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# Celebration of a century of insulin therapy in children with type 1 diabetes

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**ABSTRACT**

Insulin is the key anabolic hormone of metabolism, with clear effects on glycaemia. Near-complete insulin deficiency occurs in type 1 diabetes (T1D), the predominant form affecting children, and uniformly fatal until the discovery of insulin. By the early 20th century, it was known that T1D was caused by the lack of a factor from pancreatic islets, but isolation of this substance proved elusive. In 1921, an unusual team in Toronto comprising a surgeon, a medical student, a physiologist and a biochemist successfully isolated a glucose-lowering pancreatic endocrine secretion. They treated an emaciated 14-year-old boy in 1922, restoring his health and allowing him to live for another 13 years. Thus began an era of remarkable progress and partnership between academia and the pharmaceutical industry to produce drugs that benefit sick people. The Toronto team received the 1923 Nobel Prize, and more Nobel Prizes for work with insulin followed: for elucidation of its amino acid sequence and crystalline structure, and for its role in the development of radioimmunoassays to measure circulating hormone concentrations. Human insulin was the first hormone synthesised by recombinant methods, permitting modifications to enable improved absorption rates and alterations in duration of action. Coupled with delivery via insulin pens, programmable pumps and continuous glucose monitors, metabolic control and quality of life vastly improved and T1D in children was converted from uniformly fatal to a manageable chronic condition. We describe this remarkable ongoing story as insulin remains a paradigm for human ingenuity to heal nature's maladies.

**A BRIEF REPRISÉ TO THE FIRST USE OF INSULIN THERAPY IN 1922**

By the late 19th century, diabetes mellitus (DM) was understood as a disease associated with excess glucose and ketones, 'acid poisoning' of the blood and 'diabetic coma'. Because the urine of people with DM was glucose-rich, it was considered a condition of the kidneys or digestion.<sup>1</sup> In 1889, however, Strasbourgh physicians Joseph von Mering and Oscar Minkowski surgically removed the pancreas from a dog and observed prolific urination, with blood and urine tests confirming diabetes. Thus, the 'pancreatic theory' of diabetes took hold. In 1901, Eugene Lindsay Opie observed from autopsies that DM was associated with destruction of the islets of Langerhans, hence diabetes appeared to involve loss of an unknown pancreatic secretion.<sup>1</sup>

Until 1922, type 1 diabetes (T1D) was an inevitably fatal disease, typically striking in childhood or adolescence. The only treatment that could prolong

life was a low-carbohydrate, low-calorie, starvation diet—the Allen diet—which merely delayed coma and death from ketoacidosis.<sup>1</sup> But this situation was about to change.

**100 YEARS AGO IN TORONTO: FIRST USE OF INSULIN THERAPY**

In 1921, Canadian surgeon Fred Banting persuaded physiology professor John Macleod to allow use of laboratory facilities to pursue a research idea. Banting had read about a patient with pancreatic lithiasis in which the stone had obstructed the pancreatic duct causing acinar cells to atrophy, but with most islet cells surviving. Banting believed previous attempts to isolate the pancreatic endocrine secretion had failed due to its destruction by the exocrine pancreatic enzyme trypsin. Banting's idea, therefore, was to ligate pancreatic ducts in dogs to atrophy the exocrine pancreas before removing preserved islet-containing tissue to extract the elusive hormone.<sup>1</sup>

Macleod doubted whether Banting could succeed, as previous attempts to isolate this 'internal secretion' had failed: George Ludwig Zuelzer (1906), E L Scott (1911–1912) and Israel Kleiner (1915) had attempted similar experiments before either the First World War or lack of progress terminated their work.<sup>1</sup> Romanian scientist Nicolae Paulescu developed a pancreatic extract in 1916 that reduced blood glucose in a diabetic dog, but his work was also interrupted by the war. (Ironically, Paulescu published his research in 1921, but never received the attention afforded to the Toronto group, who referenced Paulescu in their publications but, due to mistranslation, underestimated the efficacy of his extract<sup>1</sup>).

Macleod nevertheless gave Banting practical advice, and the assistance of medical student Charles Best, who experimented with extraction procedures while Banting performed the surgery. There were many setbacks, and dogs regularly died from complications before techniques were perfected, but Banting and Best eventually showed that their 'isletin' extract lowered blood and urinary glucose in diabetic dogs, whereas liver or spleen extracts did not.<sup>1</sup> Isletin was also shown to clear urinary ketones in diabetic dogs, and to restore liver glycogen and hence carbohydrate metabolism.<sup>1</sup>

Banting and Best next turned to slaughterhouses as a source of fetal calf pancreata and, following Macleod's advice, modified their extraction method to include alcohol in order to enhance the isletin yield. Biochemist James Collip joined the team and found that the extracts effectively lowered blood



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glucose in healthy and diabetic rabbits—a more practical model than pancreatectomised dogs. The potency of extract batches was standardised, with one unit of isletin defined as the amount that would lower blood glucose in *normal* rabbits to  $\leq 46$  mg/dL ( $\leq 2.5$  mmol/L).

