

# June 1999 OAA Newsletter

## Editorial

### Happy Summer 1999!

Here's hoping the summer brings much health and happiness to your families! We've settled into our new house and Melissa is working on her social skills with the kids in the neighborhood. I'm excited about this issue of the OAA newsletter. I've heard from many families that want to share their stories and have the long-awaited article on Gene Therapy by Dr. Olaf Bodamer and Dr. Arthur Beaudet from Baylor College of Medicine in Houston. I am also happy that Dr. Arnie Strauss from the University of Washington at St. Louis has shared an article on Cardiomyopathy. If you're not familiar with this condition, it can affect organic acidemias and I wanted all families to be informed.

### Representing YOU in OAA.

I'm happy to inform you that I am representing OAA on two very important committees. In March Cindy Winiarski (OAA board member) and I attended the New England Connection PKU conference in Boston. The evening before the conference I attended a meeting to begin a National Coalition for PKU and Allied Disorders. What does this mean? As many of you know, PKU is routinely screened in all 50 states. The PKU community worked very hard to get this passed, and now want to help other allied disorders, especially metabolic disorders that have similar diets to achieve the same screening standards. Becoming a 501(c)(3) will enable the group to become more visible in the fight to expand newborn screenings. Another committee I was recently asked to join is a Board of Advisors for the Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease in Dallas, Texas. Dr. Charles Roe who is very instrumental in research for the Institute, has developed this advisory group to meet and review the Institute's progress and advise them on new directions which would serve our community and nation. I haven't attended a meeting yet, but will inform you all as to the progress going on there.

### Newborn Screening Survey Results

Here's just a brief synopsis of the newborn screening questionnaire results. While it's not a scientific survey, we hope to combine this data with the Fatty Oxidation Support groups' data and publish it for use to increase the knowledge of how newborn screening can help.

- 45 families responded before the deadline -- 15 MMA, 12 Propionic Acidemia, 4 Isovaleric Acidemia and the rest were various other organic acidemias.
- An amazing 42% were diagnosed at one week, 25% at two weeks.
- Total Cost until Diagnosis: Most respondents only had estimated cost of expenses, and the total amount estimated for all respondents was \$5,121,000.00.

Complications included: death (for 1), liver transplant, coma, seizures, motor and speech development delays, kidney failure, brain damage, feeding problems.

## From Our Families...

### Life with An Angel, by Geny Orlean

*(Jason Silverberg's Mom)*

Today completes 7 months that Jason went to his resting place, my courageous Angel. Until today, I cannot say what was the hardest thing in my life, seeing Jay going through his days of pain or having to say goodbye to my Angel of Love. A child that always had a beautiful, plentiful smile on his face, a young man that just wanted to grow up to be a clown. Like some of you may remember, Jason had Propionic Acidemia. I believe he was one of the first to go through behavior modification therapy to eat without the use of tubes. I strongly believe it was worth it. I would really like to tell more, but it is still very hard. So just remember, everyday with our angels may be the most beautiful days of our lives, doesn't matter where, or doing what, as long as we can hear .. "and then what Mom?"

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OAA wishes to express our sympathies to Bev Milligan and family for the loss of their daughter, Eseta, 15, Propionic Acidemia, who passed away in February.

And also to:

Mark & Monica Martinez, for the loss of their son, Jace, MMA, who passed away in January.

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## PHYSICIAN DEDICATION

*Dr. Mendel Tuchman, Fairview-University of Minnesota Hospital*



Our family has had been very fortunate the last 10 years to have had Dr. Mendel Tuchman as Melissa's metabolic physician. Dr. Tuchman is leaving the University of Minnesota this summer to join the metabolic staff at Washington University Children's Hospital in Washington, DC. Mendel has been very open and upfront with us as to what to expect with Melissa's disorder. We have valued the relationship we have with him over the years and plan to stay in communication with him via email. We truly feel if it weren't for Mendel and his knowledge of metabolic diseases, Melissa would not be with us now. Since it's been four years since Melissa has been metabolically unstable, we don't feel as nervous about him leaving. Thank goodness, Dorothy Markowitz, Melissa's dietician isn't leaving!

Good luck Mendel, and words can't really describe how much we appreciate you!

**Lee, Kathy & Melissa Stagni**

**Editor's Note: If you would like to include an article and picture on your families' metabolic physician, please send it to me for consideration before the next newsletter deadline, September 15, 1999.**

# Robert Bazy

## *Isovaleric Acidemia, Age 8*

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Robert is a person that has a problem called autism. He is seven. He is not that hard to deal with unless he is mad. I am his sister, Melinda. I am nine years old. Some kids in this world have autism. Autism is a type of thing that causes brain damage. Everyday, when I am away from my brother, I really miss him. Taking care of Robert is really not that bad. He understands a lot. A lot of autistic kids can understand, too, just like Robert. To tell you the truth, my brother is sweet, loving, and kind. I love him, and my whole family loves him. I really care for him a lot. I feel sorry for people that have problems like this a lot. I love my brother no matter if he is different or not. I hope he loves me, too, like I love him. I put all my care in my brother's heart because he needs it.

**by: Melinda Bazy**

# Ann-Marie Lynn Jones

## *Propionic Acidemia (PA), Age 17 months*



Ann-Marie was born on 9/29/98 at Southern New Hampshire Regional Medical Center in Nashua, N.H. She had a very traumatic birth. Her left clavicle was broken and both hips were dislocated. She was pale due to the long delivery and vacuum extraction. I was told that she "was a little shell shocked". Later, when she was brought back to me to nurse, she would not eat. They took her back to the nursery. When we tried again, she ate very well and then began to vomit all that she ate. We were told that she must have swallowed too much amniotic fluid. We did this several times with the same results.

The day we were to be dismissed, 10/1/98, I found out she had never stoolled. I questioned this but was told that it happens sometimes and not to be worried. We were sent home at 6:00 p.m. Excited to be home, but tired, we both went up stairs. I laid Ann beside me in my bed with rolls all around. I was very concerned by this point. My family has a very high rate of SIDS deaths. She continued to vomit every time she ate. I set my alarm clock for every hour so if she was going to vomit it was normally in that time frame. She finally had that black diaper I was so desperate for at 8:00 p.m. I thought all would be fine then.

