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CLINICAL PRACTICE UPDATE IN
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Celebrating 100 Years of Insulin: Past, Present and Future

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Discovery of insulin and early innovations

Before insulin was discovered, type 1 diabetes was considered to be a serious disease of childhood and early adulthood, as patients tended to die within weeks to years of its onset.

100 years ago, in the summer of 1921, Frederick Banting and Charles Best were the first to extract insulin from pancreases of dogs and to prove that it can lower blood glucose in dogs. Further research in collaboration with JJR Macleod and James Collip eventually led to the first human use. In January 1922, Banting and Best injected Leonard Thompson, a 14-year-old patient who weighed less than 30 kg, with 7.5 mL of a "thick brown muck" in each buttock. His blood glucose dropped enough to continue refining what was called "iletin" insulin. Two weeks later, a refined extract caused Leonard's blood glucose to fall from 520 to 120 mg/dL in 24 hours. Leonard lived a relatively healthy life for 13 years before dying of pneumonia (for which there was no treatment at the time) at age 27. After this initial success, further patients were treated with insulin, with similarly dramatic improvements in their health and lifespan. For this revolutionary discovery, Banting and Macleod were awarded the 1923 Nobel Prize in Physiology or Medicine, sharing the prize money with Best and Collip in recognition of their part in the discovery. This is certainly one of the most significant scientific advancements in the history of Canada, setting the stage for remarkable innovations in insulin treatments over the next 100 years. See Figure 1 for a summary of the timeline of insulin innovations over the last 100 years.

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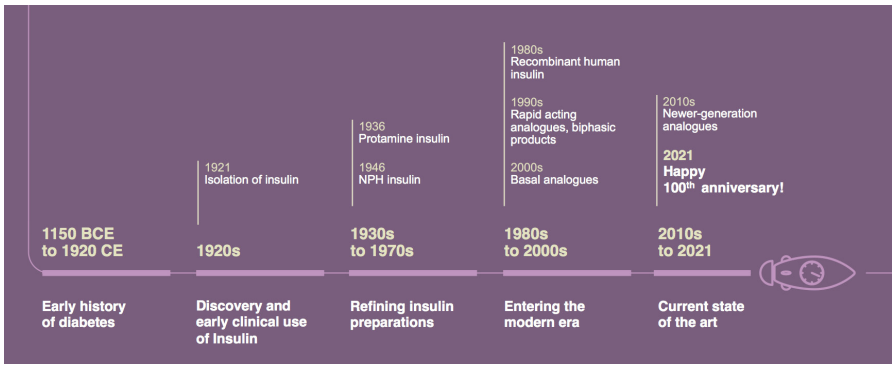

Figure 1: Timeline for insulin innovations in the last 100 years

In the beginning of the insulin era, the challenge was to satisfy the needs of thousands of people with diabetes. Insulin needed to be produced in industrial quantities

in order to cover the demands from all over the world, leading to agreements between the University of Toronto and both Eli Lilly and Company and Nordisk to start mass-producing insulin. Today, Eli Lilly and the Novo Nordisk remain two of the top three insulin-producing companies in the world.

Through the early years of insulin's clinical use, researchers tried different processes with the goals of producing purer isolates and prolonging the action of insulin products, moving towards what we now know as a basal insulin approach. In 1936, Dr Hagedorn and his colleagues at Nordisk made a breakthrough in basal insulin by combining animal insulin with protamine, which extended the duration of action to a day or more. By 1946 they succeeded in producing a crystalline protamine insulin that could be mixed with a rapid-acting insulin without any change of effect in either product. Marketed as NPH (Neutral Protamine Hagedorn) insulin, the prolonged duration of the product meant that people with diabetes needed fewer daily injections. NPH insulin became a great success and soon accounted for a large part of the Western world's consumption of basal insulin.

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By the mid-1940s, thanks to wider use of insulin and better formulations, type 1 diabetes was no longer an automatic death sentence. Even patients who were diagnosed earlier in childhood could now start to hope for better health, improved quality of life, and a longer lifespan. In 1953 Novo started marketing Lente® insulin, a prolonged-action insulin product that covered nearly one third of the world's insulin consumption for several years.