The first human recipient was Leonard Thompson, diagnosed with T1D in 1919. In December 1921, the desperately underweight 14-year-old boy was admitted to Toronto General Hospital. An injection of isletin was given on 11 January 1922, and Thompson's blood and urinary glucose levels declined somewhat, but a ketone test remained strongly positive. Due to impurities in the extract, Thompson suffered an allergic reaction and sterile abscess at the injection site. Soon afterwards, however, Collip discovered that the active component of the pancreatic extract precipitated at a certain alcohol concentration, allowing purer extracts to be made. On 23 January, Thompson began another series of treatments with this more potent extract; ketonuria ceased, glycosuria declined, and he became brighter and more active. Thompson eventually died in 1935 at the age of 27 years, his life extended by 13 years.<sup>1</sup>

By February 1922, six more patients had been treated, all with favourable results.<sup>1</sup> In April, the Toronto group published summaries of their work,<sup>2</sup> renaming their extract 'insulin'. The way had been paved for the lives of millions of children worldwide to be transformed. The 1923 Nobel Prize for Physiology or Medicine was awarded to Banting and Macleod, but tensions

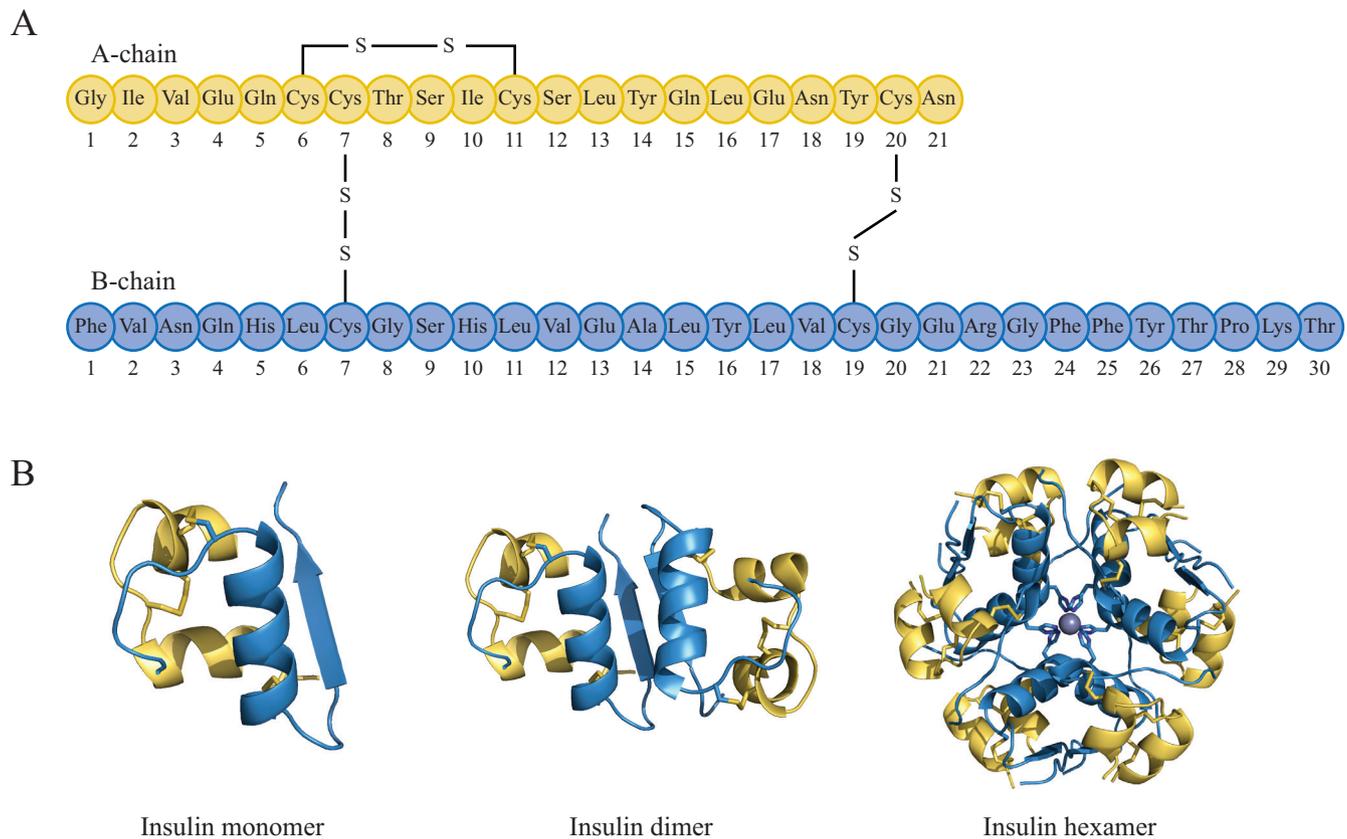
emerged within the Toronto group, particularly between Banting and Macleod, who split their prize money, respectively, with Best and Collip.<sup>1</sup>

