Tay-Sachs and other Lipid Storage Diseases

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Rarely does medical science advance in a relatively short time from little knowledge about a disease to foreseeing its complete eradication in the not-so-distant future, particularly when that disease is an inherited genetic disorder. Yet, this is precisely the outlook for Tay-Sachs disease.

A host of researchers including physicians and scientists at the National Institute of Neurological Diseases and Stroke, a component of the National Institutes of Health, have cracked the mystery of Tay-Sachs disease and are working steadily to eliminate it from the list of neurological disorders that plague man.

Caused by an abnormal gene which is responsible for the absence of a specific enzyme, Tay-Sachs disease is characterized by the accumulation of lipid material in the nerve cells of the brain and in other body cells. This accumulation of fatty material (sphingolipids) destroys the cells, thus causing severe mental retardation and eventual death.

The disease derives its name from the two men who first identified it in the 1880's. Warren Tay, a British opthalmologist, detected the telltale red spot on the retina of a victim's eye. A New York neurologist, Bernard Sachs, gave the first clinical description of the disorder.

Tay-Sachs disease can be transmitted to an infant only if both parents are carriers of the recessive, abnormal gene. A carrier can therefore marry a noncarrier without producing affected children. However, a pregnancy resulting from two carriers runs the risk of one in four children having Tay-Sachs disease and one in two of the remaining children being a carrier. The otherwise normal carriers of the gene are healthy, and no sign of the disease may be evident for generations.

Most Tay-Sachs infants appear normal until they are about 6 months old. At this time the nerve cells begin to deteriorate; there is a halt in the development of body functions controlled by the nervous system, and the baby begins to regress.

Early symptoms include the loss of power to roll over and to raise the chest and head. Later the infant is unable to extend his arms or move his legs. Inability to control the startle reflex also characterizes Tay-Sachs infants. In reaction to a sudden sound, a Tay-Sachs victim will jerk up in an exaggerated manner and then slump back. A child in final stages of the disease is likely to lie still, staring straight ahead. In the end his sight fails. Most Tay-Sachs children live only from 2 to 4 years.

Genetic Distribution

A striking feature of Tay-Sachs disease is its genetic distribution. Tay-Sachs disease is most prevalent among Jewish people of Eastern European descent. Those particularly prone to the disorder trace their ancestry to the provinces of Grodno, Kovno, Suwalki, and Vilno along the former Lithuanian - Polish - Russian border. Still other cases originate with forebears who emigrated from White Russia, the Ukraine, eastern Germany, Czechoslovakia, Hungary, Rumania, and the provinces of Bessaravia and Bucovina where Ashkenazi Jews lived in the 19th century.

The birth incidence of Tay-Sachs children is 100 times higher and the gene frequency 10 times higher among Ashkenazi Jews than among other Jewish and non-Jewish groups. Thus, approximately one of every 6,000 Jewish infants is a Tay-Sachs victim, and one of every 40 Jewish persons is a carrier of the disease.

In the United States there are an estimated ½ million carriers of Tay-Sachs disease; 10 percent of these are Jews in New York City. Each year 10 to 15 of New York City's children are born with the disease. This compares with two to four Tay-Sachs cases reported per year in the Baltimore-Washington area. This is not to say that Tay-Sachs is an exclusively Jewish disease. Many non-Jewish persons carry the abnormal gene, and cases have been reported among Swiss, Japanese, and Scandinavian children, and most recently in a Negro child.

Dr. Ntinos C. Myrianthopoulos, head of the Section on Epidemiology and Genetics, Perinatal Research Branch, NINDS, has investigated the epidemiology of Tay-Sachs disease (*1*). Grandparents of the Tay-Sachs patients, he discovered, tended to come from smaller communities in Eastern Europe, as opposed to the larger cities of Kiev, Odessa, and Warsaw.

Aronson (*1*) studied geographic marriage patterns of the grandparents. Of the cases he observed, 40 percent of the marriages included spouses from different countries; 49 percent of the couples were from the same Eastern European country but from different cities, and only 11 percent of the husband-wife combinations originated in the same community.

Myrianthopoulos also researched the epidemiology of several disorders related to Tay-Sachs. All categorized as sphingolipidoses, hereditary diseases marked by accumulation of fatty substances in various tissues, these disorders share several features with Tay-Sachs disease.

