CONGENITAL HYPOPLASTIC ANEMIA ASSOCIATED WITH MULTIPLE DEVELOPMENTAL DEFECTS (FANCONI SYNDROME)

Report of a Case

By S. Estren, M.D., John F. Suess, M.D., and William Dameshek, M.D.

The pathogenesis of congenital hypoplastic anemia is not clear. In many cases, the disorder occurs sporadically in a child who is otherwise completely well; in the absence of other etiologic agents, these cases are assumed to result from a chance defect in the chromosomal mechanism for development of the bone marrow. That this hypothesis is probably valid is suggested by the occurrence, in other individuals, of congenital aplasia of the bone marrow in siblings, and also by the occurrence of cases in which the marrow abnormality is merely one of a number of congenital aberrations. Fanconi was the first to describe examples of the latter disorder. In 1927 he reported three brothers aged 5, 6, and 7 years respectively, each of whom showed aplastic anemia, microcephaly, testicular hypoplasia, convergent strabismus, exaggerated deep tendon reflexes, and a generalized brown melanin-like pigmentation of the skin. Familial cases of this "Fanconi syndrome" were subsequently described by Émile-Weil, Hjorth, and Dacie and Gilpin. Sporadic cases of the same disorder were reported by Uehlinger, van Leeuwen, and Émile-Weil.

The purpose of the present paper is to describe an example of Fanconi's syndrome in an 11 year old American-born child. As far as we can determine, this is the first such case to be reported in the American literature. Hypoplastic anemia was associated with pigmentation of the skin, deafness, congenital heart disease, and congenital deformities of the thumbs and forearms.

CASE REPORT

H. T., an 11 year old white girl, was admitted to the Boston Floating Hospital (No. 9474) on September 10, 1946,* for investigation of anemia.

Family History. Both parents were born in France of French ancestry. The father had never had any illnesses except for unknown childhood diseases over 30 years before the patient was born. He had lived in the United States since 1924 and was 38 years old at the time of the pregnancy. The mother was well

* Referred by Dr. Earl S. Kelly, Pawtucket, Rhode Island.

From the Blood Laboratory of the J. H. Pratt Diagnostic Hospital and the Boston Dispensary, the Boston Floating Hospital and Tufts College Medical School. Aided by grants from the Charlton Fund and the Upjohn Company.
before the pregnancy except for a transient episode of "jaundice" which occurred at the age of 2 (in France), and since which time she was supposed to be anemic. Actual study of the mother showed no evidences of anemia, spherocytosis, or other defect of the hematopoietic system. The mother had lived in the United States since 1914 and was 33 years old at the time of conception. During the third month of the pregnancy, she suddenly developed faintness and dizziness, was told she had a severe "otitis media and mastoiditis," and underwent mastoidectomy. The subsequent course of the pregnancy was uneventful.

There was no history in the family of either mother or father of blood diseases, spleen disease, anemia, congenital abnormalities, pigmentation of the skin, or other similar disorders.

Birth History. The patient was an only child. The mother had never been pregnant before, and after discovering the abnormalities in her daughter refused to become pregnant again. The child was born at home of a vertex delivery in which low forceps were used. At the time of birth, it was noted that the right thumb was lacking and that the left thumb was represented by a single bony rudiment hanging by a thread of skin from the left metacarpus.

Past History. Development, in regard to weight gain and mental ability, appeared to be normal. At the age of 3 weeks the patient had pneumonia; but she was well from that time until the age of 3 years, when she developed rubella; at 4 years, she had transient pyelitis. After the first year, her general development was poor and she was frailer and smaller than other children of the same age.

Present History. In 1943, when the patient was 7 years of age, it was noted that she was extremely pale. At the same time, her skin was noticeably darker than previously, and she seemed to have some difficulty in hearing with her left ear. Pallor and increasing pigmentation continued to be present from that time on. In May 1945 the child developed fever, coryza, and cough which were interpreted as bronchitis. Sulfadiazine was given, 1.0 gram every four hours for three days, with some relief. These episodes of fever, coryza, and cough which were interpreted as bronchitis recurred in July 1945, December 1945, and February 1946; on each occasion they were treated with similar dosage schedules of sulfadiazine, with regression of the complaints. In February 1946, however, fever continued to be present after the usual course of sulfa therapy, and another similar course of sulfadiazine was given a week after the first course with good response.

