TESTIMONY

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AT THE HEARING ENTITLED

THE BATTLE AGAINST DIABETES:
PROGRESS MADE; CHALLENGES UNMET

BEFORE THE

HOUSE ENERGY AND COMMERCE COMMITTEE

SUBCOMMITTEE ON HEALTH

July 1, 2010

Chairman Pallone, Ranking Member Shimkus and Members of the Subcommittee, thank you for the opportunity to testify before you today on the state of type 1 diabetes research, the progress to date and the need for continued research along our path to a cure for this disease. I am Dr. Robert Goldstein, Senior Vice President of Scientific Affairs for the Juvenile Diabetes Research Foundation International (JDRF), and I am honored to be here today. I am also privileged to sit on the same panel with my colleagues – the American Diabetes Association and the National Indian Health Board – who are tremendous partners of JDRF's in the fight against diabetes.

JDRF is the largest charitable funder and advocate of diabetes research worldwide. Our mission is to find a cure for type 1 diabetes and its complications through the support of research. Until there is a cure, JDRF is also committed to working tirelessly to develop better treatments to improve the lives and health of people who have type 1 diabetes.

Since our founding four decades ago by parents of children with type 1 diabetes, JDRF has awarded more than $1.4 billion to diabetes research, including more than $100 million last year. To fund this research, JDRF volunteers and staff do their part every day to raise money through walks, galas and other events in communities across the nation. We are moving faster towards a cure for type 1 diabetes than ever before, thanks to the combination of federal diabetes research funding and JDRF's private investment, which is one of the world's most effective public-private partnerships focused on curing a particular disease.

Diabetes: Background on a Complex, Chronic, and Demanding Disease

About Type 1 and Type 2 Diabetes

Type 1 diabetes, often referred to as juvenile diabetes, is an autoimmune disease that causes the destruction of pancreatic beta cells, the cells in the body that make the hormone insulin. Insulin is required for people to get energy from food; therefore, people with type 1 diabetes must take multiple injections of insulin each day or continually infuse insulin through an insulin pump in order to survive. They must also monitor their blood glucose levels closely with frequent blood testing throughout the day and night and adjust their insulin levels, food intake and amount of exercise accordingly. Even with the most rigorous attention, many other factors can adversely affect a person's blood glucose levels, including stress, hormonal changes, growth spurts, medications, illnesses, and fatigue. The management of this disease is a constant battle, not only for the patients but also for their families and loved ones – low glucose causes potentially deadly medical emergencies such as seizure and coma, while high glucose causes debilitating and sometimes fatal health problems such as kidney failure, blindness, nerve damage, amputation, heart attack, stroke and pregnancy complications.

Typically, type 1 diabetes strikes in childhood, adolescence or young adulthood; however, it is not a disease one can outgrow. Warning signs of the disease include extreme thirst, frequent urination, drowsiness or lethargy, increased appetite, sudden weight loss, and vision changes. Unfortunately, diet and exercise cannot prevent the

onset of type 1 diabetes as is often the case with type 2 diabetes. Today, nothing can prevent the onset of type 1 diabetes.

Type 2 diabetes typically affects adults, although it is an increasing public health problem facing children. Injections are usually not required for people with type 2 diabetes because the pancreas produces insulin; the body just cannot process it effectively. Obesity and lack of exercise are important risk factors for type 2 diabetes. While the causes and management of type 1 and type 2 diabetes are different, the complications associated with the disease are the same. People with diabetes are two to four times more likely to have a heart attack or stroke than those without the disease. Diabetes is the leading cause of kidney disease, adult onset blindness, and non-traumatic amputations and is a leading cause of nerve damage. Overall, the risk of death for people with diabetes is about double that of people of similar age without the disease.

Incidence of Diabetes

Type 1 diabetes is the second most common chronic disease affecting children. Each year more than 15,000 children are diagnosed with diabetes in the U.S. Unfortunately, the number of new diagnoses of type 1 is increasing annually at an unprecedented rate. Historically, the diabetes research community has estimated the incidence of type 1 diabetes to increase, on average, by 2 percent per year. Currently, however, researchers believe increased incidence to be as high as 4 percent each year, with incidence of the disease rising particularly in children under the age of four.

In total, diabetes affects more than 24 million adults and children in the United States, and one out of every three Americans born in 2000 is predicted to develop some form of diabetes during his or her lifetime. Despite the staggering statistics of today, the outlook for the future is even bleaker: over the next 25 years, the number of Americans with diabetes is predicted to nearly double, while the cost of diabetes will almost triple.

