The Occurrence of Megaloblastic Erythropoiesis in Patients with Hemochromatosis

By B. J. Koszewski, M.D.

Hyperchromic megaloblastic anemia is not a disease entity. Besides the pernicious anemia of Addison-Biermer which is due to a lack of Castle's intrinsic principle in the gastric juice, there is a series of illnesses that can lead to the deficiency of the antianemic principle and subsequently typical hematologic changes. According to Castle and Minot, Rohr, Wintrobe, Bernard, Wilkinson and other investigators one can classify these symptomatic anemias by a consideration of the factors which initiate the onset, such as dietary deficiency (infantile pernicious anemia, tropical megaloblastic anemia), disturbance of absorption (sprue, Bothriocephalus latus), increased consumption (pregnancy, infections) and disturbed storage (diseases of the liver).

We have observed that hemochromatosis frequently leads to a pernicious anemia-like blood picture. This form of anemia, which also shows rather distinctive features, is little known. A detailed discussion concerning this syndrome is therefore presented.

Review of Literature

Occasional observations of extreme bronzed discoloration of the skin (without complicating insufficiency of the cortex of the adrenal) in cases of pernicious anemia has been described as early as 1877 by Muller, and later by Immermann, French and other investigators. It was only in 1915, however, that Roth reported the occurrence of pernicious anemia for the first time in an authentic case of severe hemochromatosis. The patient was a 51 year old man with megaloblastic-megalocytic anemia. Hemoglobin concentration was 30 to 36 per cent and the red cell count was between 0.98 and 1.25 million per cu.mm. The clinical diagnosis of hemochromatosis was confirmed by autopsy findings. In 1928 Seinet described 4 cases of pernicious anemia among 11 cases of anatomically proved hemosiderosis of the pancreas. In 3 cases the pathologic findings suggested hemochromatosis. In a review of 22 autopsied cases of hemochromatosis, Bork also mentioned the presence of 1 case of pernicious anemia. Then Markoff reported the detailed observation of hemochromatosis and pernicious anemia in a 60 year old man. The bone marrow, included for the first time into the description of the disease, showed an extensive deposition of hemosiderin in the reticulum cells besides typical megaloblastic erythropoiesis. Cain also described a case of pernicious anemia in hemochromatosis, which was followed clinically for quite a long time. A similar case was reported by Harvier and Mallarmé. Hotz found 4 cases of hemochromatosis in a series of 24 cases of pernicious anemia complicating cirrhosis of liver. His observations already indicate the frequent appearance of pernicious anemia in hemochromatosis.

It is remarkable that most of the literature concerning the presence of pernicious anemia in hemochromatosis appeared in Switzerland. This is perhaps caused by the generally higher incidence of pernicious anemia in this country. Very little discussion about this condition is found either in the American, English, French or in the German literature. Even recently Büchmann and Schenz denied the genesis of a real megaloblastic anemia in hemochromatosis.
OUR OWN OBSERVATIONS

Our own observations include 35 patients with hemochromatosis, who were admitted to the Department of Medicine during the last twenty years (1932 to 1951). Nine of these cases showed blood and bone marrow changes resembling pernicious anemia.

Prior to a description of their hematologic changes the clinical findings of the 9 cases can be summarized as follows:

Case report I. W. L. was a 57 year old male farmer. He was admitted October 1, died October 7, 1936. Diagnosis was chronic alcoholism. Pain and disturbed sensibility in the legs lasted for one and one-half years, ascites for one-half year. He also had anemia with burning of the tongue.

Clinical findings: pigmentation of skin, ascites, enlargement of liver, polyneuritis. No glycosuria. Total serum protein 5.2 Gm. per cent. Bilirubin 1.1 mg. per cent. Takata test positive. Weltmann's coagulation hand flocculation to 0.4 per thousand CaCl₂. Total serum cholesterol 110 mg. per cent. Severe macro-megalocytic anemia (table 1). Reticuloocyte count rose from 3.25 per cent to 8.1 per cent after liver therapy. Death due to circulatory failure.

Autopsy*: pigment cirrhosis of the liver with slight fatty degeneration. Pigment cirrhosis of the pancreas. Hemosiderosis of the spleen, mucosa of gastro-intestinal tract, myocardium, lungs, thyroid, tonsils, skin, bone marrow and abdominal and tracheobronchial lymph nodes. Hunter's glossitis. Atrophy of the gastric mucosa.

