A Neonate with Down’s Syndrome and Transient Abnormal Myelopoiesis: Serial Blood and Bone Marrow Studies

By Takeshi Nagao, Beatrice C. Lampkin and George Hug

Observations were made of the blood and bone marrow of a male infant with Down’s syndrome during the first year of life. At 4 days of age there were 36,500 myeloblasts/cu.mm. in the blood and 10.8 per cent myeloblasts in the bone marrow. Initially it appeared the patient had acute myeloblastic leukemia. However, the clinical course and kinetic and electron microscopic studies of his bone marrow cell population indicate he did not have acute leukemia.

Congenital acute myeloblastic leukemia is more common in infants with Down’s syndrome than in the general population of infants, and may undergo spontaneous and permanent remission in some of the infants. For this reason, the diagnosis of leukemia has been questioned. A neonate with Down’s syndrome who had a blood picture compatible with acute myeloblastic leukemia is described in this paper. The results of studies obtained in this patient indicate he did not have leukemia.

Materials and Methods

All routine hematologic studies were done by standard methods. The classification of blast cells was done by morphological and histochemical criteria. The proliferative capacity of samples of marrow was studied by measurement of cells in mitosis and also cells in DNA synthesis, as indicated by the ability to incorporate tritiated thymidine (labeling index). The mitotic indices were measured by the method of Japa. The number of mitotic figures per 1000 nucleated cells was counted from each of 10 cover slip preparations for each sample and was recorded as the average number of cells in mitosis per 1000 nucleated cells. To determine the labeling indices, a 1 ml. heparinized sample of bone marrow was incubated with 1 μCi. tritiated thymidine (specific activity 1.9 Ci per mmole) for 50 minutes at 37° C with constant shaking. The sample was then centrifuged at 1200 X g. for 10 minutes. Cover slip smears were made of the nucleated cell layer and autoradiographs prepared with Kodak AR-10 stripping film. After an exposure period of 13 days, the films were developed and the slides stained with Wright’s stain. At least 500 myeloid precursors, i.e. myeloblasts, promyelocytes and myelocytes, were counted for each sample, and the per

From the Department of Pediatrics, University of Cincinnati, The Children’s Hospital, and The Children’s Hospital Research Foundation, Cincinnati, Ohio.

Submitted April 8, 1970; accepted April 22, 1970.

This investigation was supported by USPHS Research Grant CA 04826 and USPHS Grant FR 00123.

This work was presented to the Midwest Society for Pediatric Research, November 6, 1969.

Takeshi Nagao, M.D.: Director, Division of Hematology, Department of Pediatrics, University of Tokyo, Japan; formerly Research Fellow, Division of Pediatric Hematology, Children’s Hospital Research Foundation, Cincinnati, Ohio. Beatrice C. Lampkin, M.D.: Associate Professor of Pediatrics, University of Cincinnati, Cincinnati, Ohio; recipient of Special Fellowship Award 1-F03-CA-42,380 from the National Cancer Institute. George Hug, M.D.: Associate Professor of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
The blasts in the blood were characterized by several prominent nucleoli and a very fine chromatin pattern. Fine azurophilic granules were present in some of the blasts. The peroxidase and sudan black B stains were positive in 4 per cent of these cells, but the PAS stain was negative. These findings are characteristic of myeloblasts. Cytoplasmic fibrillary bodies, bizarre shaped nuclei and asynchronous maturation of cytoplasmic granules are frequently seen by electron microscopy in blasts from patients with acute myeloblastic leukemia.12 These alterations were not seen in the myeloid precursors of our patients (Fig. 1).

The differential counts of serial bone marrow samples are shown in Table 1.
The results of kinetic studies are summarized in Table 2. For a period of

Fig. 1.—Comparison of electron photomicrographs of samples of bone marrow from the patient and from a 4-year-old boy with proven acute myeloblastic leukemia. A. Representative promyelocyte in the patient’s bone marrow that cannot be distinguished ultrastructurally from that of normal controls. × 19,800. B. Bone marrow of myeloblastic leukemia with disintegrating myeloid cell (upper half of the photomicrograph). This disintegration was a frequent observation in this leukemic specimen, as were cytoplasmic fibrillary bodies (arrows) that could not be detected in the patient’s marrow. × 5,500. C. Detail of the myeloid cell in the left lower corner of photomicrograph B shows part of a fibrillary body next to granules and a mitochondrion. No fibrillary bodies were found in the patient’s cells. × 38,000.

