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100 years of insulin: celebrating the past, present and future of diabetes therapy

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Abstract

The year 2021 marks the centennial of Banting and Best's landmark description of the discovery of insulin. This discovery and insulin's rapid clinical deployment effectively transformed type 1 diabetes from a fatal diagnosis into a medically manageable chronic condition. In this Review, we describe key accomplishments leading to and building on this momentous occasion in medical history, including advancements in our understanding of the role of insulin in diabetes pathophysiology, the molecular characterization of insulin and the clinical use of insulin. Achievements are also viewed through the lens of patients impacted by insulin therapy and the evolution of insulin pharmacokinetics and delivery over the past 100 years. Finally, we reflect on the future of insulin therapy and diabetes treatment, as well as challenges to be addressed moving forward, so that the full potential of this transformative discovery may be realized.

In 2021, the world celebrates the 100th anniversary of the discovery of insulin, a treatment that transformed type 1 diabetes from a once-fatal diagnosis into a chronic, medically manageable condition. Beyond its immediate therapeutic impact, insulin has served as the

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centerpiece for incredible advances in the fields of crystallography, molecular biology, prohormone processing, autoimmunity, physiology, and precision health and genetics, while forming the basis for four Nobel Prizes. In honor of this centennial, we commemorate the unlikely scientific journey that led to insulin's discovery, chronicle the subsequent molecular characterization of the insulin molecule, which has permitted new insulin-based therapeutics, and describe the parallel clinical discoveries that have forged our contemporary understanding of diabetes classification and etiology.

The discovery of insulin

The events surrounding the discovery of insulin are well chronicled. Michael Bliss summarized it perfectly in his 1982 history describing them as “richly dramatic”, both for the “medical miracle” of resurrecting people near death by a “magical elixir of life” and for the incredible scientific journey that ended with the successful extraction of pancreatic insulin and its rapid clinical use^{1,2}. The story's dramatic arc is one woven together by stubborn determination, numerous experimental failures, recurrent serendipity and, ultimately, disputed academic credit. At its center is a pair of unlikely protagonists, Frederick Banting, a surgeon with no apparent formal research experience, and Charles Best, a medical student who won a coin toss for the assignment to work with Banting on a summer research project. After reading an article on the pancreas, Banting appealed to and ultimately received support and advice from J. J. R. Macleod, a Professor of Physiology at the University of Toronto, to begin a project with a simple premise. He proposed to perform surgical ligation of the canine pancreatic duct to isolate the organ's internal secretions^{3–8}. He aimed to use these secretions for the treatment of diabetes.

At the time Banting and Best began their experiments in May 1921, diabetes was understood to be a disease of the pancreas. The name ‘diabetes’ was coined by Demetrius of Apamea around the first century BC based on the Greek term *diabainein* meaning ‘siphon’ due to the symptoms of polyuria and polydipsia⁹. In the 1600s, ‘mellitus’ was added to indicate that urine sweetness differentiated this condition from other causes of polyuria, with the idea that this sweetness might be linked to a similar finding in the blood¹⁰. However, it took nearly another century to link the polyuria and polydipsia of diabetes mellitus with excessive glucose in both the blood and urine¹¹. The first working evidence that the pancreas controlled carbohydrate metabolism would not come until 1889, when German scientists Oskar Minkowski and Joseph von Mering performed pancreatectomies on dogs who then developed hyperglycemia and diabetes¹². Almost 20 years before Minkowski and von Mering's seminal work, the first detailed histologic studies of the pancreas were published by Paul Langerhans, as a medical student. His meticulous work described nine different cell types that formed numerous “cell heaps” scattered throughout the gland¹³. The French scientist G. E. Laguesse would revisit pancreas histology in 1893 and name these collections the “îlots de Langerhans”^{14,15}. The term ‘insulin’ was subsequently coined in 1909 by the Belgian scientist J. de Meyer to describe the still-speculative internal secretion of the pancreas thought to be capable of regulating blood glucose¹⁶. At the time experiments were beginning in Toronto in the summer of 1921, a handful of other scientists throughout the world were already pursuing the goal of harnessing this mysterious substance for therapeutic use⁴.

Whereas others failed or, in the case of the Romanian scientist N. C. Paulesco, would have their work interrupted by World War I (ref. ⁴), the Toronto group in a mere 9 months successfully isolated insulin from the pancreas. They would go on to prove that the pancreatic extract regulated blood glucose levels and urinary glucose excretion by reinjecting it into pancreatectomized dogs, while keeping the longest living of these dogs, Marjorie, alive for more than 70 days. James Collip, a biochemist from the University of Alberta, on sabbatical at the University of Toronto, joined the team late in the fall of 1921 and played a critical role in developing methods to reliably isolate insulin from the pancreas using alcohol extraction. The first documented patient to receive insulin was 14-year-old Leonard Thompson. He received his first injection in January 1922, at a time when he, by all accounts, was near death. As reports of his treatment spread throughout North America, the team in Toronto received a growing number of desperate appeals from patients and their physicians for the new therapy. They struggled to scale up the production to reach this growing demand. Ultimately this problem was solved through a partnership with the pharmaceutical corporation Eli Lilly and Company in Indianapolis, Indiana. Scientists at Lilly optimized methods of isoelectric precipitation enabling the extraction of large quantities of insulin from porcine pancreata, allowing it to be purified for commercial distribution.

The capability for insulin purification quickly spread to physicians and scientists beyond North America. At a private dinner in 1922, Elliot Joslin shared the news with the Nobel Prize-winning Danish scientist August Krogh and his wife Marie Krogh, who had recently been diagnosed with adult-onset diabetes. The Kroghs extended their trip by several days to visit Macleod in Toronto, obtained a license to bring the team's insulin purification protocol to Europe, and immediately began production of insulin following their return to Copenhagen (serving as the starting foundation for what eventually became Novo Nordisk)¹⁷.

By the end of this incredible journey, the team in Toronto would be deeply fractured by conflict over who deserved scientific credit for the discovery of insulin. However, to ensure access of this lifesaving drug to patients with diabetes, the team agreed to sell their patents back to the University of Toronto for the price of CAN\$1. Ultimately Banting and Macleod were awarded the 1923 Nobel Prize in Physiology or Medicine, with Banting sharing his portion of the award with Best, and Macleod doing the same with Collip^{4,18}.

