Erythremic Myelosis (Di Guglielmo’s Disease)

Critical Review with Report of Four Cases, and Comments on Erythroleukemia

By STEVEN O. SCHWARTZ, M.D. and JOAN CRITCHLOW, M.D.

I. INTRODUCTION

The nature and occurrence of a syndrome generally designated* as erythremic myelosis or Di Guglielmo’s disease have been reported more fully in the European literature than in the English and American publications in which the relatively few references† rarely contain critical or descriptive material. For this reason, it has seemed advisable to report 4 cases encountered within the last six years, and to review and evaluate the present understanding of the disease.

Our cases were characterized by chronic refractory anemia, enlargement of the liver and spleen, and proliferation in the marrow of young erythroid cells that failed to mature.

There were the common denominators in the peripheral blood of all 4 patients: severe hypochromic or normochromic anemia, in which the red cell counts were generally below 3 million; severe anisocytosis and poikilocytosis; low reticulocyte counts that failed to rise appreciably after liver extract administration; normal to low white cell counts; a differential formula with wide variation but usually showing some degree of monocytosis; a left shift in granulocytes, with a preponderance of unsegmented forms; occasional eosinophilia; and a depressed platelet count without hemorrhagic manifestations. In 2 cases nucleated red cells occurred in small numbers.

There were the striking observations of the marrow: highly active erythropoiesis, accompanied by an apparent severe degree of maturation arrest; and prominent abnormal red cell forms, suggesting direct origin from the reticuloendothelium. Two of the cases showed, in addition, alteration in granulopoiesis, with giant band cells and large metamyelocytes, reminiscent of those seen in pernicious anemia.

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Aided by grants from the Olivia Sue Dvore, Edward Friedman, and Robert I. Goldblatt Foundations.

Submitted December 31, 1951; accepted for publication June 2, 1952.

* The Cumulative Index Medicus lists some reports of the disease under Anemia as well as Polythemia. Others are to be found under Erythroleukemia and Erythroblastemia. The nosologic problem is discussed in detail in the section on Terminology, page 767.

† More recent references in the literature, not discussed in this presentation, are listed as references 33 to 42.
There were the typical accompaniments to the disease in these patients, all women, whose duration of illness varied from ten months to eight years: low grade fever and loss of weight.

There was the inevitable course: symptomatic relief only by blood transfusions; ineffectual therapy with liver extract, folic acid and iron preparations; futility of splenectomy (performed in 2 cases in which the patients died so soon afterward that the value of splenectomy could not be fairly assessed); the fatal end. Autopsy was performed in 3 cases.

II. HISTORICAL BACKGROUND

The concept that erythremic myelosis represents a primary proliferation of the erythropoietic portion of the marrow originated with the Italian hematologists. The description of its clinical and anatomic features as well as most of the cases reported appear in the Italian literature.

Copelli as early as 1912, in an article entitled, “A Systemic Hemopathy with Erythroblastic Hyperplasia (Erythromatosis),” presented a carefully studied case characterized clinically by weakness, progressive anemia and splenomegaly. The anemia was normochromic and was accompanied by leukopenia; no nucleated red cells were found in the peripheral blood. The case presented foci of abnormal erythropoiesis in the liver, spleen, lymph nodes and marrow. Predominant in the lesions were large erythroblastic cells which Copelli compared to the primitive blood cells of Maximow. Atypical megaloblasts (normoblasts C, metarubricytes) were present in fewer numbers and normoblasts (normoblasts C, metarubricytes) were least numerous. Copelli regarded the lesions as neoplastic phenomena of the younger, more embryonal elements of the red cell line which evolved in an atypical and incomplete manner, having lost the characteristics of mobile cells and acquired those of fixed cells or tissue cells. He defined this disordered hyperplasia of the erythropoietic system as “atypical erythromatosis” and considered the possibility that a respiratory infection provided the cytoblastic stimulus.

In 1917 Di Guglielmo observed a case that he called “erythroleukopiasmia” because of an increased number of erythrocytes, leukocytes and platelets, with immature and undifferentiated forms of all three in the peripheral blood. He maintained that the erythrocytic alterations could not be considered secondary to a leukemic process, but that the lesion was primary in the myeloid tissue and affected all three cytopoietic components. From his study of this case he conceived the idea of a primary erythroblastic proliferation analogous to leukemia, and not incidentally associated with but rather the result of the same pathogenetic process. In 1923 Di Guglielmo published a case that he considered the first example of a true erythremic myelosis; this was followed in 1926 by the report of two more cases: one in a newborn child, the other in a man of 50. Of these 3 cases, reviewed in his 1928 publication, only the third warrants critical examination. In 1936 Di Guglielmo recognized about 21 cases in the Italian literature which corresponded to his interpretation of erythremic myelosis. In this article he took cognizance of the work of Cooley in the clarification of the entity known as erythroblastic anemia or Cooley’s anemia. At that time he considered both of these conditions as varieties of erythremic myelosis. In 1946
Di Guglielmo again reviewed the subject and redefined his concept of erythremic myelosis more strictly, laying down new criteria by which this condition might be differentiated from others. Discussion of the revised concept appears in succeeding sections of this presentation.

In 1937 the subject of erythremic myelosis was reviewed by Storti, and in 1938 by Baserga who collected 29 cases from the Italian literature. The subject was again reviewed by Moeschlin in 1940, and in his opinion, many cases did not stand critical evaluation either because of insufficient data or diagnostic errors. Moeschlin accepted only 5 cases as examples of true erythremic myeloses: those of Lazzaro, Benedetti, Paradiso, and 2 cases published by Di Guglielmo. In France P. Chevallier recognized the first case of erythremic myelosis in 1937, and, in the period between 1937 and 1946, Mallarmé and Moulounguet recognized 8 cases that met their diagnostic criteria.

III. TERMINOLOGY

In describing the entity that bears his name, Di Guglielmo used the terms eritrernie, eritremia, and mielosi eritrernica interchangeably. Moeschlin and Duesberg prefer the term true erythroblastosis. In France the term erythremia proved confusing because it had been used to describe polycythemia vera. The terms erythromyelosis, proposed by Chevallier, or erythromyelose maligne have been generally used in France. The advantage of these terms is that it permits one to speak of erythroleukomyelosis for intermediate cases.

Under the title erythroblastose chronique, the French, notably P. Emil-Weil, refer to a splenohepatic disease of chronic course which should not be confused with that described by Di Guglielmo. Erythroblastose chronique corresponds more accurately to the entity known in American literature as myelophthistic anemia.

Because the terms erythremia and erythroleukemia have been confused with such diverse conditions as polycythemia vera, acute hemolytic anemias, the various reticulo-endothelioses, Cooley’s anemia, pernicious anemia, acute leukemias and erythroblastosis fetalis, there have been countless misunderstandings. The confusion has been worsened by lack of a strict hematologic terminology and further compounded by a tendency to coin new terms for every purported new syndrome. In the interest of clarity, therefore, the terms erythremic myelosis and erythroleukemia are used in this presentation as defined by Di Guglielmo and Moeschlin respectively. It is believed that these terms are sufficiently descriptive and are less likely to be confused with other designations; moreover, their use gives Di Guglielmo credit for his work in developing the concept and in interrelating the condition with other dyscrasias.

IV. DEFINITIONS

Di Guglielmo defines the erythremic diseases as specific and primary entities characterized by generalized and systemic proliferations, selectively affecting the erythropoietic apparatus. The term erythremic myelosis is used to indicate the parallelism with the leukemic myeloses. According to their course there are acute and chronic forms, as well as neoplastic, anerythremic and hypoplastic or aplastic forms. In the anerythremic form, nucleated red cells are lacking from
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the peripheral blood. The hypoplastic or aplastic form shows hypoplasia or aplasia of the marrow.

Hematologic terms used by authors in cases from the literature cited here have not been changed; however, when these terms differ from ours, inserted in parentheses will be found the terms used in our laboratory and approved by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs. The terms inserted parenthetically are those understood to be equivalent stages in the red cell development, according to the following definitions:

Erythrogon—Rubriblast: The youngest recognizable cell of the erythrocyte series. Its nucleus has a fine chromatin structure which is usually stippled. Nucleoli are usually discernible. Cytoplasm is scant and dark bluish-green (May-Grunwald-Giemsa preparations).

Normoblast A—Basophilic Rubricyte: A cell of the erythrocyte series having a definite structure of the nuclear chromatin but no discernible nucleoli. The cytoplasm is dark blue and relatively more abundant than in the erythrogon.

Normoblast B—Polychromatic Rubricyte: A cell of the erythrocyte series having a well-defined structure of the nuclear chromatin with thick strands. The nuclear mass is relatively smaller than in the previous stages and the cytoplasm is gray.

Normoblast C—Metarubricyte: A cell of the erythrocyte series with a pyknotic nucleus and normochromatcytoplasm.

For the most part the terms megaloblasts and megaloblastic have not been used, except when these were the actual terms used by writers in reports in the foreign, particularly the Italian, literature. These terms are otherwise reserved for the abnormal type of hematopoiesis consequent to a deficiency of the "liver extract principle." It is recognized that in the primitive, abnormal type of erythropoiesis, seen in both erythremic myelosis and erythroleukemia, it is often difficult to draw a sharp differentiation between normoblastic and megaloblastic lines.

V. Etiology

The etiology of erythremic myelosis is unknown. In the 80 publications reviewed by Di Guglielmo neither age nor sex constituted predisposing factors, the cases having ranged from infancy to old age in both sexes. Although the cases reported occurred predominantly in Italy, the geographic factor cannot be important, for cases have been reported in Argentina, Belgium, England, France, Germany, Japan, Sweden, Switzerland and the United States. The familial factor does not have much support, for only 2 cases have been observed in the same family. Spontaneous erythremic myelosis has been noted in the cat and in fowls; in the latter the lesions are experimentally transmissible.21

The concept of erythremic myelosis as a disorder of erythropoiesis paralleling the derangement of granulopoiesis in myeloid leukemia ought not to be taken too literally. Di Guglielmo22 himself has cautioned against this view. Since the etiology of both conditions is at present unknown, nothing is to be gained by insisting on the concept of parallelism. Di Guglielmo,22 Benedetti,2 Duesberg24 and Moeschlin,22 all have advanced the view that leukemia is a neoplastic process and erythremic myelosis represents a similar disturbance in the red cell line. This view has led to a heated discussion among Italian authors as to the classification of erythremic diseases, and, in particular, whether Di Guglielmo's disease or polycythemia vera ought to be considered the counterparts of myeloid leukemia. By taking the position that until the etiology of these disorders is
clarified, no sound classification can be made, this nosologic controversy can be avoided. In any case, a discussion of the etiology of leukemia is not the present purpose. Consideration is limited here to the possible factors in the etiology of erythremic myelosis and erythroleukemia.

