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From Antiquity to Modern Times: A History of Diabetes Mellitus and Its Treatments

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Abstract
The past 200 years have brought an understanding of diabetes and its pathogenesis, as well as the development of treatments that could not have been predicted when the disorder was first clinically described 2000 years ago. Beginning in the late 19th century, the initial descriptions of the microscopic anatomy of the pancreatic islets by Langerhans led to recognition of pancreatic endocrine function. Many investigators attempted to isolate the hypoglycemic factor produced by the pancreas, but Banting, Best, Macleod, and Collip were able to extract and purify "isletin" to treat human diabetes in 1921. Rapid scientific progress over the next 100 years led to an understanding of insulin synthesis, structure and function, production of modified synthetic insulins, and the physiopathology that permitted classification of diabetes subtypes. Improvements in control of diabetes have reduced the risks of complications. In less than two hundred years, we have gone from being unable to measure glucose in blood to being able to offer people with diabetes continuous blood glucose monitoring, linked to continuous subcutaneous insulin infusion. We come ever closer with new drugs and treatments to repair the biochemical defects in type 2 diabetes and to biologically replace islets and their function in type 1 diabetes. This review addresses the history of continuing progress in diabetes care.

Introduction

Though the first-known descriptions of diabetes date back to the 1st century C.E., the earliest written account was that of Aretaeus of Cappadocia in the second century. In his text, he wrote

> "Diabetes is a remarkable affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water, but the flow is incessant, as if the opening of aquaducts. Life is too short, disgusting, and painful, thirst unquenchable, excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water; or, if for a time they abstain from drinking, their mouth becomes parched and their body dry, the viscera seems as if scorched up; they are affected with nausea, restlessness, and burning thirst, and at no distant term they expire" [1].

Various theories and descriptions of diabetes can be found in the Greek, Roman, Chinese, Arabic, and Hindu literature, but it was not until 1679 that Thomas Willis

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(1621–1675) described the distemper, diabetes as "…a swift passing of the potulen matter (or drink) or a great flux of Urin," in his treatise, "Pharmaceutice Rationalis," the first English language description of diabetes and its symptoms [2]. At that early period, diabetes mellitus was largely considered a homogeneous disorder.

Identification of the Role of the Pancreas

Our understanding of the role of the pancreas in diabetes mellitus originated in the 19th century. Paul Langerhans (1847–1888), a German pathologist, published a doctoral thesis entitled "Contribution to the Microscopic Anatomy of the Pancreas" in which he described nine different cell types which compose pancreatic islets, including those that were later found to secrete insulin [3]. These islets were named for Langerhans ("islôts de Langerhans") by Gustave Edouard Laguesse (1861–1927), a French histologist, in 1893 [4]. He turned Langerhans' description of "Zellhaüfchen" (a little heap of cells) into a functional unit, the islands of Langerhans, which presaged an understanding of their endocrine function. Laguesse hypothesized that the pancreatic islets produce a substance that could prevent glycosuria [5, 6].

Oskar Minkowski (1858–1931) and Joseph von Mering (1849–1908) conducted experiments that provided clues to the pathophysiology of what is now known as type 1 diabetes (T1D). To understand the role of free fatty acids in fat absorption, they performed a total pancreatectomy in a dog, resulting in polyuria, hyperglycemia, and glycosuria [7]. Published in 1890, they concluded that glucose concentrations in the blood were controlled by a "substance" produced by the pancreas and that in its absence, diabetes would ensue. Minkowski confirmed this hypothesis in further work published 2 years later when he showed that a subcutaneous pancreatic autograft could prevent diabetes after pancreatectomy [8].

Eugene L. Opie (1873–1971) then linked diabetes mellitus specifically with islet disruption. Opie, a medical student and later physician at Johns Hopkins, studied pancreatic anatomy, including morphological alterations, within the islets of Langerhans. He was mentored by the pathologist, William Welch (1850–1934), one of the founding professors of Johns Hopkins. Opie noted a difference in the clinical outcome in patients with pancreatitis depending on whether islets were affected. Those with islet-cell infiltration or destruction developed diabetes mellitus, whereas those with interacinar pancreatitis who retained intact islets did not [9].

Once these associations were made, scientists in many countries began to experiment with pancreatectomy to create a model of diabetes mellitus and examine the effect of treatment with pancreatic extracts. In Paris, Marcel Emile Gley (1857–1930) demonstrated that total pancreatectomy in dogs induced polyphagia, polydipsia, glycosuria, ketonuria, and the loss of liver and muscle glycogen. Incomplete pancreatectomy did not cause these signs, or they were noted only transiently. He also found, in 1884 and 1890, that diabetic dogs could be treated with the pancreatic extracts from dogs with ligated pancreatic ducts [10]. Despite his early success, he did not publish his findings until after those of Banting and Best were published in 1922 [11].

Other scientists attempted similar experiments with mixed results. In Germany, George Ludwig Zuelzer (1870–1949) (German spelling Georg Ludwig Zülzer) used calf pancreatic extract (Acomatol) experimentally in dogs and humans in the early 20th century [12, 13]. In some cases, he noted improvements in patients' glycosuria and ketonuria. However, the side effects were severe, including fever and emesis. Some undoubtedly had hypoglycemia, but it would be some years before easy measurement of glucose in the blood. Even with mixed results, Zuelzer's extract received patents in both Germany (number 201383) in 1907 and the USA (number 1027790) in 1912. Though his work was interrupted by World War I and the subsequent rise of the Nazi regime, which forced him to seek refuge in New York, his early findings pointed to insulin as a treatment for diabetes mellitus.