Niemann-Pick's disease patients, who also suffer severe mental retardation and early death, are primarily the descendants of emigrants from the Grodno-Kovno area. The cultural, marital, and occupational characteristics of Niemann-Pick grandparents are similar to those of the Tay-Sachs grandparents.

"It is unlikely that such high concentration of different deleterious genes in a population is a chance occurrence," Myrianthopoulos concluded. "It is more likely that the same or similar circumstances which favored the rise in frequency of one gene were also responsible for the concentration of the rest."

Study of Origins

In an attempt to determine which circumstances were responsible for the frequency of the sphingolipidoses among Ashkenazi Jews, Myrianthopoulos con-

sidered three hypotheses: a differential breeding pattern, a differential mutation rate, and a differential fertility rate favoring the heterozygote (*1*). He dismissed the first two hypotheses on several counts.

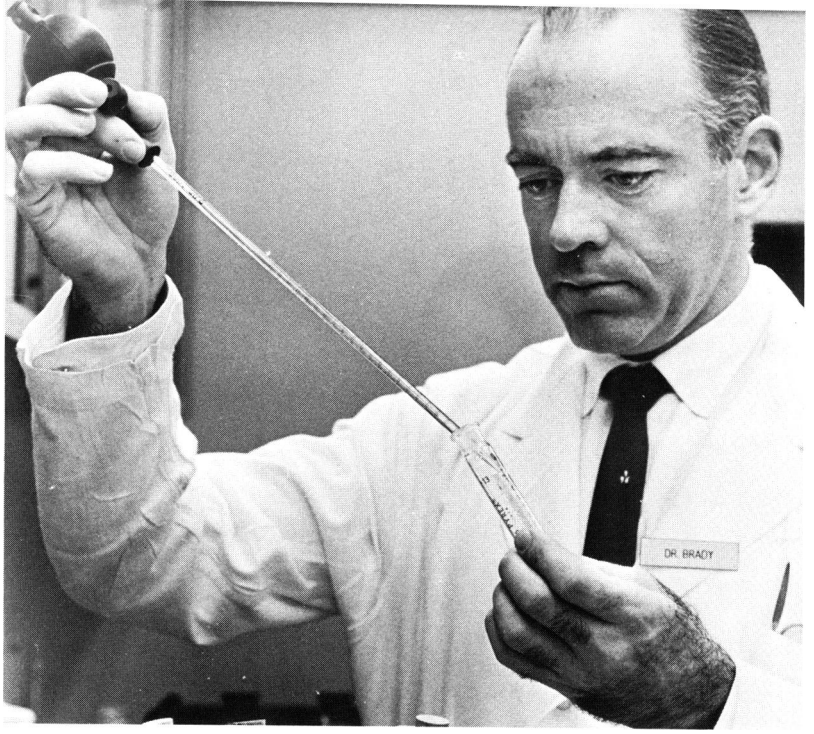
With regard to the possibility of a differential fertility rate favoring the heterozygote, comparison of reproductive performance of grandparents of Jewish Tay-Sachs infants with a control group showed a 6 percent advantage favoring the Jewish heterozygote. Myrianthopoulos determined this difference to be "small but consistent." Furthermore, he added (*1*):

> Some historical evidence also appears to corroborate this hypothesis and to place the rise of the Tay-Sachs disease gene among the Ashkenazi Jews in historical times perhaps during the early centuries of the diaspora. The kind of selective agent responsible for conferring this selective advantage is not known. But it's evident that whatever its mode of action was, it was not confined only to Tay-Sachs disease. Apparently Niemann-Pick's disease, Gaucher's disease, spongy degeneration of the nervous system, Wilson's disease and possibly other rare metabolic disorders, which were a part of the genetic pool of the Jewish communities in northeastern Europe around the turn of the century, have been subject to the influence of the same unknown selective force and shared the same polymorphic properties.

Research

While scientists such as Myrianthopoulos were attempting to unravel the historical mystery of the sphingolipidoses, others were working to treat the patients with these disorders. A campaign to diagnose, prevent, and someday cure Tay-Sachs disease and its related disorders has been underway on several fronts for nearly 20 years.