Although Di Guglielmo subscribed to the neoplastic view in the causation of erythremic myelosis, he pointed out the similarity between this condition and a spontaneous leukosis occurring in fowls. He cited the work of Ellerman in support of his view that erythremia is a counterpart of leukemia. Ellerman, using the same strain of a filtrable virus, was able to produce three different forms of the disease: a myeloid form, a lymphatic form and a third form originally designated as intravascular leukosis or erythroleukosis in fowls. In the myeloid form, white cell counts of around 2 million, as opposed to the normal figure of 30,000 were encountered; myelocytes and myeloblasts appeared in the peripheral blood, and infiltrations of these cells were found in the organs. In the lymphatic form, blood changes were less striking; but microscopic examination revealed lymphatic infiltrations in the liver, kidneys, and other organs, as well as hyperplasia of the follicles of the spleen. The erythroleukemic form, after a period of incubation, was characterized by anemia, the count about 1 million (or a third of normal). The leukocytes were generally normal and were not increased in number. Cells originally thought to be large lymphocytes but later recognized as pro-erythroblasts were seen in great number, sometimes comprising as many as 90 per cent of the nucleated cells. At autopsy the liver and spleen were found enlarged to as much as four times their normal size. Microscopically, the capillaries, especially those of the liver, spleen, kidneys and marrow, were found dilated and filled with erythrogoncs.

Pittaluga, although attributing the lesions in his case to a complex endocrine disturbance, also emphasized the theory of infection. He did not feel that an infectious process, producing a generalized lesion of the reticulo-endothelial system with hyperplasia and metaplasia, could be considered the primary disturbance in his case; nevertheless, he did not eliminate this hypothesis. In view of the pigment deposits in the spleen and the persistence of erythrophagocytic activity by the reticulum cells, Pittaluga was of the opinion that in his patient the spleen had long been the site of hyperfunction, as in familial hemolytic icterus, and, as a result of “exhaustion” and fibrosis, there was induced in the liver a vicarious hyperfunction in the process of transforming hemoglobin and the pro-pigments.

In the histories of the cases of Copelli and Benedetti, an infectious process is suggested but not substantiated.

VI. PATHOGENESIS

Di Guglielmo considers the reactivation of the hematopoietic potential of the reticulo-endothelial system the initial and indispensable phase in the pathogenesis of the erythremic myelosis. He does not believe, however, that the disease is primary to the reticulo-endothelial system, but is rather the consequence of erythropoiesis reverting to a type of embryonal, reticulo-endothelial genesis wherever reticulum cells of erythropoietic potential exist. He regards the fundamental pathologic characteristics of the disease to be hyperplasia,
anaplasia and dysplasia of the erythropoietic system. He further distinguishes the term hyperplasia as a pure proliferation affecting only the erythropoietic cells. This hyperplasia is primary rather than secondary to another process; it is systemic, in that in time the entire cellular system is affected; it is generalized, in that it is not limited to the marrow, liver, and spleen, but affects extra-hematopoietic organs as well; and it is irreversible, regressing neither spontaneously nor after therapeutic intervention. By the term anaplasia, Di Guglielmo refers to the arrest of cellular maturation of the red cells in the immature primordial phases. This phenomenon is seen especially in the acute forms of the disease in which one may observe a "hiatus erythremicus," or the disappearance of the intermediate forms of erythrocyte maturation. By dysplasia, Di Guglielmo refers to the pathologic differentiation of the red cells. The cells exhibiting atypical nuclei and cytoplasm are called para-erythroblasts. Consequent to this severe disturbance an abundance of primitive red cells is produced. However, from their failure to mature a state of anemia results, and because of their faulty development, intense anisocytosis and more fragile erythrocytes are the by-products. Owing to the presence of fragile erythrocytes, more easily destroyed than normal ones, the disease frequently assumes the aspects of hemolytic anemia. This was the explanation given by Di Guglielmo for the extreme proliferation of the reticulo-endothelial system, and the phagocytosis of erythrocytes by its cells, which is sometimes noted in this disease. He also believed that during the course of the disease the pathologic erythropoietic tissue encroached progressively, more and more, upon the normal erythropoietic tissue, and thereby hindered its regenerative capacity in maintaining the number of circulating erythrocytes.

In analyzing the pathologic changes of erythremic myelosis, one is naturally led to a consideration of the problem of extramedullary hematopoiesis. The long- vexing question confronts us again: are the foci of extramedullary blood formation, which are found in this condition as well as in other disorders, to be thought of as the result of a metastatic process or as a local hematopoietic transformation of potential cells? Brannan has written an interesting article on this subject. The chief evidence in support of the metastatic view is the presence in the peripheral blood of immature cells, among those, cells in mitosis, a condition that prevails in erythremic myelosis. That such cells might lodge in extramedullary sites, setting up daughter foci, is conceivable. On the other hand, most writers, including Brannan, ascribe to the local or autochthonous theory, and a fair number regard the condition as one of metaplasia.

The evidence supporting the metastatic view is diverse. First, there is the finding of small foci of extramedullary hematopoiesis in normal fetuses and infants. Such foci have been found in the palms and soles, in the prostate and epididymis, in the kidneys, cartilages, broad ligaments, suprarenal glands, and, more constantly, in the liver and spleen. According to Plum, these foci may be composed of erythroid elements, myeloid elements, megakaryocytes, or all three types of cells, an observation also made by Brannan. Brannan, paying particular attention to extramedullary hematopoiesis, further reviewed cases of so-called von Jaksch's anemia of infancy, a condition generally regarded as occurring
secondary to tuberculosis, syphilis, rickets, or other chronic disorders rather than as a primary entity. Among these cases, blood-forming foci were found in the liver, spleen, lymph nodes, thymus, lung, dura mater, appendix and kidneys.

In adults the occurrence of extramedullary hematopoiesis in cases of metastatic carcinoma of the marrow, in osteosclerosis, and in myelofibrosis is well known and generally regarded as a compensatory reaction. It has been less generally appreciated that the same phenomenon may also occur in conditions in which the marrow is not sclerotic but hyperplastic. Brannan,\(^4\) cites Weil (1901) who found proliferating marrow elements in the spleen, liver and lymph nodes in cases in which variola was the cause of death. Similar observations have been made in cases of pernicious anemia. In the case of a young woman who bled profusely as a result of an attempted abortion and subsequently died of a *Streptococcus viridans* septicemia, Brannan found new formation of normoblasts, megaloblasts and myeloblasts in the liver, spleen, broad ligaments and in organizing thrombi of the pelvic veins. The marrow was hyperplastic, with prominent foci of polymorphonuclear leukocytes, and large undifferentiated cells resembling myeloblasts.

From observations such as these, it seems warranted to conclude that extramedullary hematopoiesis may occur in a variety of conditions. Its presence cannot necessarily be taken as evidence of a neoplastic process.

The question arises concerning erythremic myelosis as to whether it should be considered solely as a disorder of erythropoiesis, or as a disorder primary to the reticulo-endothelial system. The first view is that advanced by Di Guglielmo, although he maintained that a reactivation of the hematopoietic potential of the reticulo-endothelial system was necessarily the initial phase in the pathogenesis of the disease. If this is the case, it seems reasonable to regard the lesions as representing a type of reticulo-endotheliosis.

The terms reticulo-endotheliosis and leukemic reticulo-endotheliosis have been used by Downey\(^3\) in referring to the Schilling type of monocytic leukemia in which there is a primary irreversible hyperplasia of the reticulo-endothelium. The designation is difficult to apply because the proliferation of the reticuloendothelium with the shedding of cells into the blood stream may occur in a variety of conditions: intoxications, granulomatous diseases (syphilis, tuberculosis, Hodgkin’s disease), in conditions of defective metabolism and in infections, such as subacute bacterial endocarditis. The presence, therefore, of histiocytes or intermediate monocyte forms in the peripheral blood may not necessarily be taken as proof of the leukemic nature of the disease. Some investigators express doubt as to the leukemic nature of this disorder: Jaffe\(^9\) believed that such cases were nonleukemic even when sepsis, or an infectious agent, could not be proved; Downey\(^3\) expressed the belief that cases of monocytic leukemia of reticulo-endothelial origin in which the leukemic nature is not obvious, the condition had better be termed reticulo-endotheliosis.

The speculations of Dameshek\(^8\) are pertinent relative to the pathogenesis of erythremic myelosis. The theory suggests that marrow response is not necessarily that of a single type cell but may be nonspecific and elicit response along multiple channels. Actually this theory is simplest to comprehend if one accepts
the "stem" cell to be multipotential and the stimulus for the production of erythremic myelosis, erythroleukemia, leukemia, or transition from one into the other28 to be nonspecific. We have long since held to the thesis that the various leukemias represent different forms of responses, if not to the same, then to similar stimuli, most likely infectious in nature, the manifestations and course being governed primarily by host response. The almost invariably acute explosive lymphoblastic response in childhood contrasted to the chronic indolent lymphocytic response of the aged best illustrates this concept.

The 4 new cases presented here as well as several of those described in the literature as erythremic myelosis and erythroleukemia might reasonably be considered as variants of reticulo-endotheliosis. The reasons for this are the following:

1. Hyperplasia of the reticulo-endothelium has been noted in several cases of erythremic myelosis and was clearly a feature of our Case III.

2. Transitional forms between reticulum cells and primitive erythroblasts are described by Di Guglielmo as a distinguishing feature of erythremic myelosis. This is in keeping with Downey's concept that in the leukemic reticulo-endothelioses, free cells differentiate toward some type of blood cell other than the monocyte.

3. In some of the cases accepted as examples of erythremic myelosis a frank monocytosis was present. This was noted in 3 of our cases.

4. The abnormalities in the granulocytes and platelets are more rationally explained in terms of a pathologic disorder of the reticulo-endothelium.

5. The close relationship between cases of erythroleukemia and erythremic myelosis is more readily understood if one views both entities as variants of reticulo-endotheliosis.

The incidence of hemosiderosis and hemochromatosis is noteworthy and it is believed that the two phenomena, which represent different stages of the same condition, are the consequences of the increased breakdown, both of the patient's own red cells and of the red cells administered by transfusions. In the first 2 cases reported in our series, the patients had developed typical "exogenous hemochromatosis." These patients received about 70 transfusions of blood each. This aspect of the condition has been previously discussed. Hemosiderosis is expected in any condition characterized by the intravital destruction of blood in which the iron is neither re-utilized nor excreted; thus, whether an additional hemolytic mechanism, which is not at all unlikely and which will ultimately be established by studies of red cell survival exists or not, the phenomenon of hemosiderosis may be expected to be found.

