Congenital Leukemia

By William G. Bernhard, M.D., Ira Gore, M.D. and Ralph A. Kilby, M.D.

Congenital leukemia is an exceedingly uncommon disease, yet there is a number of well authenticated cases in the literature indicating that the factor or factors which produce the leukemic state may operate in utero. Present day pathologists are keenly aware of the extraordinary lability of the infant's hematopoietic system. As a consequence, but somewhat paradoxically, fewer cases of this disorder are now recognized than in the past. Many of the older reports are now more accurately classified as erythroblastosis fetalis, congenital syphilis, or sepsis. Table 1 lists the 14 cases in the literature that presented acceptable documentation as to the presence of a leukemic state at birth. To these we have added 4 cases from the files of the Armed Forces Institute of Pathology (table 2). In addition to autopsy examination and microscopic study of the tissues, adequate hematologic studies had been conducted during life in each of these cases.

To fulfill the criteria of congenital leukemia, there must be manifest at birth or shortly thereafter, symptoms or signs which can be correlated with the characteristic hematologic disturbance. The recognition of the nature of the latter, however, may be delayed as in Case 4 (AFIP 234151). Significant physical manifestations are: spontaneous hemorrhages of skin and mucous membrane, nodular skin infiltrations, enlargement of spleen and liver, adenopathy, fever and pallor. The blood should reflect an alteration of the marrow by showing an undue proportion of poorly differentiated or undifferentiated cells usually of the granulocytic series; ideally there should be confirmatory bone marrow studies. In most cases considerable elevation of the white blood cell count and reduced numbers of red cells and platelets are also observed. Nucleated red cells may be present in varying number. Since changes easily confused pathologically with leukemia occur in congenital syphilis and erythroblastosis fetalis, reports of serologic studies on the mother should be available and information regarding the possibility of blood group or type incompatibility between mother and infant should be obtained.

Case Reports

Case 1, AFIP Accession 280588.* A white, full term male infant, who lived for only 19 hours, had been delivered without incident on August 18, 1948, at 2:11 P.M. The mother, aged 37, para 3, gravida 4, had been under observation for the last five and a half months of her pregnancy and had experienced an uncomplicated gestation. Serologic tests for syphilis had been negative; the blood group was O type, Rh positive. The child arrived from the delivery room in a depressed state nineteen minutes after birth. He was lethargic and cyanotic; his skin was mottled; his facies mongoloid, his liver palpable 5 cm. below the costal margin, and there were diffuse pulmonary rhonchi. Despite stimulants and artificial

*Case 1 (Acc. 280588) studied through the courtesy of Dr. Paul Russomanno, Newark, N. J.
respiration no improvement was noted; the temperature rose and the infant died less than twenty-four hours after birth.

The red blood cell count several hours before death was 4,200,000 and the hemoglobin 15.3 Gm. or 93 per cent. Color index was 1.1, and the red blood cells showed anisocytosis, poikilocytosis, macrocytosis and hyperchromia. White blood cell counts ranged between 240,500 and 181,000, uncorrected for nucleated red blood cells. The corrected white blood cell counts were 181,000 and 90,700, with 65,000 and 63,000 nucleated red blood cells. In differential counts myeloblasts made up from 19 to 25 per cent; progranulocytes 4 to 8 per cent; myelocytes, 12 to 16 per cent; metamyelocytes, 14 to 22 per cent; and segmented forms, 15 to 24 per cent. There were numerous mature and immature eosinophilic forms. The infant's red blood cells contained the Rh factor, Rh\(a\) type.

Autopsy. A full term, newborn male, 52 cm. in length, weighing 3200 Gm., presented mottled cyanosis of an otherwise unmarred skin surface. There was moderate caput succedaneum; the skull was brachycephalic; the facial features were typically mongoloid. Hypertrophy of the left buccal area and partial agenesis and deformity of the left ear were noted. The abdomen was protuberant. In the slightly enlarged heart (25 Gm.) the interatrial septum was virtually absent. The spleen and liver were considerably enlarged, weighing 35 and 210 Gm., respectively. The skull exhibited premature closure of the fontanelles; the ligaments of the major joints were unusually lax, and there was shortening of both humeri. Other findings including a patent ductus arteriosus were considered within normal limits.

