

Dr. William Knowler  
Oral History  
March 22, 2024

Addy: Good morning. Today is March 22, 2024. My name is Grayson Addy, and I'm a volunteer at the NIH Office of History and Stetten Museum. Today I have the honor of speaking with Dr. William Knowler, who was the chief of the Diabetes Epidemiology and Clinical Research Section at NIDDK [National Institute of Diabetes and Digestive and Kidney Diseases] in Phoenix for 42 years. Dr. Knowler has a multitude of accomplishments, including receiving the 2011 National Institute of Health Director's Award for Leadership in implementing novel approaches to the prevention of type 2 diabetes. Dr. Knowler will be speaking today on his early life, education, career, and accomplishments. I'm excited for this opportunity to speak with you.

Knowler: Thank you.

Addy: Okay, just to get us started, a little bit about your background. You were born in Iowa City, the son of Professor Lloyd and Faith Knowler. Could you start by telling me about your family, early life, and education through high school?

Knowler: Sure. I was born and raised in Iowa City, a college town. My father was a professor of mathematics and statistics at the university. I had a sister five years older, so we grew up as a family of four. I lived in Iowa City through high school and college, except for one year when I was 14. My father took an overseas assignment in India, where our family lived for the year. That was an eye-opening experience for me, getting outside of a college town in the Midwest. But otherwise, my education through high school was all in Iowa City Public Schools. My family valued education very highly, not surprisingly, with my father as a professor and my mother also well-educated.

Addy: Do you think that your parents' lives in education affected your views and expectations for a fulfilling, successful life?

Knowler: Yeah. Absolutely. I always saw my career being in an academic or scientific form, which is certainly how it's turned out.

Addy: You mentioned that you spent a year in Calcutta, India. What led to this decision to move, what was your impression of Calcutta at the time, and did it have a lasting impact?

Knowler: Yes. The reason for the move, as I said, was my father's work. He was a professor of math and statistics. He was very much an applied statistician and applied statistics to a number of areas, including actuarial science, engineering, manufacturing, and medical research. That, of course, had some influence on my career. Because of his work in statistical quality control in manufacturing, he was invited to come to India by the Indian Statistical Institute, although his trip was sponsored by the U.S. government, and he was a U.S. employee for that year. He was invited to work with Indian statisticians who were establishing quality control and consulting services in manufacturing throughout the country. That was a very exciting year and very challenging for him at work and for the rest of us, living in a new place. I went to a large school where I was the only foreigner. Of course, being a foreigner was a new perspective, as opposed to being in my own hometown. That really opened up my eyes to seeing that there's a lot more to the world than what I'd seen so far.

Addy: Amazing. After that, when did you become interested in mathematics and medicine? Is there anybody who especially encouraged you or had an influence on you, introducing you to these important questions and concepts?

Knowler: Of course, I was always exposed to mathematics. In addition to exposing me to his work, my father liked to tutor me as I was growing up. Math is something that I was always very good at; it came naturally. It was my major in college. Some of his applied work was at the medical school in statistics and clinical trials. I had an uncle in Iowa City whom I was pretty close to, who was a physician and also a professor at the University. I had several cousins who were physicians. Even though my immediate family had no physicians, there were quite a few in the larger family. I don't think any of them tried to talk me into going into medicine. It's just that I knew physicians in the family, so it was something that didn't seem foreign to me. I considered being a pure mathematician. I loved math and the study of philosophy and the philosophy of science, which was my favorite course in college. I felt, however, that I just didn't want to be that abstract. I wanted to do something practical, so medicine seemed like a place I could do that. A place where I could be mathematical and scientific, with a human focus, that would make some impact on people. That's how I ended up in medicine and combining medicine and my interest in mathematics.

Addy: Great, I'm glad that really added both of your interests, and you figured out a way to do that. When you were at the University of Iowa, you received the Highest Distinction and Honors in mathematics and were recognized as the most distinguished undergraduate. How did you choose the University of Iowa? And were there any additional courses that continue to influence you today? I know that you mentioned one.

