Erythroblastopenia with Giant Pro-Erythroblasts in Kwashiorkor

By Kho Lien-Keng

In 1948 Owren discovered that an anemic crisis can arise in the congenital hemolytic jaundice caused by an acute aplasia of the erythropoietic system. The reticulocytes disappeared from the peripheral blood. This aplastic crisis was followed by an excessive regeneration of the bone marrow and a reticulocytic crisis. Owren considered extrinsic factors like infections a possible cause for this condition.

Shortly afterwards Gasser described this aplastic erythroleukemia in children with other diseases than hemolytic anemia. All these children seemed to have allergic stigmata and lability of the blood apparatus (dysemia). The trigger mechanism initiating this condition was a toxic or infectious agent.

During the aplastic crisis giant cells were found with a size of 20 to 60 micron in the bone-marrow. These cells resembled reticulo-histiocytic cells with indistinct margins and a broad cytoplasm with light blue color, a large round or oval nucleus with fine, loose reticulated chromatin structure and one or more distinct big nucleoli. Most of the cells however resembled giant pro-erythroblasts both in shape and in color. The cells were considered as belonging to the red cell series. Gasser found only a few normal pro-erythroblasts and an increase of plasmacellular reticular cells and tissue mastcells in the bone-marrow. This observation was confirmed by Chernoff and Josephson in sickle-cell anemia and infectious mononucleosis.

Giant cells from the erythropoietic system more or less resembling those described above, in most instances more mature and multinucleated, were described by Limarzi and Levinson in a case of erythroblastoma, by Schleicher in lymphoblastoma, by Berman in lymphoblastoma, chronic hemorrhages, hepatitis, cirrhosis of the liver, monocytic leukemia and thrombocytopenic purpura, by others in pernicious anemia (Kienle, Scheicher, Rohr), by Goldeck in erythroleukemia and by Kho in panmyelophthisis.

It appears that erythroblastopenia with giant pro-erythroblasts in the bone-marrow is not an uncommon finding in kwashiorkor.

MATERIALS AND METHODS

The material consists of seven patients out of 92 children suffering from severe malnutrition, who were admitted to the Pediatric Clinic of the University of Indonesia, Djakarta, during the last three years. Blood examinations were applied to these children at intervals of one to two weeks. The blood examination consists of an estimation of the hemoglobin.

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ERYTHROBLASTOPENIA IN KWASHIKOR

Hematocrit determinations were done with centrifuging Wintrobe's tubes at a speed of 3,000 r.p.m. for half an hour. Thrombocytes were counted with Fonio's method, controlled by examining direct blood smears or direct method with Reese-Ecker's solution. Bone-marrow punctures were applied at intervals of approximately one month in most cases and more frequently in special cases, with a bone-marrow needle of Klima and Rosegger and 10 cc. syringe in dry state or rinsed with physiologic saline solution. In children older than two years the usual site for aspiration was the iliac crest and in younger children the head of the tibia. No more than 0.2 ml of bone-marrow material was aspirated, in most cases only the contents of the needle. Films were made on dry clean slides, fixed with methyl alcohol and stained with May-Grünwald and Giemsa stain. The cellularity of the bone-marrow was estimated by low power examination of the film, especially of the marrow particles, and with the method described by Slooff. Differentiation of the cells were made by counting 500 cells by the author himself.

RESULTS

Seven of the 92 patients admitted revealed immediately at admittance (cases 2, 3, 5, 7) or during the observation in the hospital (cases 1, 4, and 6) a bone marrow picture characterized by almost total loss of erythroblasts (erythroblastopenia, aplastic anemia) and the appearance of giant pro-erythroblasts and their precursors (reticular cells, hemocytoblasts), entirely conforming to the description by Gasser (figs. 1, 2, 3).

The number of these giant cells varied from 0.6 to 4 per one thousand nucleated bone-marrow cells. These cells are very conspicuous by their appearance with the fine chromatin structure of the nuclei, distinct light blue round nucleoli and dark

Fig. 1.—Three giant cells in one field: left, a giant reticulo-histiocytic cell; right, a giant pro-erythroblast with dark blue vacuolized cytoplasm, and below, a megakaryocyte. (Case 6.)
FIG. 2.—Left, a giant reticulo-histiocytic cell with indistinct cell margin, light blue cytoplasm without granules, oval nucleus with fine reticulated chromatin structure, and distinct large light blue nucleolus. Right, a giant cell in mitosis (case 6).

