Erythroleukemia, with Special Emphasis on the Acute or Incomplete Variety

Report of Five Cases

By William J. Martin, M.D. and Edwin D. Bayrd, M.D.

OCCASIONALLY in myeloid leukemia, there is an increase rather than a decrease in the erythrocytes. This change may occur in an early stage, and at a time when immature white cells are not present in the blood; it may occur simultaneously with a leukemic blood picture; or it may occur after the leukemic blood picture has been established.1 This concurrence of entities ordinarily considered distinct has been referred to as erythroleukemia.2 Synonyms are “panmyelosis,” “subleukemic erythremia,” “polycyteme myelogene,”3,4 and “hyperplastic panmyelopathy.”3,4 Such cases may be links in a chain characterized by excessive hemopoietic activity of the bone marrow, which may express itself clinically as a polycytemic state at one end or as granulocytic leukemia at the other end, according to whether erythropoietic or leukopoietic activity prevails.3,4

It is impossible to determine accurately the number of cases of erythroleukemia previously described in the literature, not solely because of their rarity, but because of nosologic differences.5-28 Twenty-four authors, however, have reported cases that seemed to us to exemplify the syndrome; most of the cases were cases of chronic or complete erythroleukemia.

Report of Cases

Case 1

A man, 60 years old, was admitted to the Mayo Clinic June 3, 1946, with stomach trouble of two years’ duration. The patient’s father and maternal grandfather had died of cancer of the stomach. Roentgenograms of the patient’s stomach demonstrated an ulcerating lesion on the greater curvature. Partial gastrectomy and duodenectomy were carried out on June 8, 1946. The pathologist reported reticulum cell sarcoma, grade 4 and type B (Broders’ and Dukes’ classifications). The patient subsequently received two courses of roentgen therapy. Routine examination of the patient’s blood revealed no abnormality.

The patient was seen again at the clinic in November 1946, and April 1948. Roentgenographic examination of the stomach revealed no evidence of recurrence, and routine studies of the blood revealed no abnormality. The patient remained well and active until October 1949, when progressive pallor, orthostatic edema, and exertional dyspnea developed and prompted his return to the clinic December 5, 1949.

At that time the patient was pale and orthopneic and appeared seriously ill. There was pitting edema, grade 3, of the lower extremities, genitalia, and lower half of the thorax. The border of the liver extended approximately 6 cm. below the right costal margin and was tender.

On admission, erythrocytes numbered 1,950,000 and leukocytes totaled 5600 per cu.mm.
### Table 1.—Peripheral Blood Findings Throughout Course of Disease in Cases 1 and 2

<table>
<thead>
<tr>
<th>Date</th>
<th>Case 1 *</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-46</td>
<td>4-10-47</td>
</tr>
<tr>
<td>Hemoglobin (Gm. per 100 cc.)</td>
<td>11-14.2</td>
<td>12.1-12.8</td>
</tr>
<tr>
<td>Erythrocytes (millions†)</td>
<td>4.75-4.82</td>
<td>5000-12,200</td>
</tr>
<tr>
<td>Leukocytes†</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Stem cells (%)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Progranulocytes (%)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Myelocytes (%)</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Metamyelocytes (%)</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Polymorphonuclear neutrophils (%)</td>
<td>(40% R. shift)</td>
<td>(40% R. shift)</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>52</td>
<td>32.5</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>6.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Erythrocytes, nucleated‡</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Megaloblastoid‡</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Platelets (thousands)</td>
<td>46</td>
<td>27</td>
</tr>
</tbody>
</table>

* Additional data in case 1: 4-28-48: hemoglobin 13.3 Gm.; leukocytes 3,700-5,100.
† Per cu mm. of blood.
‡ Per cent of erythrocytes.
of blood. Roentgenographic examination of the thorax showed diffuse cardiac enlargement. Roentgenographic examinations of the stomach and lumbar vertebrae gave negative results. Liver function, as indicated by the bromsulfalein test, the values for blood urea and serum proteins, the albumin-globulin ratio, urine, and electrocardiographic findings, was normal.

Treatment included a blood transfusion, digitalization, a diet containing 6.5 Gm. of sodium chloride per day and somewhat later a course of nitrogen mustard. The patient was allowed to leave the hospital December 22, 1949, but returned for re-examination on January 9, 1950, at which time pallor had decreased and orthopnea had disappeared. There was no demonstrable edema of the lower extremities. The border of the liver was barely palpable and was not tender. Two blood transfusions of 500 cc. each were administered, and the patient was dismissed.

The patient died February 28, 1950 at home. Tissues removed at necropsy were reviewed in the Section of Pathologic Anatomy at the clinic. They showed a peculiar neoplasm composed of malignant reticulum cells and immature cells of erythroblastic and myeloblastic series, with leukemic manifestations. The marrow, hilar nodes, adrenal glands, kidney, and liver were involved. Sections of stomach previously removed were reviewed and considered to show the same variation from reticulum cells of the erythroblastic and myeloblastic series (fig. 1). The lesion in the stomach undoubtedly was the same as that which caused death.

