

# Improving Lives... While Searching for a Cure



The impact of medical research on the  
quality of life of people with type 1 diabetes

**JDRF** Juvenile  
Diabetes  
Research  
Foundation  
International

*dedicated to finding a cure*

## Improving Lives...While Searching for a Cure

*Medical research to discover cures for diabetes and its complications, while not yet resulting in widespread treatments to reverse the disease, has already had a positive impact on the quality of life for people with type 1 diabetes. On the path toward therapeutic cures, research has refocused medical care on how diabetes is managed, resulting in a lower risk of complications and longer life expectancy, particularly for those diagnosed today. At the same time, the development of a range of drugs, treatments, and diagnostic tools has slowed the impact of some complications for people with type 1.*

*The research leading to improvements in quality of life—some measured, others more significant—has taken many forms. Some were large trials conducted by the NIH and other government science agencies. Others involved scientific investigation by companies that manufacture insulin, monitors, and insulin-delivery tools. And some were traditional, academic research projects looking at the causes and treatment of diabetes, as well as heart disease, kidney disease, and other complications.*

1970

1980

### Four Decades of JDRF Involvement

JDRF's primary focus is a cure: eliminating type 1 diabetes in the way that smallpox and polio have been eradicated from most of the earth. But our commitment to a cure has always focused not just on the long-term and generational needs of people with type 1 diabetes, but also on improving their lives today by reducing the life-threatening aspects of this disease. Increasingly, JDRF's cure therapeutics approach to science incorporates short-term outcomes into its longer-term vision of a cure.

## Better Quality of Life

*Despite not yet achieving a cure, research has made diabetes a different disease today than it was 50, 25, or even 10 years ago. The impact is most evident in three major areas. In general:*

**People with type 1 diabetes are living longer than they ever did before**

**The risk of complications from diabetes is declining**

**Tight control of blood glucose is more achievable than ever**

*This booklet details many of the scientific advances, most taking place in just the past few years, that have made life with diabetes a somewhat less daunting task than it was for previous generations. It outlines how standards of care, drugs, devices, and treatments are changing how—and how long—people with type 1 live.*

1990

2000

A common element in the scientific progress detailed in this booklet has been the involvement of JDRF: assuring that adequate government funds are focused on diabetes-related science, encouraging investment in the development of new products and treatments by companies serving the diabetes patient, and in many cases directly funding research that has led to improvements in quality of life. While JDRF has certainly not been the primary funder of all these advances, this timeline details some of the many scientific achievements that are already benefiting people with diabetes in which JDRF science laid the groundwork or was directly responsible (JDRF funded scientists or partnerships in parentheses).

## A Sea Change in Diabetes Research

Medical research has taken two parallel paths in diabetes over the years. The first is the effort to cure the underlying disease, prevent its occurrence and recurrence, and stop or reverse its long-term complications. Though there has been significant progress on multiple fronts, that challenge continues today. At the same time, researchers have explored methods to improve how diabetes is managed—enhancing and improving the methodology, drugs, and technology of diabetes care. More often than not, the search for a cure overlaps with research to improve how the disease is managed—discoveries in one discipline lead to treatments in another, results in patient care reinforce or challenge hypotheses in developmental scientific investigation, and drugs developed for other uses are re-employed to help treat or stall diabetes complications.

The key point of interconnection between short- and long-term research in type 1 diabetes is blood glucose control. Scientists

1970

1973

### The 1970s

- The Juvenile Diabetes Foundation is founded by a group of parents whose children have type 1 diabetes.
- Vitrectomy, an early surgical technique to treat and help halt the progression of diabetic eye disease, is pioneered by doctors at a JDRF-funded ophthalmic research center. (L'Esperance, James, Frank, Payman).

investigating both the pathology of diabetes and its complications have consistently gravitated towards glucose control as the key element in the progression of complications, from hypoglycemia to heart disease. The landmark Diabetes Control and Complications Trial (DCCT), a 10-year research study, provided solid evidence of the importance of tight blood glucose control.

