

Tay-Sachs Disease

Making a Difference Today

Tay-Sachs disease is an inherited disorder that progressively destroys the brain and central nervous system. Sadly, the most common form of the disease affects babies. Infants with Tay-Sachs appear to develop normally until a few months after birth, when they gradually cease to smile, crawl, roll over, or reach out. Eventually, they become blind, deaf, and paralyzed. Few survive past the age of five. Two rare forms of the disease affect older children and adults; the course of these diseases is generally slower and symptoms are sometimes milder, although still devastating.

Tay-Sachs is caused by a genetic defect that prevents the body from producing enough of an enzyme, called beta-hexosaminidase A or hex A, needed to breakdown an excess fatty substance, or lipid, called ganglioside. Without this enzyme, harmful quantities of ganglioside accumulate in parts of the cell called lysosomes. The excess storage is particularly severe within cells of the brain. The genetic defect associated with Tay-Sachs occurs most frequently among people of Eastern European and Ashkenazi Jewish descent. One in 30 American Jews carries the gene. Other high-risk groups include non-Jewish people of French-Canadian ancestry, members of the Cajun population of Louisiana, and Irish Americans.

Along with the roughly 50 other lysosomal storage diseases, Tay-Sachs exacts an enormous emotional and economic burden on families in the United States. Although each of these diseases is rare, together they affect approximately 1 in 5,000 Americans.

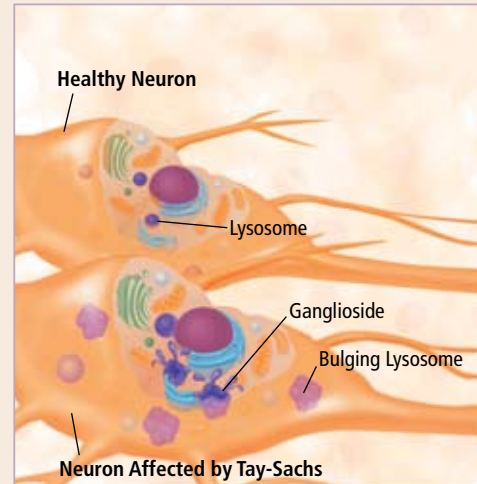
Searching for a Breakthrough

In the 1970s, an advance in genetic screening made it possible for individuals among high-risk populations to determine if they were carriers of the disease. This major development has led to a 90 percent reduction in Tay-Sachs disease among the Ashkenazi Jewish population in the United States.

However, an effective treatment for Tay-Sachs still remains elusive. With National Institutes of Health (NIH) funding, scientists are exploring a variety of therapeutic approaches. Most are aimed either at restoring the missing enzymes or at reducing the accumulation of ganglioside. All present substantial scientific hurdles.

One successful approach for patients with lysosomal diseases not involving the brain, such as Gaucher disease and Fabry disease, is intravenous enzyme replacement therapy. However, this approach doesn't benefit Tay-Sachs patients because the critical hex A enzyme is too large a molecule to cross the blood-brain barrier. Gene therapy—inserting a functional gene into brain cells to supplement the defective gene and thus restore the production of the needed enzyme—has presented similar challenges, although recent studies involving mice have produced promising results.

To decrease the toxic levels of ganglioside that accumulate in the brain cells of children with Tay-Sachs disease, scientists are investigating several therapeutic approaches, including certain chemical inhibitors to decrease ganglioside levels. One such inhibitor, miglustat, has been approved by the Food and Drug Administration for the treatment of a form of Gaucher disease. Recently, however, a two-year clinical trial of miglustat involving people with late-onset Tay-Sachs disease ended inconclusively, although promising data have emerged from the use of the same drug in a related disorder, Niemann-Pick disease type C. Although it's very unlikely that miglustat alone will help with the infantile form of Tay-Sachs, scientists continue to search for treatments that will prevent, slow or reverse the tragic outcome of Tay-Sachs disease.



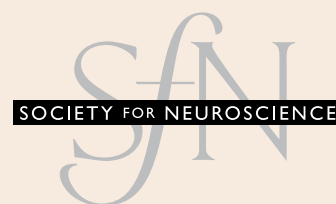
In a healthy neuron, enzymes break down cellular waste products in structures known as lysosomes. In a nerve cell affected by Tay-Sachs, a genetic defect causes one of these enzymes to become inactive, which enables a fatty waste product, or ganglioside, to accumulate and eventually destroy the cell.

