The DiGuglielmo Syndrome Revisited

By William Dameshek, M.D.

WE HAVE WRITTEN of the DiGuglielmo syndrome a number of times.1-4 Our basic concept that this variegated disorder of the bone marrow is a neoplastic disease remains unchanged and has in fact been strengthened. A number of new pieces of data suggest that such terms as "refractory anemia"5 and "refractory normoblastic anemia"6 and others such as "sideroblastic anemia"7 and "siderochrestic anemia"8 have by now become outdated. Whether the term "DiGuglielmo Syndrome" is any better is open to some question, but being sufficiently vague, it can cover a large area, and being eponymic, it too can be discarded when sufficient etiologic or pathogenetic information becomes available.

As a young man, DiGuglielmo9,10 pioneered the concept that the red cell elements of the bone marrow, like the white cells of leukemia, could proliferate abnormally, thus producing diseases which he described as "erythremic myelosis" and "erythroleukemia". Although the full implications of these abnormal disorders were not at first appreciated, there can be no question that the fundamental thought to which DiGuglielmo seemed almost singlemindedly devoted, until his death in 1961, was correct. On his deathbed, he was just completing a manuscript subsequently published in 1962 as a large and artistic folio: "Le Malattie Eritremiche ed Eritroleuemiche"11 which dealt with the subject exhaustively. We believe therefore there is sufficient reason to warrant the continuing use of the designation DiGuglielmo Syndrome.

We conceive of this condition as one of the members of the group of conditions we have called "the myeloproliferative" syndrome; these include a number of self-perpetuating disorders of the marrow.12 Since the bone marrow is productive of several kinds of cells, (erythroblasts-erythrocytes; myeloblasts-granulocytes; megakaryocytes-platelets; reticulum cells) and since these may proliferate rapidly or slowly, selectively or totally, sequentially or all at once, there is room for many variations, some of which we have previously tabulated.12,13

The DiGuglielmo syndrome may be defined as a self-perpetuating, myeloproliferative disorder of undetermined origin characterized by progressive anemia; striking erythroid hyperplasia of the bone marrow and of megaloblastic, megaloblastoid, or normoblastic types; and the gradual development,
often in the course of a number of years, of increasing numbers of myeloblasts. Eventually, in some cases, (approximately 50% in my own experience) sufficient myeloblasts are present to warrant the diagnosis of erythroleukemia and later of myeloblastic leukemia. Further criteria of the condition include hyperferremia both in the blood serum and in the marrow; the presence of large numbers of erythroblasts with iron granules (sideroblasts); the presence of large amounts of iron in the mitochondria of sideroblasts, giving rise to the picture of "ringed" sideroblasts as seen with light microscopy; "ineffective" erythropoiesis as determined by radio-iron studies (unusually rapid iron clearance; slow incorporation into non-nucleated erythrocytes); "heme diversion" as indicated by an increased output of urobilinogen in the feces without much, if any, shortening of red cell life span; a disturbance of heme synthesis, as determined from chemical studies of the marrow; a frequently low blood granulocyte alkaline phosphatase; and a variable degree of positivity of the PAS test in nucleated red cells.

Whether to use the term DiGuglielmo syndrome in the presence of what appears to be a "pure" erythroblastic hyperplasia without any indication of myeloblastosis has been the subject of some critical comment. To be sure, one cannot foretell in a given case, whether it be fulminating or slow in its development, if leukemia will eventually develop. Nevertheless, if one can rule out such "primary" disorders as cancer and chronic infection, a probable diagnosis of the syndrome may be made by putting together in one package such features as the progressive anemia with the indications of erythroblastic hyperplasia and of maturation arrest, together with the sideroblastosis and the other manifestations already noted. The course of such a case in the ensuing months or years, its progressive nature, the gradual transition from an erythroblastic to a myeloblastic bone marrow, and the complete lack of any evidence of chronic infection, tumor or other disease should support the fact that one is dealing with a "primary" neoplastic disorder.

DiGuglielmo first suggested that the disorder he described as "acute erythremic myelosis" was a leukemic-like disease of the red cell series.\textsuperscript{11} In the less violent cases, the development of anemia in the presence of striking erythroblastic proliferation, its progressive character, the presence of heme synthetic defects with apparent inability by the nucleated red cells to metabolize iron, all point to the development of a new type of red blood cell proliferation. What this is due to—an unknown deficiency state, an unknown virus, a chemical "insult," a mutation—is by no means clear.

Kiossoglu, Mitus and I in 1965\textsuperscript{14} demonstrated chromosomal abnormalities, mostly hypoploidy, in six of 16 cases of the DiGuglielmo syndrome. In a more recent study by Castoldi et al.\textsuperscript{15} of six cases, abnormalities were found in all, although no consistent patterns emerged. A common feature was a variable degree of involvement of the G group of chromosomes (five of six cases); C trisomy was found in one case. Involvement of the G group has been a common feature in various forms of myeloproliferative disease.\textsuperscript{16,17} These findings occurred even in cases of apparently "pure" erythremic myelosis and were similar, if not identical, with the chromosomal abnormalities found in acute leukemia.
In 1963, Steiner, Baldini and I described enzymatic abnormalities of heme synthesis and delta-aminolevulinic acid dehydrogenase in erythroid cells of bone marrow aspirates. Finkel, Brauer, Taub and I, in studying 49 cases, noted the frequent presence of hypergammaglobulinemia (11 of 37 cases), and a variety of autoantibodies, including the LE factor. In two cases, hemoglobin H was found. Although modifications in blood group antigens were not studied, they were observed (but not reported) in a few of the cases.

