Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Study

DCCT / EDIC

The First 30 Years

Created in recognition of the continued commitment and valuable contributions of the DCCT/EDIC participants by: Annette Barnie, Davida Kruger, Susan Hitt, Lucy Levandoski, Janie Lipps, Gayle Lorenzi, Suzanne Strowig, and Stephan Villavicencio on behalf of the DCCT/EDIC Study Group.

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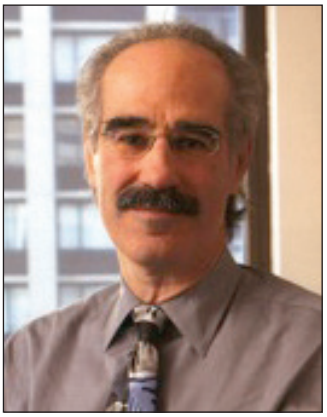
Chairmen's Corner

When we began the DCCT 30 years ago, no one could have imagined we would be celebrating a 30 year anniversary of DCCT/EDIC and marking those 30 years of accomplishments with this booklet. Our achievements have been made possible, first and foremost, by the loyal commitment and unwavering enthusiastic participation of our wonderful research volunteers. This has been coupled with a dedicated team of investigators, study coordinators, colleagues in laboratories and special reading centers, a superb data coordinating center, and unfailing support from NIDDK project scientists, leadership and staff. You should all be proud of what we have learned about type 1 diabetes and its treatment and how much that knowledge has contributed to the care of diabetes worldwide.

With deep gratitude, we dedicate this booklet to our research participants and partners.

Saul M. Genuth, MD



David M. Nathan, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

May 17, 2013

Dear DCCT/EDIC Participants,

Over the last 30 years, you have altered history. Your participation in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study has meant that millions of people with diabetes may prevent or delay debilitating and often fatal complications from the disease.

The DCCT was among the first and most successful multi-center clinical trials of diabetes run by the National Institute of Diabetes and Digestive and Kidney Diseases. The DCCT and EDIC have required a huge commitment on your part and that of your colleagues in research discovery. To commemorate that commitment, this booklet highlights your role in these groundbreaking studies. With your continued partnership, we expect many more important findings in the future.

Our collaboration over the last three decades – the longest of all such type 1 diabetes research partnerships – now serves as a model for how large-scale clinical studies should be accomplished – as a team of researchers, health care staff and participants like you, all working together, with respect for each other and our common goal of bettering the nation's health. The DCCT/EDIC and your role in them have laid the foundation for other clinical studies to prevent and treat diabetes and its complications.

Through the DCCT/EDIC, we have learned that intensive blood glucose control lowers the risk of almost all diabetes complications. Implementing such control as early as possible has long-lasting effects – often called "metabolic memory" – on both early and later-term complications. The results of the DCCT/EDIC form the basis of the standard of care for people with diabetes worldwide.

You are a pioneer. Thanks to you, the outlook for people with longstanding type 1 diabetes has been transformed, as has the understanding of type 1 diabetes and its complications. As you read through the pages of this booklet, you'll see the full breadth of scientific discoveries that you helped create.

From your colleagues at the National Institutes of Health, thank you. Thank you for your dedication to bettering human health and your professionalism in being a true research partner, both of which have led to so many crucial advances in the knowledge of diabetes and diabetes care. The effects of your extraordinary and steadfast commitment will be felt in the healthier, happier lives of people with diabetes, now and in years to come.

With best wishes for good health,

Griffin P. Rodgers, M.D., M.A.C.P.
Director, NIDDK

Judith E. Fradkin, M.D.
Director, NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases

Catherine C. Cowie, Ph.D., M.P.H.
Director, NIDDK Diabetes Epidemiology Program

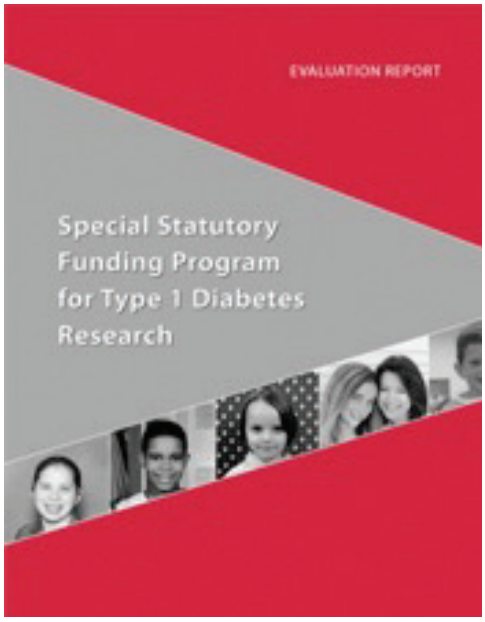
Evaluation Report:

Special Statutory Funding Program for Type 1 Diabetes Research

Prepared by the NIDDK for the U.S. Congress, 2007

The United States Congress awarded the NIDDK specific funding for type 1 diabetes research for fiscal years 1998-2008. In 2007, an evaluation report was prepared by the NIDDK summarizing the work that was being supported by this funding. Within this publication, the DCCT/EDIC was highlighted in a major article entitled: "Story of Discovery: The DCCT/EDIC Research Group".

The "dramatic and positive results have had a profound impact on clinical practice for the management of type 1 diabetes:



- It led to the development of clinical guidelines by the American Diabetes Association (ADA) and other groups;
- It spurred the creation of the National Diabetes Education Program to disseminate the findings to the public (www.ndep.nih.gov); and
- It stimulated multifaceted research efforts to develop tools and therapies that aid patients in achieving close control of blood glucose levels…"

" The DCCT and EDIC studies also demonstrate how the long-term investment in research continues to have a profound impact on the health of patients…"

This report can be accessed at:
https://catalog.niddk.nih.gov/detail.cfm?ID=1063

How It All Began

The treatment for people with type 1 diabetes has come a long way since that January day in 1922 when the first injection of a crude brown liquid, later called insulin, was given to a 14 year old boy who was hospitalized in Toronto, Canada and near death as a result of uncontrolled diabetes.

Prior to the discovery of insulin in 1921, children diagnosed with type 1 diabetes (formerly known as juvenile diabetes) lived for weeks or months, seldom for years. At that time, the only treatments available were agonizing programs of dietary restriction and extreme exercise that only delayed the inevitable. The discovery of insulin was the single most important breakthrough in diabetes therapy. It changed the course of diabetes treatment and saved countless lives.

By the late 1930's, it was clear that diabetes could be treated with insulin to prevent death, but living with diabetes was accompanied by previously unseen, disabling, and often fatal long-term complications of the disease. There was much debate and controversy about the extent to which elevated glucose (sugar) levels and other metabolic abnormalities that are the hallmark of diabetes caused or contributed to these long-term complications. It took nearly 60 years after that first insulin injection to begin the research study that could answer this question – the Diabetes Control and Complications Trial (DCCT). Why did it take so long?

The first insulin preparations contained impurities which often caused allergic reactions and skin infections. The actual amount of active insulin varied from one batch to another, making precise dosing impossible. Large volumes of this early insulin needed to be given using a very large needle that had to be sharpened by hand when it became dull. Since the first insulin preparation was short-acting (called Regular insulin), these painful injections had to be given several times per day.

Glass syringe originally used for insulin injections.

Over the next few decades, great strides were made to produce purer and longer lasting insulin in more reproducible standard concentrations. A long-acting insulin, Protamine Zinc Insulin or PZI, was marketed in 1936, followed by Neutral Protamine Hagedorn (NPH insulin) in 1950, and the Lente insulins (Lente, Semilente, and Ultralente) in 1951. Many individuals with type 1 diabetes

received just one injection per day of a long-acting insulin, with or without Regular insulin. More purified insulins were marketed in the late 1970's.

Clinitest tablet urine chart

Testing the urine for glucose, although imprecise, was the earliest primary method for monitoring diabetes control. An eye dropper was used to mix urine with a special solution which had to be provided by a doctor. The liquid was boiled for several minutes and the resulting color was compared to a standard color chart. In 1941, the Clinitest® tablet eliminated the need to apply heat to the urine solution. The first dip-and-read urine glucose test strip was marketed in 1956 which made testing more convenient but not more accurate.


Urine glucose test strips

In 1964, British investigators devised and Miles Laboratories produced the Dextrostix®, a strip for testing finger stick blood glucose levels. Five years later, the first portable glucose meter became available. Although originally marketed for use by health care professionals in the hospital setting, the meter proved to be effective for self-testing of blood glucose at home. Compared to today's meters, this device was large, difficult to use, expensive, and generally not covered by insurance.

Older home blood glucose montoring meters

By the mid to late 1970s, standard diabetes care for type 1 diabetes consisted of 1-2 insulin injections per day along with daily urine glucose testing. These treatment regimens and those that preceded them couldn't provide "physiologic" insulin replacement that imitated normal insulin secretion. The glucose levels achieved were far from normal. Some diabetes professionals were beginning to try more intensive diabetes therapy to achieve more normal insulin and glucose levels using multiple daily insulin injections of both short and long-acting insulin combined with home blood glucose monitoring and daily dose adjustments. In the late 1970's, insulin pumps were

under investigation, although early pumps were large (the size of a brick) and cumbersome to use. It was not until 1979, when the hemoglobin A1c (A1c) blood test was introduced, that the long-term impact of intensive insulin regimens on glucose control could be evaluated. The A1c test provided an objective assessment of the average blood glucose level over the previous 2-3 months. This provided health care professionals, researchers and patients with a relatively simple means of determining an individual's overall glucose control. While the A1c was a much more useful measure than a single fasting or random blood glucose test, it was not a substitute for daily blood glucose testing.

