

O'Brien J S, Okada S, Chen A & Fillerup D L. Tay-Sachs disease: detection of heterozygotes and homozygotes by serum hexosaminidase assay. *N. Engl. J. Med.* 283:15-20, 1970.
[Dept. Neurosciences, Sch. Medicine, Univ. California, La Jolla, CA]

A fluorometric method showed the activity of hexosaminidase A in human serum to be markedly deficient in serum specimens from nine patients with Tay-Sachs disease (TSD). Parents (obligate heterozygotes) of children with TSD had levels of hexosaminidase A that were intermediate between those found in affected children and those in control subjects. No overlap was found between values for this enzyme in serums from heterozygotes, healthy controls, and homozygotes. [The SCI® indicates that this paper has been cited in over 305 publications since 1970.]

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After the discovery of the absence of hexosaminidase A (Hex A) activity in Tay-Sachs disease (TSD),¹ we decided to develop methodology to detect heterozygote carriers of the mutation. We had found that carriers had reduced Hex A activity in leukocytes and fibroblasts in analysis by electrophoresis and staining for enzyme activity. We turned to serum as the enzyme source due to its availability. Exploiting the thermal lability of Hex A compared to Hex B as reported by Don Robinson and John Stirling in kidney,² we found conditions that could differentiate carriers from noncarriers over 90 percent of the time using serum.

We then ran sera from many controls and found some having significant overlap with carriers, especially hospitalized patients with liver disease and those with tissue injury such as myocardial infarction.

Our method was then automated for mass screening by both Michael Kaback's group³ and Sandy Lowden's group.⁴ It soon became evident that another obstacle to screening was pregnancy; noncarriers when pregnant had Hex A serum levels in the carrier range. Their leukocyte levels of Hex A remained normal, however, and this sample could be used to obtain the correct result.

Using automated screening and the backup leukocyte assay, approximately 450,000 individuals have been screened for the TSD carrier state worldwide. Employing prenatal diagnosis in at-risk couples and termination of pregnancy for affected fetuses, the incidence of TSD has been greatly reduced; current estimates indicate a 65-85 percent reduction in North America compared to 10 years ago. Many unaffected babies have been born who would not have been conceived without the program, bringing much happiness to their families.

I suppose this manuscript has been cited frequently because it led to a very successful program of carrier screening. Kaback and I hoped that it could serve as a prototype for screening of other genetic diseases,³ and I am pleased to see that a similar approach to effectively reduce the incidence of β -thalassemia has worked in Sardinia.⁵ My colleagues and I are gratified that our work at the bench has paid off.

1. Okada S & O'Brien J S. Tay-Sachs disease: generalized absence of a beta-D-N-acetylhexosaminidase component. *Science* 165:698-700, 1969. [See also: O'Brien J S. Citation Classic. *Current Contents/Life Sciences* 24(45):16, 9 November 1981.]
2. Robinson D & Stirling J L. N-acetyl- β -glucosaminidases in human spleen. *Biochemical J.* 107:321-7, 1968. (Cited 415 times.)
3. Kaback M M & O'Brien J S. Tay-Sachs: prototype for prevention of genetic disease. *Hosp. Pract.* 8:107-16, 1973. (Cited 20 times.)
4. Lowden J A, Skomorowski M A, Henderson F & Kaback M. Automated assay of hexosaminidases in serum. *Clin. Chem.* 19:1345-9, 1973. (Cited 45 times.)
5. Cao A, Piatas L, Lecca U, Olla G, Cosu P, Rosatelli C & Galanello R. Control of homozygous β -thalassemia by carrier screening and antenatal diagnosis in Sardinians. *Clin. Genet.* 26:12-22, 1984.