Then at 1:00 a.m. my worst nightmare. I heard her vomit. I jumped up and looked at her. She was not breathing. I screamed for my husband. "Dial 911" was all I could say. I started breathing for her and she started to breathe again. She was cold and lethargic. The Ambulance got there in the matter of minutes. By then Ann was pink, breathing fine and happy. They transported us at my request. I thought at first it was just nervous mom syndrome until she stopped breathing again. The ambulance driver floored it, the lights and siren went on. When we got there they had me wait in the ambulance while they ran her in. Then they came and got me. They sat me in a wheel chair and placed her on me. We went to the ER elevator to take us up to ICN. The doors closed and she stopped breathing again. She had come out of it again when the ICN doors opened.

I passed her off to the nurse. Ann looked at me and closed her eyes. She didn't open them for seven days. She went in to a coma. The Cat scan showed some swelling in the brain and she was having tachycardia. The neonatologist examining her noticed all of the things that were wrong including high ketones and the labored breathing. He said he was going to call a specialist up at DHMC. At 10:00 a.m. she was on her way to Children's Hospital at Dartmouth (CHAD) NICU. We had no clue what the problem was going to be when we got there.

The next morning we meet Dr. James Filiano and Lynne Wolfe. He thought she had a rare metabolic disorder called Propionic Acidemia and he wanted to run some tests to confirm it. He said he needed blood from me and Ann. They drew his blood. He was going to be the control for the test. They stuck me next, then Ann. They ran it to the lab to be sent out to Texas.

Ann progressively got worse over the next few days. Sunday October 6, at 10:00 p.m. I got a call at David's House (it's like a Ronald McDonald house). It was Dr. Jim Filiano. He said he had the diagnosis and it was Propionic Acidemia. He had already started the aggressive treatment. I ran over at 6:00 am to see her before he got there but he had never left her bedside. She showed fast improvement. Then she did something I thought I would never see again, she opened her beautiful blue eyes. She was awake and alert.

We had several set backs while we were there. She was doing great, then she got a A-line infection which was really scary. She had pneumonia and then she went back on the ventilator, but only for a couple of days. When things started to look good, Jim came in to the room and said "We have another one". Here we were trying to get our heads on straight because it was supposed to be so rare, and they had another. Ann and I met Leah's parents Jennifer and Matt in her room on Pediatrics. I remember that day like it was yesterday. They wanted to know everything and we started to compare stories. We spent many days going

back and forth, Jen coming over to pediatrics and me going over to ICN to see her. We were at CHAD for eight weeks. The weekend before Thanksgiving we came home.

Ann-Marie is now seventeen months old. Developmentally she is ten to sixteen months old. She has never really rolled over nor will she, but is starting to let us lie her on her stomach. She does sit up and play with her older sisters and watches her favorite show Blue's Clues. We get out to see Leah and her family whenever possible. The girls love to play with each other. We spend a lot of time on the phone just to see how each other is doing on a daily basis. When we have to go to Boston we always schedule them together so we have a day together.

Ann-Marie still has seizures. We are in and out of the hospital. Flu, dehydration, ear infections, seizures, and UTIs and she just got RSV and pneumonia. Her head growth is slow but it is still growing. She has OT and Speech once a week and PT once a month. She is in a medical stroller/wheel chair. We have a bath seat for her to use and a Pony Walker yet to come (it's a large baby walker). We just got rid of her Apnea monitor. She has a G-tube we use the ZEVEX pump. She is on Phenobarbital, Lamictal, Carnitor, Dexamethorphan (an experimental drug to try to decrease the Glycine in her blood and spinal fluid). She is also on a set of three antibiotics to keep the gut bacteria down which also helps her to keep her ammonia down. She uses XMTVI, Maximaid and Pedisure for her formula. She does eat. She is allowed 4.5 grams of protein by mouth per day. Each day she finds a new way of surprising us. She never gives up. She always keeps our spirits up.

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# Columbia University Seeking Patients For Cardiomyopathy Study

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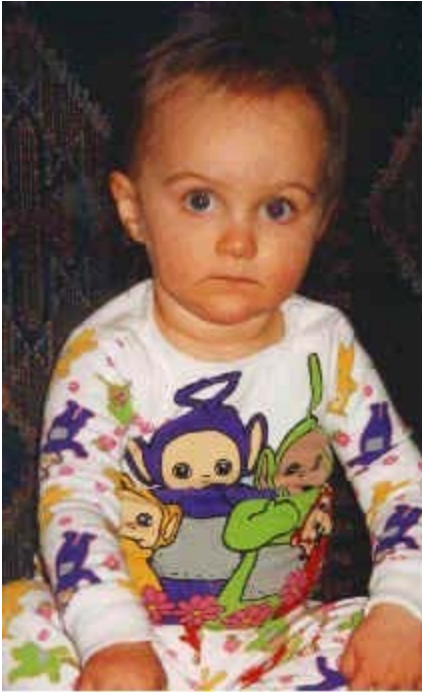
The Division of Cardiology in collaboration with the Division of Pediatric Cardiology of the College of Physicians and Surgeons of Columbia University at the Columbia-Presbyterian Medical Center in New York is recruiting patients for a federally funded study of heart blood flow and fatty acid metabolism using positron emission tomography (PET) scanning in patients with inherited or acquired cardiomyopathy (heart failure). The aim of the study is to determine the prevalence and severity of abnormal fatty acid metabolism in patients with inherited or acquired heart failure in order to gain a better understanding of how heart metabolism is affected by these disorders. Our ultimate goal is to identify and treat such cardiomyopathies with pharmacologic therapy designed to correct the metabolic abnormalities, and ultimately, in those with inherited defects, with gene replacement therapy. Under normal circumstances, fatty acids serve as the major source of energy for the heart. Some forms of inherited or familial cardiomyopathy are due to deficient or inactive enzymes involved in the metabolic pathways involving fatty acids. These abnormalities in fatty acid metabolism can lead to insufficient energy production and may also lead to heart failure because of the accumulation of certain metabolites of fatty acids in the heart muscle. PET scanning permits precise measurement of blood flow and metabolism in the heart using the administration of a small amount of radioactive fatty acids by vein. The whole procedure takes about 3 hours, but actual scan time is about 1 hour (three 20 minute scans). In subjects under 18 years of age, the amount of radioactivity administered is approximately equivalent to 1 year of background radioactivity and is considered by the FDA to be within the limits allowed for experimental procedures of the type. However, radiation risk is cumulative, so any additional radiation exposure should be carefully considered.

