PART OR ALL OF chromosome 7 is deleted during the development of a number of malignant myeloid disorders. In all age groups, monosomy 7 or del(7q) occurs in both preleukemic myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) and is particularly common in cases of MDS and AML that evolve after antineoplastic therapy with alkylating agents or occupational exposure to chemical mutagens. These abnormalities also occur in a subset of patients with severe aplastic anemia. The clinical manifestations are similar in adults and children; the response to conventional chemotherapy is relatively poor, and the outcome is frequently fatal.

An altogether different group of myeloid disorders with chromosome 7 deletions predominately occurs in children. A well-defined myeloproliferative disorder with prominent bone marrow dysplasia and hepatosplenomegaly exists in young children and has been termed monosomy 7 syndrome. This condition shares many clinical and epidemiologic features with juvenile chronic myelogenous leukemia (JCML) and acute myelogenous leukemia (AML). Monosomy 7 is also associated with an array of genetic disorders of myelopoiesis that carry a high risk of myeloid leukemia, including Fanconi anemia, severe congenital neutropenia, and Shwachman-Diamond syndrome, as well as certain multisystem constitutional conditions such as neurofibromatosis, type 1 (NF-1) and, possibly, Down syndrome. Familial bone marrow monosomy 7 has been observed in at least 10 kindreds and is associated with cerebellar ataxia in some families. Finally, a self-limited form of monosomy 7 syndrome has been reported in two children with Epstein-Barr virus infections.

The nonrandom association of monosomy 7 with myeloid leukemia is consistent with loss of function of a gene (or genes) located on chromosome 7 that regulates myeloid growth and differentiation. It is not known if inactivation of both alleles of this gene is necessary to alter the phenotype of immature myeloid cells or if deletion of a single allele might contribute to abnormal growth by reducing the concentration of a critical protein (ie, by haploinsufficiency). Although monosomy 7 or del(7q) occurs during the development of many cases of MDS and AML, the existing evidence strongly suggests that chromosome 7 loss is not sufficient for full leukemic transformation. Genetic alterations that affect signaling through the Ras proteins frequently coexist with monosomy 7 in the bone marrow of children with MDS and AML. In addition, the high incidence of monosomy 7 and del(7q) in children who are predisposed to myeloid leukemia clearly implicates chromosome 7 loss as a secondary genetic event in leukemogenesis.

We review here the epidemiology of monosomy 7 and del(7q), examine the existing biologic data in light of current ideas about leukemogenesis, and propose a model for the pathogenesis of this group of diseases. We will pay special attention to the constitutional disorders that are associated with monosomy 7 because these conditions provide an opportunity to identify and characterize genes that influence myelopoiesis. For the purpose of this review, monosomy 7 and del(7q) will be discussed as a single entity.

**EPIDEMIOLOGY**

The myeloid disorders associated with monosomy 7 develop in three contexts: (1) de novo, (2) secondary, and (3) constitutional. De novo cases arise without apparent predisposing factors. Secondary cases appear after cytotoxic chemotherapy for cancer, after occupational exposure to mutagens, and probably after immunosuppressive therapy for severe aplastic anemia (SAA). Constitutional cases arise in individuals with a genetic predisposition to leukemia. Most patients in the third group are children and adolescents.
Table 1. Demographic Features of Myeloid Disorders Associated with Monosomy 7

<table>
<thead>
<tr>
<th>De novo disorders</th>
<th>Patients With Mo7 (n)</th>
<th>Median Age at Diagnosis (range)</th>
<th>Sex Ratio (M:F)</th>
<th>No. of Patients With Mo7 at Diagnosis/Total (%)</th>
<th>Mo7 as the Only Cytogenetic Abnormality (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 yr</td>
<td>13</td>
<td>5.5</td>
<td>1.5:1</td>
<td>13/31</td>
<td>11/13</td>
<td>1-4</td>
</tr>
<tr>
<td>(0-18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;21 yr</td>
<td>88</td>
<td>54</td>
<td>2.2:1</td>
<td>88/644</td>
<td>43/88</td>
<td>6-10</td>
</tr>
<tr>
<td>(21-91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AML</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 yr</td>
<td>31</td>
<td>10.5</td>
<td>2.2:1</td>
<td>31/458</td>
<td>14/31</td>
<td>11-18</td>
</tr>
<tr>
<td>(0-20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;21 yr</td>
<td>114</td>
<td>60</td>
<td>1.4:1</td>
<td>114/1,104</td>
<td>59/114</td>
<td>10-12, 19-21</td>
</tr>
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<td>(22-80)</td>
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</tr>
<tr>
<td>Monosomy 7 syndrome</td>
<td>34</td>
<td>1.7</td>
<td>4.7:1</td>
<td>34/34</td>
<td>26/34</td>
<td>11, 17, 18, 22-26</td>
</tr>
<tr>
<td>(0.1-17)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>JCML</td>
<td>8</td>
<td>2.3</td>
<td>2.5:1</td>
<td>8/138</td>
<td>7/8</td>
<td>2, 27, 40, 41, 67-70</td>
</tr>
<tr>
<td>(0-6.8)</td>
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<tr>
<td>Secondary disorders</td>
<td>93</td>
<td>54</td>
<td>1.4:1</td>
<td>93/232</td>
<td>17/93</td>
<td>29-33</td>
</tr>
<tr>
<td>(6-86)</td>
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<td>Occupational exposure</td>
<td>23</td>
<td>54</td>
<td>3.6:1</td>
<td>23/117</td>
<td>4/23</td>
<td>34-36</td>
</tr>
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<td>(17-81)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>SAA</td>
<td>7</td>
<td>21</td>
<td>1.6:1</td>
<td>7/9</td>
<td>5/7</td>
<td>37-39, 72</td>
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<td>(3-56)</td>
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<tr>
<td>Constitutional disorders</td>
<td>16</td>
<td>21</td>
<td>1.6:1</td>
<td>16/38</td>
<td>4/16</td>
<td>42-45</td>
</tr>
<tr>
<td>(3-56)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Fanconi anemia</td>
<td>8</td>
<td>NA</td>
<td>~1:1</td>
<td>8/10</td>
<td>NA</td>
<td>45-47, 93, 97-99</td>
</tr>
<tr>
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<td></td>
<td></td>
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<tr>
<td>Kostmann’s syndrome</td>
<td>2</td>
<td>NA</td>
<td>2:0</td>
<td>2/5</td>
<td>NA</td>
<td>48</td>
</tr>
<tr>
<td>(40)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Schwachman-Diamond syndrome</td>
<td>2</td>
<td>NA</td>
<td>1:1</td>
<td>22/29</td>
<td>21/22</td>
<td>58-60, 62</td>
</tr>
<tr>
<td>(1.5-27)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Familial monosomy 7</td>
<td>22</td>
<td>10</td>
<td>1:1</td>
<td>22/29</td>
<td>21/22</td>
<td>58-60, 62</td>
</tr>
<tr>
<td>(1.5-27)</td>
<td></td>
<td></td>
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<tr>
<td>Down syndrome</td>
<td>9</td>
<td>2</td>
<td>1.2:1</td>
<td>9/103</td>
<td>0/9</td>
<td>53-57</td>
</tr>
<tr>
<td>(0-10)</td>
<td></td>
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</table>

