Erythroblastopenia (Pure Red Cell Aplasia) in Childhood in Djakarta

By L. K. Kho, O. Odang, S. Thajeb and A. H. Markum

ERYTHROBLASTOPENIA or pure red cell aplasia is a condition in which anemia develops because of a diminished number of erythroblasts in the bone marrow, without participation of the granulopoietic and the thrombopoietic systems. The first description of this entity was given in 1922 by Kaznelson, who gave the following definition: a progressive normochromic anemia with no signs of regeneration in the peripheral blood; no polychromasia, no reticulocytes, no erythroblasts; erythropoietic aplasia in the bone marrow with disappearance of all types of erythroblasts; normal leukopoiesis and thrombopoiesis and no enlargement of the spleen or lymph nodes.

The acute form of erythroblastopenia or aplastic crisis was first described by Owen in 1948 and Gasser in 1949, respectively. This is an acute anemia caused by a sudden disappearance of the erythroblasts from the bone marrow, accompanied by the disappearance or drop of the reticulocytes in the peripheral blood. This condition lasts only a few days and is followed by an erythroblastosis of the bone marrow and a reticulocytic crisis and increase of hemoglobin content of the blood. During the acute erythroblastopenia, giant proerythroblasts (erythrozones) may be observed in the bone marrow.

According to Gasser, the causative agents for this condition include intoxication by drugs (barbiturates, oleum chenopodii, santonin, calomel, aminopvirin), insect bites, viral infections (atypical pneumonia, mumps), bacteriologic infections (meningococcemia, staphylococcemia), surgical interventions (tonsillectomy, splenectomy), and allergic manifestations (eczema, asthmatic bronchitis, pseudocroup, anaphylactoid purpura and hypersensitivity reactions to drugs). Gasser described erythroblastopenia as an instability of the blood apparatus which he called "dvshaemia," and could include eosinophilia, hemolytic anemia, megaloblastic anemia and erythroblastic reactions. Kho found this condition in children with kwashiorkor, with or without infections, and in children with infections and megaloblastic anemia. Recent reports have indicated that acute erythroblastopenia is frequently encountered in Chile.

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The occurrence of pure chronic erythroblastopenia was described by Baarm in 1928 as a progressive postinfectious erythropoiesis, by Lescher as a pure red cell anemia, by Josephs and by Diamond and Blackfan under the designation of chronic (congenital) hypoplastic anemia. According to Liehmeyer, chronic erythroblastopenia is a rare condition found in adults and only a few cases have been described in the world literature. It has been noted in cases of benzol intoxication, polyarthritis, and cholecystitis. In infancy and childhood, however, this entity seems to be relatively common.

The pathogenesis of the chronic form of erythroblastopenia in children is obscure. Smith found this condition in combination with a hypoplastic and cystic kidney and presumed that there was an association between this kidney defect and the disturbance in erythropoiesis. In another infant with erythroblastosis caused by isoimmunization of a group O, Rh positive mother by a group A, Rh positive offspring, a typical pure red cell anemia developed, which was documented during the course of 10 years. According to Giblett et al., Rh antibody is able to depress the erythropoietic system in the bone marrow.

Congenital erythroblastopenia sometimes occurs as a result of a defect in tryptophan metabolism. In riboflavin deficient animals fed with tryptophan, large quantities of anthranilic acid, a metabolite formed in the breakdown of tryptophan, are excreted in the urine. Riboflavin administration in infants with congenital erythroblastopenia will decrease the excretion of anthranilic acid but will not alter the bone marrow. Observation of more than 15,000 children admitted to the Pediatric Department during the last five years has indicated that pure red cell aplasia is not at all rare in Indonesia, more popularly in Djakarta.

MATERIALS AND METHODS

From the beginning of 1954 until the end of 1959, bone marrow punctures were done in the Pediatric Department, Faculty of Medicine, University of Indonesia, in 1500 children admitted with anemia as the principal finding.

