Chapter 1
The Main Events in the History of Diabetes Mellitus

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In Antiquity

A medical condition producing excessive thirst, continuous urination, and severe weight loss has interested medical authors for over three millennia. Unfortunately, until the early part of twentieth century the prognosis for a patient with this condition was no better than it was over 3000 years ago. Since the ancient physicians described almost exclusively cases of what is today known as type 1 diabetes mellitus, the outcome was invariably fatal.

Ebers Papyrus, which was written around 1500 BC, excavated in 1862 AD from an ancient grave in Thebes, Egypt, and published by Egyptologist Georg Ebers in 1874, describes, among various other ailments and their remedies, a condition of "too great emptying of the urine" – perhaps, the reference to diabetes mellitus. For the treatment of this condition, ancient Egyptian physicians were advocating the use of wheat grains, fruit, and sweet beer.[1,2]

Physicians in India at around the same time developed what can be described as the first clinical test for diabetes. They observed that the urine from people with diabetes attracted ants and flies. They named the condition "madhumeha" or "honey urine." Indian physicians also noted that patients with "madhumeha" suffered from extreme thirst and foul breath (probably, because of ketosis). Although the polyuria associated with diabetes was well recognized, ancient clinicians could not distinguish between the polyuria due to what we now call diabetes mellitus from the polyuria due to other conditions.[3]

Around 230 BC, Apollonius of Memphis for the first time used the term "diabetes," which in Greek means "to pass through" (dia – through, betes – to go). He and his contemporaries considered diabetes a disease of the kidneys and recommended, among other ineffective treatments, such measures as bloodletting and dehydration.[3]

The first complete clinical description of diabetes appears to have been made by Aulus Cornelius Celsus (30 BC–50 AD). Often called "Cicero medicorum" for his elegant Latin, Celsus included the description of diabetes in his monumental eight-volume work entitled *De medicina*.[4,5]

Aretaeus of Cappadocia, a Greek physician who practiced in Rome and Alexandria in the second century AD, was the first to distinguish between what we now call diabetes mellitus and diabetes insipidus. In his work *On the Causes and Indications of Acute and Chronic Diseases*, he gave detailed account of diabetes mellitus and made several astute observations, noting, for example, that the onset of diabetes commonly follows acute illness, injury, or emotional stress. Aretaeus wrote:

> Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of the aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive and disproportionate to the large quantity of urine, for yet more urine is passed. . . . If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time they expire.[4,6]

Although the term "diabetes mellitus" was not firmly established until the nineteenth century, we will refer to this disease using its modern name throughout this chapter, even for the earlier periods.

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Both Aretaeus and the renowned Roman physician Galen observed that diabetes was a rare disease. In fact, Galen mentioned that he encountered only two such cases in his entire career.[6] Galen attributed the development of diabetes to weakness of the kidney and gave it a name "diarrhea of the urine" ("diarrhea urinosa").[4]

In the fifth century AD, Sushruta and Charaka, two Indian physicians, were the first to differentiate between the two types of diabetes mellitus, observing that thin individuals with diabetes developed diabetes at a younger age in contrast to heavier individuals with diabetes, who had a later onset and lived longer period of time after the diagnosis. In seventh century AD in China, Li Hsuan noted that the patients with diabetes were prone to boils and lung infections. He prescribed avoidance of sex and wine as treatment for diabetes. Avicenna, or Ibn-Sina (980–1037 AD), a court physician to Caliphs of Baghdad, compiled an exhaustive medical text ("Canon Avicennae"), which included a detailed description of diabetes. Its clinical features, such as sweet urine and increased appetite, and complications, such as diabetic gangrene and sexual dysfunction, were described by Avicenna in detail.[7]

Renaissance and After

The origin of current understanding of some aspects of diabetes can be traced to discoveries made in Europe between sixteenth and eighteenth centuries. Aureolus Theophrastus Bombastus von Hohenheim, a Swiss physician better known as Paracelsus (1494–1541), allowed the urine of patients with diabetes to evaporate and observed a white residue. He incorrectly thought that this residue consisted of salt and proceeded to attribute excessive thirst and urination in these patients to salt deposition in the kidneys.[8] In 1670, Thomas Willis in Oxford noticed the sweet taste of urine of patients with diabetes. Thomas Cawley, in 1788, was the first to suggest the link between the pancreas and diabetes after he observed that people with pancreatic injury developed diabetes.[8]

In 1776, British physiologist Matthew Dobson (1713–1784) in his *Experiments and Observations on the Urine in Diabetics* was the first to show that the sweet-tasting substance in the urine of patients with diabetes was sugar. He also noted the sweet taste of serum in these individuals and thus discovered hyperglycemia. Dobson put forward the theory that the diabetes was a systemic disease, rather than one of the kidneys.[9]

The Nineteenth and the Early Twentieth Century: Discovery of Insulin

The important elements of current understanding of diabetes mellitus can be traced to nineteenth century when modern scientific disciplines, including biochemistry and experimental physiology, acquired prominence in biological studies.

In 1815, Eugene Chevreul in Paris proved that the sugar in urine of individuals with diabetes was glucose. Von Fehling developed quantitative test for glucose in urine in 1848.[9] Thus, in the nineteenth century, glucosuria became an accepted diagnostic criterion for diabetes.

