

advantageous. Indications of the defect are present, not only in the undue hemolysis in the presence of dilute acid,⁸ but by a great reduction in red cell cholinesterase,⁹ a striking sensitivity to complement and immune antibodies,^{9, 10} a morphologic abnormality as seen by electron microscopy,¹¹ and by the presence of a shortened red cell survival time when the red cells of the patient are injected into a normal individual.¹² Thus, a certain proportion of the nucleated red cells of the bone marrow may be said to have developed an acquired, self-perpetuating abnormality which is sufficient to result in hemoglobinemia and/or hemoglobinuria. Stated in this way, PNH may be considered as a growth disturbance of the erythroblastic component of the marrow. Conceivably, it could be called "neoplastic," a new kind of growth.

Why should a previously healthy individual develop this defect involving at least a portion of his red cell series? Why should leukopenia and thrombocytopenia be so commonly present? This brings us squarely to the heart of the matter. The more than coincidental relationship of PNH to aplastic anemia and the fact that the latter disease has been commonly associated with exposure to various chemicals or ionizing radiation suggest the possibility that the same agent which results in total marrow destruction may result in injury but not total destruction of one or another component of the marrow. Thus, one may speculate that certain chemicals, which in large dosage may destroy all the elements of the marrow, may in smaller amounts result in "selective" destruction of one of the marrow components or perhaps only in the loss of a key enzyme of some cells. Such injured cells might retain the capacity to reproduce themselves despite this deletion, and in this manner the formation of a self-replicating clone of abnormal cells might be induced. PNH could thus be a form of neoplasia—of the red cell series—developing, at least in some cases, as the result of an insult to the marrow. Similar reasoning has been applied to the development of leukemia.

As cases of aplastic anemia are followed, whether these are chemically or radiologically induced, or in association with congenital defects (Fanconi syndrome, the Werner syndrome*), it becomes evident that a number of them eventually develop increasing groups of primitive leukocytes in the marrow—i.e., "acute" or primitive cell leukemia. It is conceivable that this type of leukemia is based upon the initial development of a small clone of primitive leukocytes with defective maturation; eventually such a clone may gain ecologic dominance. Thus it is evident that marrow hypoplasia may be followed in some cases by "hypoplastic" primitive cell leukemia, in others by the development of a new type of (defective) red cell growth—i.e., PNH. From this, one may infer that a sufficiently severe "insult" to the marrow—whether chemical, ionizing radiation, or viral—may result in a variable degree of injury with a variable degree of hypoplasia (hypoplastic anemia). In some cases, abnormal clones of either leukocytes or red cells could conceivably arise during the process of repair. If the preponderance of bizarre cells were of the white cell type, "leukemia" would be diagnosed; if, on the other hand, the red cell injury were sufficiently marked as to result in hemoglobinuria, then the diagnosis of PNH would necessarily be made. Thus, at least some examples of the apparently different conditions of PNH, aplastic anemia, and "hypoplastic" leukemia might have a common denominator in the form of an "insult" to the marrow. As a correlative statement, what looks like "aplastic anemia" today might be either "acute leukemia" or PNH two years from now.

⁸ Van den Bergh, A. A. H.: Ictère hémolytique avec crises hémoglobininuriques fragilité globulaire. *Rev. Med. (Paris)* 31: 63, 1911.

⁹ Ham, T. H., and Dingle, J. H.: Studies on destruction of red blood cells. II. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria; certain immunological aspects of the hemolytic mechanism with special reference to serum complement. *J. Clin. Invest.* 18: 657, 1939.

¹⁰ Rosse, W. F., and Dacie, J. V.: Immune lysis of normal human and PNH red blood cells. I. The sensitivity of PNH red blood cells to lysis by complement and specific antibody. *J. Clin. Invest.* 45: 736, 1966.

¹¹ Cecchi, E., and Conestabile, E.: Paroxysmal nocturnal hemoglobinuria. Electron-microscopic study of red blood cells. *Lancet* 2: 466, 1957.

¹² Dacie, J. V.: Diagnosis and mechanism of hemolysis in chronic hemolytic anemia with nocturnal hemoglobinuria. *Blood* 4: 1183, 1949.

*With Dr. E. Perez-Santiago and Dr. Norman Maldonado, I have recently observed, at the Centro Medico of the University of Puerto Rico, a fascinating case of pancytopenia-hypoplastic anemia occurring in a young woman with the Werner syndrome (progeria). Subsequently, she developed increasing numbers of plasma cells in the bone marrow, and the previously diffuse hypergammaglobulinemia had begun a "monoclonal" spike. It was evident that she was now developing multiple myeloma.