (Table 2). All patients included in this study had breakpoints in the long arm of chromosome 3 from bands q11 to q27 (Fig 1). Seven of the patients had relatively similar abnormalities of 3q involving either an inversion of 3q[inv(3)(q21q26.2)] (Fig 2) or a balanced reciprocal translocation involving the long arms of both chromosomes 3[t(3;3)(q11q21)] (Fig 3); three patients (No. 3, 5, and 8) had the former, and four (No. 1, 4, 7, and 12), the latter abnormality. One other patient (No. 2) had an insertion 3q21 to q26 into chromosome 5. In the inv(3), there were breaks in one chromosome 3 in bands q21 and q26, with inversion of the intervening segment. In the t(3;3), there was a break in one chromosome 3 at q26.2 and in the other at q21. The consequence of any of the three rearrangements is the abnormal juxtaposition of genes on 3q21 to those on 3q26 (Fig 4). In addition, six patients had various translocations involving 3q and other chromosomes; two of these were translocations involving chromosome 5, and the other four involved chromosomes 2, 9, 16, or 17. In patients with these translocations, the breakpoints in chromosome 3 were distributed over the long arm; only two (No. 10 and 11) of these appeared to involve the two bands (3q21 or 3q26) that were affected by either the inv(3) or the t(3;3). The breakpoints in chromosome 5 occurred at q31 or q32 in the two patients with translocations (No. 6 and 11), and at q14 in the patient (No. 2) with the 5;3 insertion.

Only two of the 14 patients (No. 4 and 6) had a rearrangement of chromosome 3 as their sole abnormality. A single additional abnormality was noted in four patients, and complex karyotypes with multiple chromosomal rearrangements were noted in the remaining eight patients. Loss of one chromosome 5 (–7) was the most frequent additional abnormality (eight patients); a –7 was noted in each of the four patients with only a single additional abnormality and in four other patients with complex karyotypes. A deletion of the long arm of chromosome 7 was seen in two other patients. Three of the 12 patients with additional rearrangements had an interstitial deletion of chromosome 5.

Morphological and cytochemical features. Granulocytic dysplasia, including hypogranular neutrophils and the pseudo–Pelger-Huet anomaly, was observed in the peripheral blood films of seven patients, including six of the 12 with ANLL. Minor red cell abnormalities in the peripheral blood films, including macrocytosis, occasional nucleated red cells, ovalocytosis, and anisopoikilocytosis, were common findings. In none of the patients were teardrop cells prominent. Platelet abnormalities, including giant platelets and hypogranular forms, were present in peripheral blood films from eight patients and were marked in three. Circulating megakaryocyte nuclei were observed in four patients. Auer rods were identified in only one case.

Upon initial evaluation, nine of the 14 patients had ANLL, and five were diagnosed as having a DMPS. Two of the five cases were classified as refractory anemia with excess blasts (RAEB); two as RAEB in transformation (RAEB-T); and a single patient (No. 2) had a prior diagnosis of idiopathic refractory sideroblastic anemia at another hospital (these slides were not available for review). In both of the patients with RAEB-T and in the patient with IRSA, the disease progressed to ANLL; this resulted in a total of 12 patients who were initially diagnosed as having ANLL, or in whom it later developed.

The classification of ANLL cases within the FAB framework was generally difficult. In most cases, there was
Table 1. Clinical and Morphologic Features of Patients With Abnormalities of Chromosome 3