Claude Bernard (1813–1878), professor of physiology at Sorbonne University, was one of the most prominent and prolific experimental physiologists in nineteenth-century Europe. Because of the scope of Bernard's interests, Louis Pasteur referred to him as "Physiology itself."[10] In the course of his work on the physiology of gastrointestinal tract, Bernard developed an experimental operation during which the pancreatic ducts were ligated. Degeneration of the pancreas followed. This technique proved invaluable for later experiments searching for pancreatic substance which controlled glucose level. In addition to developing the technique for pancreatic duct ligation, Bernard also discovered that the liver stored glycogen and secreted sugary substance into the blood. He assumed that it was an excess of this secretion that caused diabetes. Bernard's theory of sugar over-secretion leading to diabetes received wide acceptance.[11]

At the same time as researchers were looking for the cause of diabetes, clinicians were further advancing the understanding of diabetes mellitus as a systemic disease with various manifestations and complications. William Prout (1785–1850) was the first to describe diabetic coma and Wilhelm Petters in 1857 demonstrated the presence of acetone in the urine of patients with diabetes. Adolf Kussmaul (1822–1902) proposed that acetonemia was

the cause of diabetic coma. Henry Noyes in 1869 described retinopathy in a person with advanced diabetes. M. Troiser in 1871 observed diabetes in patients with hemochromatosis, naming it "bronze diabetes."[12]

John Rollo (1749–1809), surgeon general to the British Army, added the term "mellitus" (derived from the Greek word for honey) to "diabetes" in order to distinguish it from diabetes insipidus. In 1797, Rollo developed a high-protein, low-carbohydrate diet consisting of rancid meats, blood pudding, and mixture of milk and lime water for patients with diabetes.[13] It has been suggested that he prescribed anorexic agents, such as antimony, digitalis, and opium to suppress appetite in patients with diabetes.

During the years prior to insulin discovery, diabetes treatment mostly consisted of starvation diets. Frederick Allen (1879–1964), a leading American diabetologist of the time, believed that, since diabetes patients could not utilize the food efficiently, limiting the amount of food would improve the disease. The dietary restriction treatment was harsh and death from starvation was not uncommon in patients with type 1 diabetes on this therapy. On the other hand, it is easy to understand why outcomes of low-calorie diets were often quite good in patients with type 2 diabetes.[12,14]

Discovery of insulin by Frederick Banting and Charles Best was the final step in identifying the substance whose deficiency had been postulated to be responsible for development of diabetes. This milestone, however, was preceded by a number of earlier significant advances.

Oscar Minkowski (1858–1931) and Joseph von Mering (1849–1908), working in Strasbourg in 1889, observed that the dogs whose pancreas was removed developed severe thirst, excessive urination, and weight loss with increased appetite. Minkowski, suspecting that such symptoms were caused by diabetes, tested the urine of these dogs and found glucose. Since Minkowski was working in the laboratory of Bernard Naunyn (1839–1925), who was interested in carbohydrate metabolism and was a leading authority on diabetes at the time, Minkowski's research received enthusiastic endorsement by Naunyn. Work on pancreatic extraction ensued, but the investigators were not able to obtain presumed antidiabetic substance. They suspected that digestive juices produced by pancreas might have interfered with their ability to purify this substance. To prove that the absence of exocrine pancreatic secretion was not related to the development of diabetes, they ligated dog's pancreatic duct. This procedure led to the development of digestive problems but not the diabetes.[12,15]

In 1893 a very important contribution was made by French investigator Edouard Hedon (1863–1933) in Montpellier, who showed that the total pancreatectomy was necessary for the development of diabetes. After removing the pancreas, he grafted a small piece of it under the skin. No evidence of diabetes in experimental animals was present at this stage. However, removal of the graft caused the symptoms of diabetes to develop immediately. Similar results were independently obtained by Minkowski. It was becoming clear that the internal secretion of the pancreas was pivotal to the pathogenesis of diabetes mellitus.[15]

In 1893, French scientist Gustave–Edouard Laguesse (1861–1927) suggested that tiny islands of pancreatic tissue described in 1869 by Paul Langerhans might be the source of the substance involved in blood glucose control. Paul Langerhans (1847–1888), distinguished German pathologist, was a student of Rudolf Virchow. In his doctoral thesis, at the age of 22, he described small groupings of pancreatic cells that were not drained by pancreatic ducts. In 1909, the Belgian physician Jean de Mayer named the presumed substance produced by the islets of Langerhans "insulin."[16]

A number of researchers worked on isolating the active component of internal pancreatic secretion. In 1902, John Rennie and Thomas Fraser in Aberdeen, Scotland, extracted a substance from the endocrine pancreas of codfish (*Gadus callurious*) whose endocrine and exocrine pancreata are anatomically separate. They injected the extract into the dog that soon died, presumably from severe hypoglycemia. In 1907, Georg Ludwig Zuelzer (1870–1949), a German physician, removed pancreas from the dog and then injected the dog with pancreatic extract. His experiments resulted in lowered amount of glucosuria and raised blood pH. Zuelzer patented the extract in the United States under the name "acomatol." In 1908, he used it successfully to rescue a comatose diabetic patient, but, owing to likely contamination of the extract by other substances, the treatment produced severe complications and led to withdrawal of further funding of Zuelzer's work by Schering. Zuelzer continued his investigations, however, and developed a new extract for Hoffman–La Roche. The new extract produced convulsive reaction, most likely caused by hypoglycemia.[12,15] Nicolas Constantin Paulesco (1869–1931), professor of Physiology at Bucharest University in Romania, was also involved in research on pancreatic extracts. In 1916 in the course of his first experiment, he injected the diabetic dog with the pancreatic extract. The injection

resulted in the death of the animal with symptoms of hypoglycemia. During the experiment, dog's blood glucose fell from 140 to 26 mg%. Because of World War I, Paulesco did not publish the report of his experiments until 1921.[12]

