**Testimony**
**Before the Committee on Homeland Security and Governmental Affairs**
**United States Senate**

# Recent Developments in Research on Type 1 Diabetes


*Statement of*
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Chairman Collins and Members of the Committee, as Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I appreciate the invitation to testify at this hearing on type 1 diabetes, held in conjunction with the "Children's Congress" of the Juvenile Diabetes Research Foundation International (JDRF). On behalf of the NIDDK and the other Institutes and Centers of the National Institutes of Health (NIH) within the U.S. Department of Health and Human Services, I am pleased to report that we are vigorously pursuing research on type 1 diabetes and its complications. We are gaining insights into the molecular mechanisms underlying disease development, working diligently toward more effective treatment and prevention strategies, and striving for a cure.

Type 1 diabetes – which affects approximately one million Americans – strikes mainly in childhood and adolescence. An "autoimmune" disease, it mistakenly attacks the body's own immune system and destroys the insulin-producing beta cells found in clusters called "islets" within the pancreas. Thus, patients require daily administration of life-sustaining insulin in the form of injections or via an insulin pump. They must also carefully monitor their food intake and physical activity in order to manage the disease. Even with continuous and vigilant disease management, patients are still susceptible to developing serious, long-term complications. It is crucial to continue basic and clinical research to identify new ways to improve the quality of life of type 1 diabetes patients, whether through advances in islet transplantation, insulin delivery, or other avenues. Research is the key to a cure.

The NIH is focused on six broad goals in type 1 diabetes research, developed through a strategic planning process initiated in 2000: (1) to understand the genetic and environmental causes of type 1 diabetes so that we can identify who is at-risk for developing the disease; (2) to prevent or reverse the disease; (3) to develop cell replacement therapy as a cure for diabetes; (4) to prevent or reduce hypoglycemia (low blood sugar) which limits tight control of blood sugar; (5) to prevent or reduce complications; and (6) to attract new talent and apply new technologies to research on type 1 diabetes. The research that we undertake to achieve these goals is supported by our regular appropriation and by the Special Statutory Funding Program for Type 1 Diabetes Research. Earlier this year, the NIDDK convened a panel of external scientific and lay experts in type 1 diabetes and its complications to perform a mid-course assessment of research consortia and networks supported by the Special Program. The panel endorsed all of the ongoing research programs. The panel also made recommendations for future research opportunities that could be pursued with the Special Funds, as well as suggestions for enhancing ongoing efforts to maximize knowledge gained from these important studies. Recommendations from this meeting are valuable to both the NIH and the investigative research community in future priority setting.

Today, research teams are vigorously studying different aspects of the disease, such as understanding associated genetic and environmental factors; the molecular steps that lead to the development of insulin-producing beta cells; how the misdirection of the body's immune system can be corrected to spare the beta cells from immune attack; and how persistent elevation of blood sugar levels leads to the devastating disease complications that damage the eyes, kidneys, nerves, heart, and other parts of the body.

The complexity of the disease requires that researchers from diverse fields attack it from many directions. Through this multifaceted approach, we can attain a comprehensive understanding of the disease process--the foundation for future advances in treatment, prevention, and approaches to a cure.

Relative to each of our six research goals, I would now like to highlight some of the specific advances and initiatives, and also the unique, innovative, and collaborative research consortia and clinical trials networks made possible by the Special Funding Program. These efforts have involved not only partnerships among scientists with complementary expertise from multiple academic institutions, but also partnerships among many of the Institutes and Centers of the NIH, the Centers for Disease Control and Prevention (CDC), the JDRF, and the American Diabetes Association (ADA). I will highlight selected examples of our major efforts.

**Understanding the Genetic and Environmental Causes of Type 1 Diabetes**

Type 1 diabetes is caused by a combination of genetic and environmental factors. Identifying these factors is key to both prevention and cure. Already we know some of the major genes that predispose patients to develop type 1 diabetes, but identification of other key genes will provide new targets for therapy. To this end, we have formed a collaboration to collect genetic material from 2,800 families with two or more siblings having type 1 diabetes. I am pleased to report that we have already recruited over 400 families for this study, and recruitment is ongoing. This collection will be an invaluable resource to investigators in their search for culprit genes.

