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FALL 2006

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TEASING OUT ENVIRONMENTAL FACTORS IN DIABETES

Susceptibility to developing type 1 diabetes depends not only on having a high-risk genetic profile, but also on exposure to certain environmental factors. These may include diet, infections, hygiene, or something else that raises or lowers the risk of developing diabetes. The TEDDY study (The Environmental Determinants of Diabetes in the Young), which will follow more than 7,000 newborns at increased genetic risk for type 1 diabetes, will collect vast amounts of data on potential environmental factors over a 15-year period to see which ones are associated with a greater or lesser risk of developing diabetes.

By Robert S. Dinsmoor

Scientists used to think that the destruction of the insulin-producing beta cells happened suddenly, but they now realize that the whole process leading up to diabetes may start shortly after birth. Well before the age of five, often years before the clinical onset of diabetes, the immune system begins producing antibodies to proteins within islets. “Parents of a child with type 1 diabetes perceive it as an acute-onset disease, but most of these children have had islet cell antibodies for perhaps several years,” explains Åke Lernmark, Ph.D., principal investigator of the Swedish TEDDY clinical center at Lund University in Malmö, Sweden. Over the past two decades, scientists have been able to test for these antibodies and use the test results to reliably predict the probability that an individual will develop type 1 diabetes within a given period of time.

THE WEST FAMILY

Seattle, Washington

Julie West remembers all too well what it was like to be diagnosed with diabetes back in 1983. "It was the typical scenario," she says. "I lost a lot of weight, I was really thirsty, I was tired all the time, and it got to the point where I couldn't keep any food down. My parents thought I had mononucleosis, but when we went to the doctor to check it out, I was diagnosed with diabetes."

When her daughter Kendall was born at Swedish Medical Center in Seattle, Washington, researchers approached Julie and her husband, Randy, about participating in TEDDY. They were more than happy to get involved.

Volunteering has involved a certain degree of commitment of time and paperwork.

The staff of Kendall's day care center has had to keep track of her diet when she's there, but they have been very cooperative. "I think the level of difficulty is what you make it," West says. "We volunteered for the study and I plan on continuing with it as long as possible, so we will make time to be there."

West is happy to help diabetes research in any way possible, but is also reassured that Kendall is being closely monitored. "Since I have type 1 diabetes, I'm very curious as to whether she is going to get it and when," West says. "If she does wind up getting diabetes, it won't be quite as much of a shock. We'll be more prepared."

GENES AND DIABETES

Some diseases, such as Huntington's chorea and cystic fibrosis, are caused by a single gene, but type 1 diabetes is different in that a number of genes are involved in the susceptibility to the disease, with some genes raising and other genes lowering the risk. A number of genes known to confer susceptibility and resistance are located in a particular region of a certain chromosome, the HLA region. It is thought that the HLA region is responsible for about 50 percent of genetic predisposition to diabetes. "We usually say that the HLA risk types are necessary but not sufficient for the development of type 1 diabetes," Dr. Lernmark explains.

Scientists don't believe that genetics tells the whole story of diabetes risk, because only 5 to 10 percent of individuals who are genetically susceptible to type 1 diabetes ever develop the disease. "There is a misconception that type 1 diabetes is a familial disease and primarily occurs in families where there is someone with diabetes," says Marian Rewers, M.D., Ph.D., director of the clinical division at the Barbara Davis Center for Childhood Diabetes in Denver, Colorado. "Actually, about 90 percent of children who are diagnosed with type 1 diabetes have no family history of the disease."

The number of cases of type 1 diabetes is growing: "The incidence of type 1 diabetes has been doubling worldwide every 20 years, so it

is twice as high as it was in the mid-1980s. This translates into an increase of about three to five percent a year, which cannot be explained by genetic models or causes," Dr. Rewers explains.

"Something in the environment is causing that."

"Children are getting diabetes at an earlier age," Dr. Lernmark notes. "That presents a major problem for clinicians—that so many children develop diabetes as infants rather than at 10 or 14 years of age." In the area of southern Sweden where Dr. Lernmark's team does its fieldwork, the incidence of children who developed diabetes before the age of two has nearly tripled in recent years. "That doesn't happen by chance. Something in the environment is causing that."

ENVIRONMENTAL FACTORS

It was once thought that a single environmental event, such as a viral infection, must trigger the onset of diabetes, but that thinking has changed. Scientists now believe that multiple environmental factors including infections and diet may raise or lower the risk of developing diabetes throughout the period before the onset of type 1 diabetes.