Patients who are eligible for this study include those with inherited (familial) cardiomyopathy and their unaffected siblings (to determine whether perfusion and metabolism of the non-affected sibling's heart is normal), and patients with idiopathic cardiomyopathy (i.e. when no cause can be found for the heart failure) as well as their unaffected siblings (to determine whether abnormalities in heart perfusion or metabolism are normal in these children).

There is no cost to the patient. The patient's primary physician must provide a referral to Columbia-Presbyterian Medical Center for the scan. For more information, you may contact Dr. Daphne Hsu, Division of Pediatric Cardiology at (212) 305-6575, or Dr. Steven Bergmann, Division of Cardiology at (212) 305-7594. Patient scheduling is made through Melanie Phipps, R.N., at (212) 305-0897.

# Nikki Elizabeth Hrichak

## *Glutaric Acidemia, Type 1, Age 2*



Nikki was brought into this world on June 2, 1997 following an uneventful pregnancy and labor of only 3-1/2 hours. She had excellent APGAR scores and we were sent home only 4 hours after her birth. She nursed voraciously and at our 48 hour post-partum check at our home by the midwife (who delivered both of our children) took samples of blood which were taken for the routine blood screens as well as for the optional (but recommended) Supplemental Newborn Screening panel that was to be sent to NeoGen Labs, Inc. in Pittsburgh. This test would cost us \$25, as it was not covered under our Blue Cross plan. Although I had declined most of the prenatal screens and optional tests with both of my daughters, we opted to have the additional screening. We expected to receive a letter in the mail saying our child was normal, as we had 27 months earlier with our first daughter, Katya.

We did not receive a letter, instead, on June 17<sup>th</sup>, when Nikki was 15 days old, we received several urgent messages on our answering machine from our midwives and our pediatrician. I phoned the midwife first and was told our baby had a life threatening illness, that we had to get her to our Pediatrician, and that we would need to have her seen by a specialist in Strasburg. Although I had been a physical therapist for nearly a decade and was used to medical terminology and illness it was my husband, Ed who had to handle

the phone calls, as I could not even remember the initials they gave me for this disorder. We took Nikki to our local pediatrician who explained they had barely heard of the disease, let alone treated it. He suggested that Nikki should be hospitalized out of town where they treated this type of disorder routinely. We were referred to Dr. D. Holmes Morton in Strasburg, a doctor who has dedicated his life to disorders common in the Amish, such as GA1. I was put in touch with him and he recommended that Nikki be hospitalized that evening. Humbly, he explained that he was one of the top pediatric geneticists in the country, but that we could go to Children's Hospital in Philadelphia if we would rather. His calming voice and gentle reassurance made me feel as though going to Lancaster General and to Dr. Morton would be the right choice.

Nikki and I made the hour and a half drive uneventfully (though I don't remember any of it) and checked in. The next 24 hours would be the worst of my life up to that point. We met Dr. Morton and his nurse practitioner, Donna almost immediately. They could not find any immediate clinical indications that Nikki had GA1 and took blood and urine samples which Dr. Morton ran at his own lab to confirm her diagnosis. Not only did they confirm Nikki had GA1, but her levels were very high. Dr. Morton's dedication and caring were apparent immediately. He spent hours explaining to me the disorder, the implications, and what we could face in the next few years, then re-explained as much as he could to my husband over the phone, who was at home with our 27 month old.

I have never been the type of person that listens to doctor's advice or trust them implicitly. My first disagreement with Dr. Morton came over feeding. He instructed me that as of ten o'clock that night Nikki could no longer nurse since we would have to keep a careful count of her caloric intake and that she could no longer receive breast milk. Although being notified of her illness was a devastating blow, this news did me in. I am a firm believer in the health benefits of breast milk and had nursed my first daughter using a pump when I returned to work. When Dr. Morton left that night, I sobbed uncontrollably. The night became progressively worse as he did not want Nikki to have any milk and said the glucose IV's would keep her satisfied over night--they didn't. She screamed well into the night and glared at me with accusing eyes, wondering why not mother would not feed her when she was hungry. The nurses saved me and took Nikki out of the room so I could get some rest.

The next morning we had our first of many MRI's and though it showed some increased fluid around the temporal horns, her basal ganglia were intact. This started our day off on a good note and then Dr. Morton and I resolved our disagreement. He would allow me to continue to give Nikki breast milk, as long as I pumped it and gave it to her through a bottle. I ordered a double pump and for the next 17 months, fed Nikki in that manner. It was a lot of work, but to me it was worth it!

Nikki and I went home that evening and started off our new schedule of medications twice a day. Nikki had no problem adjusting to the L-Carnitine, but hated the liquid Diazepam. I discovered the medibottle that saved us a lot of fighting and allowed her to get all the necessary medication. Soon, this became routine and we traveled the 2 hours to Strasburg every 4-6 weeks for follow-ups. Although her head lag persisted to the far limits of "normal", Nikki reached every other developmental milestone on time, rolling by 3 months, sitting by 6, and walking at 11-1/2 months of age. On physical examination, Dr. Morton would always find "some slight dystonic movement" although our local pediatrician never found any.

By her 15-month visit we were really feeling we were out of the woods. Although they told us that injuries can occur up to 18-24 months, Dr. Morton told us these were usually in children who developed more slowly. By 15 months, Nikki was walking, climbing, and keeping up with her older sister. Her basal ganglia seemed to have fully developed and she had gotten through this time with only one slight cold, which I was able to manage homeopathically.

