Doomed to Die

Jewish families are still at risk from Tay-Sachs and other genetic diseases.

BY EVE GLICKSMAN

Couples say they had no idea they were at risk. Where were the doctors to warn them? Why were they given wrong information?

Meredith and Jim Margolis, both psychologists, were going the extra mile planning for their first child. Jim had a mentally retarded brother, so they wanted genetic testing for Down syndrome. But what about Tay-Sachs, a disease that can run in Jewish families? Jim was Jewish by birth, but Meredith explained to her obstetrician that she had converted. "Then don't worry about it," the physician reassured them. "Both parents have to carry the Tay-Sachs gene for a baby to get it."

Ten years later, as the Margolises replay the happy home movie of Mollie's birth, they still search for signs. There are no clues, though, that this beautiful, robust baby would never roll over or crawl in a sandbox. No indications of the severe seizures she would suffer or the stomach feeding tube she would need.

Mollie, it turned out, had infantile Tay-Sachs disease and died at age 4. The Margolises, of Allentown, Pa., were victims of the widespread ignorance that still exists about Tay-Sachs, a fatal neurological disorder. If their obstetrician in New York City was so misinformed in 1986, it can happen anywhere, anytime.

For the record, you don't have to be born Jewish to carry the Tay-Sachs gene. While Jews of Eastern European descent are far more likely to inherit it than non-Jews (1 in 27 versus 1 in 250), no ethnic group is immune. In fact, the Cajuns of southwestern Louisiana and the French Canadians along the St. Lawrence River also have a significantly elevated risk of Tay-Sachs.

Inbreeding of Jews in Eastern Europe over generations explains the disease's Jewish bloodline. As for the predominantly Catholic Cajuns, geneticist Emmanuel Shapira, of Tulane University, studied the identical Tay-Sachs mutation in the small, clannish town of Iota, La., where the carrier rate is twice as high as that among Jews. He speculates that some of the town's German settlers in the early 1700s were Ashkenazim. Another theory is that Spaniards hiding their Jewish heritage during the Inquisition may have brought over the disease.

Meredith Margolis, with Mollie, who died from Tay-Sachs.

If you are an Ashkenazi Jew (your family originated in Eastern Poland, Lithuania or western Russia), there is a 1 in 7 chance that you carry a gene for the diseases of Tay-Sachs, Canavan, Gaucher, Niemann-Pick or cystic fibrosis, according to Dr. Jerzy Tomczak, director of the Tay-Sachs Prevention Program at Thomas Jefferson University.

If you and your mate both carry the gene for the same recessive disorder, there is a 1 in 4 chance with each pregnancy of producing a boy or girl with that disease. The odds are 50 percent that the baby will be healthy but carry the gene. Chances are 1 in 4 that the child will neither have the disease nor carry the gene. If only one parent is

a carrier, there is no risk of transmitting the disorder, but there is a 50 percent chance that the child will be a carrier.

The allied diseases of Tay-Sachs, Canavan, Gaucher and Niemann-Pick are all lysosomal storage disorders, characterized by an inability to break down and dispose of waste products in the cells. Tay-Sachs, Canavan and Niemann-Pick are degenerative and always terminal; Gaucher can be mild or severe, but is often manageable with proper treatment. Cystic fibrosis, a disease that alters the permeability of cells, leading to increased mucus build-up in the lungs and other organs, used to kill children before adulthood, but treatment advances have considerably prolonged life expectancy.

Tay-Sachs is caused by the absence of the enzyme hexosaminidase A, which breaks down a fatty substance in nerve cells. The ruthless disease process begins in pregnancy, although symptoms are not apparent until several months after birth. By age 2, most Tay-Sachs children have regressed to a floppy, vegetative state. They lose motor abilities until they are eventually paralyzed, blind, deaf and mentally retarded. Even with the best of care, death by age 5 is inevitable. (There is an adult-onset form of Tay-Sachs, but it is extremely rare.)

The disease is named after Warren Tay, a British ophthalmologist who described a case in 1881, and Bernard Sachs, a New York neurologist who recognized the hereditary, Eastern European Jewish connection a few years later. The link to ophthalmology is that all Tay-Sachs children have unusual cherry-red spots on their retinas. The Margolises, in fact, had no idea Mollie had Tay-Sachs until an ophthalmologist noticed the spots during an eye exam.

