

SCID Bone Marrow Transplant: A Follow-Up After 47 Years

Maurice, held by his mother Carol, is surrounded by his four siblings, Stacie, Erin, Tamara and Michael. Tamara, nicknamed Tami, donated her bone marrow to save his life.



In 1970, shortly after my arrival at the University of California, Los Angeles (UCLA), 5-month-old Maurice Elias was referred to me with pneumonia and a mouthful of oral thrush. Little did I know this was the start of a 48-year odyssey.

By E. Richard Stiehm, MD

IN 1970, Maurice Elias was the fifth child born to a healthy mother and father; however, two maternal uncles had died in infancy. Maurice was normal at birth, and he had received his 2-month-old vaccinations without a problem. But, at 3 months old, he developed a respiratory infection and oral thrush. He was admitted to a local hospital and given ampicillin for pneumonia and nystatin for the thrush. After remaining unwell with respiratory symptoms, he was referred to UCLA at 5 months old at which time he had gained no weight and the thrush had returned. A chest X-ray disclosed bilateral pneumonia and no thymic shadow. His blood count was normal, but he had very low levels of all three immunoglobulins. His lymphocytes, although normal in number, did not proliferate when stimulated with the potent mitogen phytohemagglutinin (PHA). A needle biopsy of his lungs disclosed *Pneumocystis jiroveci*, formerly *Pneumocystis carinii* or

PCP, a rare fungal infection that only affects patients with poor immunity. He was started on Pentamidine for the pneumonia and Amphotericin for the oral thrush.

Maurice was diagnosed with SCID, also known as the bubble boy syndrome. Infants with SCID have no cellular or antibody immunity and, if unrecognized or untreated, they generally succumb from infection in the first year of life. The only cure for SCID is a bone marrow (stem cell) transplant, which at that time had been performed successfully only once in a SCID infant.¹

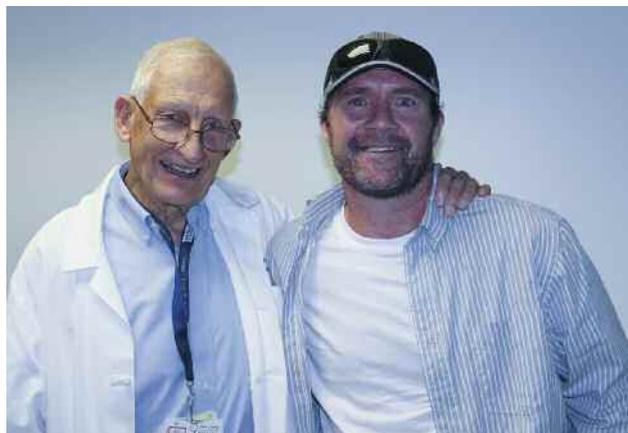
For the bone marrow transplant to be successful, Maurice would need a donor with lymphocytes that exactly matched his cells. Unlike red blood cells for which there are only four types, lymphocytes have thousands of types known as human leukocyte antigen (HLA) types. Therefore, the best chance of finding a perfect match is from a sibling with common parents.

The Need for a Bone Marrow Donor

By good fortune, UCLA had the premier tissue typing laboratory in the world, led by Paul Terasaki, MD. I spoke with Dr. Terasaki about Maurice, and he was optimistic about finding a perfect match among Maurice's four siblings. Unfortunately, repeated typing resulted in three different results, none of which matched his parents or siblings. "It's never happened before," said Dr. Terasaki. "Don't do a transplant."

Performing a mismatched transplant can cause graft-versus-host disease, which occurs when the new cells reject the patient, often resulting in death. Therefore, I delivered the sad news to Maurice's parents and sent the child home on antibiotics, antifungals and weekly immune globulin (IG) injections. Maurice remained sick, and he returned to the hospital at 9 months old with persistent vomiting. The fungal infection had extended into his esophagus, preventing him from swallowing and necessitating tube feedings.

I called Dr. Terasaki again about finding a donor, and he requested more blood. After receiving three more samples, Dr. Terasaki typed Maurice repeatedly and up to 16 different types showed up (a normal result has no more than four types, two from each parent). After comparing the typing results, he noted three types showed up repeatedly, and these were identical to his 13-year-old sister Tami. "I think Tami might be a match," Dr. Terasaki told me. We can test that by mixing their blood together to see if Tami's cells recognize Maurice's cells as foreign (a procedure known as a mixed leukocyte test). One week later, Dr. Terasaki said: "I think Tami is a perfect match. But, I can't be 100 percent sure."