Frederick Grant Banting (1891–1941) was a young (and not very successful) orthopedic surgeon when he developed interest in diabetes. A war veteran, wounded in France in 1918, he was decorated with Military Cross for heroism. After returning from Europe, he briefly practiced orthopedic surgery and then took the position as a demonstrator in Physiology at the University of Western Ontario, Canada.[17] On October 31, 1920, Banting wrote in his notebook:

> Diabetus (sic!). Ligate pancreatic ducts of the dog. Keep dog alive till acini degenerate leaving Islets. Try to isolate the internal secretion of these to relieve glycosurea[17]

The technique of pancreatic duct ligation, leading to pancreatic degeneration, was developed and used for pancreatic function studies by Claude Bernard, as discussed earlier. Banting approached John J.R. MacLeod, professor of Physiology at the University of Toronto, who agreed to provide Banting with limited space in his laboratory for the eight-week summer period in 1921. McLeod assigned a physiology student Charles Best (1899–1978) to assist Banting with the experiments (Best apparently won the opportunity to work alongside Banting on the toss of coin with another student).[17]

In July 1921, after initial delays caused by insufficient ligature of the pancreatic ducts, Banting and Best were able to harvest atrophied pancreatic glands from the dogs, chop them up, grind the tissue in the mortar, strain the solution, and inject the extract into the vein of pancreatectomized (diabetic) dog. When it was clear that the dog's condition improved, they proceeded to repeat the experiments with other diabetic dogs, with similar dramatic results. They also experimented with fresh pancreata, fetal calf pancreata, and different routes of administration (rectal, subcutaneous, and intravenous).

At the end of 1921, biochemist James Collip joined the team of Banting and Best and was instrumental in developing better extraction and purification techniques.[12] First report of successful animal experiments with Banting's pancreatic extracts was presented at Physiological Journal Club of Toronto on November 14, 1921 and American Physiological Society later that year.[18]

On January 11, 1922, Banting and Best injected Leonard Thompson, a 14-year old boy being treated for diabetes at Toronto General Hospital, with their extract. At the time Thompson's weight was only 64 lb. After having 15 cm^3 of "thick brown" substance injected into the buttocks, Thompson became acutely ill upon developing abscesses at the injection sites. Second injection, using a much improved preparation made with Collip's method, followed on January 23. This time the patient's blood glucose fell from 520 to 120 mg/dl within about 24 h and urinary ketones disappeared. Thompson received ongoing therapy and lived for another 13 years but died of pneumonia at the age of 27.[19]

On May 3, 1922, McLeod presented results of Toronto group's research to the Association of American Physicians and received standing ovation.[19] Banting and Best were not present at the meeting. In 1923, the Nobel Prize was awarded for discovery of insulin, but only to Banting and MacLeod, who shared their portions of the prize with Best and Collip, respectively.[12] The new proposed antidiabetic substance was named by Banting "isletin." The name was later changed by MacLeod to "insulin." MacLeod apparently did not know that this name had already been coined by de Mayer in 1909. Later, Banting and Best fully acknowledged this fact.[19]

In April 1922, Banting and Best accepted the offer by Eli Lilly Company to work on purification and large-scale commercial production of insulin. The Board of Governors of the University of Toronto and Eli Lilly signed the agreement, providing that Lilly would pay royalties to the University of Toronto to support research in exchange for manufacturing rights for North and South America.[20]

The announcement of insulin discovery was greeted with tremendous enthusiasm around the world. Press was bringing numerous reports of miraculous cures. Previously doomed patients were getting the new lease on life. Indeed, Ted Ryder, one of the first four children to receive insulin in 1922 in Toronto, died at the age of 76 in 1993.

Over the years, insulin purification methods improved and new insulin formulations were developed. Protamine–zinc insulin, a long-acting insulin, was introduced in the 1930s; Neutral Protamine Hagedorn (NPH) was introduced in the 1940s; and Lente series of insulin in the 1950s.[20]

Among the people who first witnessed the introduction of insulin into clinical use was a Portuguese physician Ernesto Roma, who was visiting Boston shortly after insulin became available. Upon returning to Portugal he founded the world's first organization for people with diabetes – the *Portuguese Association for Protection of Poor Diabetics*. The association provided insulin free of charge to the poor. Subsequently, the *British Diabetic Association* was founded in 1934 by Robin Lawrence, a physician with diabetes whose life was saved by insulin, and the writer H.G. Wells, who had diabetes.[21] A few years later, at a meeting of the American College of Physicians in 1937, a small group of physicians with interest in diabetes met for lunch. They felt that diabetes management was inadequately covered at regular meetings. They realized a need of a platform to share their experiences. After two years of deliberations, in April 2, 1940, delegates from local societies in the United States met and founded the *National Diabetes Association*. Both the first president of the association Dr. Cecil Striker and the vice-president Dr. Herman O. Mosenthal were very instrumental in the founding of the association. Subsequently, as per Dr. Mosenthal's suggestion, the association was renamed *American Diabetes Association* to include the Canadian physicians, there being no such association in Canada at the time as well as to pay homage to the country where insulin was discovered.[22]