Between 1914 and 1916, Nicolae Paulescu (1869–1931), a Romanian physician and physiologist, developed an aqueous pancreatic extract, pancrein, that lowered blood glucose when injected into diabetic dogs (no original documents are available, but noted in [14]). Though also affected by World War I, he succeeded in securing a patent for his extract from the Romanian Ministry of Industry and Trade in 1922 (number 6254). Similar to Gley, though his work predated the Toronto experiments, it was not reported until late 1921 [15]. Though some have sought to recognize him on par with Banting and colleagues [16], his unfortunate past as a leader in the Romanian fascist movement has overshadowed his discoveries.

In the USA, Ernest Lyman Scott (1877–1966) was a physiologist and diabetes researcher at Columbia University. He described, in his master's thesis, the isolation of an anti-diabetic substance from the pancreas when precautions were taken to prevent the effects of digestive enzymes and oxidation during preparation. Dogs were studied post-complete pancreatectomy. They had a large

decrease in urine glucose that lasted, in some cases, for 2–3 h. He was careful to note that the results did not mean that he had discovered a new hormone, as the injections were followed by a systemic reaction, and that might have been the reason for glucose lowering. Though part of his work was published in 1912 [17], his full thesis was not published until 1966 [18].

Two other investigators (both European emigres to North America) made important discoveries during this time. Israel Kleiner (1885–1966), of NY Medical College, was among the first to determine that infusing pancreatic extracts could lower glucose when co-administered with dextrose in normal dogs and induce hypoglycemia in diabetic dogs [19, 20]. He correctly identified that this extract could have therapeutic applications in humans with diabetes [20]. Moses Barron (1883–1974), a pathologist at the University of Minnesota, reported that rabbits maintained intact islets and normoglycemia without glycosuria despite ligation of the pancreatic duct, resulting in loss of pancreatic parenchyma [21]. These animals developed neither hyperglycemia nor glycosuria. The conclusion from the series of experiments was that ligation of the pancreatic duct led to slow replacement of the acinar tissue with an accumulation of connective tissue and fat, but with intact islets. This finding helped to inform the experiments subsequently conducted by Banting.

The well-known story of the discovery of insulin at the University of Toronto begins with Frederick Grant Banting (1891–1941), a surgeon practicing in rural Ontario who took on an additional job as a demonstrator in anatomy at the Western Ontario University. To prepare for a lecture on the pancreas for one of his classes, he reviewed the report of Moses Barron [21] on pancreatic islets and diabetes. This was scientifically exciting to him, and he wrote down an idea for future studies:

"Diabetes-Ligate pancreatic ducts of dogs. Keep dogs alive till Acini degenerate leaving islets. Try to isolate the internal secretion of these to alleviate glycosuria."

Banting was luckily unaware of other investigators abroad who achieved mixed results with the same plan. He could not carry out the work at Western Ontario and was advised to speak with JJR Macleod, Professor of Physiology at the University of Toronto. Macleod, an expert in carbohydrate metabolism, permitted him to use a laboratory despite Banting's obviously limited understanding of pancreatic function and diabetes. He gave him a modest budget and a student assistant (Charles H. Best) before leaving on holiday. In May 1921, Banting and Best began their experiments on dogs. There were few successes during the initial work, but eventually, some pancreatectomized dogs survived. They prepared weakly potent pancreatic extracts that could decrease hyperglycemia and glycosuria in the pancreatectomized dogs. They named their active material, "isletin" after the islets of Langerhans.

When Macleod returned, he added JB Collip, an experienced biochemist, to the team. Collip initiated the use of alcohol to precipitate the active material and developed techniques to purify isletin enough that humans would not have severe injection reactions. He also developed a reasonably stable and more precise in vivo rabbit assay for testing drug potency [22]. These contributions were critical to "isletin's" success.

Macleod then authorized the first experimental administration of "isletin" to Leonard Thompson, a 14-year-old boy admitted to Toronto General Hospital with severe diabetes and ketoacidosis. The first injection led to a sterile abscess. However, a second series of injections resulted in a decrease in glycemia, glycosuria, and ketonuria. The findings were reported in 1921 to the American Society of Physiology and published in the *Journal of Laboratory and Clinical Medicine* [23]. Banting and Macleod were awarded the Nobel Prize for Physiology or Medicine in 1923, which they shared with Best and Collip.

Insulin Structure and Measurement

Thirty years later, the molecular structure of insulin was determined through the work of Frederick Sanger (1918–2013) and colleagues at the University of Cambridge. Sanger is commonly known as the "father of genomics" and won not one, but two Nobel Prizes in chemistry. Using paper chromatography, Sanger determined the complete amino acid sequence of cattle insulin [24–27], followed by pig and sheep insulins [28], describing the projects as "building up a picture from the pieces of a jigsaw puzzle [29]." This work earned Sanger his first Nobel Prize in 1958 [30]; his second Nobel Prize in 1980 resulted from his work devising the "dideoxy" chain-termination method for DNA sequencing (known as the "Sanger Method") [31, 32]. Less than a decade later, in 1964, Dorothy Hodgkin (1910–1994), working at Oxford, was also awarded the Nobel Prize in Chemistry for her work in determining the structures of different molecules by X-ray crystallography [33]. This allowed the description of the three-dimensional structure of porcine insulin [34], which was critical in the understanding of its chemical properties, cellular functions, and receptor binding.