**Blood and marrow studies.** The findings in the peripheral blood and bone marrow in this case are summarized in tables 1 and 2. Examination of the blood smear on December 5, 1949, revealed hypochromasia, polychromasia, scattered microcytosis, occasionally a regenerative macrocyte and myeloid immaturity to the stem cell. About 10 per cent of the lymphocytes were atypical and possessed grooved nuclei. Normoblasts were present. There was basophilic stippling and thrombocytopenia.

While the peripheral blood picture was suggestive of leukemia, it was apparent from examination of the sternal marrow two days later that the main defect was in the red cell line. Erythrocyte maturation was grossly abnormal; there were giant, multinucleated, erythroid cells (6.3 to 23.4 μ in diameter; mean, 20.30 μ) which had two to six separate nuclei. Ten per cent of the cells of similar size had but one large lobulated nucleus. Thirty per cent of the cells of the red line contained mitotic figures; karyorrhexis was common and a marked left shift in the erythroid line was evident. The cytoplasm was extremely basophilic in the younger nucleated erythroid cells but became orthochromatic in many of the older cells.
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Table 2.—Findings in Sternal Marrow Throughout Course of Disease in Cases 1 to 5: Differential Count of 200 Cells (Per Cent)

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1949</td>
<td>1950</td>
<td>1951</td>
<td>1950</td>
</tr>
<tr>
<td></td>
<td>12-7</td>
<td>12-21</td>
<td>1-9</td>
<td>1-20</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>13.5</td>
</tr>
<tr>
<td>Progranulocytes</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>60.5</td>
<td>50</td>
<td>45.5</td>
<td>6</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>1</td>
<td>14</td>
<td>14</td>
<td>0.5</td>
</tr>
<tr>
<td>Polymorphonuclear neutrophils</td>
<td>9.5</td>
<td>15.5</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Eosinophils, mature</td>
<td>0.5</td>
<td>2.5</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>immature</td>
<td>3</td>
<td>3.5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Lymphocytes, mature</td>
<td>2</td>
<td>4</td>
<td>5.5</td>
<td>12.5</td>
</tr>
<tr>
<td>immature</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>Monocytes</td>
<td>9.5</td>
<td>3.5</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>1</td>
<td></td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Pronormoblasts</td>
<td>150</td>
<td>172</td>
<td>183</td>
<td>14</td>
</tr>
<tr>
<td>Normoblasts†</td>
<td>248</td>
<td>211</td>
<td>291</td>
<td>56</td>
</tr>
<tr>
<td>immature</td>
<td>31</td>
<td>56</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>orthochromatic</td>
<td>19</td>
<td>53</td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>Erythrocytes†</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>in mitosis</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>megaloblastoid</td>
<td>373</td>
<td>392</td>
<td>407</td>
<td>1</td>
</tr>
<tr>
<td>Reticulum cells</td>
<td>0.5</td>
<td>0.33</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

* 50 per cent right-shifted.
† Per 200 leukocytes.

Occasionally these cells were distinctly megaloblastoid (15 per cent). Non-nucleated erythrocytes corresponding in size to the larger orthochromatic erythroid cells were not seen, from which it was concluded that the latter did not lose their nuclei. Typical normoblasts could be traced through a series of free reticular cells. The cytoplasm of the reticular cells was deeply basophilic and frequently (20 per cent) exhibited knoblike protuberances (figs. 2 and 3). This, with the reticular nuclei, presented an appearance not unlike pathologic megakaryocytes. The reticular type of nucleus was retained for some time after differentiation into erythroid cells had begun and there seemed to be little, if any, normal erythropoiesis.

Additional blood and marrow studies showed little basic change in the picture.

Comment. The apparent subsequent evolution of this disease from a reticuloendothelial cell sarcoma of the stomach originally exhibiting a tendency to development in the red cell line is of particular interest and suggests that the process is basically a disturbance of the reticuloendothelial cell.

Case 2

A housewife, 47 years old, was first seen at the clinic on August 10, 1944, because of abdominal cramps and diarrhea of three months' duration. The medical history and family history were noncontributory. The patient stated that she passed stools two to three times a day, one to three times a week. She had lost 8 pounds (3.6 Kg.) in the preceding three months.
Fig. 2.—Case 1. Giant, multinucleated basophilic megaloblastoid cell with knobby cytoplasmic projections occupying upper left quadrant; to the left of this giant cell is a mononucleated basophilic megaloblastoid cell with knobby cytoplasmic projections, and above are three similar mononucleated basophilic megaloblastoid cells.

In the lower right quadrant near the midline is a large erythroid cell with polychromatic cytoplasm which has retained its megaloblastoid nucleus. Directly to the right of this cell are two more mononucleated basophilic megaloblastoid cells with knobby cytoplasmic projections.

