

From Thebes to Toronto and the 21st Century: An Incredible Journey

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Editor's note: This article is a transcript of the address of the American Diabetes Association President, Health Care and Education, given in June 2001 at the Association's 61st Annual Meeting and Scientific Sessions in Philadelphia, Pa.

The story of diabetes mellitus—its discovery, description, and treatment—is a remarkable chronicle covering 3,500 years of medical history. My President's Address, "From Thebes to Toronto and the 21st Century" will take you on an incredible journey through time, highlighting major milestones in the history of diabetes.

Regrettably, health care providers receive very little instruction in the history of medicine. Most medical and nursing students today have a rather limited, contemporary knowledge of diabetes. The history of advances in diabetes prior to the discovery of insulin at the University of Toronto, in 1921, has been obscured by the passage of time. Historical concepts of the causes and nature of diabetes have either been forgotten or never learned.

It is my belief that knowledge of history affords a better understanding of contemporary issues and clearer vision as we look to the future. It is my pleasure to share this thrilling story with you, and to reveal the origin of some of the discoveries that have brought us to our current understanding of diabetes at the dawn of the 21st century. Looking at this ailment over the ages makes one fact clear: the incidence of diabetes has increased dramatically, from an uncommon ailment during the period of antiquity to a worldwide epidemic expected to affect 300 million people by the year 2025.

The story of diabetes unfolds during the Age of Antiquity, where we begin to see the earliest descriptions of the symptoms of diabetes. Ancient physicians recorded their observations in an attempt to better understand the

nature of the ailment, its origin, and treatment. It is commonly believed that the history of medicine began with the Greeks, and that prior to the time of Hippocrates, there was little that could be called an art of medicine. Nevertheless, for more than 2,000 years before the birth of Hippocrates, Egyptian physicians had been striving to diagnose and treat disease. Ancient Egypt was the first civilization known to have an extensive study of medicine and to have left behind written records of its practices and procedures.

Across the Nile from Luxor, on the West Bank, sits the Necropolis of Ancient Thebes, a vast land of tombs and temples built to honor the pharaohs and other nobles. It was here, in the vicinity of Thebes, that German Egyptologist Georg Ebers acquired his famous papyrus in 1872. Named for him, the Ebers Papyrus is one of the most famous documents relating to the ancient practice of medicine. Written about 1550 BCE, abundant evidence suggests that it was copied from a series of books many centuries older. One passage dates from the First Dynasty (circa 3400 BCE).

The first reference to diabetes mellitus is attributed to the Ebers Papyrus, which mentions remedies for the treatment of excessive urination (polyuria) (Figure 1). The Ebers Papyrus contains remedies "to eliminate urine which is too plentiful." The following mixture was prescribed for the treatment of polyuria:

A measuring glass filled with Water from the Bird pond, Elderberry, Fibres of the asit plant, Fresh Milk, Beer-Swill, Flower of the Cucumber, and Green Dates
Urinary troubles in the adult were also corrected with rectal injections of olive oil, honey, sweet beer, sea salt, and seeds of the wonderfruit.

Egyptian medicine influenced the medical practices of neighboring cultures, including the culture of ancient

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Figure 1. Commemorative stamp issued by Egypt in 1971 for the World Health Organization's World Health Day. The stamp features a section of the Ebers Papyrus and a portrait of the Egyptian physician Hesy Re. (Scott catalog #864)

Greece. Although the Greek physician Hippocrates, “the father of medicine,” did not specifically mention diabetes in his writings, there are accounts in the Hippocratic writings that are consistent with the signs and symptoms of diabetes. There are references to excessive urinary flow with wasting of the body. Hippocrates promoted the concept of preventive medicine. He stressed the influence of diet, exercise, and lifestyle on health.

Galen and Aretaeus were disciples of Hippocrates. Galen, the most influential medical writer of all time, discussed diabetes in a number of his works. He described the condition as rare, as he had only seen two cases. He referred to the ailment as “diarrhea of the urine” and “the thirsty disease.”

Aretaeus, a contemporary of Galen, provided the first accurate description of the symptoms of diabetes (Figure 2). He was the first to use the term “diabetes” in connection with this ailment. The term diabetes was derived from the Greek word for siphon. Aretaeus’ classic description begins “Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine...”

The ancient Hindus were the first to coin the term “honey urine,” a thousand years before the first Europeans recognized the sweet taste of urine in patients with diabetes. The

Hindu physicians Charaka, Susruta, and Vaghbata described polyuria and glycosuria. They noted the attraction of flies and ants to the urine of those affected by this ailment.

