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DIABETIC Medicine

COMMENTARY

Centenary of Insulin

The contributions of insulin to science in medicine

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The discovery of insulin in Toronto in 1921, now 100 years ago, was nothing less than a miracle. It quite rightly stands out as one of the most significant accomplishments of modern medicine and has undoubtedly saved the lives of millions of people now able to live with diabetes. It would, however, be neglectful to imagine a world without insulin without considering the true impact of its discovery on so many other aspects in medicine and science.

The discovery of insulin can be attributed to two groups of two people, Frederick Banting and Charles Best, and John Macleod and James Collip, all four of whom played distinct roles in orchestrating or conducting the experiments that led to the successful extraction of the active hormone from pancreata and the subsequent demonstration of its life-saving effect on blood glucose in people with diabetes.[1,2] Banting and Macleod received the Nobel Prize for the discovery in 1923, and each decided to share their awards with Best and Collip, respectively. The pharmacological effect was so remarkable that it allegedly inspired one of the most renowned diabetologists at the time and in history, Elliott P Joslin, in Boston, to analogise what happened in front of him to a scene from the Old Testament in which God says 'I will attach tendons to you and make flesh come upon you and cover you with skin; I will put breath in you and you will come to life'.[2]

Since the discovery, insulin preparations and insulin regimens have been under continuous development. In the first decades, the challenge was to optimise the extraction and purification protocols and to provide longer-acting insulin preparations. The development of NPH (neutral protamine Hagedorn) insulin by Nordisk Insulin Laboratorium in Copenhagen in 1946 was an important milestone that made available a ready-to-use suspension-based product that remains widely used even today. Another major event in the history of insulin development was the advent of recombinant processes for insulin production in the late 1970s and early 1980s. This pivotal advance made it possible to produce human insulin in unlimited quantities and paved the way for engineering today's insulin analogues, offering crucial improvements in terms of, most prominently, convenience of use and the achievable magnitude of glycaemic control alongside a low risk of hypoglycaemia.

At this centenary hallmark in 2021, it is worthwhile reflecting on where science and medicine and in particular diabetes would have been without 100 years of insulin-inspired innovation. A stone's throw from the miracle that Joslin paraphrased, the discovery of insulin offered an immediate life-saving treatment for people with type 1 diabetes. Prior to its discovery in 1921, life expectancy was limited to a few years from diagnosis[3]; by 2015, a person with type 1 diabetes could expect to live for almost 50 years after a diagnosis at age 20 years, or achieve a life expectancy to within 10 years of that expected for someone without diabetes.[4] The key realisation leading to this unprecedented development was the importance of good glycaemic control to reduce the risk of microvascular complications as demonstrated in the 1980s and 1990s by the seminal DCCT[5] and UKPDS[6] studies.

Clearly, developments in insulin delivery systems combined with increasingly convenient and accurate self blood glucose monitoring, have also made a major contribution to improved outcomes. That said, the ensuing pursuance of blood glucose normalisation would have been associated with greater risks of hypoglycaemia and more limitations to life style, had new and better insulin preparations not been made possible. With the positive impact of improved glycaemic control not just on microvascular but also macrovascular complications[7,8] and numerous clinical outcomes, including, for example, pregnancy,[9] and indeed many aspects of quality of life, it is almost impossible to imagine a world without insulin.

Undoubtly, the reality of diabetes therapy and of living with diabetes would have been tremendously different had insulin not been discovered. But the full impact of the discovery of insulin goes far beyond the benefits to people with diabetes, and includes what insulin has done for a wide range of scientific disciplines, such as protein science, biotechnology and device and delivery technology. For example, insulin has been widely canonised as the scholarly example of a therapeutic protein, and many technologies have been developed based on insulin as an arguably universally applicable model among proteins. One reason has been the relatively easy access to large quantities of pure product, an obvious but often forgotten prerequisite in experimental laboratory-based protein chemistry. It is remarkable to think that it was not until 30–35 years after insulin was discovered that its molecular composition was actually identified. In the early 1950s, insulin became the first protein to be sequenced, and this milestone finally led to the realisation that proteins are composed of distinct, linear chains of amino acids.[10] This seminal work of sequencing the A and B chains of the insulin molecule, as well as identifying the three disulphide bridges, earned Fred Sanger in Cambridge, UK, his first Nobel Prize in 1958. Sanger allegedly described himself as 'just a chap who messed about in his lab'[11]; nevertheless, he later went on to win his second Nobel Prize in 1980 for sequencing DNA (shared with Walter Gilbert), establishing the pivotal recognition of the need for the genetic code for protein production to also be ordered. Without the access to large amounts of pure insulin, when would we would have concluded on the primary structure of proteins, and later gone on to understand how this links to gene translation? Moving forward, in 1964, insulin became one of the first proteins, for which the 3D structure was established; Nobel Prize laureate Dorothy Hodgkin and team solved the insulin structure, revealing the secondary, tertiary and quaternary structures.[12]