Advances in the understanding of diabetes pathophysiology.

The transformative discovery of insulin, in part, represented an inevitable culmination of a body of work performed by many investigators over many years (Fig. 1). The evolution of our understanding of diabetes pathophysiology has similarly occurred due to the collective observations of numerous clinicians and researchers. Before the clinical availability of insulin, astute observers delineated subgroups of affected individuals based on age of presentation, body habitus and survival on low-carbohydrate diets¹⁹. Once insulin therapy was available, clinicians related these differences to insulin requirements, with insulin-insensitive patients usually presenting with symptoms later in life, in association with obesity and a more insidious presentation^{20,21}. Those who were more sensitive to

insulin often presented at younger ages and required smaller doses of insulin to suppress urine glucose and become hypoglycemic²². Direct comparison of forearm arteriovenous glucose gradients after simultaneous glucose and insulin administration showed differences in lean, young patients with diabetes compared to older, overweight patients²³. These findings suggested that differences in glucose gradients may be related to forearm muscle resistance to insulin action and that those with diabetes could be separated into distinct subgroups—the first with disease resulting from insulin insufficiency and the second with disease occurring due to insulin insensitivity²³.

In the 1950s, the ability to quantify circulating insulin allowed for confirmation of insulin deficiency in certain groups of patients. Initial work used bioassays demonstrating that compared to human plasma from older obese females with nonketotic hyperglycemia, human plasma from young, ketotic patients with diabetes was unable to lower blood glucose values when injected into diabetic rats²⁴. Similarly, the extractable insulin content of pancreata was tested for its ability to induce mouse seizures. These experiments showed that pancreatic insulin was almost undetectable in young people with diabetes. This was in contrast to the nearly ~50% reduction observed in older people with diabetes relative to nondiabetic controls²⁵. Rosalyn Yalow and Solomon Berson's development of a reliable radioimmunoassay allowed for direct measurement of insulin levels, allowing for the separation of insulin-deficient versus insulin-insensitive diabetes based on measurement of circulating insulin²⁶. Yalow was awarded the 1977 Nobel Prize in Physiology or Medicine for this seminal work, becoming only the second woman to earn this award.

In search of a simple binary classification system, multiple naming iterations would be trialed, including groups I and II; types I and II; insulin sensitive and insensitive; insulin dependent and noninsulin dependent; and diabetes gras (fat) and diabetes maigre (thin)^{3,27,28}. Still the actual etiologic basis for these different disease types remained unclear. Not until the 1950s, following the discovery of an autoimmune basis for other endocrine diseases, did researchers begin to consider autoimmunity as an etiology of insulin-deficient diabetes^{29–31}. Patients with diabetes and an insulin-deficient phenotype were noted to frequently have detectable autoantibodies associated with other autoimmune diseases, including thyroid and gastric antibodies^{32,33}. In animals, injections of anti-insulin serum, or homogenized pancreatic or islet tissues, resulted in development of islet immune lesions, supporting the idea that islets could generate an immune response^{34–36}. Early reports examining small numbers of pancreatic sections from individuals with diabetes had only rarely identified examples of immune cell infiltration into the islet (that is, insulinitis)³⁷. However, in 1965, Willy Gepts analyzed a larger number of pancreatic samples obtained from children who died near the time of clinical diagnosis and showed islets with lymphocytic infiltrates in the majority of autopsy specimens, suggesting a clearer link to an immunologic origin of disease³⁸. These findings in postmortem tissue were ultimately validated by key studies showing autoimmunity using blood samples from living donors. Leukocyte migration assays demonstrated that individuals with type 1 diabetes exhibited evidence of anti-pancreatic cell-mediated immunity². In a now famous 'eureka' moment, in 1974, Franco Bottazzo, a research fellow in Deborah Doniach's laboratory in London, was the first to successfully visualize islet cell antibodies using indirect immunofluorescence, thereby confirming the presence of antibodies reactive to the islet. During experiments

originally designed to support his thesis work on Addison's disease, he observed that pancreatic islets "lit up" after incubation with sera from some patients with polyendocrine autoimmunity, most of whom had or would go on to develop diabetes^{3,5}. These findings would quickly be confirmed by multiple groups around the world³.

By the end of the 1970s, this work led to the recognition that immune-mediated loss of insulin-secreting cells was the cause of insulin-dependent diabetes³. In parallel, development of techniques to measure insulin-mediated glucose disposal allowed for direct confirmation of insulin resistance in individuals matching a noninsulin-dependent diabetes phenotype^{39–41}. Based on these findings, in 1979 the National Diabetes Data Group proposed classifying diabetes using the terms employed today: type 1 (insulin dependent), type 2 (noninsulin dependent), and 'other' denoting forms of disease not fitting into either of these two categories⁴².

Human cohorts provide a contemporary understanding of diabetes

pathophysiology.—New animal models of spontaneous disease^{43,44} and improvements in immunologic, metabolic and genetic phenotyping in human cohorts have continued to shape our understanding of type 1 and type 2 diabetes over the past half-century. The widely adopted 1986 Eisenbarth model suggested that type 1 diabetes was a chronic autoimmune disease, with genetically predisposed individuals encountering a hypothetical triggering event that activated islet autoimmunity, yielding progressive beta cell destruction and insulin deficiency⁴⁵. Although a genetic contribution to diabetes was clear based on increased prevalence among family members, analyses of kindreds were limited by lack of a reliable biomarker for 'pre-diabetes', as well as a confusing picture based on different inheritance patterns, disease presentations and phenotypes, which also pointed to environmental exposures as contributors^{6,43–45}. A theme of early twin studies indicated >90% concordance of diabetes in those diagnosed at older ages (that is, type 2 diabetes) and approximately 50% concordance of diabetes occurring in children and young adults (that is, type 1 diabetes)^{8,46,47}. The description of the critical role of human leukocyte antigen (HLA) antigen-presentation genes in the transplantation setting⁴⁸ was followed with the association of these genes with autoimmune diseases including ankylosing spondylitis, multiple sclerosis and type 1 diabetes in the early 1970s (ref. ⁶). To this day, a standout feature of many autoimmune diseases including type 1 diabetes is that a small number of HLA class 2 alleles, critical for antigen presentation by the immune system, explain a large proportion of disease heritability.