### FURTHER ADVANCES IN INSULIN AND DIABETES KNOWLEDGE

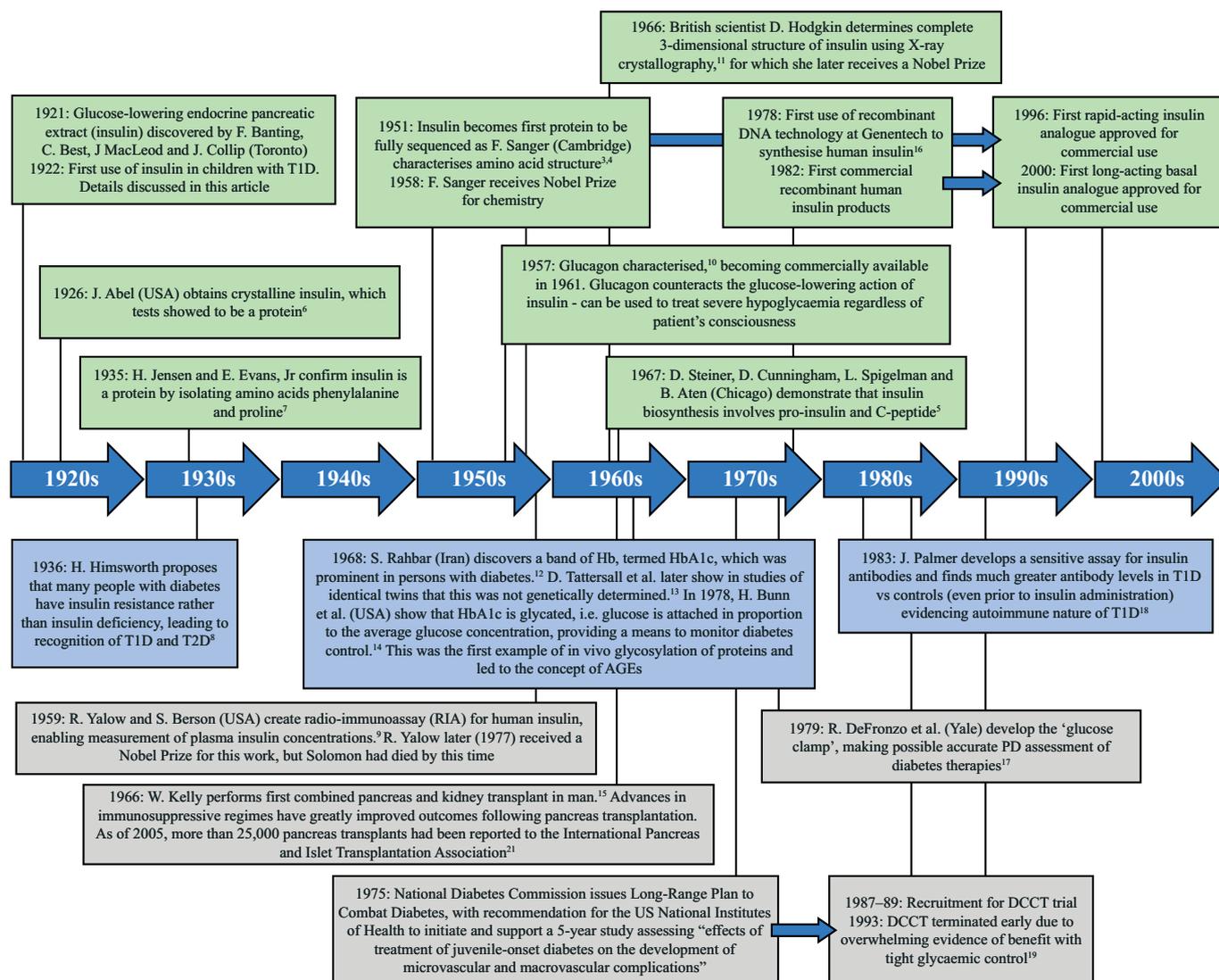
Subsequent development of insulin therapy followed numerous 20th century advances in technology and scientific understanding of insulin, the pathophysiology of T1D and its complications. Insulin was the first protein to be fully sequenced (as a 21-amino acid A-chain linked to a 30-amino acid B-chain by two disulfide bonds; [figure 1](#)),<sup>3,4</sup> by Frederick Sanger in 1951, who received the Nobel Prize in Chemistry for this research. This knowledge later enabled insulin analogues to be developed. Several other key discoveries in diabetes and insulin are summarised in [figure 2](#).<sup>3–19</sup>

