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## **100 years of insulin**

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*Published in:*  
Journal of Endocrinology

*DOI:*  
[10.1530/JOE-21-0391](https://doi.org/10.1530/JOE-21-0391)

*Publication date:*  
2022

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Cantley, J., & Eizirik, D. L. (2022). 100 years of insulin: progress, current perspectives and future challenges. *Journal of Endocrinology*, 252(3), E1-E3. <https://doi.org/10.1530/JOE-21-0391>

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## Editorial

### 100 years of insulin: progress, current perspectives and future challenges.

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Insulin secretion from pancreatic beta cells is critical to regulate blood glucose levels and maintain nutrient homeostasis (Cantley and Ashcroft 2015). Defects in insulin secretion and action lead to Diabetes Mellitus, a disease characterised by hyperglycaemia, an array of co-morbidities and increased mortality. During type 1 diabetes (T1D), beta cells are targeted by the immune system leading to a profound loss of insulin secretion. Type 2 diabetes (T2D) is the most prevalent form (~90% of cases), involving alterations in both insulin secretion and insulin sensitivity (the effectiveness of insulin): some individuals show a severe loss of insulin secretion, whereas others show obesity, insulin resistance and hyperinsulinemia, albeit insufficient to control blood glucose. In both forms of diabetes a relative or absolute beta cell failure is the central event leading to hyperglycaemia (Eizirik, et al. 2020).

Prior to the discovery of insulin, people with T1D suffered immeasurably, with uncontrolled hyperglycaemia eventually resulting in diabetic ketoacidosis and death. Desperate attempts to control the disease, such as the so-called 'starvation' diets (Allen, et al. 1919), much reduced quality of life yet were of limited efficacy. Against this backdrop, it is perhaps difficult to overstate the immediate and long-lasting impact that the discovery of insulin by Banting, Best, Collip and Macleod had on the clinical treatment of diabetes. Following the pioneering experiments conducted at the University of Toronto in 1921 (Banting and Best 1922), translation was rapid, with the introduction of bovine insulin replacement therapy resulting in a dramatic improvement in life expectancy and quality of life for people with diabetes, setting the path towards development of modern recombinant human insulin therapies in the latter 20<sup>th</sup> century.

Alongside the direct clinical impact of insulin replacement therapy, the discovery of insulin catalysed development of the nascent field of endocrinology, whilst enabling profound advances in our scientific understanding of disease aetiology. Although insulin replacement therapy has saved countless lives, turning a fatal disease into a treatable chronic one, it is important to remember that insulin replacement does not recapitulate the exquisitely nutrient-regulated insulin secretion profiles of the pancreatic beta cell. Moreover, insulin therapy introduces side effects such as weight gain and risk of hypoglycaemia, at least in part due to the need to 'hyperinsulinise' the peripheral tissues to reach physiological levels of the hormone in the portal system. Therefore, new disease-modifying therapies to protect and restore beta cell function are urgently needed (Martens, et al. 2021). A final point to note at this important anniversary is the diverse backgrounds, training, personalities and *modus operandi* of Banting, Best, Collip and Macleod (Bliss 2007), providing useful lessons about the multidisciplinary path to scientific discovery, the need for collaboration, and the importance of taking on high-risk projects where others have fallen short.

To celebrate 100 years since the discovery of insulin, the Journal of Endocrinology has commissioned a series of reviews, authored by scientists from around the globe, covering a range of perspectives

on the pathophysiology of diabetes. These articles provide a timely review of the progress made over the past century, a discussion of the latest research, along with an outlook on where the field is heading. An important theme from the series is the marked disease heterogeneity within the common classifications of T1D and T2D, and how phenotype and genotype could be better used to stratify and manage diabetes sub-types, hopefully leading to a more personalised approach that should further improve quality of life (Ahlqvist, et al. 2021; Ikle and Gloyn 2021; Martens et al. 2021; Richardson and Pugliese 2021).

The review by **Ahlqvist, Prasad and Groop** (Ahlqvist et al. 2021) considers the heterogeneity of common forms of diabetes, providing a timely update of the clustering method the group have developed to stratify subtypes of diabetes based on clinical variables. This includes key studies in wider populations, prevalence of complications and treatment responses. They also provide a historical narrative around the evolving classification of diabetes subtypes, with the discovery of insulin clearly underpinning the concepts of insulin deficiency and insulin sensitivity. The article by **Martens, Gysemans and Mathieu** (Martens et al. 2021) focuses on T1D, providing a thorough discussion of the interplay between beta cells and the immune system during disease progression. They review the heterogeneity of T1D, including age of onset, aggressiveness of autoimmunity and residual beta cell function, and discuss recent trials of immunotherapies, articulating the need for new disease modifying approaches and for improved biomarkers during the sub-clinical phase of the disease. **Richardson and Pugliese** (Richardson and Pugliese 2021) present a detailed account of the pathology of the pancreas during T1D, including the organisation of tissue banks and consortia which have underpinned key studies into disease aetiology. The authors review studies demonstrating the presence and persistence of pancreatic beta cells in T1D, and varying degrees of autoimmunity, which has important implications for efforts to protect, regenerate and restore endogenous beta cell function. A timely review of the histological evidence for inflammation, viral infection and ER stress in the aetiology of T1D is also provided. **Ikle and Gloyn** (Ikle and Gloyn 2021) discuss the genes and phenotypes that define monogenic forms of diabetes, including maturity-onset diabetes of the young, and neonatal diabetes, and how genetic and clinical insights have influenced treatment. They introduce the use of GWAS to identify gene variants linked to T2D, and predict that increasing power of genetics studies, along with clinical metrics, will improve disease stratification and treatment for polygenic forms of diabetes. Finally, **Chen and Gunton** (Chen and Gunton 2021) review the use of islet transplant therapy for T1D, including current barriers to islet graft survival and function, and the use of pre-clinical models. These authors conclude with a review of pathways that could be deployed to regenerate pancreatic beta cells *in vivo*.

The discovery of insulin has enabled many important scientific, clinical and technical advances over the past century, contributing to improvements in the management and treatment of diabetes. However, the number of people living with diabetes is at an all-time high, having recently passed half a billion (537 million worldwide; IDF 2021), with this figure projected to continue rising at an alarming rate. It is clear that new strategies to prevent or reverse the disease, focusing on maintaining a functional beta cell mass whilst fostering physical activity and maintenance of a healthy body weight, are urgently needed. If the current diabetes epidemic is approached with the same vigour as researchers and policy makers applied to tackle COVID19, then in coming decades we may finally force diabetes rates to recede.

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## Declaration of interest:

D.L.E. received grant support from Eli Lilly and Company, Indianapolis, for research on new approaches to protect pancreatic beta cells in T1D.