Case report II. N. W. was a 69 year old male worker. He was admitted January 8, died January 17, 1938. Previous hospitalization in 1932 was due to alcoholic liver disease. He suffered from fatigue and general weakness for years. He was readmitted due to hematemesis and diarrhea.

Clinical findings: brown discoloration of the skin. Liver not enlarged. Sugar negative in urine, porphyrin positive. Total serum protein 5.4 Gm. per cent. Bilirubin 5.6 mg. per cent. Takata test positive. Weltmann's coagulation band 0.3. Cholesterol 76 mg. per cent. Macro-megalocytic anemia. Reticuloocyte count rose from 3.3 per cent to 18 per cent after blood transfusions. Death in coma hepaticum.

Autopsy: atrophic pigment cirrhosis of the liver. The liver also showed many areas of focal necrosis, the nature of which was not clearly demonstrable. Pigment cirrhosis of the pancreas. Hemosiderosis and pseudomelanosis of the intestines. Chronic splenic tumor. Esophageal varices.

Case report III. St. A. was a 68 year old female housewife. She was admitted May 29, died June 1, 1941. She had alcoholism, asthenia for six months and sprue-like diarrhea for four weeks.


Case report IV. J. M. was a 72 year old female housewife. She was admitted December 29, 1947, died January 1, 1948. Chronic alcohol abuse for years. Growth of beard for twenty years. Emaciation and increased pigmentation of the skin for one year. Mental confusion.

Clinical findings: cachexia, pigmentation of the skin. Petechiae. Enlargement of the

* All autopsies were performed in the Department of Pathology (Prof. H. v. Meyenburg), School of Medicine, University of Zurich. Special stains for deposition of iron pigment in the cells were positive in all cases.
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Megablastic Erythropoiesis with Hemochromatosis

Liver. Sugar in urine negative. Serum iron 170 gamma per cent. Bilirubin 1.7 mg. per cent. Serum protein 5.1 Gm. per cent. Takata test positive. Woltmann's coagulation band 0.15. Cholesterol 217 mg. per cent. Prothrombin 40 per cent. Exitus in stupor.

Autopsy: pigment cirrhosis of the liver and the pituitary. Hemosiderosis of the pancreas, parapancreatic lymph nodes, spleen, stomach, duodenum and the right adrenal gland.


Case report VI. B. L. was a 69 year old female laundress. She was admitted May 11, died May 16, 1948. Chronic alcoholism. Extreme alcoholism. Extreme fatigue for months. Increasing pallor. "Pins and needles" in the legs.


Severe macro-megalo-ecytic anemia. Exitus in pulmonary edema.

Autopsy: pigment cirrhosis of the liver and the pancreas. Severe hemosiderosis of the spleen, intestine, para-pancreatic and para-aortal lymph nodes. Atrophy of the lingual and gastric mucosa.

Case report VII. L. A. was a 67 year old male merchant. He was admitted March 3, died March 6, 1949. Since 1949 tendency to diarrhea. Since summer 1949 persistent, increasing icterus.

Clinical findings: very poor general condition, numerous petechiae. Liver not palpable. Fatty stools. Urine sugar negative. Serum iron 215 gamma per cent. Bilirubin 1.3 mg. per cent. Serum protein 4.9 Gm. per cent. Cephalin flocculation negative. Cadmium reaction ++. Takata test positive. Woltmann's coagulation band 0.2. Total serum cholesterol 81 mg. per cent. Prothrombin 30 per cent. Bilirubin 1.7 mg. per cent. Serum iron 225 gamma per cent. Bilirubin 1.7 mg. per cent. Serum iron 170 gamma per cent. Bilirubin 1.7 mg. per cent. Serum protein 5.1 Gm. per cent. Takata test positive. Woltmann's coagulation band 0.15. Cholesterol 75 mg. per cent. Prothrombin 15 per cent. Exitus in coma hepaticum.


