The Incidence of Leukemia in Families of Patients with Hypoplasia of the Marrow

By SERGIO GARRIGA and WILLIAM H. CROSBY

DURING A STUDY of splenectomy in patients with aplastic anemia it was noticed that among the families of these patients there appeared to be a high incidence of leukemia. It is recognized that leukemia itself sometimes occurs in families. The best résumé of this problem is that of Guasch, who stated that among 8,586 cases of leukemia contributed by 81 hematologists, familial leukemia was found 39 times, a frequency of 4.54 per thousand. There also has been recognized a familial form of aplastic anemia known as Fanconi's syndrome. The syndrome is believed to be hereditary, and its transmission is attributed to a recessive gene, usually of rather low penetrance. Fanconi's syndrome is a relatively rare condition; fewer than 70 cases have been recorded in the literature. However, among these few cases it has been recorded several times that leukemia, as well as other cases of aplastic anemia, had occurred in the families of the affected children. Because the incidence of leukemia seemed exceptionally great, a review of all case reports was carried out in order to learn, if possible, how often leukemia occurred in the families in which aplastic anemia was found.

MATERIALS AND METHODS

Disorders of proliferation which can result in hypoplasia of the marrow are probably many in number and diverse in character. At present we are unable, with few exceptions to sort them one from another. Fanconi's syndrome is one such exception. Progressive atrophy of the bone marrow associated with congenital abnormalities or familial incidence of the disease, or both, permits the separation of this hypoplastic anemia from the others. Therefore, this group of patients was selected for review. All published case reports were studied and tabulated.

During the review we encountered several instances of familial hypoplastic disease of the marrow which could not be classified as Fanconi's syndrome. Davidson, Davis and Innes reported two sisters, both of whom died of aplastic anemia following treatment with gold for rheumatoid arthritis. Gianasi, Limarzi and Poncher described two brothers who died of aplastic anemia; they were the siblings of eight brothers, all of whom were reported to be anemic.

There were several families in which a coincidence of idiopathic aplastic anemia and leukemia had been recorded, but in the absence of associated congenital defects or of a familial incidence of aplastic disease, these could not be identified as Fanconi's syndrome. Erf and Rhoads described two brothers who were working in a photographic studio where benzol was used. When one of them died, evidently of aplastic anemia, the other became frightened of benzol and changed his job. Seventeen years later he came...
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again into contact with benzol and developed chronic granulocytic leukemia. Adams' reported a patient, a child with aplastic anemia, whose uncle had acute leukemia. A woman with aplastic anemia described by Heaton, Crosby and Cohen had a sister who as a child had died of acute leukemia 30 years before. A diagnosis of Fanconi's syndrome was not possible with the data provided in any of these reports.

In addition to the search for cases of leukemia in families of patients with Fanconi's syndrome, other aspects of the disease were noted and tabulated.

RESULTS

Sixty-six cases of Fanconi's syndrome were identified, involving 48 families (table 1). In 14 of the families more than one child was affected. In the absence of a familial incidence of the disease, 34 cases were identified by the association of typical congenital abnormalities with hypoplasia of the marrow. Among the 48 families there were mentioned four cases of leukemia, two of them in cousins, one in a brother, one in an uncle, and in one patient with Fanconi's syndrome acute leukemia developed after the patient had been ill for four years with hypoplastic disease of the marrow.

Developmental defects in nonanemic members of the 48 Fanconi families occurred in 15 instances. Among all members with developmental defects the skeletal faults and skin pigmentation were the most common, followed by stunting of growth, strabismus, central nervous system troubles and hypogenitalism. In some instances there were congenital defects of the kidney or urinary tract. It has not been previously noted that atrophy of the spleen may represent an associated defect of development in this disease, but in 12 cases the size of the spleen was mentioned and in nine of the twelve it was stated to be small or to have weighed less than 40 Gm. Consanguinity of the parents was found in five instances. Of the 66 cases 23 were diagnosed in the first four years of life, 22 in the second four years and 14 in the third. Seven cases occurred after the age of 12, and none was seen after 23 years of age. There were 19 females (29 per cent), 46 males (70 per cent), and in one case the sex of the patient was not stated. Beyond the age of puberty only two of seven patients were female.

DISCUSSION

Among 49 families in which Fanconi's syndrome was found, leukemia was reported four times, a rate of one in 12.2 cases. While the numbers involved are not great enough to be significant, this contrasts strikingly with the rate of familial leukemia: one in 450,23 and the rate of leukemia in the over-all population: 60 per million per year.48 The rate of leukemia in the Fanconi families seems to be astonishingly high.