### MILESTONES IN MANUFACTURING AND INSULIN THERAPY

Insulin production was first attempted locally in the Connaught Anti-Toxin Laboratories by the Toronto discovery team.<sup>1</sup> Early batches differed in potency, leading to the first hypoglycaemic episodes, then termed 'insulin reactions'. Protein impurities caused various inflammatory injection-site reactions in many patients, and salts in the solution (and reuse of needles) could make injections excruciatingly painful. Production fell short



**Figure 1** (A) Amino acid sequence and structure of human insulin. (B) Three-dimensional structure of insulin. At high concentration, two insulin monomers self-associate to form a dimer, and three dimers (with two zinc ions, shown as grey sphere in 3D hexamer image) can self-associate into hexamers for efficient storage before exocytosis (The blue arrows in the monomer and dimer represent a beta sheet—a secondary structure element in a protein in which amino acids are arranged in an elongated fashion). Adapted from [figure 2](#) in Hirsch *et al*,<sup>26</sup> distributed under the terms of the Creative Commons CC BY license, using illustrations of crystal structures (PDB ID 6S34 and PDB ID 1MSO) determined and provided by Eva Johansson, Novo Nordisk.



**Figure 2** Selected 20th century milestones, following its initial discovery in 1921, in further understanding of the insulin molecule and its physiology (green panels), and of diabetes (blue panels) and its treatment (grey panels). AGEs, advanced glycation end products; DCCT, Diabetes Control and Complications Trial; HbA1c, glycated haemoglobin; PD, pharmacodynamic; T1D, type 1 diabetes; T2D, type 2 diabetes.

of growing demand and patients continued to die from lack of availability, so the Toronto team began a collaboration with US pharmaceutical firm Eli Lilly. The University of Toronto agreed to license insulin production to commercial companies in return for royalties to support research.<sup>1</sup> Eli Lilly developed several manufacturing innovations that enabled increased output of insulin sourced from bovine or porcine pancreata. In 1922, it was discovered that isoelectric precipitation of insulin could be forced, allowing large quantities of relatively pure insulin to be extracted.<sup>1</sup> By late 1923, insulin was relatively plentiful in North America, with 20000–25000 American children receiving insulin from about 7000 physicians.<sup>1</sup>

Over the next few years, insulin manufacturing also began in Europe. Of note, 1920 Nobel Prize winner August Krogh visited Toronto from Copenhagen in late 1922 to learn about insulin and, with assistance from Hans Christian Hagedorn, set up a non-profit Nordisk Insulin Laboratory to manufacture in Denmark, where pork pancreata were plentiful. In 1936, Hagedorn developed neutral protamine Hagedorn insulin,<sup>20</sup> the added protamine-prolonging action, and other long-acting

insulin products followed in the 1950s based on the addition of zinc to the formulation (semilente, lente and ultralente).<sup>21</sup>

Compared with today's products, insulin preparations in the 1960s and 1970s remained relatively impure. After 1978, however, insulin became the first synthetic human protein manufactured through recombinant DNA techniques used by biotech firm Genentech,<sup>16</sup> which later collaborated with Eli Lilly. In 1982, this product was renamed 'human insulin' to distinguish it from animal-derived insulin products. Synthetic human insulin is free from impurities, has a standard potency and is far less likely to cause allergic reactions than animal insulins.

### THE LIMITATIONS OF SUBCUTANEOUS INSULIN THERAPY

Although initially heralded as a medical miracle, insulin brought new challenges and questions, such as whether the patient's urine should be kept glucose-free or whether some glycosuria was preferable, if this meant avoiding hypoglycaemia. It was also not known how the effects of insulin should be spread over 24 hours, or whether high blood glucose was of concern if urine was glucose-free.<sup>1</sup> Children diagnosed with diabetes

now lived longer and could abandon their starvation diets, and, with restored carbohydrate metabolism, they gained weight and vigour. However, insulin is not a cure for T1D, and prolonged life and daily insulin therapy transformed T1D from a disease of short duration, decline and premature death to a chronic condition with substantial daily burdens and concerns over later complications.

