Curse and Blessing of the Ghetto

Tay-Sachs disease is a choosy killer, one that for centuries targeted Eastern European Jews above all others. By decoding its lethal logic, we can learn a lot about how genetic diseases evolve— and how they can be conquered.

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Marie and I hated her at first sight, even though she was trying hard to be helpful. As our obstetrician's genetics counselor, she was just doing her job, explaining to us the unpleasant results that might come out of the genetic tests we were about to have performed. As a scientist, though, I already knew all I wanted to know about Tay-Sachs disease, and I didn't need to be reminded that the baby sentenced to death by it could be my own.

Fortunately, the tests would reveal that my wife and I were not carriers of the Tay-Sachs gene, and our preparenthood fears on that matter at least could be put to rest. But at the time I didn't yet know that. As I glared angrily at that poor genetics counselor, so strong was my anxiety that now, four years later, I can still clearly remember what was going through my mind: If I were an evil deity, I thought, trying to devise exquisite tortures for babies and their parents, I would be proud to have designed Tay-Sachs disease.

Tay-Sachs is completely incurable, unpreventable, and preprogrammed in the genes. A Tay-Sachs infant usually appears normal for the first few months after birth, just long enough for the parents to grow to love him. An exaggerated "startle reaction" to sounds is the first ominous sign. At about six months the baby starts to lose control of his head and can't roll over or sit without support. Later he begins to drool, breaks out into unmotivated bouts of laughter, and suffers convulsions. Then his head grows abnormally large, and he becomes blind. Perhaps what's most frightening for the parents is that their baby loses all contact with his environment and becomes virtually a vegetable. By the child's third birthday, if he's still alive, his skin will turn yellow and his hands pudgy. Most likely he will die before he's four years old.

My wife and I were tested for the Tay-Sachs gene because at the time we rated as high-risk candidates, for two reasons. First, Marie was carrying twins, so we had double the usual chance to bear a Tay-Sachs baby. Second, both she and I are of Eastern European Jewish ancestry, the population with by far the world's highest Tay-Sachs frequency.

In peoples around the world Tay-Sachs appears once in every 400,000 births. But it appears a hundred times more frequently—about once in 3,600 births—among descendants of Eastern European Jews, people known as Ashkenazim. For descendants of most other groups of Jews—Oriental Jews, chiefly from the Middle East, or Sephardic Jews, from Spain and other Mediterranean countries—the frequency of Tay-Sachs disease is no higher than in non-Jews. Faced with such a clear correlation, one cannot help but wonder: What is it about this one group of people that produces such an extraordinarily high risk of this disease?

Finding the answer to this question concerns all of us, regardless of our ancestry. Every human population is especially susceptible to certain diseases, not only because of its life-style but also because of its genetic inheritance. For example, genes put European whites at high risk for cystic fibrosis, African blacks for sickle-cell disease, Pacific Islanders for diabetes—and Eastern European Jews for ten different diseases, including Tay-Sachs. It's not that Jews are notably susceptible to genetic diseases in general; but a combination of historical factors has led to Jews' being intensively studied, and so their susceptibilities are far better known than those of, say, Pacific Islanders.

Tay-Sachs exemplifies how we can deal with such diseases; it has been the object of the most successful screening program to date. Moreover, Tay-Sachs is helping us understand how ethnic diseases evolve. Within the past couple of years discoveries by molecular biologists have provided tantalizing clues to precisely how a deadly gene can persist and spread over the centuries. Tay-Sachs may be primarily a disease of Eastern European Jews, but through this affliction of one group of people, we gain a window on how our genes simultaneously curse and bless us all.

The disease's hyphenated name comes from the two physicians—British ophthalmologist W. Tay and New York neurologist B. Sachs—who independently first recognized the disease, in 1881 and 1887, respectively. By 1896 Sachs had seen enough cases to realize that the disease was most common among Jewish children.

Not until 1962, however, were researchers able to trace the cause of the affliction to a single biochemical abnormality: the excessive accumulation in nerve cells of a fatty substance called G_{M2} ganglioside. Normally G_{M2} ganglioside is present at only modest levels in cell membranes, because it is constantly being broken down as well as synthesized. The breakdown depends on the enzyme hexosaminidase A, which is found in the tiny structures within our cells known as lysosomes. In the unfortunate Tay-Sachs victims this enzyme is lacking, and without it the ganglioside piles up and produces all the symptoms of the disease.