In the 1990s, linkage analysis of sibling pairs affected by type 1 diabetes identified an area on chromosome 11p15 (ref. ⁴⁹) that was subsequently mapped to a region upstream of the insulin gene^{50–52} as associated with type 1 diabetes. Subsequent genome-wide linkage and then genome-wide association studies of cases and controls have described more than 60 loci outside the HLA region that also contribute to type 1 diabetes genetic risk⁵³. The majority of variants point towards the role of inflammation and the immune system in type 1 diabetes pathogenesis. More recently, there has been increased focus on whether many of these variants may influence beta cell interactions with the immune system, with over 40% of genes associated with type 1 diabetes being expressed in the islet or beta cell. Coupled with molecular studies in human islets and mouse models of disease, these

genetic associations highlight an ongoing dialogue as to whether beta cell or immune system abnormalities are the key driving factor in the pathogenesis of type 1 diabetes^{54–59}, a juxtaposition first described by Bottazzo as the notion of “beta cell homicide or suicide”⁶⁰.

Contemporary and large natural history studies assembled based on HLA genotypes and family history have shown that type 1 diabetes is a heterogeneous disorder and that features beyond autoimmunity, including metabolic factors, exocrine function and environmental exposures, impact progression to clinical disease⁶¹. In addition, birth cohort studies have shed light on the timing of autoantibody development, describing a wide range but a surprising peak incidence of islet autoantibody development at 9 months of age⁶², particularly focused on insulin autoimmunity. A seminal analysis of four different birth cohorts from the USA, Finland and Germany demonstrated that the presence of a single islet autoantibody is associated with a 13% risk of developing type 1 diabetes over 15 years. In contrast, having two or more antibodies is associated with a 70% risk over 10 years of observation and an 84% risk over 15 years⁶³. These and other data led to a proposed modified staging system in 2015. Here, stage 1 diabetes is defined by two or more autoantibodies, while stage 2 diabetes is defined as the presence of multiple autoantibodies and dysglycemia. Stage 3 type 1 diabetes is defined by the progression to overt diabetes based on the American Diabetes Association standards, which include a fasting blood glucose of greater than 7.0 mmol l⁻¹ (1.26 g l⁻¹), a random glucose of >11.1 mmol l⁻¹ (2 g l⁻¹) with symptoms, an abnormal oral glucose tolerance test or a hemoglobin A1C level of >48 mmol mol⁻¹ (6.5%)⁶⁴. This staging paradigm has provided a regulatory and conceptual framework for efforts focused on disease prevention^{65,66} and for mechanistic studies focused on developing stage-specific metabolic and immune signatures.

In parallel, beautifully detailed physiologic studies using intravenous and oral glucose tolerance tests and hyperglycemic clamps have provided further insight into the metabolic underpinnings of type 2 diabetes. These studies have demonstrated that to maintain glucose homeostasis, a feedback loop exists in which decreased insulin sensitivity is tightly associated with increased insulin secretion from the beta cell, with this hyperbolic relationship between beta cell responsiveness and insulin sensitivity termed the disposition index^{67,68}. Natural history studies of cohorts progressing to type 2 diabetes have demonstrated early impairments in insulin sensitivity, which are evident more than 10 years in advance of diabetes development. Initially, beta cell function is increased, maintaining glucose levels at higher but still normal levels and below the diagnostic threshold for diabetes. However, the ability of the beta cell to maintain this response is finite in some individuals. As the beta cells undergo a process of failure that has been linked with a number of molecular processes, including oxidative and endoplasmic reticulum stress, lipotoxicity and dedifferentiation^{69–71}, beginning around 3 years before the onset of diabetes, decreasing insulin secretion and an accelerated rise in blood glucose levels are observed^{72–75}. However, the temporal relationship between changes in insulin secretion and insulin sensitivity continue to be elucidated, as insulin hypersecretion may also contribute to or exacerbate insulin resistance, and has even been documented before insulin resistance in some individuals⁷⁶.

Despite the high heritability observed in twin studies^{46,47}, it took longer to begin to identify the genetic loci responsible for the high concordance observed in twin studies of type 2 diabetes. The first associated loci, in genes including *TCF7L2*, *INSR*, *IRS1*, *GCK* and *KCNJ11* (refs.^{77,78}), were originally identified by linkage or candidate gene studies, and since the turn of the century, increasing size and depth of genome-wide association studies have rapidly expanded the list of associated loci in type 2 diabetes to more than 250 with 400 independent signals⁷⁹. The majority of associated loci are linked to beta cells, supporting the idea that impaired beta cell function is critical to type 2 diabetes pathogenesis^{78,80}. Despite the large number of associated loci, their individual contributions to overall risk are moderate, explaining just under 20% of heritability and highlighting the proportion of ‘missing heritability’ that is still to be fully elucidated. Whereas type 1 diabetes seems to be a discrete entity defined by islet autoimmunity, beta cell destruction and a relatively small group of genes, an outstanding question is whether type 2 diabetes will be resolved into multiple subtypes/clusters defined by genetic associations, mechanisms and phenotype^{81–83} and whether this approach will improve precision intervention and treatment.

Advances in the molecular characterization of insulin.

Soon after the discovery of insulin and in parallel to its application in clinical medicine, there was a steady march to shed light on the molecular characteristics of the insulin molecule. In 1935, a research fellow, Dorothy Crowfoot Hodgkins, took the first diffraction images of insulin crystals⁸⁴. She would continue her work on the insulin molecule on and off throughout her career, ultimately solving the crystal structure in 1969 and showing that insulin was a hexamer composed of three heterodimers⁸⁵. Hodgkins earned the Nobel Prize in Chemistry in 1964 for her pioneering work in crystallography, all while battling her own autoimmune condition, rheumatoid arthritis⁸⁶. In the early 1950s, Frederick Sanger determined the amino acid sequences of the A and B chains of insulin^{87–90}. By 1955, he would demonstrate the position of the two disulfide bonds linking the A and B chains and the intrachain disulfide bond within the A chain, and in 1958, he was awarded the Nobel Prize in Chemistry^{91–93}. In addition to being the first protein that was successfully sequenced, insulin was the first molecule to be characterized as a prohormone. In another moment of serendipity, Donald Steiner had the opportunity to study an insulinoma tumor removed from a patient at the University of Chicago in 1965. While analyzing extracts of the tumor and in subsequent experiments, Steiner identified proinsulin as the larger single-chain precursor of insulin, established proinsulin as the origin of C-peptide, and showed that insulin and C-peptide were secreted from the beta cell in equimolar ratios^{94,95}. In 1968, Ronald Chance at Lilly Research Laboratories in Indianapolis published the porcine sequence of the proinsulin molecule⁹⁶.