Radioimmunoassay, developed by Solomon Berson (an investigative physician) and Rosalyn Yalow (a medical physicist) at the Bronx Veteran's Administration Hospital (VA) in New York in the 1950s, enabled the measurement of hormones with extremely low circulating levels using radiotracers and antibodies [35]. Insulin was one of the first hormones they measured [36]. Perhaps they too were "lucky" that their work was conducted at the Bronx VA because they faced some skepticism when they reported that their subjects with diabetes in general had higher levels of insulin in the blood than their control subjects. This confirmed earlier work using a less sensitive in vivo bioassay by Bornstein and Lawrence [37] that the maturity-onset type of diabetes [type 2 diabetes (T2D)] was indeed different from diabetes following pancreatectomy [38].

They also faced considerable skepticism when they demonstrated that antibodies could be generated against even small polypeptide molecules, like insulin. As described later, the ability to measure insulin directly led to a better understanding of the differences in diabetes pathophysiology, specifically the concepts of insulin deficiency versus insulin insensitivity, first proposed by Harold Himsworth (1905–1993), who distinguished insulin-sensitive versus insulin-insensitive forms [39]. In 1977, Rosalyn Yalow received the Nobel Prize in Physiology or Medicine with Roger Guillemin and Andrew Schally; Solomon Berson died before the award was given [40].

Discovery of C-Peptide

Donald Steiner (1930–2014) of the University of Chicago identified proinsulin as the larger single-chain precursor of insulin in 1967 [41, 42]. Further studies confirmed that this precursor was a single polypeptide chain, which began with the B chain of insulin, continued through a connecting segment of 30–35 amino acids, and terminated with the A chain. Paired basic residues were identified at the sites of excision of the C-peptide. As soon as the structure of proinsulin was known, studies of the intact proinsulin parent molecule and its offspring, the connecting peptide or C-peptide, expanded our understanding of insulin formation and action [43]. Steiner, with Arthur Rubenstein and collaborators, was the first to show that the proinsulin C-peptide is co-secreted with insulin [44] and to develop a suitable immunoassay for measuring this peptide in plasma samples [45]. Their findings on C-peptide secretion in healthy subjects and subjects with diabetes were later confirmed by Kaneko et al. [46] and Heding and Rasmussen [47]. The scientific community recognized that the measurement of C-peptide was extremely helpful in assessing beta-cell secretory function, as the insulin immunoassay could not distinguish endogenously secreted insulin from exogenously administered insulin [48, 49]. This is now the standard of care.

Biology of Insulin Action

Soon after the discovery of insulin, scientists began postulating its mechanisms of action. An initial theory, proposed in 1924 by Vilem Laufberger (1890–1986), a Czech physician and physiologist, was that insulin had an enzymatic action in carbohydrate metabolism [50]. The more modern concept of hormones binding to a receptor to exert downstream effects came decades later. Rachmiel Levine (1910–1998), a Polish-born immigrant physician (initially to Canada, as he was denied a visa in the USA), led a series of experiments studying the relationship between insulin and glucose utilization at Michael Reese Hospital in Chicago. In 1949, he found that injecting dogs with galactose and insulin simultaneously led to greater reductions in plasma galactose levels than when galactose was administered alone [51]. Levine theorized that insulin acted on the cell membrane to prompt uptake of hexoses, like glucose, into cells, which ultimately was proven true. Levine earned the Banting Medal in 1961 for his work and is commonly referred to as the "father of modern diabetes research."

The discovery of the insulin receptor was made possible by the ability to radio-iodinate peptide hormones. Two Australian scientists, Paul D.R. House and Maurice J. Weidemann were the first to demonstrate that radioactively labeled insulin (^{125}I-Insulin) could bind to the cell membrane of rat liver cells in 1970 [52]. Shortly thereafter, two competing laboratories in the USA, that of Jesse Roth and collaborators, including Pierre Freychet, who was a Parisian visiting fellow at NIH, and that of Pedro Cuatrecasas, then at Johns Hopkins, released more detailed reports finding that ^{125}I-Insulin binds to a unique receptor on cell membranes in the liver [53] and adipose tissue [54], activating the intracellular processes which lead to glucose oxidation and suppression of lipolysis [55]. Later work identified receptor structure as a disulfide-linked heterodimer (1980) [56] which has tyrosine kinase activity (1982) [57, 58], and the correlation between the structure and function was elucidated with the cloning of the receptor cDNA by two laboratories in 1985 [59, 60].

Characterization of Diabetes

Nomenclature

Numerous clinicians and scientists first described the variability in presentations of diabetes mellitus more than a century ago, including Harley from the UK and Lancereaux from France in the 1880s, Joslin from the USA in the 1920s, and Himsworth from the UK in the 1930s [39, 61, 62]. With the ability to measure insulin, diabetes was reorganized into "juvenile-onset" (insulin appeared deficient) versus "adult-onset" (insulin appeared present) forms [37].