We have two copies of the gene that programs our supply of hexosaminidase A, one inherited from our father, the other from our mother; each of our parents, in turn, has two copies derived from their own parents. As long as we have one good copy of the gene, we can produce enough hexosaminidase A to prevent a buildup of G_{M2} ganglioside and we won't get Tay-Sachs. This genetic disease is of the sort termed recessive rather than dominant—meaning that to get it, a child must inherit a defective gene not just from one parent but from both of them. Clearly, each parent must have had one good copy of the gene along with the defective copy—if either had had two defective genes, he or she would have died of the disease long before reaching the age of reproduction. In genetic terms the diseased child is homozygous for the defective gene and both parents are heterozygous for it.

None of this yet gives any hint as to why the Tay-Sachs gene should be most common among Eastern European Jews. To come to grips with that question, we must take a short detour into history.

From their biblical home of ancient Israel, Jews spread peacefully to other Mediterranean lands, Yemen, and India. They were also dispersed violently through conquest by Assyrians, Babylonians, and Romans. Under the Carolingian kings of the eighth and ninth centuries Jews were invited to settle in France and Germany as traders and financiers. In subsequent centuries, however, persecutions triggered by the Crusades gradually drove Jews out of Western Europe; the process culminated in their total expulsion from Spain in 1492. Those Spanish Jews—called Sephardim—fled to other lands around the Mediterranean. Jews of France and Germany—the Ashkenazim—fled east to Poland and from there to Lithuania and western Russia, where they settled mostly in towns, as businessmen engaged in whatever pursuit they were allowed.

There the Jews stayed for centuries, through periods of both tolerance and oppression. But toward the end of the nineteenth century and the beginning of the twentieth, waves of murderous anti-Semitic attacks drove millions of Jews out of Eastern Europe, with most of them heading for the United States. My mother's parents, for example, fled to New York from Lithuanian pogroms of the 1880s, while my father's parents fled from the Ukrainian pogroms of 1903–6. The more modern history of Jewish migration is probably well known to you all: most Jews who remained in Eastern Europe were exterminated during World War II, while most the survivors immigrated to the United States and Israel. Of the 13 million Jews alive today, more than three-quarters are Ashkenazim, the descendants of the Eastern European Jews and the people most at risk for Tay-Sachs.

Have these Jews maintained their genetic distinctness through the thousands of years of wandering? Some scholars claim that there has been so much intermarriage and conversion that Ashkenazic Jews are now just Eastern Europeans who adopted Jewish culture. However, modern genetic studies refute that speculation.

First of all, there are those ten genetic diseases that the Ashkenazim have somehow acquired, by which they differ both from other Jews and from Eastern European non-Jews. In addition, many Ashkenazic genes turn out to be ones typical of Palestinian Arabs and other peoples of the Eastern Mediterranean areas where Jews originated. (In fact, by genetic standards the current Arab-Israeli conflict is an internecine civil war.) Other Ashkenazic genes have indeed diverged from Mediterranean ones (including genes of Sephardic and Oriental Jews) and have evolved to converge on genes of Eastern European non-Jews subject to the same local forces of natural selection. But the degree to which Ashkenazim prove to differ genetically from Eastern European non-Jews implies an intermarriage rate of only about 15 percent.

Can history help explain why the Tay-Sachs gene in particular is so much more common in Ashkenazim than in their non-Jewish neighbors or in other Jews? At the risk of spoiling a mystery, I'll tell you now that the answer is yes, but to appreciate it, you'll have to understand the four possible explanations for the persistence of the Tay-Sachs gene.

First, new copies of the gene might be arising by mutation as fast as existing copies disappear with the death of Tay-Sachs children. That's the most likely explanation for the gene's persistence in most of the world, where the disease frequency is only one in 400,000 births—that frequency reflects a typical human mutation rate. But for this explanation to apply to the Ashkenazim would require a mutation rate of at least one per 3,600 births—far above the frequency observed for any human gene. Furthermore, there would be no precedent for one particular gene mutating so much more often in one human population than in others.

As a second possibility, the Ashkenazim might have acquired the Tay-Sachs gene from some other people who already had the gene at high frequency. Arthur Koestler's controversial book *The Thirteenth Tribe*, for example, popularized the view that the Ashkenazim are really not a Semitic people but are instead descended from the Khazar, a Turkic tribe whose rulers converted to Judaism in the eighth century. Could the Khazar have brought the Tay-Sachs gene to Eastern Europe? This speculation makes good romantic reading, but there is no good evidence to support it. Moreover, it fails to explain why deaths of Tay-Sachs children didn't eliminate the gene by natural selection in the past 1,200 years, nor how the Khazar acquired high frequencies of the gene in the first place.

