

**Fox I H & Kelley W N. Phosphoribosylpyrophosphate in man: biochemical and clinical significance. *Ann. Intern. Med.* 74:424-33, 1971.**

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The intracellular concentration of phosphoribosylpyrophosphate (PRPP), a high energy, 1,5-substituted ribose sugar, has been demonstrated to have a critical role in the regulation of purine metabolism in man. Increased intracellular levels of PRPP may be important in the pathogenesis of excessive uric acid production in patients with primary gout and the Lesch-Nyhan syndrome. In addition, intracellular PRPP levels are altered by several compounds and certain trophic hormones. [The *SC<sup>i</sup>*® indicates that this paper has been cited in over 150 publications since 1971.]

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"In July 1969, my assignment at the start of my postdoctoral fellowship work was to develop an assay for phosphoribosylpyrophosphate (PRPP). William N. Kelley, who was my supervisor, believed that this compound might be important in human purine metabolism and that it would be worthwhile studying. Despite my lack of previous training in the methods of biochemical research, I enthusiastically undertook this project. In my initial attempts to develop an assay for PRPP, I followed the methods of Henderson and Khoo.<sup>1</sup> After a few months of intensive effort, the assay was established.

"In one series of studies, we attempted to understand the role of PRPP in the regulation of purine biosynthesis *de novo*. In these experiments in cultured fibroblasts, we made correlations between the rate of purine biosynthesis *de novo* and changes in the intracellular levels of PRPP. The other line of research involved studies in humans to test the hypothesis that alterations in PRPP concentrations might be important in the pathogenesis of hyperuricemia and gout. Previous work had suggested that this was possible.<sup>2-4</sup> With these

studies, we examined a large number of patients with gout. The results of these studies indicated to us that PRPP was indeed a rate-limiting substrate in *de novo* purine synthesis and that it was involved in the pathogenesis of hyperuricemia, at least in hypoxanthine-guanine phosphoribosyltransferase deficiency. We also initiated studies to observe whether the administration of various drugs or other compounds might modulate PRPP levels *in vivo*. One of our first studies with allopurinol was published in the *New England Journal of Medicine* in November 1970<sup>5</sup> and this study and others demonstrated, indeed, that specific purine and pyrimidine compounds could modulate PRPP levels *in vivo*.

"After one year's work in this area, we realized that PRPP was a critical compound in the regulation of purine synthesis in humans, was altered in some human disease states, and could be modulated by administration of drugs. To crystallize these concepts, in 1970, we began writing a review article for a medical journal which would describe the biochemistry of the compound and its alterations in different clinical states. Although it was a review article, we had performed a number of studies of PRPP metabolism in humans which had not been published. These included the evaluation of patients with gout and the administration of some purine and pyrimidine compounds which did show alterations in PRPP levels. In the course of writing this review, we added this new data to the article.

"I believe that this article has been frequently quoted because it provided clinicians and scientists, for the first time, with a description of PRPP and its relevance to human disease. The appeal of this article was reflected in the acceptance of it, virtually unchanged, within five days of our submission of the manuscript to the *Annals of Internal Medicine*. It is interesting that one or two years after the publication of this article, the discovery of a PRPP synthetase mutation with enzyme overactivity as a cause of gout was reported by Odette Spierling<sup>6</sup> in Israel and Michael Becker<sup>7</sup> in the US. The majority of the information in the article remains as correct today as it was in 1971."

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7. Becker M A, Meyer L I, Wood A W & Seegmiller J E. Purine overproduction in man associated with increased phosphoribosylpyrophosphate synthetase activity. *Science* 179:1123-6, 1973. (Cited 80 times.)