Abbreviation: NA, not available.

I summarizes the demographic features of the myeloid disorders that are associated with monosomy 7 in adults and children as reported in the literature. De novo disorders include AML, MDS, JCML, and SAA. Monosomy 7 occurs in 10% of adult AML and about 5% to 7% of childhood AML. Monosomy 7 is less common in patients with a morphologic diagnosis of aplastic anemia. Appelbaum et al. found clonal cytogenetic abnormalities in 7 of 176 consecutive cases of aplastic anemia, 3 of whom had monosomy 7. The incidence of AML, MDS, and SAA with monosomy 7 increases with age, whereas the myeloproliferative disorders JCML and monosomy 7 syndrome are almost exclusively diseases of young children. Of the latter, cases have been described before 6 months of age and 90% of patients are diagnosed before 5 years of age. When pediatric and adult cases of myeloid disorders associated with monosomy 7 are combined, a biphasic age distribution is apparent, with peaks during the first few years of life and after 60 years of age (Fig 1). In adults with monosomy 7, the male to female ratio is approximately 1.5:1, whereas 70% of affected children are boys (Table 1).

Although monosomy 5 and del(5q) are common in adults with MDS and AML, deletions of chromosome 5 are conspicuously absent in pediatric cases. Monosomy 7 is the most common cytogenetic abnormality detected in the bone marrow of children with preleukemia and it usually occurs as an isolated structural abnormality. In children and adults with AML, monosomy 7 has been associated with the French-American-British (FAB) myelomonocytic (M4) and erythroleukemia (M6) subtypes in some studies, but not in others. In older patients, MDS with monosomy 7 is usually classified as refractory anemia with excess blasts (RAEB) or refractory anemia with excess blasts in transition (RAEB-t). In the childhood syndromes, especially those of young children, myeloprolif-
The population-based incidence of de novo AML by age is from the NCI Cancer Statistics Report, 1973-1989, and the proportion of cases of AML with monosomy 7 is calculated from a number of sources. Population-based incidence of MDS in children is based on the data of Hasle et al and from Children’s Cancer Group Study 286. The proportion of children with monosomy 7 is based on published data. There are no population-based incidences of MDS in adults. Estimates of the incidence of MDS among adults are from one large series in France and from two other studies. The proportion of adults with MDS who have monosomy 7 is estimated from a number of sources. Because there are no population-based data describing the incidence of JCML and monosomy 7 syndrome (Mo 7), incidences are estimated from large institutional series.

There is also controversy about whether the monosomy 7 syndrome and JCML are distinct entities (Fig 2). JCML is diagnosed in patients who show a pattern of clinical and laboratory findings, whereas monosomy 7 is a cytogenetic abnormality that occurs in a variety of myeloid disorders, including JCML. A recent review at seven pediatric referral centers showed monosomy 7 in the bone marrow of 11 of 46 (24%) children with a clinical diagnosis of JCML (S.L.F., unpublished data), although this incidence is only 6% among cases reported in the literature (Table 1). Distinguishing monosomy 7 syndrome from JCML is problematic, because both disorders predominantly affect young male patients and are characterized by thrombocytopenia, anemia, splenomegaly, and a poor prognosis (Table 2). Children with NF-1 are predisposed to both disorders. Many children with monosomy 7 do not show the typical skin rash or increased fetal hemoglobin level that characterize JCML, and 75% to 90% of patients with JCML do not have chromosome 7 deletions in their marrows at diagnosis. However, patients with JCML may acquire monosomy 7 with disease acceleration. As shown in Fig 2, the relationship between monosomy 7 syndrome and JCML is perhaps as follows: the monosomy 7 syndrome is one of a number of distinct entities that are associated with chromosome 7 deletions, whereas JCML is a myeloproliferative disorder of infants and young children, 6% to 24% of whom show bone marrow monosomy 7 at diagnosis. The epidemiologic and clinical similarities between monosomy 7 syndrome and JCML strongly suggest that these disorders share one or more pathogenic alterations in common. Laboratory data summarized below are generally consistent with this hypothesis.

The distinct gender preference and atypical spectrum of FAB subtypes suggests that most of the sporadic childhood preleukemic syndromes have a different etiology and pathogenesis than adult MDS. The prevalence of cases in infant males implies the existence of unidentified constitutional predispositions in many patients. Although these observations suggest that the inciting genetic events that underlie the myeloid disorders associated with monosomy 7 are different in adults and young children, loss of chromosome 7 may have similar consequences for myeloid growth and differentiation in both age groups.

**Monosomy 7 in Secondary Myeloid Disorders**

**Environmental exposures to mutagens.** Many adults with monosomy 7 have a history of occupational exposure to organic solvents, pesticides, petroleum derivatives, and/or other chemical toxins. Detailed epidemiologic data regarding environmental exposures in children with monosomy 7 are lacking, but Baranger et al cite a patient with repeated exposure to kerosene. Epidemiologic studies performed by the Children’s Cancer Group showed a history of perinatal or perinatal exposure to marijuana, pesticides, recreational drugs (alcohol and/or marijuana), or other toxins in young children with monoblastic variants of AML. This group includes many patients with monosomy 7; however, no epidemiologic studies with cytogenetic correlations have been performed in children with MDS, JCML, or AML.