Microscopic examination. The liver, spleen, lungs and pancreas were extensively infiltrated with immature cells of the granulocytic series. Many of the cells contained eosinophilic granules, and a moderate number of megakaryocytes were present in the liver and spleen. The most striking changes had occurred in the liver where the intense leukemic infiltration seemed almost to have obliterated the normal histologic components. The bone marrow was hyperplastic and its cytologic pattern unduly homogeneous. Large numbers of poorly differentiated and undifferentiated cells of the granulocytic series formed the major portion of the hematopoietic tissue. Erythropoiesis was reduced to a few inconspicuous foci; megakaryocytes were sparse.

Case 2, AFIP Accession 205756.* A white female infant, who died at the age of 3 weeks with acute granulocytic leukemia, presented bilateral talipes varus, congenital shortening of the neck (Klippel-Feil syndrome), and idiopathic enlargement of the heart. The mother was 25 years of age, and pregnancy, which was of normal duration, was noteworthy only for hydramnios during the terminal two months. Serologic studies of the maternal blood were negative; the mother's blood cells contained the Rh factor. Delivery was normal. The infant weighed 4,196 Gm. at birth, January 14, 1948; the abnormalities already mentioned were apparent on physical examination. The abdomen was protuberant with a large round mass in the left upper quadrant. Difficulty in breathing was attributed to aspirated mucus and atelectasis of the left lung.

Roentgenologic examination confirmed the atelectasis and demonstrated an enlarged heart shadow. Blood counts were as follows: January 17, 1948: hemoglobin 104 per cent, erythrocytes 5,900,000, total leukocytes 32,700 segmented forms 35 per cent, bands 4 per cent, immature granulocytic forms 3 per cent, lymphocytes 57 per cent, basophils 1 per cent. February 1, 1948: hemoglobin 95 per cent, erythrocytes, 5,200,000, total leukocytes 10,300, segmented forms 21 per cent, bands 29 per cent, immature granulocytic forms 30 per cent, lymphocytes 20 per cent.

The infant steadily lost weight and a persistent pulmonary infection developed. Nasal bleeding, which had been noted at birth, still occurred on crying and exertion two weeks later and was associated with a purulent nasal infection. Death occurred at three weeks.

Autopsy. A female infant, 52 cm. in length, weighed 4025 Gm. The neck was so abnormally short as to be virtually absent; a large mass filled the left side of a distended and tympanitic abdomen, and there was bilateral talipes varus. Numerous enlarged but discrete nodes were observed in the cervical, mediastinal, peribronchial, and mesenteric and retroperitoneal