These complications were chronicled in the records of Boston diabetologist Elliott Joslin, who began his practice in 1898 and continued treating patients with diabetes until his death in 1962.<sup>22</sup> Joslin lived to see the emergence of diabetology as a specialty for thousands of healthcare professionals, catering to a rapidly growing patient population. Joslin kept thousands of meticulous medical records and letters of communication with patients, and so the Joslin Diabetes Center became a repository of information about how everyday life for children with T1D was changing over the years, and how diabetes affected them as they grew into adulthood.<sup>22</sup>

Despite many physicians' early concerns that patients might make lethal mistakes, most learnt to self-administer their injections, and self-management was championed by Joslin. Longer survival, however, led to the emergence of complications associated with poor glycaemic control: retinal damage and blindness in some patients were recognised by the mid-1930s, and deaths due to renal failure by the mid-1950s. Vascular complications (eg, ulceration, gangrene necessitating amputation, major cardiovascular events, and various microvascular and neural complications) also became apparent.<sup>22</sup> By contrast, improved care with insulin resulted in a marked decline in mortality from diabetic ketoacidosis and coma.<sup>22</sup>

As well as living with fear over complications due to diabetes, and the pain and inconvenience of injections, children with T1D endured other treatment burdens. Initially, patients were supplied with a needle, syringe and whetstone (to keep the needlepoint sharp), and sterilising the equipment required boiling or soaking in alcohol.<sup>22</sup> Only in the late 1960s did disposable needles and syringes arrive. In the 1970s, the now-uniform insulin concentration of 100 units per mL was adopted and, in the mid-1980s, the first discreet insulin pens were introduced, simplifying injections.<sup>23</sup>

Measuring the effect of insulin was also burdensome, as, for most of the 20th century, efficacy was monitored by checking urinary glucose (several times daily) using Benedict solution—a time-consuming procedure.<sup>22</sup> By the mid-1950s, simpler urine test strips were available, and in the late 1970s, home blood glucose monitoring technology was introduced.<sup>24 25</sup> Insulin therapy also did not free children from restrictive diets; indeed, as insulin therapy (and efforts to control hyperglycaemia to avoid complications) intensified, it became more important to carefully balance insulin dosing to nutrient intake and physical activity.

Specialists debated whether diabetes-related complications resulted from poor metabolic control or genetic determination. The availability of purer insulins, enhanced delivery and simplified blood glucose measurement, however, enabled the landmark Diabetes Control and Complications Trial, which assessed emergence and progression of microvascular complications in adolescents and adults with T1D, comparing an intensively treated group with standard therapy.<sup>19</sup> The results proved conclusively that glycaemic control reduced the incidence and progression of vascular complications, leading diabetologists to advocate for stricter glycaemic control through 'multiple injection therapy' basal-bolus regimens (figure 3) or use of insulin pumps. Basal-bolus therapy, however, also meant that patients

required two different types of insulin, originally drawing doses from two vials and thereby making dosing errors more likely.

Thus, by 1993, morbidities caused by impure insulin therapies had largely abated, and it was known that diabetic complications could be prevented or greatly delayed, although at the cost of increased treatment burden, more hypoglycaemic episodes and weight gain. Insulin has extended and improved the lives of millions of children globally, but children with T1D continue to face challenging lives. Furthermore, parents of children with T1D share many of these burdens and worries.