Scientists at the Isaac Albert Research Institute of Brooklyn's Kingsbrook Jewish Medical Center (formerly the Jewish Chronic Disease Hospital) have been conducting studies on the sphingolipidoses since 1952 (*2*). Their 16-bed ward for Tay-Sachs children is considered the best facility of its kind in the world.



Dr. Roscoe O. Brady incubates labeled material with tissue extract, one of the many steps in the research procedures to determine the specific metabolic defect underlying the sphingolipidoses. Photo by Jerry Hecht, National Institutes of Health

A lay institution vitally interested in treatment and prevention of the disease is the National Tay-Sachs Association in New York City. Organized in Philadelphia by only six families in 1955, the association now claims almost 1,000 members.

In recent years NINDS has taken the lead in the fight against Tay-Sachs disease. Dr. Roscoe O. Brady in the Institute's Laboratory of Neurochemistry is particularly active in Tay-Sachs research and shares credit for cracking the mystery of the disease (*3, 4*). His work on the sphingolipidoses in the mid-1960's provided the basis for his later discoveries on Tay-Sachs disease.

Related disorders. Gaucher's disease, like Tay-Sachs, is caused by a recessive genetic defect that is transmitted via parent carriers to their children. If both parents carry the defective gene, one in four children will have the disease, two will be carriers, and only one will be normal.

Brady thought that the accumulation of lipids in the spleen of Gaucher's disease patients is due to lack of an enzyme that would normally catabolize the material. He therefore chemically synthesized radioglucocerebroside and measured the amount of radioactive glucose hydrolyzed. As predicted, spleen tissue from patients with Gaucher's disease contained considerably less glucose-releasing enzyme activity (one-fiftieth) than a normal spleen tissue

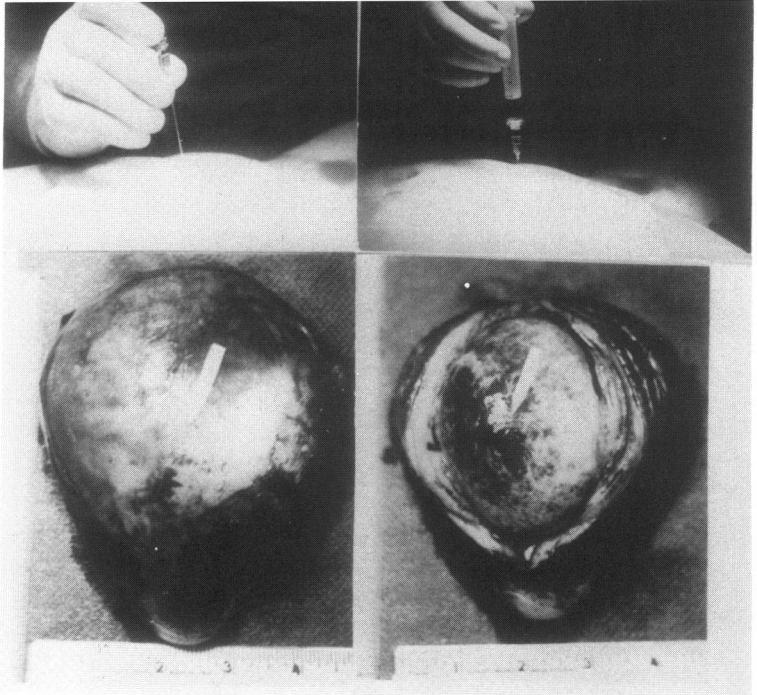
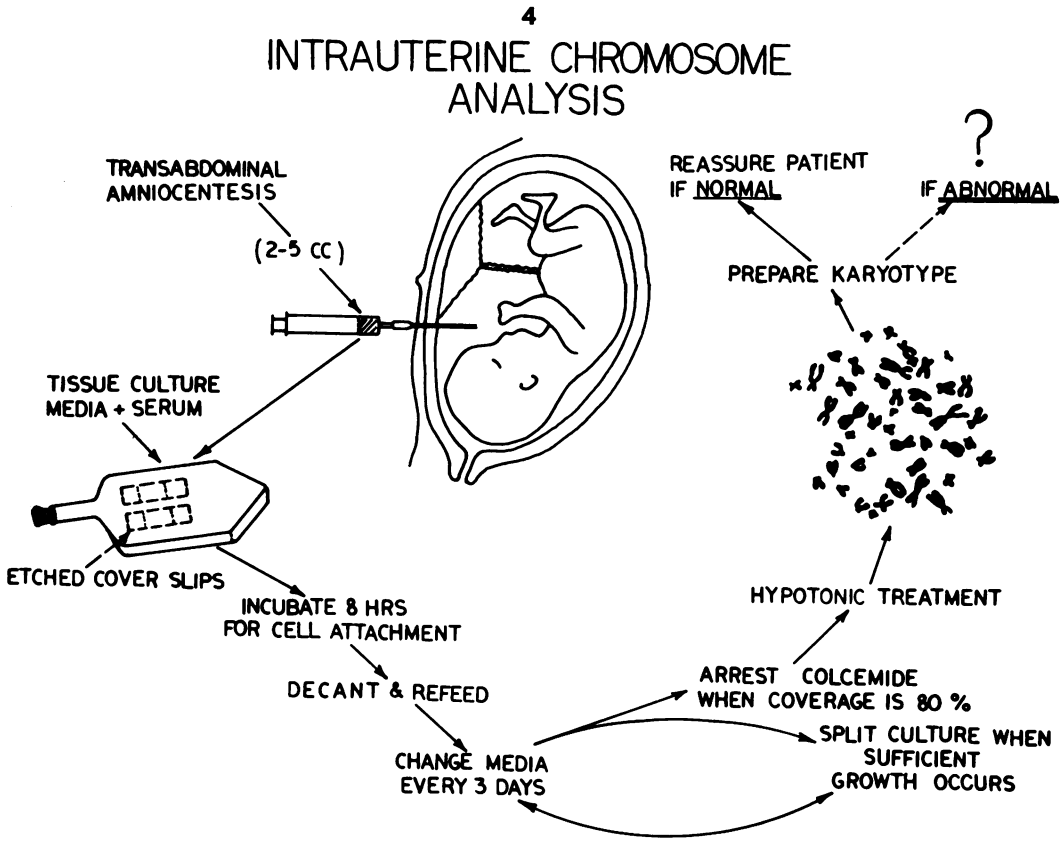