Early insulin pumps

Thus, by the late 1970s, the tools needed to conduct a study to objectively test the hypothesis that near-normal blood glucose levels would delay or prevent diabetes complications were available. At the start of the DCCT, the effect of intensive therapy on the development and progression of diabetic complications was unclear based on existing data. In 1981, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), a branch of the National Institutes of Health (NIH), gave the go-ahead to leaders in the diabetes field to design a study that would compare the effects of standard diabetes care versus intensive diabetes care on the development and/or progression of diabetes complications over 10 years. In March of 1982, the planning phase of the Diabetes Control and Complications Trial (DCCT) began. Screening of prospective candidates for the study was initiated in 1983 and in August of that year, the first participant was randomized at the Mayo Foundation in Rochester, Minnesota. The last person was randomized in 1989 at the University of Washington in Seattle . . . and the rest is history.

The Diabetes Control and Complications Trial (DCCT)

Goals and Study Design

The Diabetes Control and Complications Trial (DCCT) was designed to determine the relationship between glucose control as assessed by A1c and the long term complications of diabetes. The primary goals of the DCCT were to compare the rate of onset and/or progression of diabetic eye disease (retinopathy), nerve disease (neuropathy), kidney disease (nephropathy), and heart and blood (cardiovascular) disease between an intensive treatment group and a conventional (or standard) treatment group. Intensive treatment consisted of 3 or 4 injections of insulin per day or use of an insulin pump, frequent daily blood glucose tests, and active dose adjustments to achieve glucose levels as close to the non-diabetic range as possible. Conventional treatment consisted of 1 or 2 injections of insulin per day and less frequent glucose testing, which was the standard treatment for type 1 diabetes at the time. Each participant agreed to be randomly assigned to either the intensive or the conventional treatment group. Random assignment meant that neither the participant nor the DCCT health care team knew in advance nor could choose what the treatment assignment would be. Random assignment was necessary to ensure that the two groups were as alike as possible at the beginning of the study in order to avoid treatment selection bias which would invalidate the study results.

Screening and Testing

In 1983, members of the study group at the initial 21 DCCT Clinical Centers in the United States and Canada began screening prospective candidates between the ages of 13-39 years. In 1986, 8 additional clinical centers were added to bolster recruitment efforts. As a prospective participant, you went through a laborious series of tests over a 4 month period to determine your eligibility, and ability and willingness to perform the procedures required for the study.

Testing in the DCCT, and subsequently in EDIC, addressed the major complications associated with diabetes. Evaluations of many organs and body systems took place. Test results from participants with no evidence of eye or kidney damage would help answer the question about the role of glucose control on prevention of diabetes complications (primary prevention group), while those with mild eye or kidney damage would help answer the question about the role of glucose control on the progression of diabetes complications (secondary intervention group).

Table 1. DCCT / EDIC Clinical Centers

Clinic	Name	Location
1	Case Western Reserve University	Cleveland, Ohio
2	University of Pennsylvania	Philadelphia, Pennsylvania
3	Cornell University	New York, New York
4	Henry Ford Medical Center	Detroit, Michigan
5	Joslin Diabetes Center	Boston, Massachusetts
6	Massachusetts General Hospital	Boston, Massachusetts
7	Mayo Clinic	Rochester, Minnesota
8	Medical University of South Carolina	Charleston, South Carolina
9	International Diabetes Center	Minneapolis, Minnesota
10	University of Iowa	Iowa City, Iowa
11	University of Minnesota	Minneapolis, Minnesota
12	University of Missouri	Columbia, Missouri
13	University of Pittsburgh	Pittsburgh, Pennsylvania
14	University of Tennessee	Memphis, Tennessee
15	University of Texas Southwestern	Dallas, Texas
16	University of Toronto	Toronto, Ontario, Canada
17	University of Washington	Seattle, Washington
18	University of Western Ontario	London, Ontario, Canada
19	Vanderbilt University	Nashville, Tennessee
20	Washington University at St. Louis	St. Louis, Missouri
21	Yale University	New Haven, Connecticut
22	* Albert Einstein University	Bronx, New York
23	Northwestern University	Chicago, Illinois
24	University of California San Diego	San Diego, California
25	University of Maryland	Baltimore, Maryland
26	University of New Mexico	Albuquerque, New Mexico
27	University of South Florida	Tampa, Florida
41	University of Michigan	Ann Arbor, Michigan
42	** University of British Columbia	Vancouver, British Columbia, Canada

* Former DCCT/EDIC clinic

** Former DCCT clinic

Eye Function

Diabetes-related eye disease (retinopathy) includes the development of abnormal blood vessels in the retina (back of the eye). These abnormal blood vessels can leak and cause swelling or edema of the macula (the area of the retina that is responsible for central vision) or growth of new blood vessels that are fragile and break and bleed (proliferative retinopathy).

Before entry into the DCCT, an ophthalmologist (eye doctor) examined your eyes and a specialized photographer took photos of your retina to determine if you had any eye disease or only mild eye disease related to diabetes. Some of you had an injection in a vein in your arm of a special dye called fluorescein to provide more information about the health of the retinal blood vessels. During the DCCT, we did eye exams yearly, and we obtained eye photos every 6 months to document the first appearance (development in the primary group) or significant worsening (progression in the secondary group) of retinopathy.

General and Cardiovascular Health

Basic blood tests, along with a medical history and physical examination, were completed during the screening period. Cholesterol and triglyceride levels had to be within an acceptable range. An electrocardiogram (EKG or ECG) was done to be sure that you did not have significant heart disease.

C-peptide (a by-product of insulin production that is used as a marker of insulin secretion) levels were measured prior to entry into the study to determine if your pancreas was producing any insulin. Blood samples were obtained before and 90 minutes after you drank a milkshake-like breakfast without taking your usual morning insulin until after the test was completed. Your C-peptide levels had to be consistent with those seen in type 1 diabetes to be eligible to participate in the DCCT.

Kidney Function

Kidney function was measured by a 24-hour urine collection you completed at home (storing the container of urine in the family refrigerator was quite a challenge) and a 4-hour urine collection we obtained at the clinic. In order to be eligible for the study, you had to have normal kidney function (primary group), or only very early signs of diabetic kidney disease (secondary group). We continued to obtain a 4-hour urine collection annually during the DCCT and for many years in EDIC. You also had a special kidney procedure that involved an injection of a small amount of radioactive iodine followed by the collection of frequent timed urine and

blood samples. We performed this test three times during the DCCT. Fortunately, there are now easier and equally reliable ways to measure kidney function.

Nerve Function

There are two broad categories of neuropathy that are of special interest in diabetes: peripheral and autonomic. Peripheral neuropathy refers to damage to the nerves in the arms and legs that are involved with sensation and movement. Autonomic neuropathy refers to damage to the nerves that control body functions, such as changes in heart rate or blood pressure which are not under your conscious control.

A neurologist performed a complete neurological exam to evaluate nerve function. This included a nerve conduction test which involved applying a small electrical current to nerves in your arm and leg. These tests were done 3 times during the DCCT.

We measured autonomic ("automatic") nerve function every 2 years during the DCCT. The testing involved breathing in and out while following a "pacer" light, standing for 10 minutes while blood pressure was measured frequently, and blowing into a mouthpiece (or tube) for 20 seconds.

Cognitive Function

When the DCCT started in 1983, diabetes professionals wondered if any change in information processing ability would develop over the course of the study. More specifically, would frequent episodes of severe hypoglycemia (episodes that resulted in loss of consciousness or seizure) often associated with this treatment lead to changes in cognitive function (thinking ability) over time, especially in teenagers?

The DCCT protocol included psychometric (neurobehavioral) tests that measured learning, memory, information-processing speed, and problem-solving skills. You were asked to recall stories you were told by the psychometric tester, and you were asked to provide word definitions, put blocks in holes while blindfolded, do a finger-tapping exercise, and complete some paper and pencil tests. These tests were done 3 to 4 times during the DCCT. To some of you, the testing was reminiscent of being in school!

Dietary Assessments

The DCCT dietitians used standardized forms and interviews to determine dietary habits. The dietitians assessed your usual dietary intake with the help of plastic food models and pictures of different sizes of spoons, bowls and plates. Each year you were asked to fill out a questionnaire and recall the amount and number of times you ate various foods and took vitamin supplements. This was done to compare dietary factors with other test results, like cholesterol levels.

Self-Care Practices

During screening, you had to jump through a series of hoops to determine if you were ready to participate in the DCCT. We assessed your knowledge of diabetes management, such as how to deal with low blood glucose levels, and asked you to keep daily records of insulin injections, glucose tests, and food intake. And, then there were the ProfilSets. You were asked to collect blood from a fingerstick into a small glass tube 8 times a day (before and after each meal, bedtime, and at 3:00 AM) during screening and every 3 months during the DCCT.

Social and Family Support

One of your family members or your significant other met with members of the DCCT staff to discuss expectations and attitudes about the study. Because being in the DCCT was a very ambitious undertaking, it was important to know what kind of support family/friends could provide to help you carry out the treatment assignments. We discussed your willingness to accept random assignment to either treatment group. Your ability to follow the requirements of either treatment group for up to 10 years was also discussed at length.