In 1922, August Krogh of Denmark, winner of the Nobel Prize for his studies of capillaries, was lecturing in the United States, accompanied by his wife Marie, who had recently been diagnosed with diabetes. Krogh and his wife were informed by famous diabetologist of the time Eliot P. Joslin about new diabetes treatment developed in Toronto by Banting's group. Marie and August Krogh decided to visit Toronto and stayed as John McLeod's guests. After return to Denmark, Krogh, with H.C. Hagedorn, founded Nordisk Insulin Company, a not-for-profit concern that, together with Novo Company, was responsible for making Denmark the main insulin-producing country outside of the United States.[23]

Oral Agents in Diabetes

Oral hypoglycemic agents were discovered following the fortuitous observations of hypoglycemia as a side effect of various investigative substances. In 1918, while investigating biological effects of guanidine, C.K. Watanabe noted that guanidine, under certain condition, can cause hypoglycemia. Watanabe injected guanidine subcutaneously into rabbits, initially causing hyperglycemia followed by hypoglycemia within several hours. Inspired by these findings, E. Frank, M. Nothmann, and A. Wagner tried to modify the guanidine molecule. Several guanidine derivatives were studied, including monoguanidines and biguanidines. The biguanidines were found to have greatest hypoglycemic effect. The first commercially available guanidine derivative decamethyl–diguanidine was introduced in 1928 and marketed in Europe under the name Synthalin. In the United States, phenylethyl–biguanidine was introduced for treatment of diabetes in 1957 and was available for clinical use in 1959 under the name Phenformin. Synthalin was discontinued from the use because of liver and kidney toxicity.[24]

Celestino Ruiz and L.L. Silva of Argentina noted the hypoglycemic properties of certain sulfonamide derivatives in 1939. In 1942, in occupied France, Professor of Pharmacology at Montpellier University M.J. Janbon discovered that the sulfonylurea agent tested for the treatment of typhoid fever produced bizarre toxic side effects. Janbon correctly attributed these effects, which included confusion, cramps, and coma, to hypoglycemia.[6,24] This compound was then administered to diabetic patients, lowering their blood glucose. The researchers explored the potential mechanism of action of the substance and found that it became ineffective if experimental animal had been pancreatectomized. After well-publicized research by German investigators Hans Franke and Joachim Fuchs, sulfonylureas were studied extensively. Franke and Fuchs discovered hypoglycemic actions of sulfonylureas during testing of the new long-acting sulfonamide antibiotic. Chemists at Hoechst manufactured a compound D 860, which was marketed in the United States as tolbutamide in 1956. This compound became the first commercially available sulfonylurea agent.[24]

Many chemical substances have been studied for their hypoglycemic effect but extremely few have made it to the market. As an example, from 1962 to 1977, Boehringer–Mannheim and Hoechst studied 8000 different chemicals for hypoglycemic properties, of which 6000 produced hypoglycemia in laboratory animals. Out of

these, only five made it as far as clinical tests and ultimately only one, HB 419 (glibenclamide/glyburide), was marketed.[24]

In addition to biguanides and sulfonylureas, a number of other classes of oral hypoglycemic agents were ultimately discovered and are currently in clinical use. These are discussed in detail in Chapter 44.

Use of Radioimmunoassay for Measurement of Circulating Insulin Level

One of the most important milestones in the understanding of pathophysiology of diabetes was the development of radioimmunoassay (RIA) by Rosalyn Sussman Yalow (b. 1921) and Salomon A. Berson (1919–1972).

During her graduate studies at the University of Chicago, Yalow, a nuclear physicist, worked on the development of the device to measure radioactive substances. In 1947, she became a consultant in Nuclear Physics at Veteran Administration Hospital in the Bronx, New York. She became a full-time faculty member at the Bronx VA Hospital in 1950. Here Yalow worked with Salomon A. Berson investigating the use of radioactive isotopes in physiologic systems. Yalow and Berson developed the technique called radioimmunoassay (RIA), which allowed quantification of very small amounts of biological substances. The first report of the new technique in 1959 was largely ignored.[25]

The RIA is based on a principle of competition between the radiolabeled compound of interest and unlabeled compound in the patient's serum for limited number of binding sites on the antibody against this compound. After the incubation period, which allows for equilibrium to develop, the antibody–antigen complexes are precipitated and the amount of radioactive label attached to the antibody is measured. Because of the competition for binding sites on the antibody, the higher the concentration of unlabeled compound in the patient's serum, the smaller the amount of labeled compound that bind to the precipitated antibody.[26]

In 1959, using their method, Yalow and Berson demonstrated that patients with diabetes did not always suffer from deficiency of insulin in their blood. Thus, insulin was the first hormone measured with the new technique.[25]

For this groundbreaking work, Rosalyn Yalow was awarded many honors, including Nobel Prize in 1977, which she accepted on behalf of herself and Berson, who had died 5 years earlier. The Nobel Prize Committee called the RIA the most valuable advance in basic clinical research in the previous two decades.[25]

Yalow and Berson never patented the RIA technique, instead sparing no effort to make it more popular and accessible for use by both the clinicians and the investigators.