<table>
<thead>
<tr>
<th>Patient *</th>
<th>3q Abnormality</th>
<th>Diagnosis</th>
<th>Age/Sex</th>
<th>Mutagen Exposure</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
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<tr>
<td></td>
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<td></td>
<td>WBCs (x 10^7/L)</td>
<td>Blasts (%)</td>
<td>Hgb (g/dL)</td>
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<tr>
<td>1 (S = 25)</td>
<td>t(3;3)†</td>
<td>ANLL</td>
<td>46/F</td>
<td>RT</td>
<td>169.0</td>
<td>85</td>
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<tr>
<td>2</td>
<td>ins(5;3)†</td>
<td>ANLL/M4</td>
<td>71/M</td>
<td>None</td>
<td>6.0</td>
<td>0</td>
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<td>3 (205)</td>
<td>inv(3)†</td>
<td>ANLL/M4</td>
<td>43/M</td>
<td>None</td>
<td>14.8</td>
<td>20</td>
</tr>
<tr>
<td>4 (32)</td>
<td>t(3;3)†</td>
<td>ANLL/M4</td>
<td>39/F</td>
<td>None</td>
<td>6.4</td>
<td>34</td>
</tr>
<tr>
<td>5 (181)</td>
<td>inv(3)†</td>
<td>RAEB-T</td>
<td>30/M</td>
<td>Chemicals</td>
<td>9.1</td>
<td>22</td>
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<tr>
<td>6 (33)</td>
<td>t(3;5)</td>
<td>ANLL/M4</td>
<td>31/M</td>
<td>Chemicals</td>
<td>23.4</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>t(3;3)†</td>
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<td>76/F</td>
<td>None</td>
<td>21.1</td>
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<td>8 (S = 65)</td>
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<td>ANLL/M1</td>
<td>25/M</td>
<td>CT</td>
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Patients with increased megakaryocytes and platelets (>100 x 10^7/L)

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<th>3q Abnormality</th>
<th>Diagnosis</th>
<th>Age/Sex</th>
<th>Mutagen Exposure</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
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<tr>
<td>9 (146)</td>
<td>t(3;16)</td>
<td>RAEB-T</td>
<td>72/M</td>
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<tr>
<td>10 (S = 23)</td>
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<td>43/F</td>
<td>CT/RT</td>
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<td>98</td>
</tr>
<tr>
<td>11 (204)</td>
<td>t(3;5)</td>
<td>ANLL/M6</td>
<td>61/F</td>
<td>None</td>
<td>1.6</td>
<td>39</td>
</tr>
<tr>
<td>12 (127)</td>
<td>t(3;3)†</td>
<td>ANLL</td>
<td>61/F</td>
<td>None</td>
<td>2.4</td>
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Patients with decreased Megakaryocytes

<table>
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<th>Patient *</th>
<th>3q Abnormality</th>
<th>Diagnosis</th>
<th>Age/Sex</th>
<th>Mutagen Exposure</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
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<tbody>
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<td>13 (S = 55)</td>
<td>t(3;17)</td>
<td>RAEB</td>
<td>76/F</td>
<td>CT</td>
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<td>0</td>
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<tr>
<td>14 (S = 26)</td>
<td>t(2;3)</td>
<td>RAEB</td>
<td>64/M</td>
<td>CT</td>
<td>5.3</td>
<td>1</td>
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Table includes pretreatment specimens from which a diagnosis of DMPS or ANLL was made. For patient No. 2, slides were not available from the time of diagnosis of idiopathic refractory sideroblastic anemia. In addition, a peripheral blood count obtained after the onset of thrombocytopenia is included. Megakaryocytes per 25 1000 x fields were measured in bone smears and micromegakaryocytes were evaluated in aspirates except where noted. Abbreviations: NA, not available or not performed; CT, chemotherapy; RT, radiation therapy.