It was not until the end of the 1970s that the scientific community established formal diabetes classifications which could be used to guide therapy. The first, introduced in 1976 by the United States National Diabetes Data Group [63] and endorsed by the World Health Organization Expert Committee on Diabetes Mellitus [64], was based on the need for insulin therapy for survival. The juvenile-onset, usually ketotic type, was renamed insulin-dependent diabetes mellitus (IDDM), while the adult-onset, usually nonketotic type, was termed non-insulin-dependent diabetes (NIDDM). The classification was revised in 1997 based upon pathophysiology rather than insulin requirements, facilitated by the distinction between the autoimmunity driving insulin deficiency in IDDM and insulin resistance contributing to NIDDM. Absolute insulin-deficient states became known as T1D, with NIDDM, usually associated with insulin resistance, renamed T2D.

Today, most people with diabetes are grouped into these two classifications: T1D, characterized by the destruction of the beta cells by an autoimmune process resulting in loss of endogenous insulin production, or T2D, characterized by the lack of adequate insulin response in the presence of increasing insulin resistance. However, it is now clear that there is much more heterogeneity and overlapping of characteristics [65], which questions the common concept of categorizing diabetes by the presence or absence of islet-cell autoantibodies, as described below. In addition, we now recognize that people with monogenic autosomal dominant diabetes, formerly termed maturity-onset diabetes of the young, may make up 1–6% of those initially considered to have either T1D or T2D with decreased insulin secretion, but who are autoantibody negative [66–68]. This disorder, first characterized by Stefan Fajans in the 1950s, is composed of many genetic subtypes with different severities and treatment responses [69–72]. An understanding of the history of diabetes mellitus presupposes an understanding of this heterogeneity of presentation and treatment.

Islet Autoimmunity in T1D

Scientific discoveries in the 1960s through the 1980s further elucidated the pathogenesis of T1D. Initially, numerous reports were published suggesting an association between diabetes mellitus and several autoimmune disorders, including pernicious anemia, thyroid disease, and adrenal insufficiency [73–77]. The concept that "juvenile diabetes" could be due to an autoimmune disorder was first raised by **Dr. Robert Blizzard** (1924–2018) in the 1960s, but this was not accepted by peers [78]. Over the next 10 years, the idea grew that this disease is the ultimate result of an immunologic reaction between antigenic determinants of the endocrine pancreas and specific reactive immune cells [79].

Identification of islet-cell autoantibodies in patients with multi-endocrine deficiencies, including diabetes, supported the hypothesis of an autoimmune form of the disease as proposed by Botazzo et al. [80] in 1974. Contemporaneously, Jorn Nerup reported immune damage to the islets in similar patients [81]. Andrew Cudworth then described the role of genetic susceptibility in the association between islet autoimmunity and HLA type [82]. In 1983, Palmer and colleagues [83] in Seattle demonstrated the presence of insulin autoantibodies in patients with IDDM and their relatives before they ever received exogenous insulin. Using the same assay technology, these findings were soon confirmed in Pittsburgh by **Silva Arslanian** and **Dorothy Becker**, who also documented their greatest frequency in the youngest children [84].

Various methods were employed to assay islet-cell antibodies, as described by Ake Lernmark (University of Lund) when he was at the University of Chicago and others, including Pilcher and Elliott from New Zealand [85, 86]. The surface cell assay eventually gave way to the measurement of antibodies to glutamic acid decarboxylase (a component of islet-cell antibodies) [87–90]. Since then, other autoantibodies to beta-cell components are now used clinically, including islet antigen-2 (IA2) [91] and zinc transporter-8 (ZnT-8) [92].

Controversy starting in the 1980s surrounded the concept of whether beta-cell autoimmunity is primary in triggering the cellular destruction or whether there is innate susceptibility of the beta cell in certain populations [93–95]. This controversy still rages today. Foundational work by George S. Eisenbarth (1947–2012) demonstrated that islet autoimmunity precedes clinical T1D by years or decades and was described by his famed model [96]. This model for the natural history of T1D proposed progressive stages of pre-symptomatic T1D, including the concept of a latency period of several years before beta cells are killed

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and symptoms develop [97]. These studies and others [98–104] have allowed the development of a staging system in 2015. Stage 1 is defined as the presence of beta-cell autoimmunity as evidenced by the presence of two or more islet autoantibodies with normoglycemia and is pre-symptomatic; stage 2 is the presence of beta-cell autoimmunity with dysglycemia and is also pre-symptomatic; stage 3 is the onset of symptomatic disease [105].