* Case 2 (Acc. 205756) contributed by Dr. H. H. Leffler, Providence Hospital, Washington, D. C.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age at death</th>
<th>Clinical Picture</th>
<th>Blood Picture</th>
<th>Necropsy</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>M</td>
<td>2 months</td>
<td>Three weeks: feeding difficulty. Six weeks: enlarged axillary nodes and spleen, purpura. Termal fever. No family history of tuberculosis or syphils.</td>
<td>Six weeks: WBC 189,000, Lymphocytes 97% with excessive granulation.</td>
<td>None</td>
<td>Probable lymphoeytic</td>
</tr>
<tr>
<td>Koch (Case 2)</td>
<td>?</td>
<td>Newborn</td>
<td>Wassermann for mother negative; siblings healthy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stransky</td>
<td>M</td>
<td>3 weeks</td>
<td>At birth: leukemia skin infiltration. Three weeks: lymphadenopathy, hepatosplenomegaly. Wassermann negative.</td>
<td>Hgb. 85% RBC 4,000,000 WBC 181,000 Myeloblasts 86% WBC 421,000 at death.</td>
<td>?</td>
<td>Granulocytic</td>
</tr>
<tr>
<td>Bungeler</td>
<td>M</td>
<td>Stillborn</td>
<td>Premature (7 months) Parental and child's Wassermann negative, two healthy siblings. Hepatosplenomegaly.</td>
<td>Myeloblasts and myelocytes 80%</td>
<td></td>
<td>Granulocytic</td>
</tr>
<tr>
<td>White &amp; Burns</td>
<td>M</td>
<td>3 weeks</td>
<td>Four days: purpura, spleen and liver slightly enlarged, huge kidneys, melena, no lymphadenopathy. Family history negative for syphils or other diseases.</td>
<td>Hgb. 35% RBC 2,000,000 WBC 115,000 Lymphoblasts 99% Platelets 60,000</td>
<td></td>
<td>Limitted to kidneys: 1\times normal size, infiltrated with cells indistin- guishable from small lymphocytes, few myelocytes, many large lymphoblasts.</td>
</tr>
<tr>
<td>Name</td>
<td>Sex</td>
<td>Age</td>
<td>Symptoms</td>
<td>Initial Blood Values</td>
<td>Conclusion</td>
<td></td>
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<td>--------------------------------------------------------------------------</td>
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<tr>
<td>Giblin</td>
<td>M</td>
<td>7½    weeks</td>
<td>Feeding difficulty. Two weeks: splenomegaly. Six weeks: spleen larger, cervical &amp; axillary adenopathy. Wassermann negative in parents and baby.</td>
<td>Hgb 42% RBC 2,500,000 WBC 97,400 Myeloblasts 24% Myelocytes 15% Platelets 16,000</td>
<td>Acute granulocytic leukemia diagnosed from blood smear.</td>
<td></td>
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<tr>
<td>Kornmann</td>
<td>F</td>
<td>6     weeks</td>
<td>Icterus neonatorum, petechiae, lymphadenopathy, hepatosplenomegaly, no tuberculosis or syphilis.</td>
<td>Hgb 30% RBC 1,560,000 WBC 38600 Atypical immature cells 49% Myeloblasts ?</td>
<td>Lymphadenopathy; petechiae, serosal surfaces; hepatosplenomegaly. All organs infiltrated with myeloblasts.</td>
<td></td>
</tr>
<tr>
<td>Kelsey &amp; Anderson</td>
<td>M</td>
<td>30    days</td>
<td>Seven days: severe purpura, temperature 103.2 F., ecchymoses, hepatosplenomegaly, lymphadenopathy, tendency to bleed. Wassermann test of parents, negative.</td>
<td>Hgb 6.5 RBC 2,000,000 WBC 223,500 Myeloblasts 22% Myelocytes 68%</td>
<td>All organs infiltrated. Granulocytic Marked hepatosplenomegaly.</td>
<td></td>
</tr>
<tr>
<td>Morrison, Sanwick &amp; Rubenstein</td>
<td>F</td>
<td>10    days</td>
<td>Kline test negative. Skin tumors &amp; ecchymoses, hepatosplenomegaly. Progressive ecchymosis and vaginal bleeding. Terminal, high fever. No bone changes by x-ray.</td>
<td>Hgb. 100% WBC 300,000</td>
<td>Lymphadenopathy, hepatosplenomegaly, generalized leukemic infiltration, nodules of skin.</td>
<td></td>
</tr>
<tr>
<td>Poncher, Weir &amp; Limarzi</td>
<td>M</td>
<td>6     weeks</td>
<td>Intestinal disturbance from birth. Six weeks: spleen enlarged to nav. No familial syphilis. No bone changes by x-ray.</td>
<td>Hgb 12.5 RBC 3,850,000 WBC 275,000</td>
<td>Generalized lymphadenopathy, hepatosplenomegaly, leukemic infiltration of all organs.</td>
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</table>
Table 1.—Continued