FIG. 3.—A giant pro-erythroblast with dark blue cytoplasm, large fine reticulated chromatin structure of the nucleus and two distinct nucleoli (case 2).

blue cytoplasm in the older cells. The best method for finding these cells is by low power examination of the margins of the marrow film. We did not come across older giant cells than those described above. In some instances however we found pathologic mitotic figures (figs. 4, 5) and multinucleated giant erythroblasts (fig. 6). In five cases, where the reticulocytes were counted during the erythroblastopenia, the reticulocytes disappeared almost entirely from the peripheral
blood. In case 7 the number of the reticulocytes was 19 per cent four days after the bone-marrow puncture, while in case 4 counting at the reticulocyte has been neglected. The giant pro-erythroblasts disappeared within one week from the bone-marrow. The erythroblastopenia however lasted longer, the erythroblasts increased gradually, and became normal after a few weeks in the instances, where the children recovered from the erythroblastic crisis.

The clinical, blood and bone-marrow picture during an aplastic crisis of the cases are schematically shown in tables 1, 2 and 3 respectively. Three out of the seven patients died, case 1 five weeks, case 3 two weeks and case 7 one week after
Fig. 6.—A giant cell from the red system with multiple nucleoli (case 1).

**TABLE 1. — Clinical Picture**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (with edema)</th>
<th>Weight (without edema)</th>
<th>Edema</th>
<th>Mental changes</th>
<th>Hair changes</th>
<th>Skin changes</th>
<th>Loss of appetite</th>
<th>Abnormality of muscles</th>
<th>Pancreatic dysfunction</th>
<th>Hyperbilirubinemia</th>
<th>Fat infiltration of liver</th>
<th>Mantoux reaction</th>
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<td>Case 1</td>
<td>F</td>
<td>8</td>
<td>16.200</td>
<td>13.700</td>
<td>++</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
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<td>M</td>
<td>8</td>
<td>19.000</td>
<td>14.900</td>
<td>++</td>
<td>-</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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</tr>
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<td>5.760</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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</tr>
<tr>
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<td>6.520</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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</table>

entering the hospital. In the surviving children the condition of erythroblastopenia was followed by a high reticulo-cutaneous crisis. Case 1 was a girl 8 years of age with an almost complete kwashiorkor syndrome and a strong fat infiltration of the liver in which for the first time we came across the giant pro-erythroblasts. The Mantoux reaction was positive and the X-ray photograph showed an active tuberculous process in both lungs. Therapy consisted of INH, PAS and Streptomycin. The hemoglobin content of the blood decreased gradually from 7.6 Gm./100 ml. at admittance to 6.2 Gm. 100 ml. in one month and the bone marrow appeared to be aplastic. There were a few giant pro-erythroblasts present. The child died one week afterwards.

Case 2 was a boy of 8 years old with symptoms of kwashiorkor and a positive Mantoux skin test and a tuberculous process of the lung and a cold abscess of a rib. The bone marrow showed an erythroblastopenia with giant pro-erythroblasts. We considered these cells as identical to pro-megaloblasts so we gave to
diastase (Wholgemuth) amsd 19.2 u. hipase (Schwachmassn). The Mantoux skin
gastric juice was 32, the duodenal juice coistaed 25 u. trypsin (Gross) 25 u.
tush., urea 27 mg./100 ml., cholesterol 1 16 nsg./100 ml. thymol turbidity
Gm./100
The albumin content of the blood
vegetariams source (soya milk) with additiomsal vitamims C and

discoloration of the hair, hyper- and hypopigmentatiomi of the skin amsd atony
strotsg fat itsflltration was presemst in the liver. Edema, apathy,
test was 10.2 umsits Kimigsbury, total bilirubin 0.5 mg./100 ml. The total acidity of the
income group. The
diet has during the last six months been inadequate in pro-
marrow taketi five amid fifteen days afterwards showed a great number of eryth-

Table 2.—Blood Picture

<table>
<thead>
<tr>
<th>Case</th>
<th>Hb (gm. %)</th>
<th>Erythroblasts</th>
<th>Myelocytes</th>
<th>Metamyelocytes</th>
<th>Stab cells</th>
<th>Polym. cells</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Proerythroblasts</th>
<th>Macromegablasts</th>
<th>Megakaryoblasts</th>
<th>Megakaryocytes</th>
<th>Monocytes</th>
<th>Lymphocytes</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
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<td>+</td>
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<td>0</td>
<td>6</td>
<td>3.6</td>
<td>20</td>
<td>6</td>
<td>2</td>
<td>70</td>
<td>27</td>
<td>1</td>
<td>9</td>
<td>19</td>
<td>71</td>
<td>25</td>
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<tr>
<td>Case 2</td>
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<td>185</td>
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<td>187</td>
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<td>6</td>
<td>63</td>
<td>28</td>
<td>3</td>
<td>40</td>
<td>126</td>
<td>30</td>
<td>24</td>
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<td>90</td>
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Table 3.—Bone-Marrow Picture

