



**Testimony
Before the Committee on Indian Affairs
United States Senate**

DIABETES RESEARCH IN AMERICAN INDIANS

Statement of

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U.S. Department of Health and Human Services



**For Release on Delivery
Expected at 9:30 a.m.
Thursday, February 8, 2007**

Mr. Chairman and Members of the Committee: I am William Knowler, Chief of the Diabetes Epidemiology and Clinical Research Section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Our Institute has primary responsibility for diabetes research at the National Institutes of Health (NIH) of the Department of Health and Human Services (HHS). I am accompanied by Dr. Judith Fradkin, who is the Director of the NIDDK's extramural Division of Diabetes, Endocrinology, and Metabolic Diseases.

I am pleased to testify today regarding NIDDK's efforts to combat diabetes in American Indians, the population with the highest known rates of type 2 diabetes in the world. In addition to hitting American Indians the hardest, type 2 diabetes has become a very significant and increasing health problem nationwide. Both type 1 diabetes and type 2 diabetes are major causes of blindness, kidney failure, and cardiovascular death, and the combined economic cost of type 1 diabetes and type 2 diabetes in the U.S. is over \$130 billion annually. Reducing the incidence of diabetes would clearly reduce suffering and benefit our society.

For the past 31 years, I have conducted research on diabetes with the Gila River Indian Community at the NIDDK's Phoenix Epidemiology and Clinical Research Branch in Arizona. This Branch is a major component of NIDDK's intramural research program, and is located in Phoenix because of its emphasis on research in American Indian populations. The Branch develops and applies epidemiologic, clinical, and genetic methods in the investigation of diabetes and its complications, which are particularly common among southwestern American Indians.

Through basic and clinical research, we can gain greater insights into the genetic and environmental factors that lead to the development of type 2 diabetes, develop effective treatments, and perhaps most importantly develop strategies and programs to prevent or delay

the onset of the disease. My particular research focuses on the risk factors for type 2 diabetes and its complications (especially diabetic kidney, eye, and heart disease), obesity and its relationship to diabetes, and diagnostic criteria for diabetes.

GILA RIVER INDIAN COMMUNITY LONGITUDINAL STUDY

Most of the research of our Branch is conducted in collaboration with the members of the Gila River Indian Community (most of whom are Pima Indians) near Phoenix. Some of our programs also include other American Indians in Arizona and New Mexico. In our longitudinal population study in the Gila River Indian Community, begun in 1965, we examine community residents at regular intervals. The examinations focus on diabetes and its risk factors and complications. This study has contributed much to the world's current understanding of the causes and consequences of type 2 diabetes and its complications, for which we are all indebted to this community. The study has led to other research on obesity and physiologic problems such as insulin resistance and defects in insulin secretion that play a major role in type 2 diabetes. By carefully evaluating the relationships between plasma glucose concentrations and the specific signs of diabetes, we established criteria for diagnosing diabetes and identifying nondiabetic persons at high risk of developing diabetes. These criteria have been adopted for worldwide use. The study also led to recognizing the importance of control of high blood glucose and high blood pressure in diabetes. These are now standard components of diabetes care throughout Indian country and the entire world.

I am happy to report that these improvements in standards of care have directly benefited members of the Gila River Indian Community. Over the last 30 years there has been a rise in the percentage of people with diabetes receiving medical treatment to control blood

glucose, coinciding with a fall in average blood glucose. There has also been a marked increase in the use of blood pressure medicines accompanied by a fall in average blood pressure. The sharp increase in the use of both aspirin and cholesterol lowering agents in recent years may reduce the risk for heart disease in people with diabetes. The rates of attainment of American Diabetes Association treatment goals for diabetes are better in this Community than in the nation as a whole, thanks to the diligent efforts of the tribal health program in implementing research-based standards of care.

Finally, the research has contributed to understanding the serious long-term consequences of childhood obesity and type 2 diabetes, the importance of obesity on the development of type 2 diabetes, and the concept that type 2 diabetes and its complications can be prevented or delayed by modifying or treating factors that put people at high risk. These results stimulated the development of the Diabetes Prevention Program (DPP).

THE DIABETES PREVENTION PROGRAM (DPP)

The findings of the DPP are among the most encouraging and valuable to come from diabetes research in the past decade. I would like to tell you briefly about this clinical trial. Our Branch, along with 22 university sites, participated in the DPP to examine the effects of a lifestyle-based weight-loss intervention and pharmacologic interventions on the development of type 2 diabetes in adults with pre-diabetes. These interventions were tested because our previous research findings suggested that reducing weight or improving insulin resistance might prevent type 2 diabetes. About half of the nearly 4,000 DPP participants were from minority groups. The lifestyle intervention, that included modest weight loss and increased physical activity, resulted in a dramatically reduced risk—by 58 percent—of developing type 2

diabetes. The intervention with the drug metformin reduced diabetes risk by 31 percent. The lifestyle and metformin interventions worked well in both men and women and in all ethnic groups studied, including the American Indians. This significant finding conveys an important message to American Indians and other people at high risk for type 2 diabetes: by adopting a moderate, consistent diet and exercise weight-loss program, diabetes can be prevented or delayed. The importance of translating these results into practice is paramount. The American Indian and other DPP participants continue to be followed in the DPP Outcomes Study to assess the durability of the effects of the DPP interventions on preventing type 2 diabetes and determine their impact on development of diabetes complications.