*Numbers in parentheses are from the University of Chicago consecutive series previously reported elsewhere: patients No. 1 through 50; No. 50 through 90; No. 91 through 162; S-1 through 65; others (J.D.R., unpublished observations, February 1977 through January 1985).
†Chromosomal abnormalities that involve both 3q21 and 3q26.
‡Posttransfusion.
§Evaluated from bone core.
[Cannot be quantified.](https://www.bloodjournal.org/)
evidence of involvement of more than one cell line. Significant megakaryocyte participation was present in the bone marrow specimens of at least 12 patients (see below). Dyserythropoiesis, including megaloblastic change, premature karyorrhexis, and nuclear budding, was observed in five patients and in an additional patient who had sufficient erythroid involvement to warrant a diagnosis of acute erythroleukemia (M6). In two patients (No. 9 and 12), large collections of blasts were focally present in bone marrow specimens that otherwise showed the features of a DMPS. Marrow fibrosis was common, and thus aspirate specimens could not be obtained from four of the patients (No. 5, 7, 10, and 12) at the time of diagnosis of ANLL. Of the 12 patients with ANLL, one was classified as having acute myelogenous leukemia without maturation (M1), six as having acute myelomonocytic leukemia (M4), and one as having acute erythroleukemia (M6); four others were judged to be unclassifiable. The leukemia in five of the six patients with normal or elevated platelet counts was classified as M4; the sixth was unclassifiable. The numbers of megakaryocytes per 1,000× field in the bone core biopsies are listed in Table 1. Megakaryocytes were increased in number in 12 of the 14 patients studied, including all 12 patients with ANLL (Fig 5). Small dysplastic megakaryocytes (micromegakaryocytes) with one to
three nuclear lobes and generally well-granulated cytoplasm were identified in bone marrow specimens from each of these 12 patients. In some patients (No. 1, 3, and 5), nearly all of the identifiable megakaryocytes were micromegakaryocytes (Fig 6). Other morphological abnormalities of megakaryocytes were common including the presence of megakaryocytes with multiple separate nuclei. In two patients (No. 4 and 5), a minority of the megakaryocytes were abnormally large. In comparison with bone marrow samples of other patients studied, marrows from patients with normal or elevated platelet counts tended to show greater numbers of megakaryocytes and a higher percentage of micromegakaryocytes. The bone marrow specimen from patient No. 5,
who had a t(3;5) and a normal platelet count, contained fewer megakaryocytes, and the number of micromegakaryocytes was lower than in samples from the patients with elevated platelet counts (a bone marrow biopsy was not performed on patient No. 2 after the onset of thrombocythemia).

The platelet peroxidase reaction was carried out on peripheral blood samples from two patients. In patient No. 5, occasional circulating megakaryoblasts were identified (2% of blasts); none were observed in patient No. 7. The platelet peroxidase reaction was not performed on bone marrow samples. In patient No. 9, many of the blasts were positive for the nonspecific esterase reaction when the substrate ANA was used (partially inhibitable with NaF), but negative with ANB. This pattern may be seen in megakaryoblasts; however, the majority of blasts from this patient also showed MPX activity. Megakaryocytes were positive with ANA and negative, or only weakly staining, with ANB in those cases for which both reactions had been carried out.

**DISCUSSION**

The 14 patients studied, all of whom had abnormalities of 3q, form a heterogeneous population with regard to their clinical features, additional karyotypic abnormalities, and certain morphological characteristics. Upon review, however, significant cytogenetic-clinicoapathologic correlations are apparent. In patients with ANLL, a strong association appears to exist between abnormalities of 3q that involve bands 3q21 and 3q26 simultaneously and the presence of normal or elevated platelet counts and morphological abnormalities of thrombopoiesis.

Of the 14 patients included in this study, only the eight patients with an inv(3), t(3;3), or ins(5;3) had breakpoints in both bands 3q21 and 3q26. Seven of eight such patients had platelet counts above 100,000 per microliter; five of the eight had normal or elevated platelet counts (>150,000 per microliter); and four of the eight had significantly elevated platelet counts (>600,000 per microliter) prior to receiving chemotherapy. It is noteworthy that in one of the patients (No. 2), thrombocythemia (over 1 million per microliter) became apparent only several months after the diagnosis of ANLL, during which time he had not received chemotherapy. We can only speculate as to whether thrombocythemia would have been seen in other patients with these abnormalities of 3q if they had not been treated immediately after a diagnosis of ANLL was made.

Thrombocythemia was observed only in patients with an inv(3), t(3;3), or ins(5;3). Seven of the eight patients with platelet counts over 100,000 per microliter had one of these three cytogenetic abnormalities. Only one of our other patients had a normal platelet count, and the break in chromosome 3 in the 3;5 translocation seen in this patient was in 3q25, which is adjacent to 3q26. Because these rearrangements are sometimes difficult to define precisely, it is possible that the breakpoint in this patient was in 3q26.

