The pathogenesis of aplastic anemia is recognized to be heterogeneous. Although there is indirect evidence for an immunologic basis in many cases, the development of chronic marrow aplasia following chemical, toxin, or radiation exposure suggests that damage to the hematopoietic stem cells may cause the disease in some patients. In addition, a small number of patients with otherwise typical aplastic anemia eventually will develop an acute leukemia, suggesting the possibility that a clonal proliferation of malignant cells is resulting in aplasia, possibly through the suppression of normal hematopoiesis. Appelbaum et al reported a 4% incidence of clonal cytogenetic abnormalities in a large series of patients with typical aplastic anemia. Notably, the chromosomal abnormalities reported were those frequently observed in the myelodysplastic syndromes, including deletion of the long arm of chromosome 5, monosomy 7, and trisomy 8. We have recently identified three patients with bone marrow hypoplasia, morphologically most consistent with aplastic anemia or evolving aplastic anemia, in whom cytogenetic analysis of bone marrow cells has shown the presence of trisomy 6 as the sole clonal cytogenetic abnormality.

All three patients presented with hemorrhagic manifestations and severe thrombocytopenia. Mild macrocytic anemia was also a uniform finding, and granulocytopenia was present in two of the three patients (Table 1). The bone marrow was variably hypocellular with a reversed myeloid to erythroid ratio in each case. A lymphoplasmacytic infiltrate was observed in all patients. Although mild dysplastic features were noted in two of the cases, no patient met the standard French-American-British criteria for the diagnosis of a myelodysplastic syndrome. Cytogenetic analysis of bone marrow samples from each of the patients showed a single clonal chromosomal abnormality, trisomy 6, in 9% to 14% of the metaphase cells studied. Therapy with corticosteroids was uniformly ineffective. Anti-thymocyte globulin was prescribed without benefit in two of the patients. These two patients were subsequently treated with cyclosporine A and both responded, one with an increase in his platelet count and the other with complete recovery of his peripheral blood counts, an increase in his bone marrow cellularity to 50%, and the disappearance of the clone with the additional chromosome 6 on repeat cytogenetic analysis. The third patient has not been treated and has remained clinically stable for 2 years. A repeat cytogenetic analysis was performed in this patient and the abnormal clone was detected in 14% of the metaphase cells analyzed.

Trisomy 6 is only rarely observed as the sole cytogenetic abnormality in hematologic malignancies; this abnormality has been previously reported in only three patients with acute myeloid leukemia and two patients with myelodysplasia. Our identification of three patients with this clonal cytogenetic abnormality with similar clinical and laboratory characteristics raises the possibility that a gain of chromosome 6 may be involved in the pathogenesis of the marrow hypoplasia observed in these patients. A review of the literature discloses three additional patients with trisomy 6 who were felt to have aplastic anemia. As with our cases, all presented with severe cytopenias and none had significant hematopoietic dysplasia. This association appears to be more than coincident, although a pathophysiologic explanation is lacking at this time.

It is not clear where this entity will fit into the present classification of hematologic disorders. The rare cases of aplastic anemia with documented karyotypic abnormalities have most often had chromosomal abnormalities that are frequently observed in the myelodysplastic syndromes, suggesting they may be better defined as "hypoplastic myelodysplasia." However, patients with this presentation typically have clearly evident dysplasia of the erythroid, myeloid, and megakaryocytic precursors. In contrast, trisomy 6 is not frequently observed in myelodysplasia, and our patients displayed only minimal dysplasia, making the diagnosis of a myelodysplastic syndrome difficult. In addition, the response of two of our

### Table 1. Clinical Features of Patients With Trisomy 6 and Marrow Hypoplasia

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Hemoglobin (g/dL)</th>
<th>WBC (per L)</th>
<th>Neutrophils (per L)</th>
<th>Platelets (per L)</th>
<th>Bone marrow pathology</th>
<th>Cytogenetics</th>
<th>Therapy/Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/M</td>
<td>7.5</td>
<td>1,800</td>
<td>828</td>
<td>11,000</td>
<td>Markedly hypocellular</td>
<td>46,XY (91%)/47,XY,+6 (9%) (23 cells analyzed)</td>
<td>Prednisone—NR. ATG—NR.</td>
<td>Stable without therapy.</td>
</tr>
<tr>
<td>2</td>
<td>31/F</td>
<td>10.1</td>
<td>2,900</td>
<td>667</td>
<td>13,000</td>
<td>Markedly hypocellular (5%)</td>
<td>46,XX (87%)/47,XX,+6 (9%)/46,XX,del(11)</td>
<td>Prednisone—NR.</td>
<td>Stable without therapy.</td>
</tr>
<tr>
<td>3</td>
<td>33/M</td>
<td>12.1</td>
<td>6,600</td>
<td>3,366</td>
<td>25,000</td>
<td>Markedly hypocellular</td>
<td>46,XY (86%)/47,XY,+6 (14%) (21 cells analyzed)</td>
<td>Prednisone—NR. ATG—NR.</td>
<td>Stable without therapy.</td>
</tr>
</tbody>
</table>

Abbreviation: NR, no response.
patients to treatment directed specifically at autoimmune-mediated aplastic anemia is further evidence that this entity is distinct from the commonly defined myelodysplastic syndromes, where immunosuppressive therapy has not been shown to be beneficial. These cases demonstrate that the presence of a chromosomal abnormality does not necessarily preclude a response to immunosuppressive therapy and suggest that other patients with this clinical picture and cytogenetic abnormality should be given a trial of anti-thymocyte globulin or cyclosporine A. Our three patients with trisomy 6 have not had evolution of their disease to leukemia. Further follow-up of these three patients with serial cytogenetic studies may help determine the malignant potential of the clone bearing the additional chromosome 6.

ACKNOWLEDGMENT

We thank E. Asner, E. Davis, A. Fernald, N. Hu, and L. Synder for their technical assistance.

JILL A. MOORMEIER
CHARLES M. RUBIN
MICHELLE M. LE BEAU
JAMES W. VARDIMAN
RICHARD A. LARSON
Departments of Medicine, Pediatrics, and Pathology
The University of Chicago
JANE N. WINTER
Department of Medicine
Northwestern University
Chicago, IL

REFERENCES

Trisomy 6: a recurring cytogenetic abnormality associated with marrow hypoplasia [letter]

JA Moormeier, CM Rubin, MM Le Beau, JW Vardiman, RA Larson and JN Winter