Knowler: It wasn't really much of a choice. That was the school in the town where I lived, and it's a good university. I didn't have an incentive to look elsewhere. My parents, being products of the university, thought that it was a great place too; they never really encouraged me to go anywhere else, except for medical school. We all thought that was the time I should move on and go someplace else. When I applied to medical schools, I applied to the University of Iowa, partly because I was pretty certain I'd be accepted there and because it was and still is a great school. I applied to several others and was accepted at Harvard, where I decided to go. I decided this was the time to move on.

Addy: You talked about medical school, could you tell me about your experiences as a student at Harvard? Did you apply to medical school knowing that you'd be an epidemiologist?

Knowler: I don't think I even knew the term "epidemiology" when I applied to medical school, but I was certainly aware of medical statistics. I'd seen, indirectly, how statistics are applied in medical research and clinical trials. The medical school is located on the same campus as the Harvard School of Public Health, which has a very strong department of epidemiology. Early on, during some of my elective time, I took an epidemiology course. I got to know some of the faculty at the School of Public Health and realized, "This is the department that does what I've been thinking I wanted to do, and it's called 'epidemiology'." I took some epidemiology courses during medical school. I took an extra year and spent five years in medical school. In one of those years I did research in a laboratory. I also had time that year to take some additional courses in the School of Public Health. I ended up graduating with joint M.D. and Master of Public Health degrees. From very early in my medical training, it was pretty clear that I was heading towards some sort of epidemiologic research.

Addy: What were your main goals and perceptions of medical research early on in your career, and how did they kind of change and progress throughout?

Knowler: Early on, I did what was easily available to medical students -- taking some time for research. I worked in a behavioral lab with animals looking at physiologic responses to the different kinds of behaviors. I thought that was very interesting. One of my professors had been a Ph.D. student of B.F. Skinner at Harvard, who was the pioneer of a lot of modern behavioral science. I learned about operant conditioning, which is a basis for much of animal, and perhaps, human behavior. I learned some physiology, but I also decided during that year that, since I'm learning medicine, I would rather do my research with people rather than rats and monkeys, which I'd been working with. I've never done any animal or basic science bench research since that medical school experience. I have been working in only human research since then.

Addy: As you said, you've been at the NIDDK since pretty early, 1975, and you're still active scientifically. That's a very long-term commitment. You've seen a lot of changes. Could you tell us about some of these changes? What brought you to the NIDDK and what made you want to stay with them?

Knowler: I was an NIH employee even before 1975. For my research year, I had a research fellowship from the Public Health Service. Then, during my senior year of medical school, I was appointed as a commissioned officer in a scholarship program. The NIH paid for my senior year of medical school, which was very helpful because even though the costs were not what they are now, they were still substantial in those days. For that year, the NIH paid my tuition and a stipend that helped with living expenses. In exchange, I agreed to work for NIH after I finished my clinical training. This was what I wanted to do anyway. I knew I wanted to do some kind of human research involving mathematics and statistics. The NIH seemed like an obvious place to learn how to do that. Of course, it was and is an ideal place for that kind of research.

Addy: What kind of changes have you seen, if any, throughout the time that you've been with the NIDDK?

Knowler: There have certainly been a lot of economic changes that have affected the NIH. It was interesting that during my early years, and perhaps even for 10 or 20 years, we never seemed to have any budget questions; the budget was not a limitation. The limitation was FTEs (Full-Time Equivalent employees) -- how many people we could have. It's always been a constraint at the NIH. But given the people we had, if we needed to buy something or if we needed to spend money in the lab, that wasn't a problem. If we needed some services that could be contracted, we could contract services out. That's changed. Now, of course, the NIH has limits in both respects. There are still limits in personnel, but the major limits that I've seen have been in finances. Maybe you can hire someone, but you can't afford to pay them, or it takes so much money that even if you have staff, you can't afford for them to do anything that requires spending money, which most research does. That's been a change, just a lot more bureaucracy in terms of not just budgets, but also approving papers and research protocols. There are a lot more layers of approval. In my most recent years working at NIH, there was less time for research and more time doing a bunch of other stuff, which was less fun. That's one of the things I've really enjoyed about retiring. Being a scientist emeritus, now I can work as much or as little as I want. I still do a lot of research. All the work I do is on writing papers and helping others analyze data and write papers. That's a lot of fun, and I don't have to deal with the rest of it.