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<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age at death</th>
<th>Clinical Picture</th>
<th>Blood Picture</th>
<th>Necropsy</th>
<th>Type</th>
</tr>
</thead>
</table>
| Cross\(^3\) (Case 1) | M   | 3½ months   | Five days: bleeding from bowel. Three months: petechiae over body, hepatosplenomegaly.  
No significant family history. | Hgb. 55\(^\circ\)  
RBC 2,250,000  
WBC 112,000  
Myelocytes & myeloblasts predominate. | Leukemic infiltration,  
liver, lymph nodes,  
kidney & spleen. Patient interventricular septum. | Granulocytic                 |
| Cross\(^3\) (Case 2) | F   | 6 weeks     | Melena & purpura at birth. 1 month: crusted lesions, groin & axilla,  
hepatosplenomegaly and purpura progressive until death. Inguinal adenopathy.  
Family history negative. | Hgb. 5.9  
RBC 2,270,000  
WBC 72,500  
Metamyelocytes 6\(^\circ\) | Leukemic infiltration of  
spleen, bone marrow,  
nodes. | Granulocytic                 |
| Hamme\(^4\) | F   | 20 days     | At birth: purpura, rectal, oral, ocular hemorrhage, proptosis.  
Twentieth day: lymphadenopathy, hepatosplenomegaly. Family  
history negative. Mother had slight shift in granulocytic series. | Many blast forms.                  | Lymphadenopathy, generalized. Hepatosplenomegaly. Cerebral bleeding. Infiltration of all organs, including spinal cord. | Granulocytic                 |
| Keith\(^5\) | F   | 15 months   | Purpura noted at 3 weeks.  
Rectal bleeding at 3 months. Lymphadenopathy. Hepatosplenomegaly. Terminal  
hyperpyrexia. No reports of serologic tests. | At 3 months:  
Hgb. 8.4  
RBC 2,900,000  
WBC 29,900  
Myelocytes 3\(^\circ\)  
At 14 months:  
WBC 118,000  
Progranulocytes 10\(^\circ\)  
Metamyelocytes 8\(^\circ\)  
Myelocytes 9.5 | Multiple petechiae, hepatosplenomegaly, lymphadenopathy, leukemic infiltration of skin,  
heart, lungs, all viscera, and brain. | Granulocytic                 |
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical Picture</th>
<th>Blood Picture</th>
<th>Necropsy</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) AFIP Acc. 28068</td>
<td>M</td>
<td>Newborn</td>
<td>Lethargic, skin mottled blue, liver enlarged, mongoloid facies, spleen not palpable. Mother: serologic tests negative. Type O, Rh positive.</td>
<td>RBC 4.2 to 4.3, WBC 246,000 to 153,000, RBC (nucleated) 65,000, Myeloblasts 19%, Progranulocytes 4%, Myelocytes 12%, Metamyelocytes 22%, Segmented forms 15%.</td>
<td>Bone marrow hyperplastic, splenohepatomegaly. Leukemic infiltration, pancreas, lung, liver, spleen. Large auricular septal defect.</td>
<td>Granulocytic</td>
</tr>
<tr>
<td>(2) AFIP Acc. 205756</td>
<td>F</td>
<td>3 weeks</td>
<td>Cyanosis, hemorrhage of conjunctiva; heart enlarged to percussion with loud murmurs. Liver and spleen enlarged. Mother: Rh pos. Kahn and Wassermann neg.</td>
<td>Hgb. 95-104, RBC 5,200,000, WBC 10,300 to 32,700, Polys. 21-35, Bands 4-29, Immature granulocytic forms 3-30, Lymphs. 20-57, RBC 4,200,000, WBC 198,000, Blasts 15, Progranulocytes 16, Myelocytes 5, Metamyelocytes 4, Lymphocytes 38, Erythroblasts 4, Normoblasts 5, Segmented forms 40</td>
<td>Talipes varus, short neck, cardiac hypertrophy. Liver, spleen, heart and nodes infiltrated by immature granulocytic forms.</td>
<td>Granulocytic</td>
</tr>
<tr>
<td>(3) AFIP Acc. 189595</td>
<td>M</td>
<td>4 days</td>
<td>Bluish lumps in skin. Vomited blood; stools bloody. Hepatosplenomegaly. Serologic tests negative. Mother and infant Rh positive.</td>
<td>RBC 4,200,000, WBC 198,000, Blasts 15, Progranulocytes 16, Myelocytes 5, Metamyelocytes 4, Lymphocytes 38, Erythroblasts 4, Normoblasts 5, Segmented forms 40</td>
<td>Hepatosplenomegaly, subarachnoid hemorrhage. Nodular leukemic infiltrate of skin, intestine, liver, spleen and pancreas.</td>
<td>Granulocytic</td>
</tr>
<tr>
<td>(4) AFIP Acc. 234151</td>
<td>M</td>
<td>2 mos.</td>
<td>At birth: petechiae of skin and mucous membrane, spleen enlarged, bleeding mouth and intestine. At 42 days, more bleeding, petechiae, liver and spleen enlarged. Maternal serologic tests negative. (Rh negative?)</td>
<td>RBC 7.8 to 14 Gm, WBC 5.6 to 5.3 M, WBC 5,600 to 21,800, Polys. 21-55, Lymphs. 51-74, Monos. 1-3, Eosin. 6-14, Platelets 16,000 to 18,000.</td>
<td>Hemorrhagic diathesis skin, intestine, serous and mucous surfaces. Dextrocardia, radii absent. Marrow replaced by immature cells of granulocytic series. Leukemic infiltration in liver, spleen and nodes.</td>
<td>Granulocytic</td>
</tr>
</tbody>
</table>
regions. The thymus was visibly enlarged by hemorrhage. There was considerable enlargement of the liver, spleen (15 x 7 x 4 cm. and 10 x 4 x 2 cm., respectively; weights not given) and heart. Cardiac enlargement was entirely muscular; there were no anomalies, patencies of both the foramen ovale and the ductus arteriosus being considered within the limits of normal for a 3 week old infant.