These structural accomplishments would pave the way for studies describing the interaction of insulin with the insulin receptor⁹⁷, and would serve as a precursor to our understanding of monogenic forms of diabetes resulting from mutations in the insulin gene, which yield distinct phenotypes based on structural impacts. Altered interaction of structurally abnormal insulin with the insulin receptor leads to altered insulin action, hyperinsulinemia and adult-onset diabetes with autosomal dominant inheritance⁹⁸. In contrast, recessive

mutations impacting insulin biosynthesis result in neonatal diabetes⁹⁹. Heterozygous mutations can also impair the normal folding of insulin precursors, yielding abnormal molecules that act in a dominant-negative fashion to impair the exit of all proinsulin from the endoplasmic reticulum¹⁰⁰. This initially causes insulin deficiency, followed by severe beta cell endoplasmic reticulum stress and apoptosis^{100,101}. Molecular studies defining the biologic impact of mutant *INS* gene-induced diabetes of youth (MIDY) mutations have also yielded valuable insights into the normal molecular pathways of insulin biosynthesis, precursor processing and transit through the secretory pathway¹⁰¹, recently highlighting how certain conserved residues are critical for normal insulin folding¹⁰². Finally, decades after Steiner's original identification of proinsulin as insulin's precursor, increased proinsulin secretion relative to insulin or C-peptide is accepted as a serum proxy for beta cell stress and dysfunction and a predictive biomarker for both type 1 and type 2 diabetes^{103,104}.

Advances in the clinical use of insulin.

The molecular characterization of insulin would also dramatically shape diabetes therapy. After the first clinical use of 'regular' insulin for patients, the pancreatic extract was further purified, the source of insulin moved to pork and later beef pancreas, and the concentration was increased from the original commercially available U-5 insulin (for example, 5 units ml⁻¹) to U-10, U-20, U-40 and U-80 preparations¹⁰⁵. Later, in the early 1970s, the most common insulin preparation became U-100. More concentrated insulins also became available, and were employed for people with severe insulin resistance (U-200, U-300 and U-500); the first was U-500 beef regular insulin, which was developed in 1952.

Although exogenously administered regular insulin was lifesaving, its pharmacokinetics did not mirror that of endogenously produced human insulin. Administered insulin molecules self-associate into hexamers, which must dissociate into dimers and then monomers before entering the circulation, with typical delays of 60–90 min from injection to peak action. This contrasts with the circulating endogenous insulin peak action of approximately 15–30 min after the start of food ingestion. In addition to the delay in action, these first insulins were all short acting (Fig. 2) and required multiple injections per day.

Towards a goal of reducing the need for multiple daily injections, the first long-acting insulin was developed in the 1930s by H. C. Hagedorn. It was a suspension protamine zinc insulin that was based on the discovery that insulin action could be prolonged by adding protamine obtained from river trout semen¹⁰⁶. The action of protamine zinc insulin lasted 24–36 h. In 1946, Nordisk developed an intermediate-acting neutral protamine Hagedorn insulin that formed microcrystals, could be mixed with regular insulin and lasted 18–24 h. The first 'peakless' basal insulin, known as ultralente (belonging to the lente family of insulins), was developed during the 1950s by employing an extended zinc suspension without protamine¹⁰⁷. Ultralente was mixed with a semilente (an insulin with a different proportion of zinc and a time-action profile slightly slower than that of regular insulin) to make the intermediate-acting lente. However, because these insulins were suspension based, they had variable day-to-day action, complicating their clinical use, and they still required more than one injection a day to provide a basal coverage.

Before the 1980s, all insulin preparations were derived from animal sources. However, with increased clinical demand and tedious extraction processes (for example, more than 23,500 pancreata were needed to make 1 lb of insulin), available supplies were being outstripped¹⁰⁸. Additionally, even with the advent of highly purified monocomponent animal insulin in the 1970s¹⁰⁹, many people with diabetes continued to have allergic reactions to the formulations. A pure, scalable insulin source was needed. Just as there had been a race to isolate insulin 50 years earlier, now teams were using what had been learned in the molecular biology renaissance of the previous decade to produce human insulin using recombinant DNA technology.

Insulin cloning in bacteria was a complicated process¹¹⁰. First, the A and B chains needed to be synthesized (the B chain synthesis required cleaving the peptide into two sections). Then the A and B chains needed to be linked together. Finally, the insulin needed to be harvestable for commercial use, which required breaking off the beta-galactosidase required to insert the insulin into *Escherichia coli* bacteria. In 1978, David Goeddel, Arthur Riggs and their Genentech colleagues working at City of Hope produced the first recombinant DNA human insulin¹¹¹. Subsequently, Genentech and Lilly agreed to commercialize this new insulin and Humulin R and N insulins came to market in 1983. Novolin R (Novo Nordisk) followed in 1991 and Insuman R (Hoechst) in 1997. Although this represented an improvement in source, these insulins were still zinc-based formulations with slower pharmacokinetic profiles than natively secreted insulin.

The 1993 publication of the Diabetes Control and Complications Trial¹¹² and 1998 United Kingdom Prospective Diabetes Study^{113–115} demonstrated definitive relationships between glycemic control and microvascular complications and showed that lower A1cs were associated with higher rates of severe hypoglycemia. These observations spurred efforts focused on improving exogenously administered insulin's pharmacokinetic and pharmacodynamic properties (absorption rate, time to peak and duration of action). This has been accomplished over time (Fig. 2) using recombinant DNA technology and genetic engineering, and adding excipients. Tweaking amino acid sites/composition in the native insulin molecule changed the pharmacokinetics and permitted faster absorption, earlier peak action and faster offset. In 1988 a synthetically designed insulin was produced by replacing the B28 proline with aspartic acid, which favored a molecular conformation leading to rapid dissociation of dimerized insulin chains. The first rapid-acting insulin, insulin lispro (produced by inverting the B29 lysine and B28 proline), came to market in 1996. Next was aspart in 2000, and then glulisine in 2004. An ultrarapid-acting version of insulin aspart was subsequently developed by adding nicotinamide and L-arginine as excipients that improve the insulin's stability and rate of absorption¹¹⁶. An ultrarapid insulin lispro has also been developed by using a prostacyclin analog to enhance vasodilation and absorption and citrate to enhance local vascular permeability.