Recombinant DNA Technology and the Synthesis of Human Insulin

The groundwork for the production of large quantities of human insulin was laid by Frederick Sanger (b. 1918), who published the structural formula of bovine insulin in 1955 while working at Cambridge University. He received Nobel Prize for this work in 1958.[24] Dorothy Hodgkin (1910–1994) described the three-dimensional structure of porcine insulin in 1969 at Oxford using X-ray crystallography.[27]

Prior to the development of recombinant DNA technology, patients with diabetes mostly received bovine or porcine insulin. Although bovine insulin differs from human insulin only by three amino acids and porcine only by one amino acid, these differences are sufficient for human immune system to produce antibodies against insulin, neutralizing its action and causing local inflammatory reactions. The pharmacokinetics of insulin is altered by its binding to antibodies, resulting in increased half-life of the circulating insulin and prolongation of its action. These considerations and growing demand for insulin, coupled with the difficulties in animal insulin production (it is estimated that 8000 lb of animal pancreatic tissue is needed to produce 1 lb of insulin), prompted work on developing alternative sources of insulin.[28]

The gene coding for human insulin was cloned in 1978 by Genentech. It is located on the short arm of chromosome 11. Once incorporated in the bacterial plasmid of *E. coli*, the human insulin gene became active, resulting in the production of alpha and beta chains of insulin, which were then combined to construct complete insulin molecule.[29]

In 1978, Genentech, Inc. and City of Hope National Medical Center, a private research institution in Duarte, California, announced the successful laboratory production of human insulin using recombinant DNA technology. This was achieved by a team of scientists led by Robert Crea, Keichi Itakura, David Goeddel, Dennis Kleid, and Arthur Riggs. Insulin thus became the first genetically manufactured drug to be approved by the FDA.[28]

In July 1996, the FDA approved the first recombinant DNA human insulin analog, the insulin lispro. At present more than 300 human insulin molecule analogs have been identified, including about 70 animal insulins, 80 chemically modified insulins, and 150 biosynthetic insulins.

In January 2006, FDA approved inhaled form of insulin marketed under the name of Exubera. This was the first noninjectable form of insulin available to patients with diabetes. The device did not become popular for a variety of reasons and was withdrawn from the market by the company in 2007.

Glucose Monitoring by Physicians and Patients

Although, the chemical tests to detect sugar in blood and urine were discovered in the early nineteenth century, the concept of self-monitoring was not conceived until the 1960s. In 1965, Ames introduced a product called dextrostix created by Ernest C. Adams, at Ames Co. This was a paper strip that developed a blue color after a drop of blood was placed on it for 1 min. This blue strip was then washed with water and its color was compared with the color chart to estimate the blood glucose levels. This technique did not allow estimation of fingerstick glucose accurately. Hence, a meter that would measure the light reflected back from a test strip and would give a numerical value to it was designed. Tom Clemens, the inventor of the first blood glucose meter, started working on it in 1966 and built several prototypes for field trials in 1968. The meter became available on the market in 1970. Initially used in doctors' offices, meters and strips gradually gained popularity for patient use. Over the years, glucometer models have become smaller in size, require less blood, and have acquired a variety of user-friendly options such as memory and computer download features.[30]

An important laboratory test that has changed our approach to management of diabetes is hemoglobin A1c (HbA1c) measurement. Hemoglobin A1c was identified as one of the larger fraction of the minor components of normal adult hemoglobin in the 1950s. In 1966, Holmquist and Shroeder showed that the β-globin chain contained an unidentified compound attached to it.[31] About 2 years later, Bookchin and Gallop reported that a hexose moiety was linked to the N-terminal of β-globin chain of the hemoglobin A1c.[32] At the same time, Samuel Rahbar independently reported an abnormally fast-moving hemoglobin fraction that was present in hemoglobin of patients with diabetes in Iran.[33] Subsequently, while working as an international post-doctoral fellow at Albert Einstein College of Medicine in New York in 1969, he and his colleagues reported that this fast-moving hemoglobin in patients with diabetes was identical to the HbA1c.[34] In 1975, Tattersall et al. studied twins concordant and discordant for diabetes and suggested that hemoglobin A1c was an acquired manifestation of the metabolic abnormality in diabetes.[35] In 1976, Koenig and colleagues demonstrated that HbA1c concentration was an indicator of fasting blood glucose concentrations. HbA1c concentrations decreased as diabetes control improved with treatment.[36] Today, HbA1c measurements and use of glucometers have revolutionized management of diabetes and enhanced our understanding of effects of glycemic control on diabetes-related outcomes.

Landmark Clinical Trials in Diabetes

One of the major questions in diabetes therapy, which had remained unresolved until recently, was that of the relationship between glycemic control and development of the complications of diabetes. The evidence supporting the role of metabolic abnormalities in the development of diabetic complications had long been known. It was not clear, however, if meticulous glycemic control could prevent the development of these complications.

Two very important studies were conducted to answer this question.

Diabetes Control and Complications Trial (DCCT) was a large multicenter diabetes study conducted by NIH from 1983 to 1993. The study was designed to evaluate whether tight glucose control can prevent or reduce the rate of progression of long-term complications of diabetes. DCCT involved 1441 volunteers 13–39 years of age in 29 centers in the United States. They all had type 1 diabetes for at least 1 year but no longer than 15 years. The subjects were divided into two groups. The Primary Prevention group consisted of patients with type 1 diabetes of 1–5 years duration and no complications of diabetes. The subjects in the Secondary Intervention group had type 1 diabetes for 1–15 years. They also had mild diabetic nephropathy and retinopathy. Patients in both groups were randomized to receive either intensive or conventional therapy. The goal of intensive therapy was to keep pre-meal blood glucose between 70 and 120 mg/dl and post-meal glucose less than 180 mg/dl. In the conventional treatment group, the aim was to keep the patients free of diabetic symptoms.[37] At the conclusion, the study showed that the hemoglobin A1c (a measure of glycemic control within previous 3 months) in the intensively treated patients was almost 2% lower than in those treated conventionally. The average blood glucose level in the intensive treatment group was 155 mg/dl, as compared to average blood glucose of 231 mg/dl in the conventional treatment group. Intensive therapy resulted in 76% reduction in retinopathy, 34% reduction in the development of early nephropathy, and 69% reduction in the development of neuropathy. In the Secondary Intervention group, intensive therapy resulted in 54% reduction in progression of established eye disease. The risk of hypoglycemia, however, was increased three times in those receiving intensive therapy; this group also experienced weight gain 1.6 times more frequently.[37]