We started to let our guard down that was when tragedy struck. All along we had been worried about her caloric intake and risk of seizures from a fasting state. On October 18<sup>th</sup>, when she was 16-1/2 months old, Nikki fell off the back of a rocking horse and was rendered unconscious. She was rushed to our local trauma center where the doctors joked that they had to read up on GA1. They were in contact with Dr. Morton at my request, but were obviously unequipped to deal with her condition. A CAT scan showed a subdural bleed, something children with GA1 are at high risk for. During the course of the day, Nikki got progressively worse and we were taken by helicopter out to Lancaster General. I have never been as relieved to see someone as I was to see Dr. Morton that evening. I knew when I saw him that he would make Nikki OK. It turned out that part of Nikki's problem was that the local hospital had her glucose level four times normal and her Dilantin levels almost twice therapeutic levels.

After a few days, Nikki was walking around and seemed much better. But she continued to spike fevers in the afternoon and was sent home on Motrin every 6 hours. She screamed all the way home and as it turned out, Nikki knew best. We were back in Lancaster only 5 days later. MRI confirmed she had a second bleed and developed a strange inflammatory response to the subdural bleed, having fevers as high as 104.6 degrees. We stayed in the hospital for 3 more days, doing little more than trying to control her fevers. I was getting cabin fever, trying to keep a 16-month-old with IV's from falling on the tile floors of the hospital while she wanted to run and climb. On the third day, Dr. Morton told me we could probably go home that night, Nikki had a seizure and became paralyzed on the right side of her body. Dr. Morton and the neurosurgeon on her case were called in; she was typed and cross-matched and sent to CAT scan again. All of us had the thought that there must be pressure building in her head and that she would need surgery.

Fortunately, that was not the case. Then scan showed a slight extension of the bleed, but no pressure on the brain and no permanent damage. Throughout all this, Nikki's basal ganglia remained intact. By 4 AM the nurse woke me and let me know that Nikki was once again using her right side and seemed fine.

However, the fever persisted. Dr. Morton was baffled and spent hours on the phone and in the medical library researching her response. He finally came back and said, "let's try Decadron", a central



nervous system anti-inflammatory. This was the answer. Within 24 hours, her fevers stopped and Nikki became her normal self. We were released to go home on day 6 and this time Nikki returned home with a smile on her face.

Five months have passed since this episode. Nikki is now running and jumping and sending her parents and other relatives into panic attached everytime she jumps on the bed or climbs on a chair or "dances in the bathtub", but we never go through a day without realizing how lucky we are. Now that Nikki is closer to 24 months, the age where the imminent dance of basal ganglia injury is over, we can start to relax. I am putting any free time into the fight for mandatory expanded newborn screening. For our family, having the option to choose this additional test made a difference for which we will be eternally thankful!

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# Robbie Dey

## *Methlymalonic Acidemia (MMA), Age 2*

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Our son Robert Howard Dey, born October 31, 1996, is a very happy toddler. When I became pregnant with Robby, I was very ill. I had to go on a drug called Diceton. This drug helped me do my daily activities, for I had lost 7 lbs., and I wasn't eating or drinking, and had very little energy. I took the drug until Robby was born. Every time I tried to get off it, I became ill again. When I took this pill I would get a sick feeling that this somehow would affect our baby, but the doctor said that it was safe.

When Robby was born he weighed 7lbs. 5oz. and was beautiful. When I recovered and was placed in a room, my husband and I had to wait hours for our bundle of joy to come and join us. Apparently he had problems feeding and keeping it down. Finally he was brought in. He was a gift from God. Robby is my second child. I have one very healthy 10 year old from a previous marriage. Anyway,

everything seemed fine until the second night in the hospital. Robby became very upset and cried throughout the night. Two days later we went home.

For the first 2 months Robby ate well and was gaining weight, but he seemed to be dealing with a lot of constipation and pain. Back and forth to the family doctors we went. Finally our family doctor decided it was time for Robby to see a pediatrician. He said to change Robby's formula and add cereal to his bottles to help him push out his bowel movements. He figured that the iron in the formula was too much for Robby's system. We changed everything and things seemed to be going well for a little while, although Robby continued to have slight constipation.

Things started to go really strange when I started Robby on baby food at around 4 to 5 months of age. He would either drink all his formula or he would eat. There was really never a time when he would take all formula and food at one time. For the next 3 to 4 months Robby and I were back and forth to both our doctors with constipation, lack of food intake and what we figured was gas pains. Through all of this he was gaining weight, until he was 8 months old. Then our family doctor decided it was time for him to go to The Hospital For Sick Children.

They did numerous tests on Robby and found nothing, put him on a Lactose, a liquid form of a laxative and sent us home with a follow up in 3 weeks. Things were not going very well, but Robby continued to hang on for 2 weeks, then he halted, no food, no drinking for 4 days. The next morning we made our trip back to the hospital. The doctors said that Robby had lost 5 lbs. and he was dehydrated and it was time to admit him until they could find out what was wrong.

It took 5 days in the hospital, numerous blood and urine tests. Finally the results were in. Robby was diagnosed with Methlymalonic Acidemia (MMA). We were in shock! Never hearing anything like this before, I started to cry and ask why. They first tried vitamin B-12 oral doses, but he did not respond, so they put him on a strict low-protein diet, special formula, Carnitine and 3 grams of solid food protein per day. This made Robby feel much better. He was happy, laughing, playing and trying to walk with mom and daddy hand in hand. Five days later we went home.

Although Robby has had relapses, and we have gone back to the hospital at least 20 times, he is now a very happy normal 2 year old toddler. He still has his formula of Tang crystals, Propimex-1, Product 80056, and 5 grams of Premed (a protein supplement), plus 10 grams of solid food per day. The doctors and our family feel that there has not been any damage done to Robby's physical or mental well being. After all that time

Robby was fighting hard for his little life, he pulled through and believe me when I say he is definitely a true gift from God. We love you Robby.

"Thanks to all the doctors, hospital staff and family and friends who stood by us."

I'm looking forward to all newsletters, possible meetings regarding Genetic Metabolic Diseases, and hopefully hearing from any families living and coping with MMA.

Good-bye for now!

**Cindy, Stuart, Nicholas, and Robby Dey**  
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# Gene therapy for children with organic acidurias: reality or fiction?