The DCCT research staff conducted these detailed tests to ensure that each person who chose to become part of the DCCT was up to the challenge of being in a study that would establish the best way to manage type 1 diabetes for years to come. We continued to screen potential study volunteers until 1989. By that time, 7,304 individuals with type 1 diabetes had been screened.

Randomization

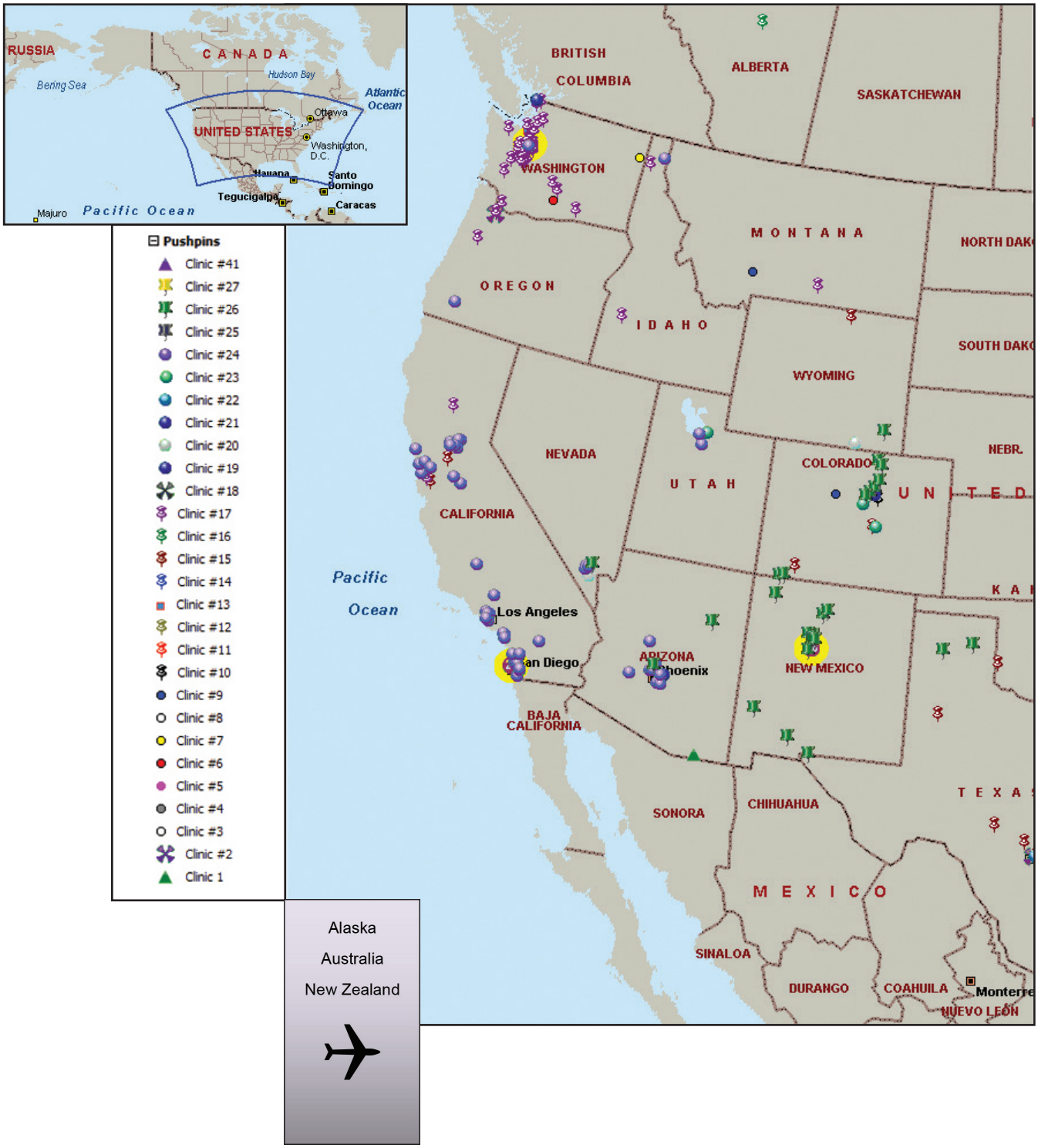
Finally, after all of the screening tests and appointments were completed, a member of the local clinic's research team made a telephone call to the Data Coordinating Center to learn your treatment group assignment – Experimental (Intensive) or Standard (Conventional) Treatment. Some participants hoped for one treatment or the other, but each of you kept your pledge to accept random assignment. Excitement, a sigh of relief, a look of disbelief, and many other emotions were observed that day. A total of 1,441 individuals entered the DCCT – 1,246 adults and 195 adolescents.

Table 2. Participant Age and Duration of Diabetes

In Years	DCCT Baseline 1983-1989	EDIC Year 1 1994	EDIC Year 20 2013
Average Age	27	34	54
Average Duration of T1DM	6	13	33

DCCT participants were randomized between 1983 and 1989. The average age and duration of type 1 diabetes at DCCT baseline represent the average age and duration of all participants when they were randomized into the trial. At the conclusion of the DCCT in 1993, participants had been in the study between 3 and 10 years.

Figure 1. Approximate Location of Participants by Zip Code (US), Postal Code (CAN), and in Other Countries (as of 2011)




CANADA
QUEBEC
NFLD. AND LAB.
MANITOBA
ONTARIO
NEW BRUNSWICK
N.S.
ME.
Montréal
Ottawa
Lake Superior
MINNESOTA
WISCONSIN
MICHIGAN
Lake Huron
Toronto
L. Ontario
Lake Erie
L. Michigan
NEW YORK
MA
Clinical Centers
New York
IOWA
ILLINOIS
INDIANA
OHIO
W. VA.
VIRGINIA
KENTUCKY
MISSOURI
NORTH CAROLINA
TENNESSEE
OKLAHOMA
ARKANSAS
MISS.
ALABAMA
GEORGIA
FLORIDA
LOUISIANA
Houston
San Antonio
Gulf of Mexico
Atlantic Ocean
Nassau
Straits of Florida
THE BAHAMAS
Egypt
England
France
Puerto Rico
United Arab Emirates

After Randomization

The DCCT staff at each clinic included doctors, nurses, dietitians, psychologists, and research and administrative assistants, who educated, supported, and helped you achieve the treatment goals of the study. Participants and staff became part of the "DCCT family". Even though many DCCT staff members had previous experience treating people with type 1 diabetes and using intensive therapy, the DCCT was a new adventure, and we (staff and participants) embarked on this learning experience together.

You dealt with many challenges along the way . . . completing school, changing jobs, moving to distant locations, having children, and coping with all of the trials and tribulations that life can bring. You drove, flew, and took trains, cabs and buses to get to the study visits. Sometimes, if getting to the center for an in-person visit was not possible, the blood and urine samples were obtained locally and your diabetes management history was reviewed by phone. Somehow we managed to work around everybody's schedules and get the job done before the availability of cell phones and email!

The available technology for taking care of diabetes during the DCCT was different than it is today. Rapid acting insulin analogs such as lispro, aspart and glulisine insulin (Humalog®, NovoLog® and Apidra®) and long-acting insulin analogs like glargine and detemir (Lantus® and Levemir®) were not available at that time. Insulin pumps were big and bulky; insulin pens only delivered insulin in 2-unit increments; meters required a much larger drop of blood and took 30-120 seconds to deliver a reading; meter memories were unavailable or difficult to use; and urine testing was still the norm for most people with diabetes as recommended by their healthcare providers.

We had DCCT social events during which you could meet and learn from one another, commiserate, or just have fun. As a team, we relied on each other's wits, determination, and camaraderie to accomplish the study goals.

Staff from all of the DCCT clinical centers met as a group at least three times a year to share information, develop strategies, and maintain motivation to make the study a success. Select DCCT staff members visited other clinics at various times during the study to monitor clinic performance, help solve problems, and provide assistance when needed. An external board of non-DCCT health care professionals monitored the study's progress, emerging results, and participant safety from the beginning.

For all of us, the DCCT provided an opportunity to work with experts in research and diabetes, and establish long-lasting friendships. After completing the work of the study together, the DCCT family proudly presented its accomplishments to the world. These were years and events we will always remember!

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England Journal of Medicine, 1993; 329:977-986.

The external board of experts that was monitoring the progress of the DCCT recommended that the study be stopped one year ahead of schedule because the results were clear and compelling. In June of 1993, while the rest of the diabetes world waited, you and your family members gathered together at individual clinics to hear the results of the DCCT. You, our research partners, had the right and deserved the honor of being the first to learn the news! Members of the study group presented the results a few days later to more than 10,000 scientists and clinicians at the annual Scientific Sessions of the American Diabetes Association and were given a standing ovation.