### DCCT research found that lowering blood glucose

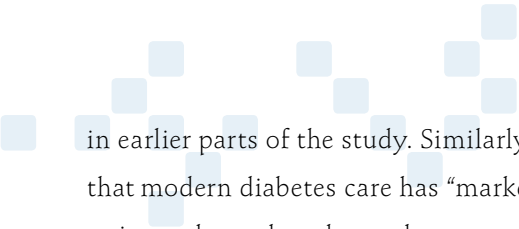
- Reduces the risk of eye disease by **76 percent**
- Reduces the risk of nerve disease by **60 percent**
- Reduces the risk of kidney disease by **50 percent**

Research continues to confirm that careful blood sugar control is a critical defense against complications. One recent study looking at survival rates of patients diagnosed from the 60s through the 80s showed that those diagnosed in the last five years of that period had significantly better long-term survival prospects than those diagnosed

1977

1977

- Hormones (and hormonal factors), including glucagon and somatostatin, that can beneficially alter the effect of insulin, are discovered, purified, and synthesized by Yale University scientists. Glucagon becomes an important treatment for hypoglycemia. (Sherwin, Honey, Ensick, Patel, Shields)
- JDRF scientists define the “tumor angiogenesis factor,” the diabetes-caused abnormal growth of new blood vessels in the eye. (Kozak, Engerman, Slonim, Bronson)
- The test to measure hemoglobin A1c levels is developed, with JDRF scientific backing. Adding to the standard blood glucose test, scientists can now determine the state of diabetic control over a period of months. (Gabay, Cerami, Banuchi-Eurite, Fluckinger)



in earlier parts of the study. Similarly, a 2004 research project concluded that modern diabetes care has “markedly reduced” the incidence of severe retinopathy and nephropathy.

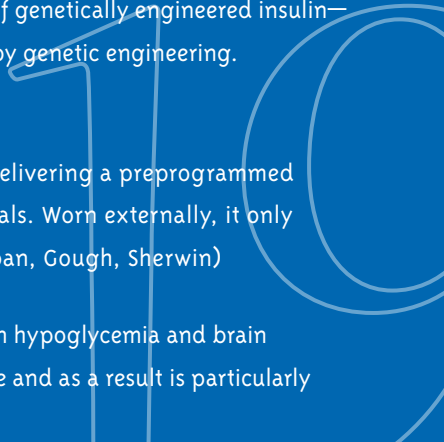
## Complications are declining, and people are living longer

### HYPOGLYCEMIA HAS BECOME LESS DIFFICULT TO AVOID

The introduction of both longer-acting and shorter-acting insulins have improved a patient’s ability to control blood glucose without levels going too low; similarly, the advanced technology of glucose monitors and insulin-delivery devices are helping many patients avoid unexpected drops.

1980

### The 1980s

- JDRF-funded science leads to the development of genetically engineered insulin—the first human protein to be cloned and made by genetic engineering. (Ullrich, Shine & Goodman)
  - An experimental insulin pump is developed, delivering a preprogrammed flow of insulin, with larger amounts before meals. Worn externally, it only needs to be removed for bathing. (Dupre, Jaspan, Gough, Sherwin)
  - JDRF scientists establish the relationship between hypoglycemia and brain metabolism—the brain is unable to store glucose and as a result is particularly
- 

## RETINOPATHY CAN OFTEN BE STOPPED EARLY IN DEVELOPMENT

Research has developed tools for curtailing retinopathy once it begins. Laser treatment can often prevent the growth of unwanted blood vessels in the retina, sealing hemorrhages in the eye and preventing further development of new blood vessels. Laser treatment now prevents 95 percent of severe vision loss, if performed promptly. Though the procedure is not perfect, and can sometimes sacrifice peripheral vision, for many patients the complication is halted before widespread damage has occurred. Research has also alerted physicians and patients to the importance of early detection of retinopathy; more frequent eye exams have contributed to lowered incidence.

1984

sensitive to rapid or prolonged hypoglycemia—helping to understand and prevent the chronic effects of hypoglycemia on the brain.

(McCall, Polonsky, Auer)

- The relationship between diabetic retinopathy and pregnancy is established. Because diabetic retinopathy may progress more rapidly during pregnancy and often reverses following delivery, the nature of the relationship between pregnancy and retinopathy had to be determined before preventive measures can be established. Scientists document the retinal lesions during pregnancy with serial photographs of the eyes. They identify patterns of specific ocular changes that herald the development of high-risk characteristics as an important therapeutic tool. (Chang, Plehwe, Kohner)

## RESEARCH HAS LED TO AGGRESSIVE TREATMENT OF DIABETES-RELATED HEART DISEASE

Diabetes is one of the four major risk factors for developing heart disease. Research shows that people with diabetes are more likely to have high blood pressure and high cholesterol, both of which cause damage to the cells lining the artery walls and lead to heart disease and stroke; researchers believe high blood glucose contributes to both of these conditions. Doctors now routinely prescribe drugs to lower blood pressure for people with diabetes. These effective medications have become more specific in the molecules they target, causing fewer side effects. Two types of blood pressure drugs have had a particularly large impact on diabetes care: ACE inhibitors, such as *captopril*, *ramipril*, and *enalapril*, which became widely adopted in the last 10 years, and ARBs, such as *irbesartan*, *telmisartan* and *losartan*, which also came on the market