Economic Impact of Diabetes

Diabetes is one of the costliest chronic diseases. In 2007, diabetes accounted for $174 billion in costs in the U.S, and 1 in 3 Medicare dollars is spent on people with the disease. The nation spends $11,744 for medical care for each person with diabetes, compared to $2,935 on people without diabetes, as of 2007. These increased costs are attributable to diabetes' role as the leading cause of kidney failure, adult blindness, and non-traumatic amputations, and a leading cause of nerve damage, stroke, and heart attacks. Continued research to better prevent, treat and cure diabetes will significantly reduce the incidence and economic impact the disease has on this country.

Progress in Type 1 Diabetes Research

Research offers the best hope for a cure for a patient with type 1 diabetes. In the forty years since JDRF's founding, we have not yet achieved a cure for this devastating disease, but investments in research have yielded new and improved therapies and treatments that now give people with type 1 diabetes greater quality of life and longer life expectancy. Today, people with type 1 diabetes have better tools to test and control

blood sugar, and significant progress has been made towards an artificial pancreas. The risks of complications are now lower than ever before, and thanks to research, doctors are beginning to have better ways to diagnose complications, slow their progression, and lessen their impact. And research has put us on a pathway towards therapies to restore the function of insulin-producing beta cells and stop the autoimmune attack that damages them. Many of the advances on the horizon would benefit not only those with type 1 diabetes but those with type 2 diabetes or other autoimmune diseases as well.

These many advances would not have been possible without the public-private partnership and steadfast commitment to diabetes research by the Congress and the federal government. On behalf of JDRF and the millions of families affected by diabetes, I want to thank the committee for its leadership in advancing diabetes research. Among your many contributions is your leadership in the Special Diabetes Program, a congressionally-mandated type 1 diabetes research program administered by the National Institutes of Health (NIH). The Special Diabetes Program provides a critical 35 percent of NIH funding for type 1 diabetes research and dedicates funding for the innovative and collaborative multi-center human clinical trials that are contributing to better therapies and treatments for people with type 1 diabetes. This public-private partnership must remain strong and stable if we are to capitalize on the advances to date and achieve our mutual goal of a cure for people with diabetes.

Immune Therapies: Research to Prevent Type 1 Diabetes

To prevent type 1 diabetes, one must know how the disease develops. Current evidence indicates that both a genetic pre-disposition and an environmental trigger cause type 1. Currently, by the time patients recognize the symptoms and receive a type 1 diabetes diagnosis, they have already suffered the devastating autoimmune attack that has destroyed most of the insulin-producing beta cells in the pancreas.

Research funded by JDRF and NIH could vastly improve the current standard of care. Thanks to research, we now know of about 40 gene regions associated with type 1 diabetes and can identify those who are genetically at risk. Long term studies are being conducted to identify the environmental trigger(s) of type 1 diabetes. And new therapies are being developed and tested to help prevent the disease altogether and enable newly diagnosed patients to preserve remaining insulin-producing beta cells and possibly even regenerate new ones. Promising research results in this area include:

- **Antibody Treatment Slows Autoimmune Attack in New Onset Type 1 Diabetes Patients:** NIH-funded researchers first identified a drug – a monoclonal antibody named anti-CD3 – that can slow the progression of type 1 diabetes. Together, JDRF and NIH funded the proof-of concept clinical trial that showed that a short 1-2 week treatment with anti-CD3 helps patients maintain or increase their ability to produce insulin naturally for several years after diagnosis. Patients on anti-CD3 therapy use less insulin and have more stable blood glucose levels for an extended period of time.

For example, Charlotte Cunningham from Maryland enrolled in the anti-CD3 trial soon after her diagnosis at the age of 10. While Charlotte now requires insulin at 15 years old, she produced her own insulin for three years after her diagnosis – helping her to better control her blood glucose levels and protect her from the complications that accompany type 1 diabetes. This success could not have been achieved without several Special Diabetes Program-funded programs at NIH, including the Immune Tolerance Network (which develops new therapies to treat/prevent autoimmune disease and to prevent or treat graft rejection in transplantation by inducing immune tolerance) and Type 1 Diabetes TrialNet (which also supports studies aimed at both preventing further destruction of insulin-producing beta cells in those newly diagnosed with type 1 diabetes, as well as developing the therapies to prevent the disease altogether).

Despite this tremendous progress, our work is not done. Pivotal phase III clinical trials on two different anti-CD3 drugs are now underway to further test their effectiveness. Continued federal support will allow for the additional research needed to determine how to prolong the effectiveness of the treatment, whether early treatment prior to disease onset can prevent diabetes or whether these therapies can be successful when given years after the onset of type 1 diabetes.