**Therapy-related AML and MDS.** Monosomy 7 is the most common cytogenetic abnormality in the leukemic cells of adults and children with therapy-related MDS and AML, but rarely occurs as an isolated finding. Monosomy 7 is strongly associated with previous exposure to alkylating agents with or without radiation therapy. The risk of secondary MDS and AML increases with age and with dose of alkylating agent, peaks 3 to 7 years after treatment, and declines thereafter. The clinical features of therapy-related MDS and AML are similar in adults and children who have monosomy 7.

**Idiopathic severe aplastic anemia (SAA).** The observation that SAA may evolve into AML was reported as early
as 1951. Monosomy 7 appears to be the most common cytogenetic abnormality in cases of MDS and AML that follow SAA. In a group of 38 patients who survived more than 2 years, 5 developed AML or MDS, 3 of whom had clonal abnormalities of chromosome 7. All 3 had normal karyotypes at the time they presented with aplastic anemia. In 1 patient, a 46,XY,inv(10) clonal abnormality appeared at 5 months; at 27 months, there were 3 abnormal clones: 46,XY,inv(10); 45,XY,-7; and 45,XY,inv(10),-7. MDS was diagnosed 3 months later. The investigators speculate that monosomy 7 may have arisen as two independent events [in both the clone with inv(10) and in a second myeloid progenitor]. Alternatively, the different karyotypes may reflect the numerical losses and gains that may occur during clonal evolution.

The European Bone Marrow Transplantation-Severe Aplastic Anemia Working Party described 15 cases of acute leukemia and 28 cases of MDS among 860 patients treated with immunosuppressive therapy for aplastic anemia and only 2 cases of leukemia among 748 patients treated by marrow transplantation. The cumulative incidence at 10 years was 9.6% for MDS and 6.6% for AML. In multivariate analysis, MDS or AML was significantly associated with androgen use, two or more courses of immunosuppressive therapy, splenectomy, and increasing age. The simplest explanation for these findings is that transplant effectively eliminates an occult clone with malignant potential that existed in a subset of patients with SAA, whereas immunosuppression has no effect. However, among the SAA patients who were transplanted, the incidence of MDS/AML is considerably less than the leukemic relapse rate of patients with de novo MDS or AML transplanted at the time of minimal residual disease. This finding provides indirect evidence that a malignant clone is not present in most patients with SAA at the time of transplantation.

An additional case report suggests a direct link between immunosuppression and the development of MDS in some patients. A young man with aplastic anemia who showed a stable 46,XY karyotype in his bone marrow for many years; at 27 months after diagnosis of SAA. All 3 initially received immunosuppressive therapy. Recombinant human granulocyte colony-stimulating factor (r-G-CSF) had been introduced to 15 months before the development of MDS and the investigators speculated that r-G-CSF may have provoked the evolution to MDS and/or AML.

Kojima et al described 3 young boys who developed a stable 46,XY karyotype in his bone marrow for 6 years developed a 46,XY,-7,+21 clonal abnormality and 5% monoblasts after initiation of intravenous cyclosporin. When oral cyclosporin replaced the intravenous drug, the blasts disappeared and the clonal abnormalities were no longer detected. Trisomy 21 and monosomy 7 recurred with resumption of intravenous cyclosporin and again resolved with discontinuation of the drug.

Kojima et al described 3 young boys who developed MDS and/or AML, with monosomy 7 between 17 and 61 months after diagnosis of SAA. All 3 initially received immunosuppressive therapy. Recombinant human granulocyte colony-stimulating factor (r-G-CSF) had been introduced 6 to 15 months before the development of MDS and the investigators speculated that r-G-CSF may have provoked the evolution to MDS and AML. Imashuku et al recently surveyed 125 pediatric patients who received r-G-CSF for chronic severe neutropenia. Of 67 children with SAA, 3 patients developed MDS or AML with bone marrow monosomy 7 between 23 and 28 months after starting on r-G-CSF. A Kaplan-Meier analysis suggested that the risk of AML or MDS was approximately 10% in children with SAA.

### Table 2. Clinical Syndromes Associated With Monosomy 7

<table>
<thead>
<tr>
<th>MDS</th>
<th>JCML</th>
<th>Monosomy 7 Syndrome</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;5 yr</td>
<td>&lt;5 yr</td>
<td>&lt;5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M &gt; F</td>
<td>M &gt; F</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>If &lt;21 yr age: M &gt; F</td>
<td>If &lt;21 yr age: M = F</td>
<td>If &lt;1 yr old, several years; if &gt;1 yr old, &lt;2 yr</td>
</tr>
<tr>
<td></td>
<td>Increase bacterial infection, no hepatosplenomegaly</td>
<td>Hepatosplenomegaly, failure to thrive, skin rash, lung infiltrates</td>
<td>Hypercellular, dyserythropoiesis, decreased megakaryocytes, dysplastic features less frequent, increased blasts but usually &lt;30%</td>
</tr>
<tr>
<td></td>
<td>Laboratory findings</td>
<td>Hepatosplenomegaly bacterial infections, skin rash</td>
<td>Hypercellular, dyserythropoiesis, mononcytosis (vacuolated), increased blasts, Pelger-Huet</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Normo or hypocellular, mostly dyserythropoiesis, dysgranulopoiesis, micromegakaryocyte, fibrosis in the adults</td>
<td>Normo or hypocellular, mostly dyserythropoiesis, dysgranulopoiesis, micromegakaryocyte, fibrosis in the adults</td>
<td>Normo or hypocellular, mostly dyserythropoiesis, dysgranulopoiesis, micromegakaryocyte, fibrosis in the adults</td>
</tr>
<tr>
<td>Progression to AML</td>
<td>&lt;1 yr</td>
<td>If &lt;6 mo old, several years; if &gt;6 mo old, several years</td>
<td>If &lt;1 yr old, may smolder several years; if &gt;1 yr old, in 1-2 yr transform into M2, M4 or M6 FAB AML</td>
</tr>
<tr>
<td>Prognosis and survival</td>
<td>&lt;2 yr, except in children &lt;6 mo at diagnosis</td>
<td>&lt;2 yr</td>
<td>&lt;1 yr</td>
</tr>
</tbody>
</table>