The significance of normal or elevated platelet counts in these patients becomes apparent if the counts are compared to values in other patients with ANLL lacking abnormalities of 3q. Adequate clinical data are available from 50 patients with ANLL recently treated at the University of Chicago. Elevated platelet counts were only observed in patients with karyotypic abnormalities involving both 3q21 and 3q26. Excluding patients with these karyotypic abnormalities, platelet counts exceeded 100,000 per microliter in ten patients. The results of the Fourth International Workshop on Chromosomes in Leukemia provide a much larger data base of clinical, cytogenetic, and morphologic information gathered from 716 patients with ANLL who were seen at 15 institutions. The median platelet count in patients studied at the Workshop was 46,000 per microliter for patients with ANLL de novo and 40,000 per microliter for those with secondary ANLL. Platelet counts exceeded 100,000 per microliter in 22% (146 of 660) of the patients in the de novo group and in 20% (11 of 56) of those with secondary ANLL. Normal or elevated platelet counts (>150,000 per microliter) were observed in 11% and 5% of patients with ANLL de novo and secondary ANLL, respectively. Elevated platelet counts (>400,000 per microliter) were seen in only 1% (7 of 660) of patients with ANLL de novo, and in a single patient with secondary ANLL. Moreover, of the eight patients with elevated platelet counts studied at the Workshop, two had abnormalities of chromosome 3 [both inv(3)], despite the fact that abnormalities of the long arm of this chromosome were observed in only 14, or 2%, of all ANLL patients. Of the remaining six patients, two had normal karyotypes and four showed a variety of unrelated karyotypic abnormalities. The highest platelet count recorded at the Workshop was 848,000 per microliter, as compared with a count of 1,731,000 per microliter in patient No. 1 of our series.

Other investigators have reported on patients with ANLL or DMPS associated with breakpoints in both 3q21 and q26-11 (Table 3). Of the 14 patients included in Table 3, all had platelet counts greater than 100,000 per microliter, and five had counts above 600,000 per microliter. Several authors have reported on patients with CML in blast crisis with
abnormalities involving 3q21 and 3q26 accompanied by normal or elevated platelet counts.8,10,12 Moir et al40 and Gonzalez et al41 have recently reported on patients with DMPS associated with t(1;3)(p35;q21). The break in chromosome 3 in these patients is in 3q21. Three of the four patients described by these authors had normal or elevated platelet counts.

Although some circulating megakaryoblasts were identified in the peripheral blood of one patient, and increased numbers of atypical megakaryocytes were present in the bone marrow of nine others, we prefer not to use the term "acute megakaryoblastic leukemia" for these cases. We reserve that diagnosis for instances in which the platelet peroxidase reaction or another method proves that the majority of blast cells are of megakaryocytic origin. Most, if not all, of the cases in our study show megakaryocytic participation as part of a panmyelosis.

Clinically, none of the patients we report in the present study appeared to have an accelerated phase of the well-recognized myeloproliferative disorders: essential thrombocytosis, polycythemia vera, CML, or myelofibrosis with myeloid metaplasia. Some marrow specimens showed histological features similar to those in cases that have been designated "acute myelofibrosis,"42,43 "acute myelosclerosis,"44 or "acute myelodysplasia with myelofibrosis."45 These disorders are generally associated with pancytopenia; however, elevated platelet counts have been noted in some of the patients.42,46

For several reasons, most of the 12 cases of ANLL were difficult to classify within the FAB framework. At present, the FAB classification does not easily accommodate leukemias with megakaryocyte participation. Furthermore, secondary ANLL is often difficult to classify47,48; five of the 12 patients with ANLL had been treated for previously diagnosed malignant disorders or had been exposed to mutagenic chemicals. Bone marrow could not be aspirated in four patients; therefore, evaluation of the cytologic features and the cytochemical reactions of the leukemic cells in these cases was impaired.

The leukemia in five of the eight patients with 3q abnormalities that involved both 3q21 and 3q26 was classified as M4 (the remaining three were unclassifiable). Five of the six patients with normal or elevated platelet counts had M4 ANLL. Because the number of patients is small, we do not know whether the apparently high prevalence of M4 leukemia is a significant finding. Moreover, the high percentage of M4 leukemia would not explain the presence of high platelet counts in these patients. At the Fourth International Workshop on Chromosomes in Leukemia, platelet counts in patients with M4 did not differ from those in patients with other types of ANLL.39