We know much less about the environmental factors that trigger onset of type 1 diabetes in a genetically susceptible individual. To address this question, an international consortium is using our knowledge of key susceptibility genes to identify infants at high-risk for developing the disease and follow them through adolescence in the search for environmental factors that may trigger disease onset. We call this study "The Environmental Determinants of Diabetes in the Young," or "TEDDY." This long-term study has recently begun recruiting patients. The Special Funding Program has also permitted us to address the important issue of whether rates of development of type 1 diabetes in America are changing over time. There are no comprehensive population-based estimates of diabetes burden among American youth. The CDC and NIDDK are supporting a population-based registry to define the prevalence and incidence of diabetes in children of diverse racial and ethnic backgrounds by diabetes type. This project, entitled "SEARCH," is identifying and following children with diabetes in six regions of the country, to help us understand how the disease strikes and unfolds.

**Reversing or Preventing Type 1 Diabetes**

To spur the testing of promising new strategies to prevent, delay, or reverse progression of type 1 diabetes, the NIDDK has established a clinical trial network, the Type 1 Diabetes TrialNet, in conjunction with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the ADA, and the JDRF. TrialNet is an international network of investigators, clinical centers, and core facilities that support the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in

new-onset patients and to prevent the disease in at-risk patients. TrialNet is currently supporting several different protocols, including a study that is testing whether two different immunosuppressive medicines are able to stop the immune system from destroying beta cells in new onset type 1 diabetes.

The NIAID-led Immune Tolerance Network (ITN) is an international consortium of scientists and physicians evaluating novel clinical approaches to achieve a state of immune tolerance for the treatment of autoimmune diseases, asthma, and allergic diseases and the prevention of graft rejection. ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. In addition, ITN and TrialNet actively collaborate to test promising interventions and strategies to prevent or reverse type 1 diabetes.

In another effort, an international NICHD-led trial addresses the role of a specific environmental factor, cow's milk, in the development of type 1 diabetes. This trial, called the "Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically-At-Risk," or "TRIGR," is comparing the development of type 1 diabetes in infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, *versus* standard cow's milk formula. TRIGR, which is currently in the patient recruitment phase, was undertaken to confirm data derived from a human pilot study in Finland that was based on evidence from rodent models implicating cow's milk proteins in the pathogenesis of type 1 diabetes.

Preclinical work to explore new approaches to prevent type 1 diabetes is being pursued in the Cooperative Study Group for Autoimmune Disease Prevention, supported by NIAID and NIDDK. This multidisciplinary consortium conducts basic and clinical

research in type 1 diabetes and other autoimmune diseases. Researchers in the Cooperative Study Group have developed molecules that can be used to identify the cells of the immune system that are involved in the development of diabetes. The Cooperative Study Group is spearheading the "NOD mouse Roadmap," a comprehensive analysis of gene and protein expression and immune function during the development of type 1 diabetes in a mouse model of human disease. These studies may potentially define and provide markers to detect early disease onset.

Currently, there is no way to measure ongoing beta cell destruction to quantitatively monitor type 1 diabetes disease progression. In research toward overcoming this major research and clinical barrier, NIH-supported scientists discovered a new, non-invasive imaging technology that enabled them to monitor disease progression due to inflammation in a mouse model. The technology uses a vascular probe containing magnetic nanoparticles that can be detected by magnetic resonance imaging (MRI). Vascular probes have already been successfully used in humans to detect prostate cancer metastases; therefore, this technology has high potential of being translated to the clinic for type 1 diabetes to detect the inflammation caused when the immune system attacks the islet cells. Importantly, if successfully applied to type 1 diabetes, this technology can facilitate clinical trials of new therapeutic agents.