*Microscopic examination.* The bone marrow was strikingly hyperplastic and its cytologic character was uniform, consisting of poorly differentiated and primitive cells of the granulocytic series. Erythropoiesis was considerably reduced and megakaryocytes were very few. Extensive infiltrates of leukemic cells in the heart, lymph nodes, liver and spleen accounted for enlargement of these organs. Less extensive deposits of similar cells were observed in the other viscera.

*Case 3, AFIP Accession 189595.* A white male infant born February 19, 1947, after a full term uncomplicated pregnancy, weighed 4,082 Gm. at birth. A number of cutaneous lumps of various sizes were noted at once. Serologic examination of the maternal blood was negative. The mother’s blood cells contained the Rh factor, as did the infant’s blood when tested subsequently. Twenty-four hours after birth the infant vomited after feeding and it was noted that the vomitus contained appreciable quantities of blood. Total leukocyte count at this time was reported to be 280,000.

Upon examination on the second day of life the infant did not appear to be acutely ill. Hard masses, varying from 1 to 2 cm. in diameter, attached to skin but not to underlying tissue, were palpable in the subcutaneous tissue. The overlying skin varied from reddish to purplish in color, the largest masses having a central area of purplish violet color surrounded by a thin ring of blue. There were many other discolored areas on the skin, approximately 1 mm. in diameter, which were deep blue with no underlying mass. Examination of head and neck, thorax and lungs was negative. The heart was not enlarged to percussion and no murmurs were heard, although the heart sounds at the apex were of a peculiar rough character; the rate was 120 per minute and the rhythm regular. The liver, which was palpable 7 cm. below the costal margin and extended across the midline to the left midepavicular line, filled

![Fig. 1.—Case 1. AFIP Neg. 280588-1, 2. Low (205 X) and high (435 X) magnifications of the liver. So intensive is the leukemic infiltrate that it is difficult to identify the organ histologically. A fair degree of granulocytic differentiation is to be observed in the higher magnification.](image-url)
a large part of the abdomen. The spleen was enlarged, being palpable 4 cm. below the costal
margin. The cord was approximately 4 cm. long and was dry and not oozing. No lymph
node enlargement or further physical abnormalities were noted.

