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HUMANITIES IN MEDICINE

On being a Doctor... ''and describe a disease not previously reported, Lesch–Nyhan disease''

Ser médico... «y describir una enfermedad no documentada anteriormente, síndrome de Lesch-Nyhan»

It has been almost 50 years since Michael Lesch and I wrote our initial publication on what has now become an eponymic disease.[1] The disease has become a favorite of teachers of Biochemistry to freshman medical students for a variety of reasons. Among them are the facts that a well-defined molecular deficiency in an enzyme of purine metabolism is associated with a recognizable pattern of abnormal behavior. Recognizable patterns of human malformations led David Smith to write the book with this name[2] and to launch the specialty of Dysmorphology. In similar fashion I coined the term ''behavioral phenotypes'' in a presidential address to the *Society for Pediatric Research* U.S. in 1972.[3] As is true for syndromes of dysmorphism, recognition of a pattern of behavior can lead the astute clinician to the diagnosis, and in the case of Lesch–Nyhan disease, to ordering the definitive confirmatory diagnostic testing. Lesch–Nyhan disease is also of special biochemical significance as the first cause of hyperuricemia to be defined with an enzymatic etiology. It is the only common cause of overproduction of hyperuricemia and gout, a disease that has been known since Hippocrates.

I entered Harvard as an undergraduate during World War II, and before I finished my sophomore year I was drafted into the U.S. Navy. It was my good luck that they needed doctors; they sent me right back to Harvard to complete my premedical studies, and at the end of my junior year, which was completed in two calendar years, they sent me to medical school in New York. Columbia University's College of Physicians and Surgeons, one of the oldest in the country, opened its doors to colonial American students in 1767.

I completed a residency in Pediatrics at Yale and undertook to learn Biochemistry under Harris Busch in the Department of Biochemistry, exploring the possibility of metabolic differences between transplanted tumors and nontumor tissues of the rat. Before the first summer was over, Harris, the lab and I moved to the University of Illinois, where in due time I received the Ph.D. I then moved to Johns Hopkins as Assistant Professor of Pediatrics, obtained a grant from the National Institutes of Health, and continued working on amino acids in cancer.

My focus changed with the admission of the first patient to be described with what we now know as propionic acidemia. We did not know that then, but knew it had to do with amino acids. Moore and Stein[4] had just published their method of separation of amino acids on cation exchange columns. I set up those very long columns according to their publication and began analyzing amino acids. From then on, our laboratory has been devoted to the study of inborn errors of metabolism, but I kept my hand in cancer research. Mike Lesch was a medical student working on nuclear proteins in cancer in my laboratory when we discovered what is now known as the Lesch–Nyhan disease.

The first of our patients was admitted to the Harriett Lane Home of the Johns Hopkins Hospital. The laboratory was on the top floor of the hospital, and the open wards for patients were on the floors beneath. It was an ideal setting in which to pursue clinical research.

The first patient was admitted at 4 years of age because of hematuria. A similar episode 5 months earlier had been

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diagnosed by a physician as hemorrhagic cystitis. In those days interns examined urine samples under the microscope in the Emergency Room. The intern was impressed by the fact that in addition to the erythrocytes, the urine was full of crystals. He and his residents pored over the clinical pathology book in which crystals were identified by their microscopic appearance. They looked just like the pictures of cystine crystals, and the patient was diagnosed as having cystinuria and admitted.

That led them on the next morning to my laboratory, where I was asked to confirm the diagnosis by amino acid analysis. Patients with cystinuria excrete not only cystine, but also the dibasic amino acids lysine, ornithine and arginine. The boy's urine had normal amounts of all these components. It soon became apparent that the crystals were composed of uric acid, and that he had hyperuricemia as well as uricosuria. It appeared that we were dealing with an inborn error of purine metabolism. This was exciting. No previous reports of inborn errors of purine metabolism, even in gout, had ever been defined on a molecular basis, and prior to our experience, gout was known as a disease exclusively of adult males and postmenopausal females.

It became even more exciting when Mike Lesch and I went downstairs to see the patient. He had all the clinical features of which we now know as the syndrome. He had been diagnosed early with cerebral palsy, and he had a movement disorder that had been referred to as choreoathetosis. Many patients with the disease continue to be categorized in this fashion. More striking than the neurologic picture was the loss of tissue about the lip which had resulted from his biting. He had thick bandages on both hands resembling boxing gloves, and under them we found mutilated fingers. We soon discovered that he had a brother in an institution in Baltimore, arranged his admission, and it was clear that he had all the same features as the brother, including the evidence of self-injurious behavior. It was obvious we had a syndrome. An implication was that we could find chemical clues to abnormal behavior. On this issue we are still looking, but we have learned quite a lot about the biochemistry of the disease.