Case report VIII. H. A. was a 74 year old male beer carrier. He was admitted October 17, died December 7, 1950. Since 1940 pernicious anemia which responded well to liver therapy. Alcohol abuse. In 1942 diagnosis of cirrhosis of liver. Histamine-refractory achylia. Worsening of general condition, edema and dyspnea appeared a few months prior to present admission.

Clinical findings: cachexia. Pigmentation of the skin. Enlargement of the liver. Ascites. Urine sugar negative. Serum iron 140 gamma per cent. Bilirubin 1.4 mg. per cent. Serum
protein 6.0 Gm. per cent. Cephalin flocculation +++. Cadmium reaction +++. Weltmann's coagulation band 0.15. Total serum cholesterol 74 mg. per cent. Prothrombin 50 per cent. Slow improvement of the anemia upon liver extract therapy. Exitus in heart failure.


Case report IX. G. E. was a 50 year old male blacksmith. He was admitted February 10, died February 16, 1951. Chronic abuse of alcohol. Anorexia for three years. Occasionally melena. Cirrhosis of the liver and hyperchromic macrocytic anemia diagnosed two years prior to admission.


As shown in our analysis most of the patients were admitted in such a poor condition that therapy was unsuccessful.

The presence of hemochromatosis could be proved by autopsy in 8 cases, so that there is no doubt about the diagnosis. In the only surviving patient (Case VI) the diagnosis, as based on the clinical findings, appears to be certain.

Pigment cirrhosis of the liver and the pancreas was found in all the autopsied cases, accompanied by extensive hemosiderosis of the gastro-intestinal tract. Most of the cases also showed hemosiderosis of the spleen and the abdominal lymph nodes.

Hemochromatosis was diagnosed intra vitam in 6 cases. In 3 cases (Cases I, VII, VIII) the combination of pernicious anemia and hemochromatosis was recognized only after autopsy.

Clinically, cirrhosis of the liver was the chief symptom. Two cases presented the picture of coma hepaticum. In 6 cases there was a distinct pigmentaion of the skin. Not a single patient was found to be diabetic. All cases showed the evidence of dysproteinemia (positive Takata, cephalin or cadmium reaction, elongated Weltmann's coagulation band) which is typical for cirrhosis of the liver.11 Hypoproteinemia could be demonstrated in 7 of 9 cases. Of 7 cases in which the serum iron level was determined it was elevated in 6. This, however, does not help to clarify the diagnosis as serum iron is increased in both cirrhosis and pernicious anemia.15, 29, 41 The total cholesterol level in serum should be elevated in cases of hemochromatosis.5, 11 It was, however, mostly lowered in our cases, a fact which possibly was due to the absence of diabetes mellitus. The prothrombin concentration of plasma was always found to be lowered, a frequent occurrence in severe liver diseases.36

The tendency to diarrhea was very conspicuous in 5 of the 9 patients. This could be explained by the extensive hemosiderosis of the gastro-intestinal tract which caused a disturbance in absorption. Stools were examined in 2 cases and were found to be sprue-like with a high fat content. Since all of the patients were very much debilitated, fractional gastric analysis was done only in 3 cases. All 3 showed achylia refractory to histamine.
MEGABLASTIC ERYTHROPOIESIS WITH HEMOCHROMATOSIS

Blood and Bone Marrow Changes

The hematologic findings are presented in table 1. The routine examinations, as usually carried out in our clinic, are listed.

The bone marrow was always taken from the sternum. The differential count of the bone marrow smears was done according to Rohr's technic, counting 300 cells of the myeloid and lymphatic series and all the cells of the erythroblastic series as well as the reticulum cells encountered during the counting of 100 cells of the white series.

The peripheral blood was investigated simultaneously with the sternal marrow puncture. The leukocyte and erythrocyte counts were done as usual by means of the Turk-Bürker counting chamber. The determination of hemoglobin was done with Sahli's hemometer. The differential count of the white blood cells was done by the cover glass method. The reticulocytes were counted according to the method of Wolfer and the thrombocytes according to Fonio's method.