7,000

The TEDDY study will follow over 7,000 newborns at increased genetic risk for type 1 diabetes.

5%–10%

Only 5 to 10 percent of individuals who are genetically susceptible to type 1 diabetes ever develop the disease.

90%

About 90 percent of children who are diagnosed with type 1 diabetes have **NO FAMILY HISTORY** of the disease

William A. Hagopian,
M.D., Ph.D.



Certain dietary components have been thought to play a role in terms of susceptibility: One hypothesis is that the introduction of cow's milk in the first few months of life may increase the risk of developing diabetes-related autoantibodies—and that breastfeeding may be protective. Some researchers have shown an association between cow's milk and insulin autoantibodies in children, but other studies such as the Diabetes Autoimmune Study of the Young (DAISY) showed no such link. Another

study (BABYDIAB) suggested that cow's milk may even be protective. Some researchers have suggested that this disparity may have to do with when cow's milk is introduced, but the issue is far from settled.

Cereals have also been implicated, but findings have been contradictory. In both the BABYDIAB study in Germany and the DAISY study in Colorado, infants who began eating cereal before the age of three months had a greater risk of having islet autoantibodies (a



x2

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sign of the type 1 diabetes autoimmune attack) after five years. However, these studies observed some differences related to delaying introduction of cereals. DAISY results showed no effect of cereal when introduced to children between four and six months of age—but found that cereal introduction after seven months did lead to increased risk of autoantibodies. In contrast, BABYDIAB found that cereal after six months of age had no effect. This may represent real differences between these populations or differences in how the data were collected, and so the role of cereals is not yet clear.

Another compelling candidate is viral infection. “One of the viruses associated with type 1 diabetes dates back to a 19th-century mumps epidemic in Norway. After the epidemic, there were several children who developed diabetes. And these kinds of case reports have continued to appear in the literature ever since,” says Dr. Lernmark. “It is believed that Coxsackie infections, or other enterovirus infections (viruses located in the intestinal tract), may accelerate an already ongoing autoimmunity. So, once you have immune activity against the beta cells, you may start to lose beta cells. Then, if you get a virus infection, the insulin demand is so high that the remaining beta cells are unable to produce enough insulin and full-blown diabetes develops.”

Modern hygiene may be partly to blame.

Another hypothesis, called the “hygiene hypothesis,” posits that improvements in sanitation may have retrained the immune system in such a way as to increase the incidence of autoimmune diseases, including type 1 diabetes. Many researchers believe that the hygiene hypothesis may explain why the incidence of type 1 diabetes is increasing in countries that were recently Westernized: According to Dr. Lernmark, the incidence is rising 5 percent per



HOW TO VOLUNTEER FOR TEDDY

The TEDDY researchers are screening newborns with and without a family history of type 1 diabetes to determine whether they have high-risk genes. If you have an infant less than 4 months of age and live near one of these study centers, you are eligible for screening and may be able to enroll your child in the study.

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www.teddystudy.org



THE GRAMMERS

Denver, Colorado

Shortly after Lauren Grammer was born at St. Joseph's Hospital in Denver, her parents, Fern and Neal, were approached by TEDDY researchers for permission to test Lauren's blood. About two weeks later the researchers called them to explain that Lauren was genetically at risk for diabetes and to invite them to be part of the study.

"It surprised me because neither of us has a family history of diabetes," Fern Grammer recalls. "They advised us that the genes represented an increased risk, but it was not really an indication that she will get it—the risk is still quite low—so we weren't upset by it."

Grammer volunteered for the study because she wanted to help researchers figure out what triggers diabetes. Participation has involved some inconveniences, such as keeping regular appointments at the TEDDY center,

5%

The incidence is rising by 5% per year in Finland and Sweden, the two countries with the highest incidence rates in the world.

Children are developing diabetes at an earlier age.

year in Finland and Sweden, the two countries that have shown the highest incidence in the world. Yet, in Poland, which was more recently modernized, newly tracked rates of incidence show an increase of 11 percent per year. "The hygiene hypothesis would suggest that recently Westernized countries are developing diabetes much faster because they now have better access to sanitation," he explains.

New hypotheses are emerging all the time. Small studies have implicated such culprits as psychological stress, artificial sweeteners, caffeine, and toxic compounds found in smoked meat and fish. However, the roles of these and other environmental factors in the development of type 1 diabetes are far from clear.

