
EDITORIAL

Some Speculations on the Myeloproliferative Syndromes

WITH ACCUMULATING EXPERIENCE, it becomes more and more evident that the bone marrow cells—erythroblasts, granulocytes, megakaryocytes—often proliferate *en masse* or as a unit rather than as single elements. Thus, leukocytosis and thrombocytosis, as well as reticulocytosis occur not only in benign reversible conditions such as hemorrhage and excessive hemolysis but in such malignant or more or less irreversible reactions as leukemia and polycythemia. Although we seem to have become conditioned to the idea that such entities as chronic granulocytic leukemia and polycythemia vera represent “pure” proliferations of one or another cell type, a revision in this thinking may be necessary. For example, in most early cases of chronic granulocytic leukemia, there is some degree of erythrocytosis and thrombocytosis. The latter may be of extraordinary degree and attended with the presence of bits of megakaryocytes in the circulation. Thrombocytosis often persists until the very end of the disease and at times may dominate the picture.

Similarly, polycythemia vera is far more than a pure red cell proliferation. The blood picture reveals pancytosis¹ (erythrocytosis, leukocytosis, thrombocytosis) and the marrow shows generalized hypercellularity often dominated by extreme increases in the megakaryocytes. Some cases of otherwise clear-cut polycythemia vera have leukocyte counts in the neighborhood of 50,000 to 100,000 with fair numbers of myelocytes in the blood. How should one classify these cases? Are they atypical granulocytic leukemia with erythrocytosis resembling polycythemia vera or are they examples of polycythemia vera with a leukemoid reaction. In some cases of polycythemia vera showing relatively slight erythrocytosis, the platelet count may reach levels of five to ten million per cu.mm. and the thrombocytocrit may be 5 to 10 per cent of the total volume. Do these cases represent a variant of polycythemia or are they perhaps a proliferative disorder of the megakaryocytes, e.g. megakaryocytic leukemia?

In about 10 to 20 per cent of all cases of polycythemia vera there is the gradual development of increasing anemia with a “leuko-erythroblastic” blood picture. The bone marrow in such cases shows a striking fibrosis and the spleen shows well defined marrow activity (myeloid metaplasia). In the past, it was simple to consider the extramedullary hematopoiesis in the spleen as being purely compensatory in nature. However, it is apparent that individuals ultimately developing myelofibrosis can often be “spotted” years in advance by the very marked degree of splenomegaly present and by the presence of small numbers of nucleated red cells and myelocytes in the blood *even when the marrow is by no means fibrotic* and the red cell count is still elevated. This brings up the distinct possibility that the splenomegaly, which is due largely to myeloid metaplasia, has been present for years. The gradually developing fibrosis of the marrow may be simply another manifestation of marrow proliferation,² in this instance involving

reticulum cells and fibroblasts rather than purely hematopoietic tissues. Rosenthal³ has recently reemphasized this view.

From such cases of apparently clear-cut polycythemia vera with terminal myelofibrosis (and myeloid metaplasia of the spleen) it is only a step to that highly controversial group of cases having such designations as agnogenic myeloid metaplasia of the spleen, leuko-erythroblastic anemia, non-leukemic myelosis and the like. Jackson and Parker⁴ have contended that these cases represent a distinct entity of "agnogenic" (i.e. idiopathic) nature, and have pointed out that some of the cases show no myelofibrosis whatever, but rather a hyperplastic bone marrow. Unfortunately, they may have included in this group cases of severe acquired hemolytic anemia showing myeloid metaplasia of the spleen at operation and some cases of undoubted leukemia. But perhaps the latter disease and myeloid metaplasia are more closely related than we have thought.

Heller, Lewisohn and Palin⁵ for example, have come to the conclusion that myeloid metaplasia of unknown origin both with and without myelofibrosis is actually a peculiar form of leukemia. Parenthetically it should be stated, however, that the therapy of leukemia and of this form of myeloid metaplasia differ considerably in that in the former disease x-ray is the treatment of choice whereas in the latter, x-ray therapy over the spleen may cause considerable anemia as the spleen becomes reduced in size and its content of "marrow" cells diminished.

Another disorder as yet not completely accepted by many is that of "erythroleukemia" "erythroblastemia," or "DiGuglielmo's syndrome."⁶ Does this represent, as DiGuglielmo has maintained, a generalized neoplastic type of erythroblastic proliferation with acute, subacute, and chronic types as in leukemia: a variant of myeloid metaplasia; or even a form of leukemia with temporary crowding of the marrow with nucleated red cells? Certainly, such cases occur, although in this country there seems to have been some reluctance in accepting them as a well defined entity.

