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Review

Biotinidase deficiency and our champagne legacy☆

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ABSTRACT

Biotinidase is the enzyme that is necessary for the recycling of the vitamin, biotin. Biotinidase deficiency is an autosomal recessively inherited metabolic disorder. If untreated, individuals with biotinidase deficiency usually develop neurological and cutaneous symptoms that can result in coma or death. Symptomatic individuals can be markedly improved by treating them with pharmacological doses of biotin; however, some clinical features may be irreversible. Fortunately, essentially all symptoms can be prevented if treatment is initiated at birth or before the symptoms develop. Because of this, the disorder is currently screened for in newborns in all states in the United States and in many countries around the world. This is the story of one laboratory's work in bringing basic science research from the discovery of the disorder to its translation into clinical medicine and its impact on the individuals with the disorder and their families.

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1. Preparation for my career

I am extremely fortunate to have been able to spend almost my entire research career investigating a single medical disorder. When I decided to pursue both M. D. and Ph. D. degrees, I hoped to work in the laboratory researching an important area of basic science, and that my work would ultimately be translatable to clinical medicine. Moreover, I thought that having both doctoral degrees would afford me credibility to more effectively collaborate and interact with clinicians and basic scientists. My expectations were answered with biotinidase deficiency. Biotinidase deficiency would be that disorder; a disorder in which symptomatic individuals would improve with appropriate treatment and asymptomatic individuals, if treated early, could be prevented from developing symptoms.

In grade school, I had no plans or desires of being a physician or a scientist. In fact, I found science dull and boring. My interest in

Abbreviations: ATG, peptide initiation codon of a messenger RNA transcript translated by a ribosome that encodes a methionine in eukaryotes; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate-activated protein kinase; BTD, designation of the gene that encodes for biotinidase; CD4, cluster of differentiation 4 is a glycoprotein found on the surface of immune cells, such as T-helper cells, monocytes, macrophages, and dendritic cells.

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science did not occur until I encountered my sixth grade science teacher, Mr. Richard Jamgochian, soon to become Dr. Jamgochian and ultimately the chair of the Department of Graduate Education at the University of California, Santa Barbara. He introduced me to the dynamic nature of science with opportunities to alter experimental conditions, test hypotheses and assess their outcomes. He asked me which area of science I might have some interest in studying. I said cancer. Because I obviously could not study animal cancers in grade school, he introduced me to plant galls, cancers in plants! This one teacher had the most important influence in causing me to pursue a career in science and medicine.

As an undergraduate student at the University of Illinois in Urbana, I was admitted into the Honors Biology curriculum of the James Scholar-Independent Study Program. This was a unique program consisting of 12 students, four freshman, including me, four sophomores and four juniors, taught by a faculty of five professors. It was in this program that I learned how to conduct research and to question scientific dogma and your own results. My college research experience started in the virology laboratory of Dr. Manfred E. Reichmann, one of the five professors, and resulted in my first two research publications. These experiences led me to pursue both a Ph. D. degree and an M. D. degree at the University of Illinois Medical Center in Chicago, Illinois.

I initially matriculated in the Department of Microbiology and Immunology for my graduate studies, but I soon became disillusioned with this area of research because the magnitude of the changes observed in the cellular immunity experiments were often less than the background differences. Although this definitely bothered me, it didn't seem to bother the professors or the other students in the department. I realized that I needed to work in a field where the experimental changes were more "definitive" and the interpretation of the results more straightforward. I, therefore, switched my major area of study to biological chemistry. My thesis project was in physical biochemistry investigating the effects of the water of hydration on the conformational changes of DNA under the direction of Dr. Mary Sue Hanlon. Near the completion of my work Sue assumed that I would want to continue my post-doctoral work in this same area; however, my major interests were directed towards translational research in pediatrics. Therefore, after completion of my degrees, I became a pediatric resident at Children's Memorial Hospital of Northwestern University in Chicago. During this time, I became interested in using my background in pediatrics and biochemistry to pursue a fellowship in inherited metabolic diseases, which at that time meant enrolling in a fellowship in Human Genetics. Although my primary interest was in inborn errors of metabolism, I realized I would have to learn all aspects of clinical genetics, including prenatal diagnosis and dysmorphology. I matriculated in the Department of Human Genetics at Yale University School of Medicine under the leadership of Dr. Leon E. Rosenberg. I initially wanted to work on the area of hyperammonemia, but my colleague, Stephanos Mantagos, had already written a review of this area prior to coming to Yale, so Leon wanted me to choose another area of research in his laboratory. I chose to work on propionic acidemia under his direction and that of Dr. Yuen "Ted" Hsia. At the time there was no set scientific agenda, so I was free to initiate investigations on my own within an environment of excellent scientists who were working on ornithine transcarbamylase deficiency, methylmalonic academia and homocystinuria. As the sole person working on propionic acidemia, I was also afforded the opportunity to address multiple research questions at the same time. Because propionic acidemia was due to a deficiency in propionyl-CoA carboxylase, an enzyme that uses biotin as its coenzyme, I also became interested in biotin metabolism.