In March 1946 the pallor became marked and the child was weak, listless, and unable to carry on her usual activities. A laboratory test was performed at this time and showed anemia. Liver and iron therapy were instituted without effect, and the patient was given two transfusions of whole blood of 500 cc. each. She felt and looked better after this treatment, but in July 1946 again became listless, pallid, and weak. Fever of 100° to 102° F. was present at this time and spontaneous ecchymoses began to appear in various parts of the body. On several occasions, spontaneous bleeding also occurred from the gums. The stools were inconstantly streaked with blood. Occasional hematuria was also noted.

Physical Examination. The child was a dull-appearing, well nourished, poorly developed white girl. The skeletal development was that of a 6 or 8 year old child.

Skin. There was a generalized brown pigmentation of the skin over the entire body, but the oral mucosa was not pigmented. Purpuric spots were present over the abdomen, legs, and arms.

Ears. Grossly, the ears were normal. Otoscopic examination showed normal drums. There was, however, definite impairment of hearing in the left ear.


Mouth. Dentition corresponded to the age of 10 years. The tongue, oral mucosa, palate, and throat were normal. There was no abnormal pigmentation.


Breasts. Although the nipples were not developed, the fatty portions of the breasts were definitely increased over normal and corresponded to the development of a 14 year old girl.

Chest. A slight pigeon-breast deformity was present.

Lungs. Normal.

Heart. The heart was enlarged to both the right and the left. There was a systolic thrill over the left border of the heart, best felt at the left sternal border over the second and third left intercostal spaces. Over the same area a very loud machinery-type murmur was present. It was continuous throughout systole and diastole but was accentuated in systole, and not well transmitted elsewhere. The murmur was well heard in the interscapular area posteriorly. A softer systolic blowing murmur was present. At
FIG. 1. GENERAL APPEARANCE OF PATIENT

Note the shortening of the right forearm, the absence of the right thumb, and the rudimentary left thumb.

FIG. 2. POSTERO-ANTERIOR X-RAY OF THE HEART

The heart shows enlargement of the left ventricle and the pulmonary conus. On fluoroscopy, the left auricle was also seen to be enlarged.
the apex, transmitted to the left sternal border and the left axilla. The sounds were of good quality, and the rhythm was regular.

Abdomen. The liver and spleen were not palpable.

Genitalia. Normal female.

Extremities (fig. 1). The right thumb was completely lacking. The left thumb consisted of a single phalanx which was attached to the left metacarpus by a thread of skin and soft tissue. There was shorten-

The right radius and ulna are shorter than those on the left. The distal epiphysis of the right radius is absent. The right hand is deviated radially. The right thumb is absent. The left thumb is underdeveloped. The number of carpal centers of ossification is less than normal.

General Laboratory Findings. The urine showed no abnormalities. The serology of the blood was negative. An electrocardiogram showed no abnormalities. X-ray and fluoroscopy of the chest showed a prominent pulmonary artery, enlargement of the left ventricle, and enlargement of the left auricle (fig. 2). X-rays of the skeletal system showed the following findings (fig. 3):