As is shown in table 1, all the patients were severely anemic on admission. The first hemoglobin values ranged from 19 to 63 per cent, with an average of 36 per cent. The RBC varied between 0.7 to 1.92 million per cu. mm, with an average of 1.23 million. The color index averaged 1.51 with a spread between 1.25 and 1.81. Morphologically the blood picture showed rather uniformly slight anisocytosis and a predominance of big hemoglobin-rich macrocytes. There was also a megalocytosis of different intensity. In a few cases erythroblasts and/or megaloblasts were seen in peripheral blood. The reticulocyte count on admission averaged 1.5 per cent, with a range of between 0.05 per cent and 3.3 per cent. The reticulocyte count did not rise in 5 patients who died a few days after admission, but in these patients the time was too short for the intensive liver therapy to take effect. Four patients who survived for more than six to eight days, showed a considerable increase in reticulocytes. In Case II, this occurred after a blood transfusion (spontaneous reticulocyte crisis), in Cases I and VI it occurred after injections of liver extract. The insufficient response of Case VIII, whose reticulocyte count rose from 1.4 per cent to only 4.0 per cent could be explained by previous treatment with liver preparations.

Most of our patients displayed leukopenia. The average white cell count was 2900, with a range of from 1200 to 7200 per cu. mm. Qualitatively, there was a lymphopenia as well as a relative neutrophilia. Only Case III, who had a lymphocytosis, was an exception. However, this absolute lymphocyte count of 874 per cu. mm. was still much below normal (1500 to 2000). In a few cases myelocytes were found in the peripheral blood. There was always a conspicuously low percentage of rhabdocytes in the differential white cell count. Only 3 patients with inflammatory complications showed a shift to the left, i.e., above 15 per cent.

Hypersegmentation of the nuclei as well as giant forms were occasionally observed among the neutrophils. There was an obvious eosinophilia in 2 cases. Monocytes were usually present in low percentage.

Thrombocyte counts were done in 8 cases. The average was 16,300 with a range from 4,300 to 27,000. The bleeding and clotting times were usually prolonged. There were hemorrhages into the skin and mucous membranes in 7 cases. Rumpel-Leede's test was positive in 5 of the 6 patients who underwent this examination.

The myelogram also presented considerable abnormalities. Most of our cases
showed an obvious hyperactivity of erythropoiesis. If 20 to 40 erythroblasts per 100 white cells is considered to be the normal ratio\textsuperscript{30} the average erythroblast–white cell ratio in these cases was often twice as high as normal. Only in 1 case (Case V) was the ratio almost normal, while a few cases had as many as 110 to 121 cells of the erythroblast series for every 100 white cells. Most of the erythroblasts, many of them in the form of macroblasts, were basophilic or polychromat. Megaloblasts were found in all 9 cases, although sometimes only in small numbers.

The leukopoiesis also showed deviation from the normal. The immature elements such as myeloblasts, promyelocytes and the so-called immature myelocytes\textsuperscript{47} were very numerous. Giant forms were seen in every stage of maturation of the white cells. Mitosis was seldom present. The number of the eosinophils in the bone marrow was mostly increased, while no parallel increase was seen in peripheral blood. Morphologically there was nothing unusual in lymphopoiesis,

although generally, the percentage of lymphocytes was reduced. The number of megakaryocytes was decreased.

The most conspicuous change was seen in the reticuloendothelium of the bone marrow, quantitatively as well as morphologically. There was an increase in the number of reticulum cells, mainly the lymphoid cells. The number of plasma cells and macrophages was also increased, and most macrophages were filled with hemosiderin. In addition, typical lymphoid cells and even the plasma cells showed a storage of pigment. The last discovery deserves some special attention as no other phagocytic processes have yet been demonstrated in the plasma cells (fig. 1).

As a conclusion we can say that the above findings pointed to the diagnosis of pernicious anemia. The presence of megaloblasts in the hyperplastic bone marrow, the simultaneous appearance of megalocytosis in peripheral blood and the reticulocyte crisis in the surviving cases represent all the findings required for the diagnosis.\textsuperscript{46} Other typical symptoms, namely a conspicuous hyperactivity of erythropoiesis with predominance of the immature elements, the shift to the left of leukopoiesis, the extreme leukopenia, the presence of the hypersegmented
neutrophils in peripheral blood as well as the thrombocytopenia were also present.\textsuperscript{14, 41, 52, 61, 62, 70}