In 238 cases (16.6 per cent of the cases) the bone marrow showed an obvious depression of the erythropoietic system. However, evaluation of a diminished number of erythroblasts in the bone marrow is not always easy, due to the following facts:

1. A diminished number of erythroblasts can be the consequence of dilution of bone marrow material with blood.
2. A diminished number of erythroblasts can be due to an increased number of other cells, i.e. granulocytes, leukemic cells, tumor cells.
3. Sometimes a relative increase in the number of erythroblasts is found because all cells in the bone marrow are diminished, but the composition of the cells does not alter or change in favor of the erythroblasts.

To prevent these errors, no more than 0.2 ml. of bone marrow material was aspirated and in cases of doubt a second biopsy was done. The presence of bone marrow particles was required in the smear. In some instances bone marrow material was fixed in formaldehyde solution, centrifuged, and the sediment put in wax to make bone marrow slides. In other instances pure bone marrow material present in the sediment or floating on the aspirate was taken out with a fine flexible paint brush and spread on a film, fixed with methyl alcohol and stained with May-Grünwald-Giemsa stain. However, we found the most important step in preventing errors to be the taking of bone marrow biopsies at weekly intervals (in some cases more and in others less frequent) and comparing the results. The site of aspiration has been: in infants the capitulum tibiae, in older children the iliac...
crest, and in bigger children or adolescents the sternum. In general, only when the percentage of the bone marrow erythroblasts was less than five were they included in this material.

Of these 238 cases, 123 were boys and 115 girls, the ages varying from newborn to 12 years of age (fig. 1).

Methods for blood examination were the same as previously used (Kho11).

Results

Of 238 cases with a diminished number of erythroblasts in the bone marrow, 56 cases were excluded from the group of pure red cell aplasia (table 1). The total number of cases of erythroblastopenia or pure aplastic anemia was 186 or 12.4 per cent of the 1500 anemias in which bone marrow punctures were performed. These cases could be divided into three groups according to the duration of the disease:

1) Acute erythroblastopenia lasting a few days to a few weeks: 20 cases.
2) Subacute erythroblastopenia with a duration of a few weeks to two months: 25 cases.
3) Subchronic or chronic erythroblastopenia with a duration of more than two months: 141 cases.

1) Acute Erythroblastopenia

This was found in 20 children, varying in age from 13 months to 12 years. However, most cases were in the age group of two and three years old. Ten were boys and ten were girls. All these children had a body weight far below the normal range for Djakarta children and most of them came from the low

![Fig. 1.—Incidence according to age of erythroblastopenia in children in Djakarata.](image)
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Table 1.— Incidence of Erythroblastopenia in Djakarta

| Number of admissions: 15,390 children |
| Number of bone marrow biopsies: in 1,500 children |
| Number of cases with diminished erythroblasts 238 (16.6%): |
| Pure aplastic anemia (erythroblastopenia) 186 (12.4%) |
| Acute leukemia 28 |
| Chronic leukemia 2 |
| Bone marrow tumors 6 |
| Reticuloendotheliosis 2 |
| Panmyelophthisis 10 |
| Agranulocytosis 2 |
| Amegakaryocytic thrombocytopenia 2 |

Table 2.—Clinical Diagnosis of 186 Cases of Erythroblastopenia

<table>
<thead>
<tr>
<th>Clinical Diagnosis of 186 Cases of Erythroblastopenia</th>
<th>Acute Erythroblastopenia (20 cases)</th>
<th>Subacute Erythroblastopenia (25 cases)</th>
<th>Subchron./Chron. Erythroblastopenia (141 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwashiorkor (malnutrition)</td>
<td>14</td>
<td>—</td>
<td>103</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td>1</td>
<td>—</td>
<td>73</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Enteritis-dehydration</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Purulent meningitis</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Ankylostomiasis</td>
<td>1</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Tetanus</td>
<td>—</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Malaria</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Furunculosis</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Idiopath. thromb. purpura</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Oligophrenia</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyreoida</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Idiopath. erythroblastopenia</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
</tbody>
</table>

income group of the population. Table 2 shows the primary diseases in these children in which acute erythroblastopenia was encountered. Allergic manifestations such as eczema, hypersensitivity to drugs, asthmatic bronchitis, and anaphylactoid purpura were not found in these children.