In the left lower quadrant are two blast cells (Wright's stain; X 675).

Fig. 3.—Case 1. Giant basophilic megaloblastoid cell with six nuclei and knobby cytoplasmic projections (X 1050).

Physical examination revealed a mass at the angle of the jaw on the right associated with the parotid gland, an adenomatous goiter, a small fibroid uterus and cervicitis, grade 1.

The hemoglobin was 12.1 Gm. per 100 cc., the erythrocytes numbered 4,330,000 per cu. mm., and the leukocytes totaled 7600. Results of urinalysis, roentgenographic examina-
tion of the thorax, colon and terminal ileum, the basal metabolic rate, examination of the stools, and cultures for the dysentery bacilli were negative or within normal limits.

On August 16, 1944, a grade I mixed tumor of the right parotid gland was removed. The bowel complaint was considered to be functional.

Examinations in 1945, 1946, and 1947, including urinalysis, blood counts, and roentgenograms of the chest, showed nothing of further significance.

The patient returned January 16, 1951. Complaints included shortness of breath of three weeks' duration, vomiting, epigastric distress, and loss of 33 pounds (15.0 Kg.) in the preceding four months. The epigastric distress which consisted of cramping and bloating, was present all day long and was not related to meals. She vomited one to four times daily. The menses had become more profuse and were painful; clots were passed.

On examination the patient was extremely pale and tottering with weakness. The goiter was unchanged. The systolic blood pressure was 140 mm. Hg and the diastolic 70 mm. The pulse rate was 130 per minute, and the respiratory rate 27 per minute. There was a soft precordial systolic murmur; the apical thrust was strong and vigorous. The liver was palpated 2 cm. below the right costal margin. There were numerous ecchymoses over the lower extremities. The patient was hospitalized.

On admission erythrocytes numbered 1,960,000 and leukocytes 7800. The urine, serum bilirubin, blood urea, roentgenograms of the chest and stomach, cholecystography, tests for occult blood in the stools, and cultures for the dysentery bacilli were negative or normal. The sedimentation rate was 55 mm. in 1 hour (Westergren method). Smears of peripheral blood and marrow were consistent with acute erythroleukemia.

Treatment with aminopterin in doses of 0.5 mg. twice daily was begun on January 24, 1951; the dosage was reduced to 0.5 mg. daily on February 4, 1951. During this interval the patient also received five transfusions of 500 cc. each of whole blood.

On February 6, 1951, ulcers were noted on the inner aspect of the left cheek and lower lip. On February 8, 1951, administration of aminopterin was stopped and treatment with 25 mg. of corticotropic (ACTH) four times daily was begun. This treatment was stopped on February 21, 1951, and 40 mg. of folic acid daily was prescribed, largely because of the megaloblastoid tendency of the erythroid line.

The patient was dismissed unimproved on February 24, 1951. Death occurred April 20, 1951 at home. Necropsy was not performed.

Blood and marrow studies. Examination of the peripheral blood smear obtained January 17, 1951 (table 1) revealed severe anemia with hypochromasia, microcytosis, scattered polychromatophilic macrocytes (10 per cent), normoblasts, and basophilic stippling. Myeloid immaturity to the stem cell was present. Twenty per cent of the normoblasts were megaloblastoid. The blood picture was suggestive of acute leukemia.

A marrow specimen obtained January 20, 1951 demonstrated marked normoblastic and megaloblastoid (40 per cent) erythropoiesis, as well as hyperactive myelopoiesis (table 2). As the study of the peripheral blood had suggested leukemia, so did study of the marrow; however, in the marrow the erythroid line appeared well ahead of the myeloid line in their wild dual flight. The picture was one of quantitative rather than qualitative wildness at this time.

Examination of the peripheral blood smear obtained January 29, 1951 revealed no essential change and was again consistent with acute leukemia. As before, the dysfunction of the myeloid line was more pronounced than that of the erythroid line in the peripheral blood, although it was now known that the converse was true in the marrow. Peripheral blood smears obtained four days later showed a distinct change. Stem cells were found with much greater difficulty, normoblastosis had been reduced in half, and there was a more striking right shift in the neutrophils. These changes apparently were associated with the administration of aminopterin. The picture was not unlike that described for von Leube's leukemia.

