DOI: http://doi.org/10.4038/jrcs.v26i1.111

100 years of Insulin

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Diabetes has been known for a ubiquity. The oldest known description of diabetes was mentioned in a papyrus dating from 1550 BC found in a sarcophagus in Luxor, Egypt.[1]In 600 BC, Sushruta and Charaka described a condition called "Madhumeha" (honey urine) in their Ayurvedic Medicine books.[1] The name 'Diabetes' was coined by Demetrius of Apamea, based on the Greek term 'diabainein" (siphon) which refers to symptoms of polyuria.[3] In the 1600s, by Thomas Wills added the name 'mellitus' to indicate sweet taste of urine.[2]

The Discovery of Insulin

By 1912, it was known that destruction of the exocrine pancreas did not produce any glycosuria, which, instead, was manifested after the destruction of the Langerhans Islands. There were many scholars in several countries that helped to arrive in this conclusion.

These prior discoveries helped scientists who we now consider as the scientists that discovered insulin; Fredrick Banting, Charles Best, James Macleod and James Collip. Surprisingly, except for Macleod none of the others had any training in endocrinology. Michel Bliss beautifully described the discovery of Insulin in his book.[3]

Fredrick Banting was trained in Orthopaedics in Canadian army medical service. During the World War 1, he was severely wounded in his arm, which barely escaped amputation. After the recovery he joined general practice in Ontario which was not successful. Therefore he worked as a demonstrator in the university as a part time job.

For medical students, he lectured carbohydrate metabolism. Since he didn't have much knowledge on this subject, he read extensively on pancreatic histology and function. On November 1st 1920, he read a paper by Moses Barron on histology and function of pancreas. In this paper it was mentioned that when stones blocked pancreatic ducts, there was gradual atrophy of acini in contrast to the islets of Langerhans.4 Banting thought that the reason for the failure to produce effective pancreatic extract by previous investigators was due to a destructive effect of trypsin on the hypothetical hormone. It could possibly be successful if the cells producing trypsin (acini) were destroyed by ligation of pancreatic ducts and the remaining part of the gland (islets of Langerhans) could then be used as the original material to reduce blood glucose in diabetic patients.

Banting outlined his idea to his Professor following day. Since facilities to conduct such research were not sufficient at the University of Ontario, He was referred to Professor John Macleod of University of Toronto. Although Macleod was skeptical about Banting's theory, Macleod accepted to take Banting for a summer project and provide an undergraduate student (Charles Best) to help him and some dogs to start with.

On May 17,1921, Banting and Best had started on their experiment. Banting operated on several dogs (either pancreatectomy or ligation of pancreatic duct). However, the results were erratic due to summer heat, because they could not keep dogs alive to conclude the experiment. First encouraging results appeared after 2 months of tiring work. Dog no. 410, who had pancreatectomy, showed reduction in blood sugar with intravenous injections of a pancreatic extract obtained from a duct-ligated dog degenerated pancreas which was sliced and chilled in Ringer solution. They named this extract as "Isletin". The first presentation of this data was done at a journal club of University of Toranto on November 14,1921. Encouraged by positive feedback from audience, Banting and Best decided to carry out longevity experiments. But they made two major changes in their experiment procedure. Due to the limited supply of duct-ligated dog pancreatic extracts, they used extracts of fetal calf and beef pancreas obtained from a nearby slaughterhouse. Also they changed the extraction procedure by using alcohol instead of Ringers solution.

The first promising results were observed in Dog no. 33 called Marjorie. She had her pancreas removed and she was first treated with 10 cc intravenous injections of filtered fetal calf followed by beef pancreatic extracts in acid-alcohol. Her urine was sugar free after 1 hour and she was kept alive for 70 days with repeated injections. A pathologist provided the proof that no pancreatic tissue remained in Marjorie.

On January 11, 1922, the same pancreatic extract used in Marjorie was administered to a 13 year-old diabetic boy, Leonard Thompson at the Toronto General Hospital. However the results weren't very promising as it produced only modest reduction (25%) in blood glucose and injection led to an abscess at the site of injection due to impurities. So Toronto team's next target

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was to produce a preparation suitable for human administration. It was on this background that James Collip who was a professor of Biochemistry, developed a method to obtain purer pancreatic extract by increasing alcohol concentration, which allowed active substance to precipitate. About, 2 weeks after the first test, Leonard Thompson received the new extract made by Collip subcutaneously and the results were excellent as indicated by disappearance of glycosuria and ketonuria and the normalization of blood glucose concentration.[5] Subsequently, six more patients were successfully treated and first report of human treatment of insulin appeared in the Journal of Canadian Medical Association in 1922.[5]

In 1923, Banting and Macleod were awarded Nobel Prize for their discovery of Insulin. They shared their prize with Best and Collip respectively. It was the first time the prize awarded for such a recent discovery (barely 2 years) and up to date Banting is still the youngest recipient of the Nobel Prize in Physiology or Medicine. It should be highlighted that although, Toronto team obtained patent rights for insulin, they handed over their patent rights back to the University for the exchange 1 dollar each to ensure access of this life saving drug to all diabetic patients across the globe.
Since Toranto team faced with difficulties to meet increasing demands, they agreed to collaborate with Eli Lilly for large scale insulin production. Other major players of insulin production were Novo Nordisk Insulin Laboratorium in Denmark, The Medical Research Council and Burroughs Wellcome in Great Britain, The National Health Institute in Poland and Hoechst A/G in Germany.