*by Olaf Bodamer, M.D. and Arthur L. Beaudet, M.D.*

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*The purpose of this article is to familiarize its reader with the concept and limitations of gene therapy without raising false hopes and unfounded speculations.*

## What is gene therapy?

Gene therapy is the introduction of genetic material (usually DNA or sometimes RNA) into tissues of patients with a genetic disease (i.e. organic acidurias). A genetic disease is characterised by a change of genetic information (gene mutation) in a way that affects normal function of the cells, tissues or organs involved. As a consequence symptoms can be observed in affected patients. Replacement of the defective gene by means of gene therapy should theoretically lead to correction of the defect and improvement of clinical symptoms. Although future complications of the disease may be prevented, none of the previous irreversible damage would be improved. Gene therapy should therefore be done as early as possible in the course of the disease.

Over the last 20 years, more than 175 clinical studies were completed world-wide with over 2000 patients already treated (report from 1996). The majority of studies were done in patients with cancer, diseases of the blood (sickle cell anemia, thalassemia) or clotting disorders (hemophilias). Only few studies were done in patients with inborn errors of metabolism, none so far in patients with organic acidurias. Overall treatment success was very limited and stable long-term correction of the defect was only achieved in exceptional circumstances.

## How does gene therapy work?

Genetic information is essential for all functions in the human organism. All the information is located on genes, which in turn encode proteins (and/or enzymes), the building blocks for each cell. Changes in genetic information (mutations) lead to enzyme deficiencies, which are the cause of inborn errors of metabolism. An example of an enzyme deficiency is the deficiency of methylmalonyl CoA mutase in children with Methylmalonic aciduria (MMA).

One important condition of gene therapy is that the gene itself and the disease causing mutations are identified. Fortunately this is the case for most of the organic acidurias, including MMA, Propionic Aciduria and Isovaleric Aciduria. However there are combined forms of MMA and homocystinuria (cblC, cblD and cblF) for which the genes are not yet identified. To deliver the correct genetic information to a child for example with MMA, the MMA gene needs to be packaged into a delivery vehicle (vector) which is given directly into a vein or tissue such as muscle. The packaging itself, which is done in the laboratory is fairly complex and cannot be described in more detail, due to space limitations. In principle there are two different types of vectors: viral and nonviral vectors.

Viruses have the ability to infect human cells, which makes them the ideal vehicle to transport genetic information. In addition each type of virus tends to infect only particular tissues or organs, such as the liver or the respiratory system. This is of importance for the group of organic acidurias as the liver is the main organ of enzyme production.

However viruses may cause inflammation and an immune response which in turn may render gene therapy ineffective. This risk has been gradually reduced as the viruses currently used for gene therapy have been much improved. It is difficult to predict for how long the corrected gene will be expressed and whether the vector has to be given at regular intervals or only once.

## **Is gene therapy feasible for organic acidurias?**

In principle, yes. As mentioned above most disease genes were identified and the vectors have reached a developmental state where they are ready for use in humans. Most vectors have been tested in animals for safety and found to have only limited, tolerable side-effects. Unfortunately, to our knowledge there are currently no approved research protocols or major efforts to embark on gene therapy for MMA, Propionic Acidemia or Isovaleric Acidemia. There may be many reasons for the lack of activity for organic acidemias. First, the development of new vectors for gene therapy is costly and time consuming, and if it can be accomplished for other diseases such as hemophilias, the technology may be quickly transferred for organic acidemias. Second, organic acidemias are relatively rare compared to disorders such as cancer, heart attacks, or diabetes, and there is little financial incentive for biotechnology or pharmaceutical companies to invest in gene therapy for rare disorders.

## **Is there cause for optimism?**

Although truly curative gene therapy has been slow to evolve, there have been a number of recent encouraging reports for delivery of genes to the liver. This work has involved the use of retroviral vectors that use safe fragments of RNA cancer viruses, lente viral vectors that use safe portions of the AIDS-like viruses, and adeno-associated viral vectors that use portions of a virus that infects the upper respiratory system; many of these studies have used animal models of hemophilia B to test the safety and the effectiveness of therapy (1-7)(PMID 9873759, 9759925, 9681416, 9883841, 9883840, 10097136, and 10074131). Our own work has focussed on the use of a modified adenovirus, most recently a new version with all of the virus genes removed; we have used mouse and cattle models of urea cycle disorders and a normal blood protein called  $\alpha_1$ -antitrypsin as a marker gene (8-10) (PMID 9462752, 9874269, 10097149). In published studies with mice and in unpublished studies with baboons, we have achieved expression of the marker gene for more than one year after a single intravenous injection, and this is quite encouraging. In addition, the newest versions of the adenoviral vectors with all of the viral genes removed have proven considerably less toxic in animals. We currently have an approved protocol for treatment of two urea cycle disorders and are seeking approval from the FDA to conduct trials in patients within the next 12-18 months. If trials in urea cycle patients were successful, it would be relatively straightforward to carry out the same treatment for most of the organic acidemias. Abstracts for all of the references can be examined through a national library of medicine resource called PubMed by entering the PMID number for each article (<http://www.ncbi.nlm.nih.gov/pubmed/>). Efforts to deliver genes to the liver using any of these four viral vectors (retroviral, AIDS-like viral, adeno-associated viral, or adenoviral) are considerably more encouraging than even a year or two ago, and we think there is good reason for optimism.

## **Are we holding out false hopes?**

Research of this type always requires longer than one would wish, and effective gene therapy for organic acidemias is certainly at least 3-5 years away, and perhaps 5-10 years away. Patients who already have impaired growth and/or neurologic development are unlikely to realize substantial benefit from the development of gene therapy, but may show improved metabolic control with a less restricted diet. Rather, this will represent a greater potential benefit for newborns diagnosed with organic acidemias. If gene therapy becomes successful, it will provide additional impetus for screening all newborns for organic acidemias using new technology (tandem mass spectroscopy) to identify all affected infants and allow early utilization of gene therapy. Although gene therapy could substantially benefit children currently affected with organic acidemias, its greater promise is for future generations.

