

## Because Of Alex...Only Connect

By Clarence E. Schutt, Ph.D.

Autism is the Rosetta Stone of human neurobiology. Deciphering autism will lead us to new insights into the origins of language, personality, and artistic vision. The very characteristics that define us as human beings—affability, communication, and intelligence—are cruelly dimmed in an autistic child. Yet, in compensation, these children seem to glimpse the world in ways shared by great artists. How else can their delightful responses to running water, spinning backgrounds, and flowing hair be understood? We must find ways to bring autism research to the forefront of modern brain science, not just to help our children, but to be able to unwrap the gift of philosophical truth these mute angels bear.



One of the most remarkable discoveries of modern neurobiology is the concept of "neuronal plasticity." The brain literally "wires itself up" during development, with neurons seeking out connections with other neurons, often situated hundreds of cell diameters away, by sending out long axonal projections tipped with highly sensitive and motile "growth cones" that can sense the subtle structural and chemical cues along the way. When they reach their target cells, growth cones restructure themselves into the receiving ends of neuronal synapses, effectively establishing direct physical communication links between neurons.

Almost a half century ago, the brilliant Canadian psychologist E. O. Hebb theorized that networks of connected neurons might store memories by strengthening frequently used synapses, while weakening those not carrying information. "Use it or lose it" expresses the idea. Today, scientists have discovered some of the protein molecules and signals that underlie the physics of synaptic strength. In my "Scenarios for a Future without Autism" lectures to parent groups, I like to refer to this phenomenon because I imagine that someday we might use this knowledge to find the means to strengthen synapses in the brains of autistic individuals. Maybe the connections continually form, but are broken down too quickly in this complex jungle of competing synapses to contribute to learned memories. Perhaps we could find a medication to shift the balance of competing influences to favor strengthening over weakening. But, can we go from mere scenarios such as this to realistic research programs that will help our children? My answer is "Yes."

There is a remarkable confluence of knowledge from many investigators supporting the notion that similar molecular mechanisms have been used over and over again during evolution to solve functional problems. For instance, the proteins actin and myosin, which generate force and movement in muscle fibers, are also found in crawling amoebae, in neuronal growth cones seeking their contact sites, and at the surfaces of macrophage cells actively ingesting foreign invaders. It appears that once Mother Nature hit upon a means of moving things around, she passed the secret on.

The tremendous power of molecular genetics to reveal, not only patterns of gene expression, but the effects of mutating or deleting particular genes, enables us to learn about human

disease directly from studies on flies, worms, and mice. These studies are necessary for the important "target validation" data required by the FDA before a new drug can enter into clinical testing.

An apt example of the power of human genomic research comes from the search for the cause of congenital deafness. Several genes have been identified recently from mapping the genomes of extended families where deafness is prevalent. In one case, the gene responsible for deafness codes for a protein that was previously discovered to be essential for the correct development of wings in the insect *Drosophila*. What is the connection between fly wings and human hearing? It turns out that, at the molecular level, the protein encoded by the deafness gene is a kind of "assembly factor" that directs the incorporation of actin molecules into extended structures. In the inner ear, there are thousands of actin-containing hair cells that convert the energy in sound waves into nerve impulses. Without the actin assembly, these hair cells fail to form, and deafness results.

What about autism? Several promising leads have been reported recently, among them the exciting news that chromosome 15 contains a genetic "hot spot" for autism. The gene responsible for Angelman's syndrome, a disease in which children exhibit many autistic-like behaviors, is also located in this gene cluster. The point, from my perspective as a structural biologist, is that we know a lot about the protein encoded by the genes in this cluster. Furthermore, GABA receptor subunits, which bind the most potent inhibitory neurotransmitters, are found in this cluster. Pharmaceutical companies have studied this "target" extensively (Valium, for example, is known to bind to GABA receptors). There is a wealth of pharmacological, toxicity, and behavioral data for thousands of promising chemical compounds that were not useful for their original purposes but could spark an idea in a mind prepared to think about autism.

New connections are being made to the pharmaceutical world, and our children are ready and waiting for them to be strengthened. When I was preparing to meet an important pharmaceutical executive recently to tell her about chromosome 15, I happened to tell my son Alex that I was going to meet someone who might help him get a medicine enabling him to talk. Alex, who cannot say much more than "Hi," went over to a drawer where vitamin tablets are hidden (from him!) and brought me a bottle to open. My wife remarked: "He wants it now."

We need to see that young scientists are trained and motivated to undertake careers in autism research. They will be the connectors that may find the way to strengthen the connections between neurons in our children's fantastic minds.

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