The primary results of the DCCT were quickly published in The New England Journal of Medicine, the most prestigious medical journal in the world, and were widely communicated to the world-wide diabetes community at scientific and medical meetings. The DCCT proved that keeping blood glucose levels as close to the non-diabetic range as safely as possible was beneficial in reducing the risk of microvascular (eye, kidney, nerve) complications associated with diabetes. Even though intensive treatment caused more hypoglycemia and weight gain, the DCCT showed that it was practical, tolerable and safe when implemented correctly. What did all this mean? For the diabetes community, it meant a significant change in the Standard of Care for type 1 diabetes. Healthcare providers and people with type 1 diabetes were encouraged to use intensive treatment strategies in order to safely bring glucose levels as close to the non-diabetic range as possible. This meant using 3 or more insulin injections per day or an insulin pump along with frequent, daily self-monitoring of blood glucose levels to make timely insulin dose adjustments. The importance of A1c monitoring every 3-4 months was emphasized as a means of tracking overall glucose control.

Importantly, lower levels of glycemic control, as measured by A1c and the frequency of episodes of hypoglycemia that resulted in coma or seizure or required the assistance of another person, were not associated with declines in cognitive function (thinking ability) in adults or teens in the study.

While many wondered whether it was realistic to expect the average person to achieve what you, the research participants, had accomplished in the DCCT, the American and the Canadian Diabetes Associations and other professional diabetes organizations advocated for people with diabetes to achieve A1c goals of less than 7% based upon the DCCT results.

The DCCT became known as THE LANDMARK STUDY for the treatment of type 1 diabetes.

Following the announcement of the DCCT results, each of you met with DCCT clinic staff to learn the results of all the tests you had done during the study. With years of data in hand, you were instructed on how to begin (if you were in the Standard Group) or were encouraged to continue using (if you were in the Experimental Group) intensive treatment strategies with the goal of achieving and maintaining glucose control as close to the non-diabetic range as was safely possible.

When the DCCT ended, the NIDDK (study sponsor) and the study group felt that it was important to continue following participants for an extended period of time in order to learn about the impact of glucose control on later-stage diabetes complications over a longer period of time. Both the investigators and you, our research partners, were eager to continue our long-term collaboration, and with the support of the NIDDK, the follow-up study of the DCCT was born.

Introducing. . .

The Epidemiology of Diabetes Interventions and Complications (EDIC) Study

EDIC was designed as an observational follow-up study. Its major goal was to examine the long term or lasting effects of previous DCCT treatment group assignment and current EDIC therapy on complications that required more time to develop than the 6.5 years of average participation during the DCCT. We wanted to determine whether the major beneficial effects we had observed with intensive therapy on early-stage complications translated into benefits with regard to more advanced small blood vessel (microvascular) complications of the eyes, kidneys and nerves, and to large blood vessel (macrovascular) complications, such as heart disease and stroke.

The beginning of EDIC brought about a number of changes.

- Each of you was taught or urged to continue intensive therapy. Together, we the DCCT research team, had proven that this was important in reducing diabetes complications.
- The DCCT center in Vancouver was closed and their participants were asked to go south to Seattle for their follow-up visits.
- There were organizational changes at the clinics to reflect the fact that visits to the clinical centers were going to be only once per year instead of every 1-3 months. Not surprisingly, this resulted in some separation anxiety!

The year 1993 was a big adjustment for everyone, staff and participants alike. However, the enthusiasm for continuing our study translated into a high level of continued participation, with more than 95% of the original DCCT research volunteers signing up for EDIC.

The DCCT/EDIC is the largest and longest study of type 1 diabetes in the world. As a group, you, the DCCT/EDIC participants represent the most extensively studied population of individuals with type 1 diabetes in history! The impressive list of publica-

tions generated by the DCCT/EDIC research group over the past 30 years is a testament to the impact that your contributions have had on the understanding and treatment of type 1 diabetes. Your extraordinary commitment to attend follow-up visits is unparalleled!

Research Team

Each DCCT/EDIC participant is a member of the DCCT/EDIC research team, along with staff at each clinical center and representatives from the NIDDK, the Clinical and Data Coordinating Centers, and several central laboratories and reading centers. Together, we are responsible for carrying out the work of this important study and sharing what has been learned with the worldwide diabetes community. The diagram in Figure 2 shows the overall organizational structure of EDIC and explains the major responsibilities of each of the DCCT/EDIC research partners.

EDIC Evaluations

Table 3 summarizes many of the assessments that have been included in or added to the EDIC study over the years.

Figure 2: Organizational Structure of EDIC Research Group

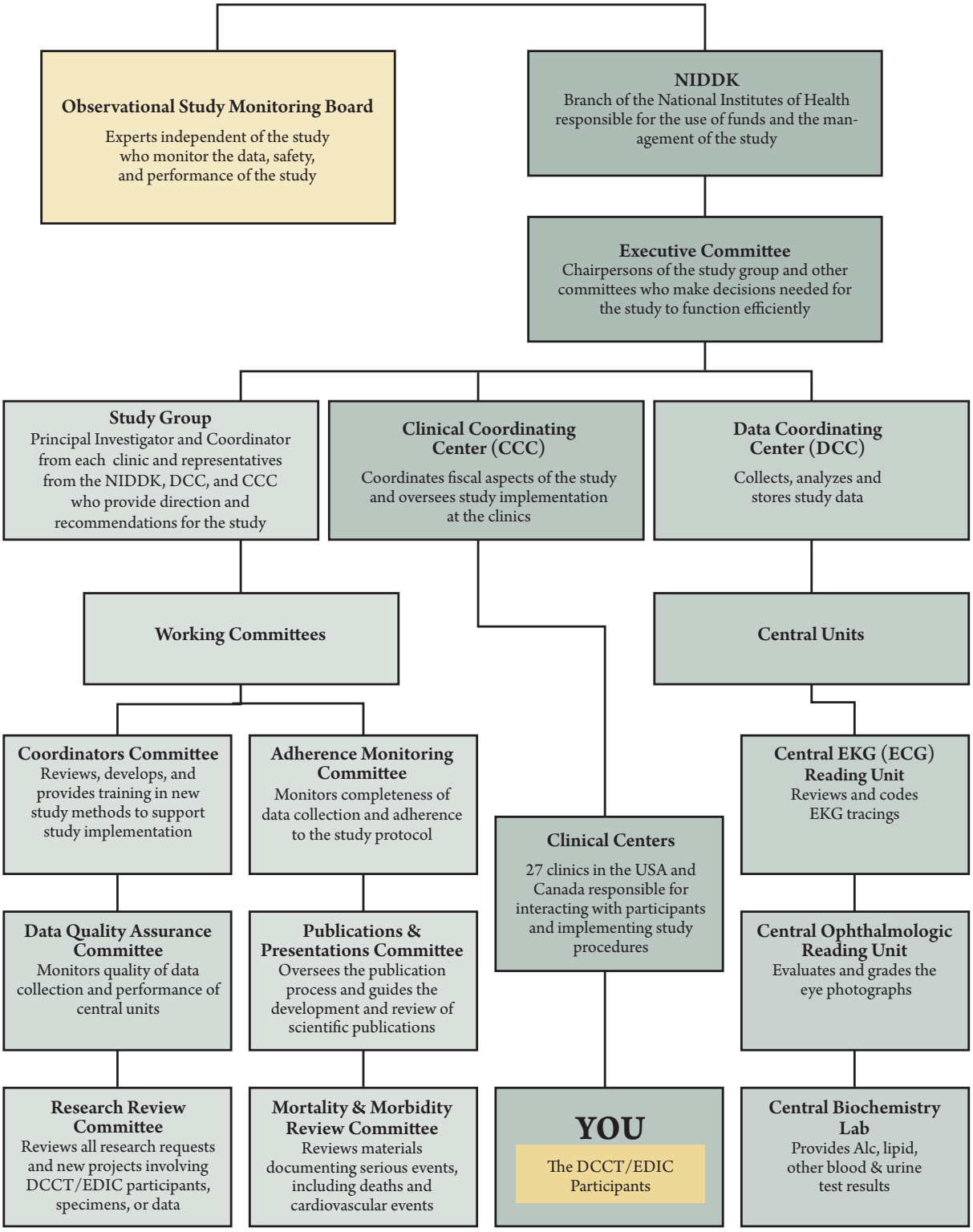
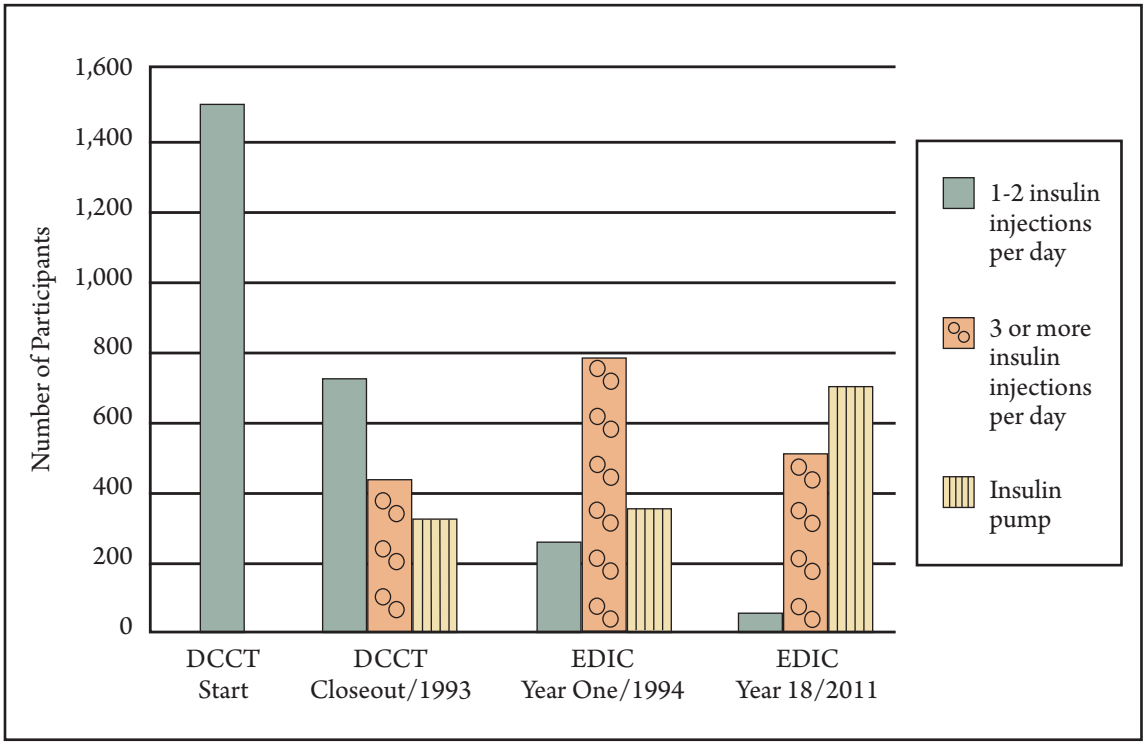