Abbreviations: Hgb F, hemoglobin F; LAP, leukocyte alkaline phosphatase.
who were 48 months from diagnosis and had received r-G-CSF for 24 months.39

This association between SAA and MDS/AML has suggested two hypotheses: (1) aplastic anemia and MDS/AML are two manifestations of the same fundamental injury to the stem cells; or (2) MDS/AML develops in patients with aplastic anemia either as a secondary effect of treatment or results from continued exposure to the same agent that induced the marrow failure. As noted above, clonal abnormalities of chromosome 7 occur rarely at diagnosis in SAA. Furthermore, some patients with SAA were exposed to toxins that are associated with the development of AML and MDS. Although it is often difficult to obtain a sufficient number of proliferating marrow cells for adequate cytogenetic analysis in patients with SAA, development of molecular probes that do not require many cells or mitotic cells may make it possible to determine if monosomy 7 and other nonrandom chromosomal abnormalities are present at the time of diagnosis. This information is especially important in children because a number of constitutional bone marrow failure syndromes are associated with a high risk of MDS and AML (see below).

**Monosomy 7 in Patients With Constitutional Disorders**

*Fanconi anemia.* Fanconi anemia is an autosomal recessive disorder characterized by spontaneous chromosome breakage and hypersensitivity to DNA cross-linking agents.42,45 Most patients are identified because of multiple physical anomalies and progressive pancytopenia developing during childhood.45 Diagnosis is confirmed by chromosomal fragility testing with diepoxybutane. Nineteen patients have been diagnosed with Fanconi anemia ex post facto after they have been treated for leukemia. In these cases, the results of marrow cytogenetic studies or extraordinarily poor tolerance of cytoreductive therapy prompted testing for Fanconi anemia.45

Leukemia arises in about 10% of Fanconi patients, usually during adolescence. Young and Alter45 cite 68 documented cases of leukemia and 27 of preleukemia or clonal hematopoiesis. Of 37 patients who had cytogenetic studies performed, 9 had abnormalities of chromosome 7 and 1 had a missing group C.45 The specific abnormalities included complete monosomy 7 in 3 cases; del(7q) in 2 cases; isochromosome 7q in 1 case; t(5;7)(p15;q22) in 1 case; and abnormalities of 7p in 3 cases. In 6 of 9 patients, the cytogenetic abnormalities were limited to chromosome 7. It has been estimated that the relative risk for development of a malignant or premalignant clonal disorder in Fanconi's patients is increased 6,500- to 15,000-fold above the general population and that the risk of clonal disorders of chromosome 7 is increased approximately 50,000- to 100,000-fold.92

*Congenital neutropenia.* The severe congenital neutropenias are a heterogeneous group of disorders of myelopoiesis that are characterized by defective neutrophil production and recurrent infections. Congenital agranulocytosis (Kostmann's syndrome) is a severe form of congenital neutropenia with onset during the first few months of life, an absolute neutrophil count less than 200/μL, and a maturation arrest at the myelocyte-promyelocyte stage of differentiation.93-95 Until r-G-CSF became available, most children with severe congenital neutropenia died from infections during the first few years of life. Treatment with pharmacologic doses of r-G-CSF is associated with an increase in neutrophil counts and a reduction in infectious complications in these children.96-98 A few cases of MDS or AML were reported in children with Kostmann's syndrome before the r-G-CSF era.95,97-99 We are aware of at least 8 additional cases of MDS or AML in patients with severe congenital neutropenia who received r-G-CSF, including 6 with Kostmann's syndrome.46,47 The marrows of 7 patients showed monosomy 7. Population-based data suggest a risk of MDS and AML of at least 5% in this group of patients, with equal numbers of affected males and females.97 These data are consistent with the experience of Imashuku et al,99 who found 1 case of MDS among 20 children with chronic neutropenia. MDS and AML have not been observed in patients with cyclic or idiopathic neutropenia who received r-G-CSF47; this finding suggests that it is the underlying hematopoietic defect rather than growth factor therapy per se that predisposes to malignant transformation.

**Shwachman-Diamond syndrome.** Monosomy 7 has been described in Shwachman-Diamond syndrome, a disorder characterized by small stature, skeletal abnormalities; deficiency of the exocrine pancreas; and neutropenia. The observed to expected risk of leukemia is estimated to be 27 times that of the general population.46 Three cases of ALL and 6 of AML have been reported in 8 boys and 1 girl at a mean age of 10 years.45 Not all had cytogenetic studies; in 1 boy, the AML was characterized by monosomy 7 plus marker 18.48 We recently learned of another boy who developed bone marrow monosomy 7 while receiving r-G-CSF (J. Priest, personal communication, 1994).

**Familial monosomy 7.** Monosomy 7 has been reported in at least 10 families in whom myeloid leukemia is the only apparent abnormality.25,58,62100 Although there have been no documented multigenerational families with this type of monosomy 7, a few kindreds with one affected child have been reported in which MDS or AML developed in one or more adults. In two other families, the tendency to develop monosomy 7 appears to coincide with cerebellar ataxia.99,100 A third similar family has been followed at the Children's Hospital of Philadelphia (B.J.L., unpublished data). The disease is apparently an autosomal dominant with variable expression such that some members may manifest the neurologic disorder with normal hematopoiesis, others the hematologic disorder, and some both. In the first family described, the father and all five children had cerebellar ataxia or atrophy.100

Familial childhood monosomy 7 differs from monosomy 7 syndrome in that females are affected as often as males and the mean age at diagnosis is higher than in de novo cases. The familial cases of monosomy 7 are distinguished from Fanconi anemia by the inheritance pattern, absence of physical anomalies associated with Fanconi anemia, and the absence of chromosomal fragility on testing. Clinicians should always consider the possibility that a child who presents with MDS or AML and monosomy 7 may be the first affected individual in a family. We are aware of one instance

...
in which monosomy 7 was detected in the bone marrow of a child who had a normal physical examination and peripheral blood counts when she was being evaluated as a transplant donor for her sibling (J. Davis and K.M.S., unpublished observation). Other children were only identified when their siblings were diagnosed with MDS or AML.92,109 As a result, we suggest that the siblings of children with de novo monosomy 7 undergo a physical examination and have a complete blood count taken. Bone marrow examination with cytogenetic studies are indicated if abnormalities are detected on the screening tests or if the sibling is being considered as a donor for bone marrow transplantation.