## MODIFYING THE PHARMACOKINETIC PROFILE OF SUBCUTANEOUS INSULIN: INSULIN ANALOGUES

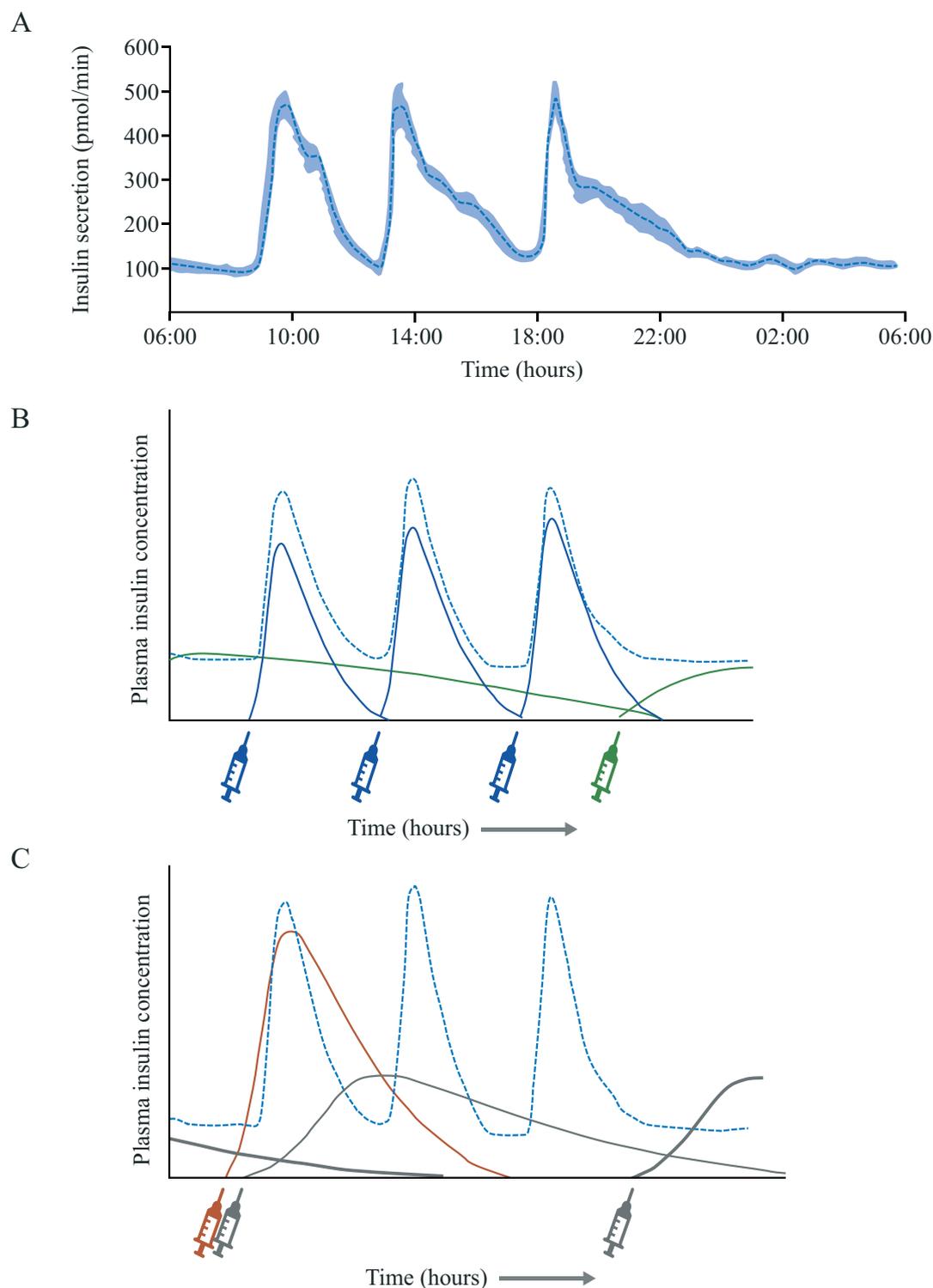
Some of the treatment burden for children with T1D occurred because subcutaneous human insulin products absorb with kinetic profiles that do not match those of physiology.<sup>26</sup> Pancreatic insulin is normally secreted at a low basal rate, with rapidly produced peaks in response to meals to regulate glycaemia tightly. However, human insulin naturally self-associates after subcutaneous administration into hexamers that subsequently dissociate slowly into monomers, which pass from the depot through capillary membranes into the circulation. The result is an absorption profile that resembles neither the constant basal insulin output nor the precisely timed physiological prandial insulin peaks (figure 3C). 'Designer' analogues of insulin have therefore been engineered with modified self-association properties and more desirable absorption profiles (table 1).<sup>26</sup>

The first of these, introduced in the 1990s, had reduced self-association, thereby becoming monomeric more readily, and absorbing faster than human insulin. Originally developed for mealtime bolus injection to minimise postprandial hyperglycaemia, these rapid-acting analogues also offer improved functioning for continuous subcutaneous insulin infusion. Several long-acting basal insulin analogues were also developed early in the 21st century, and these can be administered once daily as partners to rapid-acting insulins in basal-bolus injection therapy. Insulin analogues have improved the achievable balance between glycaemic control and tolerability, but have increased the cost of insulin therapy, and people with diabetes still need to balance mealtime bolus insulin doses with carbohydrate intake and exercise to avoid hypoglycaemia.

## FURTHER IMPROVING THE LIVES OF PATIENTS WITH T1D: CURRENT TRENDS AND FUTURE PROSPECTS

Most of the history of insulin therapy has involved subcutaneous injections. A child diagnosed with T1D at 10 years of age, treated with basal-bolus therapy and living to 70 years of age could expect to receive >90000 insulin injections (including corrective doses) and, until recently, thousands of fingerstick blood samples for glucose measurement. A long-held ambition has been to reduce this burden by automating insulin delivery and blood glucose monitoring. This has required development of discreet, miniature, reliable insulin pumps, along with technology to measure glucose continuously and accurately. The goal has been to put these elements together with control algorithms, to form a 'closed-loop' system (or 'artificial pancreas') that automatically delivers insulin as required, based on predetermined glycaemic targets.<sup>27</sup> Proof of principle for an 'artificial pancreas' was provided in 2013,<sup>28</sup> and 'closed-loop' products are in development, although no fully autonomous closed-loop system has yet received regulatory approval.