Examination of marrow on February 6, 1951 again revealed simultaneous hyperactivity of both the erythroid and myeloid lines. At this time myelopoiesis was much more left-shifted and few mature neutrophils could be located. Abundant mitotic figures (30 per cent) were observed among the normoblasts and megaloblastoid forms were more evident than
An unmarried woman, 73 years old, was first seen at the clinic on June 3, 1949, because of "low blood" noted two months earlier. She was well until November 1948, when she had
### Table 3: Findings in Peripheral Blood Throughout Course of Disease in Cases 3 to 5

<table>
<thead>
<tr>
<th>Case 3</th>
<th>1950</th>
<th>1951</th>
<th>1948</th>
<th>Case 5</th>
<th>1949</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-4</td>
<td>6-9</td>
<td>11-17</td>
<td>1-27</td>
<td>10-19</td>
</tr>
<tr>
<td>Hemoglobin, gm. per 100 cc.</td>
<td>10.6</td>
<td>10.6</td>
<td>6.4</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Erythrocytes, millions*</td>
<td>2.86</td>
<td>2.86</td>
<td>1.68</td>
<td>2.11</td>
<td>1.86</td>
</tr>
<tr>
<td>Leukocytes*</td>
<td>8100</td>
<td>2600</td>
<td>4800</td>
<td>3100</td>
<td>4100</td>
</tr>
<tr>
<td>Stem cells, %</td>
<td>13</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>5.5</td>
</tr>
<tr>
<td>Progranulocytes, %</td>
<td>1</td>
<td>4</td>
<td>0.5</td>
<td>6.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Myelocytes, %</td>
<td>4</td>
<td>0.5</td>
<td>4.5</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>Metamyelocytes, %</td>
<td>23</td>
<td>24.5</td>
<td>50</td>
<td>61</td>
<td>73.5</td>
</tr>
<tr>
<td>Polymorphonuclear neutrophils, %</td>
<td>(20%†)</td>
<td>(15%†)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>2</td>
<td>6</td>
<td>1.5</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Basophils, %</td>
<td>53</td>
<td>55</td>
<td>31</td>
<td>25.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>41</td>
<td>49</td>
<td>218</td>
<td>92</td>
<td>37</td>
</tr>
<tr>
<td>Erythrocyte, nucleated‡</td>
<td>30</td>
<td>10</td>
<td>33.3</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Megaloblastoid, %</td>
<td>360</td>
<td>310</td>
<td>42</td>
<td>61</td>
<td>27</td>
</tr>
<tr>
<td>Platelets, thousands*</td>
<td>9</td>
<td>6</td>
<td>11</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Cells per cu. mm. of blood.  
† Right-shifted.  
‡ Per cent of erythrocytes.
“flu” manifested by a dull aching in the upper portion of the chest in the midline, which had continued to give discomfort. She denied any effect of effort on this complaint. In February 1949, weakness, increased appetite, and increased frequency of urination with nocturia appeared. She was hospitalized elsewhere in April 1949, because these complaints continued and because of the development of exertional dyspnea, paresthesia in the fingers of her left hand, some blurring of vision, and loss of weight. Sugar was detected in the urine and 10 units of protamine zinc insulin was prescribed daily. While in the hospital she also received five blood transfusions for the “low blood.”

Examination revealed a pale, elderly female weighing 138 pounds (62.6 Kg.) with a temperature of 102 F. One year before she had weighed 200 pounds (90.7 Kg.). The systolic blood pressure was 174 mm. and diastolic 60 mm. The pulse rate was 86 per minute. A few small, shotty, cervical nodes were palpable bilaterally. There was a rough systolic murmur, grade 2, over the aortic area. The aortic second sound was intact; there was no thrill. An egg-sized swelling of the lateral aspect of the left deltoid area was incised and drained and the diabetes was controlled fairly well by diet and insulin. The patient was dismissed on June 14, 1950. Attempts to control the patient further have not been successful.

Blood and marrow studies. Examination of the peripheral blood smear obtained June 4, 1949 revealed hypochromasia, anisocytosis, regenerative macrocytes, and normoblastosis (table 3). There were stem cells and right-shifted neutrophils, with an intervening hiatus. The picture suggested a leukemic process, although platelets were numerous.

As in cases 1 and 2 examination of the marrow (table 2) revealed greater activity in the erythroid than the myeloid line. Erythropoiesis was bizarre with the result that there were many multinucleated, giant normoblasts containing up to six distinct nuclei. These normoblasts varied in size from 5.3 to 16.8 μ in diameter, with a mean diameter of 12.2 (fig. 5a, b, and c). Forty per cent of the erythroid cells possessed mitotic figures. The younger erythroid cells had basophilic cytoplasm, and, though about 10 per cent ultimately became orthochromatic, there were erythroid cells of similar size which had retained the basophilic cytoplasm. No mature erythrocytes of the size of the giant normoblasts were evident and thus it was presumed they retained their nuclei. Reticular cells were numerous and possessed cytoplasm similar to the earliest erythroid cells which themselves had distinctly reticular nuclei. Phagocytosis of cellular debris and pigment was conspicuous. The myeloid line was less disturbed but was distinctly hyperactive. One Auer body-containing stem cell was seen. About 50 per cent of the neutrophils were right-shifted. There was a definite hiatus between these cells and the stem cells. Again as in case 2 the eosinophils seemed to be involved in the process, for they were numerous, and the mature cells were also right-shifted. As the peripheral blood had suggested, megakaryocytes were adequate in number and normal in appearance.