Canavan disease, sometimes described as "spongy degeneration of the brain," is caused by a deficiency of the enzyme aspartoacylase. Without this enzyme, the white matter of the brain (myelin) that insulates the nerve cells is destroyed. As with Tay-Sachs, the infant appears healthy at birth but doesn't develop normally. The baby becomes unable to hold up its head and has difficulty sitting, feeding and seeing. The head becomes enlarged, and profound retardation follows. Canavan children usually die by age 10. One in 35-40 Ashkenazi Jews is believed to carry the gene.

Never heard of Canavan disease? Neither had Karen and Mike Ossip, of Wynnewood, who were relieved when they tested negative for Tay-Sachs and shocked when their daughter was diagnosed with Canavan in 1988. Named after Myrtelle Canavan, who first described its symptoms in 1931, it belongs to the family of diseases called leukodystrophies, which affect the white matter of the brain. The best known of these—adrenoleukodystrophy—was the subject of the film "Lorenzo's Oil."

Because Canavan is relatively unknown even by doctors, researchers suspect that far more children have died from it than has been reported. An estimated 85 percent of Canavan cases are among Ashkenazi Jews. Saudi Arabians, Norwegians and Spanish Gypsies make up the rest of the afflicted group, according to Dr. Reuben Matalon, of the University of Texas Medical School in Galveston, who discovered the enzyme deficiency that causes Canavan in 1988, and the responsible gene in 1993.

A simple, highly reliable blood test

introduced in 1971 can tell you if you carry the Tay-Sachs gene; carriers have less hexosaminidase A enzyme in their blood than noncarriers. Matalon's research paved the way for the more complicated DNA blood testing required to detect the Jewish Canavan mutations, a test introduced at Thomas Jefferson University Hospital in 1995.

Gaucher is the most common Jewish genetic disease. It can be harder to recognize because symptoms vary tremendously. In children, stunted growth, frequent nosebleeds, excessive bruising and a swollen stomach (indicating an enlarged spleen) are all signs. One in 10 Ashkenazi Jews is a carrier; 1 in 400 to 500 has some form of the disease, from asymptomatic to severe. DNA testing for Gaucher has just been added to the prenatal tests available through the Tay-Sachs Prevention Program at Jefferson. The testing is controversial, however, because the decision to abort for this treatable, less devastating disease is not clear-cut.

Likewise, babies found to have cystic fibrosis (1 in 30 Ashkenazim is a carrier) can live into their 40s—long enough for a cure to be found. Carrier testing is available for Niemann-Pick disease, which is similar to Tay-Sachs; but since it is so rare (1 in 100 Ashkenazi Jews carries the gene, testing is generally reserved for families with a known history of the disease.

Children's Hospital of Philadelphia (CHOP) is one of only a handful of centers in North America providing complete treatment for children and adults with Gaucher. Because of the prickly ethics involved in aborting for Gaucher, CHOP has chosen not to offer prenatal testing.

"What do you do with the information?" asks Dr. Paige Kaplan, a pediatrician-geneticist and director of CHOP's Comprehensive Gaucher Treatment Center. "Half of the people with Gaucher will never have symptoms or show signs until they're very old. The other half will have mild to severe problems, mainly in their spleen, bones or liver." While Dr. Kaplan describes the standard treatment for Gaucher as "burdensome and expensive," she says that getting intravenous insulin injections every two weeks assures a decent quality of life. Surgery may be recommended as well.

While Jefferson's Tomczak believes that all couples with one Ashkenazi Jewish spouse should be tested for Tay-Sachs and Canavan, he would agree that Gaucher testing is optional. The test can determine which mutation is present and make general predictions about severity of the adult onset form of Gaucher. Adult onset Gaucher is not fatal if treated.

Because of the tremendous success of promoting Tay-Sachs screening among Jews, its incidence is actually three to four times higher today among gentiles. Last year, in the outlying Philadelphia area, one child with Tay-Sachs died in York, Pa., and another baby was born with the disease in Northeast Philadelphia—neither of Jewish descent. Nationwide, less than 20 babies a year are born with Tay-Sachs—more than two-thirds fewer than in the years before genetic screening was available. Until Canavan screening becomes as common, Jewish children will continue to die from that disease, as did an Overbrook child in 1995.