The third hypothesis was the one preferred by a good many geneticists until recently. It invokes two genetic processes, termed the founder effect and genetic drift, that may operate in small populations. To understand these concepts, imagine that 100 couples settle in a new land and found a population that then increases. Imagine further that one parent among those original 100 couples happens to have some rare gene, one, say,

that normally occurs at a frequency of one in a million. The gene's frequency in the new population will now be one in 200 as a result of the accidental presence of that rare founder.

Or suppose again that 100 couples found a population, but that one of the 100 men happens to have lots of kids by his wife or that he is exceptionally popular with other women, while the other 99 men are childless or have few kids or are simply less popular. That one man may thereby father 10 percent rather than a more representative one percent of the next generation's babies, and their genes will disproportionately reflect that man's genes. In other words, gene frequencies will have drifted between the first and second generation.

Through these two types of genetic accidents a rare gene may occur with an unusually high frequency in a small expanding population. Eventually, if the gene is harmful, natural selection will bring its frequency back to normal by killing off gene bearers. But if the resultant disease is recessive—if heterozygous individuals don't get the disease and only the rare, homozygous individuals die of it—the gene's high frequency may persist for many generations.

These accidents do in fact account for the astonishingly high Tay-Sachs gene frequency found in one group of Pennsylvania Dutch: out of the 333 people in this group, 98 proved to carry the Tay-Sachs gene. Those 333 are all descended from one couple who settled in the United States in the eighteenth century and had 13 children. Clearly, one of that founding couple must have carried the gene. A similar accident may explain why Tay-Sachs is also relatively common among French Canadians, who number 5 million today but are descended from fewer than 6,000 French immigrants who arrived in the New World between 1638 and 1759. In the two or three centuries since both these founding events, the high Tay-Sachs gene frequency among Pennsylvania Dutch and French Canadians has not yet had enough time to decline to normal levels.

The same mechanisms were one proposed to explain the high rate of Tay-Sachs disease among the Ashkenazim. Perhaps, the reasoning went, the gene just happened to be overrepresented in the founding Jewish population that settled in Germany or Eastern Europe. Perhaps the gene just happened to drift up in frequency in the Jewish populations scattered among the isolated towns of Eastern Europe.

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But geneticists have long questioned whether the Ashkenazim population's history was really suitable for these genetic accidents to have been significant. Remember, the founder effect and genetic drift become significant only in small populations, and the founding populations of Ashkenazim may have been quite large. Moreover, Ashkenazic communities were considerably widespread; drift would have sent gene frequencies up in some towns but down in others. And, finally, natural selection has by now had a thousand years to restore gene frequencies to normal.

Granted, those doubts are based on historical data, which are not always as precise or reliable as one might want. But within the past several years the case against those accidental explanations for Tay-Sachs disease in the Ashkenazim has been bolstered by discoveries by molecular biologists.

Like all proteins, the enzyme absent in Tay-Sachs children is coded for by a piece of our DNA. Along that particular stretch of DNA there are thousands of different sites where a mutation could occur that would result in no enzyme and hence in the same set of symptoms. If molecular biologists had discovered that all cases of Tay-Sachs in Ashkenazim involved damage to DNA at the same site, that would have been strong evidence that in Ashkenazim the disease stems from a single mutation that has been multiplied by the founder effect or genetic drift—in other words, the high incidence of Tay-Sachs among Eastern European Jews is accidental.

In reality, though, several different mutations along this stretch of DNA have been identified in Ashkenazim, and two of them occur much more frequently than in non-Ashkenazim populations. It seems unlikely that genetic accidents would have pumped up the frequency of the same gene not once but twice in the same population.

And that's not the sole unlikely coincidence arguing against accidental explanations. Recall that Tay-Sachs is caused by the excessive accumulation of one fatty substance, G_{M2} ganglioside, from a defect in one enzyme, hexosaminidase A. But Tay-Sachs is one of ten genetic diseases characteristic of Ashkenazim. Among those other nine, two—Gaucher's disease and Niemann-Pick disease—result from the accumulation of two other fatty substances similar to G_{M2} ganglioside, as a result of defects in two other enzymes similar to hexosaminidase A. Yet our bodies contain thousands of different enzymes. It would have been an incredible roll of the genetic dice if, by nothing more than chance, Ashkenazim had independently acquired mutations in three closely related enzymes—and had acquired mutations in one of those enzymes twice.