<table>
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<tr>
<th>Case</th>
<th>Myeloblasts</th>
<th>Promyelocytes</th>
<th>Myelocytes</th>
<th>Metamyelocytes</th>
<th>Stab cells</th>
<th>Polym. cells</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Proerythroblasts</th>
<th>Macromegablasts</th>
<th>Megakaryoblasts</th>
<th>Megakaryocytes</th>
<th>Monocytes</th>
<th>Lymphocytes</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>MCH (fl)</th>
<th>Color index</th>
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<tbody>
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<td>18.4</td>
<td>19.2</td>
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<td>6.0</td>
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<td>0.4</td>
<td>0.4</td>
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<td>++</td>
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<td></td>
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<td>24.0</td>
<td>26.8</td>
<td>4.4</td>
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<td>26.6</td>
<td>16.0</td>
<td>13.6</td>
<td>7.8</td>
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<td>0.6</td>
<td>22.0</td>
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<td>2.8</td>
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<td>0.8</td>
<td>0.4</td>
<td>0.6</td>
<td>++</td>
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the boy daily injections of liver extract combined with 5 microgram vitamin
B12. There was only a slight reticulocytic crisis till 3 per cent, and the bone
marrow taken five and fifteen days afterwards showed a great number of eryth-
roblasts and no giant cells anymore.

The following three cases, however, show that even without “specific” treatment
the aplastic crisis can recover and that the giant cells disappear.

Figure 7 represents the course of the disease in case 4. This is a girl of one and
a half years old from healthy young parents, illiterate and from the lowest
income group. The diet has during the last six months been inadequate in pro-
teins. The albumin content of the blood was 2.29 Gm./100 ml., globulin 2.74
Gm./100 ml., urea 27 mg./100 ml., cholesterol 116 mg./100 ml. thymol turbidity
test 10.2 units Kingsbury, total bilirubin 0.5 mg./100 ml. The total acidity of the
gastric Juice was 32, the duodenal juice contained 25 u. trypsin (Gross) 25 u.
diastase (Wholgemuth) and 19.2 u. lipase (Schwachmann). The Mantoux skin
test was negative. Strong fat infiltration was present in the liver. Edema, apathy,
discoloration of the hair, hyper- and hypopigmentation of the skin and atony
of the muscles were present. Treatment consisted of a high protein diet from
vegetarian source (soya milk) with additional vitamin C and vitamin B complex
The hemoglobin content of the blood decreased gradually from 10.9 Gm./100 ml. to 5.9 Gm./100 ml. in three weeks time without any signs of increased hemolysis as jaundice or increased urobilin excretion in the urine. The reticulocytes disappeared almost entirely from the peripheral blood. The first bone marrow biopsy was applied on the tenth day and showed an almost complete disappearance of the erythroblasts and many giant pro-erythroblasts and precursors were seen. There were no megaloblasts of the ordinary size. For this aplastic crisis we did not give any specific treatment with liver extract, folic acid or vitamin B12. Nevertheless the bone marrow recovered and a reticulocytic crisis followed.

Six days after the first bone marrow biopsy the bone marrow was still aplastic, but we could not find any giant pro-erythroblasts any more. A complicated furunculosis and tonsillitis was treated successfully with penicillin. Because the condition did not improve satisfactorily soya milk was replaced by buttermilk. Treatment with folic acid 5 mg./100 ml. per day during ten days was not followed by a reticulocytic crisis and the hemoglobin content did not improve. Ferrous sulfate 600 mg./day orally gave a slight increase of the reticulocytes and the hemoglobin content of the blood increased gradually till 9.7 Gm./100 ml. in three weeks. One week after the second biopsy and two months afterwards the bone marrow was normal (fig. 7).

In figure 8 the course of blood and bone marrow picture of case 5 is summarized. This was a girl 22 months old with kwashiorkor and complicated purulent meningitis caused by Haemophilus influenzae. The aplastic crisis which was
The course of the meningitis consisted of penicillin (3,000,000 U./day), sulfadiazine (3 Gm./day) and chloramphenicol (1,600 Gm./day). The erythroblastopenia was followed by a reticulocytic crisis without any treatment with liver, folic acid or vitamin B12. The meningitis and the general condition improved, the hemoglobin content of the blood increased and the child was discharged in good condition.