## **Conclusions**

Despite shortcomings and the current limited success of human gene therapy one can be optimistic that gene therapy will eventually take off and provide a cure for most inborn errors of metabolism. However it is difficult to predict as to when the first clinical trials can be done in children with organic acidurias. This

will not the least depend on financial support by the political establishment and the availability of children who have been diagnosed early enough by newborn screening as not to have any severe complications of the disease.

## **Interest in contact with families with cblF**

Our laboratory is currently working on the molecular basis of combined Methlymalonic aciduria and homocystinuria (**cblF**). We would be very interested in receiving a small blood sample from affected children with **cblF**. Thank you for your co-operation.

### **For details please contact:**

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# Vincent Franze

## *Propionic Acidemia (PA), Age 7*



My name is Camille Franze and I am writing about my son Vincent Franze. We live in North Babylon Long Island, New York. Vincent was diagnosed with Propionic Acidemia at 4 weeks old. He is now 7 years old.

His story is very much like the stories I've read in the newsletter. He was born natural, full term and weighed 7lbs. 13oz. The very first feeding in the hospital Vincent began to vomit and with each feeding after that he was still vomiting, so the doctors switched him to Isomil (soy product) thinking he could not tolerate the milk. We were released the usual 48 hours after delivery. At about 10 days old Vincent started with apnea, he was still vomiting, not gaining weight and was also very lethargic. We took him to Schneiders Children Hospital. They took a spinal, some blood and found all the tests were normal.

He was put in ICU for the apnea spells and within a week to ten days he was released with the doctors telling us that he probably had a virus. It was approximately 3 days later that Vincent lapsed into a comatose state. We rushed him back to the hospital, they took more spinal fluid tests and then decided to do a metabolic blood chemistry test and found his ammonia level to be 1500. They called in a genetic team of doctors and told us that it was probably 1 out of 2 diseases it could be, Urea Cycle or Propionic Acidemia. At this point we needed to bring down the ammonia level so with our permission they had to give him a 3 drug I.V. that wasn't even FDA approved yet. This was so crucial at this point, so we signed the paper with hope that this would work and Vincent would come out of the coma.

Within 24 hours his ammonia level was going down and he started to wake up from his 2 day coma. His little eyes crusted shut so badly from the coma that he couldn't see us and see that we were there for him. In the meantime bloods and a skin biopsy was sent to California for the correct diagnosis and to our dismay it was Propionic Acidemia. They sat us down and told us of what we could expect of him and this terrible disease. A nurse came up to us while Vincent was in ICU and asked us if we would like to baptize him and all of sudden this nightmare became real life. We had him baptized with the whole family present. Vincent started doing well. He was drinking his special formula and began to gain weight and thrive like a 1 month old should and we were finally able to take him home.

My husband and I thought that if the hospital did a metabolic workup the first time we took him to the ER this whole thing could have been avoided. Vincent probably would not have been induced into the coma and now he is faced with the consequences of being developmentally delayed. His speech is delayed and he receives OT and PT for hypotonia. He attends a Boces program in the school (first grade) for developmentally delayed children. It's a wonderful school and he is doing very well. He is learning to read and do some math addition and he can count and write his name. His vocabulary and pronunciation have greatly improved.

We take Vincent to Mount Sinai Hospital in NYC to see Dr. Claude Sansaricq. He is a wonderful metabolic doctor. Vincent was about 2 years old when we switched doctor because Dr. Sansaricq was more experienced with treating PA and has many patients with this disease. He started Vincent on Amino Acids (Isoleucine, Valine, Threonine and Methionine) while carefully checking the levels and making sure he was getting the right amount (too low or too high was not good.) We go monthly for blood levels. Vincent's formula now consists of 8 tbl. of Propimex, 5 tbl. of Prophree, 64cc of Isoleucine, 40cc of Valine, and 8cc of Threonine and 11oz. of milk (in which he receives the Methionine). I put 8 oz. of water and some strawberry Quick for taste. It makes about a 30 oz. mix which he drinks voluntarily (sometimes with a fight). He has not been NG tubed since he was about 3 years old. His medications are 5 ml. of Carnitine and 5 ml. of Bicitra which both are taken twice a day.

Over the course of years he has been in and out of the hospital 15 to 20 times, mostly for acidosis and dehydration from vomiting with the flu virus or pneumonia. Metabolically his bloods have been good if we take him in early and let him start getting IV hydration with lipids and bicarb. if necessary. Ironically, I'm writing this in the hospital while Vincent recovers from a bout of the stomach virus that has been going

around this winter. He had also developed Pancreatitis while he was in the hospital. His lipase level reached 735. They released us because the level started to go down but when we got home he was vomiting again and still complaining of a stomach ache so 3 days later we returned to the hospital. They are now treating him with Pepcid for 2 months so we will see what happens. I read that a lot of kids with PA have gotten pancreatitis.

Vincent does like to eat and we thank God for Dr. Sansaricq for that because when he put him on the amino acids his appetite shot up. He eats low protein breads, pastas, crackers and I make him bagels, pizza, and potato croquets. We order foods through Dietary Specialties, Ener-G foods, and SHS. My insurance company pays for the foods as well as the amino acids and formula.

In spite of this terrible disease he is always a happy and playful child. We treat him as "normal" as possible and try not to make it a big deal for him. If he asks to eat something he knows he can't have (ex: meat), we ask him "Can you eat meat Vin?" and he'll say "Vincent can't eat meat because I will get a belly ache." The matter will be dropped. If we are having a birthday I will give him the frosting and a small piece of cake knowing he won't even finish it. He feels included and the whole matter is not even made an issue of. I will also make him low protein cupcakes if he wants it.

I thought when he was a baby "My God, no meat, no eggs he can't eat what we eat. What's going to happen when he attends school?". It all worked out and he doesn't feel any different. If I make him what he likes and those food distributors keep making these wonderful low protein foods for our kids it'll be great. For example, Ener-G foods came out with low protein cheddar and mozzarella cheese. Vincent always wanted a piece of cheese and now he can have it and he is happy about that. We make cheese sandwiches and we can now put mozzarella on his pizza.

We now have a little girl 9 months old named Marisa, she was tested and she does not have PA. Vincent adores her.