Acute erythroblastopenia was found soon after admission in five instances and during hospitalization in the other cases. In the latter group, bone marrow examination was done because of a sudden or rather gradual drop of the hemoglobin content of the blood without evidence of hemolysis or acute blood loss. The number of the reticulocytes was very low or in the lower normal regions. Peripheral blood data is found in table 3. The MCV values varied from 71 to 126 cμ, MCH from 32 to 35 μg. and the MCHC from 24 to 36 per cent. In all these cases the platelet count was within normal limits.
Table 3.—Data on Blood and Bone Marrow

<table>
<thead>
<tr>
<th>Hematologic Data</th>
<th>Acute Erythroblastopenia (20 cases)</th>
<th>Subacute Erythroblastopenia (25 cases)</th>
<th>Sub./Chronic Erythroblastopenia (141 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood:</td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Hb (Gm. 100 ml.)</td>
<td>2.4-13.6</td>
<td>6.7</td>
<td>3.5-11.4</td>
</tr>
<tr>
<td>RBC (million)</td>
<td>0.79-4.24</td>
<td>2.36</td>
<td>1.12-3.84</td>
</tr>
<tr>
<td>WBC (1000)</td>
<td>3.4-31.0</td>
<td>22.4</td>
<td>5.2-52.5</td>
</tr>
<tr>
<td>Reticulocytes (1000)</td>
<td>0-3.5</td>
<td>1.1</td>
<td>0.5-3.5</td>
</tr>
</tbody>
</table>

Bone marrow:

<table>
<thead>
<tr>
<th>Erythroblasts (%)</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid eryth. ratio</td>
<td>14.6-421.0</td>
<td>136.7</td>
<td>4.32-132.0</td>
<td>32.2</td>
<td>5.3-310.0</td>
<td>23.0</td>
</tr>
</tbody>
</table>

The bone marrow revealed a normal or increased quantity of cells with a diminution in fat. Megakaryocytes were found in normal quantities. During an aplastic crisis only a few erythroblasts could be found in the bone marrow and in one case no erythroblasts at all were seen. In every case giant pro-erythroblasts were easily seen under low power microscopic examination. Giant precursors of these cells, resembling reticular cells, hemocytoblasts or histioblasts were easily identified. Multi-nucleated giant cells or pathologic mitotic figures were observed (table 4). In general, we saw a tendency to an increase in monocytes, plasmocytes and reticular cells. Treatment consisted of specific therapy for the primary disease, adequate diet, blood transfusions.

Table 4.—Differentiation of Bone Marrow Cells

<table>
<thead>
<tr>
<th>Bone Marrow Cells</th>
<th>Acute Erythroblastopenia</th>
<th>Subacute Erythroblastopenia</th>
<th>Sub./Chronic Erythroblastopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>0-7.0</td>
<td>1.3</td>
<td>0-6.0</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>0-2.8</td>
<td>1.4</td>
<td>0-7.8</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>7.0-32.5</td>
<td>15.6</td>
<td>2.0-29.6</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>4.4-23.6</td>
<td>10.3</td>
<td>0.6-30.0</td>
</tr>
<tr>
<td>Stab cells</td>
<td>5.8-30.0</td>
<td>17.6</td>
<td>6.6-26.8</td>
</tr>
<tr>
<td>Polymorph. cells</td>
<td>6.4-47.2</td>
<td>22.1</td>
<td>3.2-61.2</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.2-11.2</td>
<td>3.3</td>
<td>0-14.0</td>
</tr>
<tr>
<td>Basophils</td>
<td>0-0.8</td>
<td>0.1</td>
<td>0-0.2</td>
</tr>
<tr>
<td>Proerythroblasts</td>
<td>0-0.8</td>
<td>0.3</td>
<td>0-1.6</td>
</tr>
<tr>
<td>Macronormoblasts</td>
<td>0-0.6</td>
<td>0.2</td>
<td>0-2.4</td>
</tr>
<tr>
<td>Basoph. normoblasts</td>
<td>0-0.6</td>
<td>1.2</td>
<td>0-3.6</td>
</tr>
<tr>
<td>Polych. normoblasts</td>
<td>0-2.6</td>
<td>0.4</td>
<td>0-5.0</td>
</tr>
<tr>
<td>Acidop. normoblasts</td>
<td>0-1.8</td>
<td>0.3</td>
<td>0-3.6</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>5.4-39.4</td>
<td>19.8</td>
<td>13.5-61.8</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0-5.0</td>
<td>1.7</td>
<td>0-8.4</td>
</tr>
<tr>
<td>Plasmocytes</td>
<td>0-4.6</td>
<td>1.5</td>
<td>0-8.4</td>
</tr>
<tr>
<td>Reticular cells</td>
<td>0-6.0</td>
<td>1.3</td>
<td>0-16.0</td>
</tr>
<tr>
<td>Other cells</td>
<td>0-1.4</td>
<td>1.5</td>
<td>0-14.0</td>
</tr>
</tbody>
</table>
for supportive therapy in most cases, hematinics and vitamins. Nevertheless, eight of the 20 cases (40 per cent) died during or a short time after the aplastic crisis. The following case report is an example of acute erythroblastopenia (fig. 2).

