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EDITORIAL

Celebrating 100 years of insulin

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Abbreviation

EDIC Epidemiology of Diabetes Interventions and Complications

Work in the University of Toronto (ON, Canada) during 1921 culminated in January 1922, when Leonard Thompson received his first injection of a purified pancreatic extract containing insulin. This remarkable event built on many years of groundbreaking scientific work by a number of individuals around the world, including Claude Bernard, Paul Langerhans, Oskar Minkowski, Joseph von Mering, Eugene Opie, Georg Ludwig Zülzer and Nicolas Paulesco, to name but a few. The unique achievements of the Toronto team, collaborating with industry, includes the speed at which they were able to purify, test and produce insulin in sufficient quantities for it to become a viable treatment for diabetes. These events have been described eloquently by Michael Bliss in his book: *The Discovery of Insulin* [1]. The immediate and long-term consequences of insulin therapy are life-changing for individuals with diabetes and continue to stimulate scientific research and learning.

The University of Toronto has arranged a series of events for clinicians, scientists and people with experience of diabetes to celebrate the remarkable beginning of this journey, to learn about our current knowledge and to look to future opportunities (https://insulin100.com/). *Diabetologia* is fortunate to be a partner in this venture, with a *Diabetologia* symposium on hypoglycaemia and publication of this special edition containing reviews by a number of contributors to the varied scientific symposia (https://insulin100.com/speakers). The articles included in this special issue take us through the events related to insulin discovery in Toronto in 1921/1922, the acute complications of insulin treatment, long-term complications of diabetes, and the pathophysiology, prevention and modern management of diabetes.

Fralick and Zinman [2] set the scene by recounting the story of the discovery of insulin in Toronto in 1921. They outline how, 100 years ago, Frederick Banting and Charles Best began their summer research project in the laboratory of John James Rickard Macleod, with a goal to isolate and produce a stable form of insulin that could be used to treat people with diabetes. With the help of James Collip, they miraculously achieved this goal, and on 23 January 1922, insulin was successfully administered to a 14-year-old boy with type 1 diabetes. This discovery meant that type 1 diabetes went from being a death sentence to a chronic condition.

Nonetheless, despite insulin being a life-saving medication, regrettably it is not accessible to all who need it. In fact, globally, only one in two people have access to the insulin they require. In their review, Mbanya and colleagues [3] present the different barriers to insulin access using a framework proposed by the WHO that looks at the whole pathway of a medicine, from its discovery until its use. The obstacles faced by individuals in accessing insulin are complex and occur at both global and national levels; the authors propose that major changes at societal and political levels are needed to overcome these, as well as more international collaborations. They suggest that emphasis should be laid on innovations that decrease global inequalities and should be driven by people with diabetes or designed with people with diabetes in mind, so as to effectively drive the changes needed.

For those that are fortunate enough to have access to insulin, as with the majority of drugs, its use does not come without side effects. Despite considerable advances in insulin formulation and modes of delivery in the 100 years since its discovery, hypoglycaemia remains a frequent complication of insulin therapy. A hypoglycaemic event has physiological, psychological and pathological effects, the full impact of which are not fully appreciated or understood. As part of this special issue, Stephanie Amiel [4] describes immediate and cumulative consequences of hypoglycaemia, including known and suspected circulatory, neurological, psychological and socioeconomic effects. The author concludes that good management of diabetes can only be defined when risk of

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hypoglycaemia, as well as hyperglycaemia, has been minimised.

Following on, Rory McCrimmon [5] summarises the impact of recurrent hypoglycaemia on brain function. Impaired awareness of hypoglycaemia is considered to develop owing to adaptation by the brain and peripheral organs to recurrent hypoglycaemia, which paradoxically renders insulin-treated individuals more susceptible to severe hypoglycaemia. The author also highlights that repeated hypoglycaemia and a background of chronic hyperglycaemia may lead to an acceleration of cognitive decline in diabetes, explaining why increased glycaemic variability is now commonly considered a risk factor for the complications of diabetes.

Thus, it is clear that there is a need to minimise the risk of hypoglycaemia with insulin therapy, but how can this be achieved? Chantal Mathieu [6] aims to answer this question. The author explains that, over the years, clinicians have learned to reduce the burden of hypoglycaemia through intensive patient education and coaching. In addition, the advent of insulin analogues and novel technologies for insulin administration, like insulin pumps and glucose-sensing tools, have reduced the occurrence of hypoglycaemic episodes. Use of adjunct therapies and the promise of better, preferably glucose-sensitive, insulin analogues also provide hope of reducing the risk of hypoglycaemia even further in people treated with insulin.

In order to understand how insulin therapies (both established and proposed) work, it is important to discuss the complex mechanisms that ensure that glucose levels remain in the tight range of normoglycaemia in healthy individuals. In their review, Yoon and Diano [7] focus on central glucose-sensing mechanisms involved in the regulation of glucose metabolism, underscoring the importance of specific areas of the hypothalamus. They also highlight the complexity and variety of glucose-sensing mechanisms, both at the cellular and circuit levels, and how alterations in these mechanisms affect glucose homeostasis.

Meanwhile, Kahn and colleagues [8] discuss how most people with disordered glucose metabolism exhibit insulin resistance, rather than insulin deficiency. The authors outline current and evolving concepts of insulin action and insulin resistance, specifically in type 2 diabetes. While it has been demonstrated that insulin resistance in type 2 diabetes associates with alterations in extrinsic factors, such as circulating lipids, cytokines and metabolites, the identification of intrinsic factors programmed by genetics and epigenetics that underlie the disease has been a greater challenge (these elements that manifest cell-autonomously are only now beginning to be defined). The authors conclude that understanding the primary source of metabolic disturbances and elucidating how accumulating 'multi-omics' information fits into drivers of disease remain challenging but offer important new avenues for the development of novel therapies.

