

This Week's Citation Classic

Zinkham W H & Lenhard R E, Jr. Metabolic abnormalities of erythrocytes from patients with congenital nonspherocytic hemolytic anemia. *J. Pediatrics* 55:319-36, 1959.
[Dept. Pediatrics, Johns Hopkins Sch. Med., Baltimore, MD]

Activity of glucose-6-phosphate dehydrogenase (G-6-PD) was severely reduced in red cells from four patients with a type of congenital hemolytic anemia. Although the defect was sex-linked, as in primaquine-sensitivity, the ethnic background of the patients and the extreme reduction of G-6-PD activity suggested a different genetic mutation. [The SCIP[®] indicates that this paper has been cited over 155 times since 1961.]

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"The early and mid-fifties in medicine heralded an amazingly rapid increase in our understanding of how abnormalities of the gene can cause human disease. Discoveries in the test tube were literally being carried to the bedside (or cribside), and conversely, patient problems were being explored in basic science laboratories. Our 1959 article is a product of these exciting times. Also, it reflects the mutual interest of clinical and basic scientists who contributed significantly to the work.

"Having finished residency and fellowship training in pediatrics and hematology, I entered the academic scene at Johns Hopkins with only a superficial knowledge of biochemistry. Jim Sidbury, working with V.A. Najjar at the Harriet Lane Home, was especially conscious of my biochemical ignorance. At his urging, I monitored courses at the Homewood campus under S.P. Colowick, E. Kaplan, A. Nason, and later C.L.

Markert, and attended weekly research journal seminars, the membership of which included basic scientists. Although never a full-fledged or even a partially knowledgeable biochemist, I now had an opportunity to exchange ideas with and learn methods from fellow faculty who were.

"The clinical problem which intrigued our group was the unique susceptibility of certain black children to the red cell destructive effects of naphthalene. Following up pioneering studies by A.S. Alving's group in Chicago (R.J. Dern, E. Beutler, P.E. Carson, and others) on primaquine-sensitivity we learned that naphthalene-induced hemolysis occurred only in children with deficient red cell G-6-PD activity.^{1,2} The 1959 article represents one of a series of subsequent articles, and there are possibly two reasons for its citation frequency. In the 'Methods Section' is a detailed description of our G-6-PD assay in red cells (not entirely original but incorporating some aspects of previous methods). It was probably the reproducibility of this technique in other laboratories that attracted attention. From our point of view, the significant feature of the paper was the observation that there were going to be several mutant forms of G-6-PD, some of which may shorten red cell survival without the patient being exposed to drugs or chemicals such as naphthalene.

"The physical facilities and budgetary requirements for our research were quite modest. Beginning in a wash room of 75 square feet the activity moved to larger quarters, approximately 200 square feet, equipped with \$50.00 worth of cabinets and tabletops from Sears and Roebuck, Inc. Nearby, however, both at the hospital and on the Homewood campus, were scientists interested in our work. Thus a roadway between basic and clinical research was built and during these and subsequent years was well travelled."

1. **Beutler E, Dern R J, Flanagan C L & Alving A S.** The hemolytic effect of primaquine. VII. Biochemical studies of drug-sensitive erythrocytes. *J. Lab. Clin. Med.* 45:286-95, 1955.
2. **Flanagan C L, Schrier S L, Carson P E & Alving A S.** The hemolytic effect of primaquine. VIII. The effect of drug administration on parameters of primaquine sensitivity. *J. Lab. Clin. Med.* 51:600-8, 1958.