Sot. (Case no. 2531 60) an 11-month-old boy was admitted to the Pediatric Department with fever of one month's duration, cough, and convulsions five days prior to the admission. The baby looked ill, semiconatose and demonstrated much rigidity. Examination revealed bronchopneumonic signs and an abscess in the left hip joint. The nutritional status was good (body weight 9,200 Gm.). Examination of the cerebrospinal fluid revealed a turbid fluid with positive Nonne and Pandy reaction, an increase in cells to 1064.3 per cu.mm. a decrease in glucose (45 mg./100 ml.), and an increased protein of 195 mg./100 ml. Blood examination revealed a hemoglobin content of 7.0 gm. 100 ml. and a leukocytosis of 18,000 with a differential count of 86 per cent polymnucleated cells, 12 per cent lymphocytes and 2 per cent monocytes. Mantoux reaction was negative. Treatment consisted of penicillin, chloramphenicol and sulfadiazine. The child improved. Consciousness returned and the bronchopneumonic signs and symptoms of meningitis disappeared gradually. The hemoglobin content of the blood, however, dropped to 4.1 Gm. 100 ml. and the number of reticulocytes to 2,000 cu.mm. (0.02 per cent). The erythroblasts in the bone marrow disappeared almost entirely with the appearance of giant reticular cells and giant proerythroblasts (fig. 3). Transfusion with 100 ml. blood was necessary. This condition lasted only one week. Improvement of the blood took place with the appearance of erythroblastosis in the bone marrow (fig. 4) and a reticulocytic crisis of 7.1 per cent. This was followed by a sharp rise in the hemoglobin. The bone marrow one week afterwards showed the presence of many megaloblasts, which disappeared within one week without treatment. The baby was discharged in good condition, except for stiffness of the left hip joint, six weeks after admission.

Fig. 2.—Course of the disease of an infant, 11 months old, with purulent meningitis and acute erythroblastopenia.
Subacute Erythroblastopenia

This condition is characterized by anemia, a diminished number of erythroblasts in the bone marrow without the findings of giant proerythroblasts, and a duration of the disease varying from two weeks to two months. The drop of the hemoglobin content of the blood was less sudden. The erythroblasts in the bone marrow were decreased, as well as the blood reticulocytes. The mortality of this group was high (44 per cent). This was thought to be due primarily to the severe primary infectious diseases. A typical case report of subacute erythroblastopenia is as follows (fig. 5):