1. The right thumb was absent.
<table>
<thead>
<tr>
<th>Date</th>
<th>R.B.C. (millions per cu. mm.)</th>
<th>Hemoglobin (grams per 100 cc.)</th>
<th>W.B.C. (per cu. mm.)</th>
<th>Differential count of white cells</th>
<th>Platelets (per cu. mm.)</th>
<th>Reticulocytes (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 11</td>
<td>0.73</td>
<td>2.7</td>
<td>2.700</td>
<td>P 620 (23%) L 1800 (67%) M 170 (10%)</td>
<td>21,000</td>
<td>11.1%</td>
</tr>
<tr>
<td>Sept. 13</td>
<td>1.04</td>
<td>2.7</td>
<td>2.450</td>
<td>P 760 (31%) L 1400 (56%) M 190 (12%)</td>
<td>13,500</td>
<td>9%</td>
</tr>
<tr>
<td>Sept. 17</td>
<td>1.09</td>
<td>3.4</td>
<td>1.850</td>
<td>P 350 (19%) L 1300 (71%) M 190 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept. 20</td>
<td>1.94</td>
<td>5.8</td>
<td>2.100</td>
<td>P 310 (14%) L 1600 (74%) M 140 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept. 24</td>
<td>Splenectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept. 25</td>
<td>2.41</td>
<td>7.4</td>
<td>3.450</td>
<td>P 1900 (56%) L 1000 (30%) M 500 (14%)</td>
<td>12,000</td>
<td>12.5%</td>
</tr>
<tr>
<td>Sept. 26</td>
<td>2.51</td>
<td>6.6</td>
<td>3.900</td>
<td>P 2000 (31%) L 1400 (36%) M 500 (13%)</td>
<td>12,600</td>
<td>4.3%</td>
</tr>
<tr>
<td>Sept. 28</td>
<td>2.51</td>
<td>6.7</td>
<td>2.900</td>
<td>P 1300 (43%) L 1350 (43%) M 350 (13%)</td>
<td>12,000</td>
<td></td>
</tr>
<tr>
<td>Sept. 30</td>
<td>2.40</td>
<td>5.8</td>
<td>2.300</td>
<td>P 1100 (46%) L 1200 (51%) M 50 (2%)</td>
<td>17,000</td>
<td>1.4%</td>
</tr>
<tr>
<td>Oct. 4</td>
<td>2.19</td>
<td>6.9</td>
<td>2.150</td>
<td>P 470 (12%) L 1500 (70%) M 130 (6%)</td>
<td>10,000</td>
<td>2.6%</td>
</tr>
<tr>
<td>Oct. 8</td>
<td>2.47</td>
<td>6.6</td>
<td>2.300</td>
<td>P 350 (12%) L 1800 (77%) M 150 (7%)</td>
<td>63,000</td>
<td>2.7%</td>
</tr>
<tr>
<td>Oct. 16</td>
<td>2.11</td>
<td>7.4</td>
<td>5,000</td>
<td>P 550 (11%) E 100 (2%) L 3800 (76%) M 350 (11%)</td>
<td>15.500</td>
<td>4.4%</td>
</tr>
<tr>
<td>Nov. 13</td>
<td>2.49</td>
<td>9.0</td>
<td>3.850</td>
<td>P 940 (16%) L 3500 (60%) M 1170 (10%)</td>
<td>10,000</td>
<td></td>
</tr>
</tbody>
</table>
2. The right wrist contained only 5 carpal centers of ossification (normally at this age, 8 centers are visible on x-ray).
3. The right radius and ulna were shorter than those on the left.
4. The right radius was shorter than the right ulna. The distal epiphysis of the right radius was absent.
5. The right hand was deviated toward the radial side.
6. The left thumb was underdeveloped.

Hematologic Findings. The blood counts are recorded in table 1. On admission, the red blood count was 730,000 per cu. mm.; the hemoglobin 1.7 grams per 100 cc. (18 per cent); the white blood count 2,700 per cu. mm., including 23 per cent polymorphonuclear neutrophils (640 per cu. mm.), 67 per cent lymphocytes (1,800 per cu. mm.), and 10 per cent monocytes (170 per cu. mm.). The platelets numbered 21,000 (normal 500,000) per cu. mm. The reticulocytes numbered 11 per cent of the total number of red cells. The blood smear showed variations in size and shape of the erythrocytes, some hypochromia, and virtually no platelets.