It seems evident that as more cases are described the artificial classification into acute and chronic erythremic myeloses and erythroleukemia will not be found to hold; but cases that show overlapping, and features of each of these, and perhaps even of other conditions as well, will be recognized. This characterizes the description of each new entity in medicine. At first the syndrome is described precisely, each point being clearly delineated, but as more and more examples appear, the kaleidoscopic nature of the condition is revealed. The rarer the condition, the longer this evolution takes.
A. Acute Erythremic Myelosis. The clinical features are given by Di Guglielmo as follows: severe anemia from the onset of the disease; irregular fever, usually of the remittent type; splenomegaly, almost always considerable; hepatomegaly, generally of less importance than splenomegaly; acute course, varying in duration from several weeks to about two months, with a consistently fatal termination; and hemorrhagic manifestations, frequent but variable in intensity and in time of appearance.

The distinguishing characteristics of the hematologic features are the following:

Erythrocytes: the red count, between 1.2 and 2.7 million at the onset, drops progressively in the last days of illness to about 1 million. Anemia is usually normochromic but may occasionally be hypochromic or macrocytic in type. Anisocytosis is severe and constant with no clear predominance of either macrocytes or microcytes.

Nucleated red blood cells: varying from case to case and from stage to stage, the figures range from 3,000 to 258,000 per cu. mm. The highest numbers of nucleated red cells in the peripheral blood are usually noted during the terminal stage. The nucleated red cells represent all stages of maturation but the most immature, or basophilic, forms are found in disproportionately large numbers, and this proportion progressively increases at the expense of the polychromatophilic and orthochromatic forms; thus a "hiatus erythremicus" eventually develops.

Atypical forms of nucleated red blood cells (para-erythroblasts): a number of morphologic alterations have been described. These are multilobed nuclei of irregular contours with a tendency to direct division; alteration of the nucleocytoplasmic ratio; asynchronism of nucleo-cytoplasmic maturation—cells with dense mature-appearing nuclei and basophilic cytoplasm, and the reverse, with spongy, immature nuclei and mature hemoglobin-bearing cytoplasm. Among the pro-erythroblasts (normoblast A, basophilic rubricyte), one can observe cells preserving some reticulo-endothelial characteristics, particularly in the coarsely reticular structure of their nuclear chromatin. (Descriptions of similar changes are also given by Copelli, Duesberg, Pittaluga, Heilmeyer and Schöner, Moeschlin.) Degenerative alterations also were noted by Di Guglielmo: homogenization of the nucleus, various segmented and fragmented forms of the nucleus, and a granular aspect of the cytoplasm of the basophilic erythroblasts persisting through the polychromatophilic and orthochromatic stages (also noted by Copelli). Several investigators have noted an increase in the number of mitotic figures.

Reticulocytes: in the few cases in which they were studied, reticulocytes were occasionally found to be elevated early in the disease and then dropped as the disease progressed.

Leukocytes: according to Di Guglielmo, most cases exhibit a slight leukopenia.

* Certain problems in differential diagnosis are discussed in direct conjunction with the Analysis of Cases in the Literature, Section IX of this presentation.
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**Table 1.—Summary of Differential Features**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Acute Erythremic Myelosis</th>
<th>Chronic Erythremic Myelosis</th>
<th>Erythroleukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Unimportant</td>
<td>Unimportant</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>Unimportant</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Acute, lasting from few weeks to two months</td>
<td>Irregular, lasting about two years</td>
<td>Irregular, Acute</td>
</tr>
<tr>
<td><strong>Hemorrhagic Manifestations</strong></td>
<td>Prominent</td>
<td>Not prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td><strong>Splenomegaly</strong></td>
<td>Considerable</td>
<td>Moderate to marked</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Hepatomegaly</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Hematologic Features</strong></td>
<td>1.2-1.7 million, dropping to about 1 million terminally. Considerable size and shape variation</td>
<td>Moderate anemia, progressively increasing. Considerable size and shape variation</td>
<td>Severe anemia</td>
</tr>
<tr>
<td><strong>Red Blood Cells</strong></td>
<td>Vary in number, usually primitive, many abnormal forms</td>
<td>Vary in number, usually mature forms</td>
<td>Numerous</td>
</tr>
<tr>
<td><strong>Nucleated RBC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White Blood Cells</strong></td>
<td>Usually low, may be normal or high</td>
<td>Usually normal or slightly low</td>
<td>Numerous myeloblasts</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>Diminished</td>
<td>Moderately diminished</td>
<td>Diminished</td>
</tr>
<tr>
<td><strong>Reticulocytes</strong></td>
<td>Variable</td>
<td>Usually elevated</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Reticulo-Endothelial cells</strong></td>
<td>Present in peripheral blood</td>
<td>Not prominent</td>
<td>Not prominent</td>
</tr>
<tr>
<td><strong>Marrow</strong></td>
<td>Primitive red cells predominate</td>
<td>Primitive red cells predominate, some older forms present</td>
<td>Proliferation of both primitive red cells and myeloblasts</td>
</tr>
<tr>
<td><strong>Pathologic Features</strong></td>
<td>Infiltration of hemopoietic and extrahemopoietic organs with primitive erythroid and reticulo-endothelial cells</td>
<td>Extramedullary hematopoiesis</td>
<td>Infiltration of hemopoietic and extrahemopoietic organs with primitive erythroid and myeloid cells</td>
</tr>
</tbody>
</table>

the number of white cells diminishing as the nucleated red cells increase. Rarely, the white cell count may be elevated as high as 30,000.
Platelets are always diminished, often greatly.
Reticulo-endothelial cells have been encountered in the peripheral blood in a
number of cases. Some of these cells have been described as having erythropoietic function owing to their acquisition of some pro-erythroblast (erythrogonie, rubriblast) characteristics. Others show diverse morphologic features, varying from typical voluminous reticulo-endothelial cells to small monocytoid cells. Still others are found in the process of phagocytosing erythrocytes. Mitoses have been noted among these cells as well as among the nucleated red blood cells.

Marrow: in acute erythremic myelosis, elements of the red cell series dominate both relatively and absolutely, whereas those of the white series are reduced. The nucleated red to white cell ratio is, therefore, reversed. The curve of maturation of the erythroblasts is significantly altered with a predominance of the basophilic erythroblasts (normoblasts A, basophilic rubricytes). In Pontoni's case (cited by Di Guglielmo), 93.5 per cent of the erythroblasts were basophilic, and in Baserga's case the figure was 82.7 per cent. The pro-erythroblasts (erythrogonies, rubriblasts) are proportionately increased. The appearance is that of an arrested red cell maturation. Similar changes have been revealed by splenic puncture.

Pathology: the presence of red marrow in the femur and an increase in the size of the spleen are the chief gross pathologic changes. Microscopically, infiltrations of both primitive red cells and reticulo-endothelial cells are found in both the hematopoietic and extra-hematopoietic organs, such as the kidneys, adrenals, myocardium, lungs, pancreas, testes, uterus, larynx, trachea and dura mater.

Prognosis and therapy: in the cases reviewed by Di Guglielmo, all therapy was completely ineffectiye and the end was invariably fatal.

B. Chronic erythremic myelosis. In his 1946 publication Di Guglielmo accepted 6 cases as true examples of chronic erythremic myelosis: those of Benedetti (1938), Isräels (1939), Duesberg (1940), Pittaluga (1940), Heilmeyer and Schönner (1941), and Di Guglielmo and Quattrin (1941). Abstracts of these acceptable examples from the literature appear on pages 788–791.

Di Guglielmo regarded the chronic form of the disease as differing from the acute in several particulars, the most important of which are the prolonged course, lasting about two years, and the peripheral blood findings. Whereas in the acute disease basophilic erythroblasts (normoblasts A, basophilic rubricytes) predominate over the more mature forms in the peripheral blood, the reverse is usually found in the chronic form. The reticulocytes may be greatly elevated ranging from 4.4 per cent in the case of Isräels to the high values of 80 per cent in the case of Heilmeyer and Schönner and almost 100 per cent in that of Di Guglielmo and Quattrin. There was evidence of increased hemoglobin metabolism in all these cases.

The cases of Benedetti and Copelli, abstracted on page 789 of this presentation, are remarkably similar to our own reports which follow on page 776 ff. Benedetti also presented a case which he considered a suitable prototype of chronic erythremic myelosis despite the absence of nucleated red cells in the peripheral blood. He further pointed out that cases in which a hyperplastic marrow could not be demonstrated, such as that of Griva-Angeleri, should not be accepted as examples of erythremic myelosis. Moeschlin felt that in many of the published cases, although a proliferation of erythroblasts did exist, an in-
creased proliferation of the granulocyte line was also encountered. He did not consider these cases examples of true erythremic myelosis, but rather of erythroleukemia.

C. Erythroleukemia. With the publication of his case of erythroleukoplasitryemia in 1917 Di Guglielmo is credited with the coining of the term erythroleukemia. Moeschlin and Rohr (and abstracted here on page 791 together with an example by Boni) applied the term to a case that they observed in 1936 in which the patient presented a rather fulminating disease, characterized by anemia and numerous atypical nucleated red cells as well as pathologic myeloblasts containing Auer bodies in the peripheral blood. Similar observations were noted in the marrow, the nucleated red cells outnumbering the white cells 3.45 to 1.

According to Moeschlin there must be a large number of nucleated red cells, in addition to the pathologic myeloblasts, in the marrow, and the number of these must exceed the percentage of those in the peripheral blood before the diagnosis of erythroleukemia can be made. Only by means of a marrow examination, therefore, can a true erythroleukemia be differentiated from secondary or symptomatic forms. The symptomatic form, more properly called leukemia with symptomatic erythroblastemia is seen occasionally in the course of leukemia when nucleated red cells appear in the peripheral blood as a result of the development of compensatory, extramedullary hematopoietic foci. The appearance of such foci in the spleen, with its open vascular system, facilitates entrance of immature cells into the blood stream.