Irk. (Case no. 1809/60), a boy three months old, was admitted to the Pediatric Department with fever of two days duration and the sudden appearance of coma. Body weight 4,300 Gm., length 52 cm. On physical examination the infant looked seriously ill with bulging of the fontanel and nuchal rigidity. The spleen was just palpable. No pathologic reflexes were noted. The cerebrospinal fluid was turbid, somewhat bloody with a strong Nonne and Pandy reaction and contained a great many cells (4448/3), most of them granulocytes, glucose 37 mg./100 ml., total protein 130 mg./100 ml.; culture negative. Mantoux reaction was negative. Blood examination: hemoglobin 7.0 Gm./100 ml., RBC 2.68 millions, platelets 320,000, reticulocytes 50,920/cu.mm. (1.9 per cent), WBC 5,800 (eosinophils 1 per cent, stab cells 3 per cent, polymnucleated cells 54 per cent, lymphocytes 38 per cent, monocytes 3 per cent, plasmocyte 1 per cent); PCV 27 per cent, MCV 101 cµ, MCH 28 µg., MCHC 26 per cent. Malaria negative. Treatment consisted of procaine penicillin 2 million units, chloramphenicol 800 mg., cortisone 18 mg., sulfadiazine 1,200 mg. daily.

Course of the disease: Although the physical condition improved, the body weight increased and the temperature tended to become normal, the hemoglobin dropped to 4.7 Gm. 100 ml. on the third week, with the number of erythrocytes 1.9 million and reticulo-...
Fig. 4.—Hyperactivity of erythropoiesis with the presence of a great many erythroblasts one week afterwards.

cytes 0.9 per cent (16,000 cu.mm.). The bone marrow revealed an aplasia of the erythropoietic system without the presence of giant proerythroblasts. On the fifth week of treatment the infant was discharged in fairly good condition with a hemoglobin content of 8.6 Gm./100 ml. However, the bone marrow had remained hypoplastic.

(3) Subchronic and Chronic Erythroblastopenia

A large part of this group consisted of children with kwashiorkor, salmonellosis and, in general, children with chronic infectious diseases (table 2). The grade of anemia and erythroblastopenia was, in general, not so severe as the previous groups. This was particularly true in the salmonellosis group where the erythroblastosis was very moderate. One hundred and forty-one cases were encountered in this group. The anemia was insidious at onset and the duration of the disease was at least two months. The main criterion was normochromic normocytic anemia with a rather low reticulocyte count in the peripheral blood and a diminished number of erythroblasts in the bone marrow. This anemia did not respond to iron, vitamin B₁₂ or folic acid. Blood transfusion had only a temporary effect in elevating the hemoglobin. The prognosis in this group was less severe than in the other two groups, the mortality being 27.6 per cent. While the erythroblastopenia in the case of kwashiorkor and in those caused by infections was in most cases reversible, the idiopathic erythroblastopenia or erythroblastopenia in combination with oligophrenia responded poorly to treatment. The following case is an example of chronic idiopathic erythroblastopenia (fig. 6).

F. L. (Case no. 1981/60), a baby of 11 months old, was admitted to our Department because of pallor and slight fever of two months duration. He had been hospitalized for
Fig. 5.—Course of the disease of an infant, three months old, with purulent meningitis and subacute erythroblastopenia.

one month in another children’s hospital and had received five blood transfusions without improvement. Physical examination revealed an undernourished baby with a body weight of 6,000 Gm. The parents stated he had been offered an adequate diet, but that his appetite was somewhat diminished. He looked very anemic and both feet showed edema. Lymph glands were enlarged, the spleen just palpable below the left costal arch, while the liver was palpable two fingersbreadth below the right costal arch. Mantoux reaction was negative. Blood examination revealed the following results: hemoglobin 3.8 Gm./100 ml., RBC 1.56 million, PCV 10.5 per cent, MCH 33 µg., MCHC 36 per cent, WBC 4,600 (metamyelocytes 1 per cent, stab cells 2 per cent, polynucleated cells 47 per cent, lymphocytes 46 per cent, monocytes 4 per cent, plasmocyte 1 per cent), platelets 426,000, reticulocytes 1.2 per cent (18,000 cu.mm.), alkali resistant hemoglobin 0.3 per cent. Paper electrophoretic examination revealed the presence of only Hb. A. Fragility of the red blood cells was within normal limits. Serum albumin 2.72 Gm. 100 ml., globulin 3.45 Gm. 100 ml., urea 20 mg. 100 ml., cholesterol 129 mg. 100 ml., indirect bilirubin 0.3 mg. 100 ml., direct bilirubin negative, thymol turbidity test 22 U (MacLagan).