Dr. E. Richard Stiehm (left) performed a bone marrow transplant on Maurice Elias at 1 year old to cure him of SCID.

Maurice's parents agreed to go forward with the bone-marrow transplant. The child's father, who was a Hollywood actor and stuntman, had kept his coworkers informed about his child's illness and proposed transplant. One coworker told a *Life* magazine reporter of the proposed transplant, who contacted the parents to see if they would agree to a story about Maurice before, during and after the procedure.

The Bone Marrow Transplant

With a *Life* photographer present, Tami was admitted to the hospital, where under general anesthesia, a hematologist used a large-bore needle at multiple sites to extract four ounces of marrow from her hip and breast bones. The cells were taken to Maurice's crib and injected into his abdominal cavity from where they would migrate to the bone marrow liver and spleen.

Two weeks passed, and overnight, the oral thrush disappeared. It was determined the new cells were working! But, then, there was a crash. Maurice's face and abdomen swelled, a generalized rash appeared, his breathing became labored and his liver and spleen enlarged. He was undergoing a graft-versus-host reaction.

Maurice was admitted to the intensive care unit for oxygen, antibiotics and corticosteroids. Two weeks later, he gradually improved and his body was producing immunoglobulins. A test of his lymphocytes showed them to be XX, identical to those of his donor sister. The rash and swelling disappeared, and his chest X-ray normalized.

Three months later, Maurice was discharged apparently cured.² *Life* magazine photographed every step of the transplant from admission to discharge, which appeared in the May 28, 1971, issue titled "Gift of Life From a Big Sister."

Reappearance After Three Decades

I followed Maurice through high school, and he did well, even joining the school's wrestling team. Thereafter, I lost track of him, even after hiring a student to search for him.

Last summer, at age 48, Maurice reappeared in the office of Manish Butte, MD, an immunologist and colleague of mine, to investigate why he had rejected two corneal transplants. After his hospital discharge in 1971, Maurice had been living a normal life and working as a plumber. He didn't require IG treatment or continuous antibiotics. But, he had persistent eye problems, one pneumonia, several sinus infections, poor dentition and recurrent warts. An examination showed he was normal except for the warts on his hands and toes.

Advanced immunologic studies not available in the 1970s were



Maurice Elias and members of the Elias family are reunited with Dr. E. Richard Stiehm, center, and other University of California, Los Angeles, doctors.

performed. A TREC (T cell receptor excision circles) test was negative, indicating his thymus was not producing T cells. Genetic analysis showed he had a mutation of the interleukin-2 receptor gamma chain on his X chromosome, indicating he had X-linked SCID. This is the most common form of SCID that occurs only in boys of an unaffected carrier mother. This explained the early deaths of his two maternal uncles.

The test also showed he had normal immunoglobulins and near normal T and B cells, but his natural killer cells (CD16/56) were very low. His T cells (CD3) were all from the donor, and these were functioning well, responding to PHA (a potent stimulus) and some vaccine antigens. His B cells (CD19) were those of the patient, but they were now making immunoglobulins and antibodies with the help of the donor T cells. His natural killer cells (CD16/56) were those of the patient, and they had very poor activity, probably explaining his predisposition to warts.

One interesting aspect was why his own abnormal B cells could make some antibodies. This is not uncommon when the transplant includes unfractionated marrow without pretransplant conditioning.³ We showed his B cells could respond normally to cytokines produced by normal T cells.⁴

When Maurice returned for his next visit, he was accompanied by his mother and sister Tami, the donor for his transplant 47 years ago. Since Maurice still has some immune problems, one consideration was to give him a booster transplant from his sister using a new monoclonal antibody against stem cells that will make room for the sister's cells, which may augment his less-than-perfect immune system.

Evolution of Immunodeficiency Transplants

If Maurice were born today, a SCID diagnosis would be made at birth from a heel-stick blood test, which is performed on every U.S. newborn. The TREC test would indicate he was not making T cells, and he would be referred to a center for confirmation of the SCID diagnosis and treatment by bone marrow or other stem cell source. But, in 1970, unlike today, we could not identify the genetic defect, delineate the various types of lymphocytes, assess natural killer cell function or filter the bone marrow cells for intravenous infusion.

With today's technology, if Maurice did not have a matched sibling, other donors could be used, including those from an unrelated HLA-identical adult from an international registry or from a cord blood bank of typed and stored umbilical cord blood cells. Another option would be gene therapy for this form of SCID and a few other immunodeficiencies.

Worldwide today, there have been more than 2,000 stem cell transplants and more than 200 gene therapies for patients with primary immunodeficiency. ■

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