The DPP, primarily funded by the NIDDK but also with substantial support from the Indian Health Service (IHS), has had a large impact on many IHS and tribal health programs to prevent diabetes, as I will describe later. The DPP is an outstanding collaboration between NIDDK and the IHS in a research study testing ideas that came from population research and, in turn, greatly influencing and benefiting clinical practice in Indian country and throughout the world.

COMPLICATIONS OF DIABETES

Diabetes is associated with many complications that affect the eyes, kidneys, heart, feet, gums, and blood vessels. The kidney complications of diabetes often lead to heart attacks or to the need for dialysis or kidney transplantation. Poor control of blood glucose and blood pressure, long duration of diabetes, and genetic factors increase the risk of diabetes complications such as those affecting the kidneys. We recently discovered an additional treatable factor: periodontal disease, an infection of the gums that is very common in American

Indians with diabetes. It is the major cause of tooth loss, but the risks of periodontal disease extend well beyond the mouth. Periodontal disease also increases the risk of kidney disease and is associated with higher death rates from kidney disease and heart attacks in those with diabetes.

The rate of progression to kidney failure among diabetic Gila River Indian Community members who are at least 45 years old has declined since 1990, suggesting that newer treatments for diabetic kidney disease are slowing its progression. Since 1999, a similar decline in the rate of diabetic kidney failure has been seen nationally in American Indians but not in other racial or ethnic groups. Unfortunately, the frequency of kidney failure is increasing among younger Gila River Indian Community members because of the increasing rate at which diabetes develops in youth. Five percent of Community members 15 to 19 years of age now have diabetes, and many of them will develop kidney failure or die of diabetes complications by their 40s or 50s.

Death rates from heart disease have doubled among Gila River Indian Community members with diabetes in recent years, while deaths attributed to diabetic kidney disease have declined. These changes are due primarily to improvements in dialysis care that have reduced deaths from kidney disease, while the risk of death from heart disease remains high. On the other hand, death rates from heart disease remained very low in non-diabetic Community members and have not changed over the past 40 years. This finding points to the importance of preventing diabetes and its kidney complications as a means of reducing the risk of heart disease.

LOOK AHEAD (ACTION FOR HEALTH IN DIABETES)

American Indians are part of a major NIDDK diabetes treatment clinical trial, called Look AHEAD (Action for Health in Diabetes), which is a multicenter randomized clinical trial examining the long-term effects of a lifestyle weight-loss intervention on the development of cardiovascular disease and other complications of diabetes. A Southwest American Indian Look AHEAD clinical center at our Branch includes participants from American Indian communities in Arizona and New Mexico.

OVERWEIGHT AND OBESITY

Because obesity is an important and modifiable risk factor for the development of type 2 diabetes, we seek to understand in more detail why some people become overweight or obese. We also conduct research on better ways of preventing or reversing these conditions. Much of this research is conducted in our inpatient clinical research unit in the Phoenix Indian Medical Center. Specifically, we are studying genetic and other causes of why some people overeat and exercise too little, because these are the major factors causing obesity, not “slow metabolism” or abnormalities of resting energy expenditure. We are also studying factors that predict which people respond best to weight-loss interventions by achieving and, more importantly, maintaining weight loss.

GENETICS RESEARCH

Most of the research I have described has had large and immediate impacts on the prevention and treatment of type 2 diabetes. To achieve even greater progress or to eliminate the disease altogether, we believe that a more fundamental understanding of its causes and

biological mechanisms is needed. To this end, we have also pursued research in the genetic susceptibility factors for obesity, type 2 diabetes, and its complications, including diabetic kidney disease.

There is a large body of scientific evidence that obesity and type 2 diabetes have major genetic determinants, and there have been considerable advances in technologies to identify genes for such complex health conditions. These new methods need to be applied across various populations and individual American Indian communities, because different genes, or different variants within the same gene, may increase the risk of these conditions in different groups.

In the past year a major type 2 diabetes susceptibility gene was identified in Iceland, and it appears to be a major gene for diabetes in Whites around the world, but not, for example, in the Pimas of the Gila River Indian Community. We are testing the possibility that polymorphisms (i.e., common variations in the sequence of DNA among individuals) in other genes in the same metabolic pathway increase the risk of diabetes among the Pimas. Conversely, a genetic polymorphism that is unique to the Ojee Cree tribe in Canada was found to greatly increase their risk of diabetes. By contrast, our previous discovery of a region on chromosome 1 that contains a gene or genes involved in diabetes susceptibility in the Pima Indians has been widely replicated around the world. We work with an international consortium of scientists to precisely identify this gene.