The reality is that Tay-Sachs and Canavan will always exist because the gene doesn't disappear from families. Tomczak is particularly worried about Russian Jews, who rarely seek screening. "We published brochures about Tay-Sachs in Russian and organized educational meetings in Northeast Philadelphia, but no one responded," says Tomczak. Perhaps it's a fear of being stigmatized or punished in some way if they are found to be carriers, he speculates. Many Russian Jews learned to survive, after all, by not acknowledging their religion.

While the odds of having a Tay-Sachs or Canavan baby are low, the disorders are terrible enough that not getting tested is unconscionable to those who have experienced the horror of a child's agonizing death firsthand. "Who cares about the numbers?" says Meredith Margolis, "Just one child is too many. I think about Mollie every single day. Her birthday and yahrzeit are especially difficult."

"Doomed from the moment of conception" is how Sedra Schiffman puts it. Schiffman did not have the option of Tay-Sachs screening when her daughter, Caron, was born with the disease in 1967. "The doctor told me to find a nursing facility for Caron as far away from home as possible. I asked when he wanted to see her again, and he said, 'What for?'"

At the time, Schiffman knew no one to turn to for support or advice. No family should have to suffer that anguish alone, she says. In 1969, after attending meetings of the National Tay-Sachs and Allied Diseases Association in New York, the young mother turned her sor-

row into usefulness. "I had time, energy and a whole lot of guilt," she explains. Schiffman gathered a group of women in her Willow Grove living room to launch the Delaware Valley Chapter of the National Tay-Sachs & Allied Diseases Association (NTSAD-DV).

Just finding out you carry the gene for Tay-Sachs or Canavan is devastating, notes Vivian Weinblatt, senior genetic counselor at Thomas Jefferson Medical College. Weinblatt must often explain to people who test positive that carrying the gene will not affect their life expectancy or health. But if both prospective parents carry the gene, there is often guilt because they can transmit the disease.

As a genetic counselor for the Tay-Sachs Prevention Program at Jefferson, Weinblatt sees approximately 25 expectant couples a year, where both partners are carriers. If the fetus is found to be affected, it is rare for parents not to terminate the pregnancy, although "everyone revisits the decision after it happens," says Weinblatt.

When the news is bad, she continues, "Many couples have a hard time telling their extended families. This is threatening news with implications for the entire family." Couples who decide to abort may also isolate themselves, fearing opposition from their relatives.

The trauma is that much worse when children are unexpectedly born with these diseases. The correct diagnosis may be long in coming. The Margolises were told by their physician that Mollie was big and that was why she was developing more slowly than her peers.

The Schiffmans' anxieties were not taken seriously until Caron's seizures began. Once diagnosed with Tay-Sachs at the age of 1, she deteriorated rapidly. Sedra spent two to three hours each meal trying to feed Caron, who had difficulty swallowing. In a short time, Caron became blind and lost nearly all responsiveness to her environment; she was even unable to recognize her parents.

The baby's medical demands left the Schiffmans little time and energy for their healthy 4-year-old. The grief-stricken couple placed their 19-month-old daughter in Kingsbrook Jewish Medical Center in New York, which had the only Tay-Sachs unit in the world. "It was a difficult thing for me to do. I felt like I was abandoning my baby," says Schiffman, still struggling with guilt 27 years later. But in 1969, most Tay-Sachs children were hospitalized or placed in nursing homes because home health care was virtually non-existent then.

By the time Mollie Margolis was diagnosed in 1988, doctors had a more enlightened view of home care. The Margolises cared for Mollie at home, although it meant daily battles with their health insurance company. After Mollie's seizures made using baby-sitters impossible, they hired an eight-hour nurse. By the time Mollie was 3 years old, 24-hour care was necessary.

"Someone was always working on Mollie," says Meredith Margolis, who seems to have made peace with the nightmare. Mollie needed suctioning to remove mucus and phlegm, as well as constant turning to prevent bedsores. Unlike Caron, Mollie remained responsive to people. The family made sure someone was always there to read to her, sing to her or hold her. Still, there was not much quality to the last year of her life, her mother concedes.

The Parent Peer Group Network, funded by the National Tay-Sachs and Allied Diseases Association (NTSAD), was the Margolises' lifeline during those excruciating years. NTSAD established the Parent Peer Group to ensure that Tay-Sachs and Canavan families have free access to parents around the world who have been touched by the diseases. Today, Meredith Margolis is the president of NTSAD. "Staying involved helps me keep Mollie's memory alive in a positive way."