Many pump products are available, however, that control glycaemia by modifying insulin delivery rate through user input



**Figure 3** Pharmacokinetic profiles of subcutaneously absorbed insulin products versus normal physiological secretion. (A) Insulin secretion in healthy subjects eating three meals per day. Republished with permission of American Society for Clinical Investigation, from Polonsky *et al*<sup>39</sup>; permission conveyed through Copyright Clearance Center. (B) A near-normal profile of insulin secretion can be reproduced (dotted light blue line) by using basal-bolus therapy: injections of a rapid-acting insulin analogue at mealtimes (dark blue) and a once-daily injection of a long-acting insulin analogue (green line). Alternatively, a rapid-acting insulin analogue can be used in a CSII pump to reproduce the desired profile. ISPAD now recommends intensive individualised insulin therapy given by multiple daily injections or CSII pump for paediatric patients with T1D of all ages.<sup>40</sup> (C) The pharmacokinetic profiles of human insulin products given subcutaneously are suboptimal. Soluble human insulin (orange line) is too long-acting to accurately recreate the prandial insulin response of normal physiology. It must be injected in advance of meals to coordinate the peak effect with glucose absorption, but the prolonged action can risk postprandial hypoglycaemia. Longer-acting human insulin-based products, such as NPH insulin (grey line), poorly recreate basal insulin secretion, having a peak effect and being too short-acting. NPH insulin is therefore usually administered two times per day. Note that all traces in B and C are hypothetical schematics. CSII, continuous subcutaneous insulin infusion; ISPAD, International Society for Pediatric and Adolescent Diabetes; NPH, neutral protamine Hagedorn; T1D, type 1 diabetes.

**Table 1** Summary of currently available insulin analogue products

Insulin (unit concentration)	Year of first commercial introduction	Dosing	Onset of action	Peak effect	Duration	Mechanism of acceleration/protraction	Notes
<b>Mealtime insulin products</b>							
Regular human insulin (U100)	1982	30 min before start of meal	30–60 min	2–4 hours	5–8 hours	None (structurally identical to human insulin)	Slower onset and protracted action requires dosing in advance of meals, thereby reducing scope for tailoring dose to carbohydrate content
Insulin lispro (U100)	1996	15 min before or immediately after start of meal	15–30 min	0.5–2 hours	≤5 hours	Reversal of two amino acid residues in the B-chain terminus to decrease strength of self-association	
Insulin aspart (U100)	1999	5–10 min before start of meal	15 min	1–3 hours	3–5 hours	Substitution of one amino acid in the B-chain terminus (aspart for proline at position B28) to decrease strength of self-association	
Insulin glulisine (U100)	2004	Inject within 15 min before or within 20 min after start of meal	12–30 min	1.5 hours	~5.3 hours	Substitution of two amino acid residues in the B-chain to decrease strength of self-association	
Fast-acting insulin aspart (U100)	2017	Inject at the start of meal, or within 20 min of starting	~16–20 min	~1.5–2.2 hours	~5–7 hours	Insulin aspart with niacinamide and L-arginine to further accelerate subcutaneous absorption	Very rapid action may be advantageous in pump administration, where acceleration of absorption is demonstrated to be faster than with subcutaneous injection
Fast-acting insulin lispro (U100)	2020	At start of meal or within 20 min of starting	~15–~17 min	~2–3 hours	~5–7 hours	Insulin lispro with citrate and treprostinil to further accelerate subcutaneous absorption	Very rapid action may be advantageous in pump administration
<b>Basal insulin products</b>							
NPH insulin (Humulin N) (U100)	1982	Usually twice daily	1–2 hours	2–8 hours	14–24 hours	Addition of protamine to the formulation results in a crystallised suspension of insulin	NPH insulin must be thoroughly resuspended prior to injection to ensure dosing accuracy. Patient failure to do this might contribute to a well-documented variability in glucose-lowering effect from injection to injection
Insulin glargine (U100)	2000	Once daily, same time each day	N/A	No pronounced peak	~24 hours	One amino acid substitution in the A-chain and two additions to the B-chain terminus cause isoelectric precipitation after subcutaneous injection, to slow absorption	Soluble at pH 4
Insulin detemir (U100)	2004	Once or twice daily	N/A	No pronounced peak	Up to 24 hours	Removal of terminal B-chain amino acid and acylation with a 14-carbon fatty acid chain results in an insulin that reversibly binds albumin in the depot and circulation, retarding kinetics	Detemir causes less weight gain than other insulins by mechanisms not fully understood, and it has been shown to have a relatively predictable action from dose to dose. The frequent need for twice-daily dosing due to shorter duration of action than other basal analogues has limited its uptake in T1D
Insulin degludec (U100 and U200)	2013	Once daily—dose times can be anytime of day for adults and the same time every day for paediatric patients, but should be a minimum of 8 hours apart	N/A	No pronounced peak	42 hours	Removal of terminal B-chain amino acid and acylation with a 16-carbon fatty diacid results in an insulin that forms multihexamer chains in the depot and reversibly binds albumin in the circulation, retarding kinetics	Degludec has a half-life of 25 hours. This means that, at steady-state, it has a very low peak:trough ratio, hence a very predictable and near-flat action profile