The practice of medicine in the Middle Ages (350 CE to about 1450 CE) was fundamentally a restatement and acceptance of Greco-Roman teachings. Arabian physicians translated the works of Hippocrates and Galen and offered minor modifications.

Two prominent medieval physicians who contributed to the knowledge of diabetes in the 11th and 12th centuries were Avicenna and Moses Maimonides. Maimonides was a renowned medieval physician, rabbi, and philosopher. Although Galen wrote that diabetes was rare and that he had seen only two cases of this illness, Maimonides claimed to have seen more than 20 cases. He proposed that diabetes was caused by the sweet waters of the Nile and the prevailing heat that spreads over the kidneys.

No further progress was made in the understanding of diabetes until the 16th century, when the Renaissance physician Paracelsus challenged the medical doctrine of the time and attempted to reform medical thinking. Osler described Paracelsus as the “Luther of medicine,” the embodiment of the spirit of revolt. In medicine, there was an

exhilarating revision of medical and scientific concepts. Renaissance physicians and scientists questioned conventional thinking with a renewed spirit of curiosity, objectivity, and experimentation. This period accomplished three things in medicine: 1) it shattered authority, 2) it laid the foundation for an accurate knowledge of anatomy, and 3) it demonstrated how the body’s functions should be studied intelligently.

It was Thomas Willis’s observations of diabetes in 1674 and Matthew Dobson’s experiments in 1776 that conclusively established the diagnosis of diabetes in the presence of sugar in the urine and blood. Diabetes was no longer considered a rare ailment. Willis referred to diabetes as the “pissing evil” and noted that in patients with diabetes, “the urine is wonderfully sweet, as if it were imbued with honey or sugar.” He claimed that diabetes was primarily a disease of the blood and not the kidneys. Willis proposed that the sweetness first appeared in the blood and was later found in the urine.

Dobson provided experimental evidence that people with diabetes eliminate sugar in their urine. He gently heated two quarts of urine to dryness. The remaining residue was a whitish cake, which, Dobson wrote, “was

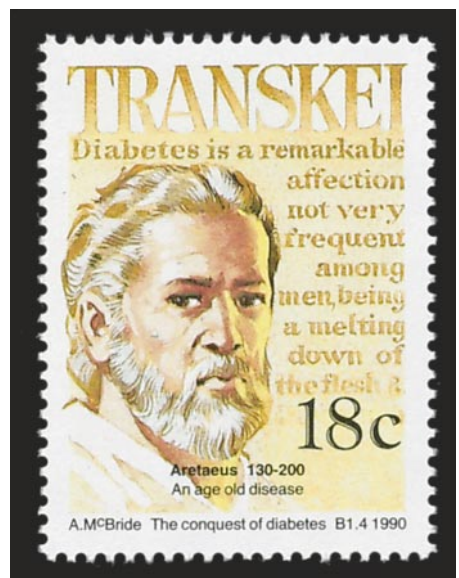


Figure 2. This stamp issued by Transkei in 1990 features the image of Aretaeus and a brief section of his description of diabetes. (Scott catalog #235)

granulated and broke easily between the fingers; it smelled sweet like brown sugar, neither could it be distinguished from sugar, except that the sweetness left a slight sense of coolness on the palate." Dobson detailed his findings in a paper presented to the medical society of London in 1776. Prior to presentation of his findings, Dobson consulted with William Cullen, one of Britain's foremost clinicians, consultants, and educators.

It was Cullen who was the first to distinguish between diabetes mellitus and diabetes insipidus. In 1769, Cullen published an elaborate classification of human diseases. In this classification, we see for the first time a distinction between diabetes (mellitus), with the urine of "the smell, color and flavor of honey," and diabetes (insipidus), with limpid but not sweet urine. It was Cullen who added the descriptive adjective mellitus, from the Latin word for honey. Cullen wrote to Dobson, "You have done something in putting it beyond all doubt by your experiments... I have only to add that I wish you would examine both by taste and evaporation what might be called the Urina Potus or that copius limpid urine which runs in some people after their drinking largely of water or watery liquors."

The Experimental Period in the history of diabetes began in the first half of the 19th century with the experiments of Claude Bernard. Bernard discovered that the liver releases a substance that affects blood sugar levels. In 1857, he isolated a starch-like substance that he called "glycogen," which was the precursor of glucose, "the internal secretion" of the liver. This observation established the liver's role as a vital organ in diabetes.