Insulin Resistance

The term "insulin resistance" was introduced in 1929 by Howard Root (1890–1967), a physician and the first Medical Director of the Joslin Clinic, to explain the variable insulin requirements to manage hyperglycemia among individuals with diabetes [106]. Root described several cases in which more insulin was required than would be expected for individual patients, and the desired outcome for urinary glucose was not achieved. He concluded that these cases indicate disordered action of insulin in the liver, muscle, or other tissues. In addition to laying the groundwork for our understanding of the pathophysiology of T2D and insulin resistance in T1D, this concept helped us understand how defects in the insulin receptor contribute to glucose intolerance and other disturbances. The first description of a syndrome of severe insulin resistance was by William Donohue (1906–1985), a Canadian pathologist, in 1948 [107]. Donohue described a full-term female infant who presented at 4 weeks of life with emaciation, hepatomegaly, hypertrichosis, and a peculiar facial appearance; following her demise at 46 days of life, an autopsy revealed histologic changes in the ovaries, mammary tissue, pancreas, and liver. In the absence of any previous descriptions of similar infants, the general term "dysendocrinism" was applied to suggest the multitude of possible endocrine abnormalities. In 1954, Donohue and Irene Uchida (1917–2013) described a similar presentation in the sibling of this infant, arriving at the conclusion that a rare, homozygous mutation in a recessive gene was likely the cause [108]. With the characteristic features of both infants, including prominent eyes, low-set, and posteriorly rotated ears, thick lips and skin, and the absence of subcutaneous fat, they termed this condition "leprechaunism." However, given its pejorative nature, this term has fallen out of favor and the condition is now referred to as Donohue Syndrome. Two years later, Rabson, a pathologist, and Mendenhall, a general practitioner both in Fort Wayne, IN, described three siblings with many overlapping clinical features of Donohue Syndrome, in addition to dysplastic teeth, gingival hyperplasia, and pineal hyperplasia (Rabson-Mendenhall syndrome) [109]. These children survived into early childhood when they developed IDDM and died of complications from ketoacidosis. These overlapping conditions were later found to be due to defective insulin binding in cultured fibroblasts or other cell types, first in 1979 for Donohue Syndrome by Schilling et al. [110] and in 1986 for Rabson-Mendehall Syndrome by Takata et al. [111]. Around the same time, C. Ronald Kahn at the NIH published a case series of patients with severe insulin resistance who had a marked decrease in insulin binding to receptors in circulating monocytes which did not improve with fasting [112]. Named "Type A" insulin resistance, these patients presented with variable glucose intolerance, hyperinsulinemia, and a polycystic ovary syndrome-like phenotype in lean women. This was later found to be associated with milder defects in the receptor, likely moderated by other genes and environmental factors. "Type A" was used to distinguish this condition from Insulin Type B Resistance Syndrome, a disorder caused by circulating insulin receptor antibodies, which block insulin binding, which was first reported in 1976 [113–115].

Insulin resistance in more common forms of diabetes was recognized to be largely post-receptor in nature by groups including those of Jerry Olefsky at the University of California in San Diego in 1980 [116], Jerry Reaven at Stanford in 1984 [117], and Jack Gerich at Mayo Clinic in the same year [118]. Although T2D was long thought of as a disease of adults only, pioneering work by **Arlan Rosenbloom**, published in 1970, demonstrated that mild "chemical diabetes" in children could be treated with sulfonylureas [119]. A symposium organized by **Rosenbloom**, and other pediatric endocrinologists, including **Allan Drash** (1931–2009) and **Richard Guthrie** (1935–2020), identified the presence of diabetes responsive to oral hypoglycemic agents in children with obesity, presaging the later identification of T2D in children by **Rosenbloom** and colleagues [120, 121] as well as other investigators. This work led to the TODAY study of treatment of T2D in youth (2004–2011) and a clearer understanding of the difficulties of treating this increasingly common problem [122, 123].

Therapeutic Advances in Diabetes

Commercialization of Insulin and Analogs

Not long after Banting, Best, Collip, and Macleod presented their initial evidence that an alcoholic extract derived from the pancreas had a hypoglycemic effect, they

were approached by George Clowes (1877–1958), the first research director of Eli Lilly, who suggested that his company could commercialize production [124]. The investigators gave away the rights to the patent for this discovery because they felt that they were helping mankind. Insulin from pig and beef sources first became available for patients with diabetes in 1923.

Similarly, August Krogh, a Nobel prize-winning physiologist in Denmark, obtained the rights to the production of insulin. He and Hans Hagedorn developed the Nordisk insulin laboratories and received the rights to develop a manufacturing process for insulin in Europe. Nordisk would later merge with Novo to form Novo-Nordisk in 1989. Hagedorn eventually became the chief physician at the Steno Memorial Hospital and continued an active research career [125]. In the 1930s, Hagedorn and colleagues [126] went on to develop the first longer-acting insulin by combining insulin with protamine. This preparation, NPH or neutral protamine Hagedorn insulin, has continued to prove useful [126]. These were the first examples of rapid commercialization of a hormone after initial proof of principle by academic research. Later development of modified and synthetic human insulins was almost entirely driven by pharmaceutical company research after the development of recombinant-DNA technology.

Insulin Treatment for T1D

Over the past several decades, groundbreaking research has identified that "intensive insulin therapy" is key to the treatment of T1D. A few observational studies reported that relatively short periods of markedly improved control resulted in improved ocular function [127, 128], lipids [129], and microalbuminuria [130]. Though these studies found an association between hyperglycemia and complications, they did not determine a causal relationship. In the mid-1970s, before the advent of home glucose monitoring, controversy raged between clinicians advocating tight glycemic control (e.g., absence of glycosuria) and others who were concerned about the risks of hypoglycemia and psychological trauma before a cause and effect were proven [131]. Selected randomized, clinical trials also sought to elucidate the relationship between hyperglycemia and complications [132, 133]; however, these studies had shortcomings, including a small sample size and shorter duration of diabetes, among others [134]. The availability of self-glucose monitoring in the early 1980s provided the tools to create a large, well-designed, and adequately powered intervention trial of diabetes, including intensive insulin therapy, to answer the question in humans with T1D whether tight control was achievable and effective in delaying or preventing microvascular complications of diabetes.