Case 4

An unmarried woman, 19 years old, was first seen at the clinic on November 16, 1950. She had apparently been well until May 1950, when she had suffered for about two weeks from abdominal pain localized in the right lower quadrant. Appendectomy was performed and subacute appendicitis was reported. The patient had not felt well since. In August 1950, her hemoglobin was 40 per cent. Nausea and vomiting also began in August; vomiting
occurred every two to three days and sometimes twice a day, and was usually more evident in the morning. She had noted bleeding from the gums, but from no other source. She believed that she had bruised more easily during the past year. She had noted exertional dyspnea since August 1950. For the last month before admission she had had transient occipital and frontal headaches associated with blurring of vision lasting ten to fifteen minutes.

Two weeks prior to admission, the patient had been hospitalized because of vomiting and fever to 100 F. Transfusion of blood and injections of liver and penicillin were given. A sternal aspiration showed very active erythropoiesis.

Physical examination at the clinic revealed pallor of the skin, mucous membranes, and nail beds. The temperature was 101 F., the blood pressure was 120 mm. Hg systolic and 50 diastolic, and the pulse rate was 96 per minute. The spleen was not palpable.

Examination disclosed 6.4 Gm. of hemoglobin per 100 cc., 1,680,000 erythrocytes, and 4800 leukocytes per cu.mm. Urinalysis and the serologic test for syphilis were negative. The concentration of direct reacting serum bilirubin was 0 and of indirect type 1.3 mg. per 100 cc. Fragility of erythrocytes was normal. The Coombs test gave negative results. Roentgenographic examination of the chest was not remarkable. Smears of the blood and
bone marrow were consistent with acute erythroleukemia. The marrow exhibited prominent megaloblastoid activity. The patient was given folic acid (folvite) 15 mg. intramuscularly daily to observe the effect on the bone marrow. She was dismissed November 30, 1950, without evident improvement.

Death occurred December 5, 1951 at home. Postmortem examination was not performed. Terminally, bleeding from the bodily orifices was noted with marked progressive enlargement of the spleen.

Blood and marrow studies (tables 2 and 3). Initial peripheral blood smears were suggestive of leukemia; they revealed hypochromasia and polychromasia, as well as anisocytosis of the erythroid line. There were many normoblasts, approximately a third of which were megaloblastoid. The neutrophils were granule-poor, and there was an hiatus between them and stem cells containing Auer bodies. Lymphocytes too possessed reticular nuclei. There were abundant chromatin rests and thrombocytopenia.

Smears of marrow obtained on admission revealed evidence of exuberant erythropoiesis (table 2). The normoblasts did not reach excessive size, but about 40 per cent were undergoing mitosis, and 50 per cent were binucleated. Slightly more normoblasts were basophilic than orthochromatic on November 24 and there were about five times as many polychromatic normoblasts as these combined. Reticulum cells were readily seen. Myelopoiesis was hyperactive and left-shifted; about a third of the stem cells contained Auer bodies (fig. 6).

The condition of the marrow obtained on November 16 and 24 was essentially the same. Examination of a specimen of marrow sent us about three months later revealed several unexpected changes. Megaloblastoid cells were now 10 per cent in contrast to 30 per cent earlier. Myelopoiesis was still left-shifted, but neutrophils were more numerous. Auer bodies were present in 30 per cent of the stem cells. Megakaryocytes were present. The question arose whether or not folvite might have contributed to the conversion of the megaloblastoid cells, but it was difficult to explain.

Case 5

A 42 year old married stenographer first visited the clinic October 4, 1948, because of “slowing up in work” and “tiring easily,” of four months’ duration. On July 12, 1948, she
was seen by her local physician because of weakness and swelling of the arms, hands, and feet. He noted pallor and found marked anemia. About one month prior to coming to the clinic she had had a rash from her waist to her feet, like a crop of "mosquito bites," which were red, hot, hard, and painful. Recurrent fever up to 104 F. had been present since the onset of her illness and would come and go for a week or longer at a time. On one occasion, associated with a febrile episode, she had had a generalized rash of tiny, painless, red lesions lasting only one night and disappearing without residua. She had received numerous blood transfusions at home; the last, about one month previously. She had also received liver, iron, penicillin, and sulfonamide therapy. She had lost 20 pounds (9.1 Kg.).

Physical examination at the clinic revealed marked pallor of the skin and mucous membranes with a suggestion of a yellowish hue. The mucosa of the tongue appeared slightly atrophic. The blood pressure was 110 systolic and 60 diastolic. The pulse rate was 92 per minute. A soft blowing precordial systolic murmur not obliterated by deep inspiration was heard best when the patient was supine. A small cervical polyp prolapsed from the os. There were multiple small petechiae on the skin of the legs amid numerous subcutaneous hematomas. The spleen was palpable.

