PATIENT PROFILE

Jodie and Dillon Distel

Participating in Clinical Research To Fight against Type 1 Diabetes

Jodie Distel had just given birth to her son, Dillon, at St. Joseph's Hospital in Denver, Colorado, when she was asked if she would like to participate in something called the Diabetes Autoimmunity Study in the Young, or DAISY. The study, she was told, would initially involve a fairly simple test: Blood from her newborn son's umbilical cord would be screened for genes that could indicate whether he was at high risk for developing type 1 diabetes.

"I didn't know very much about the disease," says Jodie, "but I figured that if taking part in the study might benefit someone else's child or my own son, that it was okay with me." She signed up for the study on the spot.

Within a week after Dillon's birth, Jodie was taken totally by surprise to learn that test results indicated that Dillon was at high risk for developing type 1 diabetes. Later, Jodie recalls, study staff alerted her that it was extremely likely that Dillon would have the disease by the time he was eight years of age. In fact, exactly three days after his seventh birthday, Dillon was formally diagnosed as having the disease.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

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About Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that destroys a person's ability to produce insulin, a critical hormone the body needs in order to convert sugar from food into life-sustaining energy. Type 1 diabetes most frequently strikes people in childhood, adolescence, or young adulthood. It is characterized by elevated levels of blood glucose, or sugar, which lead to other serious health complications, including eye, kidney, and nerve disease. Adults with type 1 diabetes are also at much greater risk of death from heart disease than adults without diabetes.

Because there is not yet a cure for the disease, people with type 1 diabetes face a daily struggle to manage their disease and prevent complications over the long-term. They must monitor their blood sugar levels and administer insulin via shots or an insulin "pump" every day to enable muscle, fat, and other tissues to absorb sugar from the blood for conversion to energy, and to try to keep blood sugar levels in a stable, healthy range. To help patients, their families,

and people at risk for the disease, the NIH is supporting research on type 1 diabetes with the aim of disease prevention, improved interventions, and, ultimately, a cure.

What Is DAISY?

DAISY is one in a group of epidemiological studies that researchers are pursuing to better understand the underlying causes of type 1 diabetes. The study is based at the University of Colorado Health Sciences Center in Denver. Marian Rewers, MD, the lead investigator for the study, says: "With DAISY, we have two primary objectives. One is to find out what causes [type 1] diabetes; the other is to find ways to prevent it."

To those ends, DAISY researchers are following two groups of children at risk for type 1 diabetes. One group was identified through screening a general population of newborns—which is how Jodie and Dillon got involved in the study. The other group consists of children who have a parent or sibling with type 1 diabetes.

Children who participate in DAISY are followed until they receive a clinical diagnosis of type 1 diabetes or until age 15, whichever comes first. Follow-up includes interviews with the parents to determine a child's diet and exposure to certain viruses, as well as periodic blood tests for three different antibodies against insulin-producing pancreatic islet cells, starting at nine months of age. Like the initial genetic screening, the antibody tests are used to predict risk of developing type 1 diabetes. The presence of antibodies indicates that the autoimmune process has begun. Dillon's blood tests were negative for antibodies against the insulin-producing islet cells until he reached the age of two, at which time he began showing an elevated level of one antibody. Subsequently, his blood was tested more frequently, every 3 to 6 months. At three-and-a-half years of age, he began showing an elevated level of two antibodies. Other markers for diabetes began to change, as well. Over time, Dillon's levels of a marker called HbA1c began to show an upward trend. Finally, his blood sugar levels became elevated. On December 13, 2004, Dillon was diagnosed with type 1 diabetes. He started on a low dose of insulin, and is currently doing very well; as of January 2006, he has never been hospitalized for diabetes-related conditions. With only about one-quarter of the insulin dose it usually takes at his age, physicians are currently able to keep Dillon's levels of the HbA1c marker at a level consistent with improved long-term health outcomes in persons with type 1 diabetes.

Dillon's case appears to support previous observations that early diagnosis helps, to some degree, to preserve the body's own insulin production. This may be in part due to avoiding a condition called diabetic ketoacidosis (DKA). DKA is a dangerous metabolic condition caused by profound insulin deficiency. Prior to diagnosis, many patients with undetected type 1 diabetes will develop DKA, which, if untreated, places them at risk of diabetic coma and death. However, the severe metabolic disturbance of DKA is not only life-threatening, but also further damages any residual insulin-producing cells. Early detection thus helped Dillon to avert both DKA and DKA's negative impact on his already compromised ability to produce insulin—and, by doing so, likely contributed to his need for less aggressive insulin therapy at diagnosis.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Dillon's mother, Jodie. Now, looking back, she adds that: "participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

The benefits of early detection and preservation of the body's capacity to produce insulin can last many years. In the landmark Diabetes Control and Complications Trial (DCCT), for example, participants who had preserved insulin secretion not only had better blood glucose control and lower insulin requirements, but also had a 50

percent lower risk of eye complications and a 65 percent lower risk of severe hypoglycemia, or low blood sugar (a risk patients face as a result of insulin treatment).

Thus, early detection of type 1 diabetes can provide both immediate and longer term health benefits. "Dillon is in a much better situation than if we had not participated in the study," says Jodie. In addition to testing a child's blood for antibodies and elevated sugar levels, the families of the children who participate in DAISY are educated about what to expect in the way of symptoms, how to do blood sugar tests at home, and more.