In 1937 Penati published a case that he called leukemia megaloblastica. Moeschlin reviewed the marrow and peripheral blood in this case and found them remarkably similar to his own, there being numerous large megaloblastoid cells side by side with typical pathologic myeloblasts, the abnormal nucleated red cells predominating. Moeschlin regards this case as one of true erythroleukemia. Bianchi's case, in which cells described as histiocytes or reticulo-endothelial cells, in addition to the immature nucleated red cells, appeared in the blood, marrow, and other organs, is also regarded by Moeschlin as true erythroleukemia. Similar cases were described by Boni as "acute total hyperplastic myelosis," and by the French investigators, Harvier, Le Melletier, La Vergne and Lamotte, under the title acute erythroleukomyelosis. A case more difficult to classify is that of Isræls in which the NRBC:WBC ratio of the marrow was 66.6 to 33.4, but in the relative proportions of cells of different ages, no maturation arrest is evident in either granulopoiesis or erythropoiesis. Marrow myeloblasts numbered 1.4 per cent of the total of nucleated cells, which was within normal limits despite their appearance. Myeloblasts, along with other immature granulocytes, were found in the peripheral blood. Di Guglielmo regards this case as an example of chronic erythremic myelosis, although it was presented by Isræls as one of probable erythroleukemia. From the descriptions, one cannot be sure that it is either.

VIII. REPORT OF FOUR CASES

Case I. V. G. A Negro housewife, aged 47, was admitted to the Cook County Hospital on November 7, 1944, chiefly because of weakness.

History: the patient was known to have been anemic since 1936. Relief could be had only by blood transfusions. She estimated that during the eight year period, she had received at
least 50 transfusions, the last one about three weeks before admission. She had progressively increasing dyspnea on exertion, occasional nausea and vomiting, poor appetite, and a weight loss of 37 pounds. In 1940, when previously hospitalized in the Cook County Hospital, the patient reported occasional epistaxis and one episode of hematemesis. At that time she had 12 per cent (1.8 Gm.) hemoglobin; 700,000 red blood cell count and 9,300 white blood cells, with neutrophils 71 per cent (bands 15); eosinophils 6 per cent; basophils 2 per cent; lymphocytes 21 per cent. There was no sickling.

Several years before her last admission, the patient had undergone antisyphilitic therapy, and in 1912 she had had "typhoid malaria." Her one child died in infancy and her parents were dead of unknown causes.

Examination: the patient was found to be somewhat malnourished and moderately dyspneic. Her temperature was 100.2 F; pulse 106; respirations were 28 per minute; blood pressure, 120 systolic and 0 diastolic. There was pallor but no jaundice. The tongue appeared normal. The heart was enlarged to the left and right, with systolic and presystolic murmurs audible over the apex. The liver was firm, tender and enlarged so as to fill the entire upper portion of the abdomen and extend almost to the umbilicus. The spleen was easily palpable on deep inspiration. There was slight edema of the legs but no enlargement of superficial lymph nodes. Patellar and achilles tendon reflexes were absent. There was an equivocal decrease in vibratory sense.

Laboratory observations: the urine was normal; the icteric index, 14 and 7; total serum proteins 4.8; albumin 3.2; globulin 1.6 Gm. per 100 cc.; the blood and spinal fluid Wassermann reaction was negative; spinal fluid protein, 10 mg. per 100 cc.; occult blood was not found on repeated examinations of the stool; gastric analysis showed 40 degree free, 60 degree combined hydrochloric acid.

Hematologic observations: blood counts are given in table 2.

Analysis of marrow: the marrow was highly cellular. Megakaryocytes were present in increased numbers and did not show remarkable cytologic changes. Nucleated red blood cell to white cell ratio was about 6 to 4. Erythropoiesis was characterized by a decided left

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<td>11/13/44 Blood transfusions—1,000 cc. Liver extract—120 units intra-muscularly. Ferrous sulfate</td>
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<td>11/28/44 Blood transfusions—1,000 cc. Signed release from hospital.</td>
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For personal use only. By guest on September 24, 2017. For personal use only.
shift with erythrogones (rubriblasts) and normoblasts A (basophilic rubricytes) predominating. There were scarcely any normoblasts B (polychromatophilic rubricytes) or C (metarubricyte). Reticulo-endothelial cells, histiocytes and macrocytes were numerous. Mitotic figures and nuclear fragments in the red cells were prominent numerically. Granulopoiesis was characterized by the presence of many giant band cells and metamyelocytes. Eosinophilia was remarkable. Cells that represented intermediate forms between reticulo-endothelial cells and primitive red cells were seen everywhere.

Diagnostic considerations: in 1940 the impression was that the patient had pernicious anemia complicated by chronic blood loss. This impression, however, could not be substantiated. During hospitalization in 1944, several possibilities were considered. One was that the eosinophilia and the abnormal myelopoiesis were the result of an intestinal aberration, such as parasitism or the presence of a neoplasm. A second consideration was that the eosinophilia represented a sensitization phenomenon which also accounted for the lack of red cell maturation. The third possibility was that the symptoms were caused by "hyper-splenism."

Course: the patient remained in the hospital for three weeks. During that time she was febrile, with the temperature ranging up to 100 F. She was given seven blood transfusions of 300 cc. each. Because of the extreme left shift in erythropoiesis and the presence of giant metamyelocytes and band forms in the marrow, a course of liver extract was instituted. No appreciable reticulo-endothelial response resulted from the administration of 120 units. Ferrous sulfate was also given. During this period the red blood cell count reached a maximum of 1.66 million and the hemoglobin, 28 per cent. At this point the patient left the hospital against advice. Two weeks later she returned, with a red blood cell count of 0.88 million, and hemoglobin, 12 per cent. Although admittedly a poor surgical risk, under the tentative diagnosis of "hyper-splenism," the patient was prepared for splenectomy. Preoperatively, over a period of twelve days, 4,500 cc. of blood were given. At operation the spleen was found to be four or five times its normal size; the liver appeared cirrhotic, and there was a great deal of ascitic fluid in the abdominal cavity. Dense adhesions between the spleen and the diaphragm made the operation difficult. During removal of the spleen the patient's condition deteriorated, and it was necessary to close the abdomen, with several clamps protruding from the wound. The postoperative course was stormy, characterized by fever and signs of heart failure. Despite digitalization, antibiotic therapy, and transfusions there was a downhill course and the patient died on the eighth postoperative day.

Pathology: the spleen weighed 780 Gm. It was firm and its capsule was covered with fibrous tags. The sectioned surface was light red, mottled with small confluent dark red areas. Microscopic examination revealed diffuse fibrosis, narrow sinusoids and small malpighian bodies.

Autopsy: there was no jaundice. There was slight edema of the lower extremities. About 100 cc. of clear fluid were found in the abdominal cavity, about 35 cc. in each pleural cavity. The heart weighed 300 Gm., was of normal size and configuration. The valves were delicate; the myocardium was light brownish red with a few yellow streaks over the papillary muscles. The lungs showed glistening pleural surfaces with frothy fluid escaping from the cut section. There were many foci of red consolidation in all lobes. Accessory spleens numbered about 30, each measured from 2 mm. to 4 cm. in diameter, and altogether, they weighed 80 Gm. They were firm, the cut surfaces light red and smooth. One of these, measuring 12 mm. in diameter, was necrotic and the corresponding branch of the splenic artery was thrombosed. The main stem of the splenic artery and vein was not thrombosed. The liver weighed 3100 Gm.; was greatly enlarged; the margin, rounded; the capsule covered with adhesions between the surface of the liver and the diaphragm. The surface was smooth and dark brown; consistency was firm and somewhat doughy. The cut surface showed the liver lobules with dark brown centers and lighter yellow-brown peripheries. The gallbladder was large and well filled. Lymph nodes along the aorta were brown and only slightly enlarged. The axillary and hilar nodes revealed no discoloration. The pancreas weighed 40 Gm. It was firm, brown, and of normal lobulation. The kidneys weighed 375 Gm. The capsules stripped easily, a smooth pale surface being left. Cut sections were normal. The marrow in the right femur was purplish red.
Microscopic observations: the liver showed typical portal cirrhosis with proliferation of connective tissue and bile capillaries. There was complete reconstruction of the liver tissue with foci of regeneration forming pseudolobules. There was a large amount of pigment, which gave a positive iron reaction, in the connective tissue as well as in Kupffer cells and the liver cells. The pancreas revealed interstitial fibrosis with huge deposits of iron pigment, most of which were found within the cells of the acini and Langerhans cells. The lymph nodes likewise had huge deposits of iron pigment in the sinusoids; the adrenal gland contained iron pigment in the cells of the zona glomerulosa; the thyroid gland had small deposits of iron pigment in the interstitial tissue. There was diffuse fibrosis of the accessory spleen with dilatation of the sinusoids which were empty. The follicles were small. Iron pigment was not demonstrable here or in the heart or skin.

Case I: Summary and Comments (Chronic Erythremic Myelosis)

A Negro woman, aged 47, had had a history of anemia for at least eight years. The only other significant symptoms were weight loss, severe hepatomegaly, and moderate splenomegaly. The patient had been treated with iron, liver, and about 70 blood transfusions, each of 500 cc. Anemia was severe and of the normochromic type. There was no reticulocytosis. Some leukocytosis, with a left shift in granulocytes, and eosinophilia were characteristic. The marrow was hypercellular and the erythroid series showed extensive proliferation of primitive red cells. Because a hypersplenic effect was thought responsible for the absence of red cell maturation and delivery, splenectomy was performed. The patient died soon after operation. Autopsy revealed fibrosis and hemosiderosis of the liver and pancreas with considerable hemosiderosis of the other organs.

It is felt that the terminal hemochromatosis was the end result of the many transfusions; but because of the interference with organ function, hemochromatosis may have been an important factor in the fatal outcome of splenectomy.

In retrospect the case fits the symptom complex of chronic erythremic myelosis.

Case II: C. K. A white woman, aged 49, experienced weakness, palpitation and dyspnea for three years before her admission to the Cook County Hospital on January 31, 1944. During those three years, she was treated for anemia which was relieved only by blood transfusions. Iron preparations and parenteral liver extract had been ineffectual. In the six months prior to admission the patient had lost 30 pounds and had had an episode of jaundice, the details of which she could not recall. Inquiry into systemic disorders revealed no other pertinent symptoms. Menopause had occurred at the age of 47. Her three children were living and well.

Examination: the patient was intelligent and appeared well nourished, although there was some evidence of loss of weight. The blood pressure was 140 systolic and 78 diastolic; pulse 108, temperature 99 F., and respirations were 24. The skin was moist and pale with a faint icteric hue; sclerae were subicteric. The tongue was pale but uncoated. There was moderate atrophy of the papillae. The heart was moderately enlarged to the left, with systolic murmurs audible at the apex and base and transmitted up the carotids. The spleen was rather hard, descending 2 cm. below the costal margin. The liver margin was 3 cm. below the costal margin. Pelvic, rectal, and neurologic examinations revealed no abnormalities.