- **Vaccine to Prevent Type 1 Diabetes Onset:** Research toward the development of a vaccine to reverse the immune attack that causes diabetes holds great promise for type 1 diabetes patients. NIH- and JDRF-funded researchers have successfully cured and prevented type 1 diabetes in mice using a vaccine made of nanoparticles thousands of times smaller than the size of a cell, coated with proteins involved in immune cell communication. Thanks to NIH funds from the Special Diabetes Program, researchers have shown that these particles are safe for use in humans.

  The NIH, JDRF and privately-funded researchers are also working on promising vaccine therapies to preserve beta cell function in people newly diagnosed with type 1 diabetes.

Beta Cell Therapies: Research to Restore Insulin Production

Therapies to restore insulin production by beta cells in the pancreas would benefit all patients with type 1 diabetes and many with advanced forms of type 2. Researchers are focusing on replacing diseased beta cells with functioning ones from a human donor or from animals like pigs, as well as by changing different types of cells, such as liver cells, into becoming insulin-producing cells. Researchers are also investigating therapies to regenerate insulin producing cells either by copying existing cells or encouraging the pancreas to create new ones. While more work is needed to fulfill the promise of regenerative medicine, recent research toward that end includes:

- **Continued Progress in Islet Transplantation:** Researchers continue to improve the efficiency of procedures for transplanting islets from human donors to people with difficult-to-control or “brittle” diabetes. Thanks to efforts by the NIH and

JDRF, islet transplantation researchers worldwide are sharing information learned with each new procedure, and helping to quickly disseminate this knowledge.

- **Identification of the Gene Critical to Beta Cell Development:** Researchers have identified a gene, called Rfx6, which is required for the development of insulin-producing beta cells and other cell types in the pancreas. Mice lacking the gene failed to regenerate beta cells and most other cells in the pancreas. In people, deficiency of the gene resulted in diabetes in newborns. Research on beta cell development may help identify potential new treatments that could be used in both type 1 and type 2 diabetes.

- **Potential of Other Pancreas Cells to Convert into Insulin-Producing Cells:** A JDRF-funded researcher recently found that "alpha" cells in the pancreas – specialized cells that produce glucagon, not insulin – can spontaneously convert into insulin-producing beta cells without genetic manipulation. This finding is significant, especially since the alteration of genes is a process that cannot be easily translated into therapies for people. More research into alpha cells would be particularly beneficial for people who have long struggled with diabetes and have few or no remaining beta cells.

Glucose Control: Research to Advance an Artificial Pancreas

Until there is a cure, people with diabetes will need better tools to control their blood glucose levels, as better control will keep people healthier and help them avoid diabetic complications. The federally-funded Diabetes Control and Complications Trial (DCCT), a clinical trial of almost 1,500 people with type 1 diabetes conducted between 1983-1993, demonstrated that tight control of blood glucose levels through intensive insulin therapy could significantly reduce or delay many diabetic complications. A follow-up study – which was funded by the Special Diabetes Program and the results of which were published in *The New England Journal of Medicine* – found that intensive diabetes therapy aimed at achieving better glucose control reduced the risk of any heart disease event by 42 percent, and the risk of nonfatal myocardial infarction, stroke, or death from heart disease by 57 percent.

Despite the clear benefits of glucose control demonstrated by these studies, far too many patients with diabetes cannot achieve tight glucose control with traditional diabetes tools. For example, a 2005 study found diabetes patients who tested their blood glucose on average of nine times a day – far above the national average – spent less than 30 percent of the day in normal glucose range (between 90-130). These patients had higher than acceptable blood glucose ranges (over 180) for eight hours of the day and low ranges (less than 90) for two hours per day.

JDRF is working in partnership with the National Institutes of Health and private sector partners to accelerate the development and availability of new technologies to improve glucose control. These devices include the continuous glucose monitor (CGM) and the artificial pancreas (a closed-loop device that will consist of a continuous glucose monitor, an insulin pump and software to link the two) and will enable a person with diabetes to

maintain normal glucose levels by providing the correct amount of insulin at the appropriate time. Promising research includes:

- **Advancements in Glucose Monitoring Technologies:** Just within the past few years, new glucose sensing technologies that can monitor glucose levels continuously have come on the market. These CGM devices are a critical part of an artificial pancreas system, and have been shown to improve glucose control when used alone. NIH funded the original glucose sensor research which was developed by the private sector into CGM products. The NIH DirecNet program then tested the products and demonstrated benefits in children. JDRF then funded a larger trial including children and adults with type 1, whose results were published in *The New England Journal of Medicine*, which led to insurance coverage by major health plans. This public-private effort by NIH, JDRF and the private sector has enabled wide spread adoption of this beneficial technology. However, research has also shown there are limits to the benefits of CGM technology, which require the patients to respond manually to the data, something difficult to do continuously throughout the day and especially at night while sleeping. Thus, a parallel effort has been underway to accelerate the development of an automated artificial pancreas system.