1986

- JDRF scientists find that blood sugar control is paramount to fetal development, leading to treatment standards that are invaluable to the delivery of a healthy baby to diabetic mothers. (Levitsky, Tuch)
- Researchers, funded by JDRF, advance the understanding of the type of blood vessel cell involved in diabetes-induced arteriosclerosis (hardening of the arteries). (Wang-Iverson)

1988

in the 1990s. In addition, the development in the 1990s of statins such as *atorvastatin*, *fluvastatin*, and *lovastatin*, have revolutionized the management of cholesterol, in general, and doctors routinely prescribe them to people with diabetes. 2003 research showed that the use of statins can substantially reduce the risk of heart disease people with type 1 diabetes.

## **NEPHROPATHY IS DIAGNOSED EARLIER AND CAN OFTEN BE SLOWED DOWN CONSIDERABLY**

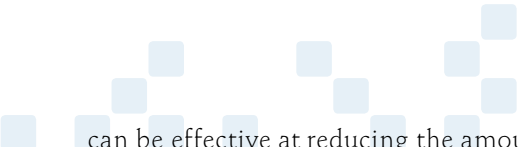
Due to development and adoption of the microalbuminuria test, diabetic kidney disease is more frequently being halted or delayed in its earlier stages: detection of protein in the urine is no longer a sure sign that serious kidney disease will inevitably follow a few years later. The newer blood pressure drugs, including ACE inhibitors and ARBs, are having a positive effect on nephropathy. Research shows that blood pressure drugs can often lower localized blood pressure within the kidney, and

1990

1992

### **The 1990s**

- In their efforts to prevent diabetic arteriosclerosis, scientists find that a prototype new drug—aminoguanidine—keeps “sticky” glucose (AGE formation) from blocking blood vessels. The drug blocks AGEs from interacting with nearby leaked plasma proteins, which is the main cause of diabetic vascular narrowing. (Brownlee)
- JDRF research establishes the causal relationship between diabetic retinopathy and glycosylated hemoglobin levels, well before the DCCT findings are published in 1993. (Klein)



can be effective at reducing the amount of protein in the urine. People with detectable microalbuminuria are now automatically placed on these medications, with increasingly positive results.

### **MULTIPLE DRUGS CAN COUNTERACT NEUROPATHY**

For peripheral neuropathy (numbness, tingling, pain), research has shown that drugs originally prescribed for other ailments can often be effective. Recent studies showed that some anti-epileptic drugs, such as *topiramate* and *gabapentin*, often relieve pain and improve nerve function. The newer class of antidepressants, *paroxetine*, *fluoxetine*, and *sertraline*, have also relieved pain in some diabetes patients.

1994

- The success rate of pancreatic transplants increases, as the procedures for transplanting whole or partial pancreases advances. As the number of post-transplant patients who have remained healthy continues to grow, researchers begin to evaluate its potential for younger, healthier diabetes patients (Sutherland, Morris, Schulak)

1996

- JDRF makes islet transplantation a priority by establishing the JDRF Center for Islet Transplantation at Harvard Medical School, the first of many such centers JDRF will launch that focus on a specific aspect of curing type 1 diabetes.

In addition, the FDA just last year also approved capsules of the anti-epileptic drug *pregabalin* and the antidepressant *duloxetine* as treatments for peripheral neuropathy. For autonomic neuropathy, which attacks the nerves that control organ and glandular systems, research has produced drugs that can often relieve many symptoms of the disorder. For example, drugs now exist for gastrointestinal problems such as gastroparesis, common to people with diabetes, including *erythromycin*, *metoclopramide*, and in some countries, *domperidone*. And in the last few years, another condition caused by diabetic autonomic neuropathy, sexual dysfunction, became much more treatable with the availability of *sildenafil*, *tadalafil*, and *vardenafile*.

1998

- JDRF establishes the Human Islet Distribution Programs to meet increased demand for islets for both clinical transplantation and basic research. This increased demand is a direct result of the success of the Edmonton protocol that was quickly replicated by JDRF-supported groups at several U.S. locations. Later, the Islet Distribution Programs become part of NIH's Islet Cell Resource (ICR) Centers.