My husband and I are truly blessed with 2 beautiful children. Our family is wonderful and very supportive and is always there for us. We thank them for that. I never before had a motto in life but I now say "You have to take each day one at a time and never look into the future because you can really make yourself crazy by thinking too much". Thanks for listening. God Bless our children!

Sincerely,

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# Megan Ladwig

## *Glutaric Acidemia, Type 2, Age 21 months*



Our first child was born September 2, 1997. We named her Megan and were delighted to have a little girl. The only problem we had initially was that Megan was a poor eater. We were told all newborns have some trouble figuring out how to feed, but she would be fine. And, we were sent home with a healthy baby girl, as far as anyone could tell.

Megan continued to have little or no appetite, could not be roused for feeding, and was extremely lethargic. We were told to just keep trying to feed her. After six weeks of maternity leave, I, sadly, had to return to work. This prospect worried me greatly knowing how difficult it was for me to get her to consume even small amounts of milk. I took Megan to a new doctor at this time to get a different opinion. She was seen by an occupational therapist to evaluate her feeding skill. The therapist said Megan looked like she was doing fine, although displaying a weaker than normal suck. Megan was examined by a third doctor who agreed to authorize a barium swallow test to be done. Result: No abnormality seen.

Megan's feeding skill had even further deteriorated and she was not hitting other developmental milestones. She choked every time a bottle was put to her mouth, her lungs and throat were consumed by mucus, and she would turn blue due to lack of oxygen. We brought Megan to the ER, where the doctor looked at her, listened briefly to our concerns, and simply sent us home with no testing and no help. Again, there was no follow-up done by Megan's doctor to determine what was wrong with her, so I took her to a fifth doctor. His diagnosis was a sinus infection. Her problems only got worse and I resigned from my job.

I was appalled that these doctors collectively made light of my concerns when there was truly something wrong with my baby. I suggested she be seen by an Ear, Nose, and Throat specialist, but the pediatrician did not think that was necessary. I, however, made it happen. This was the sixth doctor that had an opportunity to examine Megan. He decided to perform a bronchoscopy, but thought it could wait until after the Christmas holiday. He was wrong.

On Christmas Eve 1997, we drove four hours in the middle of the night to get Megan to The Children's Hospital of Minneapolis emergency room. We were not sure she would make it. She was so weak. She could not consume any milk. She could not breath through the mucus, although I suctioned her constantly. She was pale and completely lifeless. At the ER, we were made to wait endlessly. When the doctor did arrive, he deep suctioned what he described as huge amounts of mucus from her throat and lungs. I desperately tried to convey to him how urgent it was Megan receive help. He didn't agree. His advice was to take her home and continue trying to feed her. We objected and asked that she be hospitalized. He said the hospital would be the worst place for her since there were several kids with RSV (very contagious) as patients. We even asked that he call Megan's pediatrician in the hope that we would get some action. The pediatrician said he trusted the ER doctor's recommendation that we go home. We were devastated and too naive to fight against the doctors, so, we took our sickly infant home. We returned to the hospital the next day and Megan had the bronchoscopy done. The result: No abnormal structures.

The first turning point came that night, while Megan was in recovery from the procedure. A nurse, Andi, observed my husband trying to bottle feed Megan. Andi saw Megan choke and gasp for air immediately. She told us Megan was drowning in the milk and made the call to finally have her admitted to the hospital. Andi was exactly right. Megan's muscles did not work properly to direct the milk to her stomach. The milk was going directly into her lungs, and the doctors missed this! She had pneumonia on top of the underlying condition yet to be determined. An NG was placed while several swallow studies and many invasive tests were done to determine the cause of her muscle problem. A test for organic acids was never done.

She was released after two weeks with a GT, a heart/apnea monitor, and a suction machine. No further follow-up was done on the part of the doctors. We were told that hopefully Megan would "grow out of" her eating disorder.

We tried to go on with our lives as best we could. Megan started therapy, as it had become quite obvious she was not developing. At four months she could not even lift her head. Megan had no muscle tone, no reflexes. She made no sounds and had almost no facial expression for months. Megan made little progress in occupational therapy. I pushed her pediatrician to get me a different infant formula, since both the milk and soy formulas caused Megan to throw up. Nutramigen is a formula that has the protein in it already broke down. This formula worked much better for Megan. By nine months, she was able to have tastes of baby food.

When Megan was a year old, we moved to Wisconsin and found a new pediatrician. Dr. Prieto agreed with me that Megan's delays and problems had been caused by something and we had to know the cause! Megan was seen by the Neurology physicians at Children's Hospital of Milwaukee, where urine and blood tests were ordered. We received word on February 1, 1999 that Megan had a disease called Glutaric Acidemia Type II. Megan was 17 months old. At long last, we knew what was wrong. We had a lot to learn about this disease. However, literature was hard to come by. It is amazing how once we finally had an answer, the pieces of the puzzle came together and her problems over that past year and a half made sense.

Within two weeks of being on a diet that restricts fat and protein, Megan could crawl for the first time! Within a month, she was babbling, showing some muscle tone, and able to move her body with more ease. It has now been just two months since her diagnosis, and Megan can transition from sitting to crawling or laying, and back again. She can pull up as far as her knees, and walks with speed and stability. She is also saying some words. Megan now has a big, beautiful smile that we are blessed with seeing every day.

I am still bitter about the incompetence we experienced from the numerous doctors that examined Megan. But, I know the most important thing is that we still have Megan with us despite the undue suffering she went through.

Megan is the greatest joy in our lives and we are so thankful to have her.

**Stacy and Michael Ladwig**  
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# Elizabeth Kell

## *Isovaleric Acidemia, Age 17*



Last night I arrived home after a 16-hour drive, returning from BYU (in Utah) to our home in the San Francisco Bay Area. I was attending Sariah's college commencement, which was in April, although she actually graduated in December (when she was 19 years old). Sariah was not the only Kell to finish a degree in December. Elizabeth completed the requirements for an AA in Liberal Studies just before Christmas, when she was still 16. She will receive the degree this May, a day before her high school diploma. She has been accepted to University of California campuses at Davis, San Diego, and Berkeley, as well as BYU (which was really her 1<sup>st</sup> choice).