My prior experiences as an undergraduate and graduate student prepared me well for my subsequent career. I learned that when you work on rare disorders, it is often difficult to get other clinicians and investigators as excited about collaboration as they would if the projects were more topical and perhaps more relevant. On the other hand, when investigators pursue research on a rare disorder, they have more time to make mistakes and learn new technologies that can be incorporated into their research without the competition from other investigators or laboratories. Our laboratory at Yale was well known for working on disorders, such as propionic acidemia, so samples from children with the disorder were constantly sent to us for confirming the diagnosis and investigation. Moreover, it afforded me an opportunity to meet colleagues who looked to our laboratory and ultimately to me as an "expert" about the disorder. I successfully published multiple papers dealing with propionic acidemia during my fellowship.

When I completed my fellowship, Leon allowed me to take my projects dealing with propionic academia with me. This provided me with the necessary preliminary data to write my first major grant proposals when I moved to my first academic position as Assistant Professor of Human Genetics and Pediatrics at the Medical College of Virginia at Virginia Commonwealth University in Richmond. Dr. Walter Nance had been recruited to build a new Department of Human Genetics several years before I arrived. I was recruited to be a clinical and biochemical geneticist in the Departments of Human Genetics and Pediatrics. Walter expected me to have my first grant submitted before I arrived in Richmond in the summer of 1978. That didn't happen! In addition, I was immediately required to design and teach a full semester course in biochemical genetics for graduate students and subsequently for genetic counseling students. I was given sufficient protected time to initially establish and develop my research program. To meet Walter's requirements of writing grants and getting funded, I wrote five grants in less than three months. Amazingly, in less than a year, four of them were funded; two NIH RO1 grants, a Basil O'Connor-March of Dimes grant and an NIH Career Development Award, which paid my entire salary for five years. The one grant that was not funded was from the American Egg Board. Although the grant was approved, I had requested more money than the organization apparently had to support all its research, so it wasn't funded.

2. The primary enzyme defect

Although my work on propionic acidemia with the help of graduate students, Cathy McKeon, Jerry Feldman and Debra Weiner, went well, after Dr. Frantisek Kalousek in Leon's laboratory purified human propionyl-CoA carboxylase, I began to move away from the competition with the Yale laboratory. I redirected my research to aspects of biotin metabolism and its relationship to metabolic disease with graduate students, Sharon Suchy and Paula Awrich. My laboratory had been working on the biotin-responsive multiple carboxylase deficiencies (Wolf et al., 1981; Feldman et al., 1981; Wolf and Feldman, 1982) and confirming the diagnosis by measuring the various mitochondrial carboxylase activities in lymphocytes and fibroblasts from children suspected of having isolated and multiple carboxylase deficiencies. At that time, there were two forms of multiple carboxylase deficiency. The first form was known as the early-onset or infantile multiple carboxylase deficiency. Individuals with this disorder usually presented with symptoms during the first month of life. They exhibited urinary organic acids consistent with multiple carboxylase deficiency and the diagnosis was confirmed by finding deficiencies of the three mitochondrial carboxylases in lymphocytes prior to treatment with biotin or in fibroblasts incubated in medium with a low concentration of biotin. The carboxylase activities increase markedly when the medium was supplemented with high concentrations of biotin. Subsequently, it was shown that these individuals have a deficiency of biotin holocarboxylase synthetase (Burri et al., 1981; Saunders et al., 1982), the enzyme which covalently binds biotin to the various apocarboxylases forming active holocarboxylases. The other form was referred to as the late-onset or juvenile multiple carboxylase deficiency. Symptomatic individuals with this disorder usually also exhibited urinary organic acids consistent with multiple carboxylase deficiency. However, even prior to biotin treatment, the mitochondrial carboxylase activities are normal when incubated in basic culture medium or in medium with a low concentration of biotin.