## The 2000s

- JDRF helps establish the Immune Tolerance Network, a seven year, \$144 million project co-funded with the NIH, devoted to research that leads to tolerance of transplanted tissue and prevention of autoimmune conditions.

2000

# Tight control of blood glucose is much more achievable

## GLUCOSE-MONITORING TECHNOLOGY HAS IMPROVED

Just a few decades ago, blood glucose testing was restricted to a doctor's office, meaning there was no method for patients to monitor their blood sugar levels on a day-to-day basis. Industry innovation and a push for patients to take control of their care have resulted in the introduction of home glucose testing. While patients have been able to track their blood sugar levels each day and follow guidelines to keep levels within a normal range, today's home glucose tests calibrate readings with levels of accuracy unavailable to even physician's monitoring devices just a few decades ago—within a matter of seconds. And the lancing devices used to produce the drop of blood for analysis have been designed and redesigned to cause as little discomfort as possible.

2001

- JDRF researchers develop the Edmonton Protocol for islet transplantation, which uses less-toxic immune-suppressing drugs and greatly improves the success rate. (Shapiro, Lakey, Ryan)
- JDRF partners with the Department of Defense to develop better glucose sensing technology. The Technologies for Metabolic Monitoring research program (TMM) is a joint initiative with three U.S. agencies to develop new approaches to noninvasive glucose monitoring, to improve current approaches for monitoring metabolism. (TMM)

## NEW DRUGS HELP KEEP BLOOD SUGAR LEVELS LOW

As a result of industry research, new insulin formulations have been developed, with longer- or shorter-term effects to provide patients with more spontaneity and flexibility. The longer-acting insulins, such as *glargine*, can provide more predictable metabolism of food, and help bring about lower HbA1c levels with less risk of hypoglycemia. Shorter-acting insulins, such as *aspart*, *lispro*, and the newly approved insulin supplement *amylin*, offer patients better and more flexible control around meals. Their use helps patients maintain finer control of blood glucose to limit the occurrence of hypoglycemia, as well as the longer-term impact of complications.

2002

- JDRF research shows that the initial stimulus for diabetic retinopathy comes not only from the body's blood vessels, but also from the nervous system and the neural components in the retina itself—providing an opportunity to interfere in the process at a very early stage. (Leith, Gardner)
- A JDRF-funded human clinical trial shows that treating newly diagnosed type 1 diabetes patients with a drug called an anti-CD3 antibody can preserve residual beta cell function for up to 18 months. This is an important step toward arresting the disease in its early stages and possibly preventing it.



## PUMPS PROVIDE EFFICIENT ALTERNATIVES TO MULTIPLE INJECTIONS

The introduction of the insulin pump has provided patients with greater flexibility in diets and sleep schedules, and a somewhat greater degree of freedom to pursue activities without constant worry over rising or falling blood sugar levels. Pumps, manufactured now by a handful of medical device companies, are a direct outgrowth of increased understanding of the biology of the pancreas, providing a steady flow of insulin that more closely mimics pancreatic secretions. And mirroring the enhanced standards of care now encouraged for type 1 patients, the newer models record data that can be downloaded and studied at a doctor's office to better understand insulin requirements.

2005

2007

- Military, government, academic, and industry researchers work together to develop better methods to deliver insulin and monitor glucose, focusing on technologies that can be applied to the care and long-term health maintenance of people with diabetes, including research with biodegradable polymers to produce nanoparticles—tiny particles a few tens of atoms across—for controlled insulin delivery, injected under the skin. Other research includes clinical tests of fluorescent dyes placed under the skin that could be read to indicate glucose levels. (JDRF-NASA-NIH partnership)

## CONTINUOUS GLUCOSE MONITORS HERALD AN IMPROVED WORLD OF DISEASE MANAGEMENT

Over the years, miniaturization has produced glucose meters that are more portable and less obtrusive devices, yet capable of analyzing minute amounts of blood. The next step, slowly being introduced into everyday use, are continuous glucose monitors, which could revolutionize how patients manage their disease by tracking glucose-level trends over time (not just at the specific time of a finger-prick).

2009

- Research shows that insulin itself is a key target in the autoimmune attack on pancreatic beta cells. (Hafler-Eisenbarth)
- Clinical trials to use new technologies and treatments to reduce the risk of severe hypoglycemia in children, and to best use advanced technology to measure and clarify how diabetes, insulin therapy, and age affect hypoglycemia's impact on the brain and central nervous system. (JDRF-Yale Center)

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For more information:

[www.jdrf.org](http://www.jdrf.org)

Juvenile Diabetes Research Foundation International  
120 Wall Street New York, NY 10005