Evaluation of the relationship between the various abnormalities of 3q and the morphologic abnormalities of thrombopoiesis is hampered by the presence, in most patients, of factors known to be associated with abnormalities of megakaryocytes, such as prior radiation and/or chemotherapy and exposure to mutagenic chemicals. In addition, ten patients had abnormalities involving chromosome 7 (loss of the chromosome in eight patients, deletion of the long arm in two others). Each of these factors has been associated with megakaryocytic dysplasia, including the presence of micromegakaryocytes, in ANLL.47,49,50 Although the morphological features observed in the bone marrows of patients with abnormalities of 3q are not specific, the extremely high numbers of micromegakaryocytes observed in several of our patients with an inv(3) or with a t(3;3) appear to exceed what we have generally observed in secondary ANLL, or in ANLL associated with abnormalities of chromosome 7. Furthermore, of the seven patients with an inv(3), t(3;3), or ins(3;3) who were reported on by Bernstein et al,7 Pinto et al,8 and Pintado et al,9 all were noted to have numerous micromegakaryocytes, whereas only one had a monosomy 7, and a second (gold miner) had a history of possible mutagen exposure. We therefore believe that the inv(3) and t(3;3), each with breakpoints in 3q21 and 3q26, are most likely to be associated with disordered megakaryocyte proliferation. The influence of other abnormalities of 3q on megakaryocytopoiesis is unclear.

Although dysmegakaryocytopoiesis is common in therapy-related ANLL and in patients with abnormalities of chromosome 7, these factors do not, by themselves, appear to have a significant impact on platelet counts. As indicated above, at the Fourth International Workshop on Chromosomes in Leukemia, the platelet counts in patients with secondary ANLL were found to be no higher than those in patients with ANLL de novo. For patients who had ANLL de novo with abnormalities involving chromosome 7, the median platelet count was 41,000 per microliter. Eighteen percent had platelet counts above 100,000 per microliter, and one of 28 patients had an elevated platelet count.39

We had previously interpreted the structural rearrangement involving both chromosomes 3 as an insertion. Based on chromosomes with improved banding, we have reinterpreted these rearrangements as reciprocal translocations; this is in

*Author’s designation.

MK = Megakaryoblastic.

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>3q Abnormality*</th>
<th>Platelet Count (x 10^3/μL)</th>
<th>Reference</th>
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<tbody>
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<td>ANLL/M1</td>
<td>inv(3q)</td>
<td>611,000</td>
<td>Bernstein et al</td>
</tr>
<tr>
<td>ANLL/M2</td>
<td>inv(3q)</td>
<td>628,000</td>
<td>Bernstein et al</td>
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<td>inv(3q)</td>
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<td>Norrby et al</td>
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*Two of the four patients of Pintado et al are included in an addendum to their report, and they are not described in detail.
agreement with the findings of others. Although the inv(3), t(3;3), and ins(5;3) all involve breaks in bands 3q21 and 3q26, the exact nature of the gene rearrangements differ. The inversion places the proximal part of band 3q21 adjacent to the proximal part of 3q26 and brings the distal segments of each band into apposition (Fig 4). In contrast, in the 3;3 translocation, the proximal part of 3q21 is adjacent to the distal part of 3q26 in the 3q– chromosome, whereas the proximal region of 3q26 is adjacent to the distal part of 3q21 in the 3q+ chromosome. In the patient with the 5;3 insertion, the 3q– chromosome was similar to the 3q– chromosome described for the t(3;3). These observations suggest that, at least for the t(3;3) and the ins(5;3) rearrangements, the juxtaposition of the proximal part of q21 and the distal segment of q26 is the consistent and therefore essential rearrangement.

As we have learned with other consistent chromosomal rearrangements, the location of the breakpoint is a critical factor in the development of the specific morphologic and clinical features of certain hematologic malignancies. Our data and the findings of others indicate that genes present on the long arm of chromosome 3 may be important in the abnormalities of thrombopoiesis that are observed in a subset of patients with ANLL. More specifically, the abnormal juxtaposition of genes on 3q21 and 3q26 appears to be the critical event. The mechanisms by which these rearrangements might ultimately result in thrombocythemia is unclear at present. A thorough understanding of the pathogenesis of the abnormal thrombopoiesis observed in association with these specific chromosomal rearrangements will require careful study of the structure and function of the genetic material on the long arm of chromosome 3.

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Rearrangements of chromosome 3 involving bands 3q21 and 3q26 are associated with normal or elevated platelet counts in acute nonlymphocytic leukemia

MA Bitter, ME Neilly, MM Le Beau, MG Pearson and JD Rowley