Initially there were 2,110,000 erythrocytes and 4100 leukocytes per cu.mm. of blood. Urine was normal. The Kline test gave a negative result and the value for direct reacting serum bilirubin was 0, but that of the indirect type 1.8 mg. per 100 cc. (normal 0.6 mg. per 100 cc.). The cell volume varied from 13 to 20 per cent, the prothrombin time from 22 to 25 seconds. There was no increased fragility of the erythrocytes. Studies failed to disclose irregular antibodies and autoagglutinins. The value for total protein was 6.2 Gm. per 100 cc. with 3.7 Gm. of albumin and 2.5 Gm. of globulin. A bromsulfalein test disclosed normal liver function and stools were negative for occult blood. Excretion of fecal urobilinogen was increased (646.5 mg. per 24 hours). Blood cultures were negative. The value for blood urea was 26 mg. per 100 cc. The roentgenogram of the thorax was negative. Peripheral blood smears and marrow aspirate, although showing some abnormality, were not considered diagnostic.

Because of the evidence of increased hemolysis, splenectomy was performed on October 23, 1948. The spleen weighed 495 Gm. The pathologist considered the histologic pattern of the spleen to be consistent with a hemolytic process.

The patient was dismissed November 9, 1948. Peripheral blood smears were forwarded to the clinic periodically by her home physician. (There were three such smears which bear the date of examination at the clinic.) After dismissal from the clinic transfusions of 500 to 600 cc. of blood were necessary every two to six weeks. Despite such transfusions hemoglobin did not rise to more than 8.5 Gm.

Blood and marrow studies (tables 2 and 3). Examination of the peripheral blood smear obtained October 5, 1948 revealed marked anisocytosis, with about 45 per cent of the cells being microcytes and 25 per cent regenerative macrocytes, and hypochromasia and polychromasia. Poikilocytosis was rather marked. Of nucleated erythrocytes about a third were megaloblastoid. There was myeloid immaturity to the stem cell. Platelets were reduced in number. It seems possible that this was a leukemic process, with a hemolytic factor. In addition there was a surprising number of reticular cells and small, round, granular, basophilic bodies with a narrow rim of lighter-staining cytoplasm. Most of these cells had large centrally placed, light-staining nucleoli. The intervening nucleus, like the rim of the cytoplasm, was lighter-staining, and was grooved. They seemed quite distinct from the lymphocytes.

Erythroid activity predominated in the marrow. It was left-shifted and abnormal. There were giant normoblasts measuring up to 19.1 μ in diameter. Twenty per cent of nucleated erythroid cells had megaloblastoid features; about 30 per cent contained mitotic figures; and 15 per cent were binucleated. Jolly bodies and karyorrhexis were evident. It seemed possible to trace both the normoblastic and megaloblastoid branches of the erythroid line back to the same precursors. Myelopoiesis was overactive but overshadowed. One stem cell subsequently observed contained an Auer body. There was somewhat of an hiatus between the stem and mature neutrophilic cells (fig. 7a and b).
Fig. 7. Case 5. a. In the left upper quadrant a large erythroid cell is undergoing mitosis. The most prominent cells in the right half of the picture are four large megaloblastoid cells, grouped together (Wright’s stain; × 960).  

b. The center of the picture is occupied by two megaloblastoid cells; the upper and smaller having one nucleus, the lower and larger cell possessing three nuclei. To the left of the upper cell there is a polychromatic normoblast; to the right of the lower cell, a chromatic normoblast is undergoing mitosis (Wright’s stain; × 960).

The peripheral blood smears after splenectomy were remarkable principally for an appreciable increase in nucleated erythrocytes.

Six months after operation, blood smears showed increased numbers of lymphocytes and reticular cells. At times it was difficult to differentiate the two, but both cell types were present. It will be recalled that a disturbance of the reticulum was noted in each of the preceding cases. An Auer body-containing stem cell was also seen.

Examination of the peripheral blood smear obtained November 21, 1949, thirteen months after operation, was notable for two reasons: (1) the presence of a small megakaryocyte and (2) an appreciable increase in the number of stem cells, two of which contained Auer bodies.

Examination of the peripheral blood smear dated December 28 revealed that the smear
was literally overrun by the small, round, granular, basophilic reticular cells. They were about twice as frequent as erythroid cells, which were themselves prodigiously hyperactive. Stem cells containing Auer bodies were located without difficulty.