After completion of the DCCT, researchers continued to follow DCCT subjects to assess long-term implications of intensive glycemic control during the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. After the DCCT study, the conventional treatment group was offered intensive management of diabetes and then asked to follow up with their health-care providers. During the fourth year after the DCCT, the gap in glycosylated hemoglobin values between the conventional therapy and the intensive therapy group narrowed from average 9.1 and 7.2% to 8.2 and 7.9%, respectively ($p < 0.001$). However, the proportion of patients who had progression of retinopathy was significantly lower in the intensive treatment group (odds reduction 75%). The proportion of patients with an increase in urinary albumin was significantly lower in the intensive treatment group.[38] Furthermore, during the 11-year post-DCCT follow-up, the intensive treatment group continued to exhibit a 57% reduction in risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease compared to the conventional treatment group. This occurred in spite of very minor differences in glycosylated hemoglobin values ($8.0 \pm 1.2\%$ vs. $8.2 \pm 1.2\%$, respectively; $p = 0.03$). The pathophysiological mechanism responsible for this sustained beneficial effect of tight glycemic control remains unclear and is now referred to as "metabolic memory."[39]

The United Kingdom Prospective Diabetes Study (UKPDS), completed in 1998, was the largest study of patients with type 2 diabetes mellitus. The study was designed to observe the effects of glycemic control on long-term complications of diabetes. Researchers enrolled 5102 patients with newly diagnosed type 2 diabetes and followed them for a median of 11 years. Intensive treatment (insulin or oral agents or both) was compared to conventional therapy (diet and, if necessary, pharmacological therapy). Median level of HbA1c in intensively treated group was 7.0%; it was 7.9% in conventionally treated group. Intensive treatment significantly decreased risk (by 12%) of aggregated diabetes-related endpoints (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, or cataract extraction). Risk reduction for progression of retinopathy was 21% and for appearance of microalbuminuria was 30%. However, individual cardiovascular events did not decrease significantly.[40] Tight blood pressure control (mean blood pressure 144/82 mmHg) compared to less tight control (mean blood pressure 154/87 mmHg) significantly reduced the risk of microvascular and macrovascular complications by 37 and 34%, respectively.[41] Adding metformin to the diet in overweight patients lowered the risk of any diabetes-related endpoints, diabetes-related death, and all-cause mortality and did not induce weight gain.[42]

Collectively, DCCT and UKPDS, along with other studies (discussed in detail in Chapters 39 and 45), established that improvement in the control of metabolic abnormalities decreases the risk of the development of dreaded complications responsible for severe and chronic disabilities associated with the disease, such as blindness and renal failure. However, the effects of tight glycemic control on cardiovascular outcomes remain unclear.

ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial sponsored by the National Heart, Lung and Kidney Institute is being conducted to study effects of tight glycemic control, blood pressure treatment, and lipid control on cardiovascular outcomes in individuals with type 2 diabetes. In February 2008, the ACCORD investigators halted the intensive glycemic control arm (hemoglobin A1c goal less than 6%) because of increased risk of death in this arm. Although details of this study are not published, at the time of this writing it appears that this group consisted of individuals who had type 2 diabetes for an average of 10 years with at least two risk factors for heart disease other than diabetes or a previous history of heart disease. Among 10,251 participants, the rates of death in intensive and conventional group were 257 and 203, respectively, over 4 years of treatment. The incidence of deaths in this study (11 deaths/1000 patients per year in conventional treatment group versus 14 deaths/1000 patients per year in intensive treatment group over 4 years) is lower than death rates found in similar population in other studies. At this point, the cause for increased death is not clear and is under investigation. The other treatment arms are being continued and the study is scheduled to conclude in June 2009.[43]

Patients with diabetes are typically counseled to lose weight and exercise. However, long-term consequences of intentional weight loss are unknown. Look AHEAD is the first randomized controlled trial to assess whether weight reduction, combined with increased physical activity in overweight individuals with type 2 diabetes, reduces cardiovascular morbidity and mortality. The study began in 2001 and is scheduled to conclude in 2012.[44]

Attempts to Cure Diabetes: Whole Pancreas and Pancreatic Islet Cell Transplantation

Majority of the treatment methods available for the management of diabetes offer means of controlling the disease. The ultimate goal of the physicians treating patients with diabetes is to achieve cure. There have been many attempts to develop the safe and effective methods of curing diabetes. Although very intensive research is being conducted in this field, current protocols still have only limited applications.

In 1966, University of Minnesota surgeons performed the first cadaver pancreas transplant. The first living donor transplant was performed in 1978. With improved surgical techniques, newer immunosuppressive agents, and healthier recipients, the graft survival rate has remarkably improved. In experienced centers, the 1- and 5-year pancreas graft survival rates have increased significantly from 29 and 11% (1976–1985) to 73 and 46% (1996–2006), respectively.[45] Although the risk of the procedure and the rates of the graft failure have declined, the complications associated with prolonged immunosuppression limit the use of this procedure to a small number of patients with type 1 diabetes.