The third case (case 6) of erythroblastopenia with giant pro-erythroblasts in which blood and bone marrow recovered without any “specific treatment” was a girl of three years and 8 months old with severe malnutrition and purulent pleurisy. Culture for microorganisms of the pleura exudate was negative. The child was treated with penicillin and streptomycin. The x-ray picture of the lung showed symptoms of a tuberculous process and indeed two and a half months afterwards the Mantoux skin test became positive and the child was treated with INH, PAS and streptomycin. We suspected an aplastic crisis because the hemoglobin content of the blood, the number of the erythrocytes and reticulocytes decreased gradually (fig. 9). Bone marrow biopsy showed an aplastic marrow of the red system with many giant pro-erythroblasts. There were no Ehrlich’s megaloblasts present. Four days afterwards the bone marrow showed many erythroblasts and no giant pro-erythroblasts. The reticulocytic crisis reached its summit at 25.4 per cent. The diet consisted of a high protein diet with ½ liter milk a day with additional vitamin C and B complex. The child could be discharged in good condition after half a year.

In case 3 and case 7 death came rather suddenly after erythroblastopenia had been diagnosed, so therapeutic measures could not be tried. Case 3 was a boy of one year and 7 months old with full kwashiorkor syndrome, and xeroph-
thrombocytopenia and hemorrhagic diatheses. Case 7 was a girl of five years and three months old, with kwashiorkor, keratomalacia, pneumonia and otitis media.

**Discussion**

Kwashiorkor is a form of protein malnutrition first described as an entity by Williams in 1933, and afterwards by many others from different parts of the world. Other factors as infection and intestinal parasites may aggravate the condition. Since not only protein deficiency, but lack of many vitamins may occur, symptoms of different kinds of vitamin deficiencies may be manifest. The joint FAO/WHO expert committee on nutrition stated in 1953 that severe kwashiorkor might be diagnosed in a child that presents a certain combination of the signs to be referred to below. The diagnosis should be made only after due attention has been given to the history of the disorder and the preceding diet and after a full clinical examination, together with observation of the biochemical and pathologic changes and the response of the signs and changes to treatment. Characteristic of kwashiorkor are the following: the weight is always markedly subnormal; mental apathy is always present; edema is sometimes present; the pancreatic enzymes are always severely reduced and the stools usually loose; the muscles are always wasted; the appetite is in many cases decreased; the hair and skin show dyspigmentation in varying degrees (discoloration of the hair, easy to pull off, "crazy pavement" dermatosis, hyper- and hypopigmentation, cracked skin); the serum albumen is always seriously reduced; at a certain stage in the illness, fat accumulates in the periphery of the lobules of the liver; moderate
anemia usually occurs, usually normocytic, but may be macrocytic in terms of mean corpuscular volume; the disease is common among weanlings; the diet before illness contained a low ratio of protein in proportion to its calory content; the child is always seriously ill and there is a high mortality rate in untreated cases; vitamin deficiencies may occur. There are many names for this disease in different parts of the world; “dystrophy de farineux” in France, “nutritional dystrophy” in India, “síndrome policariential en las infancias” in Latin America, “infantile pellagra” in South Africa, “malignant malnutrition” in East Africa “sugar baby” in Jamaica, “syndrome dépigmentation-oedème” in Belgian Congo and “malnutrition” in Mexico.

In a previous communication of 50 children with kwashiorkor, the author and collaborators found edema in 82 per cent, mental changes, loss of appetite and muscle atony in almost all cases, loose stools in 64 per cent, skin changes in 84 per cent, hair changes in 90 per cent, serum albumin below 3.0 Gm./100 ml. in 93 per cent, decreased hydrochloric acid of the gastric juice, trypsin, lipase and amylase content of the duodenal fluid in all cases examined, in 34 cases, in which liver biopsy was done, 28 had fat infiltration, 6 had fibrosis and 3 necrosis of the liver. Blood urea and cholesterol were in many cases far below the normal values. These children came from the lowest income group of the population and all had insufficient protein in their diet at home.