**Analysis of Cases**

These five cases showed the combined features of acute erythremia and leukopenic leukemia. In all five, anemia of moderate to severe intensity was present. Hypochromasia, polychromasia, microcytosis, regenerative macrocytosis, and poikilocytosis were noted in the peripheral blood smears in all cases. Hemolytic anemia was sufficiently severe to prompt splenectomy in case 5. Extreme immaturity of the red cell line together with bizarre derangement of the erythrocytes was a notable feature in both the marrow and peripheral blood. Megaloblastoid cells were noted in the blood or marrow in all except case 3. The percentage of megaloblastoid cells varied from 10 to 60 in the peripheral blood smears, and from 10 to 55 in the sternal marrow. In cases 1, 3, and 5 erythroid cells reached gigantic proportion in the marrow. Erythrocytes comparable in size to the giant orthochromic blast cells were not seen in the blood; this suggests that the giant cells did not lose their nuclei. Mitosis was frequent among the erythrocyte cells in the marrow in all cases and varied in percentage from 15 to 40 in different specimens. Multinucleated erythroid cells were noted in the marrow in all cases except case 2; in cases 1 and 3 the number of nuclei varied from 2 to 6; in cases 4 and 5, 15 to 50 per cent of the erythroid cells were binucleated. Knoblike cytoplasmic protuberances of the erythroid cells were especially notable in the sternal aspiration specimens in case 1 in which they occurred in about 20 per cent of the cells.

Leukocytosis was present only in case 2 and was transient even there. In case 5 leukocyte counts were usually within the normal range. The remaining cases (cases 1, 3, and 4) were eventually characterized by leukopenia. Immaturity of the stem cell was noted in the peripheral blood in all cases. Auer bodies and megakaryocytes were noted in the peripheral blood in two cases (cases 4 and 5). An additional case (case 3) was characterized by the presence of Auer bodies in the sternal marrow. Right-shifted polymorphonuclear neutrophils were noted in the peripheral blood in two cases (cases 2 and 3) and eosinophilia, in the sternal aspiration specimens of these same two cases (cases 2 and 3).

Thrombocytopenia was present in cases 1, 2, 4, and 5. Atypical lymphocytes with grooved nuclei were noted in the blood in case 1.

Reticulum cells were noted in the peripheral blood smears in case 5 only, but were abundantly present in the sternal marrow in all the other cases, except case 2, and seemed to vary with the nucleated erythroid cells.

The lesion in the wall of the stomach resembling reticulum cell sarcoma three years before the recognizable onset of erythroleukemia in case 1 is most unusual and points again to a relationship between the reticuloendothelial system and acute erythroleukemia. Although the duration of life would be expected to be short in patients who have such a lesion, the relatively prolonged life of the patient in case 1, who apparently did not die until some six years after the onset of the neoplasm, should be noted.

The chief complaints varied as follows: stomach trouble in case 1, abdominal cramps in case 2, “low blood” in case 3, anemia and vomiting in case 4 and weak-
ness, rash and anemia in case 5. Our clinical findings of note were: fever in three cases, pallor in four, malaise and weakness in five, loss of weight in three and not assessed in cases 1 and 5 because of edema, dyspnea in five, paresthesia in two, blurred vision in one, heart murmur in five, splenomegaly in two, hepatomegaly in two, and hemorrhagic tendencies in three.

Including our five cases, it would appear that not more than fifteen cases of acute erythroleukemia have been presented to date.

**Pathogenetic Aspects**

Erythroleukemia, rather than being a manifestation of concomitant diseases, probably is a bidirectional expression of the uncontrolled efforts of the common blast cell.

Multidirectional involvement of blast cells is frequently noted. For instance, in cases of polycythemia vera leukocytosis is frequent, a leukemoid reaction is noted occasionally, terminal leukemia is not too uncommon, and megakaryocytosis has been noted. At necropsy in cases of polycythemia vera, although the leukocyte count has been normal, granulocytic tissue may exceed erythroblastic tissue in the bone marrow. Thus, polycythemia vera cannot be considered solely an erythropoietic disease.

Leitner reported “hyperplasia of all three systems” in the bone marrow of most of his patients with polycythemia vera. Türk, Weber, and Minot and Buckman pointed out that leukogenic tissues share in the overactivity of the erythrogenic tissues in polycythemia vera. Megakaryocytes and platelets also may be greatly increased in number. Di Guglielmo and Pianesi referred to such a condition as “eritro-leuco-piastrinemia.”

Leukemic states may be accompanied by disturbances in the erythroid line just as polycythemic states are accompanied by disturbances in the leukocytes. Thus, leukemia may be associated with normoblastosis or more rarely with megaloblastosis. In a few cases the blood picture has vacillated between leukemia and polycythemia vera.

In leukemia the megakaryocytic elements of the marrow may be relatively more numerous than the granulocytic elements. In such a condition the blood may be flooded with megakaryocytes and their derivatives, the platelets, so that for a time the disease process appears to be confined to the megakaryocytes.

In granulocytic leukemia Jaffé noted that erythropoiesis was often nearly as prominent a feature of the marrow as leukopoiesis. The stimulated and abnormal activity of the red-cell-forming tissue in some cases may antedate manifestations of leukemia by long intervals. Profound anemia likewise may long precede definite evidences of leukemia. Collins and Rose wrote: “It is certain that in both acute and chronic granulocytic leukemia, erythropoiesis and leukopoiesis should not be considered apart from each other and it is inaccurate to dismiss the anemia in these diseases, simply as a secondary phenomenon.”