Continued

Table 1 Continued

Insulin (unit concentration)	Year of first commercial introduction	Dosing	Onset of action	Peak effect	Duration	Mechanism of acceleration/protraction	Notes
Insulin glargine (U300)	2015	Once daily at the same time each day	~6 hours	No pronounced peak	10.8–>24 hours	When formulated at a three-times-greater molar concentration than the original formulation, the absorption of the insulin glargine precipitate is further retarded	U300 glargine has a flatter and more predictable PK/PD effect than U100 glargine, but up to 20% lower molar potency, possibly due to increased subcutaneous metabolism with its slower dissolution

Human soluble insulin and NPH insulin (not analogues) are included as comparators to illustrate how the pharmacokinetic properties of the analogues represent improvements. Information derived from Hirsch *et al*<sup>26</sup> and manufacturers' labels.  
N/A, not applicable; NPH, neutral protamine Hagedorn; PD, pharmacodynamic; PK, pharmacokinetic; T1D, type 1 diabetes.

and/or continuous glucose monitoring (CGM) data. This technology is improving rapidly and is increasingly used by patients with T1D. Wider use of CGM technology has led to new assessments of glycaemic control. The previous gold standard of glycated haemoglobin (HbA1c) gives a crude estimate of average glucose exposure over the previous 2–3 months; similar HbA1c values could be obtained for two patients with different dynamic glucose profiles because HbA1c informs about average glycaemia rather than episodes of hyperglycaemia and hypoglycaemia, or glucose variability. But with CGM, metrics such as 'time in range' (ie, 3.9–10 mmol/L, ideally for 70% of a 24-hour day) can be assessed, and treatment better individualised.<sup>29</sup> Furthermore, many currently available devices enable CGM data to be shared remotely, via electronic technology, with parents, school nurses and others to aid in a child's care when away from home, or overnight.

Finally, there remains scope for new insulin products that improve convenience, efficacy and tolerability. Under study are a rapid-acting, short-duration inhaled insulin preparation in children,<sup>30</sup> once-weekly basal insulin analogues<sup>31 32</sup> and a glucose-sensitive insulin that adjusts biological activity to ambient glucose levels.<sup>33</sup> 'Functionally selective' insulins, engineered to act selectively more in the liver than in muscle and adipose tissue, are also being explored. Theoretically, these would more accurately replicate the physiology of endogenous insulin, which is secreted into the portal vein, with about 50% acting upon and being extracted by the liver.<sup>34</sup>

## REFLECTIONS ON A CENTURY OF INSULIN THERAPY

In this centenary tribute to the discovery of insulin, and reflecting on its unfolding history, we wish to highlight the profound influence this hormone has had in the field of diabetes and endocrinology. As summarised in [figure 2](#), its discovery and subsequent research led to several Nobel Prizes. Innovations made in the pursuit of an understanding of insulin have been applied to other hormones, leading to advances in their respective fields. In particular, radioimmunoassays revolutionised endocrinology, permitting precise, reproducible measurements of chemicals in various biological fluids or tissues, and eliminating complex, imprecise bioassays. Indeed, radioimmunoassay was the driving force of discovery in endocrinology until the mid-1980s, before molecular and genetic techniques. Here, too, insulin was prominent, being the first hormone synthesised by recombinant techniques, which would later enable modifications of the hormone to improve its pharmacokinetic/pharmacodynamic properties. Recent technological advances, combining CGM with pump therapy, and insulin

analogues have revolutionised diabetes treatment, leading to improved glycaemic control, fewer long-term complications and preserved quality of life.

Ongoing developments continue, with 'designer' insulins, including preparations administered by inhalation or ingestion.<sup>35</sup> Prediction of those at risk of diabetes may permit delay or prevention of the disease and its complications,<sup>36</sup> while other research aims to create replaceable beta-cells—from stem cells, for example—this being a potentially curative approach.<sup>37</sup>

Regrettably, however, issues of equity persist, especially in developing countries where economic challenges can lead to insulin shortages. Given the explosion of treatment advances today, using costly technologies, and the future prospect of beta-cell replacement, it is imperative that the medical community, advocacy groups, private and public payers, and patients collectively ensure equal access to avoid repeating the environment of 1922, when patients continued to die as a result of shortages of the newly discovered life-saving insulin.<sup>38</sup>

Nevertheless, the century of advances outlined here (1921–2022) represents remarkable medical success achieved through numerous contributions from physicians, academia and commercial organisations. This triumph highlights how collaborative, innovative medical science can overcome challenges of disease. The extraordinary speed with which progress was made a century ago is reminiscent of the recent success in developing vaccines against COVID-19. Insulin's story is one that gives hope, although not yet one of conquest, but of increasing containment. Yet T1D has been transformed into a challenging, but manageable, chronic condition. The quality of life and longevity expected for children diagnosed with T1D today now approach those of children without diabetes, with every prospect that remaining gaps will continue to close.

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