Recent exciting reports have suggested that the naturally produced hormone insulin is itself the critical initiator of the autoimmune destruction of pancreatic beta cells leading to type 1 diabetes. Although patients with the disease are known to have antibodies directed against insulin, and these antibodies are used to identify individuals at risk for the disorder, it was unclear whether insulin itself was the "key" autoantigen that

triggers the autoimmune attack. Two new lines of evidence, one in a genetically engineered mouse model of diabetes and the other using isolated T-cells (a type of cell in the immune system) from pancreatic lymph nodes of people with and without type 1 diabetes, strongly suggest that insulin is the key protein required for initiating the development of type 1 diabetes. This finding has important implications for development of new therapies. The NIH recently completed a clinical trial in which individuals at risk for type 1 diabetes were given insulin orally in an attempt to desensitize them to this potential trigger of autoimmunity. Although there was no benefit in the entire group of people studied, additional analyses have suggested that a subset of the study population--the group with the highest titers of antibodies directed against insulin--may have benefited from the therapy. We will soon begin a clinical trial to test whether insulin administered orally in this population can delay or prevent onset of type 1 diabetes.

## Developing Cell Replacement Therapy

Insulin therapy, via daily injections or a pump, is a poor substitute for the body's exquisitely precise regulation of blood glucose by insulin-producing pancreatic beta cells. In contrast to insulin administration, a real cure could emerge from cell-based therapy, such as the transplantation of insulin-producing cells. A breakthrough protocol pioneered in Edmonton, Canada, yielded short-term insulin independence in up to 90% of patients with type 1 diabetes who received islet transplantation. This protocol was subsequently replicated in the NIDDK intramural research program and then in a multi-center international trial conducted by the ITN at nine sites in the United States, Canada, and Europe. Although the success rate varied among the centers, this study showed that the

new procedure can relieve some patients of the burden of daily insulin injections. However, the immunosuppressive drugs of the new protocol do carry significant side effects, and the long-term results have yet to be established. The NIDDK-supported Collaborative Islet Transplant Registry (CITR) published its first annual report last year. The report included data from 12 medical centers in the U.S. and Canada that performed islet transplants on 86 patients. The report showed that, at one year after the last islet infusion, 58 percent of recipients no longer had to inject insulin but were relying on the transplanted cells to meet their bodies' needs for the hormone. To further bolster research efforts on islet transplantation, the NIDDK and NIAID co-sponsor a major new Clinical Islet Transplantation (CIT) consortium. The group consists of five clinical centers in the U.S., Canada, and Sweden. The CIT will also conduct a clinical trial on islet transplantation in Medicare recipients as mandated in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

A major barrier in the field of islet transplantation that limits its widespread use in clinical application is an inadequate supply of islets. NIDDK has teamed with the National Center for Research Resources (NCRR) and the JDRF to form the Islet Cell Resource Center consortium to provide human islets for both clinical transplantation protocols and basic research studies and to optimize the production methodologies. In addition, we are accelerating research on many aspects of beta cell development and function with the goal of increasing the supply of islets for transplantation. A key component of this effort is the NIDDK-sponsored Beta Cell Biology Consortium. This collaboration is providing scientists with access to information, resources, technologies, expertise, and reagents that are beyond the means of a single research effort. It represents

an unprecedented initiative to delineate each step in the pathway that leads to formation of beta cells that have the unique capacity for appropriately regulated insulin secretion and to develop methods to create ample supplies of these vital cells. Researchers in this consortium have generated a research tool, called Human PancChip 1.0, which contains over 12,000 human genes that are expressed in human pancreatic islets. They have also developed a Mouse PancChip 6.0, which contains over 13,000 mouse genes expressed in the pancreatic islets, and a tool called PromoterChip BCBC 3.0, containing regions controlling expression of 3,500 mouse genes involved in beta cell development and function.

The NIDDK is also supporting a new initiative to build on recent research demonstrating that beta cells can divide to produce more beta cells (or "regenerate"). If beta cells can be "coaxed" to form more sister cells, then this could be a potential therapy to reverse new onset type 1 diabetes or lessen the number of donor pancreata required for transplantation. In addition, the NIAID and NIDDK are sponsoring a new initiative to support studies of methods for transplanting islets from pigs to non-human primates. This is one aspect of xenotransplantation research, which involves the transfer of cells, tissues, or organs from one species to another.

A very exciting result was recently reported by scientists in the NIDDK Intramural Research Program. These scientists have induced human cadaveric insulin-producing cells to revert to islet precursor cells, proliferate, and then differentiate into islet-like cells again in which insulin production is regulated by glucose levels. With additional research, this work may help to clarify the natural lifecycle of the beta cell and may eventually have implications for cell replacement therapy.