Paul Langerhan's most famous histological finding, the pancreatic islets, was presented in his doctoral dissertation at the University of Berlin in 1869. Langerhans acknowledged that he did not know the function of these ductless cells, which were later named "islets of Langerhans," in his honor by the French histologist Laguesse.

At the close of the 19th century, Oscar Minkowski demonstrated conclusively that removal of the pancreas from a dog results in the production of fatal diabetes. This was the turning point in determining the endocrine function of the pancreas.

The discovery and isolation of insulin at the University of Toronto in 1921-22 was one of the greatest events in the history of medicine. Insulin therapy would soon commute the death sentence associated with the diagnosis of type 1 diabetes.

Despite initial rebuffs by JJR Macleod, professor of physiology at the University of Toronto, the persistent Frederick Banting was finally allowed to begin his research in Macleod's laboratory in May 1921. Macleod doubted that Banting would be able to isolate the internal secretion of the pancreas because of the destructive effects of the pancreatic juice. Banting was assigned laboratory space, research animals, and a 22-year-old research assistant named Charles Herbert Best. Later, Macleod

recruited a young biochemist, James Bertram Collip, to assist Banting and Best in obtaining a pancreatic extract.

An article written in 1920 by Moses Barron stimulated Banting's research interests. Barron described the rare case of a pancreatic stone that blocked the main pancreatic duct. The blockage resulted in degeneration of the acinar glandular cells but not the islet cells. Banting wrote the following words in his research notebook (Figure 3):

"Diabetus

Ligate pancreatic ducts of dog.

Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretion of these to relieve glycosurea."

The spelling errors, "diabetus" and "glycosurea" are Banting's. It goes to show that brilliance and success are not necessarily tied to spelling proficiency.

Banting and Best are the figures that history has most closely associated with the discovery of insulin. Yet the 1923 Nobel Prize in Medicine was not awarded to Banting and Best, but rather to Banting and Macleod. In an attempt to remedy this injustice, Banting publicly acknowledged Best's role in the discovery of insulin and shared the monetary prize with him. Macleod agreed to do the same with Collip.

In 1926, John Jacob Abel purified insulin and isolated its crystalline structure. The rhombohedral crystals of insulin fascinated him (Figure 4). His studies of insulin helped to develop modern concepts of protein chemistry. In 1958, Frederick Sanger was awarded the Nobel Prize in Chemistry "for his work on the structure of proteins, especially that of insulin." It was Sanger who was the first to discover the exact amino acid sequence of the protein insulin. Sanger determined that the insulin molecule was composed of two different chains of 51 amino acids held together by two bridges of sulfur atoms.

In 1977, Rosalyn Sussman Yalow won the Nobel Prize in Medicine for "the development of radioimmunoassays of peptide



Figure 3. Frederick G. Banting and Charles H. Best are seen on this commemorative stamp issued by Canada in 1999. In the background is a page from Banting's research notebook, in which he plans his experimental approach to obtaining the internal secretion of the pancreas. (Scott catalog #1822a)



Figure 4. Insulin crystals are represented on this commemorative stamp issued by Japan in 1994 for the 15th International Diabetes Federation Congress, held in Kobe. (Scott catalog #2433)

hormones.” Working together with Sol Berson, these investigators developed a tool that would stimulate a revolution in biological and medical research.

The pig has played an important role in the history of diabetes as a source of insulin and life for people with diabetes. For many years, beef/pork insulins were the only source of insulin. Human insulin became available in the early 1980s and was the first commercial product developed by recombinant DNA technology. The origin of the term “insulin” is from the Latin word for island: insula.

The discovery and therapeutic application of insulin in the 1920s was a miraculous development in the treatment of diabetes that enabled individuals affected by this disease to live an almost-normal life. It soon became apparent, however, that insulin did not cure diabetes. As people began to live longer, they experienced complications that had not previously been seen. Elliot P. Joslin noted that “The era of coma as the central problem of diabetes has given way to the era of complications. People with diabetes are at increased risk for the development of serious complications, including blindness,

kidney failure, heart disease, stroke, and amputations.”