Laboratory observations: there were three periods during which laboratory observations were made: the first two at the Cook County Hospital from December 31, 1944 until January 30, 1945 and from June 14 to July 8, 1945, and the third, at another hospital, from August 23 until December 23, 1945. These reports are presented together in summary: Urine showed from a trace to 2 plus albumin and a few white cells in sediment. Kahn and Wassermann reactions were negative. Blood, ova, cysts, parasites, or pathogenic organisms were
not present on repeated examination of stools. Gastric analysis did not reveal free acid after histamine administration. Roentgenologic studies of the chest showed an increased cardio-thoracic ratio with a boot-shaped contour of the heart; increased hilar markings; normal lung fields and gastro-intestinal tract. An intravenous pyelogram was taken and excretion of the dye was normal on the left but delayed on the right. The pelvis, lumbar spine and skull were normal. An electrocardiogram disclosed no significant abnormalities. The basal metabolic rates were plus 29, plus 40 and plus 39; the icterus index was from 4 to 9 units. Chemical analysis of the blood showed nonprotein nitrogen, glucose, and calcium and phosphorus levels within normal limits. In September of 1945 the alkaline phosphatase levels were repeatedly elevated, from 9.4 to 9.8 units. The blood cholesterol was 223 mg. per 100 cc. with 61 per cent esters on September 21. The serum proteins 7.4 Gm. per 100 cc. on January 18, 1945 dropped to 4.6, the albumin-globuln ratio 3.2:1.4 on September 7, 1945. Morphologic examination of the red cells showed anisocytosis from 1 plus to 3 plus; poikilocytosis 2 plus to 3 plus; hypochromia 1 plus to 2 plus, and occasional stippled red cells. Auto-agglutination was noted on August 27 in the counting chamber and after that rouleau formation was frequently found. Platelets were often noted to be decreased on the films; values of 170,000 and 125,000 were obtained on January 22 and November 17 respectively. Occasionally giant platelets were seen. The sedimentation rate on January 4 was 18 mm. per 29 minutes; on September 24, 43 mm. per hour. Daily reticulocyte counts were made after the administration of parenteral liver extract. The highest value, 2 per cent, was reached on the tenth day. There was no response as measured by the red cell counts and hemoglobin.

Marrow was extremely hypercellular. Megakaryocytes were present in somewhat diminished numbers but showed no significant qualitative changes. Approximately half the cells could be identified as belonging to the erythroid series. More than two-thirds of these were erythroblasts (rubriblasts) and normoblasts A (basophilic rubricytes). The remainder were normoblasts B (polychromatic rubricytes). Only a rare normoblast C (metarubricyte) was encountered. Reticulo-endothelial cells and cells suggesting a transition from these into primitive erythroid cells were numerous throughout. Their number could not be fixed because they showed more fragmentation than the other cells, undoubtedly as part of their primiveness. Multiple nuclei and mitotic figures were common among these cells. In the granulocyte series metamyelocytes and band forms were most numerous. These showed nothing remarkable. A slight increase was seen in eosinophils and their precursors.

Course and diagnosis: during the periods of observation there was a low grade fever, occasionally rising slightly above 100 F.

Three diagnostic possibilities were considered on the basis of the first marrow observations: The first was chronic bleeding with a severe iron deficiency. This was also suggested by an analysis of the peripheral blood, but was ruled out by the absence of a history of bleeding, the lack of response to numerous transfusions, and the absence of small nucleated red cells in the marrow. The second possibility, that of atypical hemolytic anemia, was ruled out by the absence of spherocytes, the extensive morphologic changes in the red cells, and the left shift in nucleated red cells without significant numbers of late forms or reticulocytes. The final possibility, that of marrow inhibition, was considered most likely. This, however, failed to explain the severe morphologic changes in the cells. These changes are rarely encountered in conditions other than those of iron deficiency, sometimes in Hodgkin's disease, and occasionally in treated cases of leukemia. The possibility was entertained, therefore, that inhibition was secondary to Hodgkin's disease whose primary focus was the spleen.

After the second marrow examination the entirely different clinical impression was that of a rapidly progressing myeloid leukemia. The patient was then given roentgen therapy.

During the third admission, blood transfusions alone relieved the patient of symptoms; however, she began to have reactions of chills, fever and aching followed by the passage of dark urine. A brownish discoloration of the skin was noted in September of 1945. An attempt at splenic puncture was unsuccessful.

In December of 1945 the patient entered another hospital. There she died in April of
1946, approximately six weeks after a splenectomy was performed. The extirpated spleen weighed 520 Gm. and revealed some capsular and trabecular fibrous thickening. The lymphoïd follicles were fairly large but widely separated, and some showed irregular central fibrosis and many histiocytes. The pulp was characterized by wide sinusoids lined by prominent endothelium, and some of the sinusoids were filled with young hematopoietic cells. Between the malpighian corpuscles the degree of cellularity varied from field to field. In addition to the usual cells, however, there were collections of larger cells and histiocytes laden with hemosiderin. Most of the young cell forms revealed little evidence of maturation. There was an occasional multinucleated cell with megakaryocytic qualities.

Autopsy: there was a walled-off abscess beneath the left hemidiaphragm; hemosiderosis of the liver, pancreas, stomach, adrenals, and lymph nodes; pigmentary cirrhosis of the liver; interstitial fibrosis of the pancreas; fatty degeneration of the heart and kidneys, and hyperplasia of the marrow.

### Table 3.—Case II. C. K. Hematologic Data

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### Case II: Summary and Comment (Chronic Erythremic Myelosis)

A white woman, aged 49, whose history of anemia was of at least three years' duration, presented fever and weight loss as the only other chief symptoms. She had been treated with liver, iron, and by transfusions; but only transfusions were effective. The peripheral blood was characterized by anemia, with significant changes in size, shape and color in the red cells. There was an inconstant white cell count with a decided left shift in granulocytes; monocytosis, and a leukemoid reaction; and slight thrombopenia. The marrow was extremely cellular. Approximately half the cells were of the erythroid series, and of these more than two-thirds were erythroblasts (rubriblasts) and normoblasts A (basophilic rubriblasts). Reticulo-endothelial cells were numerous, many of them showing transition to erythroid cells.

Splenectomy proved fatal in six weeks, but inasmuch as a subdiaphragmatic abscess was found, it is again difficult to evaluate the efficacy or failure of splen-
ECT ERYTHEMIC MYELOSIS (DI GUGLIELMO'S DISEASE)

nectomy. As in Case I the patient had had an extensive hemochromatosis as a consequence of many transfusions over a span of three years.

This case fits the description of chronic erythremic myelosis.

Case III: E. L. A white woman, aged 56, entered the Cook County Hospital five months after the onset of an illness characterized chiefly by weakness. Two weeks prior to admission, dyspnea and orthopnea became prominent and the weakness was so profound that the patient was unable to walk. For a few days, all ingested food was vomited. Although she bruised easily, the patient noticed no abnormal tendency to bleed. She had no pain or weight loss. Some years before, she had undergone a cholecystectomy. Since then, except for "arthritis," she had enjoyed good health.

Because pernicious anemia was suggested at the onset of illness, a series of liver extract injections was prescribed, but this was without beneficial effect.

Examination: the patient was obese and acutely ill. She appeared older than her stated age. Respirations were deep and grunting. Temperature was elevated to 101.2 F.; the pulse was 120, and blood pressure 110 systolic, 60 diastolic. The skin and mucous membranes were pale but not icteric. Neither petechiae nor ecchymoses were present. Lymph nodes were palpable. The tongue was normal; the heart, slightly enlarged to the left with a soft apical systolic murmur transmitted along the left sternal border. There were a few moist rales in both lung bases. It was uncertain whether the liver edge was palpable. Neurologic examination revealed no abnormalities.

Laboratory reports: the urine showed 3 plus albumin and many red blood cells. A roentgenogram of the chest revealed cardiac enlargement and passive congestion of the lungs. Hematologic observations showed hemoglobin 41 per cent (6.3 Gm.); the red blood cell count 2.21; white blood cells 2,500; neutrophils 51; lymphocytes 39; monocytes 10; platelets decreased. The red cells showed anisocytosis, poikilocytosis, polychromatophilia, and macrocytosis. Subsequent counts taken on September 9, 1947 were similar.

Sternal marrow: the marrow was highly cellular. Megakaryocytes were present in essentially normal numbers, and although an occasional normal form was seen, most appeared abnormal. Abnormalities included dark blue cytoplasm, naked nuclei and prominent nucleoli. The ratio of erythroid to granulocytic cells was 6 or 8 to 1. Granulopoiesis was abnormal and resembled that seen in pernicious anemia, with large metamyelocytes and band cells. There were few segmented cells. Reticulo-endothelial cells, frequently occurring in sheet-like syncytial groups, were seen throughout. Cells apparently metamorphosing into erythroid forms were numerous. These cells measured as large as from 50 micra to 75 micra in diameter and often contained multiple nuclei, mitotic figures, and large distinct nucleoli. The chromatin of these cells was finely stippled and rather light. Transition from these cells into erythroid cells could be traced through distinctly normoblastic stages, although the resultant late forms were large. Hardly any normoblasts B (polychromatic rubricytes) and C (metarubricytes) were found. There were many histiocytes and monocytes.

Clinical course: during the nineteen days of her hospitalization the patient was febrile despite penicillin therapy. On the fourteenth day the temperature rose to 104 F. and the patient experienced difficulty in breathing and pain in the right side of the chest. There was no evidence of pulmonary consolidation. Blood transfusions of 500 cc. each were given on the second, fifth, eighth, twelfth and eighteenth days. Digitoxin, folic acid, and ferrous sulfate were also administered. The clinical condition steadily deteriorated, with lapse into a semi-coma; a shock-like state with oliguria ensued, and on the nineteenth hospital day, the patient died.

Autopsy: examination showed a well developed, obese body. The skin was dry and extremely pale and yellowish. The sclerae were faintly tinged with yellow. There were no external hemorrhages or palpable lymph nodes and there was no edema. The spleen weighed 250 Gm., was moderately enlarged; softer than normal; its surface was purplish red, and its capsule was smooth. On the cut section, the follicles and trabecular network were obscured. The liver weighed 1800 Gm., was moderately enlarged, soft and had a blunt inferior edge. It was grayish-brown with a yellow hue. The lobular markings of the cut section were obscured. The bile ducts were patent and the gall bladder was absent (post-cholecystectomy).
None of the lymph nodes was significantly enlarged. The heart weighed 300 Gm. The epicardium was covered by a moderate amount of fibrinous exudate which showed no signs of organization. The myocardium was extremely flabby, pale and gray. The ventricles were dilated and the coronary arteries showed some sclerosis. The other organs showed no remarkable gross abnormalities. The sternum, vertebræ, ribs, calvarium and the shaft of the femur were examined. All contained dark red marrow.

