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This Week's Citation Classic™

Layzer R B, Rowland L P & Ranney H M. Muscle phosphofructokinase deficiency. *Arch. Neurol.* 17:512-23, 1967.
[Dept. Neurol., Coll. Physicians and Surgeons, Columbia Univ.; Neurological Clinical Res. Ctr., Neurological Inst., Columbia-Presbyterian Medical Ctr.; and Heredity Clinic and Dept. Medicine, Albert Einstein Coll. Medicine, Yeshiva Univ., New York, NY]

Clinical and biochemical studies of a patient with muscle phosphofructokinase (PFK) deficiency confirmed the presence of a block in muscle glycolysis at the PFK step. Immunologic studies suggested that the disease was caused by hereditary absence of the muscle-type subunit of PFK, which is normally present in red cells but not in white cells. [The *SCI*® indicates that this paper has been cited in over 160 publications since 1967.]

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"This was my second scientific article, and for the most part it was not very original. It reported a second family with muscle phosphofructokinase (PFK) deficiency, a rare hereditary disorder with symptoms resembling those of McArdle's disease (muscle phosphorylase deficiency). The first such family had been reported not long before in an excellent paper by Tarui *et al.*[1] and many of our studies merely confirmed their results.

"We did make some new observations, however. Tarui *et al.* had shown that red-cell PFK was about half of normal in affected persons; we found that PFK activity was normal in white blood cells. At that date (1966), nothing was known about PFK isoenzymes. We realized that the simplest hypothesis to explain the different degrees of PFK deficiency in muscle, red cells, and white cells was that PFK existed in multiple molecular forms composed of at least two nonidentical subunits, only one of which (the muscle type) was affected by the genetic defect. By this theory, muscle PFK should contain only muscle-type subunits; red-cell PFK should contain both the muscle-type subunit and another type; and white-cell PFK should contain no muscle-type subunits.

"To test this hypothesis, we prepared antiserum to purified human muscle PFK and checked its ability to inhibit the PFK activity of muscle and red-cell extracts. Sure enough, the antiserum inhibited the PFK activity of normal muscle and red cells but did not inhibit the patient's red-cell PFK. We also found no immunologically cross-reactive material in the patient's muscle extracts. These results came through just in time to be included as 'unpublished data' in the last paragraph of the article. We were nervous about not having repeated the experiment, but we wanted to scoop Tarui's group, who, we suspected, might be working along similar lines. Fortunately, the results turned out to be repeatable and were later confirmed by the Japanese workers.[2]

"This research helped me to obtain a National Institutes of Health Career Development Award in 1968. I worked on PFK isoenzymes for several years after that and succeeded in separating the two subunits of red-cell PFK, though others eventually did a better job of elucidating the subunit composition of PFK isoenzymes.[3] Meanwhile, many new metabolic myopathies were discovered, and medical interest in PFK deficiency dwindled, while the rise of nucleic acid chemistry made isoenzyme biochemistry seem quaintly out of date. Why, then, has this paper been cited so often? I really have no idea, unless it is because the paper was very well written."

1. **Tarui S, Okuno G, Ikura Y, Tanaka T, Suda M & Nishikawa M.** Phosphofructokinase deficiency in skeletal muscle. A new type of glycogenosis. *Biochem. Biophys. Res. Commun.* 19:517-23, 1965. [See also: **Tarui S.** Citation Classic. *Current Contents/Clinical Practice* 12(47):20, 19 November 1984.]
2. **Tarui S, Kono N, Nasu T & Nishikawa M.** Enzymatic basis for the coexistence of myopathy and hemolytic disease in inherited muscle phosphofructokinase deficiency. *Biochem. Biophys. Res. Commun.* 34:77-83, 1969. (Cited 75 times.)
3. **Vora S, Corash L, Engel W K, Durham S, Seaman C & Piomelli S.** The molecular mechanism of the inherited phosphofructokinase deficiency associated with hemolysis and myopathy. *Blood* 55:629-35, 1980.