All these facts bring us to the fourth possible explanation of why the Tay-Sachs gene is so prevalent among Ashkenazim: namely, that something about them favored accumulation of G_{M2} ganglioside and related fats.

For comparison, suppose that a friend doubles her money on one stock while you are getting wiped out with your investments. Taken alone, that could just mean she was lucky on that one occasion. But suppose that she doubles her money on each of two different stocks and at the same time rings up big profits in real estate while also making a killing in bonds. That implies more than lady luck; it suggests that something about your friend—like shrewd judgment—favors financial success.

What could be the blessings of fat accumulation in Eastern European Jews? At first this question sounds weird. After all, that fat accumulation was noticed only because of the curses it bestows: Tay-Sachs, Gaucher's, or Niemann-Pick disease. But many of our common genetic diseases may persist because they bring both blessings and curses (see "The Cruel Logic of Our

Genes," *Discover*, November 1989). They kill or impair individuals who inherit two copies of the faulty gene, but they help those who receive only one defective gene by protecting them against other diseases. The best understood example is the sickle-cell gene of African blacks, which often kills homozygotes but protects heterozygotes against malaria. Natural selection sustains such genes because more heterozygotes than normal individuals survive to pass on their genes, and those extra gene copies offset the copies lost through the deaths of homozygotes.

So let us refine our question and ask, What blessing could the Tay-Sachs gene bring to those individuals who are heterozygous for it? A clue first emerged back in 1972, with the publication of the results of a questionnaire that had asked U.S. Ashkenzaic parents of Tay-Sachs children what their own Eastern European-born parents had died of. Keep in mind that since these unfortunate children had to be homozygotes, with two copies of the Tay-Sachs gene, all their parents had to be heterozygotes, with one copy, and half of the parents' parents also had to be heterozygotes.

As it turned out, most of those Tay-Sachs grandparents had died of the usual causes: heart disease, stroke, cancer, and diabetes. But strikingly, only one of the 306 grandparents had died of tuberculosis, even though TB was generally one of the big killers in these grandparents' time. Indeed, among the general population of large Eastern European cities in the early twentieth century, TB caused up to 20 percent of all deaths.

This big discrepancy suggested that Tay-Sachs heterozygotes might somehow have been protected against TB. Interestingly, it was already well known that Ashkenazim in general had some such protection: even when Jews and non-Jews were compared within the same European city, class, and occupational group (for example, Warsaw garment workers), Jews had only half the TB death rate of non-Jews, despite their being equally susceptible to infection. Perhaps, one could reason, the Tay-Sachs gene furnished part of that well-established Jewish resistance.

We're not a melting pot, and we won't be for a long time. Each ethnic group has some characteristic genes of its own, a legacy of its distinct history.

A second clue to a heterozygote advantage conveyed by the Tay-Sachs gene emerged in 1983, with a fresh look at the data concerning the distributions of TB and the Tay-Sachs gene within Europe. The statistics showed that the Tay-Sachs gene was nearly three times more frequent among Jews originating from Austria, Hungary, and Czechoslovakia—areas where an amazing 9 to 10 percent of the population were heterozygotes—than among Jews from Poland, Russia, and Germany. At the same time records from an old Jewish TB sanatorium in Denver in 1904 showed that among patients born in Europe between 1860 and 1910, Jews from Austria and Hungary were overrepresented.

Initially, in putting together these two pieces of information, you might be tempted to conclude that because the highest frequency of the Tay-Sachs gene appeared in the same geographic region that produced the most cases of TB, the gene in fact offers no protection whatsoever. Indeed, this was precisely the mistaken conclusion of many researchers who had looked at these data before. But you have to pay careful attention to the numbers here: even at its highest frequency the Tay-Sachs gene was carried by far fewer people than would be infected by TB. What the statistics really indicate is that where TB is the biggest threat, natural selection produces the biggest response.

Think of it this way: You arrive at an island where you find that all the inhabitants of the north end wear suits of armor, while all the inhabitants of the south end wear only cloth shirts. You'd be pretty safe in assuming that warfare is more prevalent in the north—and that war-related injuries account for far more deaths there than in the south. Thus, if the Tay-Sachs gene does indeed lend heterozygotes some protection against TB, you would expect to find the gene most often precisely where you find TB most often. Similarly, the sickle-cell gene reaches its highest frequencies in those parts of Africa where malaria is the biggest risk.