Another barrier that limits widespread use of islet transplantation is the lifelong immunosuppressive drug treatments that are currently required to prevent rejection of transplanted islets, as well as recurrence of the underlying autoimmunity that caused type 1 diabetes initially. Both the Immune Tolerance Network and the Clinical Islet Transplantation Consortium are testing approaches to altering the immune system in human transplantation studies that may be safer or have fewer side effects than the drugs currently used. Another research consortium jointly led by NIAID and NIDDK, the Non-human Primate Transplantation Tolerance Cooperative Study Group, is evaluating the safety and efficacy of novel methods to induce immune tolerance to transplanted kidneys and islets in non-human primates to achieve long-term graft survival. This tolerance induction approach would avoid lifelong immunosuppressive therapies that can have deleterious and often life-threatening side effects.

Through this multifaceted bench-to-bedside approach, combining shared resources, collaborative fundamental basic research, preclinical development in animal models, and multicenter clinical trials, the NIH is pursuing every avenue toward progress in islet transplantation that can directly translate into potential therapies for type 1 diabetes patients.

## Reducing or Preventing Hypoglycemia in Type 1 Diabetes

Perhaps the most distressing, acute complication in patients with type 1 diabetes is hypoglycemia, or low blood sugar. It is caused by excessive treatment with insulin relative to food intake and physical activity. The potential for hypoglycemic episodes has impeded the use of intensive insulin therapy even though major clinical trials have shown

that such therapy can significantly reduce the risks of longer-term diabetic complications. Hypoglycemia is a particular problem in young children, who may not be able to realize and communicate their symptoms to parents. For these reasons, a key goal of ours is to attain greater understanding of hypoglycemia and develop new approaches to mitigate this problem. We have established research programs to address these important issues.

We have established a network, called "DirecNet," which is led by NICHD, to investigate the use of technological advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia. DirecNet has recently completed a study examining the impact of exercise on the incidence of nocturnal hypoglycemia in children with type 1 diabetes. The data, which are still being analyzed, indicate that exercise affects glucose levels in children over a longer period than previously appreciated; there is a strong association between exercise and delayed overnight hypoglycemia.

Because of the importance of the brain in sensing blood sugar levels, the NIDDK, in collaboration with National Institute of Neurological Disorders and Stroke (NINDS), is supporting an initiative to promote research on how the brain and other critical tissues sense and respond to hypoglycemia; understand the effects of hypoglycemia on brain function; and develop more effective methodologies to prevent hypoglycemia. These approaches are all directed toward improved management of the disease.

**Preventing or Reducing the Complications of Type 1 Diabetes**

The complications of diabetes affect virtually every system of the body. Diabetes increases the risk of blindness, kidney failure, chronic wounds and skin ulcers, nerve pain

and other neurological problems, lower limb amputation, heart disease and heart attacks, stroke, high blood pressure, gum disease, and pregnancy-related problems. Diabetes and its complications can shorten average life expectancy by up to 15 years. However, the good news is that patients with type 1 diabetes are living longer than ever before. Data from Allegheny County, Pennsylvania, have shown that the long-term survival of children with type 1 diabetes has improved over time, most likely representing better glycemic and blood pressure control since the early 1980's. In addition, clinical trials, including the Diabetes Control and Complications Trial (DCCT), have demonstrated that intensive control of glucose is extremely effective in preventing complications. Long-term results from the follow-on study to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC), now show that a finite period of good glucose control provides benefits that endure more than a decade after the trial ended. Therefore, further reductions in mortality can be expected as the findings of this landmark study are incorporated into practice.

The NIDDK continues to foster exciting new opportunities for the research community to intensify the study of diabetic complications. Support of these efforts comes from both our regularly appropriated funds and the Special Statutory Funding Program for Type 1 Diabetes Research.

Patients with type 1 diabetes have a four- to nine-fold increased risk of developing cardiovascular disease (CVD), and 75 percent will die from CVD, the leading cause of mortality in these patients. The National Heart, Lung, and Blood Institute (NHLBI) and the NIDDK have spearheaded a new initiative that supports basic and clinical studies to increase understanding of the effects of type 1 diabetes and its

metabolic complications on the early development and accelerated progression of CVD in these patients. New studies will also evaluate imaging techniques that might be used as endpoints in future clinical trials, reducing the time needed to see an effect of therapy.