The anemia, however, presented some peculiarities which required further explanation. For instance, there was a severe hemorrhagic diathesis in all cases investigated, whereas this is usually absent in ordinary pernicious anemia in spite of the ever present thrombocytopenia. The peripheral blood did not reveal that degree of anisocytosis and poikilocytosis characteristic of ordinary pernicious anemia. There was a preponderance of great round macrocytes in the peripheral blood and of macroblasts in the bone marrow. Both were quite different from megalocytes and megaloblasts\textsuperscript{31, 50, 62, 72}; their presence could not solely be explained by deficiency of antiperinicious anemia factor.\textsuperscript{31, 40, 45, 53} The increase in bone marrow reticulum with extremely abundant hemosiderin phagocytosis was also unexpected. Therefore, it was important to study other factors which could be responsible for these changes, especially the role of hemochromatosis.

\textit{Pathogenesis of Megaloblastic Anemia in Hemochromatosis}

According to Gram,\textsuperscript{27} Schulten and Malamos,\textsuperscript{55} Gamma,\textsuperscript{24} Fellinger and Klima,\textsuperscript{29} Wintrobe and Shumacker\textsuperscript{69} and other investigators,\textsuperscript{31, 33, 47} macrocytosis of the peripheral blood and macroblastosis of the bone marrow are typical findings in cirrhosis of the liver. Likewise, an increase in marrow reticulum indicates advanced hepatic cirrhosis.\textsuperscript{3, 31, 50, 63} Thus these findings in our cases were caused by pigment cirrhosis of the liver and may rightly be attributed to the symptomatology of hemochromatosis.

Rohr\textsuperscript{29} and Hotz\textsuperscript{31} emphasize the fact that the simultaneous occurrence of cirrhosis of the liver and megaloblastic anemia in the same patient is encountered not infrequently and therefore appears to be more than a mere coincidence of the two conditions. According to these authors, liver cirrhosis with its gastrointestinal complications often results in the hindrance of the storage of the anti-anemic factor as well as disturbance of its formation and absorption. Since one-fourth of all our cases of hemochromatosis showed a pernicious anemia-like blood picture, we have to assume that there is a cause-and-effect relation between pigment cirrhosis and megalocytic anemia. The morphologic findings in peripheral blood and bone marrow also support this hypothesis.

The severe macrocytosis of peripheral blood, the partly macroblastic, partly megaloblastic erythropoiesis and the hyperplasia of the reticulum of the bone marrow suggest that the terminal megaloblastic anemia had evolved from a macrocytic anemia of pigment cirrhosis of the liver. This mechanism is particularly well illustrated by Case VI, in which there was a progressively severe macrocytic anemia for years, which finally developed into megalocytosis. The liver therapy led to a compensation of the anemia with disappearance of megaloblasts in the bone marrow and of megalocytes in the peripheral blood, but the macrocytosis remained unchanged. Case VIII, in which pernicious anemia was present for eight years, while the hemochromatosis remained unsuspected until autopsy, did not contradict this explanation either. Although clinical evidence of liver cirrhosis appeared rather late, there were from the onset in peripheral blood, as the first sign of cirrhosis, many big round macrocytes besides megalocytes.
The constant presence of hemorrhagic diathesis, which was due partly to a thrombocytopenia, partly to a hypoprothrombinemia also indicated the important role of the pigment cirrhosis in the genesis of this anemia.

In all our cases a severe, decompensated liver cirrhosis existed which by itself was able to cause a deficiency in the storage of antianemic substances (vitamin $B_12$, folic acid). However, this was not the only cause. Simultaneously there was also present an extensive hemosiderosis of the gastro-intestinal tract, which could be responsible for the disturbance of the formation and absorption of the antianemic factor. Five of our 9 patients had a tendency to diarrhea, and all 3 cases in which gastric analysis was carried out, showed histamine refractory achylia.

Therefore, we have to assume that the pathogenesis of megaloblastic anemia in hemochromatosis, as in liver cirrhosis, is a very complex one. Disturbance in storage as well as in formation and absorption plays a certain part in it. Only when all these factors are present for a long time, does a lack of the antianemic factor ensue. This explains why only some cases of hemochromatosis develop blood changes resembling pernicious anemia.