NF-1. Children with NF-1 are at increased risk of developing malignant myeloid disorders, including AML with monosomy 7, monosomy 7 syndrome, and JCML.43,49,51,83 Children who present with JCML and normal bone marrow cytogenetic findings may acquire monosomy 7 during the course of their disease.72 There is a preponderance of affected males among children with NF-1 who develop monosomy 7 or JCML.52,101 In addition, there appears to be a higher risk of leukemia among children who inherited NF-1 from their mothers as opposed to their fathers.49 Of 11 consecutive cases of malignant myeloid disorders in children with NF-1 included in a recent series, 10 were diagnosed before 5 years of age.103 A striking and peculiar feature of the association between NF-1 and leukemia is that it is restricted to the first few years of life and there is no evidence that adults with NF-1 are predisposed to MDS or AML.102 Three of 37 patients with JCML had NF-1 in the series of Castro-Malaspina et al,41 and their experience is consistent with our own (K.M.S., unpublished data), suggesting that the risk of malignant myeloid disorders is increased 200- to 500-fold in children with NF-1.

Down syndrome. The risk of leukemia in Down syndrome is 10 to 20 times that of the general age-matched population.103 Kaneko et al37 reported no abnormalities of chromosome 7 in 46 cases of leukemia arising in patients with Down syndrome; Alimena et al37 did not detect monosomy 7 in 3 more cases. Hecht et al26 cite 1 case with a rearrangement of chromosome 7 among 23 cases of AML in patients with Down syndrome, whereas the Groupe Francais de Cytenogenique Hematologique reported 3 patients with monosomy 7 among 25 patients with either acute leukemia or transient myeloproliferative syndrome.55,56 Four other cases of MDS with monosomy 7 preceding acute megakaryoblastic leukemia have been reported55,56 and one more has been treated at the Children's Hospital of Philadelphia (B.J.L., unpublished data). In one case of leukemia in a child with Down syndrome, interphase cytogenetic analysis of cells stimulated to stimulate in vitro showed that monosomy 7 was restricted to the megakaryocytic lineage.104 It is not clear that the incidence of monosomy 7 among Down syndrome patients with AML is higher than that in the general pediatric population with AML. Interestingly, of 3 patients treated with modern AML therapy, all achieved remission and none has had a recurrence (B.J.L., unpublished data). These limited data suggest that generally good prognosis of patients with Down syndrome who develop AML apparently includes those with monosomy 7.

Monosomy 7: An “Opportunistic” Cytogenetic Abnormality?

Although monosomy 7 is only one of many nonrandom cytogenetic alterations seen in human cancer cells, its strong association with a variety of inherited and acquired predispositions to MDS and AML (summarized in Table 1) is remarkable. Taken together, these findings implicate monosomy 7 as the cytogenetic equivalent of the opportunistic infections that occur in immunodeficient patients. As such, monosomy 7 may be a cytogenetic marker for myeloid leukemias that develop in the context of constitutional genetic instability or acquired genotoxic damage. The presence of monosomy 7 should thus provoke a careful inquiry to ascertain the existence of a predisposing condition.

The broad spectrum of underlying predispositions that are associated with monosomy 7 suggests that these deletions are secondary events that contribute to leukemogenesis. The high incidence of monosomy 7 during the first 2 years of life implicate constitutional factors in the pathogenesis of many of the de novo cases, whereas the epidemiologic data in adults and in secondary monosomy 7 argue for an etiologic role of chemical toxins. A male preponderance exists in monosomy 7 syndrome and in cases that arise in patients with NF-1 and Shwachman-Diamond syndrome. In contrast, almost equal number of boys and girls are affected when monosomy 7 develops in the context of previous cytotoxic or immunosuppressive therapy, Fanconi anemia, severe congenital neutropenia, and familial predisposition. It thus appears that certain strong genetic or environmental factors can override the male predisposition typical of de novo cases.

BIOLOGY

The epidemiologic data showing that monosomy 7 is a pervasive abnormality in myeloid neoplasia give rise to a number of questions. First, what myeloid progenitor is the target cell? Second, loss of precisely what gene (or genes) on chromosome 7 contributes to leukemogenesis? Third, how do chromosome 7 deletions contribute to leukemogenesis? Fourth, is there an etiologic or pathogenetic link between cases of monosomy 7 that arise de novo and those that appear in patients with known acquired or constitutional predisposition? And fifth, can investigation of childhood monosomy 7 provide insights that are applicable to the more common disorders of myeloipoiesis that develop later in life? Laboratory data that address some of these questions are reviewed below.

Studies of Malignant Progenitor Colony Growth

Cytogenetic analysis of colonies derived from erythroid (burst-forming unit-erythroid [BFU-E]) and myeloid (colony-forming unit–granulocyte-macrophage [CFU-GM]) progenitors have shown primary involvement of both lineages.105 Lymphoid cells are normal when examined cytogenetically12 and lymphoblastoid cell lines derived from adults with monosomy 7 consistently retain heterozygosity for polymorphic chromosome 7 markers.50 Gerristen et al106 used fluorescent in situ hybridization (FISH) to investigate subpopulations of blood and bone marrow cells from patients...
with monosomy 7 and found that the cytogenetic abnormality was generally restricted to the myeloid lineage. Although these results suggest that malignant transformation in most patients with monosomy 7 occurs in a partially committed cell that is capable of giving rise to erythroid, myeloid, and megakaryocytic progeny, but not to lymphocytes, other data implicate involvement of an earlier, multilineage progenitor. Some cases of leukemia associated with monosomy 7 present with immunophenotypic evidence of multilineage involvement and the phenotype of the blast population may switch lineages during therapy. Lau et al recently described a 2-month-old child with JCML, whose terminal course was characterized by a lymphoid blast crisis and monosomy 7. The immunophenotype of his blasts were consistent with pre-B-cell leukemia and there was a rearrangement of the Ig heavy chain. Taken together, the existing data suggest that chromosome 7 deletions are not restricted to myeloid leukemia in all cases, but may contribute to deregulated growth in hematopoietic cells at various levels of differentiation, including multilineage progenitors.