ALONG COMES TEDDY

To help understand the ways these environmental factors interact with individuals' genes, the National Institutes of Health (NIH), JDRF, and the Centers for Disease Control and Prevention (CDC) initiated the TEDDY study in 2002.

TEDDY is designed to follow newborn infants until they reach the age of 15, taking note of which environmental factors—and their timing—are associated with an increased or decreased risk of developing type 1 diabetes.

"Many different groups have been trying to study the environmental factors involved in the development of type 1 diabetes, but none of the groups alone had sufficient statistical power and they were not collecting data in a coordinated, standardized way," explains Beena Akolkar, Ph.D., director of the immunopathogenesis and genetics of type 1 diabetes program at the NIH in Bethesda, Maryland, and program officer of TEDDY. "We decided to put together a consortium of different clinical centers to take part and collect the samples so that all the study criteria would be the same. That would give us the statistical power to properly analyze the data."

TEDDY is pooling the patients, data, and resources of several participating clinical centers (see sidebar, page 28) and a data coordinating center at the University of South Florida in Tampa. The clinical centers will screen newborn babies from the general population who have high-risk HLA types as well as newborn babies with first-degree relatives (a parent or sibling) with type 1 diabetes.

"From an epidemiology standpoint, the best way to look at and analyze risk factors is to



collecting stool samples, having Lauren's blood tested, and also keeping a detailed record of her diet. "It's a little tough to keep track of everything one eats over three days. Once you start looking at what you eat, you realize how complicated spaghetti sauce can be, considering all of the ingredients that go into it," she says.

Still, for her, the benefits of participating far outweigh the drawbacks. "Everyone at TEDDY has been helpful, friendly, and accommodating, and they seem so excited about their project. If Lauren were ever to develop diabetes, I hope that we would be able to identify the cause sooner than later and have access to really good information from an expert source," she says. "When she grows up, participating in the study will be the basis for talking about volunteering and being a good citizen."

"It surprised me because neither of us has a family history of diabetes."

study a group that is at an elevated risk. That way we get to see enough 'events'—that is, children who develop autoimmunity or diabetes. If we were to study a low-risk group, we would need to study many thousands more to register an equal amount of events. So, we're studying first-degree relatives, who have a tenfold risk of developing diabetes compared with the general population," explains Jeffrey Krischer, Ph.D., co-chair of the TEDDY study group and professor in the department of pediatrics at the University of South Florida. "On the other hand, most cases of type 1 diabetes occur sporadically in the general population, so we need to look at both groups. Then we can look at the gene and environmental interactions to see what factors appear to either initiate or promote the process throughout the first 15 years of life."

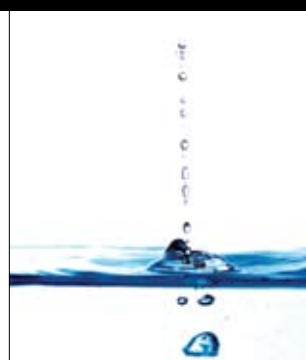
TEDDY researchers hope to recruit 6,000 newborn babies from the general population who have been identified with certain high-risk genes, and 1,100 newborns who have first-degree relatives with type 1 diabetes and high-risk genes. Over the course of the 15-year follow-up of these newborns, the TEDDY researchers will continually monitor the introduction of certain foods in the infant's diet, including cow's milk, cereal products, and vitamin D; the development of viral infections such as enteroviral infections; pesticide exposure; vaccinations; exposure to

pets; and psychosocial issues such as stress. They will see who develops diabetes-related autoantibodies or full-blown type 1 diabetes, and take note of any statistical links between these environmental factors and the risk of developing diabetes.

"Past studies helped us formulate the hypotheses for the TEDDY study," says Dr. Krischer. "Previous studies were limited in size and could not follow patients for a long period of time. We have a much larger cohort here, followed in a much more systematic fashion. Here we can look at not only individual environmental exposures that others have examined, but also the combinations of various exposures. And we're able to do that in a much more systematic way."

High genetic risk does not mean a guarantee of developing the disease.

"In previous studies, we were getting answers but it was taking a long time," says Dr. Rewers, who is principal investigator of the Barbara Davis Center TEDDY site in Denver. "Now, when we combine forces from centers



15 years

Over the course of the 15-year follow-up of these newborns, the TEDDY researchers will continually monitor the introduction of certain foods in the infant's diet, including cow's milk, wheat products, and vitamin D; the development of viral infections such as rubella, mumps, and Coxsackie virus; pesticide exposure; vaccinations; exposure to pets; and psychosocial issues such as stress.