In 1972, Paul Lacy and coworkers published the paper on methods of isolation of intact pancreatic islet cells.[46] First attempts at islet cell transplants were performed in animals with experimental diabetes and resulted in the reversal of hyperglycemia.

First autologous islet cell transplant was performed by surgeons at the University of Minnesota in 1977.[47] Autologous islet cell transplants are reported to have 75% long-term success rate. Autologous transplants are usually used in the setting of chronic pancreatitis requiring removal of pancreas.

Success with autologous cell transplants has foreshadowed the recent very promising developments in the field of allogeneic islet cell transplants. Early experience with human allogeneic transplants was not promising. It is thought that the poor success rate with the early allogeneic transplants was related to the use of immunosuppressants like prednisone, which is diabetogenic. That may have been compounded by insufficient number of islets used for transplantation.

In 1999, a group of researchers from Edmonton in Alberta, Canada, reported successful experience (defined by insulin independence up to a median time of 11 months) in seven patients with type 1 diabetes mellitus that had a history of severe recurrent hypoglycemia and poor metabolic control. These patients received islet cell transplants from non-HLA (human leukocyte antigen)-matched cadaveric pancreata, with the use of glucocorticoid-free immunosuppressive regimen.[48] A 5-year follow-up from the same center reported data on 65 patients who received islet cell transplant as of November 2004. Majority (80%) had c-peptide present, but only a minority (10%) maintained insulin independence. The median duration of insulin independence was 15 months.

The HbA1c was lower in patients who were off insulin or on insulin but c-peptide positive and higher in those who lost all graft function. Furthermore, the hypoglycemic episodes and the amplitude of glycemic excursions improved post-transplant.[49]

The most serious limitation to the use of donor islet cells is the shortage of available donors. This limitation has led to a search for alternative islet cell sources. Porcine cells have been suggested as a potential source of islet cells for the transplant. The development of transgenic pigs (expressing human genes to diminish immunological reaction) might decrease the need for immunosuppression after the transplant procedure. The disadvantage of using cells from transgenic pigs involves the risk of cross-species infection with porcine retroviruses, which can adapt to human hosts. These concerns have led the FDA to halt trials of porcine xenografts until those patients who have already received grafts are assessed for possible infections.[50]

Other possible sources of islet cells under investigation are human pancreatic duct cells, fetal pancreatic stem cells, and embryonic stem cells.[50]

Diabetes Prevention

In 1921 Eliot P. Joslin wrote:

> It is proper at the present time to devote not alone to treatment but still more to prevention of diabetes. The results may not be as striking or immediate, but they are sure to come and to be important.

Studies have clearly demonstrated that diet and exercise improve glycemic control and some patients with diabetes treated with diet and exercise alone enter a sustained remission state lasting up to 5 years. Data from two NHANES (National Health and Nutrition Examination Survey) surveys show that among adults aged 20–74 years, the prevalence of obesity increased from 15.0% (in the 1976–1980 survey) to 32.9% (in the 2003–2004 survey). Thirty-four percent of adults aged 20–70 are overweight.[51] This can be partly attributed to a significant increase in total calories and carbohydrate consumption in the past 30 years.[52]

The Physician Health Study has demonstrated inverse relationship between physical activity and rate of development of diabetes.[53] Similar results were reported from Nurses' Health Study.[54] National Health Interview Survey completed in 1990 has shown that diabetic individuals were less likely to participate in regular physical exercise than were people without diabetes.[55]

Several clinical studies present the evidence suggesting that diet and exercise can reduce the incidence of type 2 diabetes. Tuomilehto and coworkers demonstrated that the individuals on a consistent diet and exercise program had 10% incidence of diabetes during 4 years of follow-up compared to 22% for patients in the control group who met only once a year with the dietician and the physician.[56] A 6-year randomized trial conducted by Pan and colleagues demonstrated that exercise resulted in 46% reduction in the incidence of diabetes in patients with impaired glucose tolerance.[57] Helmrich and coworkers administered questionnaires evaluating the pattern of physical activity to 5990 male alumni of University of Pennsylvania. The researchers found that the leisure time activity (like walking, stair climbing, and participation in sports) during 14-year follow-up was inversely related to the risk of development of type 2 diabetes. The protective effect was strongest among the people at the highest risk for diabetes.[58] Study by Manson and coworkers followed 87,253 women (aged 34–59) free of diabetes, cardiovascular disease, or cancer for 8 years. Women who engaged in vigorous exercise at least once per week, after adjusting for age, family history, body mass index, and other factors, had 46% relative risk reduction for development of diabetes.[54]

In 1993, National Institute of Diabetes and Digestive and Kidney Diseases initiated a multicenter study with the objective of developing methods to prevent new cases of type 2 diabetes in adults. The study was named Diabetes Prevention Program (DPP). DPP was a 27-center randomized clinical trial designed to evaluate the safety and efficacy of interventions that may delay or prevent development of diabetes in people with increased risk. Three thousand two hundred and thirty-four obese patients with impaired glucose tolerance and fasting plasma glucose of 5.3–6.9 mmol/l were randomized into three groups: intensive lifestyle modification, standard care plus metformin, and standard care plus placebo. Trial was terminated 1 year prematurely because the data had clearly addressed main research objectives. Results of DPP were reported in 2001. About 29% of DPP

control subjects developed diabetes during the average follow-up period of 3 years. In contrast, 14% of the diet and exercise subgroup and 22% in metformin arm developed diabetes. Volunteers in the diet and exercise arm achieved average weight loss of about 5% during the duration of the study.[59]