Limited data exist on myeloid progenitor colony growth in children with monosomy 7 syndrome, but this question has been investigated extensively in JCML and these studies included some patients with chromosome 7 deletions. Weiss et al found aberrant myeloid progenitor colony (CFU-GM) development characterized by an abnormal pattern of cluster and colony growth and by colony formation without feeder layers as a source of exogenous colony-stimulating activity in 8 preleukemic children with monosomy 7. Abnormal growth of CFU-GM is also characteristic of JCML. Marrows are labeled by monoclonal antibodies that react with immature monocytic cells and consistently show excessive proliferation of monocyte/macrophage colonies that is independent of exogenous growth factors. The “spontaneous” proliferation of JCML cells is abolished by removing adherent cells before culture or by antibodies to granulocyte-macrophage colony stimulating factor (GM-CSF). Emanuel et al found that JCML CFU-GM are selectively hypersensitive to GM-CSF but proliferate normally when stimulated with interleukin-3 (IL-3) or G-CSF. Freedman et al reported abnormal proliferation of JCML cells in response to both GM-CSF, IL-1, and tumor necrosis factor α. Another recent study implicates IL-1β as important in the autonomous pattern of in vitro growth seen in JCML. The role of GM-CSF in the pathogenesis of JCML is further supported by the finding that transgenic mice that overexpress the GM-CSF gene develop a clinical syndrome with some features of JCML. Recent data from studies of X-inactivation in females with JCML are consistent with monoclonal proliferation.

In summary, a large body of experimental evidence implicates hypersensitivity to GM-CSF and perhaps to other growth factors in the abnormal pattern of proliferation that is characteristic of JCML. The limited data from studies of children with monosomy 7 syndrome are consistent with a pattern of aberrant proliferation that is similar to JCML. A major focus of future research in childhood preleukemia will be to define the genetic alterations that deregulate growth factor production and responses in leukemic cells and to understand how these genetic changes perturb biochemical signals transduced from specific growth factor receptors to the nucleus.

**Cytogenetics and Deletion Mapping**

Complete monosomy 7 is the only cytogenetic abnormality identified in the bone marrow of most affected children (Table 1). As in adults, the q22-pter region is involved most often in patients with partial deletions. It is of interest that the marrow of a child with NF-1 and MDS showed a partial deletion of the long arm and another patient with familial monosomy 7 had an interstitial deletion of the same region (B.J.L., K.M.S., and J. Davis, unpublished data). These data suggest that the same gene or genes contribute to deregulated myeloid growth in children with and without genetic predispositions. Four children had cytogenetic abnormalities of chromosome 3 in addition to monosomy 7.

Figure 3 shows a number of loci on chromosome 7 that have been examined in the mapping experiments reported to date. The extent of chromosome 7 deletions in children...
Studies of Chromosome 7 in Therapy-Related Leukemia and JCML

Demonstrating allelic loss in malignancies that do not show detectable cytogenetic deletions implicates loss of function of tumor-suppressor genes in tumorigenesis and may help to localize critical regions within specific DNA segments. Patients with therapy-related MDS or AML and children with JCML who do not have monosomy 7 have been analyzed for loss of heterozygosity with chromosome 7 probes. Neuman et al studied the bone marrow of 10 patients with secondary MDS or AML without cytogenetic evidence of chromosome 7 deletions. They detected loss of heterozygosity with multiple probes located near CFTR in 1 patient. None of 40 patients with de novo AML had cryptic involvement of chromosome 7. A similar analysis in 23 children with MDS or MPS, including 19 with JCML, found no evidence for loss of constitutional heterozygosity. Taken together, the data from these studies indicate that submicroscopic loss of large segments of chromosome 7 DNA are

uncommon in patients whose marrow does not show overt structural abnormalities, but does not exclude a small region of overlapping deletions located between the existing polymorphic markers.

The Tumor-Suppressor Model and Familial Monosomy 7

The peculiar epidemiology of monosomy 7 and 7q- could be explained by the model of recessive cancer genes proposed by Knudson. Familial cases would arise when affected siblings inherit the same abnormal allele from one parent. In young children with the nonfamilial type of monosomy 7, the initial mutation might occur in a parental gamete or during embryogenesis (similar to the mechanism in sporadic cases of retinoblastoma). In patients who develop AML as a second cancer, the initial mutation is presumably induced by exposure to the carcinogen. The high spontaneous mutation rate in Fanconi anemia would increase the likelihood of a random mutation of the critical gene in a susceptible cell. In all of these circumstances, subsequent deletion of the homologous normal allele in a hematopoietic progenitor would lead to deregulated growth and clonal expansion. The
Knudson model predicts that DNA from the same (abnormal) parental chromosome 7 will be retained in the bone marrow of siblings if the familial predisposition to leukemia is caused by a germline mutation affecting one allele of a tumor-suppressor gene located on chromosome 7 (similar to familial retinoblastoma). However, multipoint linkage analysis in 3 pairs of siblings with childhood monosomy 7 showed consistent retention of alleles from different parental chromosomes (Fig 4). The surprising result that the familial predisposition to develop monosomy 7 is apparently not linked to chromosome 7 implicates at least two interacting mutational events in the development of familial monosomy 7. This idea is consistent with the fact that children with familial monosomy 7 are generally older at diagnosis than patients with nonfamilial disease (Table 1), a finding that is in marked contrast to the earlier age at disease onset in patients with germline mutations such as the tumor-suppressor genes RB1, WT1, and P53.123124 There are no published molecular data from kindreds in which the predisposition to monosomy 7 is associated with cerebellar ataxia.

