September 1999 Issue | Mary Megson, MD, FAAP

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Welcome to *Functional Medicine Update*™ for September 1999. I begin this month by paying honor to Dr. Charles Edwin Butterworth, Jr., who has made incredible contributions to the emergence of functional medicine. Dr. Butterworth fought a vigilant battle regarding folic acid and cervical dysplasia. His career has spanned a range of activity, only one aspect of which was the folic acid/cervical dysplasia debate. Dr. Butterworth passed away last year at the age of 75.

One of Dr. Butterworth's major contributions was a landmark paper titled "The Skeleton in the Hospital Closet," which appeared in *Nutrition Today* in 1974.[1] This paper revealed the high level of malnutrition among hospitalized patients and led to many positive changes in the management of nutritional interventions during the vulnerable period of hospitalization. Most of us would say there is still a lot of room for improvement and continued progress in this area, but at least it was brought to our attention in the medical nutritional community.

Dr. Butterworth conducted a number of clinical and basic research studies in the interface between medicine and nutrition. He was co-editor of a book titled ***Micronutrients in Health and In Disease Prevention***, which was ahead of its time. At the time it was published, the importance of micronutrients in preventive medicine was a concept that was not widely believed. He wrote, discussed, and conducted research across a range of areas, focusing principally on mucosal cell integrity and its relationship to nutrition. His view was that the mucosal cells that line the surfaces of various organ-specific systems, such as the mucosa in the mouth or the intestinal tract, are early warning markers for undernutritional status. By evaluating mucosal integrity, either by direct visual observation of the tongue, gingiva, and soft tissue in the mouth, or by biopsy or scoping, he believed we could better understand systemic nutritional imbalances. His concept of dysplastic conditions related to nutritional imbalances focused on epithelial tissue integrity, and it is a hallmark of the emerging view of the importance of nutritional assessment.

Dr. Butterworth focused on the folate nutrients, folic acid/B12/B6. His work converges with that of Dr. Kilmer McCully, who is working from a different perspective. Dr. McCully is a pathologist focusing on atherosclerotic disease, again with the folate/B12/B6 connection. We have heard much talk of his work with hyperhomocysteinemia over the last several years. Dr. Butterworth was looking at epithelial tissue dysregulation, hypertrophy, and the relationships to dysplasia that occur from not from frank deficiency but from insufficiencies of these same nutrients, the folate pool nutrients, folic acid/B12/B6.

This convergence has resulted in our recognizing that a common mechanism may account for a range of health effects, due to the insufficiency of these nutrients. We have often discussed methyl transfer reactions. The methylation reactions involve the transfer of a methyl group, a reaction essential for

nucleic acid biosynthesis involved in cell replication, differentiation, and development. Without an appropriate level of folate and vitamins B12/B6, the folate cycle is interrupted. That interruption can have an adverse impact on methyl transfer reactions, changing the availability of the nucleotide pool for nucleic acid synthesis and altering the morphology and function of cells involved with active mitotic turnover. Those cells, in part, are the blood cells, the cells of the immune system, and those of the mucosa. The importance of this cycle may best be appreciated when one considers that antifolate therapy is a mainstay of cancer chemotherapy.

Both Dr. Butterworth and Dr. McCully, unbeknownst to one another, probably in the early phases of their work, were working on the same thing, approaching it from different directions. Dr. Butterworth recognized that cervical dysplasia appeared to be related to statistically lower levels of folate in the plasma of women. He started talking about the role of folate in proper cervical mucosal integrity. This is beyond the story of vitamin A, zinc, or other nutrients, the importance of which has been suggested.

Late in his career Dr. Butterworth strongly urged improved folate nutrition and even folate intervention in individuals with dysplasia. He was starting to talk about folate levels from 800µ g to 1000 µ g or higher. If we look at Dr. Butterworth's background as a medical doctor, who later, as a professor emeritus of nutritional science at the University of Alabama at Birmingham, focused on nutrition, we would not have expected him to make these observations. Nor would we expect Dr. McCully to make the observation of homocysteine and heart disease, and then the connect it to the B vitamins. Some people have unique the genius to make observations and connect the dots in a way that allows us to jump forward in our knowledge. We owe Dr. Butterworth a recognition and honor for his contribution related to mucosal surface integrity, its interrelationship to nutritional status, and how that interrelates to the folate cycle nutrients – folic acid/B12/B6.

Another report of historical consequence is a discussion of Wernicke's encephalopathy, which appeared recently in the ***Lancet***.[2] The Wernicke Korsakoff syndrome is often associated with the excess consumption of alcohol. This neurological condition, traditionally considered irreversible, leads to the dementia of alcoholism. In the early 1980s, as part of his research on Wernicke's encephalopathy, Dr. Pierre Dreyfus, a neurologist at the University of California at Davis, did some studies on moderate drinkers of alcohol. He had come to the conclusion that some individuals with unique biochemistries ran a risk of developing Wernicke's encephalopathy with even moderate alcohol consumption, or what we might call social drinking. The increased risk was a consequence of insufficiencies of vitamin B1 in these individuals.[3] He could actually determine sensitivity on the basis of the erythrocyte transketolase test.