Figure 1. Transabdominal amniocentesis is most safely performed at the 16-week gestation stage. Under sterile technique a 23-gauge needle is inserted in the midline near the top of the fundus and below the umbilicus.

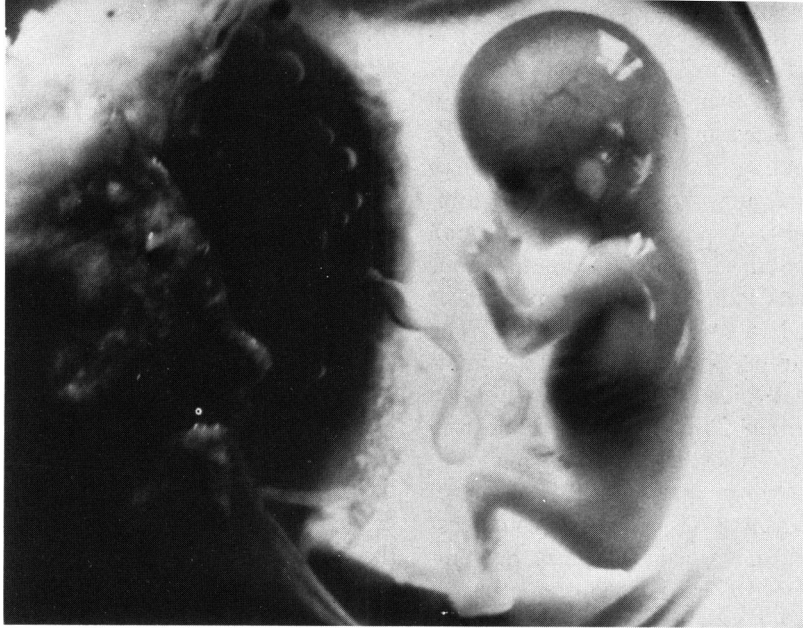
Figure 2. Amniotic fluid is withdrawn into a sterile, siliconized syringe. Fluid should be clear and free and flowing.