A bone marrow puncture showed hypopcellularity. Megakaryocytes were virtually absent from the preparations. Granulocytopoiesis was qualitatively normal, but quantitatively reduced. Erythropoiesis was normoblastic in type and orderly in development, but also quantitatively much reduced. There was a slight relative increase in the numbers of lymphocytes and plasma cells. Differential count of the marrow cells gave the following results:

Blasts ............. 0.4%  Erythroblasts .......... 0.4%  Promyelocytes ...... 1.6%  Normoblasts (basophilic) .... 3.0%
Myelocytes ........... 3.6%  Normoblasts (polychromatophilic) .10.0%
Band forms .......... 8.1%  Normoblasts (orthochromatic) .... 50.2%
Polymorphonuclears 6.4%  Ratio of granulocytes to erythrocytes =
Lymphocytes ......... 10.6%  1:1.5 (normal 1.5:1)
Plasma cells .......... 3.0%  Histiocytes ............ 4.2%

Course in Hospital. There was no response to liver and iron therapy. Three transfusions of blood totaling 700 cc. were given on September 11, 17, and 18 and had little effect on the symptoms of weakness and fatigue or on the blood values (table 1). Because the patient was going progressively downhill, and because splenectomy has occasionally given beneficial effects in hypoplastic anemia,6 removal of the spleen was undertaken on September 24. An additional 550 cc. of blood were given at this time. The spleen weighed 49 grams and showed large numbers of follicles. The sinuses were conspicuous. There was diffuse but slight hemosiderosis. No evidences of hematopoiesis were present. Vessels, capsule, and trabeculae were normal.

The patient's convalescence was uneventful. One month postoperatively there were no essential changes in the neutrophil or platelet counts, although a slight lymphocytosis had resulted in a total white count of 5,000 (table 1). The red count level was at a higher level than the patient's pretransfusion levels (5.2 M. as compared to 1.0 M.). Although the role of splenectomy in this regard could not yet be definitely stated, it seemed that the patient was able to maintain a higher level of erythrocyte count than before splenectomy.

DISCUSSION

The presentation of this patient as an example of the syndrome described by Fanconi is based upon the co-occurrence of multiple congenital abnormalities including hypoplasia of the hematopoietic system. The patient showed the following defects:

1. Skeletal system. There was underdevelopment of the bones, so that the skeletal age was two to four years less than the chronological age. There was
hypogenesis of the left thumb and agenesis of the right thumb and two carpal bones of the right hand. There was maldevelopment of the bones of the right forearm.

2. Central nervous system. There were no obvious abnormalities of the nervous system, with the exception of the deafness of the left ear. The etiology of this deafness was obscure; although it had been definitely noted only in the three years before admission, the parents recalled that the child always had some difficulty in hearing, so that it is likely that the deafness too was a developmental abnormality.

3. Cardiovascular system. The heart was grossly enlarged both clinically and by x-ray examination. A murmur and thrill were present which were variously interpreted as indicative of patent ductus arteriosus, interauricular septal defect, or a combination of both lesions. Although the exact nature of the cardiac lesion was uncertain, the presence of some form of congenital heart defect was definite.

4. Skin. Brownish pigmentation of the skin was present, but did not involve the mucous membranes. Again, the parents had noted pigmentation for only three years, but its presence before that time seemed likely.

5. Endocrine system. Gynecomastia was present.

6. Hematopoietic system. The patient showed anemia, leukopenia and neutropenia, and thrombocytopenia (pancytopenia). The cause for the pancytopenia appeared in the bone marrow, which showed hypoplasia of erythropoietic, granulocytopoietic, and thrombocytopoietic elements.

The etiology of the underdevelopment of the hematopoietic system could not be attributed to benzol, x-ray, sulfonamides, or any of the other external agents known to produce hypoplasia or aplasia of the marrow in certain instances. The fact that pallor and weakness were already present before the initial dose of sulfadiazine was given for the upper respiratory infections indicates that hypoplastic anemia was already present prior to sulfonamide medication. It is possible, however, that the sulfonamide caused an accentuation of the already existing hypoplasia, which was probably a developmental defect explicable on the same basis as the other developmental defects; i.e., chromosomal abnormalities. The blood picture was typical of idiopathic hypoplastic anemia showing a normochromic normocytic anemia, neutropenia and leukopenia, and thrombocytopenia. The presence of reticulocytosis in certain cases of this disorder, notably those that are congenital in onset, has been noted. Such a disorder would not be expected to respond to treatment with liver or iron, and actually in this patient these medications were without effect on the clinical or hematological status. Splenectomy in hypoplastic anemia is occasionally beneficial, especially in cases in which marked thrombocytopenia is present despite the occurrence of megakaryocytes in the marrow.