THE NATIONAL DIABETES EDUCATION PROGRAM (NDEP)

To disseminate the important findings of the DPP to people at risk for diabetes, the NDEP developed the “Small Steps, Big Rewards, Prevent Type 2 Diabetes” education

campaign. The NDEP is sponsored by the NIDDK, the Centers for Disease Control and Prevention (CDC), and over 200 partners. The campaign, which includes material tailored to American Indians, emphasizes the practical application of the DPP findings and includes lifestyle-change tools for those at risk, patient education materials for healthcare providers, web-based resources for healthcare providers and consumers, and public service announcements. In addition to educational material on diabetes prevention, the NDEP has developed culturally-specific messages on the importance of controlling blood glucose levels to prevent life-threatening diabetes complications for American Indians already diagnosed with diabetes. The NIDDK is committed to continuing these types of educational efforts to disseminate the positive results of its clinical trials to benefit public health.

NIDDK-IHS PARTNERSHIPS

Mr. Chairman, I'm pleased to tell you that the NIDDK works closely with the Indian Health Service to improve the health and quality of life of American Indians. The NIDDK's extramural Division of Diabetes, Endocrinology, and Metabolic Diseases, which Dr. Fradkin heads, has worked closely with the IHS' Division of Diabetes Treatment and Prevention in the development of the "Special Diabetes Program for Indians Competitive Grant Program," which has developed a DPP-like lifestyle intervention program for American Indians diagnosed with pre-diabetes, for implementation testing at 36 Tribal grantee sites. Since the awarding of the 36 grants, including one to the Gila River Indian Community, NIDDK has participated in the Steering Committee for this program. In addition, the Director of the IHS' Division of Diabetes Treatment and Prevention and its National Diabetes Program, Dr. Kelly Acton, serves as a member of the statutory Diabetes Mellitus Interagency Coordinating Committee, which is

chaired by the NIDDK. This Committee serves an important function by coordinating activities of all Federal programs related to diabetes and its complications.

In addition, the NIDDK, IHS, CDC, Tribal Colleges and Universities, and the Tribal Leaders Diabetes Committee joined together to develop “Diabetes-Based Science Education in Tribal Schools,” which is an educational curriculum development program to enhance understanding and appreciation of diabetes, and within this framework, to increase knowledge of the biomedical sciences in Tribal elementary, middle, and high schools. One goal of the program is to enhance awareness and understanding of diabetes among students, families, community members, and teachers to prevent the disease and to help affected Tribal members better manage their diabetes. Another objective of the program is to increase the numbers of American Indians who enter the health research professions. The IHS continues to make critical personnel and financial contributions to the successful and influential prevention research program, the DPP and the DPP Outcomes Study.

CONCLUSION

Mr. Chairman and Members of the Committee, I hope that these few examples convey the firm commitment of the NIH and NIDDK, in partnership with our sister agencies, to combating diabetes in American Indians. The central mission of the NIH is to conduct and support biomedical research aimed at decreasing the burden of disease in the United States. In diabetes, I believe that the NIH’s mission is being well served and that the future is encouraging for the ultimate control and prevention of diabetes in American Indians and all Americans. Let me conclude with a note of special thanks to the members of the United States Senate on behalf of the community of scientists who work in diabetes. Thank you for the

continuing encouragement of biomedical research through which we hope to improve the health of all Americans.

I appreciate the opportunity to address the Committee on behalf of the NIH and NIDDK and would be pleased to respond to any questions you may have.



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Dr. William C. Knowler has worked with American Indians in the Southwestern U.S. for the last 31 years as a research physician with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). He is Chief of the Diabetes Epidemiology and Clinical Research Section of NIDDK in Phoenix, AZ, where he conducts research in type 2 diabetes, complications of diabetes, obesity, and other health concerns of American Indians. He also serves with two national diabetes clinical trials evaluating the best ways to prevent the development of type 2 diabetes and the occurrence of cardiovascular complications of the disease and in a national study of the hereditary factors in the development of diabetic kidney disease.

Dr. Knowler was born and educated in Iowa City, receiving his BA in mathematics from the University of Iowa. He then received doctoral degrees in medicine and public health from Harvard University and further clinical training in Boston before moving to the NIDDK in Arizona in 1975. He is widely recognized for his research in the causes and prevention of type 2 diabetes and its complications. His research findings have been widely implemented in clinical practice, in particular in Indian Health Service and tribal programs serving American Indians.

Dr. Knowler is widely sought as a lecturer and teacher, has published over 400 medical research articles and book chapters, and serves as a reviewer or editor for several medical journals. He is recognized as one of the world's 250 most highly cited researchers in clinical medicine and in biology and biochemistry. He has been honored for his research and its clinical applications with many awards, most notably the Kelly West Award for Epidemiology from the American Diabetes Association, the Tribal Leaders Diabetes Committee award for research in treatment and prevention of diabetes in American Indians, and the NIDDK Director's Award for national leadership in diabetes prevention.

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