

Conley C L, Weatherall D J, Richardson S N, Shepard M K & Charache S.  
Hereditary persistence of fetal hemoglobin: a study of 79 affected persons in 15  
Negro families in Baltimore. *Blood* 21:261-81, 1963.  
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This paper describes the authors' extensive experience with a unique hemoglobinopathy. The results of clinical, genetic, biochemical, and physiologic investigations are reported and interpreted. [The SCI® indicates that this paper has been cited in over 155 publications since 1963.]

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In 1959 Emery C. Herman, Jr., then a research fellow in our Hematology Division, discovered that a black woman in the gynecology ward had an electrophoretic pattern of hemoglobin indistinguishable from that of sickle cell anemia, although she was not anemic. Study of the patient and her family established that she was heterozygous for sickle hemoglobin (HbS) and for hereditary persistence of fetal hemoglobin (HPFH), a condition first described by Edington and Lehmann in 1955.<sup>1</sup> The disorder presented a genetic enigma, for the persistent fetal hemoglobin appeared to be inherited as if determined by a gene at the ASC locus, although it was known that the genes for HbS and fetal hemoglobin (HbF) are not alleles. We proposed that HPFH could be accounted for by deletion of a gene at the ASC locus, with compensatory production of HbF.<sup>2</sup> That hypothesis, rejected by many geneticists at the time, was subsequently shown to be correct.

Intense interest centered on the absence of anemia in persons heterozygous for both HbS and HPFH, whose red cell hemolysates

contain about 70 percent HbS and 30 percent HbF. Similar values are encountered in some patients with severe sickle cell anemia. Thomas B. Bradley, Jr., a research fellow, James N. Brawner III, a medical student, and I found that in S-HPFH the HbF is uniformly distributed among the red cells, so that each cell is protected from sickling by the high concentration of HbF. In contrast, HbF is heterogeneously distributed in the red cells in sickle cell anemia, leaving many cells susceptible to sickling at physiologic oxygen tensions.<sup>3</sup>

Many studies of HPFH were conducted by members of our group. Biochemical analyses were performed principally by David J. Weatherall, then a research fellow and now Nuffield professor of clinical medicine in the University of Oxford. Stuart N. Richardson, also a research fellow and subsequently a professor of medicine at the Medical University of South Carolina, was involved with family studies. Analysis of the distribution of HbF among the red cells in HPFH and other disorders was performed by Marguerite K. Shepard, a medical student who is now a professor of obstetrics and gynecology in the University of Indiana School of Medicine. Pathophysiological studies were carried out by Samuel Charache, a research fellow who became a professor of medicine and of laboratory medicine at Johns Hopkins. During the course of these investigations the first person identified as homozygous for HPFH was discovered.<sup>4</sup>

I think that our paper has been cited frequently because we assembled all that was known about a unique hemoglobinopathy of unusual genetic and pathophysiological significance. Interest in HPFH has persisted over the years and has been intensified by the demonstration that sickle cell anemia could be ameliorated if it were possible to increase the concentration of HbF in all of the erythrocytes to the levels that occur in S-HPFH heterozygotes. Variants of HPFH have been described and genetic mechanisms worked out in detail. The subject has been reviewed recently.<sup>5</sup>

1. Edington G M & Lehmann H. Expression of the sickle-cell gene in Africa. *Brit. Med. J.* 2:1328-9, 1955. (Cited 75 times.)
2. Herman E C, Jr. & Conley C L. Hereditary persistence of fetal hemoglobin. A family study. *Amer. J. Med.* 29:9-17, 1960. (Cited 60 times.)
3. Bradley T B, Jr., Brawner J N III & Conley C L. Further observations on an inherited anomaly characterized by persistence of fetal hemoglobin. *Bull. Johns Hopkins Hosp.* 108:242-57, 1961.
4. Wheeler J T & Krevans J R. The homozygous state of persistent fetal hemoglobin and the interaction of persistent fetal hemoglobin with thalassemia. *Bull. Johns Hopkins Hosp.* 109:217-33, 1961. (Cited 75 times.)
5. Weatherall D J & Clegg J B. Hereditary persistence of fetal haemoglobin. *The thalassaemia syndromes.* Oxford: Blackwell Scientific Publications, 1981. p. 450-507.