Addy: Thank you so much for the insights, and I admire the work that you're doing. For most of your career, you have been partnering with Southwest American indigenous communities. Tell me about this partnership and how you became involved with this study.

Knowler: Again, I became involved in 1975, when I joined the study that had already been going on for 10 years. I had applied for the early commissioning program that paid for my senior year of medical school. There was a matching program where I looked at many different NIH programs that were participating, and the directors of those programs interviewed me. We had a match, and I ended up with this program in Phoenix. Of course, most

of these programs were in Bethesda. Phoenix was my first choice for several reasons. I've always been drawn to the western U.S. Even though I grew up in the Midwest, my family traveled extensively. Most of our vacation trips were in the West, either in the Mountains, the West Coast, or Western Canada. I've always liked mountains and being adjacent to the wilderness. Although there's a lot of nice wilderness in New England and around Boston, where I lived during medical school, I felt more attracted to the western U.S. than to New England. So I thought, "Gee, that sounds interesting to go to Arizona." I think ever since my experience living in India, I've been interested in working with people who are different from me and have different backgrounds. For these reasons, my wife and I chose the Phoenix branch of NIDDK. Because of my scholarship, I had a two-year commitment to work in Phoenix, and we fully intended to fulfill the two-year commitment, and then go somewhere else. We didn't really know what we were going to do next. But as the two years went on, I got involved in a lot of projects, which, of course, I couldn't finish in two years, I felt, "Well, can we stay another year or two and finish up some of this stuff?" My wife was getting into work that she liked and getting good colleagues. Of course, we and our children were making friends in the area. Over 40 years later, my wife and I were still there. Things just work out that way. Your plans don't always go as you think they will.

Addy: That makes a lot of sense. I think it's great that you just stayed and that you found the place that you wanted to be. You said that you're most proud of your collaborations with your American Indigenous partners, especially since they volunteered to be in the study since they believed that their participation would benefit not only their own health but [also] those of others. Was it ever difficult to retain or find participants? How did you all address these issues? And why did you find that kind of inclusion of Indigenous Americans so important in these studies?

Knowler: Well, that's a mouthful of questions. Let me try to answer a few at a time. You mentioned in the introduction that I had received the NIH Director's Award, which was probably the most visible award that I've received, but the one that means the most to me was an award from the Tribal Leaders Diabetes Committee. I worked very closely with the Indian Health Service, and the Albuquerque area of the Indian Health Service was very supportive of the Diabetes Prevention Program, one of my most important research projects. I spent a lot of time in Albuquerque, which fortunately was only an hour's flight away, to work with the Indian Health Service and Tribal committees dealing with diabetes. At one of these meetings, the Tribal Leaders Diabetes Committee gave me their award for diabetes prevention work in American Indian communities. This was important because you want your research to be appreciated by the people who are participating in it, not just by the scientific community at large. That was my most important recognition. In terms of recruitment, it's mixed. We're always able to recruit for studies, but there are also people who don't want to have anything to do with research. There are research detractors. There are people who have said publicly and even in the press that we created or perpetuated diabetes so we could study it. Fortunately, I think that view has been in a minority, and most people have appreciated the research. There have been disappointments, however, because some people thought that we're going to undertake this big research program and then in a few years there will be no more diabetes. That was an unrealistic expectation, but I think some people hold it against us and other researchers that, "You've been doing all this research, and diabetes is still here." Now, unfortunately, that's a fact of life. There have been lots of improvements, lots of ways to prevent diabetes, and better ways to treat it, but it is still here.

Addy: I think that's understandable. You have accomplished a lot, especially with all the research you've done. One of the things that you accomplished is that you were instrumental in the development of national and international criteria for identifying risk factors in diagnosing type 2 diabetes. Could you talk a little bit about these achievements and what was known about diabetes when you first began studying it?