The infant was placed on a formula of amigen and glucose (5 per cent) in 1/1 ratio. Most
of the feedings were vomited promptly; the vomitus, at first “coffee ground” in appearance,
later became streaked with bright red blood. The infant was given a subcutaneous infusion
of 1.6 molar sodium lactate and glucose (2.5 per cent) in a physiologic solution of sodium
chloride. The stools regularly contained bright red blood and tarry material. On the after-
noon of February 21, the infant’s respirations became more rapid and labored and he was
placed in an oxygen tent. At 7:30 P.M., February 23, respirations were so slight as not to be
noticeable, and a short time later the pulse became imperceptible. The infant was pro-
nounced dead seven days after birth.

Erythrocytes numbered 4,200,000; leukocytes 108,000, with blasts 15 per cent, progranulo-
cytes 16 per cent, myelocytes 5 per cent, metamyelocytes 2 per cent, bands 2 per cent, fila-
ments 4 per cent, lymphocytes 8 per cent, smudges 38 per cent, erythroblasts 3 per cent,
normoblasts 5 per cent and unidentified forms 1 per cent. Bleeding time was fifteen minutes
and prothrombin time was five minutes. One of the large skin nodules was removed and
bone marrow puncture was performed to obtain material for pathologic examination.
Roentgenograms of skull and long bones were negative.

Autopsy. A well developed, newborn white male of 7 days, weighed 3800 Gm. and mea-
sured 51.5 cm. in length. Numerous superficial firm nodular elevations of the skin, varying
in size from 1 cm. to 4.5 cm., and in color from gray to purple and hemorrhagic, were noted
over the entire body surface. Axillary and inguinal nodes were enlarged.

Liver and spleen were greatly enlarged, weighing 300 and 37.5 Gm., respectively. The
heart, which weighed 27.7 Gm., presented several gray-yellow, poorly circumscribed,
nodular elevations of the epicardium. Similar discrete lesions were present in the small
intestine and bladder, and involvement of the first portion of the ascending colon was
diffuse. Hemorrhages were present in the intestinal mucosa, the renal pelves and the lepto-
meninges over the left cerebrum. Except for discrete enlargement of the lymph nodes and
patchy consolidation of the lungs, there were no other positive findings. With the exception
of bronchopneumonia, all gross changes could be related to a leukemic process.

Fig. 2.—Case 2. A.F.I.P. Neg. 205756-1, 7. Low (205x) and high (435x) magnifications
of the bone marrow illustrating the homogeneous and undifferentiated cellular growth.
CONGENITAL LEUKEMIA

Microscopic examination. The bone marrow was occupied by a uniform growth of primitive and poorly differentiated cells of the granulocytic series. Erythropoiesis was considerably reduced and megakaryocytes were few. Liver sections were scarcely recognizable, so intense was the leukemic cellular infiltration. The spleen and lymph nodes were diffusely involved and the nodular lesions of skin, heart, intestine and bladder proved to be cellular masses identical in character with the bone marrow. Less intensive deposits were present in all tissues.

An incidental finding was a small (microscopic) adrenal rest in the epididymis.

Case 4, AFIP Accession 234151. A white male infant, who weighed 3005 Gm. at birth, presented dextrocardia and bilaterally absent radii, as well as evidence of hematologic disturbance. Petechiae of the skin, the mucous membrane, and the conjunctivae were observed on the first day of life. The spleen was palpably enlarged. Evidence of gastrointestinal bleeding was found in both the stool and vomitus, but the episode of bleeding was apparently transitory. On the tenth day circumcision was accomplished without difficulty. Blood count was reported as normal and the infant was released from the hospital on the seventeenth day.

On the forty-second day of life the child, who exhibited only a slight gain in weight, was admitted to the hospital because of considerable bleeding from the rectum for the preceding three days. There was marked pallor; petechiae were observed on the palate, and the child appeared moribund. The liver was enlarged but the spleen was not palpable. Blood count was: erythrocytes 1,500,000; total leukocytes 12,000 to 17,000; platelets 80,000. Bleeding and clotting times were reported normal. Rectal bleeding continued after two transfusions. On the sixty-eighth day of life the child was transferred to another hospital, where extensive skin petechiae and ecchymoses were noted. Spleen and liver were found to be enlarged and intestinal bleeding continued. Despite multiple transfusions, the infant died.