Microscopic examination of the spleen showed the follicles normal sized and almost devoid of germinative centers; the reticulum was extensively hyalinized; the walls of the sheathed arteries were thickened. Blood was present both inside and outside the sinusoids, the endothelium of which showed some proliferation. In addition to the proliferation of the reticulum cells within the pulp cords there were large cells which had vesicular nuclei with sharply defined chromatin and occasional small nucleoli. The cytoplasm of these cells was abundant and stained homogeneous purple (hematoxylin eosin). Transitional forms between these cells and the reticulum cells were noted. In the transitional cells the nuclei were smaller, often indented and contained well defined nucleoli. In foci surrounding these cells moderate numbers of nucleated red cells were found. The liver had well preserved architecture; the central areas of the hepatic lobules were edematous. The liver cells contained wear-and-tear pigment and those at the periphery of the lobules often revealed fatty metamorphosis and circumscribed foci of polymorphonuclear cells which were seen at the sites of disintegrating liver cells. A few nucleated red blood cells were present. The periportal areas were normal.

The marrow of the femur was extremely cellular. Many of the cells were large with vesicular nuclei and well defined nucleoli. In some of these cells the nucleus was extremely large, hyperchromatic, and without nucleoli. Occasionally two or three such nuclei, some of them indented, were found in one cell. The cytoplasm of some of these cells was purplish-blue and the cells assumed the character of erythroblasts. Nucleated cells were present in large numbers, most of them still with vesicular nuclei. In general large mononuclear or multinuclear cells which resembled proliferated reticulum cells or erythroblasts were prominent. In circumscribed foci, small cells of a lymphocytic character predominated. Myelopoiesis appeared somewhat suppressed. Megakaryocytes were present in moderate numbers. The marrow in a rib was similar but even more cellular. The bone showed evidence of sclerosis.

The architecture in the several lymph nodes examined was well preserved. In the medullary cords and to some degree in the peripheral sinuses were large cells resembling the large cells of the marrow. The transition to nucleated red cells was also seen here. In addition there was an increase of reticulum cells. The capsule was nowhere invaded.

Case III: Summary and Comment (Chronic Erythremic Myelosis)

A white woman, aged 56, had had a relatively short course of illness, lasting only about six months from the time of onset of symptoms, the most prominent of which were those secondary to anemia. She was acutely ill during her entire hospitalization, and manifested no response to liver extract, iron or folic acid. The peripheral blood was characterized by anemia, leukopenia and thrombocytopenia, with the red cells showing severe anisocytosis, poikilocytosis, polychromatophilia and macrocytosis. The marrow was highly cellular. Erythroid elements far outnumbered white cells. Reticuloendothelial cells were numerous and their evolution into red cells could be traced readily. Most of the latter were basophilic rubriblasts.

The spleen was not remarkably enlarged at autopsy (250 Gm.). Many of the organs showed proliferation of reticulum cells and transitional cells. Extramedullary hematopoiesis, with primitive nucleated red cells predominating, was seen in several of the organs.

This case may be classified as one of chronic erythremic myelosis notwithstanding the relatively brief clinical course.
**ERYTHREMIC MYELOSIS (DI GUGLIELMO’S DISEASE)**

**Case IV: H. M.** A white woman, aged 34, entered the Cook County Hospital on July 1, 1948, the day after the appearance of a tender swelling in the left side of the jaw. She was referred by a private physician under whose care she had been for several months. His diagnosis was “acute leukemia, probably myelogenous,” and treatment had consisted of blood transfusions and liver extract. During the antecedent five months the patient had experienced anorexia and a loss of 15 pounds. Weakness and a cough appeared about one month before admission and she had had an episode of pain in the right lower abdominal quadrant which lasted for two days. Inquiry into systemic disorders revealed nothing contributory except the fact that the patient bruised rather easily and that as a child she had had an illness that was diagnosed as “infantile paralysis,” as a result of which, despite subsequent surgical intervention, the left leg had remained shorter than the right.

Examination: the patient was 4 feet 4 inches tall, with short stubby fingers and the appearance of an achondroplastic dwarf. The lower half of her body was rather obese. The temperature was 99.8 F.; pulse 88; respirations were 24; blood pressure was 120 systolic and 70 diastolic. The skin was pale; the tongue pink and well papillated. There was a tender walnut size swelling in the left side of the lower jaw and the teeth on this side were carious. The liver and spleen were just palpable. There was an old operative scar on the shorter left knee.

Laboratory reports: the urine showed no albumin or urobilinogen. Roentgenograms of the chest and abdomen were normal; the spleen was not visualized. An electrocardiogram showed a right axis shift. The Kahn reaction was negative and the basal metabolic rates plus 34 and plus 42, according to the referring physician who also reported “stood negative for blood and parasites; icterus index, 20 units.” The blood counts are summarized in Table 4.

The red blood cells showed: anisocytosis from 2 plus to 4 plus; poikilocytosis from 1 plus to 4 plus; polymorphonuclear leukocytes from 1 plus to 3 plus; occasional target cells and stippled red cells. The referring physician likewise reported: “Fragility test: hemolysis began at 0.42 per cent and was complete at 0.34 per cent; bleeding time, 8.5 minutes; clotting time, 2.5 minutes; prothrombin concentration, 40 per cent (Quick).”

Marrow (sternal puncture): the marrow was extremely hypercellular. Megakaryocytes were present in slightly increased numbers. Many were young and multinucleated, resembling giant cells. The nucleated red cells and reticuloendothelial cells outnumbered the white cells approximately 2 to 1. The reticuloendothelial cells together with the erythropoiesis (rubriblasts) and cells which appeared to be transitional forms from the former to the latter accounted for 30 per cent to 40 per cent of all cells seen. This group of cells measured between 20 and 30 micra in diameter, had nuclei that occupied from 75 to 80 per cent of the cell volume, finely stippled chromatin and 3 or 4 prominent nucleoli. The cytoplasm was dark blue and granular, paling in the perinuclear area with the maturing of the cell. The nuclei were often double, and in mitosis. Red cells at the maturation level of normoblasts A (basophilic rubricytes) were present in moderate numbers; normoblasts B (polychromatophilic rubricytes) and C (metarubricytes) were also encountered, although somewhat less frequently. In these the nuclei often assumed bizarre shapes, were sometimes multiple and fragmented. The granulocytes, although scant in number, appeared normal. Eosinophils in all stages of maturation were distinctly increased.

Clinical course: the patient was given penicillin and the carious teeth were extracted. Following this the swelling of the jaw subsided. A therapeutic trial of folic acid (45 mg. per day) was instituted but there was no hematologic response or change in the marrow. After a month in the hospital the patient was discharged to the outpatient clinic where she received 30 units weekly of liver extract. The hemoglobin and red cell values steadily decreased during the antecedent five months the patient had experienced anorexia and a loss of 15 pounds. Weakness and a cough appeared about one month before admission and she had had an episode of pain in the right lower abdominal quadrant which lasted for two days. Inquiry into systemic disorders revealed nothing contributory except the fact that the patient bruised rather easily and that as a child she had had an illness that was diagnosed as “infantile paralysis,” as a result of which, despite subsequent surgical intervention, the left leg had remained shorter than the right.

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On October 25, 1948 the patient was rehospitalized because of fatigue and swelling of the hands and face. At this time she presented anasarca on examination. The liver edge was palpable 6 cm. below the costal margin, but the spleen was not palpable. Petechiae were noted on the mucous membranes of the mouth, and flame-shaped hemorrhages were seen in the left eye. Laboratory reports at this time were as follows: The urine showed a trace of urobilinogen and occasional white blood cells; stools gave a 4 plus positive benzidine reaction; nonprotein nitrogen 30; total protein 5.0, albumin 3.1; globulin 1.9; icterus index 5; basal metabolic rate plus 13. Blood culture was negative. A roentgenogram of the mastoids...
revealed sclerosis; of the chest, a slight increase in the transverse diameter of the heart. The marrow was examined again on September 23 and November 1, but the observations were in no way dissimilar to those of July 14.

Therapy consisted of blood transfusions, and because infection of the upper part of the respiratory tract was present, penicillin was given prophylactically; nevertheless, the patient developed acute otitis media of the right ear which gradually cleared, only to be followed by furunculosis of the external canal. The course was relentlessly downhill, with some temporary waning of the anasarca only to reappear preterminally. The patient was given thyroid for about a month, starting on November 17, because of the suggestion of myxedema in her appearance and the nephrotic-like appearance on the last admission. There was no demonstrable improvement as a result of this regimen. Death occurred on December 22, 1948. Permission could not be obtained to perform an autopsy.

Table 4.—Case IV. H. M. Hematologic Data

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Case IV: Summary and Comment (Erythremic Myelosis)

A white woman, aged 34, had symptoms referable to the presence of anemia and thrombopenia. The duration of the disease from the onset of symptoms was approximately one year. She had prominent hepatomegaly but splenomegaly was not of clinical significance. Anasarca was unique in this series. Weight loss and fever occurred in the other cases as well. There was no response to liver, folic acid, or thyroid.

Anemia was essentially normochromic in type; the white cell count ranged from low to normal; there was moderately severe thrombopenia. The red cells showed significant changes in size and shape and both stippled and nucleated red
ERYTHREMIC MYELOSIS (DI GUGLIELMO'S DISEASE)

Blood cells were prominent. The leukocyte condition was characterized by a leukemoid reaction. The marrow was extremely hypercellular. Reticulo-endothelial and red cell precursors outnumbered the white cells 2 to 1. The former could be seen to develop into the latter. Bizarre nuclei were seen in all the red cells, most of which were young forms, encompassing rubriblasts and basophilic rubricytes.

Although not so typical as the other cases in this series in that there was relatively less marrow involvement by the primitive erythroid cells, which unfortunately could not be verified by autopsy, it is believed that this case belongs to the group of erythremic myelosis.

IX. Analysis of Cases in the Literature

In the evaluation of cases presented as erythremic myelosis or as erythroleukemia, the greatest difficulty lies in differentiating them from various forms of hemolytic anemia. At one time, for instance, Cooley’s anemia and erythroblastosis fetalis were considered by Di Guglielmo and others to be examples of erythremic myelosis, but this is no longer believed.

From the clinical point of view acute erythremic myelosis has several features in common with acute forms of hemolytic anemia; notably, fever, splenomegaly, severe anemia, and a course of a month or six weeks. Jaundice, on the other hand, is not listed as a prominent sign but has been noted in several of the chronic cases.