The first long-acting once-daily basal insulin, glargine, was approved in 2000 (ref. ¹¹⁷). It was designed to have an extended duration of action through amino acid modifications in both chains (A chain A21 asparagine substituted by glycine and B chain elongated by adding two arginines). These changes achieved a prolonged duration by shifting the isoelectric point to make the insulin soluble at an acidic pH but precipitate at the injection

site at a pH of 7.4, allowing for slow dissociation. The next long-acting basal insulin, detemir, was approved in 2005 (ref. ¹¹⁸). Detemir has a fatty-acid (myristic acid) side chain bound to position B29 that facilitates self-association and an affinity for albumin allowing for prolonged duration of action without peaks. Insulin degludec followed a decade later; degludec forms a depot of soluble multihexamers at the injection site giving it an ultralong (>42 h) glucose-lowering effect¹¹⁹.

Improvements in insulin therapy have also been realized by changes in the method of delivery. Initially, insulin was available only through administration via vials and syringes. In 1985 the first insulin pen was launched by Novo Nordisk¹²⁰. More recently developed ‘smart’ insulin pens allow for tracking of insulin dosing, and integration with smartphone applications to provide reminders, integrate with blood glucose data and provide dosing recommendations¹²⁰. Advances in insulin delivery have also included the development of inhaled insulin with a faster onset of action and offset of effect than any of the injected insulins¹²¹. The first, Exubera, came to market in 2006, but was rapidly withdrawn due to poor market uptake. Inhaled technosphere insulin, Afrezza, was launched commercially in the next decade by Mannkind, although cost, limited dosing flexibility and continued concern about pulmonary effects have limited its clinical uptake and use.

Arguably, the most impactful technology-driven advances in insulin delivery have revolved around the technology of continuous subcutaneous insulin infusion using insulin pumps¹²². The first closed-loop insulin pump that incorporated automatic blood glucose sensing was designed by Arnold Kadish in 1963 (ref. ¹²³). It was large (like an “army backpack”) and impractical for daily use. The first bedside computer-controlled closed-loop system, the Biostator, was invented by Miles Laboratory (Elkhart IN) in 1974 (ref. ¹²⁴). During the late 1970s, rigorous testing of insulin pumps began in earnest—leading to the first wearable systems, including the ‘big blue brick.’ By the 1980s, continuous subcutaneous insulin infusion had become a viable alternative means of delivering insulin¹²². In 1983, MiniMed brought the first commercial pump to market. Improvements over the next several decades have included the emergence of new pump models by multiple manufacturers, including tubeless patch pump models, the ability to modify the timing/duration of insulin bolus delivery and improvements in device usability. The development of reliable and accurate continuous glucose monitors allowed for the possibility of integration of glucose data with pump insulin delivery and sparked a flurry of interest to develop safe and effective algorithms for closed-loop systems, notably championed by do-it-yourself movements from the diabetes community itself^{122,125}. Now, increasingly, many pumps employ hybrid closed-loop technologies with automatic insulin dosing by the pump based on continuous glucose readings and trends.

What does the future hold?

In the 100 years since the discovery of insulin, there has been remarkable progress in our ability to treat type 1 and type 2 diabetes, facilitated by an improved understanding of the pathophysiology of the disease and improvements in insulin formulation and delivery. This progress is captured in an impressive series of scientific accomplishments summarized in this Review and shown in Fig. 1, several of them recognized by the most prestigious awards

in Medicine, Physiology and Chemistry. However, the true impact of these achievements is best illustrated by the voices of patients who have seen dramatic changes in the management of their type 1 diabetes (Fig. 3).

What do the next 100 years hold for insulin and those who depend on it (Fig. 4)? Furthermore and importantly, will treatment with exogenous insulin therapy become another note in the history books? For type 1 diabetes, this goal is a centerpiece of clinical trials testing disease-modifying interventions, including work that is ongoing in several large networks such as Type 1 Diabetes TrialNet, the Immune Tolerance Network and INNODIA. In 2019, following a nearly three-decade search for successful disease prevention, the Type 1 Diabetes TrialNet study of the anti-CD3 antibody teplizumab showed that a single 14-day course of drug could delay the onset of clinical diabetes (that is, stage 3 type 1 diabetes) by a median of 32.5 months in high-risk multiple-autoantibody-positive individuals with dysglycemia (that is, stage 2 type 1 diabetes)^{126,127}. Results from this seminal study have underscored the importance of identifying the correct therapeutic window for intervention, but have also raised the practical question of how to identify at-risk individuals outside a research setting. In this regard, population-based screening is now being increasingly performed in several countries and regions, and is based on autoantibody measurement and, in some cases, assessment of genetic risk. Genetic risk stratification has focused on assessment of HLA risk or more recently calculation of polygenic genetic risk scores that sum the effects of a large number of variants¹²⁸. The education and anticipatory guidance provided as part of these programs have been shown to significantly reduce the risk of ketoacidosis at the onset of stage 3 type 1 diabetes¹²⁹. However, additional research will be needed to identify the ideal timing and frequency of screening and how to prioritize at-risk individuals for interventions. For type 2 diabetes, complementary disease-modifying therapies that may reduce or eliminate the need for insulin administration have also represented a rapidly expanding field of interest^{130–132}.

In addition to efforts focused on disease modification, there are continuing efforts to improve insulin therapies and there is still much to be refined in our approach to exogenous insulin delivery. There is a hope for development of better insulins including: insulins with even faster pharmacokinetics, once-weekly insulin, oral insulin and, ultimately, glucose-responsive ‘smart’ insulins that increase circulating concentrations under conditions of hyperglycemia. Additional technological advancements on the horizon include improved algorithms for automated insulin delivery devices, implantable devices and dual-hormonal systems that combine automated delivery of insulin and glucagon^{133,134}. Finally, there is also considerable interest in developing renewable, cellular sources of insulin through the generation of beta-like cells from either induced pluripotent stem cells or embryonic stem cells. While a beta-like cell with behavior that fully recapitulates the physiology of a normal beta cell is yet to be realized, there has been a steady series of improvements to directed differentiation strategies over the past 20 years^{135–138}. In parallel, a large body of work has focused on developing the ideal cellular niche and encapsulation strategies to support normal patterns of hormone secretion while also protecting these cellular implants from autoimmune destruction^{139,140}. Improvements in insulin delivery and monitoring and alternative cell-based sources of insulin have the potential to broadly impact diabetes

management and will benefit individuals with type 1 and type 2 diabetes, as well as rarer forms of the disease.