<table>
<thead>
<tr>
<th>Date</th>
<th>RBC (Millions)</th>
<th>Hgb</th>
<th>WBC</th>
<th>P</th>
<th>L</th>
<th>M</th>
<th>E</th>
<th>B</th>
<th>Clotting Time</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/12/48</td>
<td>2.47</td>
<td>50%</td>
<td>13,500</td>
<td>42</td>
<td>51</td>
<td>1</td>
<td>6</td>
<td>2’30”</td>
<td>4’10”</td>
<td>None seen</td>
</tr>
<tr>
<td>4/13/48</td>
<td>3.75</td>
<td>78%</td>
<td>9,800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4’15”</td>
<td>3’40”</td>
<td>None seen</td>
</tr>
<tr>
<td>4/14/48</td>
<td>3.6</td>
<td>68%</td>
<td>21,800</td>
<td>35</td>
<td>64</td>
<td>1</td>
<td></td>
<td>6’30”</td>
<td>5’35”</td>
<td>None seen</td>
</tr>
<tr>
<td>4/15/48</td>
<td>3.6</td>
<td>50%</td>
<td>5,600</td>
<td>30</td>
<td>55</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/16/48</td>
<td>5.36</td>
<td>95%</td>
<td>18,750</td>
<td>21</td>
<td>74</td>
<td>3</td>
<td>1</td>
<td>2’55”</td>
<td>3’40”</td>
<td>16,000</td>
</tr>
<tr>
<td>4/22/48</td>
<td>5.36</td>
<td>95%</td>
<td>14.8 Gm.</td>
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Tests of the maternal blood for syphilis during pregnancy had been negative. The Rh factor had not been ascertained in either the mother or the infant.

Autopsy. Dextrocardia and bilateral absence of the radii had already been noted on physical examination. Petechiae and ecchymotic hemorrhages were found in the skin, intestinal tract and other serous and mucous surfaces. Body weight was 3500 Gm.; that of the liver, 150 Gm.; of the spleen, 13 Gm. The lymph nodes of the cervical and mediastinal regions were large and prominent.

Microscopic examination. There was considerable though uniform hyperplasia of the marrow. Nearly all of the cells were of the granulocytic series and many were poorly differentiated. There was a fairly rich component of eosinophilic myelocytes; erythropoiesis was considerably reduced, and megakaryocytes were exceedingly scarce. Granulocytic metaplasia was conspicuous in the spleen and in the lymph nodes, and apparent in the liver. The viscera showed small intravascular foci of erythropoiesis.
Discussion

It seems more than a coincidence that 3 of our 4 cases of congenital leukemia presented multiple developmental anomalies. Farber has observed examples of congenital leukemia associated with mongolism, and there is, therefore, a basis for speculating that the factors responsible for the latter may also have been influential in causing the blood dyscrasia. According to Ingalls, the crucial developmental period for the production of mongolism is the sixth to the ninth week of fetal life. It is his opinion that occasionally during this period, and less frequently than other structures, the bone marrow sustains an injury which culminates in leukemia. Although there was only 1 case (Case 1) of mongolism, it is interesting that all of the other anomalies noted entailed damage at approximately the same period of embryonic development (table 3). Of the 14 cases of congenital leukemia recorded in the literature only one presented an associated anomaly, but the cursory reports of the postmortem examinations in 11 instances led to the suspicion that a malformation might have gone unrecorded. At any rate such obvious growth disturbances lead to speculation regarding the presence of the leukemic process or some more fundamental disorder during the morphogenesis of the various structures. From the account of Clatworthy and Anderson, it appears that the disturbance must have occurred early in fetal life, between the fifth and fourteenth weeks. Tabulated above are some of the observed anomalies correlated with the period of fetal life during which they were presumably initiated.