Genomic Imprinting and Parent of Origin Effects

Genomic imprinting refers to the observation that the functions of homologous alleles may differ depending on whether they were transmitted by the father or mother.126 Because the allele that is inherited from one parent is functionally inactive because it is imprinted, malignancies in which tumor-suppressor genes are inactivated by imprinting would be expected to show preferential retention of alleles inherited from one of the parents. This theory is true in a number of pediatric cancers, including Wilms' tumor and familial rhabdomyosarcoma.127128 Segments of the mouse genome that are homologous to regions of the long arm of chromosome 7 are imprinted,129 and studies of patients with cystic fibrosis that are homologous to regions of the long arm of chromosome 7 are imprinted.129 and studies of patients with cystic fibrosis suggest that this is also true in humans.130131 Two groups used polymorphic markers to determine whether monosomy 7 bone marrow preferentially retains paternal or maternal chromosomes. Katz et al132 found loss of paternal alleles in 7 of 8 children with preleukemia and monosomy 7 and suggested that imprinting might be important. However, a recent study of 12 patients showed preferential retention of maternal chromosomes.133 The ratio of retained DNA segments derived from maternal and paternal chromosomes was 1:1 when data from these studies were combined.132133 The apparent lack of a parent-of-origin effect in childhood monosomy 7 provides indirect evidence that imprinting of chromosome 7 is not involved in leukemogenesis.

Mutations in the ras Pathway in Childhood Preleukemia

RAS mutations are observed in the marrow of 25% to 50% of adults with MDS and in a similar proportion of adults and children with AML.134135 As summarized in Table 3, 20% to 30% of childhood preleukemias show RAS mutations. These alterations usually affect codons 12 and 13 of KRAS or NRAS and the incidence is approximately equal in monosomy 7 and JCML (Table 3).82136138 An activating RAS mutation was reported in the bone marrow of one child with familial monosomy 7.136 We recently found a mutation in the bone marrow of one of two sisters with monosomy 7 (R. Kalra and K. M.S., unpublished data). We have also detected activating RAS mutations in the bone marrow of some patients with severe congenital neutropenia who developed malignant myeloid disorders associated with bone marrow monosomy 7.137

The presence of RAS mutations in many patients with monosomy 7 is of particular interest because children with NF-1 are at increased risk of developing monosomy 7 and JCML.140495183101 The NF-1 gene (NFI) includes a domain that shares sequence homology with GTPase activating proteins (GAPs).179140 GAPs negatively regulate the biologic activity of Ras proteins by accelerating GTP hydrolysis; genetic and biochemical evidence are consistent with the idea that NFI functions as a tumor suppressor in neural crest cells.139140 Similarly, a study of 11 children with NF-1 who developed malignant myeloid disorders showed loss of the normal NFI allele in 5 cases, including 2 patients with JCML and 1 with monosomy 7 (Fig 5).101 Furthermore, activating RAS mutations appear to be restricted to the subset of children with preleukemia who do not have NF-1.138 Taken together, these data provide strong genetic evidence that the tumor-suppressor activity of NFI is mediated through its effects on Ras in hematopoietic cells. Mutant NFI alleles transmitted by either parent may be retained in the marrows of children with NF-1 who develop malignant myeloid disorders; this suggests that NFI is not imprinted in myeloid cells.101

Two groups used homologous recombination in embryonic stem cells to construct mouse strains with germline disruptions of NFI. Homozygous inactivation of NFI is an

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>RAS Mutations/No. of Cases*</th>
<th>Percentage With RAS Mutations (%)</th>
<th>Type(s) of RAS Mutations†</th>
</tr>
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<tbody>
<tr>
<td>Neubauer et al136</td>
<td>Mo 7</td>
<td>2/11</td>
<td>18</td>
<td>N12ASP (1) K13ASP (1)</td>
</tr>
<tr>
<td>Lubbert et al137</td>
<td>Mo 7 MDS</td>
<td>2/6</td>
<td>33</td>
<td>N12 (2)†</td>
</tr>
<tr>
<td>Miyauchi et al138</td>
<td>JCML</td>
<td>1/3</td>
<td>33</td>
<td>N61 (1)</td>
</tr>
<tr>
<td>Kalra et al139</td>
<td>JCML MPS</td>
<td>4/27</td>
<td>14</td>
<td>N12ASP (2) K12ASP (2)</td>
</tr>
<tr>
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<td>JCML</td>
<td>5/24</td>
<td>20</td>
<td>N12SER (1) K12VAL (2)</td>
</tr>
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* Does not include 3 patients with NF-1 in the study of Neubauer et al136 and 16 patients with NF-1 in the study of Kalra et al.138 None of these patients had RAS mutations. See text for further details.
† The abbreviations refer to the RAS gene (NRAS or KRAS), the codon mutated (12, 13, or 61), and the amino acid substitution resulting from the mutation.
‡ The studies of Lubbert et al137 and Miyauchi et al138 were limited to NRAS.
§ Four of the JCML patients in this study had bone marrow monosomy 7.
∥ Miyauchi et al139 and Kalra et al138 each identified 1 patient with two independent RAS mutations.
A-1994 C-child with JCML. A highly polymorphic repeat located in an intron of lung biopsy (L) but is lost in the bone marrow (BM). We are indebted to Dr Eric Sieven for referring this patient for study.

Fig 5. Loss of the normal NF1 allele from the bone marrow of a child with JCML. A highly polymorphic repeat located in an intron of NF1\textsuperscript{TN} was amplified using the polymerase chain reaction as described elsewhere; the products were separated on a polyacrylamide gel. The normal maternal allele is seen in tissue obtained at diagnostic lung biopsy (L) but is lost in the bone marrow (BM). We are indebted to Dr Eric Sievers for referring this patient for study.

A-1994 C-child with JCML. A highly polymorphic repeat located in an intron of lung biopsy (L) but is lost in the bone marrow (BM). We are indebted to Dr Eric Sieven for referring this patient for study.

The normal maternal allele is seen in tissue obtained at diagnostic lung biopsy (L) but is lost in the bone marrow (BM). We are indebted to Dr Eric Sievers for referring this patient for study.

embryonic lethal trait with prominent vascular and cardiac anomalies.\textsuperscript{141,142} Interestingly, heterozygous animals are susceptible to the development of malignant myeloid disorders during the second year of life.\textsuperscript{141} Molecular analysis of these leukemias consistently showed loss of the wild-type allele.\textsuperscript{141} These animals provide a valuable experimental system for characterizing the biochemical consequences of loss of NF1 function and to investigate what additional genetic events contribute to leukemogenesis.