The same problem is presented in the evaluation of blood observations. The presence of anemia characterized chiefly by severe anisocytosis and the outpouring of nucleated red cells may be seen in both conditions. The interpretation of the reticulocyte counts presents even greater difficulty. In the few cases of erythremic myelosis that Moeschlin accepted, the reticulocyte count was either not given, or, as in the case of Paradiso, was listed as “not over 20 per cent.” Among the cases accepted by Di Guglielmo as examples of chronic erythremic myelosis, reticulocyte counts ranged to high levels and there was in addition evidence of accelerated blood destruction. The presence of a high serum bilirubin, increased fecal urobilinogen, a positive indirect van den Bergh reaction, combined with reticulocytosis of 95 per cent and extremely diminished osmotic resistance of the red cells would thus place Di Guglielmo’s and Quattrin’s case clearly in the category of hemolytic anemia or of presenting a hemolytic component. The case of Heilmeyer and Schöné presented an increase in urinary and fecal urobilinogen, serum bilirubin values of from 3 mg. to 4 mg. per cent, and reticulocyte counts up to 80 per cent. With such evidence the possibility of a primary hemolytic disease cannot be ignored. A similar objection can be raised against the case reported by Duesberg in which moderate amounts of bilirubinemia and urobilinuria and a reticulocyte count of 70 per cent were found. If the chief feature of erythremic myelosis is erythropoietic proliferation combined with maturation arrest, then a severe reticulocytosis, indicating accelerated erythropoiesis is incompatible with the diagnosis by definition.

Di Guglielmo advanced two explanations for the hemolytic component in erythremic myelosis: (1) that the abnormal erythropoietic tissue produced red cells more fragile than normal; hence, more subject to hemolysis, and (2) that the level of circulating erythrocytes is maintained, not by the pathologic tissue,
but by the remaining uninvaded normal erythropoietic tissue. Neither explanation seems to be sufficient to account for reticulocyte counts of the magnitude mentioned.

Pittaluga\textsuperscript{27} in the presentation of his case, stressed the dissociation of the erythroblastic reaction from the reticulocyte reaction. He believed that the number of erythroblasts in the peripheral blood is regulated by factors entirely different from those that govern the new formation of reticulocytes and the normal maturation of erythroblasts. It is known that in conditions such as leukemia and myelophthistic anemia the relative proportions of reticulocytes and erythroblasts appearing in the peripheral blood may show a significant disproportion. Whether this phenomenon occurs as a result of marrow “irritation” or, as Moeschlin and Rohr\textsuperscript{23} believe, by the entrance of immature cells into the blood stream from extramedullary foci, is not of so much concern here as the problem of the interpretation of the elevated reticulocyte counts. Since in erythremic myeloses the increase in reticulocytes is usually irregular and modest, not necessarily indicating accelerated hematopoiesis, some increase in their number is acceptable; but whenever the rise is either sustained or pronounced, a primary hemolytic process must be ruled out.

In cases such as that of Isræls,\textsuperscript{18} in which reticulocytosis is not a prominent feature (4.8 per cent), the differentiation of erythremic myelosis from hemolytic anemia is not so difficult. In the cases of Benedetti\textsuperscript{2} and Copelli,\textsuperscript{8} which correspond most nearly to our 4 cases, reticulocyte counts unfortunately are not given; but the information that there was no polychromatophilia suggests that blood production was not accelerated.

In the examination of the marrow the same problem in differential diagnosis exists. The finding of a hypercellular marrow with the predominance of erythroblasts is seen in both erythremic myelosis and hemolytic anemia. The maturation arrest and the presence of atypical erythroblasts are features that serve to distinguish erythremic myelosis. These criteria, given by Di Guglielmo\textsuperscript{11} in his 1946 publication, are the sine qua non of the diagnosis. Recently, however, we have been made aware by Owen\textsuperscript{24} that even the criterion of maturation arrest is not foolproof, because during crises in hemolytic anemia there may be an “aplastic” phase during which only the primitive red cell precursors remain in the marrow. This has been found to be true also in several cases of sickle cell anemia which we have studied during crisis.\textsuperscript{30} This is unimportant from the differential diagnostic standpoint in all but the acute conditions inasmuch as the aplastic phase is transient, lasting only a few days.

In the case of Benedetti the marrow showed a predominance of erythroblasts in the ratio of NRBC:WBC of approximately 9:1, and 72.6 per cent of the erythroblasts were basophilic, a maturation arrest of such severity that the case is readily singled out of other hemopathies. The case of Paradiso, cited by Moeschlin,\textsuperscript{22} showed 88.2 per cent of all the nucleated cells in the marrow to be erythroblasts and 83 per cent of these were basophilic. In this case, despite the evidence of increased blood destruction (positive indirect van den Bergh reaction, slightly reduced resistance of the red cells to hypotonic saline solution, reticulocytes 20 per cent), it is hard to attribute a left shift in erythropoiesis of this degree to a primary hemolytic process. In the case of Stodmeister\textsuperscript{32} the ratio of nucleated red cells to white cells (77.8:100), although exceeding the
normal range, did not reach the proportions seen in other cases. A left shift in erythropoiesis was clearly demonstrated, with 62.8 of the 77.8 nucleated red cells basophilic.

Using a clear-cut left shift in erythropoiesis in the marrow as one criterion for the differentiation of erythremic myelosis, one must still allow for personal differences in the classification of immature cells. Of the cases under consideration, such a left shift or failure in maturation is seen in the chronic cases reported by Benedetti,2 Duesberg,14 Pittaluga27 and Heilmeyer and Schöner.17 Among the acute cases, Di Guglielmo's,10 Stodmeister's,32 and Paradiso's25 meet this qualification.

Is such a criterion valid for the differentiation of erythremic myelosis from hemolytic anemia? Under ordinary circumstances, it would seem so. But of these 7 cases, we are still confronted with strong evidence of accelerated blood destruction in 4. In severe and prolonged hemolytic anemia coupled with or leading to nutritional or hemopoietic principle deficiencies, might not a left shift be produced as a result of the exhaustion of these substances? Such a mechanism could conceivably account for the changes described in the case of Heilmeyer and Schöner.17

Another distinguishing feature lies in the atypical forms of the erythroblasts (rubriblasts). These changes, similar to those seen in the megaloblasts of pernicious anemia, are emphasized by most writers on the subject. Besides megaloblasts, Di Guglielmo15 described primitive erythroblasts bearing evidences of reticulo-endothelial genesis, and transitional forms between reticulo-endothelial cells and basophilic erythroblasts. In Moeschlin's22 case the cells are referred to as “megaloblastoid,” whereas Copelli8 spoke of them as “atypical megaloblasts.” The abnormal cells in Stodmeister's case32 could not be distinguished from the megaloblasts of pernicious anemia. Other features, notably dissociation between the maturity of the nucleus and cytoplasm make the similarity to the marrow in pernicious anemia even more striking. The changes in erythremic myelosis are, at least morphologically, apparently similar but more severe and bizarre than those of pernicious anemia. Pernicious anemia could be ruled out, at least in more recent cases, by a trial with liver therapy.

The presence of reticulo-endothelial cells or histiocytes in the process of erythrophagocytosis in the peripheral blood and in the organs has been stressed as another feature. This phenomenon can be given little weight in differential diagnosis inasmuch as it also occurs in various anemias and in subacute bacterial endocarditis.

Cases that fulfill, in our opinion, the criteria of erythremic myelosis are abstracted in the following section. This is not intended to represent a definitive list of acceptable cases. It does represent most examples of the disease reported in the literature in which the diagnosis seems warranted.

X. Acceptable Cases in the Literature: Abstracts of Examples*

1. Acute Erythremic Myelosis

Case A: Di Guglielmo9 (1928) 50 year old male. Observed four days before death. Seven weeks illness with lack of appetite, lassitude, fever, sweating, yellowish pallor and dryness

*The limitation of space has compelled the abbreviation of the abstracts to the point where much interesting material is excluded. For details, and especially for each author's interpretation of his case, the reader is warmly urged to consult the original article.
and burning of the mouth. Severely prostrated, pale; painful stomatitis and glossitis; diffuse bronchial rales; spleen three fingerbreadths, liver 6 cm. below costal arch. RBC 1.16 to 1.5; WBC 3,200 to 4,000; Hgb. 32 to 40 per cent; nucleated RBC on the first day only; myelocytes, metamyelocytes and endothelial cells. Platelets reduced.

Autopsy: pallor, 1,700 Gm. spleen, hepatomegaly. Marrow: basophilic and polychromatophilic rubricytes in clusters; metarubricytes almost completely lacking. Histioid cells with voluminous cytoplasm and spongy, nucleolated nuclei, transitional forms between hemo-histioblasts and “megaloblasts,” and reticulo-endothelial cells in the process of macrophagocytosis. Granulocytes scarce; groups of eosinophils. Liver and spleen: foci of reticulo-endothelial and erythroblastic cells.

Case B: Lazzaro* (1933) 23 year old male. Profuse bleeding after tooth extraction, frequent epistaxes; sore throat with fever, swelling of the eyelids. Pale; vestiges of a hemorrhagic diathesis. Liver two fingerbreadths, spleen one fingerbreadth below costal margin. Died nine days after admission. RBC 2.1; Hgb. 29 per cent; platelets 8,000; nucleated cells 38,000. Basophilic rubricytes 5.4; polychromatophilic rubricytes 14.2; metarubricytes 30.2; neutrophilic myelocytes 4.3; metamyelocytes 15.2; neutrophils 4.4; lymphocytes 5.6; monocytes and monocytoid cells 8.4; reticulo-endothelial cells 12.4.

Autopsy: pallor, petechiae, pachymeningitis iuemerhhagica, fibrinous pericarditis, splenomegaly (550 Gm.), hepatomegaly (2310 Gm.). Liver: portal spaces infiltrated with histiocytes and cells of the erythroblastic series. Spleen: foci of erythroblasts. Marrow: hyperplastic; granulocytes and megakaryocytes scarce; cells of the erythroblastic series and reticulo-endothelial elements increased in volume and number.

Case C: Stodmeister2 (1941) 37 year old female. Admitted febrile and dying, four days postpartum; died the same day. Pale; rales in the chest. Spleen at the umbilicus; liver edge three fingerbreadths below costal margin; fundus of the uterus midway to the umbilicus. Hgb. 25 per cent; RBC 0.94; WBC 7,200; "macroblasts," basophilic 10, polychromatophilic 4.5, orthochromatic 0.5; "normoblasts," basophilic 4.5, polychromatophilic 4.5; two mitotic figures for every 100 WBC. Thrombocytes diminished. Marrow: moderately cellular; megakaryocytes diminished; myeloblasts 0.8; myelocytes, “unripe” 4.4; “half ripe” 25.0; “ripe” 6.6; metamyelocytes 35.4; bands 13.2; polymorphonuclears 12.4; eosinophils, unripe 0.8, ripe 0.4; lymphocytes 1.0. Reticulo-endothelial cells per 100 white blood cells; pigment phagocytosis 0.6; granular reticular cells 0.8; nongranular reticular cells 2.8; plasma cell 1.4. Nucleated red blood cells per 100 white blood cells: macroblasts, basophilic 39.4, polychromatophilic 3.8; normoblasts, basophilic 23.4, polychromatophilic 8.6, orthochromatic 2.6. The young macroblasts resembled the megaloblasts of pernicious anemia.