Course of the disease: During a hospitalization period of four months, there was no improvement either of the physical condition or of the hematologic state. Eight transfusions of 125–150 cc. of blood each were given without improvement. Cortisone treatment (45–90 mg. daily) during one month appeared to have no effect on the erythroblastopenia, and the child is still under observation in the hospital.

Discussion

Most of our 20 cases of acute erythroblastopenia were characterized by a decrease in body weight. In fact many were in a severe state of malnutrition (kwashiorkor), with or without severe infections and parasitic infestations of the intestines. The principal symptoms of kwashiorkor were decrease in body weight, edema, skin changes (pellagroid, "crazy pavement" dermatosis, hyper- and hypopigmentation), hair changes (discoloration, depilation), changes in the liver (fatty infiltration, fibrosis, necrosis), changes in the pancreas (fibrosis; decreased excretion of trypsin, lipase and amylase), anemia, hypoprotein-
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Fig. 6.—Course of the disease of an infant, 11 months old, with idiopathic chronic erythroblastopenia.

...emia, hypocholesterolemia, bone marrow changes and symptoms of vitamin deficiencies. A moderate drop in the hemoglobin after the first or second week of hospitalization was quite common in most of our patients. We consider as one of the important causes of this drop in hemoglobin the adjustment or improvement of the blood volume and blood electrolytes under treatment, with resulting blood dilution and a relative decrease of the hemoglobin content of the blood. Hemoconcentration in the children admitted to the hospital was explained by the fact that most of these children were suffering from diarrhea and fluid loss without adequate fluid intake. Thus, some of these patients were admitted to the hospital in a serious condition with dystrophia, dehydration, acidosis and occasionally in a state of shock. The treatment in these cases was directed at combating the shock and dehydration with blood transfusions and parenteral fluid therapy with adequate electrolytes. As stated above, only in a small percentage was acute erythroblastopenia encountered during the first week of hospitalization. This period was critical. If the child survived this period, improvement of the physical condition occurred rapidly and the stress on the bone marrow became very great. Either the bone marrow could then fulfill its task for production of sufficient quantities of red blood cells or, lacking one or more known or unknown erythropoietic substances, it was unable to respond effectively. Thus, a temporary shortage of protein or of one or more amino acids probably plays an important part. It is also our experience, that an insufficiency of iron or folic acid with the resulting hypochromic anemia or megaloblastic anemia occurs after a certain period of hospitalization in which the physical condition appears to improve. It is cer-
tain, too, that infection plays an important part in provoking an erythroblastopenia. Another factor may be a marked deficiency in the production or availability of erythropoietin.²

It is well known from tissue culture studies that enlargement of tissue cells occurs when there is a deficiency of one of the factors necessary for growth of the tissue. The formation of giant hemocytoblasts and the giant proerythroblasts as found in acute erythroblastopenia may be an attempt of the erythropoietic system to accelerate red cell production by polyploidal division. Polyploid mitotic figures of giant cells were quite common findings in acute erythroblastopenia.

It must be said that the subdivision of subacute erythroblastopenia is very arbitrary. It is made only to distinguish this group from the acute ones, since not only is the duration of the condition longer than that in acute erythroblastopenia, but it is also distinguished by the lack of giant red cell precursors in the bone marrow. As most of these children had serious infectious diseases such as purulent meningitis, pneumonia, tetanus, diphtheria, viral hepatitis and acute enteral infections (shigella, pathogenic Coli), we are of the opinion that in this group infection plays the most important part in the pathogenesis. Whether antibiotics and chemotherapeutic agents (chloramphenicol, penicillin, streptomycin, tetracyclin, sulfadrugs) played an important role, was not established with certainty. It is a fact that the erythroblastopenia improved despite continuation of treatment with antibiotics and sulfa drugs.