A Diabetes Prevention Trial (DPT-1) was conducted to determine if subcutaneous or oral insulin administration can delay or prevent diabetes in nondiabetic relatives of patients with diabetes. This was a large multicenter study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases in cooperation with the National Center for Research Resources, the Juvenile Diabetes Foundation International, and the American Diabetes Association. There was no decrease in incidence of development of type 1 diabetes with parenteral or oral insulin administration.[60,61]

Genome-Wide Association Studies

The susceptibility to develop diabetes is determined by a combination of genetic and environmental factors. Given the polygenic etiology of type 2 diabetes, the genes responsible for the disease are not yet identified. However, with the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers are now able to quickly analyze the whole genome for single-nucleotide polymorphisms (SNPs) in large populations. Genomic areas with variations in SNPs between populations with and without diabetes are then studied in greater details. The most comprehensive genome-wide association study for type 2 diabetes was reported in April 2007 by three groups working in close collaboration – US–Finnish team, US–Swiss team, and a British group. These studies identified four new genetic variants and confirmed existence of another six.[62–64] The significance of these variants is currently under investigation. Once new genetic associations are recognized, the information can be utilized to better understand pathophysiology of diabetes and develop better strategies to detect, treat, and prevent the disease.

Summary

Diabetes mellitus has been observed and reported throughout written history since at least 1500 BC. It is only relatively recently that the perception of this disease has changed. Type 1 diabetes no longer carries the stigma of inevitably fast progressing and deadly disease. Intensive scientific research worldwide has brought new insight into this disease with modern management methods. Yet, much remains to be done and the cure has remained elusive. With improving standard of living and increasing affluence, the western world is now witnessing the rising epidemic of obesity predisposing to type 2 diabetes. As the disease itself and its complications impose great social and economical burdens, attention of medical professionals should increasingly be directed toward raising awareness of diabetes and promoting healthy lifestyle to prevent the development of this disease. Ultimately, with effective strategies for prevention and cure of diabetes, this disease will be eliminated.

Diabetes Timeline

Circa 1500 BC, Ebers Papyrus	First written reference to diabetes by ancient Egyptian physicians
230 BC, Apollonius of Memphis	The name diabetes (from Greek “to pass through”) given to the disease
First century AD, Aulus Cornelius Celsus	First clinical description of diabetes
Fifth century AD, Susruta and Charaka, India	First distinction between type 1 and type 2 diabetes mellitus
1776, Mathew Dobson, England	Determined that the sweet-tasting substance in the urine of diabetic individuals is sugar

Diabetes Timeline (continued)

1788, Thomas Cowley, England	First link between diabetes and pancreas
1869, Paul Langerhans, Germany	Discovery of small cell clusters in the pancreas, not drained by the pancreatic ducts. These cell clusters later named "islets of Langerhans"
1889, Oscar Minkowski, Joseph von Mehring, Germany	Removal of the pancreas in the dogs causing immediate development of diabetes
1893, Edouard Laguesse, France	Islets of Langerhans might be the source of anti-diabetic substance
1907, Georg Zuelzer, Germany	Pancreatic extract "acomatol," produced by Zuelzer, decreased glucosuria and raised blood pH in diabetic dogs
1921–1922, Frederick Banting, Charles Best, James Collip, and John J.R. Macleod, Canada	Dog's pancreatic extracts shown to decrease glucosuria. First successful clinical use of refined pancreatic extract for diabetic patient. Eli Lilly Company begins the work on the commercial development of insulin
1928, Germany	Synthalin–a guanidine derivative administered orally for treatment of diabetes
1939, C. Ruiz, L.L. Silva, Argentina	Hypoglycemic properties of sulfonamide antibiotics observed for the first time
1958, Frederic Sanger, Great Britain	Nobel prize for the structural formula of bovine insulin
1959, Rosalyn Yalow and Salomon Berson, USA	Development of radioimmunoassay. Rosalyn Yalow received Nobel Prize for RIA in 1977
1966, University of Minnesota, USA	First transplant of the pancreas performed
1969, Dorothy Hodgkin, Great Britain	Description of the three-dimensional structure of porcine insulin using X-ray crystallography
1978, Robert Crea, David Goeddel, USA	Human insulin production using recombinant DNA technology
1993, Diabetes Control and Complications Trial, USA	Relation of the metabolic control of type 1 diabetes to the development of diabetic complications
1998, United Kingdom Prospective Diabetes Study, Great Britain	Relation of the metabolic control of type 2 diabetes to the development of diabetic complications
2001, Diabetes Prevention Program, USA	Relation of diet and exercise to the rate of development of type 2 diabetes in high-risk population
2003, Human Genome Project	Sequencing of human genome
2007, First Genome-Wide Association Studies for Diabetes	Novel loci identified in association with type 2 diabetes

Internet Resources

1. http://nobelprize.org
2. http://www.genome.gov/
3. http://utdol.com
4. www.crystalinks.com/egyptmedicine.html – ancient Egyptian medicine, Ebers papyrus
5. www.uic.edu – Claude Bernard
6. www.britannica.com – Claude Bernard
7. www.nobel.se – August Krogh
8. http://web.mit.edu/invent/iow/yalow.html
9. www.gene.com – press release September 6, 1978
10. http://www.mendosa.com/history.htm
11. Prevalence of Overweight and Obesity Among Adults: United States, 2003–2004. National Center for Health Statistics www.cdc.gov
12. www.niddk.nih.gov – results of Diabetes Prevention Program, Diabetes Prevention Trial.

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11. www.britannica.com – Claude Bernard.
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