Autopsy: spleen 1050 Gm.; large nucleated elements with large round, chromatin-poor nuclei throughout. Marrow: erythroid and myeloid hyperplasia, with large round nucleated cells throughout.

2. Chronic Erythremic Myelosis

Case A: Copelli8 (1912) 60 year old male. In 1908 “bronchitis,” fever, splenomegaly. In 1909 recurrence with anemia and weakness. Third recurrence with dyspepsia, and icterus in 1910. Final illness lasting eight months. Weak, pale, semicomatose. Spleen normal size. Hgb. 16 per cent; RBC 0.85; platelets 8,000; nucleated cells 8,000; lymphocytes 16; mononucleated cells 2; polymorphonuclear neutrophils 82.

Autopsy: Spleen 16 x 11 x 6 cm.; follicles hyperplastic; nodular focci of nucleated red cells which in some areas destroyed the trabecular reticulum, follicles and capsules. Three types of red cells distinguished: (1) Large (from 15 to 35 micro) erythroblastic cells, (2) Megaloblastic cells, (3) Normoblasts. Marrow: uniformly increased at the expense of the bony tissue. Liver: numerous small groups of erythroblastic cells scattered within the lobules.

Case B: Benedetti (1938) 46 year old female. Observed for three months prior to death. Six years before admission an ill-defined respiratory infection followed by attacks of bronchitis, pallor, weakness and fever. Three years before admission enlarged spleen and severe anemia. Extreme pallor; liver two fingerbreadths below the costal margin; spleen 6 cm. above the pubis. Hgb. 35 per cent; RBC 1.725, WBC 1,800; platelets 110,000; poly. 33; lymphs. 62; monos. 5. Marrow: intensely erythroblastic with predominantly basophilic
ERYTHREMIC MYELOSIS (DI GUGLIELMO'S DISEASE)

erythroblasts (72.6 per cent). Biopsy of spleen: numbers of immature basophilic erythroblasts, occasionally in bunches.

Splenic artery ligated. Died a few days later.

Autopsy: accessory spleen contained mature and some immature red cells; hyperplasia of the pulp.

Case C: Israels (1939) 42 year old female. Exhaustion, dyspnea nine months. Pallor, edema, spleen below the umbilicus, liver 2 inches below costal margin. Hgb. 45 per cent; RBC 3.03; WBC 149,000; nucleated RBC 9,000; nuclei of red blood cells 79,000 of which normoblasts A 0.5 per cent, normoblasts B 15 per cent, normoblasts C, 55 per cent, megaloblasts B, 25 per cent, megaloblasts C, 4.5. Marrow: polys. 15.4; baso. 0.4; metamyel. 3.4; myeloblasts 1.4; myelocytes 7.4; mono. 1.8; lymphs. 3.4; plasma cells 0.2; normoblasts A (basophilic rubricytes), 3.2; normoblasts B (polychromatophilic rubricytes), 12.0; normoblasts C (metarubricytes), 37.2; megaloblasts B, 9.5; megaloblasts C, 5.2.

Died four months after admission.

Case D: Pittaluga (1940) 42 year old male. Jaundice in 1938. July, painful edema; entered hospital in August; died in January 1939. Pale, gross edema, liver extremely enlarged, spleen "enormous". Hgb. 65 per cent, RBC 1,300 to 4,000; nucleated RBC 800; polys. 69; eosin. 2; mono. 9; lymphs. 14; promyelocytes 6. Reticulocytes 11 to 14 per cent. Platelets 100,000 to 120,000. Marrow: normoblasts and erythroblasts 38 per cent; proerythroblasts (basophilic) 18 per cent; macroerythroblasts 29 per cent.


Case E: Duesberg (1940) 50 year old male. Ill for two years; under observation last five months of life. Weakness, weight loss; enlargement of liver and spleen. Hgb. 40 per cent; WBC about 1,000; 5 normoblasts per 100 WBC; platelets from 20,000 to 50,000. Marrow: 79 per cent erythroblasts.

Autopsy: marrow: cellular, abundant macroblasts and normoblasts, frequent reticulum cells, granulopoiesis reduced. Liver: 2,020 Gm., distinct infiltrations in portal fields and about the central vein by cells resembling erythrocytes. Spleen: 850 Gm.; structure indistinct; marked infiltration of cells similar to those in the liver.

Case F: Heilmeyer and Schoner (1941) 75 year old male. Pallor and lack of appetite, 1938. Fatigue, weakness, complete loss of appetite, feet greatly swollen, March. 1939. Pale, wasted, edema of legs, ecchymoses. Abdomen distended; liver edge 7 cm. below costal margin, spleen 3 cm. below the umbilicus. Hgb. 45 per cent; RBC 2.1; nucleated cells 5,200; reticulocytes 80 per cent; myelocytes 16; young forms 10; stab cells 8, segmented 20, baso. 1, mono. 2, lymphs. 45; 14 nucleated red blood cells per 100 white blood cells, of which proerythroblasts constituted 2, erythroblasts (macroblasts) 7, and normoblasts 5. Marrow: abundant. Erythroblasts (macroblasts) accounted for most of the nucleated red cells. The ratio of nucleated red to white cells rose from 41 to 3,260 per hundred white blood cells. Parallel increase in reticulum cells. Similar change in the peripheral blood, with 2,230 nucleated red cells and 1,770 white cells per cubic millimeter terminally.

In the first splenic puncture nucleated red cells exceeded the white cells by 20 per cent; in the second, the chief cells were the nucleated reds. Liver puncture showed erythroblastic proliferation.

Died after eight months' observation.

Autopsy: great enlargement of the liver and spleen; red marrow in the femur; ascites; edema; wasting. Liver: nucleated RBC between the cords and the capillaries. Spleen: erythroblasts, normoblasts and undifferentiated cells.

Case G: Di Guglielmo and Quattrini (1942) 12 year old female. Eighteen month illness. Jaundice, anemia, fever, and gastrointestinal disturbances. Spleen 2 fingerbreadths below the umbilicus. Hgb. 20 per cent; RBC 0.95; nucleated cells 38,128; erythroblasts 15,538; white blood cells 12,500; reticulocytes 900,250. Marrow: 76.1 per cent of the cells belonged to the erythropoietic line. Post-splenectomy the reticuloocyte count dropped to 18 per cent, the red blood cells rose to 3.6 million, nucleated red cells in the peripheral blood
dropped to 8,068 and the serum bilirubin declined. Four months after the operation recurrence of anemia and jaundice: death.

Autopsy: liver: diffuse perilobular infiltrations of histio-erythroblastic tissue and erythroblasts in various stages of maturation. Similar infiltrations in the lymph nodes, kidneys, heart, and pancreas.

3. Erythroleukemia

Case A: Moeschlin and Rohr23 (1939) 31 year old female. Fatigue; pallor; bleeding, swollen and ulcerated gums, November, 1935. Liver enlarged; spleen 2 fingerbreadths below rib margin. Hgb. 25 per cent; RBC 1.1; nucleated cells 12,900; nucleated RBC 5,900; platelets decreased. Twenty-eight normoblasts and 140 macroblasts per 200 WBC. Differential count myeloblasts 5.5; mature myelocytes 1; neutrophils 65; eosinophils 2.5; monocytes 5.5; lymphocytes 20.5. Many myeloblasts contained Auer bodies. Marrow: 345 erythroblasts per 100 WBC, divided as follows: basophilic erythroblasts 35; polychromatophilic erythroblasts 205; and orthochromatic erythroblasts 105. WBC: 16 myeloblasts, 1.5 unripe and 5.0 half ripe, 12.0 mature myelocytes, 24 metamyelocytes, 28 neutrophilic stabs, 6.5 eosinophils and 3 lymphocytes. Megakaryocytes were rare. Died after an illness of about 8 months.

Autopsy: anemia; enlargement of liver (2150 Gm.), spleen (350 Gm.), and lymph nodes of thorax and abdomen. Spleen contained myeloblasts and clearly distinguished nests of normoblasts. Myeloblastic metaplasia and occasional erythroblastic foci in lymph nodes.

Case B: Boni' (1942) 30 year old female. Fever, gastro-intestinal symptoms, four months. Pale; spleen palpable 1 fingerbreadth below costal margin. Died soon after admission. Hgb. 14 per cent; RBC .750; platelets 4,500; nucleated cells 40,000, of which 30 per cent were erythroblasts; myeloblasts 29, promyelocytes 64, myelocytes 1.4, metamyelo. 0.1, polymorph. 0.4; lymphs. 4.5; megakaryocytes and megakaryoblasts 0.1; plasma cells 0.5; phagocytic mononuclear cells 0.1 per cent. Of the red series there were eight pro-erythroblasts, 17.7 basophils, 10 polychromat and 4 orthochromatic erythroblasts, 0.3 basophilic binucleated cells, and 58 lymphocyte-like cells.

Autopsy: lymph nodes and liver enlarged; spleen one and a half times normal size. Liver, spleen, kidneys infiltrated with myeloid connective tissue and erythroblastic type cells. Immature cells of the red and white series, the hyperplasia of the red cells exceeding that of the white cells, were found in the marrow.

XI. Summary

This article represents a critical attempt to survey the cumulative information of the rare syndrome ordinarily called Di Guglielmo's disease. The historical background lies predominately in Europe, more particularly in Italy, where the recording of cases has been fairly extensive and where interpretation has been pioneered.

The present study does not presume to be definitive. It attempts to trace the thinking that has gone before, and to define the terms of reference so as not to compound nosologic confusion. It presents examples of cases in the literature acceptable diagnostically by definition. Criteria for the differential diagnosis of acute and chronic erythremic myelosis and erythroleukemia are offered. These three conditions are regarded as variants of reticulo-endotheliosis. This conclusion is based on what is known of the pathogenesis, and on what has been observed clinically and hematologically.

All evaluation is necessarily offered with the reservations that must be held regarding a rare disease of unknown etiology.

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STEVEN O. SCHWARTZ AND JOAN CRITCHLOW

Erythremic Myelosis (Di Guglielmo's Disease): Critical Review with Report of Four Cases, and Comments on Erythroleukemia

STEVEN O. SCHWARTZ and JOAN CRITCHLOW

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