Until he was 3 weeks of age, the per cent of myeloblasts was higher than normally present, but never exceeded 15 per cent. The per cent of myelocytes was relatively constant, with the exception of the marrow obtained at 5 weeks of age. This sample of marrow was hypocellular and preceded the transient neutropenia and mild anemia. The erythroid series and megakaryocytes were not affected.

The results of kinetic studies are summarized in Table 2. For a period of
Table 1.—Differential Count of Bone Marrow

<table>
<thead>
<tr>
<th>Cell Types</th>
<th>6</th>
<th>8</th>
<th>21</th>
<th>35</th>
<th>84</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloblast</td>
<td>10.8</td>
<td>9.2</td>
<td>14.8</td>
<td>2.8</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Promyelocyte</td>
<td>7.6</td>
<td>5.6</td>
<td>6.8</td>
<td>0.8</td>
<td>3.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Myelocyte</td>
<td>15.6</td>
<td>13.2</td>
<td>17.6</td>
<td>4.0</td>
<td>12.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Mature neutrophil</td>
<td>50.4</td>
<td>50.6</td>
<td>18.4</td>
<td>43.2</td>
<td>32.4</td>
<td>53.2</td>
</tr>
<tr>
<td>Erythroid precursor</td>
<td>4.0</td>
<td>9.6</td>
<td>7.6</td>
<td>14.0</td>
<td>28.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Lymphocyte and others</td>
<td>11.6</td>
<td>11.6</td>
<td>31.2</td>
<td>36.0</td>
<td>24.8</td>
<td>20.2</td>
</tr>
</tbody>
</table>

| Cellularity     | + + | + + | + + | Hypo | + + | + + |

Table 2.—Kinetic Studies

<table>
<thead>
<tr>
<th>Age of Patient (Days)</th>
<th>Mitotic index (per 1,000 cells)</th>
<th>Labeling index of myeloid precursors in bone marrow (per 100 cells)</th>
<th>Labeling index of blasts in blood (per 100 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4.3</td>
<td>18.8</td>
<td>13.4</td>
</tr>
<tr>
<td>8</td>
<td>2.8</td>
<td>17.8</td>
<td>12.4</td>
</tr>
<tr>
<td>21</td>
<td>5.8</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>3.0</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12 weeks, the labeling and mitotic indices were low, as compared to reported results of samples of marrow from normal persons. These values were particularly low since a relatively high per cent of myeloblasts were present.

At 5 months, the labeling and mitotic indices were normal. Labeling indices of blasts in blood were obtained on two occasions and were almost identical but lower than the values of samples of marrow.

**Discussion**

Some infants with Down's syndrome who were reported to have a blood picture compatible with acute myeloblastic leukemia subsequently were considered to have had a leukemoid reaction secondary to hemolytic disease of the newborn, congenital syphilis, and other severe infections, or a folic acid deficiency. These diagnoses as a cause for the blood findings in our patient were excluded by the absence of a blood incompatibility with the mother, negative VDRL, normal IgM level, negative bacterial cultures and no megaloblastic changes in the bone marrow aspirate.

The large number of myeloblasts in the blood, hepatosplenomegaly and low labeling and mitotic indices found in our patient are findings compatible with the diagnosis of acute myeloblastic leukemia. However, the presence of only 15 per cent myeloblasts in the marrow and the absence of anemia, neutropenia or thrombocytopenia when there were many myeloblasts in the blood are findings against the diagnosis of acute leukemia. The spontaneous remission which has lasted over 1 year, the return to normal of the labeling and mitotic indices of the marrow and the absence of electron microscopic changes consistent with leukemia make the diagnosis of acute leukemia even less acceptable.

Further studies of the type reported in this paper may be helpful in defining the nature of the abnormal myelopoiesis which may be seen in infants with Down's syndrome.
ACKNOWLEDGMENTS

We thank Dr. Shirley Soukup for doing the chromosomal analysis and Dr. Alvin M. Mauer for his helpful suggestions regarding the manuscript. We acknowledge the technical assistance of Miss Virginia Fisher and Miss Claire Anderson.

REFERENCES

A Neonate with Down’s Syndrome and Transient Abnormal Myelopoiesis: Serial Blood and Bone Marrow Studies

TAKESHI NAGAO, BEATRICE C. LAMPKIN and GEORGE HUG