But you may believe there's still a hole in the argument: If Tay-Sachs heterozygotes are protected against TB, you may be asking, why is the gene common just in the Ashkenazim? Why did it not become common in the non-Jewish populations also exposed to TB in Austria, Hungary, and Czechoslovakia?

At this point we must recall the peculiar circumstances in which the Jews of Eastern Europe were forced to live. They were unique among the world's ethnic groups in having been virtually confined to towns for most of the past 2,000 years. Being forbidden to own land, Eastern European Jews were not peasant farmers living in the countryside, but businesspeople forced to live in crowded ghettos, in an environment where tuberculosis thrived.

Of course, until recent improvements in sanitation, these towns were not very healthy places for non-Jews either. Indeed, their populations couldn't sustain themselves: deaths exceeded births, and the number of dead had to be balanced by continued emigration from the countryside. For non-Jews, therefore, there was no genetically distinct urban population. For ghetto-bound Jews, however, there could be no emigration from the countryside; thus the Jewish population was under the strongest selection to evolve genetic resistance to TB.

Those are the conditions that probably led to Jewish TB resistance, whatever particular genetic factors prove to underlie it. I'd speculate that G_{M2} and related fats accumulate at slightly higher-than-normal levels in heterozygotes, although not at the lethal levels seen in homozygotes. (The fat accumulation in heterozygotes probably takes place in the cell membrane, the cell's "armor.") I'd also speculate that the accumulation provides heterozygotes with some protection against TB, and that that's why the genes for Tay-Sachs, Gaucher's, and Niemann-Pick disease reached high frequencies in the Ashkenazim.

Having thus stated the case, let me make clear that I don't want to overstate it. The evidence is still speculative. Depending on how you do the calculation, the low frequency of TB deaths in Tay-Sachs grandparents either barely reaches or doesn't quite reach the level of proof that statisticians require to accept an effect as real rather than as one that's arisen by chance. Moreover, we have no idea of the biochemical mechanism by which fat accumulation might confer resistance against TB. For the moment, I'd say that the evidence points to some selective advantage of Tay-Sachs heterozygotes among the Ashkenazim, and that TB resistance is the only plausible hypothesis yet proposed.

For now Tay-Sachs remains a speculative model for the evolution of ethnic diseases. But it's already a proven model of what to do about them. Twenty years ago a test was developed to identify Tay-Sachs heterozygotes, based on their lower-than-normal levels of hexosaminidase A. The test is simple, cheap, and accurate: all I did was to donate a small sample of my blood, pay $35, and wait a few days to receive the results.

If that test shows that at least one member of a couple is not a Tay-Sachs heterozygote, then any child of theirs can't be a Tay-Sachs homozygote. If both parents prove to be heterozygotes, there's a one-in-four chance of their child being a homozygote; that can then be determined by other tests performed on the mother early in pregnancy. If the results are positive, it's early enough for her to abort, should she choose to. That critical bit of knowledge has enabled parents who had gone through the agony of bearing a Tay-Sachs baby and watching him die to find the courage to try again.

The Tay-Sachs screening program launched in the United States in 1971 was targeted at the high-risk population: Ashkenazic Jewish couples of childbearing age. So successful has this approach been that the number of Tay-Sachs babies born each year in this country has declined tenfold. Today, in fact, more Tay-Sachs cases appear here in non-Jews than in Jews, because only the latter couples are routinely tested. Thus, what used to be the classic genetic disease of Jews is so no longer.

There's also a broader message to the Tay-Sachs story. We commonly refer to the United States as a melting pot, and in many ways that metaphor is apt. But in other ways we're not a melting pot, and we won't be for a long time. Each ethnic group has some characteristic genes of its own, a legacy of its distinct history. Tuberculosis and malaria are not major causes of death in the United States, but the genes that some of us evolved to protect ourselves against them are still frequent. Those genes are frequent only in certain ethnic groups, though, and they'll be slow to melt through the population.

With modern advances in molecular genetics, we can expect to see more, not less, ethnically targeted practice of medicine. Genetic screening for cystic fibrosis in European whites, for example, is one program that has been much discussed recently; when it comes, it will surely be based on the Tay-Sachs experience. Of course, what that may mean someday is more anxiety-ridden parents-to-be glowering at more dedicated genetics counselors. It will also mean fewer babies doomed to the agonies of diseases we may understand but that we'll never be able to accept.

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