The occurrence of hypoplasia or aplasia of the bone marrow in association with other congenital defects designates this case as an example of Fanconi’s syndrome. In the absence of a history of any similar disorder in either parent or their families, the case must be regarded as a genetic ‘‘sport’’ due to chance aberration in one or more of the hereditary genes which have to do with development of the bone marrow, skeletal system, heart, etc.
The patient was an only child, and the absence of siblings leaves open the question whether such an occurrence would repeat itself in this family. It is of interest that abnormalities of the thumbs were mentioned in relation to 3 of the 6 reports of Fanconi's syndrome in the literature: the thumbs were absent in a cousin of the cases reported by Hjorth; one thumb was absent in Uehlinger's patient; and one thumb was deformed in van Leeuwen's case.

The rationale of splenectomy in congenital hypoplastic anemia has been discussed elsewhere. Splenectomy is of occasional benefit in this disorder, especially in cases in which a hemorrhagic diathesis due to thrombocytopenia is the chief complaint, and at the same time the megakaryocytes in the bone marrow are not completely absent. The improvement following removal of the spleen is probably due to the removal of the normal inhibitory or regulatory mechanism exerted by the spleen upon the elements produced within the bone marrow. Following splenectomy, and probably as a result of elimination of this regulatory factor, the delivery of platelets from the marrow into the peripheral blood may increase sufficiently so that the resulting platelet count, although still less than normal, may suffice to prevent the hemorrhagic diathesis. In the present case, thrombocytopenic purpura was a prominent finding and gave rise to a marked bleeding diathesis; but very few megakaryocytes were seen on marrow specimens. Splenectomy was nevertheless undertaken because the patient was going rapidly downhill and it was felt that the operation offered the only chance of improvement. The procedure was followed by a well defined reduction in the necessity for frequent transfusions, although the platelet level did not rise appreciably. The red cell and hemoglobin levels were well maintained and perhaps even favorably influenced. There are two reports of splenectomy in the Fanconi syndrome. In van Leeuwen's patient, who was a 14 year old female child, splenectomy was without effect on the symptoms or signs, but the patient lived for three years after the operation. Splenectomy was also carried out in one of Dacie and Gilpin's patients and was followed by sustained improvement, so that transfusions (which had had to be given regularly preoperatively) were no longer required after the operation. Death here also occurred three years later.

It is of interest to speculate upon the possible relationship of the mother's acute otitis media and mastoiditis, during the third month of pregnancy, to the occurrence of the congenital abnormalities in her child. Recent reports have emphasized certain congenital defects following infections early during pregnancy. The most prominent of these concern congenital cataracts in children born of a pregnancy complicated by rubella. Others report eye lesions, heart lesions, deaf mutism, microcephaly, etc., following rubella, chicken pox, mumps, etc. In virtually all reports only virus diseases have been implicated in giving rise to congenital abnormalities, and in all reports the disease affected the mother before the third month of pregnancy. In the present case, it is probable that the infection was completely unrelated to the subsequent abnormalities in the fetus.

**SUMMARY**

A sporadic example of Fanconi syndrome (congenital hypoplastic anemia in association with other congenital defects) is reported.
The significance of the simultaneous occurrence of multiple congenital defects in the pathogenesis of congenital hypoplastic anemia is discussed.

REFERENCES

CONGENITAL HYPOPLASTIC ANEMIA ASSOCIATED WITH MULTIPLE DEVELOPMENTAL DEFECTS (FANCONI SYNDROME): REPORT OF A CASE

S. ESTREN, JOHN F. SUESS and WILLIAM DAMESHEK