Attorney Mike Ossip, president of NTSAD-DV since 1993, became an activist, too, after his daughter, Alison, was diagnosed. Mike's wife, Karen, suspected something was wrong with the baby early on, but a neurologist told her that everything was fine. By the time Alison was six months old, specialists weren't as reassuring. Alison was unable to sit up or hold up her head. "Just make her as comfortable as possible," the doctors said when the grim diagnosis was finally made after her first birthday.

Alison Ossip died at age 4, weighing 20 pounds. Brian, her brother, was 6 then. This year, he will be donating a portion of his Bar Mitzvah gifts to NTSAD-DV. His parents also have been major contributors to Canavan research and education efforts.

Prevention, the Only Medicine

At a time when medical miracles are almost commonplace, there is little optimism about a cure for Tay-Sachs or Canavan anytime soon. Enzyme and gene replacements are possible in theo-

ry, but scientists have a long way to go, says Jefferson's Tomczak. Physical therapy, nursing care and medication have enabled some Canavan children to live into their early teens, but these extra years can make the inevitable death more heartbreaking, Tomczak notes.

One recent development is the ability to detect Tay-Sachs in newly fertilized eggs. Scientists at the Jones Institute at Eastern Virginia Medical School in Norfolk performed a biopsy on four preembryos after a carrier couple's sperm and egg were mixed in a test tube; one was found to have Tay-Sachs. Doctors then implanted the three disease-free fertilized eggs in the mother, who had previously lost a daughter to Tay-Sachs. She delivered a healthy child in 1994. Tomczak warns patients, however, that this is a complicated, impractical procedure that is still very experimental and is likely to cost over $10,000.

With no cure on the horizon, carrier screening and genetic counseling are the only weapons against these diseases. It may not seem like good news to find out you are both carriers, but it's much better than giving birth to an affected baby, says Tomczak, who knows first-hand the distraught reactions of young couples upon learning they are both Tay-Sachs carriers.

Knowing their risk in advance, carrier couples are able to plan a strategy of prevention. Once pregnant, a woman can have early prenatal testing. A chorionic villus sampling (CVS) can be done at 10 weeks, or amniocentesis can be performed at 16 weeks to detect whether an unborn child has Tay-Sachs or Canavan. In this way, if the fetus is found to be affected, the couple can choose to terminate the pregnancy. Monitoring each pregnancy enables high-risk couples to give birth selectively to healthy babies. At Jefferson, results of the Tay-Sachs test are available within an hour following a CVS, and a day after an amniocentesis. For Canavan, several days are required for both tests.

Thanks to today's prenatal tests, most families, like the Margolises, courageously get on with family planning. "Our experience was more of a tragedy because it was so easily preventable," Meredith Margolis reflects. Not long after Mollie was diagnosed, Meredith became pregnant again, underwent a CVS, which showed no evidence of the disease, and had a healthy son, now 7. She went on to have a daughter, now 6, and another son, now 3. She and Jim aborted one other pregnancy at 10 weeks after discovering the fetus had Tay-Sachs.

The Schiffmans, who didn't have the benefit of prenatal testing in 1970, adopted a daughter. In the early '90s, before Canavan testing was perfected, the Ossips decided not to risk having another child. Other families solve the dilemma with artificial insemination of sperm from a confirmed noncarrier.

Religious Practices

Both Reform and Conservative Judaism support therapeutic abortion of fetuses with Tay-Sachs or Canavan. For Orthodox Jews or Catholics who do not, however, prenatal testing is not a solution, nor is artificial insemination, which is also frowned upon.

In the Dor Yeshurim program of Hasidic Jews in Israel and the United States, Tay-Sachs testing is given to young adults whose marriages are arranged and must be approved by the rabbi. Results of the test are made available only to the rabbi. This way, the rabbi can take genetic information into account when considering a union and no one is stigmatized. While it is not openly sanctioned, some Orthodox rabbis interpret Jewish law as allowing abortion if performed by the 40th day.

The important thing is knowing. Lisa Leibowitz, executive director of NTSAD-DV, says the office fields calls all the time from people asking why their doctor never told them about Tay-Sachs testing, or specifically told them it wasn't necessary because only one spouse was Jewish.