Table 3. EDIC Evaluations

EVALUATION	METHOD	FREQUENCY
Retinopathy (eyes)	Dilated eye exam and eye photos	Every 4 years, plus 1996 and 2006
Nephropathy (kidneys)	Urine and blood collection to assess kidney function	Alternate years
Neuropathy (nervous system)	Symptom questions; measurement of reflexes, sensation, and vibration in lower extremities	Every year
	Vibration test on toes and fingers	2005–2007
	Nerve conduction studies	2005–2007
	Autonomic nervous system testing (paced breathing, blowing in "tube", repeated standing blood pressure)	2005–2007 2009–2011
Cardiovascular	EKG/ECG, sitting blood pressure measurements	Every year
	Ankle:arm blood pressure measurements	Every other year
	Fasting lipid profile	Alternate years
	Carotid ultrasound (blood vessels in neck)	1993, 1996, 2005
	Cardiac calcium computer tomography (CT) scan	2001–2002
	Cardiac magnetic resonance imaging (CMRI)	2008
Cognition	Assessment of thinking, memory, manual dexterity	2004 – 2006
Cheirorthropathy	Hand and shoulder measurements	2011–2012
Genetics	Blood collection from participants and family members	2001–2004
	Epigenetics (in a small group of participants)	2009
Pancreatic Islet Cell Function	C-peptide pilot study to measure insulin secretion	2011–2012
Risk Assessment for Diabetic Complications	Ultraviolet measurement of skin reflectance	2010–2011
	Skin biopsy (in a small number of participants)	1991–1992
Urology	Questionnaires about urinary tract, sexual function	2002–2003; every year since 2010
	Testosterone and prostate-specific antigen (PSA) levels (men)	2010–2011
Retention Survey	Questionnaire about your participation in the study	2009
Health Status and Quality of Life	Self-administered questionnaires	Every 1–2 years

Figure 3. Insulin Delivery During the DCCT and EDIC



Retinopathy (Eyes)

The dilated eye exams and photographs of your retina (back of the eye) provide critical information about the status of your eyes and identify the presence of any diabetes-related eye disease.

The DCCT demonstrated that keeping blood glucose levels close to the non-diabetic range significantly decreased the risk of either developing retinopathy (if it was absent at the beginning) or experiencing further progression of existing retinopathy (if some retinopathy was already present) by more than half. During EDIC, we are learning that intensive glucose control makes a difference in retinopathy, not only in the short term (a few years), but more importantly, it lessens retinopathy in the long run, with persistent benefits seen more than a decade later. We call this effect "metabolic memory" or more simply said: "an ounce of prevention is worth a pound of cure". These results continue to support the importance of good glucose control to reduce and possibly improve the impact of diabetes on the eyes. While the treatment of diabetic retinopathy continues to advance with improved laser treatment and eye injections, the results from the DCCT/EDIC demonstrate that preventing complications, such as

retinopathy, with better glucose control in the first place is far better than any treatment currently available for late diabetes-related complications.

Nephropathy (Kidneys)

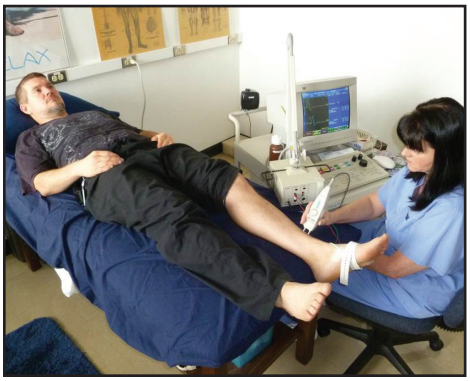
The major function of the kidneys is to filter waste materials from the body. The first and earliest sign of nephropathy is the leakage of a protein, called albumin, into the urine. A little bit of albumin leakage is called "microalbuminuria" and a larger amount is called "macroalbuminuria". Albuminuria (microalbuminuria and macroalbuminuria) is measured in the urine collections you continue to do. If filtering is severely impaired, kidney failure requiring dialysis or transplantation may occur.

The DCCT demonstrated that the leakage of albumin in the urine was decreased by almost half with intensive therapy. Your commitment to the DCCT/EDIC allows evaluation of the continued effects of glucose control over time on the kidneys. A DCCT/EDIC paper, published in the New England Journal of Medicine in 2011, describes the benefits of better glucose control on diabetic kidney disease (nephropathy).

Our long-term follow-up now proves that intensive therapy reduces not only the early stages of kidney disease but importantly, reduces further loss of kidney function. Our results also showed that lower A1c increased the probability of persistent microalbuminuia regressing (improving) to normal albumin excretion. It is likely that this will translate into fewer people requiring dialysis or kidney transplant during their lifetime.

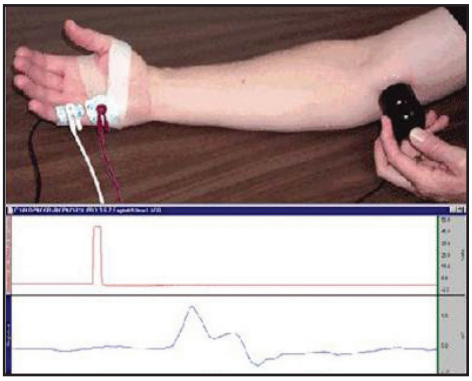
Neuropathy (Nervous System)

Neuropathy is a general term used for nerve damage, and diabetes is among the leading causes of neuropathy. Some studies suggest that as many as two-thirds of all people with diabetes will develop some degree of measurable neuropathy over time. Because neuropathy is such a common complication of diabetes, it was important to measure it during the DCCT and to continue to do so during the EDIC study.



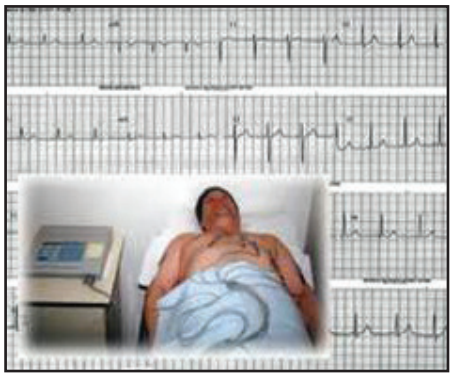
During the DCCT, your peripheral nerve function was measured 2 to 3 times. This was done with an exam by a neurologist (a doctor specializing in the nervous system) and with nerve conduction studies of your leg and arm. Autonomic (automatic) nervous system testing was also done during the DCCT. The DCCT proved that better glucose control prevented or slowed the development and progression of neuropathy by more than half. However, very few of you had developed peripheral or autonomic neuropathy during the DCCT, and in most cases, the signs and symptoms of neuropathy were mild, or there were no symptoms at all.

Repeating some of the DCCT measures of neuropathy and adding some new ones such as questionnaires and more advanced vibration testing during EDIC allowed us to determine the longer-term effects of diabetes and of intensive therapy on peripheral and/or autonomic nerve function. These results continue to support the importance of good glucose control to reduce and possibly improve the impact of diabetes on the nervous system.



Electrocardiogram (ECG or EKG)

Electrocardiograms (ECGs) are the most common method to measure whether someone has had heart damage, such as from a myocardial infarction (heart attack). At the end of the DCCT, very few of you had experienced a heart attack and as a group, you represented a relatively young and healthy population of study participants. After an average of 17 years of follow-up in the DCCT and EDIC, the original intensive therapy group had about a two-thirds reduction in the occurrence of any cardiovascular disease event including heart attacks, strokes, or the need for angioplasty (a procedure to widen or open narrowed or clogged arteries), placement of stent(s) (a tube that is inserted into a clogged artery to improve circulation through the artery), or coronary artery bypass surgery.



Carotid Ultrasound

Several tests to examine abnormalities of the blood vessels that supply the brain and heart have been performed during the DCCT and EDIC. The carotid ultrasound utilizes sound waves (like sonar on a submarine) to measure the thickness of the lining of the carotid arteries in the neck which are the major blood vessels supplying blood to your brain. Thickening of these vessels is part of atherosclerosis or hardening of the arteries, the abnormality that underlies stroke and heart attacks. We looked at the early changes of these vessels in your neck to determine whether intensive therapy slows the thickening that occurs in everyone as they age.

