

OVER THE PAST SEVERAL DECADES, RESEARCHERS HAVE DEVELOPED SCREENING TOOLS THAT HAVE REDUCED THE OCCURRENCE OF TAY-SACHS DISEASE IN CERTAIN POPULATIONS. CONTINUED RESEARCH HAS HELPED IDENTIFY SOME MECHANISMS OF THE DISEASE. NOW, ANIMAL STUDIES INDICATE THAT COMBINING TREATMENTS CAN MULTIPLY THERAPEUTIC BENEFITS. SOME SCIENTISTS THINK THIS APPROACH WILL HELP THE MOST DIFFICULT CASES.

TREATING TAY-SACHS DISEASE

Children with Tay-Sachs, a progressive neurodegenerative disease that attacks nerve cells, usually die before age 5. More gradual and less severe forms can also affect young children, teens, and people in their 20s and 30s.

The most severe form of Tay-Sachs disease begins to affect babies when they are only a few months old. Initially, their development is delayed. They begin to lose vision and react abnormally when startled. Paralysis gradually sets in. They may go deaf, have seizures, and, ultimately, become unable to swallow or breathe.

Currently there is no cure or effective way to delay the progression of the disease. Scientists around the world are investigating a range of treatment options for a number of diseases, including Tay-Sachs, that stem from excess cell products building up in nerve cells or other cell types. Research has revealed commonalities among these diseases, increasing the likelihood that advances in one area will increase our understanding of them all. Already the crossover effect of this research has led to a broader understanding of how cells work normally and could contribute

to treatments across this range of diseases.

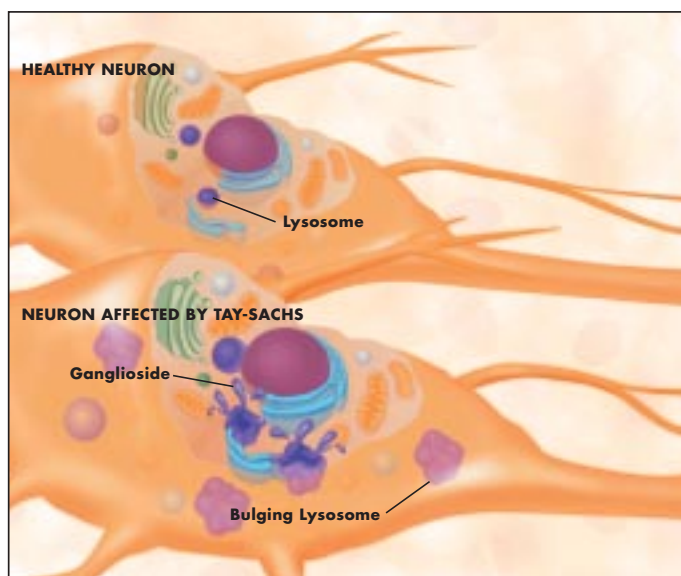
Advances are leading to:

- Possible treatments for disorders related to problems with storage within cells.
- A greater understanding of how healthy cells—in particular, nerve cells—function.
- Clues to how Tay-Sachs and related disorders share characteristics with diseases such as Alzheimer's and Parkinson's.

Tay-Sachs disease, first identified in 1881, stems from problems in lysosomes, the waste processing centers of the cell. Mutated genes produce enzymes that are less effective than normal at breaking down fatty cell products known as

gangliosides. As a result, gangliosides build up in the lysosomes and overload cells. Their buildup ultimately causes damage to nerve cells.

Tay-Sachs is one of nearly 50 diseases in which faulty waste processing and excess storage in lysosomes are common features; in the 1960s, they were identified as lysosomal storage disorders. Each disorder affects different areas and organs of the body, and they strike at different ages. In Tay-Sachs disease, the excess storage is particularly severe within cells of the brain. While they are quite rare individually, together these disorders affect as many as 1 in 5,000 people.



▲ IN A HEALTHY NEURON, TOP, LYSOSOMES ACT AS THE WASTE RECYCLING CENTER OF THE CELL. IN TAY-SACHS DISEASE, GENETIC DEFICIENCIES HOBBLE LYSOSOME ENZYMES THAT BREAK DOWN FATTY CELL PRODUCTS, ALSO KNOWN AS GANGLIOSIDES, WHICH BUILD UP AND DESTROY THE CELL.

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The genetic mutation associated with Tay-Sachs disease occurs most frequently among people of Eastern European and Ashkenazi Jewish descent. About one in 30 American Jews carries the gene for Tay-Sachs. Other high-risk groups include non-Jewish people of French-Canadian ancestry, members of the Cajun population of Louisiana, and Irish Americans.

Clinicians consider efforts targeting Tay-Sachs disease over the last generation a huge success. Programs for screening potential parents for the gene known to cause Tay-Sachs disease and prenatal testing for the presence of the enzyme produced by the gene were established in the 1970s. Screening programs directed at the Ashkenazi Jewish population in the United States and Canada have led to a 90 percent reduction in Tay-Sachs disease.

Yet Tay-Sachs remains a disease without a cure. Agencies in the United States and other countries have approved treat-

ments for lysosomal storage disorders affecting other parts of the body, but the brain has proven more difficult to reach. As scientists learn more about their similarities, lysosomal storage disorders reveal clues that could help in the development of common treatments.

One treatment tactic aims to prevent or slow the production of the gangliosides that build up, reducing them to a level the deficient enzymes can handle. Experiments that successfully blocked the toxic buildup of gangliosides in animals led to trials in humans. Early results from testing on adults and infants have been inconclusive, and additional trials are ongoing.

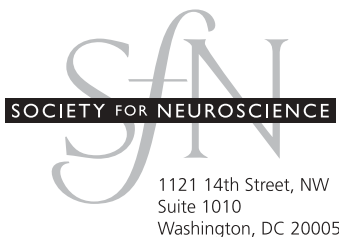
Recent studies on mice show that gene therapy, where normal genes are delivered to the brain to increase the breakdown of gangliosides, delayed the onset of the disease, decreased inflammation, improved function, and extended their life. Other studies are ex-

amining whether cutting calories delays the disease, the potential benefit of transplanting stem cells, and the role of inflammation, which is triggered in Tay-Sachs.

But there may be no single key to treating Tay-Sachs disease. Researchers are encouraged by animal research showing that combining treatments brings improved outcomes. For example, one study of mice modeling Sandhoff disease, a disorder very similar to Tay-Sachs, showed that combining bone marrow transplant with a drug therapy produced a benefit greater than the sum of the benefits of each treatment alone.

Scientists hope that this combination approach will ultimately lead to more effective treatment than any single approach. Such synergy may multiply the prospects for effective treatments for children with the most severe cases.

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