However, from the morphologic standpoint, we can no longer assume that the megalocytic anemia in hemochromatosis is just another form of pernicious anemia in hepatic cirrhosis. The severe hyperplasia of the reticulum of the bone marrow with increased pigment phagocytosis, which appeared even in the plasma cells, makes this anemia quite unique and distinguishes it from the other pathogenetically related conditions.

**Phagocytosis of Hemosiderin in Plasma Cells of the Bone Marrow**

Although the plasma cells are generally classified with the reticulum cells, their phagocytic activity has not been demonstrated as yet. The different inclusion bodies, as vacuoles, amyloid granules, Russell bodies and azurophilic rods, which often appear in myeloma and plasma cell leukemia, are related to disturbances in protein production and can by no means be considered as evidence for phagocytic activity. Following the injection of India ink into the bone marrow, Dubois-Ferrière reported a minimal storage of India ink in the plasma cells. However, considering his procedure, and the fact that the myelocytes and the neutrophils also have stored the pigment, the possibility of artifacts must be kept in mind. Many hematologists still consider the plasma cells to represent a special cell group characterized by an individual process of development and distinctive method of reaction. However, our observation of phagocytized hemosiderin in the plasma cells makes it certain that they do belong to the reticulo-endothelial system of the bone marrow. This kind of phagocytosis was present in all our cases of hemochromatosis with megaloblastic anemia. We did not observe this finding in cases of idiopathic pernicious anemia (24 cases), and megaloblastic anemia in hepatic cirrhosis (12 cases), in sprue (4 cases) or after gastric resection (5 cases). These comparative investigations and the fact that iron pigment in plasma cells was present in all 9 cases of megaloblastic anemia in hemochromatosis excluded the possibility of artifacts. The presence of hemosiderin was proved...
in all cases after development of a new stain for iron pigment, which permitted us to examine the May-Gr"unwald-Giemsa stained preparations for their iron contents.

Phagocytosis of hemosiderin in plasma cells of the bone marrow could seldom be seen in cases of uncomplicated hemochromatosis. In studying the puncture specimens of the sternal bone marrow in 10 cases of simple hemochromatosis, slight storage of hemosiderin in the plasma cells was encountered only in 2 instances. Thus it appears to us that numerous hemosiderin inclusions in the plasma cells seem to be pathognomonic for the megalocytic anemia in hemochromatosis. This finding enables us to distinguish megaloblastic anemia in hemochromatosis from the other forms of megaloblastic anemia.

The etiology of this phenomenon is unknown. Basically, the disturbance of the iron metabolism in both diseases could be responsible for it. In hemochromatosis the abnormal regulatory process leads to a pathologically extensive iron storage in the body, so that many internal organs, including the bone marrow, contain a great deal of iron positive pigments. On the other hand, there is also an increased hemosiderin formation in megalocytic anemias. Therefore, one can assume that the already burdened bone marrow of a patient with hemochromatosis is unable to cope with the overwhelming supply of hemosiderin due to megalocytic anemia, and has to use all its varied capacities to effect an adequate disposition of the iron. Under this condition, the plasma cells, which ordinarily are charged with the function of building plasma proteins, begin to phagocytize.

Only a part of the plasma cells in the bone marrow are loaded with hemosiderin. Morphologically, these phagocytizing cells (fig. 2) do not appear to differ from the pigment-free plasma cells. It is difficult to suppose that these cells have been fundamentally changed. It would seem to us that the plasma cells are capable of phagocytosis under certain conditions and constitute an integral part of the reticulo-endothelial system of the bone marrow.

**SUMMARY**

The occurrence of megaloblastic anemia in hemochromatosis was observed in 9 patients. The anemia was characterized by a macromegalocytic blood picture,
a hyperactive macromegaloblastic erythropoiesis as well as a positive response to liver therapy. The bone marrow reticulum was hyperplastic and showed extensive hemosiderin phagocytosis. The hemosiderin was also stored in the plasma cells. This unusual finding is pathognomonic for megaloblastic anemia of hemochromatosis and distinguishes it from the other symptomatic megaloblastic anemias.

Megalocytic anemia occurs relatively frequently in hemochromatosis. Pigment cirrhosis of the liver and hemosiderotic changes in the gastrointestinal tract seem to be responsible for its genesis. Disturbance in storage, absorption and formation of the antianemic principle favors the accompanying hematologic changes.

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