By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

As part of the DAISY research efforts, "one of the best things we do is to educate families, from the time their child's screening indicates high risk, straight through to diagnosis, if that should end up being the case," says Michelle Hoffman, RN, the clinical coordinator for DAISY.

Benefits of the DAISY Study

Since December 1993, the DAISY study has screened more than 33,000 newborns in the Denver, Colorado area for genetic markers that would indicate high risk for type 1 diabetes. Of those, the study has followed more than 2,000 children whose genetic screenings indicated that they were at high risk for developing the disease. Of those, 143 children developed islet cell autoimmunity (ICA)—a condition present in the majority of cases of type 1 diabetes, although people with ICA do not always progress to onset of the disease. Of those 143, 48 have developed type 1 diabetes.[1]

"It should be noted," says Dr. Rewers, "that 90 percent of children in the United States diagnosed with type 1 diabetes are hospitalized at the onset of the disease, and nearly one-third of those enter the hospital with diabetic ketoacidosis (DKA)." According to Dr. Rewers, approximately 100 children die each year of DKA. However, of the 48 children in the DAISY study who went on to develop full-blown type 1 diabetes, only one—an 11-month-old infant—needed to be hospitalized at disease onset.

Therein lies one of the benefits for participants in the DAISY study: By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Jodie lived for seven years with the hope that Dillon would never be diagnosed with type 1 diabetes. However, when the diagnosis came, she was knowledgeable. "Because of the DAISY program I think Dillon and I were prepared to handle Dillon's being diagnosed, and I think we had to go through far less than any other child and family who do not have the benefit of learning and recognizing early indications of this life-changing disease," she says. "From day one, I was told what symptoms to look for and I mentally prepared myself for this day and how I would help Dillon from that day."

Because diabetes is an insidious disease, "most families are blindsided; they don't know what to look for to recognize onset of the disease," says Dr. Rewers. "When eventually diagnosed, the overwhelming majority of these children end up in the hospital, and many are fighting for their lives—at great emotional expense to themselves and their families, and financial expense to our society." He adds, however, that until researchers can discover and develop prevention strategies to arrest disease onset, they do not currently recommend extending screening programs outside of the research setting.

Research Findings

In addition to refining ways to recognize a genetic predisposition to diabetes and to pursue effective family follow-up, DAISY also has been responsible for a number of significant findings. "For example," says Dr. Rewers, "by closely following these children, we've been able to rule out quite a few environmental factors once suspected as triggers for the onset of diabetes."

DAISY has also opened up new areas for investigation. Researchers, for example, are currently investigating whether the introduction of baby cereals may have something to do with the onset of inflammation in the pancreas that leads to diabetes. "We've discovered through DAISY that if babies at increased risk of type 1 diabetes first eat cereal regularly in their diets before four months of age, or after six months, their risk of islet autoimmunity is four to five times higher than if they begin eating cereal between four and six months of age," says Dr. Rewers. (The current American Academy of Pediatrics recommendation is to breast-feed babies and begin introducing iron-enriched solid foods, such as cereal, beginning at six months of age, if the child is ready.[2]) For children who have a specific genetic marker that is known to strongly predispose individuals to type 1 diabetes, the risk appears to be even greater. According to Dr. Rewers, "these children have an overall increased risk of islet autoimmunity six times higher if fed cereal before age four months, and twelve times higher if cereal is delayed beyond six months, than if they are started on cereal at age four to six months." Research is ongoing to tease out the answers to this and other challenging issues regarding possible causes of type 1 diabetes and factors contributing to its onset.

TEDDY—A Collaborative Effort

In addition to DAISY, other studies have contributed many important insights to advance research on environmental factors in type 1 diabetes. However, there are limitations to smaller studies, such as the number of patients that can be recruited in a given location.

To overcome these limitations, the NIH spearheaded the launch of a long-term, international, collaborative effort to identify environmental triggers of type 1 diabetes. This effort, begun in 2002, is called "The Environmental Determinants of Diabetes in the Young," or TEDDY. Funded by the Special Statutory Funding Program for Type 1 Diabetes Research (see *http://www.T1Diabetes.nih.gov*), TEDDY consists of six centers in the U.S., Finland, Sweden and Germany. The creation of the TEDDY consortium allows for a coordinated, multidisciplinary approach; collection of data and information in a standardized manner; greater statistical power than can be achieved in smaller studies; and the creation of a central repository that includes data and biological samples for use by the scientific community.

Researchers participating in TEDDY—including the Denver investigators who have conducted DAISY—are recruiting newborns who are genetically predisposed to developing type 1 diabetes. They are screening newborns from the general population, as well as newborns who have parents or siblings with the disease. The children will be followed until they are 15 years old or until they develop islet autoimmunity or type 1 diabetes. This long-term study will amass the largest data set and samples on newborns at risk for type 1 diabetes anywhere in the world.

"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.

TEDDY was established by the NIDDK, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, the Juvenile Diabetes Research Foundation, and the American Diabetes Association.

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[1]*These numbers are current as of December 2005.*
[2]*http://aappolicy.aappublications.org/cgi/content/full/pediatrics;115/2/496*

TEDDY is currently enrolling patients. TEDDY enrollment sites in the United States are located in Georgia, Florida, Colorado and Washington state. For more information on enrolling in TEDDY, please see:
http://www.niddk.nih.gov/fund/diabetesspecialfunds/t1d_ctcr/study.asp?StudyID=121