Diabetes is the leading cause of new cases of blindness in adults aged 20 to 74 years. The prevalence of retinopathy is strongly related to the duration of diabetes and uncontrolled high blood glucose levels. After 20 years, nearly all people with type 1 diabetes and nearly two-thirds of people with type 2 diabetes have some evidence of diabetic retinopathy. Diabetes is also the leading cause of end-stage renal disease in the United States and Europe. The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study have shown conclusively that intensive diabetes therapy significantly reduces the risk of developing retinopathy and kidney disease in people with diabetes.

Abundant evidence shows that people with diabetes are at high risk for cardiovascular disease: coronary heart disease, stroke, peripheral arterial disease, and cardiomyopathy. Heart disease is the leading cause of diabetes-related deaths and hospitalizations. Adults with diabetes have heart disease death rates about two to four times as high as those of adults without diabetes. The risk of stroke is four times higher in people with diabetes. Therefore, having diabetes is itself a risk factor for developing cardiovascular disease.

In 1934, Joslin wrote a paper, “The Menace of Diabetic Gangrene,” published in the *New England Journal of Medicine*. Joslin noted that following the introduction of insulin, mortality from diabetic coma had fallen significantly from 60 to 5%. Yet, deaths from diabetic gangrene (of the foot and leg) had risen significantly. The reason for this complication, Joslin alleged, was that physicians were not aggressive enough in their treatment of diabetes.

Joslin firmly believed that gangrene and amputations were

preventable (Figure 5). Hopefulness in the treatment of gangrene was possible. He wrote, “Consequently, it has been forced upon me that gangrene is not Heaven-sent but is earth-born.” His remedy was a team approach to diabetes care, which included patient education in foot care, medical nutrition therapy, exercise, prompt treatment of foot infections, and, when necessary, specialized surgical care.

Public awareness of the serious nature of diabetes and its complications remains very limited, despite the fact that diabetes is one of the leading causes of death and disability in the United States. The message to “Know More About Diabetes” is important for all people. However, it is most critical for those who are at high risk for diabetes and who have not as yet been diagnosed. This message is also important for health maintenance organizations and hospital administrators, government officials, and third-party payers.

Scientific evidence demonstrates that much of the morbidity and mortality of diabetes can be reduced by aggressive treatment with diet, exercise, and improved blood glucose control. Diabetes self-management education with self-monitoring of blood glucose is the cornerstone of care for all people with diabetes (Figure 6). Unfortunately, there is still a significant disparity between current and desired diabetes care and practices.



Figure 5. The Dominican Republic issued a series of stamps, *Lucha Contra La Diabetes* (Fight Against Diabetes) in 1974 to raise awareness of the serious complications of diabetes. This stamp calls attention to lower limb amputations. (Scott catalog #725-726)

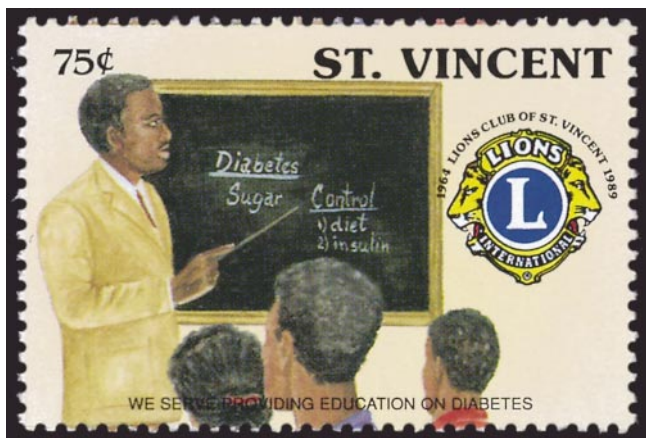


Figure 6. The cornerstone of care for people with diabetes is self-management education. St. Vincent issued this stamp in 1989, raising awareness of the importance of diabetes education and commemorating the 25th Anniversary of the Lions Club of St. Vincent. (Scott catalog #1305)

In its 1998 report, the congressionally mandated Diabetes Research Working Group recognized the great urgency and extraordinary opportunities facing us today in diabetes research. Mapping of the human genome marks a new era in medical research, paving the way for the treatment and cure of many serious diseases. In the 21st century, we are witnessing an exciting new chapter being

written in the history of diabetes. There is genuine optimism in our search for a cure.

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Proceeds from Dr. Sanders' book The Philatelic History of Diabetes: In Search of a Cure are being donated to the American Diabetes Association Research Foundation. The book can be ordered in paperback for \$14.95 or in hardback for \$24.95 by calling 1-800-232-6733 or visiting the Association's online bookstore at store.diabetes.org.

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