The NIDDK, in collaboration with the NINDS, NHLBI, and the National Eye Institute (NEI), has sponsored a new initiative to stimulate research on the abnormal formation of new blood vessels observed in the development of complications of type 1 diabetes. Research on blood vessel formation (angiogenesis) has already yielded new therapies for cancer, and we are conducting basic and clinical research on angiogenesis in order to develop therapies, biomarkers, and imaging tools to improve the diagnosis and treatment of diabetic complications.

Another focus of research has been the development of animal models that faithfully replicate development of complications of diabetes in humans. This type of work is being done through the Animal Models of Diabetic Complications Consortium, which is supported by the NIDDK and the NHLBI. The Consortium has already developed a number of promising models for complications involving the heart, kidney, and nervous system. Development of animal models is essential for preclinical drug development.

In addition to clinical studies, basic research is under way to identify the genes that may increase a person's susceptibility to developing complications of diabetes. For example, DNA collected from patients in the DCCT/EDIC study and their family members is being analyzed in order to find genes associated with the development of diabetic complications. The CDC and JDRF-led Genetics of Kidneys and Diabetes Study (GoKinD) has accrued the largest single collection of biosamples and data for research on

the genetic causes of kidney disease in type 1 diabetes. Researchers from this consortium recently announced the availability of these biosamples and data to the broad research community so that investigators could conduct studies to identify genetic risk factors for diabetic kidney disease. In addition, the Special Funding Program has allowed the Family Investigation of Nephropathy and Diabetes (FIND) study to expand its focus to include the genetic determinants of diabetic retinopathy. Identifying the genetic basis of disease complications will reveal new targets for therapy.

## Attracting New Talent and Applying New Technologies to Research on Type 1 Diabetes

Type 1 diabetes research spans an extraordinarily broad range of scientific disciplines. For this reason, a cadre of exceptionally talented and dedicated researchers is needed to bring expertise to bear on understanding, treating, preventing, and curing type 1 diabetes. As more research is being done in the laboratory, or at the "bench," there is a need to rapidly move those results into the clinic, or "bedside," to benefit patients directly. For this reason, the NIH is sponsoring "bench-to-bedside" initiatives, in which teams of basic scientists and clinical researchers are successfully working together on translational research projects focused on type 1 diabetes. The funded research projects represent a broad spectrum of science related to the disease and its complications. Another important translational research effort that is supported by the NIDDK and the National Cancer Institute (NCI) is the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program. T1D-RAID provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in type 1

diabetes clinical trials. The goal of T1D-RAID is to facilitate translation from the lab to the clinic of novel, scientifically meritorious therapeutic interventions for type 1 diabetes and its complications.

In addition, we are supporting the research training and career development of pediatric endocrinologists. Due to heavy clinical demands, it is especially challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers, yet their clinical expertise is invaluable to type 1 diabetes research. The NIDDK, in collaboration with the ADA and the JDRF, is therefore supporting research training and career development programs in pediatric endocrinology to increase the number of independent investigators who can contribute to research in this area. This program has already seen success: seven of the trainees have successfully competed for an individual NIH career development award, and two of the trainees have attained tenure-track faculty positions at other universities.

New and innovative technologies are continually being developed. Examples include technologies to describe the dynamics of protein interactions ("proteomics") and technologies to study cellular metabolites, such as lipids, amino acids, and carbohydrates ("metabolomics"). In order to capitalize on these new and emerging technologies, the NIDDK has developed an initiative to support studies on proteomics and metabolomics technologies to enhance understanding of type 1 diabetes and its complications. These types of studies, which can be performed at different times during disease development, could lead to invaluable insights into the etiology and development of type 1 diabetes and its complications.

## Conclusion

I am grateful for the opportunity to share with you these few highlights of ongoing research efforts. In order to inform the priority-setting process for NIH-supported type 1 diabetes research in the years ahead, the NIDDK is spearheading a new strategic planning effort under the aegis of the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). With extensive input from external scientific and lay experts, the Plan will summarize recent advances in the field, and set forth short-, intermediate-, and long-range objectives for research on type 1 diabetes and its complications. The Strategic Plan is expected to be released next summer.