Knowler: Yes. Starting in the 1960s and early 1970s, a lot of people were proposing criteria for diagnosing diabetes, mostly based on the glucose tolerance test. The test itself was somewhat standardized, although not completely. Different people used different doses of glucose. People came up with different cut points. "What level do we call diabetes?" Then, later on, new intermediate terms came out: intermediate hyperglycemia, impaired glucose tolerance, impaired glucose regulation, prediabetes, etc., all with somewhat different criteria, and that's because there really wasn't a good database for establishing these cut points. Ideally, to say how high glucose should be called diabetes might depend on what's the prognosis of that level of glucose. That's where our studies in the southwest provided data that were very scarce anywhere else and were very influential in developing criteria because we studied the same people for decades. When the standardized criteria came out in the late 1970s and early 1980s, our study had been going on for 10 to 15 years. That was long enough to have good prognostic data that at these levels, people are much more likely to develop diabetic eye and kidney disease, complications that are generally recognized as diabetes. They can still occur at lower glucose levels but much less frequently. Our group proposed diagnostic criteria on these bases. Then, later on, there were other longitudinal studies producing similar data that came up with similar results, and our results were adopted. The major turning point, I think it was in 1980 when the WHO (World Health Organization) adopted the criteria that we had proposed. They've subsequently been modified slightly over the years by WHO and the American Diabetes Association. Those two groups still don't agree on all the fine points. I think that's somewhat deliberate; neither organization wants to recognize that the other one's right and adopt the other one's criteria, but they're very similar. Our study really laid the groundwork for those criteria.

Addy: Interesting. With all of these kinds of accomplishments and advancements that you just talked about, do you think that these studies achieved their aims?

Knowler: Yes, many of the aims. You mentioned the diagnostic criteria. Another important area of our research pertained to diagnosis and classification of diabetes type. We made very early contributions to the distinction between type 1 and type 2 diabetes. In the 1960s or 1970s, it was generally thought that all diabetes occurring in children and teenagers was type 1 diabetes, which we now recognize as being due to complete or nearly complete islet cell destruction and lack of insulin production. It became clear from our studies that children and adolescents could develop diabetes that looked almost identical to what had been called adult-onset diabetes. These kids secreted lots of insulin, but the body didn't respond normally to the insulin, a condition we now call insulin resistance. For the most part, they didn't have the autoimmune evidence of islet cell destruction, so they looked much more like typical adult-onset diabetes than juvenile-onset diabetes, using terminology of that time. The terms subsequently changed, however. What had been called juvenile-onset was changed to insulin-dependent or, currently, type 1, and what had been called adult-onset became type 2, because both of those forms of diabetes can occur at any age. Our research was very important in pointing out the existence of type 2 diabetes in children and that it should not be assumed to be type 1 and treated as type 1 diabetes. Subsequently, there's been a lot of good research done elsewhere, finding other categories of diabetes that often affect children and are due to single gene variants. Diagnosing them is also important because they respond better to different treatments than those usually used in children with diabetes. Over the years, the importance of classifying the type of diabetes has come to the forefront and plays an important therapeutic role.

Another contribution of our research was identifying many of the predictors of who gets diabetes, or what we call risk factors for diabetes. That's helped with understanding the physiology and the intermediate steps towards the development of diabetes, such as gradual increases in blood sugar that don't meet diagnostic criteria but identify people at high risk of diabetes. It turns out, through clinical trials with people at high risk of developing diabetes, that you can treat them and reduce their rate of developing diabetes. That's been a very important part of our research, as well as research done elsewhere. Understanding predictors of diabetes, many

of which can be modified by medicines or behavior change, led to the concept that type 2 diabetes may be preventable. This was a concept that came to the fore really in the 1970s and 1980s. A lot of people were talking about it, but the research on this really got going in the 1980s and 1990s. We weren't the first to do clinical trials in diabetes prevention; some smaller pioneering studies were done in Sweden, England, China, Finland, and elsewhere. We learned from those experiences, but when we started the Diabetes Prevention Program or DPP in the late 1990s, this was the first large United States study of diabetes prevention, which has turned out to be one of the most influential ones.

