Foreword and a Proposal for considering Paroxysmal Nocturnal Hemoglobinuria (PNH) as a “Candidate” Myeloproliferative Disorder

THE PRESENT “BONUS” ISSUE of Blood represents another attempt to whittle down our rather impressive backlog. Like a woman with obesity, our journal is always battling with the problem of too many tempting morsels—in our case, submitted papers. For this there are only two remedies: one, a further increase in rejection rate (now well over 50 per cent, or an increase in pages. We have rejected a third approach, i.e., a “bare bones” journal comprising only submitted articles sans editorials, reviews, or topical material. With the ever-increasing quantity and quality of submitted papers, it becomes increasingly more difficult to turn away good papers. Unlike the obese woman, our journal can, however, afford to expand girth a bit—but not its backlog—through an extra issue from time to time or by other printing technics presently under consideration. In the meantime, our publisher, Henry Stratton, has again given us the opportunity of publishing an extra issue on leukemia. This is highlighted not only by a deserved tribute to Dr. Edwin E. Osgood together with a recent “opinion” on Acute Monocytic Leukemia but by three reports of single cases of paroxysmal nocturnal hemoglobinuria (PNH) terminating as acute myeloblastic leukemia.

And thereby hangs a tale! Dacie and co-workers and I have alluded to the close relationships of PNH with aplastic anemia. I have speculated that hypothetical (and not so hypothetical) “insults,” e.g., chemicals, ionizing radiation, might induce not only bone marrow hypoplasia but in its wake, either PNH or primitive cell leukemia. There is much to indicate that PNH is not simply a peculiar hemolytic anemia, but rather a disorder of the entire bone marrow. It seems clearly evident that a new form of erythroblastic proliferation has developed with the result that mature red cells are produced showing a variety of abnormalities: ready destruction within the circulation via complement; unusual reactivity with such antibodies as anti-I (cold hemagglutinin); increased sensitivity to minor reductions in PH; reduced acetyl cholinesterase activity. These abnormalities appear to be clonal in variety, with indications that a relatively small percentage of abnormal red cells is present early in the disease, increasing with time. But red cell abnormalities including hemolytic anemia are not alone: usually pancytopenia is present, with well-defined leukopenia, granulocytopenia, and thrombocytopenia. The leukocyte alkaline phosphatase is unusually low as in chronic granulocytic leukemia and in some cases of MMM. The platelets are unusually reactive to platelet antibodies. Thus, it may be said—without stretching the point too much—that a generalized growth abnormality of the bone marrow, i.e., a myeloproliferative disorder has developed.

We have previously emphasized that the end result of the myeloproliferative
disorders may well be acute leukemia, as in myelosclerosis with myeloid metaplasia, polycythemia vera, and the DiGuglielmo syndrome. In the latter condition, what is at first apparently only a peculiar kind of anemia often becomes, in the course of time, primitive cell leukemia. Could PNH conceivably eventuate in acute leukemia? In discussing these concepts at various meetings, three such cases came to light (two entirely “new”—those of MacFarland and of Lichtman; Hartmann’s case had already been reported in abstract form). Hartmann, MacFarland and Lichtman agreed to report their cases together, and thus the appearance of all three in the present issue.

It is evident from the observations recorded here that the development of acute leukemia in PNH is by no means a rare event. Certainly the number of reported cases of aplastic anemia occurring in sequential relationship to PNH has increased far beyond the realm of coincidence; perhaps with time, the same may happen for primitive cell leukemia. As yet, I know of no case which has shown the three different expressions of bone marrow disease of aplastic anemia, PNH, and acute leukemia, but perhaps this rare “postage stamp” will soon be found. In any event, the point already made in a previous editorial seems clear enough: the marrow may react in different ways to the same “insult.” This variability in reaction is perhaps due to individual genetic differences, or simply to chance as to which group of injured cells has retained the capacity to grow and perpetuate its kind, eventually producing an abnormal or neoplastic clone.

At this point, one must consider the possibility of including PNH as a “candidate” for inclusion amongst presently accepted myeloproliferative disorders. Thus, I can see no difficulty in thinking about PNH as a form of erythremic myelosis or a variant of the DiGuglielmo syndrome. Could we have some other opinions?

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