The last or chronic group, being the largest one, consisted of two subgroups, the first being children with malnutrition and chronic infections (kwashiorkor, tuberculosis, salmonellosis), the second consisting of children with chronic erythroblastopenia in combination with mental retardation of unknown origin. While in the first group the erythroblastopenia was reversible depending on the improvement of the primary disease, the erythroblastopenia of the second group was resistant to all treatment. Protein deficiency, and caloric deficiency as well as infections played an important part. Vitamin deficiencies were frequently observed especially in children with malnutrition: deficiency of vitamin A consisting of hemeralopia, xerosis conjunctivae, Bitot spots or keratomalacia, deficiency of vitamin B₁ consisting of paraesthesia, areflexia, circulatory or cardiac disturbances, vitamin B complex deficiency, consisting of pellagroid skin changes, angular stomatitis or mucosal changes. Vitamin C and vitamin D deficiencies were very uncommon. As stated previously,¹⁸ anemia caused by deficiency of iron and folic acid or vitamin B₁₂ was frequently found in our patients. The pathogenesis of many cases of anemia, however, including both anemia in combination with erythroblastopenia and anemias which did not react satisfactorily to treatment with iron, folic acid or vitamin B₁₂, remains unknown. Most of these were normochromic normocytic anemias with an active normoblastic bone marrow without megaloblasts. It was evident that at least some of these cases presented maturation arrest of the erythropoietic system, due to deficiencies of one or more unknown erythrocyte maturity or stimulating factors. Erythroblastopenia, as described here, is a condition in which maturation arrest occurs at the earliest red cell precursors. It is our opinion that in addition to protein deficiency, there may be a deficiency of one or more unknown factors.
ERYTHROBLASTOPENIA IN CHILDHOOD

Summary

Erythroblastopenia or pure red cell aplasia was encountered in 186 children during an observation period of five years in the Pediatric Department in Djakarta, Indonesia. Twenty cases were of the acute type of erythroblastopenia, distinguished by a sudden drop of the hemoglobin content of the blood, reticulocytopenia, and disappearance of the erythroblasts in the bone marrow. Giant red cell precursors (giant reticular cells and proerythroblasts) appeared in the bone marrow. This condition lasted two days to two weeks.

A subacute type of erythroblastopenia with a duration of two weeks to two months was found in 25 cases. The last group consisted of 141 cases of subchronic or chronic erythroblastopenia with a duration of more than two months. Malnutrition, infections and vitamin deficiencies were the main clinical findings in these children. The authors are of the opinion that erythroblastopenia is a maturation arrest of the erythropoietic system caused by protein deficiency and/or temporary deficiencies of one or more erythrocyte maturation or stimulating factors.

Summary in Interlingua

Erythroblastopenia o aplasia erythrocytic pur esseva incontrate in 186 juveniles in le curso de un periodo quinquenne de observation in le Departmento de Pediatria al Universitate de Djakarta in Indonesia. Vinti del casos esseva del typo acute de erythroblastopenia, distinguite per un declino rapide del contento de hemoglobina in le sanguine, per reticulocytopenia, e per le disparition del erythroblastos ab le medulla ossee. Gigante precursores de erythrocytos (gigante cellulas reticular e proerythroblastos) appareva in le medulla de osso. Iste condition durava inter duo dies e duo septimanas.

Un typo subacute de erythroblastopenia con un duration de inter duo septimanas e duo menses esseva incontrate in 25 casos. Le ultime grupo consisteva de 141 casos de erythroblastopenia subchronic o chronic con un duration de plus que duo menses. Malnutrition, infections, e carentias de vitamina esseva le major constatationes clinic in iste juveniles. Le autores opina que erythroblastopenia es un arresto del maturation in le sistema erythropoietic causate per carentia de proteina e/o carentias temporari de un o plure factores de maturation o stimulation erythrocytic.

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Erythroblastopenia (Pure Red Cell Aplasia) in Childhood in Djakarta

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