Continued funding for research could lead to:

- Better diagnostic testing for carriers.
- New mechanisms for the successful delivery of lysosomal enzymes into the brain.
- Further advances in gene therapy delivery into the brain.
- Drugs targeting the accumulation of fatty waste products in cells.
- Developing novel approaches for treating Tay-Sachs and related disorders.
- Better understanding of other lysosomal storage diseases.

For more information please email brss@sfn.org.

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Tay-Sachs Disease

Making a Difference Tomorrow

Scientists have learned a great deal in recent years about Tay-Sachs disease and its effects on the brain, but they have yet to discover a cure. Tay-Sachs continues to devastate children and their families. Did you know that:

- Even under the best of care, children born with Tay-Sachs disease usually die by age 5.
- About 1 in 30 Jewish Americans and about 1 in 50 Irish Americans carries the Tay-Sachs gene. Other high-risk populations include individuals of French-Canadian ancestry and members of the Cajun population in Louisiana.
- There is no effective treatment for Tay-Sachs disease.

Federally funded basic research is helping scientists better understand the neurobiological complexities of Tay-Sachs and other lysosomal storage diseases. Continued funding will enable scientists to translate this knowledge into therapeutic breakthroughs.

Research Brings Hope for the Future

During the past two decades, National Institutes of Health funding for basic research has enabled scientists to clone the genes responsible for Tay-Sachs disease and to identify the disease-causing mutations on those genes that affect enzyme production and lead to the destruction of brain cells. Scientists have also created Tay-Sachs animal models that can be used to study the course of the disease and to explore treatment options.

One of the latest treatments being investigated for Tay-Sachs involves neural stem cells that are genetically modified to produce and secrete the missing hex A enzyme. When inserted in the brains of mice, such cells were able to break down ganglioside and prevent its accumulation. However, clinical trials of neural stem cell therapy in Tay-Sachs patients is still many years away. Bone marrow transplantation is also being explored as a way of introducing the missing enzyme into the brain.

Another treatment approach under study—molecular chaperone therapy—focuses on the enzyme-producing proteins that become “misfolded” in the brain cells of some people with Tay-Sachs disease because of the genetic mutation. Misfolded proteins are usually destroyed by their cells’ quality control system—a process that then decreases the amount of enzyme transferred to the cells’ lysosomes. Molecular chaperone therapy introduces small molecules into the cells to correct the misshaped proteins. Clinical trials of this therapy are currently underway for other lysosomal storage diseases, and trials for Tay-Sachs may soon follow.

Scientists are also investigating substrate reduction therapy drugs as a potential treatment for Tay-Sachs disease. These drugs are designed to decrease the production of gangliosides so that it matches the amount of residual hex A enzyme in the nerve cells of Tay-Sachs patients.

Because Tay-Sachs is such a complicated neurological disorder, researchers believe no single technique holds the answers for a cure. Most likely a combination of therapies will be needed to halt or even reverse its destructive and tragic effects.

Hope for Other Diseases

Research into Tay-Sachs disease adds to our understanding of the other 50 or so inherited lysosomal storage diseases, including Fabry, Gaucher, Sandhoff, and Niemann-Pick. An estimated 1 in 5,000 Americans is affected by one of these diseases. Studies of Tay-Sachs are also adding to our general knowledge of human genetics, complex lipid metabolism, and brain function—knowledge that promises to lead to new therapeutic advances for many brain disorders, including Alzheimer’s disease.

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Substrate Reduction Therapy (Trickle-Down Therapy)

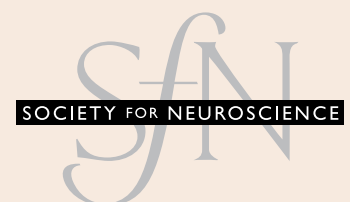


- a) healthy neuron
- b) neuron affected by Tay-Sachs
- c) neuron treated with substrate reduction compound

Substrate reduction therapy helps prevent gangliosides from building up to toxic levels by using drugs designed to decrease their production. This helps bring levels of gangliosides closer to levels of the hex A enzyme, which processes gangliosides but is deficient in the nerve cells of Tay-Sachs patients.

Already research has led to:

- Identifying the disease-causing mutations on the genes responsible for Tay-Sachs
- Genetic screening tests to identify high-risk populations
- Clinical trials for potential therapies to treat Tay-Sachs and other lysosomal storage diseases



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