Insulin products had become still more pure since the 1920s, but there were still many problems to be solved. Studies showed that all insulin users developed antibodies against insulin and there were cases of patients becoming allergic to insulin. Researchers at both Novo Nordisk and Eli Lilly concentrated on reducing the impurities in animal insulins, with the goal of decreasing antibody formation.

The modern era of insulin therapies

One of the key early research priorities was to create an insulin that would be identical to that produced by the human body, with the goal of reducing immunogenicity and side effects. In 1978, scientists at the Genentech company succeeded at introducing a human insulin gene into E. coli and having the bacteria produce the protein. This set the stage for the mass production of recombinant human insulins. Eli Lilly and Genentech collaborated to launch the first recombinant human insulins in 1982, under the Humulin name. That same year, scientists at Novo developed a process for converting porcine insulin to human insulin by replacing a single amino acid. Both Novo and Nordisk brought products to market in the early 1980s that used this technology, before moving to recombinant products later in the decade.

When thinking about clinically relevant directions for further innovations in insulin treatment, one of the key remaining questions at this point in history was, how can we effectively mimic normal endogenous insulin activity? As a quick review, normal physiologic insulin secretion includes both continuous low-level basal secretion, as well as incremental secretion following meals. The existing insulin preparations were developed to alter time-action profiles in an attempt to make insulin replacement follow the pattern of the body's own insulin release, as much as possible. This time-action profile incorporates three key elements: the onset of insulin action, the peak or time to maximum effect, and the duration of action.

In the 1990s and 2000s, genetic engineering techniques allowed the design and creation analogue insulins, in which the native composition of insulin is altered to give it different properties with regard to absorption, metabolism, and/or excretion. With analogue insulins it is possible to better imitate the body's natural regulation of blood glucose and ensure better blood glucose control. The first analogue that was designed to have a faster onset of action, insulin lispro, was introduced by Eli Lilly and Company in 1996; several other rapid-acting analogues soon followed. Conversely, several analogues that were designed to have a longer action and provide the basal component of insulin activity were introduced in the 2000s, the first being insulin glargine in 2000.

In terms of basal insulins, our progress has led us towards longer- and longer-acting analogues, in an effort

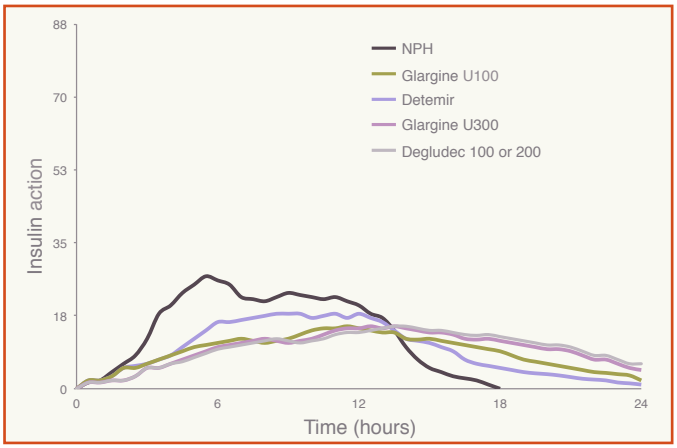

Figure 2: Insulin action profiles of currently approved basal insulin

to match the natural biological profile of endogenous human insulin as closely as possible. Ideally, an ultra-long-acting basal insulin should provide good glycemic control, with flexible and simple dosing, and predictable levels of blood glucose leading to a low risk of hypoglycemia. In terms of pharmacological profile, it would be advantageous to have a flat time–action profile with low glycemic variability, resulting in a predictable insulin. These analogues proved to have evident clinical benefits in terms of glycemic control, on the level of within-subject variability, changes in HbA1c, and rates of hypoglycemia. With the recent development of insulin analogues with even longer half-lives, our progress towards the ideal basal insulin has now brought us even closer to the profile of normal physiologic insulin activity. The ultra-long-acting basal insulin analogues (degludec, glargine U300) have an even longer duration of action and flatter profile than the first-generation analogues (figure 2) with clinical benefits in terms of overall glycemic control and lower rates of hypoglycemia.