Diabetes Control and Complications Trial

The landmark Diabetes Control and Complications Trial (DCCT) was designed initially as a 2-year feasibility trial beginning in 1986 [to prove that it was possible to lower hemoglobin A1c (HbA1c)] and then continued until 1993 when it was stopped prematurely because of demonstrated effectiveness. The DCCT was a randomized, controlled clinical trial designed to assess the relationship between glycemic control and early microvascular complications in persons with T1D. It consisted of a primary prevention study and a secondary intervention study. Participants were randomly assigned to intensive diabetes therapy or therapy with no or optional blood glucose testing, as was typical treatment at that time [121]. After 6.5 years, the study proved that tight glycemic control, as assessed by HbA1c measurements, was effective in preventing retinopathy, nephropathy, and neuropathy. In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria and clinical neuropathy [135].

The DCCT also showed that intensive insulin therapy helped preserve C-peptide secretion which was associated with a reduced risk of long-term complications and hypoglycemia [136, 137]. Over the last few decades, C-peptide concentration has emerged as a marker for the progression, diagnosis, and classification of diabetes.

Development of Non-Insulin Drug Therapies

Sulfonylureas

In Montpellier in 1942, Auguste Loubatieres, a Belgian graduate student in physiology, surmised that adverse hypoglycemic side effects reported after administration of some newly developed sulfonamide antibiotics might make them useful anti-diabetes agents. He confirmed that the drugs lowered blood glucose and then proved that these agents could lower blood glucose in normal fasting dogs, but not in those that had complete pancreatectomies. He hypothesized that the drug stimulated the pancreatic release of insulin, but had no effect in the absence of pancreatic islets [138]. Within 10 years of the end of World War II, sulfonylurea derivatives, the first oral agents for the treatment of diabetes, were being tried as a treatment for T2D [139, 140]. They have also been useful in the treatment of some monogenic forms of diabetes, particularly those related to HNF-1 alpha mutations [141].

Biguanides

Extracts of French lilac, also known as goat's rue and false indigo (*Galega officinalis*), were used in medieval medicine for the treatment of symptoms, which likely were those of T2D. An herbal treatise, published by Nicholas Culpepper in England in the 17th century, lists extracts of these plants as accepted treatments for diabetes symptoms. The plant contains galegine and an excess of guanidine with action, similar to modern synthetic biguanides like metformin, but is much more toxic [142, 143]. Among others, Jean Sterne, a Parisian clinical pharmacologist and physician (1909–1997), identified metformin, which had initially been synthesized by Werner and Bell in 1922 [144], for clinical development in the 1950s [145]. Although used in Europe in the 1960s, it was not until 1995 that metformin was approved for use in the USA. The delay in approval followed the recognition of severe lactic acidosis induced by a cognate drug, phenformin, which was withdrawn from use in the USA in 1978. Metformin is now an important drug for the treatment of T2D, but there may also be a role for it in T1D, as recently published studies headed by **Ingrid Libman** and **Kristen Nadeau**, demonstrated improved insulin sensitivity in young people with T1D, though without effect on HbA1c [146, 147].

Amylin Analogs

Deposits of hyaline material within the pancreatic islets were first reported by Opie in 1901 [9] and identified as amyloid in 1943 by Ahronheim in Michigan [148]. Several groups, notably that of Per Westermark in Upsala, recognized that this protein was a polymerization product of a small beta-cell peptide in the 1960s [149]. Several laboratories worked out the chemical structure and identified the amylin gene in the late 1980s [150]. Amylin, which is co-secreted with insulin from the beta cell, has direct effects within the islet, but the biological effect of circulating amylin on gastric emptying and appetite led to the development of analogs for diabetes treatment. A synthetic, water-soluble derivative, pramlintide, has had limited therapeutic success [151].

SGLT Inhibitors

Familial renal glycosuria, first described in the 1920s as a benign disorder, set the stage for the later use of SGLT inhibitors for T2D [152]. The first-known drug in this class, Phlorizin, was isolated from the bark of an apple tree by chemists in France over 150 years ago [153]. Josef Von Mering, the German physician who helped to identify that a pancreatic product was important for control of diabetes with Minkowski, also reported that phlorizin induced glycosuria in 1886 [154]. Pflorizin was utilized in rat studies almost 40 years ago by DeFronzo and colleagues [155, 156] in San Antonio to demonstrate that inhibition of glucose reabsorption by the renal tubule in an experimental diabetes model improved glycemic control.