Figure 3. Hysterectomy specimens taken during pregnancy show the absence of uterine bleeding or amniotic fluid leakage following a transabdominal amniocentesis.

Figure 4. Prenatal diagnosis encompasses obtaining amniotic fluid, tissue culture for cell growth, and utilization of cell cultures for chromosomal analysis or biochemical studies.



Photos on pages 772 and 773 are from the Reproductive Genetics Unit, George Washington University Medical Center, Washington, D.C.



A human hysterectomy specimen at 16 weeks' gestation is maintained in vitro following transabdominal amniocentesis. The placenta occupies less than 30 percent of the circumference, and the fetus occupies less than 20 percent of the volume.

treated the same way. Brady found no activity whatsoever in the tissues from patients with the infantile form of Gaucher's disease, only 10 to 30 percent activity in less-severe juvenile and adult forms, and 75 percent activity in white blood cells and cultured skin fibroblasts in carriers of the disease.

More recently, the NINDS researcher used a cerebrosidase assay to monitor the condition of an unborn child susceptible to Gaucher's disease (*5*). By extracting a few cells in the third month of pregnancy from the amniotic fluid surrounding the fetus, he was able to culture the cells for a month and then predict whether the infant would be born with Gaucher's disease, have a juvenile or an adult form of the disease, be a carrier, or be normal.

Brady next turned his attention to Niemann-Pick's disease. Another sphingolipidosis, this disorder is characterized by accumulation of the lipid sphingomyelin in the spleen and liver and erosion of the bone cortex. In the more prevalent infantile form, Niemann-Pick's disease also causes severe mental retardation. Some cases, however, do occur among adults.

Following procedures similar to his work on Gaucher's disease, Brady showed the culprit of Niemann-Pick's disease to be a deficiency of the enzyme sphingomyelinase.

There are more than a half-dozen related disorders of amaurotic idiocy, and Brady's work in the sphingolipidoses led him to characterize still another disorder. Fabry's disease, also a hereditary enzyme deficiency, differs from Gaucher's and Niemann-Pick's diseases in that it is sex-linked to the extra X chromosome in women. As with hemophilia, only the mother can be a carrier, but she has a 50 percent chance of transmitting the disease to her male children. Whether or not the father is a carrier of the Fabry gene is irrelevant.

Fabry's disease patients do not show signs of mental retardation but suffer cataracts, high fever, pain in the extremities, kidney failure, and a reddish purple maculopapular rash. In contrast to other sphingolipidoses, Fabry's disease patients usually live until middle age.

Brady, using the amniocentesis methods he developed in his Niemann-Pick's disease research, diagnosed a case of Fabry's disease in utero. Assays of cells from the subsequently aborted fetus confirmed his diagnosis.

Tay-Sachs. These advancements and discoveries led Brady to the most prevalent of all sphingolipidoses, Tay-Sachs disease. After a series of experiments, the biochemist and his associates hypothesized that the defect in Tay-Sachs disease is due to the lack of a catabolic enzyme responsible for splitting the amino sugar from the ganglioside.

The fatal lipid accumulation caused by this lack is a Tay-Sachs ganglioside [N-acetylgalactosaminyl - (N-acetylneuraminyl) galactosylglucosyl ceramide] or otherwise known as GM_2. Because both the galactosamine and neuraminic acid portions of the molecule are theoretically subject to attack by catabolic enzymes, Brady had to determine which end of the molecule is responsible. He spent 2½ years making the neuraminic acid end of the ganglioside radioactive. Testing of muscle tissue from Tay-Sachs patients and normal control patients, however, showed the same enzyme activity for both. He then turned to the galactosamine end of the molecule.

At this time two NINDS grantees, Dr. John S. O'Brien and Dr. Shintaro Okada (*6*) at the University of California at San Diego, found through the use of

an artificial substrate that the enzyme missing in the blood and tissue of Tay-Sachs patients is hexosaminidase component A. Carriers of the disease, they further discovered, have only half as much of that enzyme in their blood as normal controls.

The California scientists' work required confirmation by examining the metabolism of the ganglioside which accumulates in the brain and tissues of Tay-Sachs patients. Brady and his co-workers, therefore, directed their efforts to confirming the O'Brien-Okada report. Through investigations with Tay-Sachs ganglioside radioactively labeled in the hexosaminyl portion of the molecule, they demonstrated the absence of this ganglioside, hexosaminidase component A, in tissues of patients with Tay-Sachs disease.