Since quantitatively significant granulocytopoiesis does not appear until the fourth month of intrauterine life (Wintrobe), it does not seem likely that leukemia could exist before that time. However, the relative abundance of recognizable differentiation in the leukemic cells found in the tissues at autopsy indicates that the process must certainly have been present during an appreciable portion of fetal life. Histologically, at least in this respect, the granulocytic leukemic process in most of these cases of the congenital variety resembles the chronic counterpart in the adult. The acute clinical course is a measure only of the observable part of the disease. Since Farber found that 98 per cent of the leukemias of children under ten years of age were of the acute variety (196 of 200), it would appear fruitful to compare the process in newborns having congenital anomalies with that in normally formed infants. The reports in the literature are inadequate for such a study and the 4 cases in this study are too few to permit conclusions.

Most cases seem to have offered little diagnostic difficulty. The prevalent use

<table>
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<th>Anomaly</th>
<th>Critical Period</th>
<th>Case</th>
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<tr>
<td>Mongolism</td>
<td>6th-9th week</td>
<td>Case 1</td>
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<tr>
<td>Interatrial Septal Defect</td>
<td>5th-7th week</td>
<td>Case 1</td>
</tr>
<tr>
<td>Agenesis of Ear</td>
<td>10th-14th week</td>
<td>Case 1</td>
</tr>
<tr>
<td>Klippel-Feil Syndrome</td>
<td>9th week</td>
<td>Case 2</td>
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<td>Dextrocardia</td>
<td>5th week</td>
<td>Case 4</td>
</tr>
<tr>
<td>Absence of Radii</td>
<td>6th-8th week</td>
<td>Case 4</td>
</tr>
<tr>
<td>Patent Interventricular Septum</td>
<td>5th-7th week</td>
<td>Cross (Case 1)</td>
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of serologic tests for syphilis and the current alertness to the factors producing erythroblastosis have minimized the problem that confronted earlier pathologists. In these conditions and also in sepsis a considerable amount of extra-medullary hematopoiesis is to be observed. When there is appreciable associated proliferation of reticulo-endothelial cells, distinction from leukemia may not be easy. In general, however, the process in the former conforms to the normal architecture of such structures as liver, spleen and lymph nodes, and though this may also be true in leukemia, actual tumorlike aggregates and colonies may, and often do, completely efface normal histologic structures. In Case 4 (AFIP Accession 234151) a diagnosis of congenital thrombocytopenic purpura was entertained during life but could not be substantiated by postmortem observations. Hematopoiesis was virtually all of poorly differentiated granulocytic character. Erythropoiesis was considerably reduced and megakaryocytes were almost absent, contrary to what would be expected in thrombocytopenic purpura.

It is of academic interest that all but 2 of the reported cases of congenital leukemia were of the granulocytic variety. That of White and Burns is questionable and although incompletely studied possibly represents lymphocytic leukemia. Later in childhood, classification of the usually acute leukemia is handicapped by the virtual absence of cellular differentiation. Zuelzer, for that matter, questions the validity of attempts to distinguish the cell type in the acute disease. Nevertheless, it would seem appropriate to entertain some reservations regarding the frequently stated generalization that the majority of leukemias in infants and children are lymphocytic.

Maternal influences which might have contributed to the onset of the leukemic process were not apparent in this material. None of the mothers were leukemic, and since there are many reported cases of normal children born to frankly leukemic women, the presence of a blood dyscrasia in the mother does not appear to be of etiologic significance.

SUMMARY

Four new cases of congenital leukemia reported here may be added to the 14 acceptable cases in the literature. In all except 1 of these cases cells of the granulocytic series were involved; males predominated over females in a ratio of more than 2 to 1. Congenital anomalies were present in 3 of the 4 cases we have reported, indicating a growth disturbance early in fetal life. Contrary to the usual finding in childhood leukemia, cells of the granulocytic series in the 4 cases reported here exhibited a fair degree of differentiation and in this respect are similar to those which characterize the chronic form of the disease. It seems likely, therefore, that the leukemia existed during a significant portion of intrauterine life.

REFERENCES

4 Farber, S.: Personal communication.
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8 —: Personal communication.
Congenital Leukemia

WILLIAM G. BERNHARD, IRA GORE and RALPH A. KILBY