Hereditary Benign Erythroreticulosis

By Ingmar Bergström and Lennart Jacobsson

In the province of Västerbotten, North Sweden, we have observed a hitherto undescribed anomaly of erythropoiesis, characterized by: (1) a nonhemolytic normochromic anemia with a low or normal reticulocyte count and without indications of reduced activity of either granulocytopoiesis or thrombocytopoiesis; (2) a characteristic bone marrow picture, corresponding to that seen in the di Guglielmo disorder of erythremic myelosis; (3) an abnormal hemoglobin in the red blood cells; (4) a benign clinical course, but refractory to therapy; (5) a hereditary component.

The reports of the first two cases are briefly summarized below:

Case 1. In 1954–1955, a 35 year old man was admitted to the Medical Department, Umea, with symptoms of anemia. Physical examination was essentially negative, and there was no apparent enlargement of liver, spleen, or peripheral lymph node. Peripheral blood studies revealed a normochromic anemia with pronounced anisocytosis. The bone marrow picture disclosed changes similar to the di Guglielmo disorder, as seen in figures 3–6. Five years later, however, the patient was in the same condition with hemoglobin values of 7.9–9.5 Gm. per cent (Case No. 5 in Table 1).

Case 2. A 32 year old woman was admitted to hospital in October 1957 following an abortion. She had been anemic since childhood. The hemoglobin value was 7.9 Gm. per cent and the serum iron level was high. The preliminary diagnosis was megaloblastic anemia of pregnancy. The bone marrow smear showed, however, a picture resembling the di Guglielmo disorder. This woman was a niece of the above patient (Case No. 8 in Table 1).

As patients with such a bone marrow picture are extremely rare, we considered the appearance of two cases in one family so remarkable that a more detailed investigation of the family was carried out. A study of the family records going back to the middle of the 18th Century is pictured in Figure 1.

The cases are geographically centered mainly in and around the parish of Degerfors in the south of Västerbotten, and belong to the agricultural population. No admixture of Lapp or foreign blood has been found. There is no definite evidence of increased infant mortality or incidence of abortion. No congenital malformations are reported and there are no cases of mental disease. Judging from the records, the frequency of cancer appears to be high. There is one case of a first cousin marriage.

Figure 2 represents the number of persons examined, and amongst these, fifteen were found with the characteristic features of the disease. Blue eyes and brown hair were found characteristically in the family, particularly among those suffering from the disease. The mode of inheritance is as yet uncertain. The disease affects both sexes equally. The age at which clinical manifestations appear is variable, but two children, aged two and nine, were found among
Fig. 1.—The structure of the family. Brothers and sisters on the same horizontal line, the eldest to the left. The first two observed cases of the disease = ● ■; □ = male, ○ = female; △ = sex unknown.
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**Table 1.** A Summary of the Laboratory Data in 15 Clinically Affected Members of the Family.
those with typical signs. As a rule, liver, spleen and lymph node enlargement does not occur. The prognosis appears to be favorable. Until now no deaths have occurred among the known cases. Some patients are over 70 years of age.

The laboratory findings are summarized in table 1. The blood picture was characterized by a moderate normochromic anemia. The erythrocytes revealed a pronounced anisocytosis with a number of unusually large cells, some of which contained nuclear remnants. The reticulocyte counts were low or normal. The osmotic fragility was unchanged. The Coombs' test was negative. The leukocytes and the thrombocytes were not affected. The serum iron level was normal or somewhat elevated and the total iron-binding capacity was normal. In three cases, the incorporation of iron in the red corpuscles was studied with Fe²⁺ and revealed a somewhat increased renewal rate. The life span of the erythrocytes was determined with radioactive chromium and was found to be normal. The acidity of the gastric juice was normal in the majority of cases, but a diminished secretion of hydrochloric acid was occasionally observed. Cases in which the Schilling test was performed gave normal results. Porphyrinuria was not observed.

The most typical changes occurred in the bone marrow. Erythropoiesis was hyperplastic with abundant gigantoblasts, which resulted from division of the nuclei without simultaneous cytokinesis. This led to monstrous forms having a diameter of 50 to 60 μ containing up to 10 to 12 nuclei. These gigantoblasts were seen at all stages of maturation. There was a dissociation in the maturation between the nucleus and the cytoplasm as in the megaloblast. Di-, tetra- and polyploid mitoses were common, and so was karyorrhexis. No essential changes were seen in granulocytopoiesis or thrombocytopoiesis. On the other hand, abnormal gigantic reticulum cells and transitional forms between these and the erythroblasts were seen.

Sixteen members of the family, eight clinically affected and eight clinically healthy, were examined for the occurrence of abnormal hemoglobin by chromatography on ion-exchange column (Amberlite IRC 50) according to a modification of the technic described by Boardman and Partridge, and by electrophoresis on filter paper. The resistance to alkali denaturation was investigated in some cases where the method for the demonstration of fetal hemoglobin in the erythrocytes by Kleihauer et al. was also used.