Closing.

In the 1920s, having developed a transformative and lifesaving therapy, the Toronto team faced an almost impossible challenge, and they struggled at the outset to produce enough insulin to meet a rapidly growing demand and to distribute insulin in a fashion that was equitable¹. As we celebrate this remarkable centennial anniversary and the subsequent discoveries that have improved life expectancy and quality of life for those with diabetes (Fig. 3), there are continued challenges with accessibility and equity, which have only been exacerbated by advances in diabetes care technology. In a recent analysis of children and adults with type 1 diabetes in the USA, the average cost associated with diabetes totaled nearly US\$800 per month, with nearly 50% driven by pharmacy costs¹⁴¹. Even the most basic component of diabetes management, insulin itself, has become unaffordable for many¹⁴². From 2012 to 2016, the average list price of insulins increased by 14–17% per year in the USA. These increases are often driven by gaps between the list price and the net price ultimately received by manufacturers, which have been largely attributed to rebates and discounts negotiated between stakeholders in a supply chain with poor transparency¹⁴³. As members of the Toronto team arranged to sell their patents for insulin back to the University of Toronto for CAN\$1, Banting is reported to have remarked, “Insulin belongs to the world, not to me.” Thus, while we envision a future of possibilities for those who require insulin to survive, it is important that we not forget Banting’s altruism and become complacent to this most basic and fundamental challenge of the present. Only once equal access for patients around the globe is established will the remarkable achievements surrounding insulin over the past century truly realize their greatest impact^{144–150}.

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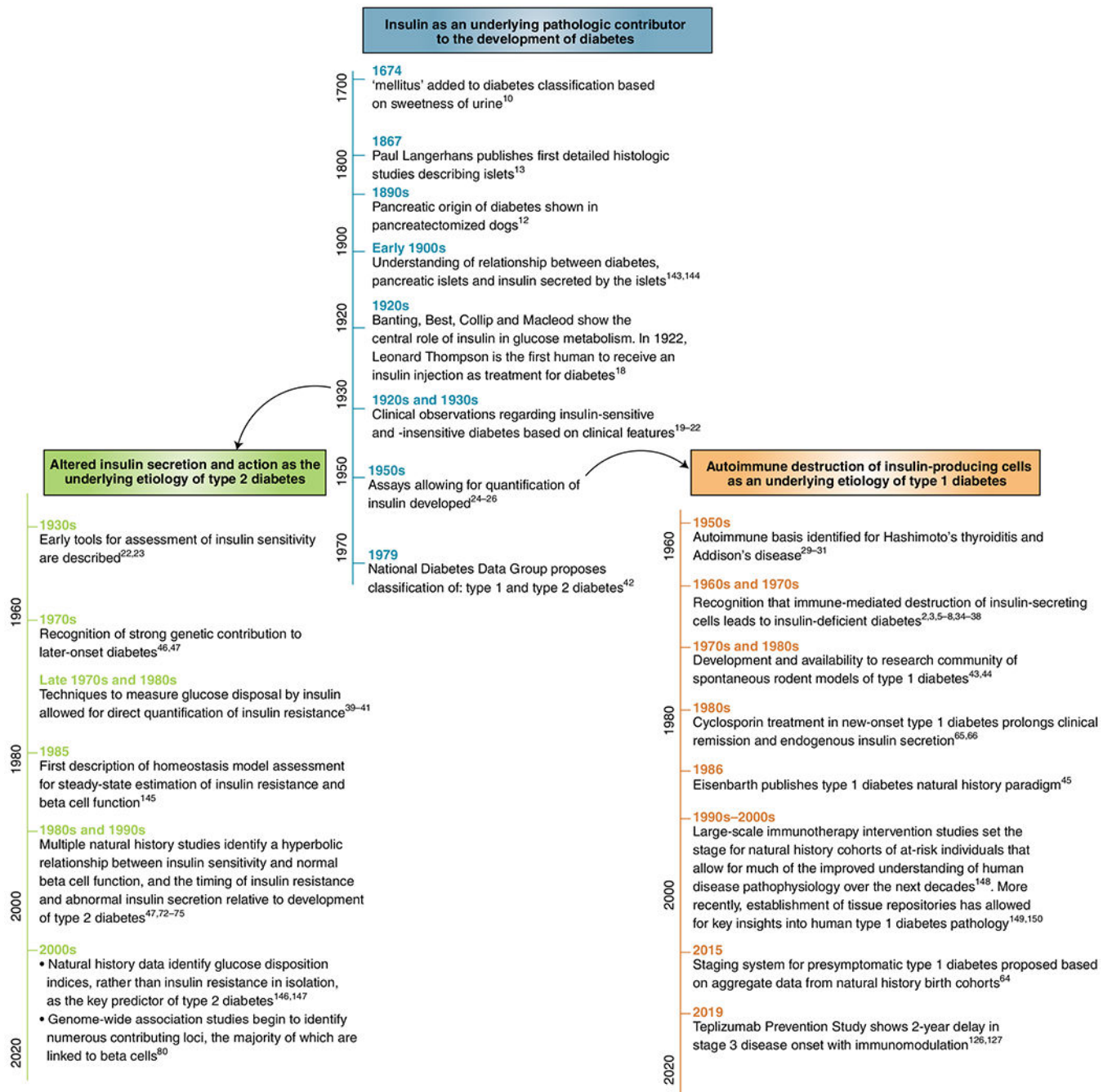


Fig. 1 | A timeline of key discoveries in our understanding of insulin and diabetes pathophysiology.

Shown in the main branch of the timeline are key discoveries in our understanding of insulin as a central contributor to diabetes pathophysiology^{10,12,13,18-22,24-26,42,143,144}.