Di Guglielmo considered that erythroleukemia did not result from the fortuitous association of polycythemia vera and granulocytic leukemia, but rather from a single force acting on the multipotent blast cell and producing two simultaneous effects.
The hematologic disease entities for which the multipotent blast cell may be responsible are presented in Table 4.

Acute erythremia of Di Guglielmo (Table 4) is a rare malignant erythroblastic hyperplasia with severe anemia. Moeschlin, in 1940, stated that only five reported cases of acute erythremia could withstand critical scrutiny. Later, Leitner described a case. Acute or incomplete erythroleukemia is acute erythremia plus leukemia.

**Comment**

Loosely speaking, any combination of polycythemia vera and leukemia may be referred to as "erythroleukemia." The leukemia may be leukopenic or non-leukopenic. In polycythemia the erythrocytes may not show any great evidence of immaturity, or acute erythremia may be present. Gradations between these extremes of either leukemia or polycythemia vera may be encountered.

There are two types of erythroleukemia, that is, acute (or incomplete) and chronic (or complete). Di Guglielmo classified erythroleukemia as complete (chronic is the term we prefer) if there was an increase in mature and immature leukocytes and erythrocytes in the circulating blood and as incomplete (acute) if the blood picture was the same except for the presence of anemia instead of erythremia.

Most of the cases reported in the literature are of the chronic variety, but there are some of the acute type. The five cases reported by us are examples of acute erythroleukemia. The leukemia may precede, coexist with, or supplant the erythrocytic abnormality in the chronic form. It appears that thus far only the coexistent form of the acute variety has been described. The types and sub-
types of erythroleukemia may be classed as follows:

I. Acute erythroleukemia (incomplete erythroleukemia of Di Guglielmo)
   1. Leukemia → acute erythremia
   2. Leukemia + acute erythremia
   3. Acute erythremia → leukemia

II. Chronic erythroleukemia (complete erythroleukemia of Di Guglielmo)
   1. Leukemia → polycythemia vera
   2. Leukemia + polycythemia vera
   3. Polycythemia vera → leukemia

This concurrence of entities ordinarily considered distinct is not a mere chance association but rather represents simultaneous excessive activity of the common blast cell in two directions.

SUMMARY

Five cases of erythroleukemia of the acute or incomplete variety form the basis of this report. Four of the patients were women. The ages of these five patients ranged from 19 to 73 years at time of admission to the Mayo Clinic. Studies were made on the blood and peripheral marrow for varying periods throughout the course of the disease. All five patients had anemia and extreme immaturity of the erythrocytes in the peripheral blood and bone marrow. Leukopenia was eventually present in four cases as was thrombopenia. Splenectomy was performed on one patient.

One patient lived six years after the condition developed, two died within thirteen months of the time of diagnosis, one was not followed, and the fifth was still living at last report.

Relatively few cases of erythroleukemia have been reported in the literature and most of those reported have been cases of the chronic variety. The erythrocytic picture in the chronic variety differs from that in the acute variety. In the acute type acute erythremia is associated with leukemia and in the chronic type polycythemia is associated with it. Either the erythrocytic abnormality or the leukocytic may appear first. Our studies and those reported in the literature suggest excessive activity of the blast cell in two directions.

SUMMARIO IN INTERLINGUA

Cinque casos de erythroleueemia del varietate acute o incomplete forma le base de iste reporto. Le etates del patientes variava inter 19 e 73 annos al tempore de lor admission al Clinica Mayo. Quatro esseva feminas.

Le sanguine peripheric e le medulla ossee del cinque patientes esseva studiata pro periodos de varie durationes in le curso del morbo. Omne le cinque esseva anemic. In omnes un extreme immaturitate del erythrocytos in le sanguine peripheric e le medulla ossee esseva observeate. In quatro del casos leucopenia adveniva in le curso del tempore. Thrombopenia se deklarava etiam in quatro casos. In un caso splenectomy esseva executeate.

Un del patientes viveva pro 6 annos post le declaration del morbo, duo moriva intra 13 menses post le diagnose, super uno nulle reportos subsequente esseva obtenite, e le quinte viveva ancora al tempore del ultime reportos.

Comparativemente pauc casos de erythroleueemia ha essite reportate in le
ACUTE OR INCOMPLETE ERYTHROLEUKEMIA

litteratura, e le majoritate de istos esseva casos del varictate ('hm'omuio'. Jc svmidrome erythrocytic imi le forma chronic differe de illo del forma acute. In le typo acute, erythremia acute es associate con leucemia; in le typo chronic, polycythaemia es associate con illo. Le prime manifestation pote esser o le anormalitate erythrocytic o le anormalitate leucocyte. Nostre studios, assi como le studios reportate in le litteratura, conduce al conclusion que le duo typos representa activitates excessive del blasto in duo directiones.

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Erythroleukemia, with Special Emphasis on the Acute or Incomplete Variety: Report of Five Cases

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