Addy: You've worked on a multitude of long-lasting multicenter programs. They're kind of difficult to touch on since we have just a short time. But they definitely demand additional recognition. You mentioned the Diabetes Prevention Program. If you could either talk about the FIND (Family Investigation of Nephropathy and Diabetes) program, diabetes prevention, or one of your other programs, [and give] a summary of your involvement and the results of it. I know it is very long-lasting and hard to summarize.

Knowler: I'll talk a little bit about one of our other multicenter clinical trials called Look AHEAD, short for Action for Health in Diabetes. This study was patterned after the DPP in terms of looking at lifestyle intervention. Instead of preventing diabetes, it was a study in adults who already had diabetes. It was to see if a weight loss intervention patterned after the one in the DPP could improve outcomes in people with type 2 diabetes. This was another multicenter study done at several university centers around the U.S. sponsored by NIDDK. We had a Southwest American Indian Center with several participating clinics in Arizona and one in New Mexico. The primary question was whether a weight loss intervention would reduce cardiovascular disease events: heart attacks, strokes, heart failure, and death from these illnesses. Unfortunately, it did not, which was surprising because the intervention did reduce most of the known risk factors for these outcomes but still didn't reduce the event rates. However, it benefited almost everything else that we studied, other than what we had declared as the primary outcome. The moral of that story is if you want your clinical trial to be considered successful, you have to pick the right primary outcome because that's what most people judge a study by, even if it has a lot of other benefits. My particular interest was in the kidney complications of diabetes. We found that the people who had the weight loss intervention did better in terms of advancing kidney disease in the study.

You asked, "Why was it important to include American Indians in these studies?" Of course, from a personal standpoint, my work was with American Indians. Obviously, for me to be involved with the people with whom I did research, the studies had to include American Indians. Fortunately, the NIDDK leadership has always recognized the importance of including American Indians and groups other than the major non-Hispanic White part of the population in medical research because they're such important parts of the population, and often those that are more highly affected by diabetes. It's very important to include a wide variety of people in our major clinical trials and research programs, especially those groups that are most affected by diabetes, even though they are smaller in number in terms of the entire population.

Addy: Amazing. You have had a long-lasting career. I would like to touch on how your research or career may have been influenced or guided by various historical events that have occurred throughout your studies, if any.

Knowler: One of the most important developments in the research over my career in the epidemiology of type 2 diabetes has been the transition from non-interventional epidemiology (taking measurements, following people, referring them for treatment according to standard of care at the time) to randomized clinical trials, where instead of using only the standard of care of treatment, new approaches to treatment are tested. My research had a heavy emphasis on lifestyle modification approaches, which have always been given lip service in medicine but not usually given the necessary resources to implement them. You can't simply hand somebody a diet book and say, "Go away and lose weight." That doesn't work, except for very few people. The science of

weight loss is very difficult, and we're not always successful, although we certainly demonstrated with the DPP and Look AHEAD that there is some success and that success in weight loss has good health outcomes. I think one of the really important advances in the last few years is the development of new drugs that are very effective in weight loss. They may be very effective for preventing diabetes, treating diabetes, or treating obesity as a whole and preventing adverse consequences of obesity. These drugs are new enough that we don't have many answers yet, although the clinical trials look very promising in the short-term, a matter of a few years. One always worries about long-term effects with a new drug, especially a drug that may be used for a lifetime. That also raises big questions about costs, which the country and healthcare payers are very concerned about. You would rather not put someone on a drug for life unless you're pretty sure it will help them. These drugs look very promising, but it's just too soon to know how they're going to work in the long term.

Addy: That's really interesting. I look forward to seeing how that unfolds. To get back to more of a personal aspect, if you don't mind, what would you say are some personal benefits that this career has brought you?