- **Accelerating the Development of an Artificial Pancreas:** Early research funded by JDRF at Yale had shown that, by using sophisticated software in a hospital setting, CGM data could be used to effectively direct insulin delivery, creating an early artificial pancreas system. In 2006, JDRF funded a worldwide consortium of diabetes researchers, mathematicians, and engineers to develop and test the software algorithms for a first generation artificial pancreas. This consortium has developed, tested, and refined algorithms needed to automatically deliver insulin in various situations (e.g., during overnight, meals, exercise) in hospital-based clinical trials, and results to date show a first generation artificial pancreas system can improve glucose control throughout the day and lower the risk of blood glucose emergencies at night. Additional research is underway to further hone these software algorithms so they can be used in real life situations and tested to ensure safety and effectiveness. In 2009, the NIH funded multiple grants to help accelerate this process which are complementary to the JDRF funded research and funded through the Special Diabetes Program. As a result of this promising research, companies have announced plans to develop and commercialize artificial pancreas systems, a development that holds great promise for those with type 1 diabetes.

Complications Therapies: Research to Reverse Costly Diabetes Complications
Thanks to the public-private diabetes research partnership, diabetic complications are declining, and people with diabetes are living longer. The introduction of longer and shorter acting insulins and improved technologies – such as insulin pumps and CGMs – are helping many patients avoid unexpected and dangerous low blood sugars. Research funded by JDRF and the federal government has increased our understanding of how diabetes causes complications, and led to the development of new drugs and treatments to

stop, prevent or reverse the various complications. These complications include eye disease, nerve damage, kidney disease, heart disease and stroke, and they place a tremendous economic burden on society. Some of the exciting recent advances in this field include:

- **Reversing Diabetic Eye Disease:** Recent research has confirmed the ability to halt and reverse diabetic eye disease, a major complication of diabetes and the leading cause of adult-onset blindness. Research supported by the Special Diabetes Program and JDRF has shown that a treatment combining a drug and laser therapy is almost twice as likely to improve vision in people who have diabetic macular edema as laser therapy alone (50% vs. 28%). Improved vision was defined as being able to read two lines better on the eye chart, an improvement that could be the difference between being able to see well enough to drive, or hold a job – or not. The result of this research brings us one step closer to a new and much-needed treatment for diabetic eye disease, the first in almost 25 years.

- **New Gene Identified with Diabetic Kidney Disease:** Kidney disease is a devastating complication of diabetes and develops in 40 percent of patients with the disease. Researchers have identified a gene, called ELM01, that identifies people with type 1 diabetes who are at greater risk of developing kidney disease. More research is needed so that doctors can eventually identify type 1 patients with low, medium, and high risk for kidney disease and take steps earlier to mitigate the onset of kidney disease and its progression.

- **Reversing and Repairing Nerve Damage:** Research has shown the ability to reverse and repair diabetic nerve disease in the legs. People with diabetic neuropathy who were given a drug therapy had a significant increase in the number of small nerve fibers in the skin, which are responsible for sensation and motor function and are lost in diabetes patients with neuropathy complications.

Conclusion

As JDRF looks back on the last forty years since its founding, there is much to be proud of in the field of type 1 diabetes research. Tremendous research advancements have produced a number of new therapies and technologies that are undoubtedly improving the lives of people with type 1 diabetes. This progress, however, has yet to lead us to a cure for this devastating disease. We must redouble our efforts on both the federal level and in the private sector to ensure continued momentum toward our goal of a cure.

The renewal of the Special Diabetes Program is a key element of our continued success, and I would like to thank Rep. Diana DeGette for introducing H.R. 3668, which would provide a multi-year renewal of the program. I would also like to thank Ranking Member Shimkus for his contribution to the program's success, as he was the lead sponsor of legislation to renew the Special Diabetes Program in 2002. Additionally, JDRF is grateful to the majority of the Energy and Commerce Committee for co-sponsoring the bill and for the tremendous support you have given patients with type 1 and their loved

ones. JDRF wholeheartedly endorses this legislation, which has currently 281 bipartisan cosponsors, and knows all too well the program's importance in our mutual effort to understand, treat and eventually cure type 1 diabetes. JDRF will keep doing its part in this fight, and we hope that we can count on Congress to continue funding the medical research that will be necessary to maximize research opportunities and capitalize on the federal investment made in type 1 diabetes research to date. We have come too far along our path to a cure to turn back now.

Thank you again Chairman Pallone, Ranking Member Shimkus and Members of the Subcommittee for holding this hearing. I am happy to answer any questions you may have.