A tale of two brothers

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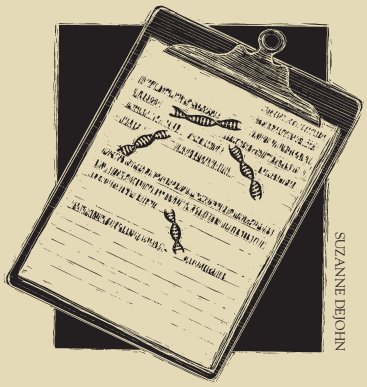

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Recently, I had the opportunity to visit two patients—siblings whom I've known and stayed in touch with since their birth, back when I was a fellow in biochemical genetics at the National Institute of Child Health and Human Development. They're now in their late twenties, and their story encapsulates the history of biochemical genetics—successes wrought by medical advances, and challenges presented by those successes to patients and society.

Both boys were born with acidosis and hemolytic anemia. In the early 1970s, using then-new analytical tools, we found excessive amounts of 5-oxoproline in the urine of Alex, the older of the boys. Based on the understanding of metabolism at the time, we developed enzyme assays confirming a defect in the enzyme glutathione synthetase. There had been several patients described in Europe with similar problems, but Alex was the first in the U.S. (To date, there have been fewer than a dozen reported worldwide.) It was more than a decade before molecular tools allowed us to clone and sequence the gene for glutathione synthetase and to determine the specific mutations that Alex and his younger brother, Joe, had inherited.

Eternal quandary: Today, we take for granted molecular tools that we only dreamed of in the 1970s. It is worth reminding ourselves that today's tools will soon seem primitive. This is medicine's eternal quandary—acting in the here and now, while keeping an eye on the future. Over the years, we have treated Alex and Joe with medicines to adjust their blood acid and with antioxidants, since one role of glutathione is to act as an antioxidant. The hope of molecular approaches (such as gene- or enzyme-replacement therapies) remains elusive for genetic diseases like theirs. We're rapidly gaining knowledge about the human genome and protein structure, yet converting our understanding of mechanisms into therapies remains a daunting task. The sheer number of inborn metabolic errors, each represented by only a few patients, increases the challenge.

Alex and Joe have other problems. Both have significant learning problems, speech difficulties, and other neurologic conditions that we do not understand. Yet despite having the same genetic defect, they are radically different. Alex has congenital heart disease, spinal curvature, and never-before-described retinal abnormalities. An ophthalmologist who saw pictures of his retina once declared that he was blind; in fact, he can see—a lesson in talking with and examining a patient, not just relying on laboratory tests. Despite Alex's handicaps, he works every day and is a delightful, positive person—someone whom people immediately admire. Joe, on the other hand, has no cardiac, orthopaedic, or ocular problems but struggles with depression and behavioral problems and is, as his mother puts it, an "acquired taste." That's another lesson—genetic defects have a profound impact on people's health but are not the sole determinant of who a person is.

Over the years, I have learned from Alex and Joe's parents about the trials and tribulations of advocacy for chronically ill children and young adults. From the educational system to health insurance, from employment to transportation, the challenges are immense. Often, the "system" fails to take into account individual differences, applying dogma instead of creative empiricism. Alex and Joe, though they bear the same "label" of glutathione synthetase deficiency, are very different people, with different needs for medical and social services.

Great ironies: It is one of the great ironies of improved outcomes for children with a range of handicaps that as they have grown up to become young adults, medicine and society are faced with people who never before existed as adults. We do not know what to expect as they age. Sometimes we find new problems, such as early-onset Alzheimer's disease in 20-year-olds with Down syndrome. The "system" is not set up to serve such patients. And the situation is confounded by the fact that there are not many patients with each of these unusual diagnoses. Furthermore, there are few physicians trained to treat young adults with what we formerly thought of as pediatric diseases, be they inborn errors of metabolism, congenital heart conditions, or problems related to extreme prematurity.

Yet it is crucial that we figure out how to serve patients like Alex and Joe. There are growing numbers of such pediatric "successes," and their parents are getting older. As a society, we have not yet addressed how to help these families as the parents age. A recent *Wall Street Journal* article profiled an 85-year-old man who cares for his 50-something autistic son. As with so many aspects of medicine and life, one solution won't fit all. Yet we must address these issues.

Mentors: At DMS's 2004 Class Day, Dr. Judah Folkman spoke to our graduates about patients as mentors. Once the rigors of classroom science give way to learning—a lifetime of learning—at the bedside and in the clinic, it is patients who become the teachers. Molecular biology, proteomics, technology, physiology, translational science, clinical investigation, evaluative sciences, economics, sociology, and on and on—all these are part of medicine's "tool box." But I would argue that it is interactions with patients that help doctors grow in understanding, wisdom, and passion to improve the system. As we grapple with the challenges besetting health care today, all of us—doctors and patients alike—would do well to remember that. It is Alex and Joe and all of my patients who have helped me to be a doctor. ■

"For the Record" offers timely commentary from the dean of Dartmouth Medical School. Spielberg, a pediatrician and a pharmacologist, is in his second year as DMS's dean.