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This Week's Citation Classic

Tanaka K R, Valentine W N & Miwa S. Pyruvate kinase (PK) deficiency hereditary nonspherocytic hemolytic anemia. *Blood* **19**:267-95, 1962.
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The paper describes a specific deficiency of the glycolytic enzyme pyruvate kinase (PK) in the erythrocytes of seven patients with congenital nonspherocytic hemolytic anemia. Family studies indicate that PK deficiency is transmitted as an autosomal recessive trait. [The *SCI*® indicates that this paper has been cited over 265 times since 1962.]

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"I am indebted to William Valentine of UCLA for providing me, as a junior research hematologist, the opportunity in July 1957 of joining his laboratory located in a Quonset hut. In the early fall of 1960, we began to set up assays for each enzymatic step of the glycolytic pathway to study the nonspherocytic hemolytic anemias because (1) of Dacie's earlier report on autohemolysis,[1] (2) G6PD deficiency had been recently described as a cause of hemolytic anemia,[2] and (3) purified enzymes and substrates had become more readily available.

"In February 1961, very shortly after the PK assay had been established, I obtained a sample of blood from a 26-year-old Caucasian veteran who had been admitted to Wadsworth Hospital for investigation of his chronic anemia. Essentially no PK enzyme activity was obtained on the hemolysate of this patient; the leukocytes were found to have normal activity. We quickly found that the erythrocytes of the patient's son and daughter and parents had about half of normal activity consistent with heterozygosity for the defect. Two brothers with chronic hemolytic anemia were recalled for study and were found to be deficient in erythrocyte PK. The data on these three patients were submitted to *Science*, but the manuscript was rejected on the basis of lacking broad interest.

"Valentine wrote to the president of the Association of American Physicians, Cecil J. Watson, about our studies on the three subjects. The paper[3] was accepted for the annual session in Atlantic City on May 2, 1961, less than three months after our initial results. A total of seven patients were soon found to have a specific deficiency in the red cell glycolytic enzyme PK. This formed the basis of the manuscript published in *Blood*. Many other cases of PK deficiency were soon reported from all over the world.

"Meanwhile, I became chief of hematology at Harbor-UCLA Medical Center, and have continued to work in the field of red cell enzymology and metabolism during the past 20 years. However, I collaborated with Valentine for a number of years and we still write reviews together.[4] Miwa, who was a research fellow at the time, returned to Japan shortly thereafter and has become the leading investigator of red cell enzyme deficiency hemolytic anemias in Japan.

"The probable reasons for the frequent citation of our paper are these. Our initial brief paper on PK deficiency was published in *Transactions of the Association of American Physicians*,[3] but this is not as widely circulated as *Blood*. The paper in *Blood* defined the entity of PK deficiency hemolytic anemia, which has proven to be the first described, best studied, and most common of the hemolytic anemias resulting from an enzyme defect in the Embden-Meyerhof pathway. The discovery of PK deficiency excited interest in hereditary hemolytic anemias and led to the rapid subsequent finding of other enzyme deficiency hemolytic anemias, many in Valentine's laboratory.

"The first patient with PK deficiency hemolytic anemia has been living for a number of years in Sanger, California, where I spent the first 15 years of my life. His red cell PK enzyme was characterized recently and named PK 'Sanger.' "[5]

1. **Selwyn J G & Dacie J V.** Autohemolysis and other changes resulting from the incubation in vitro of red cells from patients with congenital hemolytic anemia. *Blood* **9**:414-38, 1954.
2. **Carson P E, Flanagan C L, Ickes C E & Alving A S.** Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science* **124**:484-5, 1956.
3. **Valentine W N, Tanaka K R & Miwa S.** A specific erythrocyte enzyme defect (pyruvate kinase) in three subjects with congenital non-spherocytic hemolytic anemia. *Trans. Assn. Amer. Physicians* **74**:100-10, 1961.
[The *SCI* indicates that this paper has been cited over 125 times since 1961.]
4. **Valentine W N & Tanaka K R.** Pyruvate kinase and other enzyme deficiency hereditary hemolytic anemias. (Stanbury J B, Wyngaarden J B & Fredrickson D S, eds.) *The metabolic basis of inherited disease*. New York: McGraw-Hill, 1978. p. 1410-29.
5. **Shinohara K & Tanaka K R.** Pyruvate kinase deficiency hemolytic anemia. Enzymatic characterization studies in twelve patients. *Hemoglobin* **4**:611-25, 1980.