Included in the left branch of the timeline are important milestones that have enabled the understanding of type 2 diabetes as a disease of impaired insulin secretion and action^{22,23,39-41,46,47,67,72-75,80,145-147}. The right branch highlights notable discoveries that have led to the understanding of type 1 diabetes as an autoimmune disease^{2,3,5-8,29-31,34-38,43-45,64-66,126,127,148-150}.

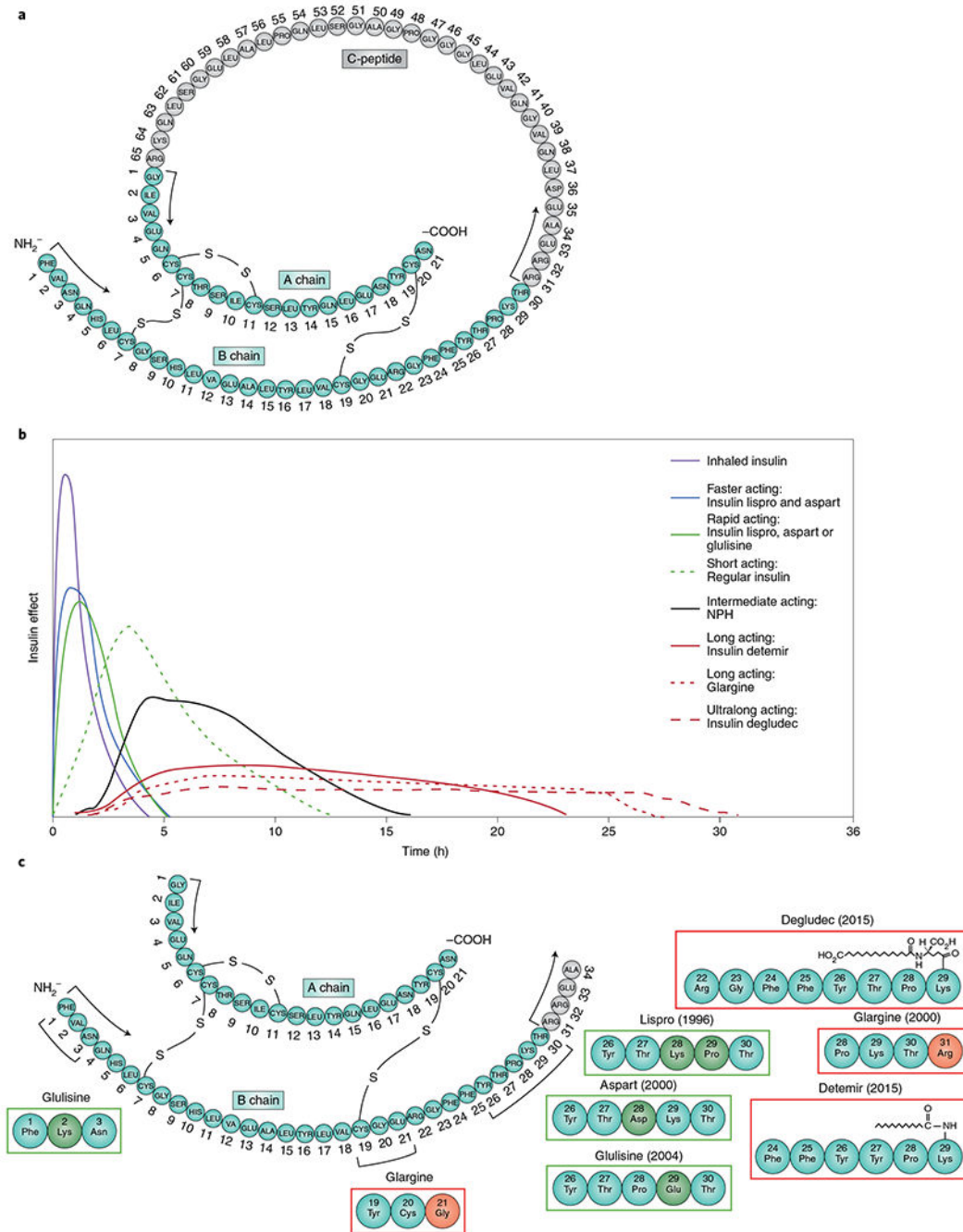


Fig. 2 |. The evolution of improvements in insulin pharmacokinetics.

a, The native structure of human proinsulin. **b**, Representative pharmacokinetic profiles of available insulins administered subcutaneously. **c**, Structural changes of insulin analogs and years of introduction in the USA including rapid-acting insulin analogs (green boxes) and long-acting insulin analogs (red boxes)^{96,106,151–154}.