Glucose transport across the gut and other tissues was characterized beginning in the 1960s. Early work by Vogel and others in Germany demonstrated that sodium was required for this transport [157]. In the 1980s, the human sodium-glucose cotransporters (SGLT) were cloned, expressed, and characterized, leading to our understanding that familial glycosuria results from mutations in SGLT2, while SGLT1 is largely a gut transporter with an adjunctive role in the kidney tubule. Investigators from UCLA played an important role in cloning and understanding many of these genes [158]. These studies have led to the present-day development of inhibitors of SGLT2 alone as well as combined SGLT1-SGLT2 drugs to improve glycemic control and decrease long-term complications of diabetes [159, 160]. Because of the risk of diabetic ketoacidosis, whether these agents will find a role in the management of T1D remains unclear.

Incretins

In 1906, Moore, Edie, and Abram from Liverpool proposed, with rather uneven data, that an acid extract of the duodenal mucous membrane could improve glycemic control, suggesting that the duodenum supplies a "chemical excitant for the internal secretion of the pancreas" [161]. The concept of an incretin stimulating the internal secretions of the pancreas was first suggested by LaBarre and colleagues [162, 163] from Brussels and the University of Chicago in the 1930s using cross-circulation experiments. John Dupre and others initially demonstrated that the human body can more rapidly clear an oral glucose load compared with an intravenous one, and that gut mucosal extract can improve glucose clearance following an intravenous glucose load [164]. With the availability of immunoassays for insulin, investigators such as Michael Perley and David Kipnis at Washington University demonstrated that oral glucose challenge elicited a much larger insulin response than did intravenous glucose, confirming the existence of gut factors enhancing insulin release [165]. The concept of a so-called enteroinsulin axis was popularized by Roger Unger at the University of Texas, Southwestern, in response to this and similar studies [166]. These studies led to the pioneering work of Daniel Drucker in Toronto, Joel Habener in Boston, and Jens

Holst in Copenhagen, with their many colleagues, in the identification of glucagon-like peptides, and glucose-dependent insulinotropic polypeptides leading to their therapeutic application in the treatment of T2D [167, 168].

Thiazolidinediones

This class of drugs was initially synthesized by Takeda Pharmaceuticals in the 1980s to develop lipid-lowering drugs. However, screening revealed that this group of agents lowered both glucose and insulin in animal models, leading to their investigation and commercialization as insulin sensitizers by Takeda in initial collaboration with Upjohn [169, 170].

These drugs were identified to be PPAR gamma agonists, among other targets, and therefore had pleiotropic actions. However, liver failure was associated with one of the earliest approved agents (troglitazone), and there was concern about adverse cardiac effects with some of the other agents (e.g., rosiglitazone, pioglitazone). Ongoing regulatory concerns have led to decreased use of these drugs [171]. Although rosiglitazone was chosen as one of the drug treatment arms in the TODAY study of treatment of T2D in youth, it was only slightly more effective than metformin alone or metformin with intensive lifestyle modification [122].

Monitoring Glycemic Control

Measurement of Sugars in Urine and Blood

It was not until 1838 that George Rees, a physician in London (Guy's Hospital), definitively isolated sugar from the blood of a patient with diabetes [172, 173]. In the mid-1840s, Trommer and Fehling independently reported chemical methods for the detection of sugar in the urine based on its reducing properties [174, 175]. Indeed, a French physician Edme Jule Maumene developed the first strip test with a wool-impregnated stannous chloride reagent, which could rapidly detect the presence of sugar [176]. Before that time, identification of sweet urine was a matter for the ants and the tastebuds [177].

In 1908, Stanley Benedict developed a more easily utilizable, quantitative test using a solution of copper sulfate combined with other agents which changed color when heated. Named Benedict's solution, this was the first clinical laboratory glucose test to come into full use. It was modified by others for use in urine and blood and eventually reformulated by chemists from Ames Laboratories into a solid and compact form, the Clinitest tablet, which did not require heating. Clinitest offered people with diabetes a semiquantitative understanding of their urine glucose excretion and was made available for patient use in 1945 [178].

There was a gradual switch in reagent use from those relying on chemical reduction and color change to those dependent on a chromogen-linked enzymatic reaction (initially glucose oxidase) to measure urine and then blood glucose. However, blood glucose test strips were developed by Miles (Ames) laboratories and Boehringer Mannheim for home use only in the late 1960s and glucose meters in the 1970s. This changed the focus of self-glucose monitoring from urine glucose "spilling" to actual blood glucose measurements.

Quantitative Point of Care Blood Glucose Tests

The first of these tests, introduced in 1964 by the Ames company, was the Dextrostix, a strip impregnated with glucose oxidase and other active reagents that changed color when a drop of blood was placed on the test area. This strip and others required careful timing and then washing with water before reading a color change. If used meticulously, they were relatively accurate at approximating blood glucose within a wide range (40–250 mg/dL) [179]. The same company introduced a reflectance meter a few years later. This meter was also relatively accurate when used precisely [180].

These and similar prototype operator-dependent strips and devices (1970s) [181] gradually improved to the point that it was possible to review multiple, daily, self-monitored blood glucose levels and correlate them with hemoglobin A1c, described below [182]. These devices also led to the availability in 2004 of subcutaneous continuous glucose monitoring (CGM) devices that measure glucose in an extracellular fluid using electrochemical detection [181]. Almost 50% of children in the developed world use continuous subcutaneous insulin infusion (CSII) [183] and over 60% use CGM either linked with CSII or separately [184]. With the increasing ease of these devices, they are becoming the benchmarks for diabetes management.

