

This Week's Citation Classic

CC/NUMBER 45
NOVEMBER 9, 1981

Okada S & O'Brien J S. Tay-Sachs disease: generalized absence of a beta-D-N-acetylhexosaminidase component. *Science* **165**:698-700, 1969.

[Dept. Neurosciences, Sch. Medicine, Univ. California, La Jolla, CA]

The primary defect in Tay-Sachs disease is the absence of the lysosomal enzyme, hexosaminidase A. Deficiency of this enzyme leads to the storage of ganglioside GM₂ in neurons and resultant cerebral degeneration. Carrier detection and prenatal diagnosis by enzyme assay have led to a large reduction in the incidence of Tay-Sachs disease in North America in the past decade. [The SC[®] indicates that this paper has been cited over 475 times since 1969.]

John S. O'Brien
Department of Neurosciences
School of Medicine
University of California
La Jolla, CA 92093

September 11, 1981

"Shintaro Okada and I were pleased to learn that this publication has become a *Citation Classic*. Okada joined my laboratory in 1967 and we began to work on the enzyme defects in hereditary ganglioside storage diseases. In 1968 we discovered the primary defect in GM₁ gangliosidosis, a deficiency of β -galactosidase.¹ We then turned to the problem of Tay-Sachs disease, a GM₂ gangliosidosis.

"At that time little was known about enzymes which degraded gangliosides. I strongly suspected a defect of ganglioside degradation in Tay-Sachs disease, a hexosaminidase deficiency being most likely. We began to work on human hexosaminidases using synthetic substrates for assay. I became aware of the work of Don Robinson and John Stirling² at Queen Elizabeth's College in London, who demonstrated two different electrophoretic forms of hexosaminidase in human tissues, an acidic form, hexosaminidase A, and a basic form, hexosaminidase B. Okada carried out starch gel electrophoresis of hexosaminidase A and B and found that hex A was absent in Tay-Sachs disease tissues. We next demonstrated the defect in freshly prepared leukocytes from patients and found a partial

deficiency of hex A in serum from carriers, confirming the hereditary transmission of the defect.

"We were then at University of California, San Diego, working in temporary quonset huts situated on the cliffs overlooking Black's beach in La Jolla. Okada and I celebrated our discovery with some Old Bushmills. As the sun set on the blue Pacific, we contemplated upon a Japanese and an Irishman cracking a Jewish disease.

"We sent our manuscript to *Science* and I presented our findings at the Cordon Conference on Lysosomes in June 1969. There I learned that Konrad Sandhoff had found the same deficiency but was not sure it was the primary defect. After hearing our work, he published his findings.³

"We then perfected the carrier test using serum⁴ and established a reliable prenatal test for Tay-Sachs disease using amniotic cells.⁵

"I believe this article has been widely cited because it led to the first prospective prevention program for a human genetic disease by carrier screening of an at-risk population. Michael Kaback organized and led the first screening program for Tay-Sachs carriers among the Jewish citizens of Baltimore and Washington in 1971. In ten years, more than 312,000 individuals have been screened worldwide in 73 cities from 13 countries, using an improved automated version of our serum test.⁴ This has led to the identification of 12,763 carriers and 268 at-risk couples, none of whom had a previous family history of Tay-Sachs disease. Tay-Sachs disease has been diagnosed before birth in 175 of 814 pregnancies; 639 unaffected babies have been born. A recent calculation⁶ indicates that the program has resulted in a 65-85 percent reduction of Tay-Sachs disease in North America within the past decade.

"Okada is now associate professor of pediatrics at Osaka University and is still active in research in human biochemical genetics. Both of us are extremely gratified that our work has helped to diminish the suffering caused by this fatal disease."

1. Okada S & O'Brien J S. Generalized gangliosidosis: beta-galactosidase deficiency. *Science* **160**:1002-4, 1968.
2. Robinson D & Stirling J L. N-acetyl- β -glucosaminidases in human spleen. *Biochemical J.* **107**:321-7, 1968.
3. Sandhoff K. Variation of β -N-acetyl-hexosaminidase pattern in Tay-Sachs disease. *FEBS Lett.* **4**:351-4, 1969.
4. O'Brien J S, Okada S, Chen A & Fillierap D L. Tay-Sachs disease: detection of heterozygotes and homozygotes by serum hexosaminidase assay. *N. Engl. J. Med.* **283**:15-20, 1970.
5. O'Brien J S, Okada S, Fillierap D L, Veath M L, Adornato B & Brenner P H. Tay-Sachs disease: prenatal diagnosis. *Science* **172**:61-4, 1971.
6. Kaback M M. Unpublished data. Los Angeles CA:University of California 1980.