Carotid ultrasounds were performed in 1994, 1999 and 2006. We found that the average A1c levels during the DCCT and EDIC are strongly related to the thickness and progression of thickening in the carotid arteries, meaning that lower A1c levels decrease the progression of atherosclerosis. Blood pressure also influences carotid artery thickness, with higher blood pressure values being associated with the progression of cardiovascular disease, regardless of the level of glucose control.

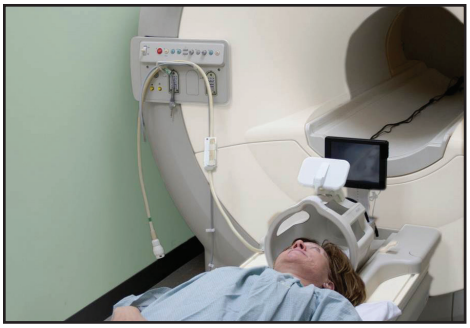
Heart Computed Tomography (CT) Scan

Coronary artery computed tomography (a CT scan of the heart) measures calcification (calcium build-up) in the coronary arteries that supply blood to the heart. This is another indicator of atherosclerosis. This scan was done once between 2000 and 2002.

The results showed that lower A1c levels during the DCCT and EDIC are associated with lower scores or less calcification in the coronary arteries, and that previous intensive therapy reduces atherosclerosis in the heart, as it does in the vessels supplying the brain. Excess fat in the abdomen (measured using the annual waist and hip measurements), smoking, high blood pressure, and high cholesterol levels are also significantly associated with higher coronary artery calcium scores.

Cardiac Magnetic Resonance Imaging (CMRI)

Between 2007 and 2009, cardiac magnetic resonance imaging (CMRI) was performed to assess the structure and function of your heart. Those of you who participated were asked to lie flat on a table and the table entered a tube with whirling noises that can be claustrophobic for some. Many of you also received an injection of an image-enhancing dye to determine if there were any scars in the heart that would suggest a previous undetected injury or silent heart attack. Silent heart attacks occur more commonly in people with diabetes.



Higher average A1c levels during the DCCT and EDIC along with other risk factors such as high blood pressure, smoking, and albumin in the urine (an early indicator of diabetic kidney disease) had a slight but significant adverse effect on the structure and function of the heart. These results not only support the importance of lowering A1c levels, but also the need to address other cardiovascular risk factors such as smoking, high blood pressure, high cholesterol levels, and high urine albumin levels. Despite the average diabetes duration of over 25 years, very few of you have experienced serious heart problems.

Urologic and Sexual Function (URO-EDIC I and II)

The original URO-EDIC project started in 2003 and consisted of a confidential questionnaire we asked you to complete at your annual visit. The purpose of this questionnaire was to learn more about bladder and sexual function problems that both men and women with diabetes may face as they age. We are grateful that so many of you have been willing to provide this personal and private information.

The findings are noteworthy. While one in five men in EDIC reported significant bladder problems, this is less than what is reported in the age-matched general population. In addition, it does not appear that overall lower A1c levels help to reduce the impact of this complication, as it does with other diabetes complications. On the other hand, higher average A1c levels do increase the risk of erectile dysfunction or ED, a form of autonomic neuropathy. Based on information obtained from your responses to the questionnaire administered in 2003, less than a quarter of men reported experiencing erectile dysfunction. The take home message for men… … diabetes control is very important to help prevent or reduce the severity of erectile dysfunction.

For women in EDIC, sexual problems are related to depression, but not to the level of diabetes control as measured by A1c. Urinary tract infections (UTIs) are not related to glucose control. Bladder problems (leaking urine) in women are associated with being older, overweight, and having had previous urinary tract infections. The take home message for women . . . losing weight and properly treating UTIs may help prevent or reduce the severity of bladder problems.

The URO-EDIC II, started in 2010, will continue to investigate bladder and sexual function in the DCCT/EDIC group. Blood samples for testosterone (male hormone) and prostate specific antigen (PSA) were obtained in men. We will continue to ask you, both men and women, to complete a brief questionnaire every year for the next few years to further explore bladder and sexual health issues and their impact on your quality of life. In addition, we hope to be able to study hormonal changes in EDIC women in the future.

Cognition (Information Processing by the Brain)

The DCCT utilized a detailed and demanding evaluation of cognitive performance (how the brain processes information). This detailed testing was needed to determine if there was a difference in cognitive function over time between the two diabetes treatment groups. The good news at the end of the DCCT was that there was no difference in cognitive function between the treatment groups in both adults and adolescents.

The same evaluation was repeated 12 years after EDIC began. The results of this evaluation were similar to those in the DCCT. Specifically, there are no differences in cognitive function in adults or adolescents between those of you in the former intensive group compared to the conventional treatment group, or in those of you who had experienced multiple episodes of severe hypoglycemia during the DCCT/EDIC. What we did find was that persistently high blood glucose levels, as measured by A1c over the course of the DCCT/EDIC study, lead to modest decreases in performance on tests that require mental and motor speed. This finding has also been reported in other studies comparing individuals with diabetes to those without diabetes. Those of you with more advanced retinopathy and kidney disease also showed modest decreases in performance on tests requiring mental and motor speed.

Quality of Life

Assessing quality of life is important as it provides insight into the impact that diabetes and its treatment has on emotional well-being and the balance between the perceived benefit and burden of therapy. As we now know, intensive therapy prevents or slows the development of complications, but it requires greater effort to achieve near-normal glucose levels and is associated with more frequent hypoglycemia which could affect quality of life. You have completed the Diabetes Quality of Life (DQOL) questionnaire at least every two years to better understand the impact of diabetes and its treatment on your quality of life. Your responses to these questionnaires indicate that intensifying treatment using pumps and multiple daily injections has not had a negative impact on your overall quality of life or general well-being.

Advanced Glycation End-products (AGEs)

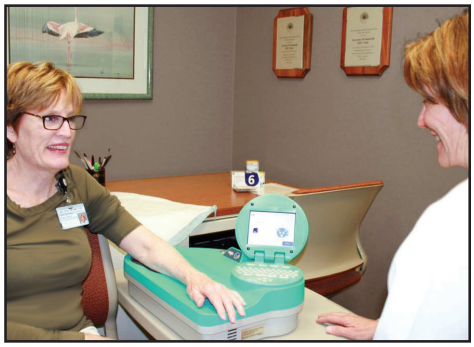
Glucose combines with body proteins to form substances called advanced glycation end products or AGEs. These AGEs are a measure of metabolic stress and form at a slow, constant rate in everybody regardless of whether diabetes is present. This is part of the normal aging process. However, the formation of AGEs is accelerated in people with diabetes because there is more glucose present in the tissues of the body. The build-up of AGEs is thought to contribute to a variety of diabetic complications. During DCCT/EDIC, you have participated in several tests that measured advanced glycation end-products (Skin Biopsy and SCOUT studies) or measured the effects of increased advanced glycation end-products on body function (cheiroarthropathy).

Skin Biopsy Study

Near the end of the DCCT (1991-1992), 216 of you (from 8 DCCT clinics) volunteered to have a skin biopsy taken from your gluteus maximus or derrière: the memorable "butt biopsy". The skin biopsies allowed us to measure advanced glycation end products or AGEs in the skin and to examine their relationship to complications, similar to our analyses of A1c levels and complications.

The results of this study showed that AGEs are increased in proportion to the A1c levels. Moreover, individuals with complications (retinopathy, nephropathy, and neuropathy) had higher levels of these AGEs than individuals without complications. Even more importantly, the AGE levels appear to be a more powerful predictor of complications than the A1c levels, suggesting that the attachment of glucose to structural proteins may be the cause of complications. Finally, individuals with higher levels of AGEs appear to be more likely to develop or experience worsening of complications over time. The DCCT/EDIC is one of the few studies in type 1 diabetes that helps explain the mechanism by which high blood glucose levels lead to complications. Our improved understanding may lead to new interventions to prevent complications.

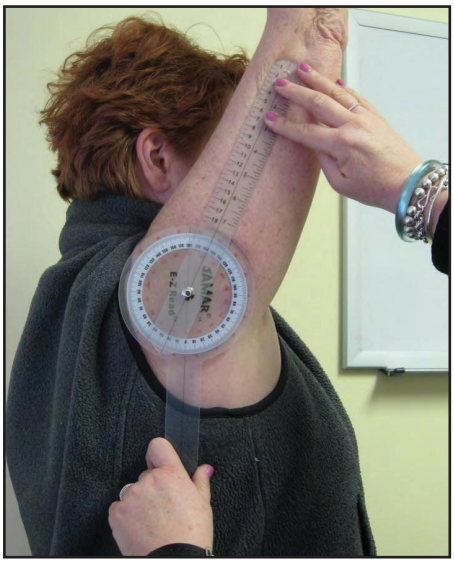
Measurement of AGEs using Reflectance of Ultraviolet Light (SCOUT Study)



Although a skin biopsy provides valuable scientific information, it is not a practical way to determine which individuals with type 1 diabetes are at greatest risk of developing or experiencing worsening of diabetes-related complications. After careful review of a new device that could quickly, accurately, and non-invasively measure AGEs, the EDIC study used this new device to measure AGEs using ultra-violet light. AGEs in the skin are assessed by measuring the amount of light that passes through the skin on the underside of the left arm. The initial analysis showed that the measurement of skin reflectance correlates with the average A1c levels over time. The results are a bit disappointing in that the measurements do not sharply separate those with complications from those without complications. We plan to reanalyze the original measurements mathematically to see if this simple procedure can enhance our ability to predict the future risk of complications and the impact of intensive diabetes treatment on this risk.