It was clear that this was a more important project for Mike Lesch, and he began working on it full time. Our first paper in the American Journal of Medicine[5] set out the biochemical features of the disease. The enormous quantities of uric acid being made were greater than anyone had encountered in patients with gout. Study of the *de novo* pathway of purine synthesis *via* the incorporation of labeled glycine into urinary uric acid *in vivo* indicated rates of overproduction appreciably greater than any previously reported.

The first clues to the site of the molecular defect came from studies on the effects of azathioprine.[6] Azathioprine, the immunosuppressant, lowers concentrations of uric acid, but it does not in Lesch–Nyhan disease. Azathioprine is converted to 6-mercaptopurine which must be converted to its ribose monophosphate before it becomes active. The enzyme that catalyzes this conversion is hypoxanthine guanine phosphoribosyltransferase (HPRT) (Fig. 1). Seegmiller and colleagues in 1967[7] reported that the activity of this enzyme was defective in this disease. In erythrocytes, the activity of the enzyme approximates zero. This assay is the gold standard for diagnosis; we carry it out on spots of dried blood on filter paper.

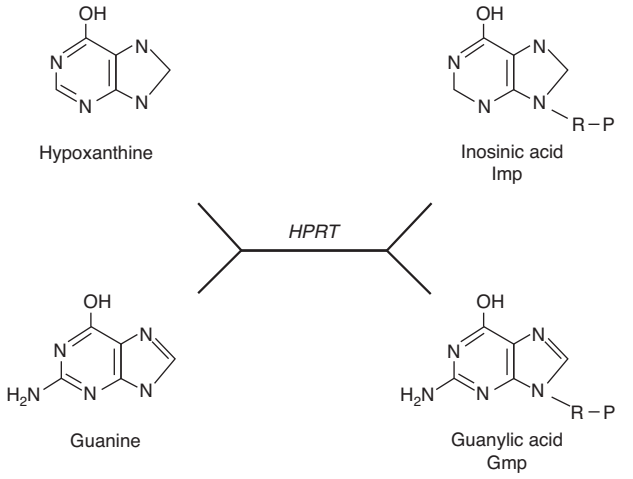

Figure 1 The hypoxanthine guanine phosphoribosyltransferase (HPRT) reaction. This enzyme is the molecular defect in the Lesch–Nyhan disease.

The discovery of the disease had major effects on my life and those of others. I soon gave up cancer research and devoted my efforts to the field of biochemical genetics, when the field was just beginning to explode. I have been fortunate over the years to have had a continuous progression of students, fellows, and colleagues with whom we have been able to move the field forward. The advent of recombinant DNA technology and the ability to define mutations have enormously expanded our approaches to this disease and other disorders of metabolism.

It was in studies of cell cultures established from the original family that Barbara Migeon, an early colleague at Johns Hopkins, was able to provide the first biochemical proof of the Lyon Hypothesis in man. She cloned single cells from the mother and sister of the two boys and established the fact that there were two populations of cells, one HPRT positive and one HPRT negative.[8] More recently, Laura DeGregorio[9] found the mutation, a complicated insertion in the original family (Table 1).

Mike Lesch went on to become a Professor of Medicine and a cardiologist. He was recently the Chairman of Medicine at St. Luke's Hospital in New York. His untimely death in 2008 occurred on a fly fishing trip to Patagonia.

Richard Preston writes novels with biologic themes. His book, *The Cobra Event*, has a central theme of HPRT deficiency and the Lesch–Nyhan disease. More recently he has written an article in the New Yorker entitled, *An Error in the Code*, in the Annals of Medicine series.[10] This provides the best available insight into the disease in adults, an area that is becoming of great interest as our patients are now becoming adults.

Table 1 Mutation in original proband.

Insertion-CCTTATGC at nt 576 results in frame shift skipping Exon 8

Over the years my colleagues and I have been able to establish the molecular enzymatic defect in a number of previously elusive diseases. With Larry Sweetman and Betty Burri we found that the disease known as 3-methylcrotonylglycinuria, a disorder of leucine metabolism, was actually a multiple carboxylase deficiency, and that the fundamental defect was in holocarboxylase synthetase. With Michael Gibson we found that 4-hydroxybutyric aciduria, another disorder in which there are behavioral features, was caused by deficiency of succinic semialdehyde dehydrogenase. With Kazuhiko Narisawa we found that the defective enzyme was 3-methylglutaconylCoA hydratase in a subset of patients with 3-methylglutaconic aciduria. With Georg Hoffmann we found the defect in mevalonic aciduria in mevalonic acid kinase, the first defect to be discovered in the pathway of cholesterol biosynthesis.

I remain active as Professor of Pediatrics at UCSD. I continue to see patients and to supervise the Biochemical Genetics Laboratory. The 3rd edition of our *Atlas of Inherited Metabolic Disease* will be published in early 2012 by Hodder Arnold, London.

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