The erythrocyte transketolase test is a biochemical *in vitro* analysis of *in situ* need for B vitamins. Blood is taken, and red blood cells are spun down and resuspended. A substrate is added to measure the activity of the enzyme involved in a form of carbohydrate metabolism called transketolase, which is part of the hexose monophosphate shunt pathway.

INTERVIEW TRANSCRIPT

Clinician of the Month:
Mary Megson, MD, FAAP

JB: This month's Clinician of the Month is Mary Norfleet Megson, MD, a pediatrician who earned her medical degree at the University of Virginia and did her residency and internship at Boston Floating Hospital at Tufts in Boston. For the past nine years she has been Director of Developmental Pediatrics at Children's Hospital in Richmond, Virginia. Recently, however, she began a private developmental pediatric practice. I met Dr. Megson at a recent meeting of the American College for the Advancement of Medicine. Although our conversation was brief, I was fascinated by the work she is doing with autism and the model she is developing, which may apply to other childhood brain-related dysfunction.

Dr. Megson, how did you enter the field of autism and brain chemistry?

MM: I trained in Developmental Pediatrics for three years after residency and worked only with children with developmental disabilities, such as learning disabilities. When I saw a t.v. show about secretin, I thought most people would be thinking about secretin and how it affects the brain as a neurotransmitter—like we found in substance P. I went in a different direction. I asked myself what secretin would do in the gastrointestinal tract. It stimulates CCK (cholecystokinin), which stimulates bile production. If patients are not making any bile or are in liver failure, it's very important to supplement with the fat-soluble vitamins.

I began to ask questions related to deficiency of fat-soluble vitamins. My practice deals largely with autism, or communication disorders. I found that in 54 of 60 families I've studied, or 90 percent, night blindness was present in one parent. Four more had retinitis pigmentosa in the mother. I heard this again and again. Then, within one week, I had no history of night blindness in three families in a row. In all three cases, however, one parent had recently been treated for a pituitary adenoma.

JB: Your experience relates to the interview we had with Dr. Jeffrey Kopelson, who described his experience with the use of secretin in autistic children. Also, Dr. Michael Lyon spoke about ADHD and his observations with brain chemistry in children. Finally, Dr. Sidney Baker talked about children's brain chemistry and behavior. We seem to be taking the next step with you. Tell us how a signaling molecule like retinol or a retinoid like vitamin A could be related to what is observed with these brain chemistry problems in autism.

MM: Several years ago, Margaret Bauman at Massachusetts General did research looking at cellular differentiation in the hippocampus. She had autopsy studies from children at 11 or 12 months of age, and the cells were small. There were problems of connections. But they were not so differentiated. Then she looked at a population of children who had abnormal language development, and the cells appeared the same at age three. In children with normal language development, there was a dropout of connections and more branching of synapses.

I started to think about vitamin A and cell growth and differentiation—this is all ectodermal tissue. I started to get more thorough family histories that reflected again and again the same sorts of medical problems—hyperthyroidism, night blindness, rheumatoid arthritis, and even gold nephropathy. Most of these diseases are associated with major histocompatibility complex tissue type HLA-DR3. Direct repeat sequences are known to have high affinity for retinoid receptors.

B: In the abstract of a paper you recently submitted for publication, you report in 36 families a parent of

the autistic child, usually the mother, had history of night blindness and difficulty driving in dim light at dusk, in the rain, at night, or in fog. You state this clearly indicates a potential for vitamin A insufficiency. However, if you do diet-recall studies on these individuals, I presume you would find they were "adequate in vitamin A from their diet." I presume you are describing something else that is genetically related to either the absorption or the utilization of vitamin A.

MM: Yes, you're exactly right. I looked at vitamin A metabolism to try to figure out how these children were absorbing it, because they did not consistently present with a malabsorption picture—fatty stools, etc. And the children appeared to be growing normally. So I asked myself how these well-nourished children offered a variety of foods could have a vitamin A deficiency emerging before 30 months of age.

The enzyme that helps split vitamin A palmitate is in the microvilli of the gut. What I found in my research was that if you have gut mucosal damage, and if the child has a single adenoviral or rhinoviral infection before 15 months of age, the mucosal cells are sloughed off so that enzyme might not be available for use. Vitamin A palmitate has to be in the presence of bile, and the right pH for absorption. Gut mucosal integrity is damaged. At 15 months they get a MMR vaccine.

The measles antigen cross-reacts with intermediate filaments that are important in gap junctions and tight junctions. Mucosal cell integrity is also important for absorption of CoA, which is the critical enzyme when choline is converted to acetylcholine. The precursor for this reaction is s-adenosyl methionine (SAMe), now touted as the "cure all" nutrient. If the CoA pathway is blocked, choline is diverted to production of homocysteine. Are we effectively blocking G-alpha inhibitor of G stimulatory alpha pathways, increasing cAMP cells, causing lipolysis, and blocking production of acetylcholine? Many of these patients have elevated cholesterol and VLDL/LDL. These are 2-year-old children eating three fruits and two vegetables, and chicken nuggets, and they have serum cholesterols over 200 mg/dl.

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