An excellent example of a novel therapeutic approach for diabetes is the closed-loop insulin-delivery system, which is starting to transform the management of type 1 diabetes in children and adults. In their review, Boughton and Hovorka [9] summarise the supporting evidence for currently available closed-loop systems, whilst also highlighting the benefits of and challenges surrounding non-regulated 'do-it-yourself' closed-loop systems. Successful clinical adoption of these systems, however, requires training of healthcare professionals and users alike, and equitable access should be prioritised. The authors explain that challenges remain with regard to management of postprandial glucose excursions and blood glucose levels upon physical activity with insulin-delivery systems, with some systems having usability issues. They propose that future closed-loop systems would benefit from improved components to minimise device burden, and faster-acting insulin analogues or dual-hormone approaches to enhance performance towards development of fully closed-loop systems.

Developing the 'technology' theme, Weiss and colleagues [10] take us into the fascinating world of 'smart' insulin-delivery devices and molecular technologies designed to exploit feedback regulation. Whilst current pump-based closed-loop systems exploit algorithmic control based on the output of a continuous glucose monitor, the authors highlight the promise of molecular strategies to provide intrinsic in vivo feedback based on glucose-regulated insulin bioavailability or bioactivity. They also discuss strategies and prospects for unimolecular glucose-responsive insulin analogues in the treatment of diabetes.

But what if we were able to take away the need for insulin altogether? Douglas Melton [11] explores this by discussing the promise of stem cell-derived islet replacement therapy for individuals with diabetes. The fact that cadaveric islet transplantation achieves insulin independence for some patients with type 1 diabetes has motivated the search for a reproducible and inexhaustible supply of functional human beta cells. Human pluripotent stem cells, having a virtually unlimited capacity for self-renewal and differentiation, provide an excellent starting material to solve this problem. Excitingly, it is now possible to direct the differentiation of human pluripotent stem cells in vitro into functional islet endocrine cells, including beta cells. Melton reviews the recent history of making beta cells from stem cells, points to areas for potential improvements and outlines the challenges ahead as stem cell-derived islets enter clinical trials.

Another approach to avoid the need for insulin therapy would be to prevent the destruction of beta cells in the first place. In type 1 diabetes, autoimmune processes destroy the insulin-producing beta cells, leading to hyperglycaemia. In their review, von Herrath and colleagues [12] give a concise overview of current and potential future therapeutics that may help to prevent and better manage the disease. Previous

attempts to preserve functional beta cells have been partially successful and a reinforced focus on the beta cell incites hope that novel therapies will, at least, be able to slow down the rate of beta cell demise. For example, vaccination against beta cell antigens or various stress-relief approaches may help to ensure that the beta cell is not targeted by immune cell populations. The authors state that complications associated with established type 1 diabetes, including cardiorenal risk and increased body weight, could also be managed using drugs already approved in type 2 diabetes.

Turning to the long-term complications of diabetes, David Nathan [13] writes about the long-term promise of insulin therapy using findings from the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study. The DCCT demonstrated that, compared with conventional treatment, intensive insulin therapy reduced retinopathy, nephropathy and neuropathy by 34–76%. Moreover, a strong, continuous relationship was demonstrated between mean HbA_{1c} levels and complications. Longer-term follow-up during the EDIC study showed persistent effects of the original DCCT interventions, even though the separation of HbA_{1c} levels observed during the DCCT dissipated. The persistent effect of prior HbA_{1c} levels was termed 'metabolic memory'. Nathan states that the more than 28 years of EDIC follow-up to date have shown a significant ~50% reduction in severe eye and kidney complications and CVD events, and a 33% reduction in mortality, with intensive therapy. The author concludes that DCCT/EDIC have shown how insulin therapy ameliorates the long-term complications of type 1 diabetes.

In summary, the tremendous advances in the therapy of type 1 diabetes have seen type 1 diabetes move from a fatal illness to a manageable chronic condition. These advances encompass the continuous sensing of glucose to the development and automated delivery of new insulin analogues. To complete this special series celebrating the discovery of insulin a century ago, Daniel Drucker [14] looks to the future by examining emerging areas of transformational science. In doing so, Drucker highlights the potential of smart insulins, fully automated insulin delivery, reprogramming of the immune system and the generation of fully functional differentiated stem cell-derived islets to alter the natural history and treatment of type 1 diabetes.

Conclusions

Almost like no other condition, the ramifications of diabetes cross all societal, medical and scientific boundaries. The events in Toronto in 1921 were led by a science student, a surgeon, a physiologist and a biochemist, latterly in collaboration with Eli Lilly and company. The articles in this special issue illustrate how improvements in our understanding and management of diabetes until now has rested on such multidisciplinary input, and how further advances will depend on continued strong cross-disciplinary collaborations, sometimes from unexpected sources. It has truly been a remarkable journey, and the new developments to come suggest even more exciting progress. However, my enthusiasm for our increasing knowledge and technological advances is tempered by the shameful fact that many individuals worldwide do not have access even to basic diabetes care, including regular, reliable provision of insulin. The best treatment in the world is useless if people who need it are denied access. As we push our scientific endeavours forward, we must also all collaborate to ensure that everyone has equitable access to the best possible diabetes care.

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