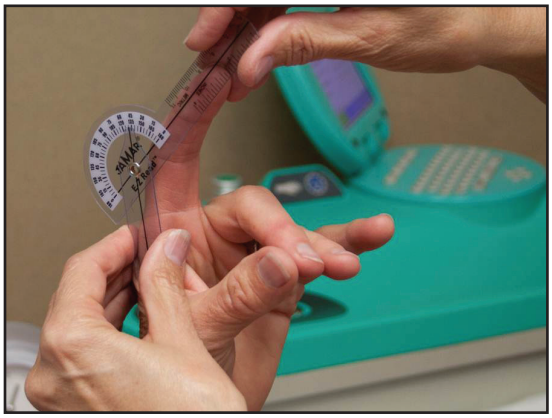
Cheiroarthropathy (Shoulders and Hands)

Cheiroarthropathy is a condition that causes limited joint mobility in people with diabetes due to thickening of the tissue in the hands and shoulders. Cheiroarthropathy leads to stiffness in the joints and in some cases, it can be painful. Other conditions associated with cheiroarthropathy are adhesive capsulitis (frozen shoulder), carpal tunnel syndrome, flexor tenosynovitis (trigger finger) and Dupuytren's contracture (finger[s] that cannot be straightened even with force).



There are very few studies that have carefully measured cheiroarthropathy in individuals with type 1 diabetes. While the exact cause of cheiroarthropathy is unknown, the most popular theory is that it is caused by long-term exposure to high glucose levels.

During 2011-2012, a careful evaluation was completed to determine if you had any history of cheiroarthropathy and related symptoms and treatment. We measured range of motion in your fingers and shoulders. The purpose of this study was to understand the relationship between signs and symptoms of cheiroarthropathy and overall glucose control. We wanted to learn if cheiroarthropathy occurs more often when other complications such as kidney, eye or nerve problems are present. We also wanted to know whether other factors such as elevated blood lipids (cholesterol), smoking, and longer duration of diabetes increase the risk of developing cheiroarthropathy.



Although all the data have not been completely analyzed yet, the early results suggest that cheiroarthropathy is very common in people with type 1 diabetes and that longer diabetes duration and higher average glucose levels increase the risk for its development.

Pancreatic Islet Cell Function (C-Peptide)

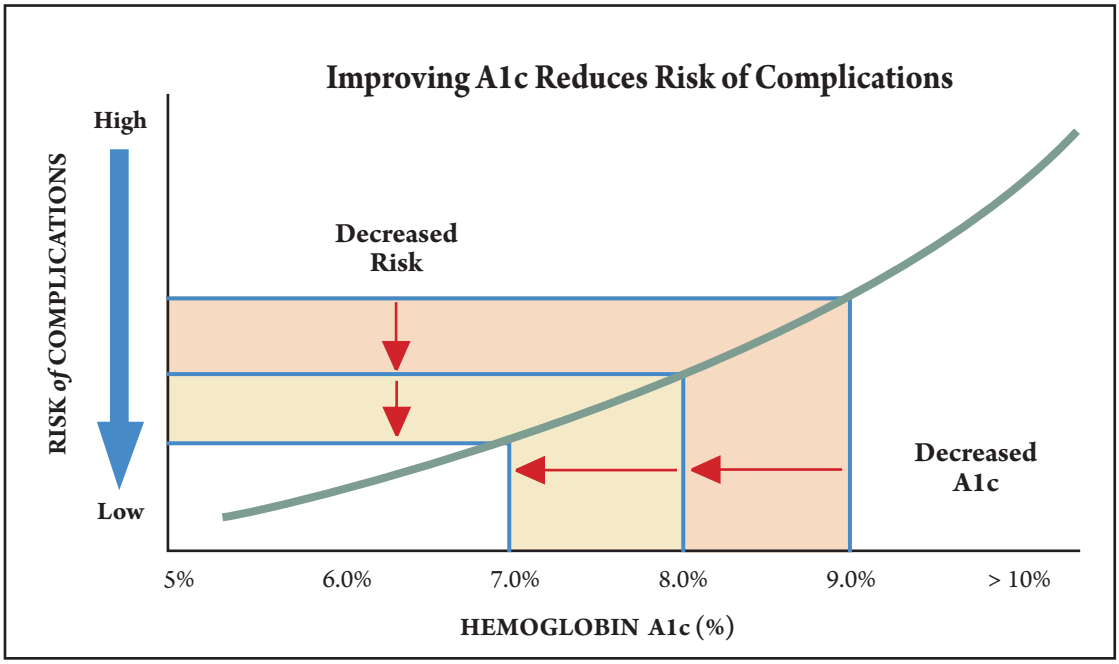
At the beginning of the DCCT, a test was performed to measure how much, if any, insulin was still being produced by your pancreas. In some of you who had diabetes for less than 5 years at the start of the DCCT, the pancreas continued to produce a small amount of insulin. For those who continued to make a little bit of insulin, the amount of insulin was small and eventually disappeared, but it seemed to be important. At that time, it appeared that preserved insulin secretion was associated with lower A1c levels, less hypoglycemia (low blood glucose), and less retinopathy and nephropathy.

More sensitive testing methods are now able to detect even smaller amounts of C-Peptide. EDIC will be doing a test similar to the one done during the DCCT to determine if the pancreas continues to produce some insulin many years after the diagnosis of type 1 diabetes. The main question is whether continued production of even tiny amounts of insulin is an important factor in determining the severity of diabetes complications and the risk of hypoglycemia.

Glycemic Threshold

The results of the DCCT demonstrated the importance of glucose control in preventing and reducing complications associated with diabetes. But, one of the most encouraging messages from the DCCT was that ANY degree of improvement in glucose control was beneficial. Risk was reduced with the lowering of A1c and the degree of risk reduction was proportional to the degree of A1c reduction. There was not a specific A1c number or threshold that had to be reached to reap benefit. For each 10% reduction in A1c, the risk of complications was reduced on average by 44%. For example, if your A1c improved from 9.0% to 8.1% or from 8.0% to 7.2% (a 10% reduction in A1c), your risk for complications would decrease by about 44%. This is shown in the following graph.

Figure 4. Reducing Risk of Complications



Metabolic Memory

During the DCCT, the average A1c, which was measured at least every 3 months, was about 7% in the intensive treatment group and about 9% in the conventional treatment group. At the end of the DCCT, each of you was encouraged to use intensive treatment methods to maintain blood glucose levels as close to the non-diabetic range as was safely possible.

As you worked with your own diabetes care providers to manage your diabetes, the average A1c in the former conventional treatment group dropped to an average of 8%, while the average A1c in the former intensive treatment group rose to about the same level. During EDIC, tests of your eyes, kidneys, nervous system and heart show that the differences in risk of complications seen in the DCCT continue despite both groups having similar levels of glucose control for most of EDIC. This finding is called "metabolic memory".

This finding was not expected . . . and what does it mean? Simply, it means that the earlier intensive treatment is begun and the lower the A1c is kept, the better. This DCCT/EDIC finding is one of our most important contributions to the management of diabetes worldwide – and it grows in importance with each passing year! All individuals with type 1 diabetes (and probably type 2 as well) now and in the future will benefit from your contribution to the DCCT/EDIC study.

Genetics

The field of genetic research is rapidly developing and new information is emerging constantly. Rarely a week goes by without a news headline proclaiming that the gene for a particular disease has been discovered. The problem with such headlines is that the biology of diabetes and its complications is not so simple. The genetic risk factors for diabetes and its complications are almost certainly "polygenic", meaning that several, and perhaps many, genes are involved.

Through the availability of a number of new technologies, and based on the knowledge of the DNA sequence of the human genome (the whole set of human genes), it is now possible to find genetic variations that are associated with many traits and diseases in humans. Diabetes has led the way in this regard. At last count, there are over 40 different genetic variations associated with the risk of developing type 1 diabetes, and a similar number of different variations have been identified for type 2 diabetes.

A major focus of the DCCT/EDIC has been on the genetics of diabetes complications, which may be very different than the genes associated with diabetes itself. DNA obtained from blood samples that you and your relatives provided as part of the DCCT/EDIC Family and Genetics studies, have been used to identify some previously unidentified genetic variations that are associated with the risk for the development of complications. What have the results of these genetic studies revealed so far? The DCCT/EDIC family study provided evidence that familial factors influence the severity of diabetic retinopathy (eyes) in DCCT participants, and confirmed the existence of familial effects on the presence of diabetic nephropathy (kidneys). We have also learned or confirmed that certain genes influence whether a person with type 1 diabetes develops early retinopathy, severe later retinopathy or early nephropathy. Interestingly, we have also identified a place in the genome on chromosome #10 that has an effect on the level of glucose control achieved with intensive or with conventional treatment. The effect is small, however, and usually has no important clinical meaning, but it may explain rare unexpected instances where the A1c seems out of proportion to the personal effort being made to control glucose.