The majority of the bone marrows are normoblastic, only a few megaloblastic or intermediate megaloblastic (five cases). The decrease of cellularity, especially of the erythropoietic system of the majority and increase of reticulo-histiocytic system, was striking. The decrease of erythroblasts of the bone marrow is evident through the high myeloid-erythroid ratio of 13.4 in comparison to a ratio of 3.4 in a control group of 12 children and low reticulocytes count in many instances. The granulopoietic system is characterized by a relative increase of the granulocytes and the presence of pathologic cells as giant stab cells, vacuolization and hypersegmentation in many cases. Pathologic megakaryocytes, like hypersegmentation of the nucleus and vacuolization are detected in many instances, associated with thrombocytopenia in some cases. The mean hemoglobin content of the blood is 7.17 Gm./100 ml., and the number of erythrocytes 2.52 million. In regard to the pathogenesis we propose the following considerations of the main types of anemia in kwashiorkor seen in Djakarta:

1) a normochromic normocytic anemia due to bone marrow insufficiency (hypo or aplastic anemia);
2) a macrocytic/normochromic or hypochromic anemia with a normoblastic bone marrow as a consequence of the highly damaged liver (fat infiltration, fibrosis);
3) a hypochromic microcytic or normocytic anemia due to “iron deficiency”;
4) a macrocytic anemia with a megaloblastic bone marrow (Tropical macrocytic anemia) caused by lack of substances active in pernicious anemia syndrome. Other factors as infections, intestinal parasites, inadequate digestion, absorption and utilization of the food may play an important part too.

The seven children described in this article have all symptoms of kwashiorkor and came from the same material as the fifty cases mentioned above.

Gasser considered lability of the erythropoietic system as one of the main
causes for acute erythroblastopenia, while Chernoff and Josephson\textsuperscript{4} were of the opinion, that frequent infections and allergic processes were important factors. Dameshek and Bloom\textsuperscript{23} stated that the acute hemolytic crisis could be explained by exaggeration of the hemolytic mechanism and maturation arrest of the red cell precursors in the bone marrow induced by a pathologically hyperactive spleen. None of our cases showed splenomegaly.

The pathogenesis of the acute erythroblastopenia in our cases is still obscure, but we consider chronic protein deficiency with superimposed frequent infections as one of the important factors. All these children had at one or other time diarrhea with mucus or leukocytes in the stool (bacillary dysentery), three of the seven had a positive Mantoux reaction of which two had an active lung tuberculosis (case 1 and 2), another pleurisy (case 6), a fourth suffered from purulent meningitis caused by H. influenzae (case 5) and a fifth was suffering from pneumonia and otitis media (case 7).

The giant proerythroblasts are according to Undritz\textsuperscript{24} a product of abnormal and incomplete mitosis of the earliest red-cell progenitors, while Lüdin\textsuperscript{25} considered these cells as a form of disturbance of maturation of the erythropoiesis.

We are of the opinion that the giant proerythroblasts are pathologic forms of the erythropoiesis. It is possible that there exists a lack of unknown maturing factors in our cases. We consider these giant proerythroblasts not to be identical to megaloblasts for the following reasons:

1) These giant cells appear only for a short period in the bone marrow during an aplastic crisis (acute erythroblastopenia). In most cases they disappear a few days or at the longest period one week after the first bone marrow biopsy.

2) These giant proerythroblasts are not accompanied by megaloblasts of the ordinary size or more mature megaloblasts, and are not always accompanied by macrocytosis in terms of M.C.V. larger than 96 $\mu$.

3) These giant cells disappeared without any treatment with liver extract, folic acid or vitamin B$_{12}$.

**Summary**

Description of seven cases of kwashiorkor in children of one and a half to eight years of age, in which at one time or other an aplastic crisis (erythroblastopenia) occurred with the appearance of giant proerythroblasts or their precursors in the bone marrow. This condition independent of the treatment—reversed to normal in four cases and was followed by a reticulocytic crisis. Three of the children died during or shortly after the aplastic crisis. The author considers erythroblastopenia in these cases as due to insufficiency of the bone-marrow (lability) caused by chronic protein deficiency superimposed by frequent infections. The giant proerythroblasts are pathologic forms of erythropoiesis and are not identical with Ehrlich’s megaloblasts.

**Summario in Interlingua**

Es presentate un description de septe casos de kwashiorkor in infantes de inter un e medie e octo annos de etate. In omnes un crise aplastic (erythroblastopenia) occurreva a un tempore o un altre, insimul con le apparition de gigante proerythroblastos o lor precursores in le medulla ossee. Iste condition non esseva in-
ERYTHROBLASTOPENIA IN KWASHIORKOR

fluentiata per le tractamento. Illo returnava al stato normal in quatro casos e
esseva sequte per un crise reticuloctic. Tres del patientes moriva durante o
brevemente post le crise aplastic. Le autor considera le erythroblastopenia in
iste casos como effectuate per un insufficientia (labilitate) del medulla ossee que
habeva su causa in chronic carentia de proteina con le superimposition de fre-
quente infectiones. Le proerythroblastos es formas pathologic de erythropoiese
e non es identic con le megaloblastos de Ehrlich.

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