

To Feel Pain and Cry Again

MICHAEL BRENNER WAS BORN WITH a mystifying constellation of symptoms: feeding problems, persistent vomiting, delayed development. For two years, his parents trailed along with him from doctor to doctor until a neurologist finally told them that he suspected that their boy had familial dysautonomia (FD), a rare genetic disease that occurs in one in 3,000 live births in the Ashkenazi Jewish population. The prognosis was grim: Michael was unlikely to live beyond the age of five.

Today Michael is 20 years old, and while he has learning disabilities, his health is stable, and he has beaten the odds. His father, David Brenner, is the executive director of the Dysautonomia Foundation. He was appointed to his present position in 2006 after 16 years of volunteering for the organization. His dedication, he says, was inspired in part by the care and compassion of Michael's physician, Felicia B. Axelrod, M.D., the Carl Seaman Family Professor of Dysautonomia Treatment and Research and professor of pediatrics and neurology. As the world's foremost expert on the disorder, she has devoted 37 years to investigating the causes and the treatment of FD. That persistence has finally paid off: she and her colleagues at NYU's Dysautonomia Treatment and Evaluation Center may have discovered a compound, kinetin, that could potentially correct the FD gene mutation.

It was Dr. Axelrod who definitively diagnosed Michael when he was two years old and immediately suggested surgery to prevent food regurgitation, and the insertion of a feeding tube into his stomach to ensure adequate nutrition. These measures have enabled Michael and many others with FD to reach adulthood. In fact, 50 percent of those diagnosed with the disorder now reach the age of 40.

It was not always so. FD affects the autonomic nervous system, the "orchestra leader" that keeps the rest of the nervous system in balance. A mutation on chromosome 9 — identified in 2001 in collaboration with Harvard geneticists — inhibits the ability of a gene called *IKBKAP* to make a protein called IKAP, which controls the development of neurons. One in 27 Ashkenazi Jews carries one copy of

the mutation, which is recessive; in other words, an affected child must have two copies, one inherited from each parent. Symptoms of FD include partial or complete inability to feel pain, heat, or cold; lack of overflow tears (leading to abrasion of the cornea); and repeated bouts of pneumonia due to aspiration of food particles into the lungs. Although surgery and drugs can ameliorate some of these symptoms, the disease progresses relentlessly as patients age.

It was with this adult population in mind that Dr. Axelrod sought a drug to modify the mutant gene in order to treat symptoms. These days, fewer than five children with FD are born each year (down from 15 to 20 per year) thanks to carrier and fetal screening. "But what do you do for the patient who already has it?" asks Dr. Axelrod. That's why she collaborated with human geneticist Susan Slaugenhaupt, Ph.D., of Massachusetts General Hospital to screen therapeutic drugs, examining about 100 until they found a plant hormone called kinetin that corrects the FD gene's activity in cell culture. Kinetin enhances the production of normal IKAP, which itself is part of a protein complex called Elongator that regulates the

expression of about 100 other genes, some of which are involved in cell migration and development. A subsequent study at NYU on the effect of kinetin on carrier parents (who have only one copy of the gene) shows similarly promising results. Thus kinetin, and possibly other drugs, can modify the FD gene's expression and offer patients like Michael new therapies.

But genetic intervention is just one of the center's goals. Last fall, a \$2.5 million grant from the Dysautonomia Foundation enabled Dr. Axelrod to recruit Horacio Kaufmann, M.D., the Felicia B. Axelrod Professor of Dysautonomia Research and professor of medicine, pediatrics, and neurology. An eminent researcher who specializes in autonomic disorders, he will treat adults with FD. In addition to being named co-director of the center, Dr. Kaufmann is also director of a new Dysautonomia Research Laboratory. The grant will also fund the expansion of the center, doubling its current space.

Dr. Axelrod has started testing kinetin, as well as some other promising drugs, on FD patients and hopes, in the long term, to stop the progression of the disease — or even cure it. "Within my lifetime," she says, "a disease has been described, the gene has been identified, and probably before I retire I'll see a definitive therapy for this disorder. That is an amazing thing." ●

▶ Michael Brenner and Felicia B. Axelrod, M.D.