Measurement of Glycated Hemoglobin

Rahbar, Cerami, and others recognized that glycated hemoglobin could serve as a marker for glycemic control, enabling investigators to examine health outcomes in relation to a relatively objective measure of glycemia over time. Sam Rahbar was working as a hemoglobin researcher in Tehran in the 1960s when he noted a fuzzy electrophoretic band associated with Hemoglobin A in the discarded blood of a woman with diabetes. He quickly found

the same band in multiple people with diabetes [185]. As a research fellow in New York at the Albert Einstein College of Medicine, he collaborated with an experienced hemoglobin researcher, Dr. Helen Ranney (1920–2010). They termed this new finding HbA1c and speculated that the unknown component of the hemoglobin was an amino sugar [186]. Ranney continued these studies with others in her laboratory. In 1971, she and colleagues noted that the amount of the unusual hemoglobin varied between patients with diabetes, though it did not correlate with complications or other disease characteristics [187].

Within a few years, Anthony Cerami, a hematologic investigator at the Rockefeller Institute, in collaboration with diabetology colleagues, demonstrated in a small study that HbA1c correlated with glycemic control [188]. Other investigators, notably at the University of Chicago and Harvard University, performed similar studies so that by 1980 it was clear that HbA1c could be used as a marker for glycemic control [189, 190]. HbA1c became the major marker for glycemic control employed in the DCCT trial [191].

Continuous Glucose Monitoring and the Insulin Pump

In the early 1960s, Arnold Kadish, a physician working at Loma Linda University, with the assistance of engineers from the Pacific Telephone and Telegraph Company, developed a closed-loop device for blood glucose control using a double lumen autoanalyzer to measure blood glucose linked to an intravenous insulin infusion pump. Although it worked, from transcripts of comments at a presentation to an artificial organ society, it was considered so bulky, worn as a backpack, and complicated, that it was never commercialized [192, 193].

The Biostator, developed in 1974, was a large desk-sized device that used computerized algorithms to infuse intravenous insulin based on sampled blood glucose. Because of its size and complexity, it was used in research studies but was never adapted to long-term clinical use [194, 195]. Development of CSII techniques then separated from development of continuous glucose monitors until the methodology for measurement of subcutaneous tissue fluid glucose became stable.

A number of investigators, including John C. Pickup in the UK and **William Tamborlane** at Yale, adapted available, rather cumbersome medical infusers to the subcutaneous infusion of insulin via pumps, finding improvements in both diabetes control and, to some degree, patient satisfaction in children and adults [196, 197]. Infusion pumps have become smaller and easier to use and are now the standard of care for diabetes management in the developed world [173, 198].

Beta-Cell Insulin Therapy

Subcutaneously injected or infused insulin, while effective, is intrusive and non-physiologic, spurring the search for a more physiologic source of insulin, initially with pancreas transplantation. The first transplant was performed in 1966 in Minnesota by a group led by Fred Goetz [199]. Over subsequent years, success rates increased dramatically with improvements in immunosuppression and surgical techniques. Because of the greater success when performed together with a kidney transplant, this surgery is very rare in children. To overcome some of these disadvantages, islet-cell transplantation was pursued with cadaver islets infused into the portal vein, resulting in insulin delivery into the liver. The concept is almost half a century old with current techniques based on modification of the work by Paul Lacy in the 1960s [200]. In 1972, Ballinger and Lacy reported the first reversal of diabetes in rodents by transplanting islets [201]. This work paved the way for the first successful human islet transplantation by Thomas Starzl's (1926–2017) group in Pittsburgh in 1990 [202]. At first, success was limited, but a high proportion of grafts now have long-term survival and insulin secretory capacity as a result of modifications to the isolation of islets and immunosuppression regiments, as reported in large cohorts [203–205].

Successful long-term survival and insulin secretion require adequate islet numbers, immunosuppression, and vascularization of the islets, as well as a variety of favorable host characteristics. The first major advance was in 1988 when Camillo Ricordi developed an automated method of pancreas dissociation [206]. Another milestone was the development of the Edmonton protocol in 2000 for more successful and less damaging immunosuppression than previously used [207]. The field has progressed gradually, but challenges remain. Islet transplantation remains a relatively uncommon procedure in the USA, although numbers and successes are growing.

Conclusion

The discovery and sequencing of insulin and its receptor unlocked insights into both common and rare diseases. We have come a long way from the first human injection of animal insulin to the current possibility of engineered cells that make insulin for the treatment of diabetes perhaps by induced human pluripotent stem cells [208]. However, optimism is tempered by inequities

in access to insulin, which is one of the most expensive components of diabetes care. Multilevel barriers in manufacturing, approval, pricing, supply and prescribing practices limit access to this life-saving therapy [61]. Limited studies have examined the feasibility of alternative insulin management strategies in low- and middle-income countries [62]. In addition to lack of insulin, inadequate access to blood glucose measurement, HbA1c testing, and health care generally impair the ability to diagnose and manage T1D. The World Health Organization updated its essential medications list in 2021 to include long-acting insulin analogs, in addition to human insulin and NPH, to lower prices and improve availability [63]. As improvements in management accelerate, we need to ensure equitable access to insulin and other management tools globally.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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