Thus, if we examine these various syndromes, all of them originating from bone marrow cells, as a group, we find it difficult to draw any clear-cut dividing lines; in fact, so many "transition forms" exist that one may with equal reasonableness call a single condition by at least two different terms. Polycythemia vera, undoubtedly a panmyelopathy, has variants which cannot be distinguished from chronic granulocytic leukemia or myeloid metaplasia. The diagnosis as between certain cases of chronic granulocytic leukemia and myeloid metaplasia is sometimes a matter of taste. Cases showing extreme thrombocytopenia may be due to benign megakaryocytic hyperplasia, but on the other hand, they may indicate a neoplastic proliferation of the megakaryocytes (megakaryocytic leukemia), or simply a variant of chronic granulocytic leukemia or polycythemia. Similar confusion exists for cases showing large numbers of nucleated red cells in the blood. In recent years the tendency has been to group them all in the rather vague syndrome of "agnogenic myeloid metaplasia."

Perhaps it is possible to resolve all of these dilemmas, conflicts, antagonisms and confusions by considering, not that the various conditions listed are differ-

ent, but that they are closely interrelated. It is possible that these various conditions—"myeloproliferative disorders"—are all somewhat variable manifestations of proliferative activity of the bone marrow cells, perhaps due to a hitherto undiscovered stimulus. This may affect the marrow cells diffusely or irregularly with the result that various syndromes, either clear-cut or transitional, result. Among them are the following: chronic granulocytic leukemia, polycythemia vera, idiopathic or "agnogenic" myeloid metaplasia of the spleen (and liver), thrombocythemia, megakaryocytic leukemia and erythroleukemia (diGuglielmo's syndrome.) These more or less different types of cellular proliferation of the marrow are listed in table 1.

TABLE 1.—*The Myeloproliferative Disorders*
Myelostimulatory Factor's

Syndromes	Bone marrow				Potential bone marrow
	Erythroblasts	Granulocytes	Megakaryocytes	Fibroblasts	Myeloid metaplasia of spleen and liver
Chronic Granulocytic Leukemia	±	+++	+ to +++	+	++
Polycythemia Vera	+++	++	++ to +++	+ to +++	+ to +++
Idiopathic or Agnogenic Myeloid Metaplasia of Spleen	±	±	+++	+ to +++	+++
Megakaryocytic Leukemia	±	±	+++	+	+ to +++
Erythroleukemia (including diGuglielmo syndrome)	+++	+	±	±	+ to +++

Degrees of Proliferation: + slight
 ++ moderate
 +++ marked

Regarding the hypothetical myelostimulatory factor, speculation may be made that it is conceivably highly potent since under its influence not only do normal marrow cells become highly proliferative, but sites of embryonic or potential hematopoiesis as in the spleen and liver may become activated. One must now ask whether the stimulatory factor is perhaps related to the adrenocorticotrophic hormone. Certainly the administration of purified ACTH alone results in a definite myelostimulatory effect with reticulocytosis, thrombocytosis and the like.⁷ The continued administration of crude pituitary extracts, along with testosterone, has been shown to result in myeloid metaplasia.⁸

Many observers have cited the reciprocal or antagonistic relationship between granulocytic and lymphocytic hyperplasias and proliferations. These are noted, not only in infectious diseases but in the leukemias. Wiseman, Doan and Erf⁹ were among the first to emphasize the "fundamental reciprocal relationship between myeloid and lymphoid tissues" which has recently come to the forefront with knowledge of the lymphocytolytic effects of ACTH and cortisone.⁷

In line with these concepts are the investigations of F. R. Miller and his collaborators. These workers have succeeded in extracting from urine¹⁰ and more recently from serum¹¹ steroid-like principles which they have termed "myelokentric" and "lymphokentric" acids. When these materials were injected in the normal animal leukemoid effects of myeloid and lymphocytic types respectively were obtained. Miller et al.¹² have even used myelokentric acid for the treatment of acute lymphocytic leukemia and lymphokentric acid in acute granulocytic leukemia. With the present widespread interest in the steroid hormones and their undeniable relationships to the blood forming organs it seems that these observations must be considered with closer attention.

In any event, the concept of a myelostimulatory principle, perhaps hormonal or steroid in type, and of a variety of more or less closely related myeloproliferative disorders deserve our increasing consideration. To put together such apparently dissimilar diseases as chronic granulocytic leukemia, polycythemia, myeloid metaplasia and diGuglielmo's syndrome may conceivably be without foundation, but for the moment at least, this may prove useful and even productive.

What more can one ask of a theory?

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