In recent studies by Dreyfus and collaborators, many new observations and some extensions of previous ones have been made. These were the subject of a symposium published in the January-February 1969 issue of *Nouvelle Revue Francaise d'Hematologie* under the general heading of “The Refractory Anemias.” Dreyfus and collaborators describe chromosome abnormalities, modification of red cell and leukocyte antigens, enzymatic abnormalities in both red and white cell series, and in enzymes concerned with heme synthesis. Electron microscope studies by Bessie, Dreyfus, et al. of 11 cases of “refractory anemia” and eight having erythromyeloblastosis showed similar irregularities, including nuclear abnormalities, asynchrony of nucleocyttoplasmic development, abnormal granulation of the granulocytes, and excessive glycogen in nucleated red cells, megakaryocytes, and platelets. Salmon et al. demonstrated modifications in the quantities of blood-group antigens A, A, B.H.I and i, identical with those already described in acute leukemia. Anomalies in platelet function were also observed. These various findings led Dreyfus and his collaborators to the general conclusion that far from being an innocuous disorder, “refractory anemia” or “chronic erythremic myelosis” was actually a neoplastic disease having many of the features seen in acute leukemia. Involvement of all three myeloid lines suggested origin from an abnormal group of stem cells.

Conceivably the erythroleukemia of mice inoculated with the Friend virus may represent an experimental model for the human disease. This form of leukemia has many features setting it apart from the usual leukemic disease of mice: marked erythremic myelosis, a well-defined increase in the number of myeloblasts, and eventually the characteristic features of myeloblastic leukemia. Although the disease of mice is induced by a virus, this does not necessarily indicate a viral etiology for the human DiGuglielmo syndrome, although a viral etiology for at least some cases is by no means excluded.

Of further interest is the recent finding that some cases of the full-fledged erythroleukemic disease (i.e., mixed erythremic and leukemic proliferation) respond to the administration of the antimetabolite cytosine arabinoside with definite, and even complete remission, lasting for two months to two years. Further studies in this area are warranted.

To conclude this “new look” at the DiGuglielmo syndrome: (1) it seems desirable to discard such terms as refractory anemia, refractory normoblastic anemia, sideroblastic anemia, and sideroachrestic anemia as either meaningless or of limited conceptuality. They certainly offer no new insights. What is more, sideroblastosis occurs in a wide variety of entities. Surely the inability to incorporate iron into the heme structure (“siderochrestia”) is simply a symptom...
and not a pathognomonic feature of the disease. To my mind, all that these terms offer are perhaps a not very laudable caution and a degree of evasion of the central problem of the disease, i.e. what it means and its pathogenesis.

(2) It seems best to think of the DiGuglielmo syndrome as a highly variable but generalized myeloproliferative disorder in which erythremic myelosis, erythroleukemia, and myeloblastic leukemia may all appear either sequentially or in a “mix” which is difficult to classify.

(3) The abnormal growth process in the marrow, with its numerous and variable morphologic, metabolic, and antigenic abnormalities may be considered as a neoplasm, perhaps of the bone marrow stem cells, often eventuating in myeloblastic leukemia.

(4) Like pernicious anemia, it is conceivable that the DiGuglielmo syndrome may represent a defect in DNA replication; unlike pernicious anemia, the latter disease has thus far been largely irreversible, perhaps because of the development of an acquired, self-perpetuating genetic defect (neoplasm) which is no longer subject to the usual control mechanisms. To be sure, a hitherto undefined vitamin deficiency may one day be uncovered, as was the case with the seemingly neoplastic disease of pernicious anemia. At any rate, the “progressive pernicious anemia” of the past is no longer “pernicious,” but the DiGuglielmo disorder of the present day surely is. Although etiology and pathogenesis of the human disease have not yet been elucidated, the presence of numerous, highly variable defects in consecutive series of cases suggest that highly potent etiologic agent(s) may have been involved. On this note, Clarke, Cooper, Hackett, et al. have demonstrated at the Battelle-Northwest Clinic that various forms of myeloproliferative disorders may be induced in a special strain of swine by the chronic ingestion of Strontium. Similar results have been obtained in beagles by Dungworth, Goldman, Fritz, Norris, et al. Gradually, knowledge of the DiGuglielmo syndrome and its related myeloproliferative disorders has piled up. The therapeutic era should not be too far away.

In this admittedly controversial field, some of our readers with different or better ideas might care to comment. We should be delighted to receive “Letters to the Editor” for publication and discussion.

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REFERENCES

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