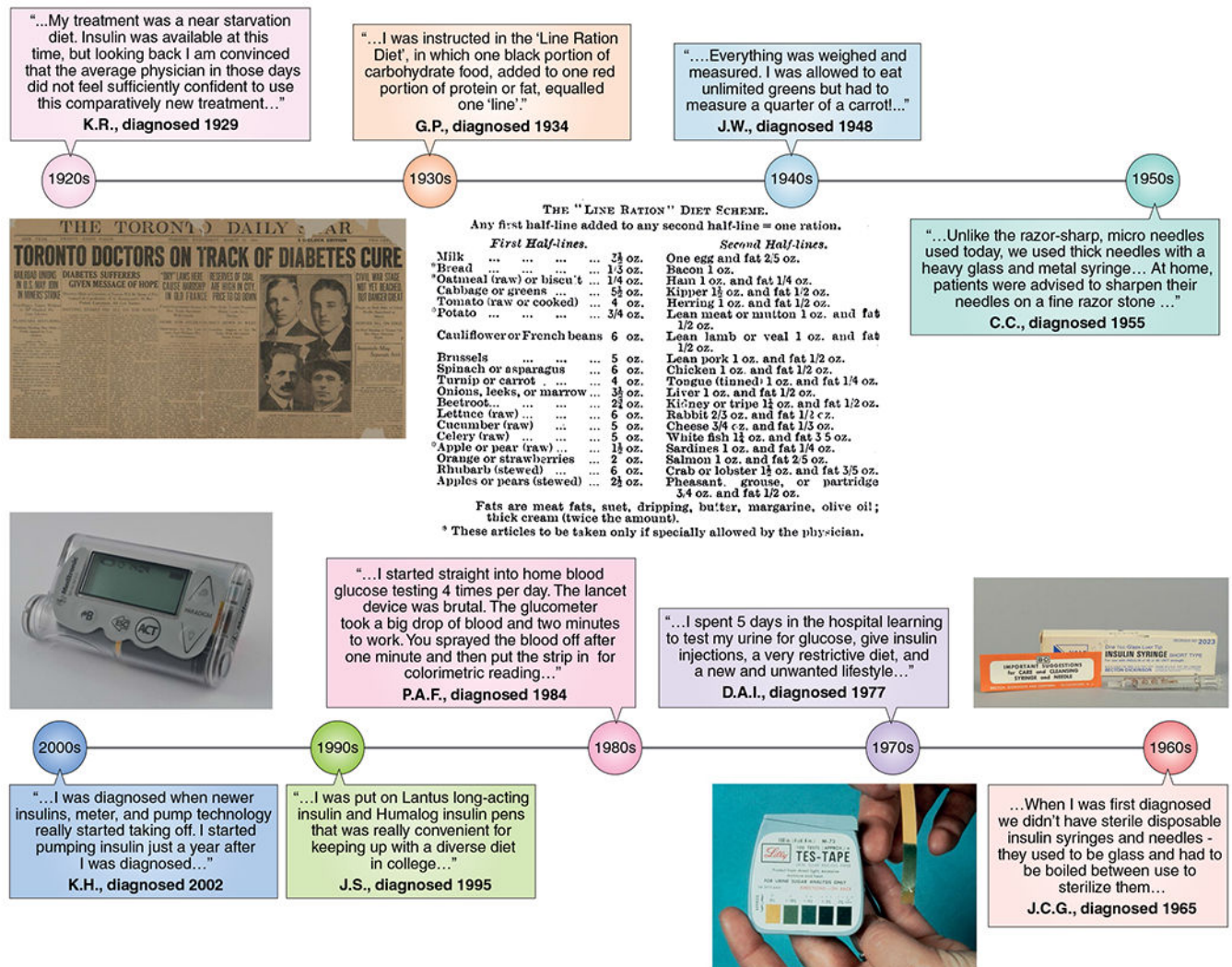


Fig. 3 |. Advances in diabetes management viewed through the lens of individuals with type 1 diabetes.

The full names of contributing individuals for the years 1965–2006 are included in the Acknowledgements. The quotes from K.R. (diagnosed 1929) and G.P. (diagnosed 1934) are from ref. ¹⁵⁵. The quote from J.W. (diagnosed 1948) is from ref. ¹⁵⁶. The quote from C.C. (diagnosed 1955) is from ref. ¹⁵⁷.

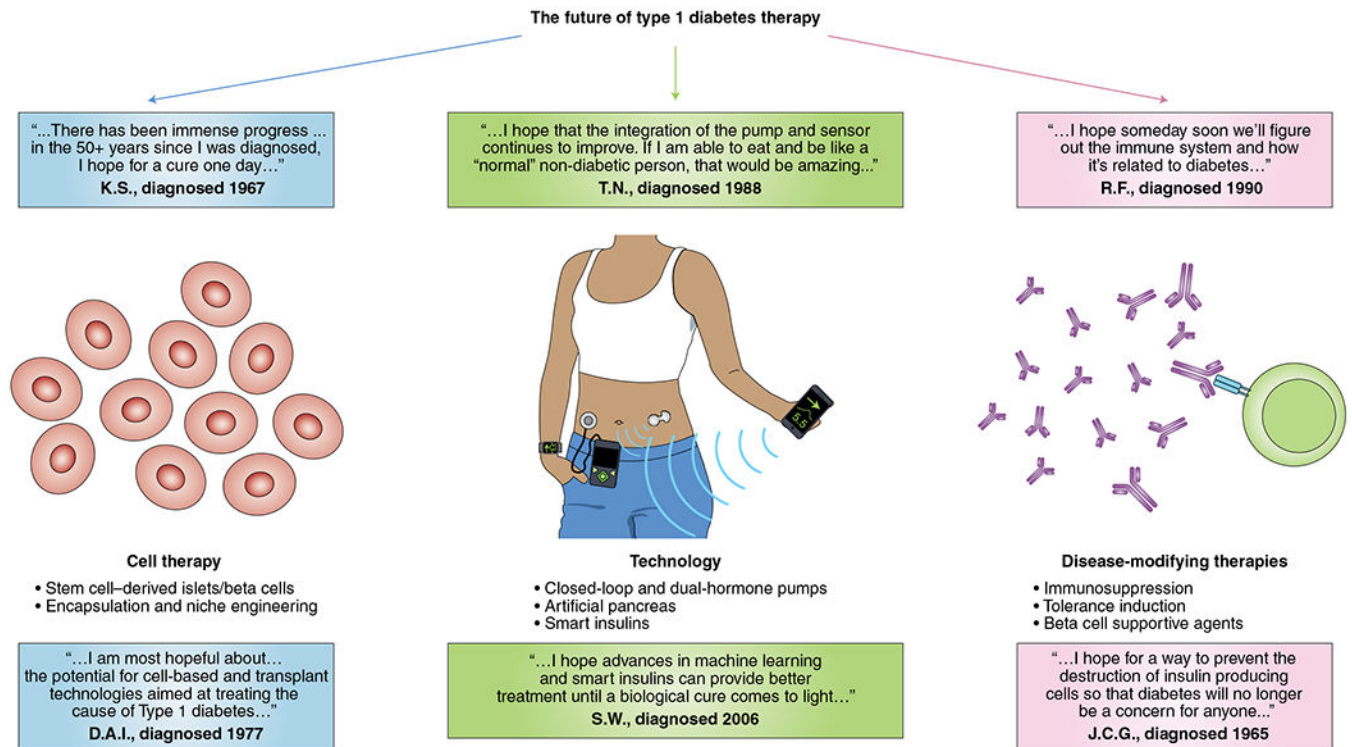


Fig. 4 |. The future of insulin and diabetes therapy.

The future of diabetes therapy and prevention includes efforts focused on: the development of a renewable, cellular source of insulin; improvements in technology, including better insulins and novel insulin delivery platforms; and disease-modifying therapies, including immune-modulating therapies and beta cell supportive agents. Quotes are included from individuals who depend on insulin, expressing their hopes surrounding the future of diabetes therapy. Image originally created using biorender.com and AutoDesk SketchBook.