Diabetes is a devastating illness for patients and their families. We continue to be inspired by the dedicated efforts of individuals affected by the disease, and by organizations that represent them, such as the Juvenile Diabetes Research Foundation International. We are grateful for the full range of appropriations for type 1 diabetes research. We continue to be diligent in our fight against diabetes so that we can help all the children in this room and the many other type 1 diabetes patients throughout America whom they represent here today. Improving their quality-of-life—with the ultimate goal of curing their disease—is the driving force behind our efforts. I am pleased to answer any questions you may have.

**Allen M. Spiegel, M.D.**

Appointed director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in November 1999, Dr. Allen M. Spiegel oversees a staff of 625 full-time employees and a $1.7 billion budget in Fiscal Year 2005. The Institute conducts research on some of the most serious and chronic diseases affecting the Nation's health at its intramural facilities in Bethesda, Maryland, and Phoenix, Arizona, and it supports the work of about 3,300 investigators in medical centers, universities, and laboratories throughout the United States. "Throughout my career, I've tried to forge strong links between fundamental science and clinical medicine," Spiegel says. "As NIDDK director, I'm committed to continuing our strong support for basic science because it offers the greatest promise for acquiring new knowledge of human disease. At the same time, we vigorously support efforts to apply this new knowledge so that it rapidly reaches patients and measurably improves their lives."

Before becoming director, Spiegel served as NIDDK's scientific director for 9 years, leading one of the largest and most productive intramural research programs at the National Institutes of Health (NIH). In this post, he oversaw 21 laboratories and branches that study diabetes, metabolic disease, sickle cell disease and other red blood cell disorders, endocrinology, hepatitis B and C, genetics, biochemistry and molecular, cellular, developmental, and structural biology. He created a new branch to study the pathogenesis of type 1 diabetes and to test new immunomodulatory treatments aimed at reducing the need for global immunosuppression in patients who undergo kidney and pancreatic islet transplantation.

Spiegel is an internationally recognized researcher and endocrinologist whose work on signal transduction helped to clarify the genetic basis of several endocrine diseases. His research showed that defects in G proteins, the intermediaries between hormone receptors and effectors, could cause inherited disease. Spiegel and colleagues at NIH have identified mutations in G proteins that result in disrupted cell signaling and cause disorders such as pseudohypoparathyroidism type la and McCune-Albright syndrome.

Spiegel and colleagues also found mutations in G protein-coupled receptors that lead to either hormone resistance in diseases such as nephrogenic diabetes insipidus or excessive hormonal production in diseases such as familial male precocious puberty. His ongoing studies on a G protein-coupled calcium-sensing receptor may help researchers develop treatment for hyperparathyroidism and other disorders involving this receptor.

Spiegel and a team of researchers from NIDDK and the National Human Genome Research Institute (NHGRI) also cloned the multiple endocrine neoplasia type 1 (MEN 1) tumor suppressor gene. A mutated form of the MEN 1 gene causes this inherited tumor predisposition syndrome, as well as sporadic, noninherited forms of endocrine tumor. As chief of the Molecular Pathophysiology Section, Spiegel continues to collaborate with the NIDDK and NHGRI team, which is studying the structure and function of the MEN 1 gene and its encoded protein, menin.

Spiegel earned his bachelor's degree, summa cum laude, from Columbia University in 1967, and his medical degree, cum laude, from Harvard Medical School in 1971. Spiegel completed an internship and residency in internal medicine at Massachusetts General Hospital in Boston in 1973, and then came to NIDDK's Endocrinology Research Training Program under the mentorship of the late Gerald Aurbach, M.D. He became a senior investigator in the Metabolic Diseases Branch, in 1985 was promoted to chief of the Molecular Pathophysiology Section, and in 1988 to chief of the Metabolic Diseases Branch.

The author of over 350 scientific papers and two books, Spiegel has received many awards recognizing his accomplishments, including the Jacobaeus Prize of the Novo Nordisk Insulin Foundation in 1990, the 1996 Komrower Memorial Lecture Award from the Society for the Study of Inborn Errors in Metabolism, and the 1998 Edwin B. Astwood Lecture Award from the Endocrine Society. He has been elected to membership in the American Society for Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the National Academies.