In all the eight affected individuals and in five of the clinically healthy ones,
Figs. 3-6.—See legends, facing page.
a fast moving hemoglobin fraction was isolated from the chromatography column. The content of hemoglobin of this fraction varied from 6 to 31 per cent of the total amount eluted. The mobility was of the same magnitude as fetal hemoglobin. The resistance to alkali denaturation, however, was low and similar to adult hemoglobin. The mobility on paper electrophoresis at pH 8.6 was also like that of adult hemoglobin. No fetal hemoglobin could be demonstrated in the erythrocytes according to the technic of Kleihauer et al.

As regards therapy, which was used in five cases, iron was without effect. Liver extract and vitamin B₁₂ therapy led to no improvement, nor did folic acid. Supplementary blood transfusions remain so far the only treatment in the cases having severe anemia. ACTH and cortisone were not tried.

**DISCUSSION**

Hereditary anemias, except for hereditary spherocytosis, are rare in Sweden. In the hemolytic conditions the bone marrow is characterized by hyperactive erythropoiesis without specific qualitative changes.

Since 1917, di Guglielmo has in several papers described a disease which bears his name. Three instances of this disorder have been described in Scandinavia. The morphologic picture is characterized by a pronounced hyperplasia of erythropoiesis, often with striking qualitative changes, including megaloblastosis, and multinucleated erythrocyte precursors. The disease is not hereditary, and all indications point to a leukemic-like disease, or one which progresses to leukemia, as Dameshek and collaborators have pointed out. Some cases have a very lengthy course, however.

Emile-Weil, Rohr, Moeschlin, and Schleicher described cases of hypoplastic bone marrow characterized by atypical erythropoiesis with gigantoblasts. These were cases of osteosclerosis or metastatic bone disease—probably with compensatory extramedullary blood formation. This syndrome was named variously, “erythroblastose chroniques des adultes,” “leukoerythroblastosis,” “crypto-” or “pseudoerythroblastosis.”

In 1951 Wolff and von Hofe reported a pathologic bone marrow with gigantoblasts in a 31 year old woman and her three children—the only analogous hereditary condition we have found in the literature. Kho Lien-Keng observed in the bone marrow of seven children with kwashiorkor an abundance of gigantoblasts which appeared transiently. A temporary occurrence of gigantoblasts in children is also reported by Gasser.

A familial reticulopathia in the North of Sweden was studied by Kostmann. It is a congenital disorder with excessive proliferation of the reticuloendothelial system. The bone marrow dysplasia leads to granulocytopenia. Severe infections result in a rapid fatal course. In this disease no specific changes occur in

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*Fig. 3.—Bone marrow smear. Abnormal gigantic reticulum cell.*

*Fig. 4.—Bone marrow smear. Transitional form between reticulum cell and abnormal erythroblast and polychromatophilic gigantoblast.*

*Fig. 5.—Bone marrow smear. Basophilic gigantic erythroblast with five nuclei.*

*Fig. 6.—Polychromatophilic gigantic and orthochromatophilic erythroblasts.*

*Further evaluations of this abnormal hemoglobin are being carried out.*
erythropoiesis. However, there may be some connection with the disorder described by us. It is inherited and occurs in the same region. Both conditions might conceivably be due to grave disturbances of the reticuloendothelial system.

The di Guglielmo disorder and cryptoerythroblastosis may be excluded in our cases because of the pronounced hereditary pattern and the benign course. Wolff's and von Hobe's cases showed a tendency towards granulo- and thrombocytopenia. They observed no polyploid mitoses. In contradistinction to the non-hereditary conditions described by Gasser and by Kho Lien-Keng, the malformation of the erythroblasts reported by us was stationary over a long period of observation.

We propose to name this disorder hereditary benign erythroreticulosis.

SUMMARY

In the province of Västerbotten, Northern Sweden, we have observed a blood disease formerly unknown in Europe. It is characterized by:

1. A non-hemolytic normochromic anemia with a low or normal reticulocyte count and without indications of reduced or increased activity of either granulocytopoiesis or thrombocytopoiesis.
2. A characteristic bone marrow picture corresponding to the di Guglielmo disorder.
3. An abnormal hemoglobin.
4. A favorable clinical course, but refractory to therapy.
5. An hereditary component.

SUMMARIO IN INTERLINGUA

In le provincia Västerbotten, al nord de Sveda, nos has observate un previemente non describite anormalitate erythropoietic con le sequente characteristicas:

1. Un non-hemolytic anemia normochromic con basse o normal numeration reticulocytic e le absentia de indicationes de un reduction o un augmento in le activitate granulo- e thrombocytopoietic.
2. Un tableau characteristic del medulla ossee, in correspondentia con illo del disordine de di Guglielmo.
3. Un hemoglobina anormal.
4. Un favorable curso clinic, con refractorietate therapeutic.
5. Un componente hereditari.

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HEREDITARY BENIGN ERYTHRORETICULOSIS

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