

This Week's Citation Classic

Lesch M & Nyhan W L. A familial disorder of uric acid metabolism and central nervous system function. *Amer. J. Med.* 36:561-70, 1964. [Dept. Pediat., Johns Hopkins Univ. Sch. Med., Baltimore, MD and Univ. Miami Sch. Med., Miami, FL]

A syndrome consisting of hyperuricemia, choreoathetosis, self-destructive behavior, and mental retardation is described. Marked abnormalities, quantitatively greater than any previously reported, of urate synthetic rates are described. [The **SCF**[®] indicates that this paper has been cited over 460 times since 1964.]

Michael Lesch
Department of Medicine
Northwestern University
Medical School
Northwestern Memorial Hospital
Chicago, IL 60611

July 23, 1981

"As a freshman medical student I applied for a student research position too late to work in the biochemistry department. The dean suggested I speak to a young assistant professor of pediatrics whose research interests were in biochemistry. I made the appointment with Bill Nyhan and on arrival, found that he barely had any area that could be called an office. Moreover, my interview began by talking to a pair of feet, the rest of Nyhan's body being submerged in the 'innards' of an early model Beckman amino acid analyzer.

"When he crawled out of the machine, I met a man to whom I took an instant liking and, as I recall, I was immediately hired. That summer I worked for Nyhan trying to separate various nucleoproteins isolated from the nuclei of an experimental tumor. The summer passed rapidly; I accomplished little other than to ruin some glassware but Nyhan and I became close friends. He entered me into a Hopkins program that allowed me to spend an entire year between my sophomore and junior years in his laboratory but still graduate with my class. The following summer I reported to his lab ready to isolate those 'damn' proteins once and for all.

"Work on this project progressed slowly. Part of our laboratory effort was related to Nyhan's interests in disorders of amino acid metabolism and, as such, the laboratory

provided a 'service' function to the pediatrics department and frequently performed routine blood and urine amino acid analyses. One such specimen was sent to the laboratory labeled 'cystinuria' but we could find no cystine in the specimen. Nyhan, who trusted his Beckman more than he did the clinical judgment of a pediatrics house officer, insisted on seeing the patient. In a short time he recognized the crystals in the urine to be urate. The rarity of gout in the pediatric age group, coupled with the child's obvious bizarre neurologic deficit, suggested something of significance to Nyhan. This suspicion was heightened when the mother said, 'You think this kid is something, you should see the other one I have at home.'

"My work on nucleoproteins was immediately halted and Nyhan asked me to read up on methods of studying urate metabolism. At that time, such studies included determination of pool size and turnover time, and injection of labeled glycine to determine incorporation rates of glycine into urate. The two brothers were admitted, appropriate control subjects were identified, and I became a urate chemist for six months. The work progressed smoothly as we were utilizing previously published methods.¹² It took me almost two months to write and rewrite the manuscript, which was accepted without change.

"In retrospect, my contribution to the discovery of the Lesch-Nyhan syndrome was marginal. I simply was fortunate to be in the right place at the right time and to be working for a senior investigator who was gracious enough to allow a medical student to be first author on a manuscript.

"The publication laid the groundwork for the subsequent discovery³ in J. Seegmiller's laboratory of the absence of hypoxanthine-guanine phosphoribosyl transferase in these children which in turn opened new concepts as to the regulation of purine metabolism. For this reason and the obvious features of a 'new' genetic disease, this paper has been often quoted. See *The Metabolic Basis of Inherited Disease* for more recent work in the field."⁴

1. **Benedict J D, Forsham P H & Stetten D, Jr.** The metabolism of uric acid in the normal and gouty human studied with the aid of isotopic uric acid. *J. Biol. Chem.* 181:183-93, 1949.
2. **Benedict J D, Roche M, Yü T F, Bien E J, Gutman A B & Stetten D, Jr.** Incorporation of glycine nitrogen into uric acid in normal and gouty man. *Metabolism* 1:3-12, 1952.
3. **Seegmiller J R, Rosenbloom F M & Kelley W N.** An enzyme defect associated with a sex linked human neurological disorder and excessive purine synthesis. *Science* 155:1682-4, 1967.
4. **Kelley W N & Wyngaarden J B.** The Lesch-Nyhan syndrome. (Stanbury J B, Wyngaarden J B & Fredrickson D S, eds.) *The metabolic basis of inherited disease*. New York: McGraw Hill. 1978. p. 1011-36.