On the converse side from the basal picture, it is also important to try to reflect the physiological profile of native insulin when developing a subcutaneously injected mealtime insulin. The first generation of fast-acting insulins has an improved action profile as compared wit the regular human insulin, but there was still a gap to the ideal one. Ultra-fast-acting insulins help to reduce this gap and provide clinical benefits.

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In summary, over the last 100 years we have gone from diabetes being an incurable, rapidly fatal disease to having a wide range of insulin options that can be tailored to meet our patients' clinical needs and goals and to improve their quantity and quality of life dramatically.

Insulin innovations for the future

Administration of daily basal insulin can be burdensome and inconvenient. This can result in clinical inertia, including delays in insulin initiation, and poor insulin self-management and persistence in T2D. Once-weekly basal insulin may offer benefits versus more frequent dosing: greater convenience and improved self-management, improved health-related quality of life and reduced treatment burden for patients and caregivers. Insulin icodec and basal insulin Fc (BIF) are once-weekly insulins in development that may eventually offer a convenient option for basal insulin treated patients with diabetes.
Work on orally administered insulin is a work in progress. The challenge of poor bioavailability has led to the preclinical exploration of newer technologies for the oral delivery of the insulin peptide. Options being explored include a self-orienting millimetre-scale applicator (SOMA), based on the shape of the leopard tortoise, such that the insulin capsule will consistently orient towards the gastric mucosa and allow for injection of compressed insulin via milliposts. Other technologies in preclinical research include a high velocity liquid injection, a passive hooking method and a dissolvable needle in an enteric capsule. See figure 3 for a summary of technologies in preclinical development regarding an oral insulin.

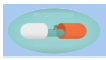
Technology	Method	Image
Self-orienting millimetre-scale applicator (SOMA)	The SOMA orients toward the tissue and injects the drug into the mucosa	 Brigham and Women's Hospital, MIT, Novo Nordisk
High velocity liquid injection	The capsule dissolves, injecting fluid into the gut	 Baywind Bioventures Propel Biologics™ JetCAP™
Passive hooking method	A tiny spike with drug pushes safely into the gut wall	 Biograil BIONDD®
Dissolvable microneedle in enteric capsule	An inflating balloon injects drug into the intestine	 Rani Therapeutics RaniPill®

Figure 3: Oral insulin technologies in preclinical development

A "smart" insulin that is only active in the presence of hyperglycemia will allow for insulin administration with the potential for elimination of hypoglycemia. This is being studied by including a glucose sensor, either intrinsic to the insulin molecule, or as a part of a polymeric matrix. One of these glucose-sensitive insulins is currently in phase 1 of development.

Just like we have seen tremendous accomplishments in insulin innovations over the last 100 years, we can look forward to even further improvements in insulin therapies over the years to come. We should celebrate accomplishments over the past 100 years and look forward to the next 100 years in insulin innovations.

LMC Healthcare

C. Mark Angelo

President & CEO
LMC Healthcare

November is Diabetes Awareness Month, a time when we honour all those involved in the fight against diabetes – patients, their families, healthcare professionals, researchers and staff. This year's Diabetes Awareness Month is even more special given that we're also celebrating the 100th year anniversary of the discovery of insulin. This first life-saving treatment for diabetes was discovered in Toronto in 1921 by a Canadian team of researchers (Banting, Best, Macloed and Collip). While insulin is not a cure, it did transform diabetes from a fatal diagnosis into a medically manageable chronic condition.

Managing diabetes continues to be a struggle for millions of Canadians across the country. Whether it access to specialists, fragmented care or lack of coverage, many Canadians still don't have the support they need to manage their chronic condition with confidence. That's why LMC's core purpose is centered around Making Healthy Easier for those living with diabetes and transforming diabetes care to make it more accessible, comprehensive, proactive and patient-centric than ever before.

Thank you for everything you do, day in and day out, to care for your patients and support our communities. It is all of you who allow LMC's unique care model to deliver life-changing care and support to over 50,000 patients living with diabetes each year.

HAPPY DIABETES AWARENESS MONTH!

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