"Obstetricians generally take care of healthy people and it is not their specialty to know about genetic risks," Jefferson's genetic counselor Weinblatt explains. "And if you've never seen a couple at risk, you're less inclined to worry a family over something so rare. Canavan affects about 1 in 6,000 Jewish pregnancies. Not many obstetricians see 6,000 Jewish couples in their practice."

Joye Lesser, a spokesperson for NTSAD-DV, says that public misconceptions abound, too: "People think that the marriage license blood test includes Tay-Sachs testing, that a Tay-Sachs test is part of routine health care, that Tay-Sachs is an old disease that has faded away, that there is a cure for Tay-Sachs." Wrong, wrong and wrong again. And did you know that routine amniocentesis and CVS do not rule out Tay-Sachs or Canavan unless testing for them is specifically requested ?

Since 1991, the American College of Obstetricians and Gynecologists has rec-

ommended Tay-Sachs testing not only for Jewish couples, but also for couples with only one partner of Jewish descent. There is no recommendation at all about Canavan testing. Educating doctors and health insurers about Canavan will take longer, says Weinblatt.

Despite increased awareness about Tay-Sachs, there are still gaps. A 1993 study in the *Journal of the American College of Obstetrics and Gynecology* revealed that 35 percent of Jewish couples had not obtained screening by the seventeenth week of pregnancy. The conclusion was that many health-care providers still don't discuss Tay-Sachs risks during pre-conception or prenatal visits."

"Tay-Sachs was always a part of my life," says Mindy Levin Feldstein, a member of the NTSAD-DV board who, as a child, was present at the first Philadelphia Tay-Sachs screening, in 1972. Her grandparents, Morris and Nettie Levin, were among the founding members of the first organized Tay-Sachs effort in the United States, after losing a son—her father's brother—to Tay-Sachs in the 1950s.

Feldstein tells of making toys which were sold to relatives on the High Holidays to raise money for Tay-Sachs research. As children, she and her cousins also appeared in a television spot about Tay-Sachs with Joan Rivers. "It was a hot issue then, but now people feel they can ignore it," says Feldstein, a wife, mother and attorney in Ambler.

If people are ignorant about Tay-Sachs, they know even less about Canavan. While most insurers cover Tay-Sachs screening, most do not cover Canavan testing because it is so new, or they pay only some portion of the $125 cost of the very labor-intensive DNA test. The much simpler blood serum test to detect Tay-Sachs costs $75 at Jefferson.

There is grave concern at NTSAD-DV that today's young couples are not informed about Tay-Sachs and Canavan. Further, increasing rates of intermarriage are producing more children with less awareness of their genetic risks. "Part of the problem is our own success," comments Ossip. "The incidence of Tay-Sachs disease in the Jewish population is way down, so people think it is not a problem anymore. Every generation produces the same number of carriers, though, so testing must be ongoing. Otherwise, we're ticking time bombs."

Schiffman, now on the national Tay-Sachs Association board, addressed 100 Jewish Federation leaders five years ago about Tay-Sachs. "Haven't we really solved this problem?" she was asked after the presentation. Yet, when Schiffman requested a show of hands of those who had been tested, only half went up.

"There are too many things in this world you can do nothing about, but a few things are simple. During pregnancy, you shouldn't drink, you shouldn't smoke and you should get genetic tests," Schiffman asserts. "It's a piece of information everyone should have, like their blood type." Further, the advice for women is to get screened before pregnancy because testing during pregnancy is much more complex and less conclusive.

"Just because you don't hear about new cases doesn't mean you can rest now," Tomczak says. While he was performing screenings at a Cherry Hill synagogue last year, a group of teenage girls attending religious classes stopped by and asked him what was going on. "They had never heard of Tay-Sachs," he exclaims, shocked and upset anew as he relates this.

"We're not through with this," he warns. ■

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RESOURCES:

National Tay-Sachs & Allied Diseases Association of Delaware Valley
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Tay-Sachs Prevention Program
Thomas Jefferson University
1100 Walnut St., 4th fl., Phila., PA 19107. (215-955-8328)

Comprehensive Gaucher Treatment Center
Children's Hospital of Philadelphia
34th St. and Civic Center Blvd., Phila., PA 19104. (215-590-3376)

United Leukodystrophy Foundation (for Canavan Disease)
2304 Highland Drive, Sycamore, IL 60178. (800-728-5483)