Knowler: It's been fun. It's let me do the kind of work I enjoy doing, working with people, data, and writing papers. I've always enjoyed writing. I know a lot of people hate writing, but to me, it's one of the fun parts of research. That may have come from the good education I had in Iowa City where I had many classes that involved a lot of writing. Working at NIH has allowed me to have a good lifestyle. An advantage of working in the intramural program at NIH, at least until recently, when things have changed, is that I didn't need to worry about funding. I didn't need to write grant applications or wonder, "Will I be able to continue this project next year when this grant runs out?" A lot of my colleagues at universities have that sort of worry. It was very nice just to be able to focus on medical and scientific issues. That's been the great joy of working in the intramural research program. One of the downsides, which may come as a surprise to a lot of people, despite the fact that we raised our family in Phoenix and we lived there for so many years, is that we really got tired of Phoenix. That's one of the major reasons we decided to retire a few years ago. Living in Phoenix has gotten more and more difficult. Maybe we don't want to show this to our Phoenix city leaders, but the climate is just unbearable. Many people love to go to the southwest in the winter, where it's delightful, but the summer can mean five or six months of unrelenting heat and many days over 110 degrees Fahrenheit. It just finally got more than we could bear. As I said, that was one of our major reasons for deciding to retire, aside from being old enough to retire and that it was time to do something else. We have family in Washington state where we moved. I've always loved the mountains of the West, the Northwest in particular. The chance to finally live here was a big draw. Retiring and leaving have been difficult in many respects. Giving up the job and day-to-day contact with my colleagues and our friends in Phoenix has been very difficult. But being close to family and living in a climate and geography that we love have been real benefits.

Addy: Understandable. You mentioned loving the mountains, and you are a very experienced longtime climber, what has kind of been your most challenging and impactful climb? And what do you most enjoy about the sport?

Knowler: The highlight of my climbing was when I was in college many years ago. And that's not too surprising because climbing is very athletic, and you must be in great shape. You need to spend a lot of time working at it unless you're just a natural athlete, which I'm not. Some people might be surprised that I developed this passion for climbing while living in the flat Midwest, but there are actually good reasons for that. The University of Iowa had a very active mountaineering club, and the head of that club lived around the corner from me in Iowa City; he had a son who was my age and was a good friend of mine. Through that family, I was introduced to climbing. The Midwest actually has a lot of good rock climbing. There are rock cliffs along the riverbanks, and probably the best climbing area in the Midwest is in southwestern Wisconsin, which was within weekend range of Iowa City where I lived. I learned rock climbing when I was in high school and college, when I could spend a lot of weekends climbing. I started going on the mountaineering club's North American trips. Then I met other

climbers, and we did summer climbing in a more informal setting. During my college years, I was able to climb a lot. My most exciting climb was between my junior and senior years of college, in the Bugaboo mountains in British Columbia, which are known to a lot of climbers and back-country skiers. It's a very remote wilderness area that has amazing topography. It's heavily glaciated with rock pinnacles sticking up out of the glaciers. The climbing there is a mixture of glacier crossing, ice climbing, and rock climbing at the end -- very exciting. One of the climbs I did there was a two-day climb. We had to spend the night tying ourselves onto a tiny ledge partway up the mountain. It was exciting enough that I wrote an article about it, which was published in the Canadian Alpine Journal. That's my favorite publication. It has nothing to do with my medical research, but it's probably the most interesting paper I've ever written. I've not been able to do that kind of climbing since then. When I started medical school, there was a lot less free time. I got married, and we had kids. We have always been very avid hikers and took our children hiking and camping in the mountains. When our kids were in college, they discovered climbing for themselves. Our son and one of our sons-in-law are very good climbers, and we really enjoy it when we can climb with them, and they can lead. Lead climbing is dangerous and something you have to be very good at. I haven't done it in years. I love to do big climbs if someone else will lead the way, but that's very limiting. Now we settle for indoor climbing at a rock gym which is much safer and more convenient. We still really enjoy getting outdoors and hiking in the mountains, and where we live now, along the ocean. Now we live on an island in Puget Sound surrounded by water, and it's a gorgeous place.

Addy: Incredibly interesting, I think I would be terrified, personally. I think we are at the end of our time, but is there anything that you would like to touch more on, talk about, or add to anything that we discussed today?

Knowler: Oh, no, I think we've covered things pretty well. Perfect.

Addy: It was so great to talk to you and have this time. Thank you so much.

Knowler: No, I enjoyed it too. Thank you.