Prevention possible. Discoveries by Brady, O'Brien, and Okada, together with Dr. Bruno Volk, director of the Isaac Albert Research Institute, led to a simple diagnostic test for patients and carriers of the sphingolipidoses, including Tay-Sachs disease. In utero diagnosis of the lipid storage diseases is possible through amniocentesis. When such a diagnosis is made, prospective parents have the opportunity to consider therapeutic abortion. Determination of carriers is possible also by a simple blood test.

The first mass screening program to detect Tay-Sachs carriers, thus hopeful of preventing future occurrence of the disorder, is underway in the Baltimore-Washington area (*7,8*). An affiliate of Johns Hopkins University, the John F. Kennedy Institute, is sponsoring this unprecedented pilot program.

Dr. Michael M. Kaback, an assistant professor of pediatrics at the Johns Hopkins University School of Medicine and a former researcher in the Laboratory of Molecular Biology, NINDS, is directing the Tay-Sachs screening program. The test takes 10 minutes. A physician draws a small amount of blood from the arm, puts it in a test tube, and places it in a rack for refrigeration. The sample is later analyzed automatically, and the patient is notified within 2 to 3 months if he is a carrier of the defective gene.

More than 5,000 Baltimore-Washington Jewish volunteers will have been tested by September 1971. The entire program will continue until 1973, when an estimated 60,000 volunteers will have been tested. A minimum of 8,000 carriers are expected to be identified in this pilot program. Of these, approximately 100 to 200 couples will be at risk of conceiving a Tay-Sachs child. Initial tests have already turned up some carriers of the disease.

The cost of the Baltimore-Washington program is estimated at $200,000—less than the amount necessary to care for two Tay-Sachs patients (*8*). Those tested are asked to contribute $5 to offset the project's cost.

Three characteristics of Tay-Sachs disease make mass screening possible: the disease affects a specific subpopulation; carriers can be identified by a simple, economic test; and diagnosis is also possible in utero. Physicians hope that procedures developed in the Tay-Sachs program may eventually be extended for mass screening of other inherited diseases such as sickle cell anemia and cystic fibrosis.

Hope for Cure

With detection and prevention of Tay-Sachs disease possible, the question of a cure arises. The logical consideration is enzyme replacement, thus returning the lipid metabolism to its normal state.

In Tay-Sachs and infantile forms of Gaucher's disease, however, this theory would be difficult to institute because the protective blood-brain barrier is so effective and the brain cells are already severely damaged. However, in a recent interview, Brady said, "I believe we can now modify the enzyme so it can get into the brain." For juvenile Gaucher's and Fabry's disease patients, this may also be beneficial.

With medical science already able to prevent certain inborn errors of metabolism and hopeful of correcting others, it may soon be possible to strike many disorders from man's list of neurological ailments.

REFERENCES

(*1*) Myrianthopoulos, N. C., and Aronson, S. M.: Population dynamics of Tay-Sachs disease. 1. Reproductive fitness and selection. Am J Hum Genet 18: 313–327, July 1966.

(*2*) On the track of a mysterious killer. Med World News 10: 18, 18A, Sept. 19, 1969.

(*3*) Henanhan, J. F.: The chemical innovators. Roscoe O. Brady, unearthing a biochemical Rosetta Stone. Chem Engineering News 49: 42–45, Feb. 22, 1971.

(*4*) Brady, R. O.: Medical progress, the sphingolipidoses. N Engl J Med 275: 312–318, Aug. 11, 1966.

(*5*) Brady, R. O.: Prenatal diagnosis of lipid storage diseases. Clin Chem 16: 811–815 (1970).

(*6*) O'Brien, J. S., et. al.: Tay-Sachs disease: prenatal diagnosis. Science 172: 61–64, Apr. 2, 1971.

(*7*) Medical news, 'clinical genetics' gain notice. JAMA 213: 2168–2171, Sept. 28, 1970.

(*8*) Mass tests begin to find Tay-Sachs gene carriers. JAMA 216: 1097–1098, May 17, 1971.