Following the identification of its amino acid sequence, insulin has been widely claimed as being the first protein to be chemically synthesised.[13] Insulin was also among the polypeptides to be synthesised by Bruce Merrifield's pioneering solid phase approach,[14] a method that revolutionised peptide and protein synthesis and also awarded Merrifield a Nobel Prize in chemistry in 1984. Moreover, proinsulin, which was discovered by Don Steiner and published in a seminal paper in 1967,[15] was the first prohormone to be isolated and sequenced. Steiner outlined the biosynthetic pathway for insulin production via proinsulin in the beta cells in the islets of Langerhans in the pancreas, and we have later come to understand the more general significance of prohormones in protein expression and secretion. Paving the way for the crucial quantification of substances in biological fluids, insulin was also among the first peptide hormones to be measured with high sensitivity and specificity by radioimmunoassay, contributing to Rosalyn Yalow winning the Nobel Prize in physiology and medicine in 1977.

As a consequence of its history, it is not unreasonable to conclude that the reach of insulin, as a model compound, has extended from medicine to biology and to chemical technology.

But probably the greatest example of insulin as a model compound with implications for both medicine and technology is the successful production of the hormone by genetic engineering, when it became the first application of recombinant technology for large-scale protein production. It was shown in 1978 that bacteria could be induced to produce proinsulin.[16] The first process to be taken forward in an industrial setting was developed by researchers at Genentech and published in 1979,[17] and was based on separate cloning in *Escherichia coli* of the insulin A and B chains, followed by recombination of the two individual chains. This process was expanded on to an industrial scale by Eli Lilly, whereas Novo Nordisk in 1985 published a recombinant technology to produce single-chain insulin precursors in yeast followed by enzymatic conversion to insulin.[18] Since that time, recombinant production of peptides and proteins has become an integrated part of biopharmaceutical and biotechnological research and development with far-reaching impacts on medicine and beyond.

Genetic engineering above all has allowed for the rational design of protein drugs. In the field of insulin, it has allowed for the intricate design of analogues with tailored time-action profiles with associated benefits on convenience, glycaemic control and risk of hypoglycaemia. Starting with insulin, integration of recombinant technology and chemical protein modification, such as acylation with fatty acids,[19] has been successfully applied to extend the stability and thereby the duration of action to 1 day or 1 week and possibly even longer for several licensed and in-development drugs such as insulin degludec,[20] insulin icodec[21] and glucagon-like peptide-1 (GLP-1) analogues including liraglutide and semaglutide,[22] as well as tirzepatide.[23] Finally, completing the quest for a holy grail that has been going on since the advent of protein-based pharmaceuticals, the technologies have recently been shown to facilitate oral delivery of proteins such as GLP-1 analogues[24] and insulin itself.[25]

Lastly, because of its narrow therapeutic window and the ensuing need for timely delivery to regulate blood glucose and maximising time in range, insulin has also been the prime example within development of device and delivery technologies. Technologies built around insulin include pen injection devices, first commercially introduced in 1985,[26] which in the present age of digitalisation are also made available in versions with memory functions and connectivity for data transfer. Together with data from glucose monitoring systems, connected pens allow for more informed dialogue between patient and physician about compliance and control. Starting with insulin, pen-like injection devices have later been developed for other injectable therapies as well. Moreover, insulin has also been the first target for development of advanced pump systems, so far culminating in the recent development of 'hybrid closed loop' systems that provide automatic feedback from a continuous glucose sensor to regulate the rate of insulin delivery.[27,28] Taken together, insulin also holds promise to be spearheading the application of digital technologies for delivery and dialogue in a world where data and information gets more and more critical for individualised therapy.

Their brilliance notwithstanding, the chance was little that the four scientists whose group was honoured by the Nobel Prize in 1923 could have foreseen what would be the expansive consequences of their discovery a century ago. We are allowed to hope that future science will be as impactful on both technological development and patient care in diabetes and beyond.

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CONFLICTS OF INTEREST

Both authors are employees of Novo Nordisk A/S.

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