THE BROWN FAMILY

Denver, Colorado

"Since my husband has diabetes, we knew that there was a chance that we would have a child or children who would either be a carrier or would actually develop diabetes," says Sonja Brown, who lives with her husband Chris, one-and-a-half-year-old son Keller, and two chocolate Labradors, in the Denver area. As it turns out, Keller does have a genetic profile that puts him at increased risk for type 1 diabetes.

"Keller's pediatrician, whose son was actually in the DAISY study, suggested that we go and have Keller tested for diabetes-related genes. That's how we found out that, lo and behold, Keller does have high-risk genes," Brown says.

She and Chris decided to enroll Keller in TEDDY not only to help the cause of diabetes research but also to have Keller closely monitored for the development of the disease. She keeps detailed records of any medications he



50,000

TEDDY centers in four countries are screening 50,000 children each year. The size of the study provides the statistical power to rule out causes of disease with better accuracy.

"Something is turning our immune systems against us, and we have to find it. Not only to prevent the disease, but also to invent a cure."

in four countries, we're screening 50,000 children each year. The size gives us the power to detect or rule out causes of disease much faster and much more accurately than any single-center study could do."

According to Dr. Krischer, the differences between Europe and North America may be very valuable in terms of collecting data. "There are different customs, and those differences really help us. If everybody introduced food in exactly the same way, it would be impossible to see whether food really plays a role. If we have one group receiving cow's milk and another group that emphasizes breastfeeding, and early introductions of cereals versus later introduction, it will allow us to see which of these factors plays a role."

"One important issue in previous studies was recall bias," says Dr. Rewers. Imagine a situation where a child is diagnosed with diabetes and you ask the parents, 'When did you start giving wheat or cow's milk formula to

your child?' Often this will be ten or fifteen years after the fact, so the recall is understandably poor. Our advantage is that TEDDY is a prospective study, which means that we record events such as viral infections and dietary changes as we go along."

According to Dr. Krischer, the database and repository of serum, plasma, stool, toenail, and other samples they collect will make it possible for researchers to test new hypotheses in the future.

"There is currently no disease that has been prevented through high-tech instruments or gene therapy," admits Dr. Rewers. "On the other hand, we have prevented a lot of death and disease by immunization and hygiene and removal of environmental factors that can cause disease. Something is turning our immune systems against us. Whatever it is, it's in the environment and we have to find it—not only to prevent childhood diabetes, but also to invent a cure, because that's where we're headed."

is given, when various foods are introduced into his diet, and the symptoms of any illnesses he has. Four times a year, they go to the TEDDY clinic so that Keller can be examined.

The Browns find Keller's involvement in the study reassuring. "When Chris developed diabetes, he lost a lot of weight, got very thirsty, and felt generally awful. No one knew that it was because of diabetes. With Keller, if any of his antibodies change, we'll know he'll probably have diabetes within a couple of years. This way, if any of the symptoms show up, it won't be a guessing game," Sonja says.

Whereas some parents might be on pins and needles waiting for test results, the Browns take it all in stride. "Chris has had diabetes for 28 years and is still healthy, so we know that there are worse diseases out there. Diabetes is at least manageable," says Brown. "We both feel that, if he gets it he gets it—and if he doesn't, that's even better!"

The Browns find the study reassuring. "If any of the symptoms show up, it won't be a guessing game."

THE BENEFITS OF VOLUNTEERING

According to William A. Hagopian, M.D., Ph.D., principal scientist at the Pacific Northwest Research Institute and clinical associate professor of medicine at the University of Washington in Seattle, TEDDY researchers are especially eager to find participants who have first-degree relatives with diabetes. He offers a number of benefits of volunteering for TEDDY.

"Just going through the screening process tells you whether your child has a one in thirty chance of getting diabetes, based on HLA type, or no more risk than the average child, which should put your mind at ease. Those who are enrolled in the study have their antibodies tested every three months. If the antibody tests continue to be negative, you can be reassured that the child is not at increased risk. If your child tests positive for antibodies, you can look for the warning signs of diabetes. That way, if your child is diagnosed with diabetes, the diagnosis comes earlier rather than later. Studies

have proven that early diagnosis decreases the likelihood of hospitalization, decreases illness at onset, increases residual beta cell function, and decreases the long-term insulin dose while improving glycemic control," Dr. Hagopian says. "Some of our families also find it very exciting to participate in research that they strongly feel will make a real difference ten or more years down the line." ●



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