As you may know, Elizabeth has a restricted protein diet. She eats about 20 gm protein from normal food, and the rest comes from her formula, I-Valex 2. On her last diet record, that translated to only about 1000 kcal/day from food. I was trying to get a reduced price on the dorm meals at the various universities for her, since the UC system charges \$7,500 for 3 quarters, and BYU charges \$4,500 for 2 semesters. Unfortunately, we got an unexpected result from UC.

After talking to the food services nutritionist at UCSD, we were hopeful that they would work with us. She had worked with an inborn error of metabolism child during her training, and UCSD has a medical school, which would mean that the people there might be familiar with the organic acidemias. The next week, the bureaucratic secretary called back. She said that the dorms and meal plans were set up exactly opposite to what Beth needed. Apartments were impossible because of Beth's young age, but maybe the disability office could force the University to do something. Any changes would have to be done after Beth registered with the disability office and they would have to do them, not us.

She kept saying Beth had an eating disorder (which as you all know is not the problem, and is not what I said in my letter). She mentioned that a co-worker's child had gone to BYU, and that it was a good school. Basically, despite the good conversation I had with the nutritionist the week before, the impression I received was that UCSD did not want Beth as a student: that they didn't want to deal with her diet.

What a difference from the conversations I had with the directors of housing and dining services at BYU. They agreed to allow Beth to live in the dorms where she wanted. BYU would special order anything she needed to eat, and "sell" it to her at their cost, credited to her meal plan "dining dollars" account. She will have an appointment with one of the 3 dining services nutritionists when she arrives, who will have nutritional analyses for all the cafeteria dishes served. In reality, the meal plans are similar: the difference was that they were willing to work with us. They even agreed to reevaluate the amount she actually "spends" on food, and did not rule out a possible refund after a few months, to be fair to both us and the university.

Plus, having big sister on staff at the university during Beth's first year will be a plus, and will help with any unforeseen problems.

My father reminded me that this is not the first time my concern for warning people about Beth's diet has backfired. When she was 8 years old, he had bought tickets for a Caribbean cruise, which were cancelled when I sent the cruise line a copy of her medical protocol letter. I no longer send the letter, although she carries a copy of it on trips, just in case. She has not been hospitalized since starting formula at age 8, and gets by on normal foods. Still, Isovaleric Acidemia is a condition not heard of, and thus not understood by, most people.

On the social front, Beth has served this year as president of her church youth group, is substitute teaching this week for her 6 am religion class, was high school yearbook editor, and student representative to the West Contra Costa District school board. She has taken weight training , bowling, swing dance, and even tried indoor rock climbing. She was in a play at the college, doing a group dance and singing a solo. She has also found that second semester college physics (electricity & magnetism) required more work than most of her college classes. She even has a boy-friend, and talks on the phone with him for hours every night.

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# Cardiomyopathy and Organic Acidemias

*by Arnold W. Strauss, M.D.*

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## What is cardiomyopathy:

Cardiomyopathy is a disease of the heart muscle, in which the heart loses its ability to pump blood and, in some instances, heart rhythm is disturbed, leading to irregular heartbeats, or arrhythmias. There may be multiple causes of cardiomyopathy, including viral infections. Sometimes, the exact cause of the muscle disease is never found.

Inherited disorders of enzymes and protein essential for metabolism have many different manifestations, i.e. phenotypes. Disorders causing accumulation of organic acids in the blood include defects in the mitochondrial fatty acid oxidation (FAO pathway, see [www.cinternet.net/FOD](http://www.cinternet.net/FOD)). Breakdown of fatty acids is essential for energy generation in the heart and other tissues with high energy requirements and oxygen consumption, such as kidney and skeletal muscle. In addition, metabolism of fatty acids in the liver is critical for the generation of ketone bodies, short chain fatty acids such as butyrate and acetoacetate, that are essential sources of energy for the brain.

Therefore, it is not surprising that FAO defects cause liver, heart, and muscle dysfunction. Heart muscle dysfunction, or cardiomyopathy, is rare in infants and children, but is usually serious and often leads to death. Cardiomyopathy may be of the hypertrophic (thick muscle) or dilated (enlarged heart with poor function) types. Cardiomyopathy undoubtedly has many different causes, but it has recently been recognized that metabolic and other genetic disorders may account for up to 50% of cases. Thus, careful analysis for metabolic disorders by study of acyl-carnitines (fatty acids bound to the amino acid, L-carnitine) and organic acids by tandem mass spectrometry is an essential part of the evaluation of children with cardiomyopathy.

Conversely, it is clear that many inherited metabolic disorders, including organic acidemias, may be complicated by heart muscle dysfunction, cardiomyopathy. A partial list of known associations includes:

1. Abnormalities of amino acid metabolism:

Propionic Acidemia.

2. Disorders of sugar metabolism and storage diseases:

glycogen storage diseases (Pompe's disease-type II, debranching-Type III, and branching-Type IV, phosphorylase kinase B-type IX), pyruvate dehydrogenase deficiency (Leigh's disease), mucopolysaccharidoses (all types, although usually these have valve disease, not muscle dysfunction), Refsum's disease, and mucopolysaccharidoses (GM1 and GM2 gangliosidoses).

3. Mitochondrial fatty acid oxidation disorders:

very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, long chain 3-hydroxy-acyl-CoA dehydrogenase deficiency (LCHAD), trifunctional protein deficiency, carnitine acyl-carnitine translocase (CAT) deficiency, carnitine palmitoyl-transferase deficiency, carnitine uptake or transporter (OCTN2) deficiency.

4. Mitochondrial energy production (oxidative phosphorylation) disorders:

MELAS syndrome; Kearns-Sayre syndrome; MERRF syndrome; Barth's syndrome (3-methylglutaconic aciduria).

It is important to note that not all patients with these examination of the heart by high frequency ultrasound, allows precise measurements of heart structure, size, and function. Because echo is non-invasive, it can easily be repeated frequently. Cardiomyopathy may develop long after other manifestations of metabolic disorders, and so heart dysfunction should be looked for during follow-up visits to genetics or metabolic clinics. When cardiomyopathy develops, many different treatment options are available, depending upon the type of heart muscle dysfunction and its severity. As a last resort, heart transplantation can be considered in such patients.