

Because of Alex....My Odyssey from Denial to NAAR

By Clarence E. Schutt, Ph.D.

My son Alexander is eleven years old. It was not until he was about four that I ceased thinking that he was 'just like me'—bull-headed and slow-to-speak as a toddler, disruptive and inconsiderate in grade school—and accepted his diagnosis.

The long process of arranging for schooling and adapting our family and home to Alex's needs and behaviors helped us appreciate the achievements of those pioneers whose autistic children are now adults. They generously shared their experience, even as they continued to exhaust themselves in giving primary care.

Although Alex was benefiting from the programs and rights for which they had had to fight, I couldn't imagine how I could give even a fraction of the time so many of them gave to improving the lives of our children. As a scientist, I was committed to spending many long hours in the laboratory, and I wondered how my wife could cope, not only with Alex, who "was a handful" (as my mother used to say of me), but with our raising his three older and very talented sisters.

Like many parents, I read everything I could about autism and its causes. I also read broadly in the scientific literature, looking for a way in to the problem. But I couldn't find any sure touchstone within the modern sciences of molecular and cell biology. I knew that many diseases could be understood in terms of specific protein molecules, such as the insulin receptor in the case of diabetes, or a certain dopamine-producing enzyme that was absent in patients suffering from Parkinson's disease. What the cold phrase "autism has no known etiology" meant to me was that we didn't have a clue.

Worse, understanding autism seemed tantamount to grasping the secrets of the brain itself, probably the most complicated structure in the universe. At a minimum, to solve the riddle of autism is to explain our ability to use language in social communication, a task as daunting as trying to find out what it means to be human. Where to begin?

Pharmaceutical companies employ very smart people in important positions, such as Vice-President of Discovery, to define new markets, and to think of strategies for developing new drugs. As a Professor of Chemistry in a university situated at the epicenter of the world's greatest concentration of pharmaceutical research laboratories, I have the opportunity to meet with these influential people. I ask them: "Why not autism?"

The answer, never unsympathetic, is invariably: "We don't know the targets". *Targets* are molecules that control the flow of information, energy, and material through cells. The storied development of antihypertensives (by Ondetti at Squibb and Patchett at Merck) flowed from the discovery that inhibiting a single protein molecule, ACE (angiotensin converting enzyme), could reduce blood pressure. Ondetti and Patchett knew the target they were looking for, the ACE protein. These drugs have saved countless lives. In the field of mental health Prozac works by binding to a class of proteins known as serotonin reuptake transporters...again, the target was known.



These drugs would never have been developed without clearly defined protein molecules for the medicinal chemists to target. So, the question for me, as a parent and a scientist, was: How do we find targets in autism, and thus engage the major pharmaceutical companies in our quest for a cure?

My field of specialization is structural biology, a branch of structural chemistry that aims at discovering and "seeing" (with x-ray detectors and computers) the molecules of life. With these instruments, we can discern the arrangements of atoms on the surfaces of

protein targets of interest. Armed with this knowledge, medicinal chemists can use powerful computer algorithms to design molecules that fit neatly into the atomic crevasses and valleys forming the molecular landscape. In some cases, these designed molecules will occupy these sites, substituting for a missing signal — or competing with a signal that appears in excess, perhaps over-exciting a nerve cell.

Eventually the best ones can be optimized into drugs ready to meet the strict requirements of the FDA. The price of developing a drug is estimated to be about \$400,000,000, roughly one thousand dollars for each person suffering from autism in this country, small when compared to the annual costs of care and schooling.

I began to speak with my fellow structural biologists about autism and the need for targets. About five years ago, Dr. Florante Quiocho of Baylor Medical School drew my attention to a protein he was working on called "the memory enzyme". I was stunned! An individual protein molecule, important for long-term memory, perhaps for learning as well! Could this be the target?

After all, some autistic individuals learn slowly, others remember practically everything. Maybe autism was all about memory and its control and access. The more I read about this protein (CAM-Kinase-II), the more intrigued I became. I found studies describing experiments where mice, trained to carry out complicated spatio-temporal tasks, would easily get confused if the *single* gene encoding for this protein was inactivated. (A major advance in molecular biology is the discovery of how to breed "transgenic mice"—normal except that they lack one or two specific genes.) More specifically, the inactivated or mutated gene was located in cells of the hippocampus, considered to play an important role in conscious memory. The hippocampus seems to integrate our senses and produce "maps" of our surroundings. It is thought by some neurobiologists that these interior "maps" of what we perceive are continuously compared with maps of what we expect to see. In this way, memory and perception become intertwined during the earliest stages of cognition.

Imagine my astonishment, then, at first hearing that Margaret Bauman's celebrated autopsy studies had showed less well-developed arborizations (connections) of nerve cells in the hippocampi of autistic individuals! (In a future column, I will discuss "neuronal plasticity" and other ideas, such as neuronal migration, that are the basis of my private hopes that more



and more useful targets will be discovered in autism, especially as the Human Genome Project unfolds.)

I impulsively told Dr. David Holmes, the Director of the Eden Programs Serving Children and Adults with Autism, where Alex attends school, about these developments. He said, "Why don't you tell our parents and staff about this at our next Membership Meeting?"

To make a long story short, these "messages of hope, scenarios for a future without autism" gave rise to the annual Princeton-Eden Lecture Series, to which we invite leading scientists and service providers to speak each year at Princeton University. My lecture "Because of Alex...", opening the Eden Lecture Series, was a call for more research, for parent involvement in fund raising and advocacy at the National Institutes of Health.

At the end of that lecture, Karen London approached me and introduced herself. The National Alliance for Autism Research was still in embryonic form, but her vision for it perfectly matched the organization I had dreamed about but could see no way of starting myself. Most important for me was the quality and integrity of the scientific review process. Without peer review, no pharmaceutical executive or NIH program officer would ever take us seriously at the next stage.

My wife and I discussed whether I could make the time commitment that a Board position on NAAR would entail. I thought of my son Alex, working "bull-headedly" to make sense of the world from the prison of autism. Could I do anything less? I recalled Jesse Jackson's stirring speech to the Democratic National Convention on the homeless – "They work hard. They work hard everyday. They get up. They look for a job. They work hard. They work hard everyday" – and I reflected on the staggering effort expended everyday by autistic children to open the doors and windows of their imprisoned minds. Maybe NAAR could provide the keys to unlock the closed gates—and I knew where to find the locksmiths.

At some point during NAAR's first Scientific Advisory Board meeting last December at the Harvard Faculty Club, my eyes suddenly welled up in tears at the sight of these world-class scientists, some of whom had encountered the mystery of autism only because of NAAR, applying the wisdom of their years to autism. After relieving Martha Denckla as Chair of the SAB for the evaluation of a particular proposal, I returned the gavel to her with the observation "Now I know what it's like to drive a Maserati!"

As the SAB meeting was ending, and all of these great scientists were rushing back to their labs, energized as I was, I thought back to the day two years before when I first met Karen London at the end of my "Because of Alex..." lecture. She had said then, as she now does almost every day "I have something very interesting to discuss with you." ♦

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