Work continues to better understand the association between variations in specific genes and the risk of type 1 diabetes and its complications.

Participant Retention

Every year since 1993, at least 90% of all EDIC participants have returned to one of 27 clinics across the United States and Canada for their EDIC exams and evaluations. The high level of retention parallels the extraordinary results during the DCCT when 99% of participants completed the study. Despite moves to different locations and the major life events and challenges that many of you have experienced, the retention rate in EDIC is unequalled. You, the DCCT/EDIC participants, are a particularly dedicated and committed group of research partners. Without you, there is no DCCT/EDIC study and the worldwide diabetes community would be the poorer for it.

At the end of the DCCT, a questionnaire was administered that asked for your impressions of the study. In 2008, a survey based on that DCCT questionnaire was redesigned to ask: "Why do you continue to participate in the DCCT/EDIC after all of these years?" Each participant was asked to rank the reasons for continuing in EDIC in six different areas; 86% of you completed this anonymous confidential questionnaire. What did we learn? The primary reasons you identified for your continued high level of commitment emphasize the importance of expert medical care, supportive staff-participant relationships, and involvement with clinically and scientifically meaningful research. Seventy nine percent (79%) of you (more women than men) indicated that "cutting edge tests", such as the cardiac MRI, are a top reason for continuing in EDIC, and 68% of you (more men than women) identified annual diabetes evaluations as a major reason. Those with three or more complications identified "annual evaluations" as a major reason for continued involvement more often than did those with fewer complications. Over 60% of you indicated that the desire to help others and better care for your own diabetes were other major reasons for returning each year, and over 40% of you provided additional write-in comments, many of which highlighted the importance of your long term relationships with EDIC staff.

Why is a study of participant retention so important? A high level of retention is critical to all studies; if too many participants drop out of a study, the scientific value of the study results are jeopardized. Your commitment to return to your clinic every year has resulted in hundreds of manuscripts and presentations that are highly valued by the scientific and health care community because of the superior quality of the data we have collected. The DCCT/EDIC will continue to be successful due to your dedication and understanding of the value of this research program.

Summary

The results of the DCCT were published in the New England Journal of Medicine in 1993 and set the course for new standards of care and management for type 1 diabetes. EDIC continues to lead the way in furthering our understanding of the relationship between glucose control and diabetes related complications. The 30 years of the DCCT/EDIC follow-up continue to provide an understanding of type 1 diabetes that is unmatched in the annals of clinical science.

The strong and continued impact of the DCCT/EDIC is a tribute to each of you and your ongoing commitment to diabetes research. The DCCT/EDIC investigators are honored to work with such a dedicated group of volunteers and are grateful for our continued research partnership.

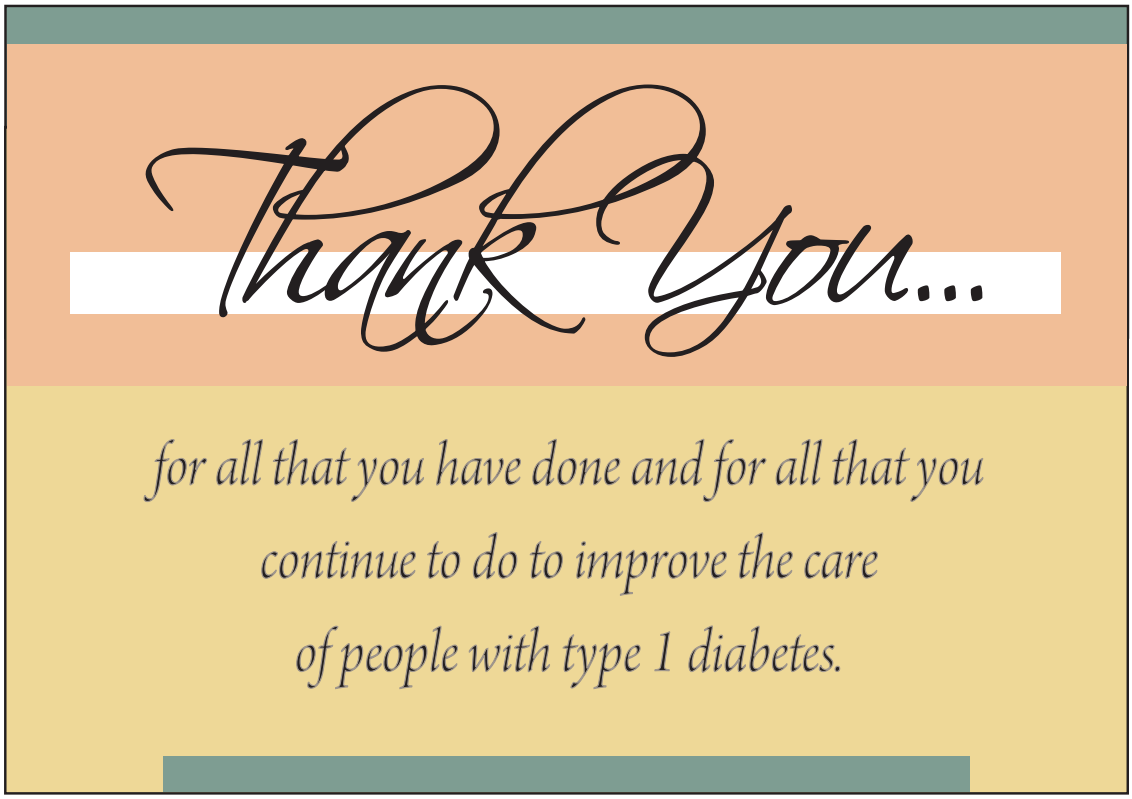
Theodore Roosevelt once observed that life's greatest gift is the opportunity to work hard at work worth doing. The NIDDK provided the opportunity but YOU have made it possible, and we and the diabetes community are grateful.

The first 30 years of the DCCT/EDIC have provided many answers about type 1 diabetes . . . but many questions still remain. We hope that each of you is proud of what has been accomplished by the DCCT/EDIC research family and is committed to continuing active participation in this historic study.

Moving Forward . . .

A wealth of knowledge has come from the DCCT/EDIC. As commonly occurs, the more you learn, the more there is to learn. With your continued dedication and involvement in the study, we hope to gain an even greater understanding of the impact of diabetes and glucose control on the heart, blood vessels, eyes, kidneys and nervous system. We hope to explore new areas such as hearing, gastrointestinal function (i.e. how your body processes and uses the food you eat), the impact of nocturnal hypoglycemia on overall health, and continued production of small amounts of insulin (C-peptide study). In addition, with your permission, the blood and urine samples collected throughout DCCT/EDIC that are stored in the NIDDK Central Repository will continue to be shared with the greater scientific diabetes community. This enables other investigators to submit additional study proposals that are reviewed by experts and, if deemed meritorious, will continue to complement and expand the work of the DCCT/EDIC and support continued scientific discovery about type 1 diabetes for years to come.

Every time a participant comes to a DCCT/EDIC clinic visit, it helps to increase the knowledge of type 1 diabetes, its treatment and the complications. We look forward to your ongoing enthusiasm and participation in the DCCT/EDIC. Together, we will continue to strengthen and expand our understanding of diabetes and work to improve the lives of all who have type 1 diabetes.



The "faces" included throughout this publication
represent only approximately 676 of the DCCT/EDIC participants.
But, without doubt, the success of the DCCT/EDIC
is due to the tremendous efforts of every one of the participants.

Acknowledgements

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Trial Registration: www.clinicaltrials.gov; identifiers NCT00360815 and NCT00360893.

Supporting Contributors

Over time, the DCCT/EDIC study has been supported by several commercial entities that have provided free or discounted supplies or equipment for participant use. These include:

Abbott Diabetes Care - *Alameda, CA*
Animas® Corporation - *Westchester, PA*
Bayer HealthCare LLC Diabetes Care, North America Headquarters - *Tarrytown, NY*
Becton Dickinson and Company - *Franklin Lakes, NJ*
Dex4® (formerly CanAm) - *Atlanta, GA*
Eli Lilly and Company - *Indianapolis, IN*
Genentech - *San Francisco, CA*
Lifescan - *Milpitas, CA*
Medtronic MiniMed, Inc. - *Minneapolis, MI*
Omron Corporation - *Shelton, CT*
OmniPod® Insulin Management System - *Bedford, MA*
Roche Diabetes Care - *Indianapolis, IN*
Sanofi-Aventis U.S. LLC - *Bridgewater, NJ*

These commercial entities were not involved in the design or conduct of the DCCT/EDIC.

Our Special Thanks To . . .

Eli Lilly and Company and Medtronic Diabetes for the education grants received to support the printing and distribution of this historical perspective for the DCCT/EDIC participants.

DCCT/EDIC Publications

The publications included on the next pages represent a sampling from over 200 peer-reviewed scientific and medical publications by the DCCT/EDIC Research Group.

GENERAL RESULTS

The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of the feasibility study. *Diabetes Care*, 10:1-19, 1987.

The DCCT Research Group. Are continuing studies of metabolic control and microvascular complications in insulin-dependent diabetes mellitus justified? The Diabetes Control and Complications Trial. *The New England Journal of Medicine,* 318:246-250, 1988.

★ **The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine*, 329:977-986, 1993.**

The Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: The perspective of the Diabetes Control and Complications Trial. *Diabetes*, 45:1289-1298, 1996.

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