**SPECULATIONS AND FUTURE PERSPECTIVES**

The existing data are most consistent with the idea that chromosome 7 deletions are not the initiating event in childhood MDS and AML, particularly because this deletion arises in so many situations in which there is already a well-defined predisposing condition. Epidemiologic evidence that chromosome 7 deletions are secondary events are consistent with data in familial monosomy 7 showing that the inherited predisposition is not linked to chromosome 7. The coexistence of chromosome 7 deletions and mutations that perturb Ras-mediated signaling in many cases of MDS and AML suggest that these alterations cooperate in the outgrowth of a malignant clone.

It is likely that monosomy 7 contributes to leukemogenesis because it results in loss of function of a critical gene (or genes) located on 7q. However, it is unknown if inactivation of both alleles of the putative gene (or genes) is essential or if monosomy 7 might act by dosage. This is a crucial question and the experiments performed to date are remarkably uninformative. The fact that the predisposition to leukemia is not linked to chromosome 7 in children with familial monosomy 7 does not exclude the possibility that inactivation of both alleles of a tumor-suppressor gene is a late event in leukemogenesis. Similarly, the existence of either alternative genetic events or of a small "critical region" between the probes used to date might explain the failure to detect loss of heterozygosity on chromosome 7 in patients with secondary AML or JCML without cytogenetic evidence of deletions. The best evidence of a tumor-suppressor locus on the long arm of chromosome 7 are derived from genetic mapping and microcell fusion experiments in immortalized, nontumorigenic fibroblast cell lines.\textsuperscript{143} Two lines showed loss of heterozygosity on 7q (one by deletion); the introduction of chromosome 7 induced senescence.\textsuperscript{143} The relevance of these data to hematopoietic cells is unknown.

With little direct evidence that functional inactivation of both alleles of a putative tumor-suppressor gene is an essential step in leukemogenesis in monosomy 7, it is reasonable to consider the idea that loss of one allele confers a growth advantage by reducing the concentration of a critical protein (ie, by gene dosage or haploinsufficiency). As reviewed recently, two copies of some genes are essential for a normal phenotype; genetic disorders result when one allele is inactivated.\textsuperscript{144} There is no direct evidence that monosomy 7 contributes to leukemogenesis by this mechanism, but the idea of haploinsufficiency is consistent with data in de novo monosomy 7, in familial monosomy 7, and in patients who do not show overt cytogenetic deletions. Inasmuch as it is highly unlikely that loss of one allele of a single autosomal gene would have severe phenotypic consequences for myeloid growth control, it is striking that monosomy 7 is strongly associated with occupational or medical exposure to genotoxins, with a variety of constitutional predispositions to leukemia, and coexists with alterations of genes involved in Ras signaling in many patients. Deletions of 5q31 are common in adults with MDS; this syndrome has been investigated intensively over the past few years.\textsuperscript{145,146} Despite a well-defined "critical region" and contiguous genomic clones spanning the DNA segment of interest, convincing evidence that both alleles of a tumor-suppressor gene are inactivated have not emerged in patients with 5q deletions, and haploinsufficiency has been suggested as a plausible explanation.\textsuperscript{145,146}

The tumor-suppressor and haploinsufficiency models are not mutually exclusive. For example, it is possible that one allele of the critical gene is lost during the development of MDS with monosomy 7 and that progression to AML is associated with an acquired mutation of the remaining normal homologue. If monosomy 7 contributes to leukemogenesis by haploinsufficiency, proving that this is true and excluding the existence of a "classic" tumor-suppressor gene is a formidable experimental challenge.

Deregulation of signal transduction through Ras proteins is a common underlying event in many types of myeloid
leukemia. As recently reviewed by Sawyers and Denny, this apparently occurs by a number of different genetic mechanisms, including (1) activating point mutation of KRAS or NRAS; (2) loss of the normal NFI allele; (3) interaction between the chimeric Bcr-Abl protein and Grb-2 in CML; and (4) involvement of the intracellular domain of the PDGFβ receptor in the (5;12) translocation of CMML. The presence of RAS mutations in the bone marrow of some patients with monosomy 7 suggests that aberrant Ras-mediated signaling and chromosome 7 deletions cooperate in leukemogenesis, probably by deregulating different biochemical pathways involved in myeloid growth and differentiation. Importantly, the presence of both alterations in the bone marrow of some children with constitutional predispositions to leukemia indicates that leukemogenesis in these cases involves the same secondary genetic events as in de novo MDS and AML. This finding, in turn, suggests that these disorders predispose to myeloid leukemia by increasing the likelihood of acquiring common secondary alterations rather than through novel mechanisms.

Figure 6 is styled after the genetic paradigm developed by Fearon and Vogelstein as they have defined the molecular events that underlie colon carcinogenesis. In our model, alterations of the RAS pathway precede chromosome 7 deletions for two reasons: (1) NF-1 is associated with a clear constitutional predisposition to myeloid leukemia; and (2) the data in familial monosomy 7 implicate loss of chromosome 7 as a "late" genetic event in leukemogenesis. It is likely that the constellation of genetic alterations is more important than the order in which they are acquired and that this sequence varies in individual patients.

Finally, the clinical features of adults and children with monosomy 7 and cytogenetic findings in patients with partial del(7q) are consistent with the hypothesis that the same gene (or genes) contributes to leukemogenesis in both age groups, irrespective of whether the predominant clinical pattern is hyperproliferative or dysplastic. Identification of the putative gene on the long arm of chromosome 7; characterization of the mechanism involved in leukemogenesis (ie, recessive inactivation of both alleles or haploinsufficiency); and establishing the biochemical activities of its protein product are important goals. This is particularly true because conventional treatment approaches are unsatisfactory in patients of all ages who have bone marrow monosomy 7.

**ACKNOWLEDGMENT**

We are indebted to Drs Sherri Brown, Jeff Davis, Peter Emanuel, Tyler Jacks, and Jack Priest for sharing their unpublished data with us and to our colleagues Ruby Kalra, Katherine Matthy, Kristin Olson, and Dorothy Palenaga.

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Childhood monosomy 7: epidemiology, biology, and mechanistic implications

S Luna-Fineman, KM Shannon and BJ Lange