At present it cannot be said that this coincidence is not due to chance. Our purpose is to point out the possibility that occurrence of aplastic anemia and leukemia in families may be the consequence of some hereditary fault. It is known that certain agents such as benzol may cause aplastic disease in some susceptible people and leukemia in others.29 The atomic bombs at Hiroshima and Nagasaki caused an increased rate of leukemia in the exposed population,41 and there were also cases of aplastic disease which appeared a few years after the bombing.36 Among the thousands of people exposed
### Table 1.—Associated Defects Recorded in the Reported Cases of Fanconi's Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Case No.</th>
<th>Sex</th>
<th>Age at onset</th>
<th>Growth retarded</th>
<th>Pigmentation</th>
<th>Renal failure</th>
<th>Skeletal malformations</th>
<th>Ocular defects</th>
<th>Familial Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al.</td>
<td>1</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>S: in siblings</td>
</tr>
<tr>
<td>Van-Bruinen</td>
<td>1</td>
<td>M</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1, 2, and 3 were brothers</td>
</tr>
<tr>
<td>Van Lueven</td>
<td>2</td>
<td>M</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Emile-Well</td>
<td>3</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hjorth et al.</td>
<td>4</td>
<td>M</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 and 2 were siblings</td>
</tr>
<tr>
<td>Rocha-Brito</td>
<td>5</td>
<td>F</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Heuyer et al.</td>
<td>6</td>
<td>M</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Zellweger et al.</td>
<td>7</td>
<td>M</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>P: skeletal</td>
</tr>
<tr>
<td>Jimenez de Asua</td>
<td>8</td>
<td>M</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>M: dermal</td>
</tr>
<tr>
<td>Estren et al.</td>
<td>9</td>
<td>M</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Rohr et al.</td>
<td>10</td>
<td>M</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 and 2 were brothers</td>
</tr>
<tr>
<td>Feuilleen</td>
<td>11</td>
<td>M</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Diamond</td>
<td>12</td>
<td>F</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Beautyman</td>
<td>13</td>
<td>M</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Baumann</td>
<td>14</td>
<td>M</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Reinhold et al.</td>
<td>15</td>
<td>M</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 and 2 were sisters</td>
</tr>
<tr>
<td>Cassimos et al.</td>
<td>16</td>
<td>M</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>S: mental, ocular, A cousin had acute leukemia</td>
</tr>
<tr>
<td>Guinard-Doniol</td>
<td>17</td>
<td>M</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>S: developmental, genital</td>
</tr>
<tr>
<td>Genzini</td>
<td>18</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>S: dermal, skeletal Parents were cousins</td>
</tr>
<tr>
<td>Demirag</td>
<td>19</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None recorded</td>
</tr>
<tr>
<td>Crissi et al.</td>
<td>20</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 and 2 were brothers</td>
</tr>
<tr>
<td>Levy et al.</td>
<td>21</td>
<td>M</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Volpe et al.</td>
<td>22</td>
<td>M</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Silver et al.</td>
<td>23</td>
<td>F</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kuenzler</td>
<td>24</td>
<td>F</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Jimenez-Diaz et al.</td>
<td>25</td>
<td>M</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 and 2 were brothers</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>A sister died of aplastic anemia, 3 and 4 no abnormalities</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Althoff</td>
<td>28</td>
<td>F</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>M: developmental</td>
</tr>
<tr>
<td>Higashi et al.</td>
<td>29</td>
<td>F</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>M: deaf</td>
</tr>
</tbody>
</table>

**Familial Conditions**
- M: on maternal side
- P: on paternal side
- S: in siblings

**Hypogenitalia**
- very small

**Splenic size**
- approx 20 Gm.
- 30 Gm.
to benzol and irradiation the few who developed diseases of the marrow are somehow different; we may call them predisposed. It is possible that the hereditary fault which permits development of Fanconi's syndrome may also cause a predisposition to leukemia, even among those in whom the gene is not so completely expressed as to cause Fanconi's syndrome.

**SUMMARY**

The authors have reviewed the published cases of Fanconi's syndrome of hypoplasia of the bone marrow. They have tabulated the features of the syndrome, pointing out that atrophy of the spleen is a common fault and may reflect a generalized dystrophy of the tissues of mesenchymal origin.

Of special interest is the demonstration of a high incidence of leukemia in the families of patients with hereditary hypoplasia of the bone marrow.

**SUMMARIO IN INTERLINGUA**

Esseva effectuate un revista del casos publicate del syndrome de Fanconi de hypoplasia del medulla ossee. Esseva tabulate le caracteristicas del sy-
drome. Es signalate que atrophia del splen es un defecto commun que reflecte possibilemente un dystrophia generalisate del histos de origine mesenchymal.

De interesse special es le demonstration de un alte incidentia de leucemia in le familias de patientes con hypoplasia hereditari del medulla ossee.

REFERENCES

24. Guinard-Doniol, J. and The, F.: Pan- myelopatic constitutionelle infantile
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