Advances in clinical use of insulin

a) Changes in the insulin source

Before the 1980s, all Insulin preparations were of animal origin. Pork and beef insulin differs from human Insulin by one amino acid and three amino acids respectively. Main disadvantages of animal Insulin were the development of allergic reactions and production of insulin antibodies. Also due to tedious extraction procedure, there weren't enough supply of animal insulin to meet increasing clinical demand.
In 1978, David Goeddel, Arthur Riggs and their Genentech colleagues produced the first human Insulin using recombinant DNA technology.[6] Humulin that was the first commercially available human Insulin came to the market in 1983. Novolin and Insuman were introduced subsequently in 1991 and 1997 respectively.

b) Production of concentrated insulin

Original commercially available preparation was U-5 insulin (5 U per ml). The concentration of insulin was increased over time from U-10 to U-80.[7] In the early 1970s, the most common insulin preparation was U-100. More concentrated insulins were introduced for patients with severe insulin resistance who require more than 200 units per day. U-500 contains 500 U of regular insulin in 1ml and its pharmacokinetics is quite similar to NPH insulin.

c) Production of insulins with prolonged duration of action

Initial insulins were short acting and had to be given as multiple daily injections. In 1936, the first long-acting insulin (Protamine Zn Insulin) was developed by H.C. Hagedorn to overcome this defect. Addition of protamine delayed the action of Insulin and Zn caused crystallization of Insulin.
In 1946, Nordisk produced neutral protamine Hagedorn (NPH) insulin that was a crystallized suspension of human insulin, protamine and zinc in a neutral buffer. NPH Insulin has the advantage of being able to mix with regular insulin without changing the pharmacokinetics of both. The first 'peakless' basal insulin, known as ultralente, was developed during the 1950s by employing an extended zinc suspension without protamine.[8] The commonly used intermediate acting Lente Insulin was aInsulin Zn suspension which contained 30% semilente and 70% ultralente. Lente insulin is no longer produced due to the availability of long acting insulin analogues.

d) Introduction of rapid acting insulin analogues

In 1998 United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight glycemic control was associated with reduced incidence of microvascular complications.[9]However Accord Trial showed that lower HbA1cs were associated with higher mortality.[10]

So there was a need to produce exogenous insulin, which has similar pharmacokinetic/dynamic characteristics of endogenous insulin. Tweaking amino acid sites/composition in the native insulin molecule produced insulin analogues with faster absorption, earlier peak action and faster offset. Insulin lispro, which was the first rapid acting insulin analogue, came to the market in 1996. Subsequently, Insulin aspart and Insulin glulisine were introduced in 2000 and 2004 respectively.

e) Production of long acting basal insulin

Similarly, long acting basal insulins were produced to replace NPH Insulin and Protamine Zn Insulin. In 2000, insulin glargine was introduced as the first long acting basal insulin. This was followed by insulin determine in 2005. Insulin degludec which has an ultralong duration of action (>42 hrs) was approved in 2015.

f) Advances in the method of insulin delivery

Initially, insulin was administered using only vials and syringes. Novo Nordisk launched the first insulin pen in 1985.11 More recently smart Insulin pens, which have the ability to calculate and tracks doses, provide helpful reminders and integrate with blood glucose data and provide dosing recommendations were developed.

Inhaled insulin was an attractive option that could prevent the need for injections. Exubera and afreeza were intro-

duced into the market as inhaled insulins. But the cost, limited dosing flexibility and continued concern about pulmonary effects had limited its clinical use.

Continuous subcutaneous Insulin infusion (CSII) using insulin pump was a key development in the method of insulin delivery. In 1963, Arnold Kadish designed the first insulin pump but it was difficult to use due to the size like an army backpack.[12] The"Big-blue Brick" which was the first wearable pump was developed in 1976 and Medtronic introduced the first commercial pump to the market in 1983. Another major milestone was the introduction of closed-loop system in which glucose readings by continuous glucose monitor (CGM) would allow insulin pump to deliver automated insulin doses accordingly. Currently commercially available pumps such as Medtronic, Omnipod and Tandem are hybrid closed-loop systems that allow delivery of both automated and manual insulin doses.

Insulin use in Sri Lanka

Lente Insulin was widely available in Sri Lanka for few decades although exact date of introduction was uncertain. Recombinant human insulin (Regular, Isophane and Premixed) has been available in Sri Lanka since 1994. Rapid acting insulin analogues and long acting insulin analogues were introduced into Sri Lanka in 1999 and 2007 respectively. In the government sector, only recombinant human insulin is available as vials. In the private sector, diabetic patients can buy both recombinant human insulin and rapid/long acting insulin analogues in the form of cartridges, which can be used in insulin pens. Introduction of insulin pump to Sri Lanka is delayed due to financial constraints.

Possible future developments of insulin

For the past 100 years, there has been a tremendous development in insulin formulation and delivery. We expect similar improvements in the next 100 years also. There is a hope for the development of better insulins with even faster pharmacokinetics, once weekly insulin and oral insulin. If we could produce glucose responsive 'smart' insulin that increase circulating concentrations under conditions of hyperglycemia, diabetic patients could avoid strict dietary patterns that limit carbohydrate intake.

Possible technological improvements in insulin delivery include improved algorithms for fully automated insulin delivery devices, implantable devices and dual hormone systems that deliver both insulin and glucagon.[13]

Conclusion

Although, we have made huge strides after the discovery of insulin in the management of diabetes, there are several challenges in which we could not find a definitive answer. Despite extensive research, we could not find a cure for Type 1 Diabetes. Also we seem impotent to control the current raging pandemic of Type 2 Diabetes and Obesity. In addition, we could not find an effective mechanism in which accessibility for insulin is guaranteed for all diabetic patients across the world.

Also it should be noted that Toronto team sold their patents for insulin back to the University of Toronto for 1 Canadian Dollar each and Banting is reported to have remarked, "Insulin belongs to the world, not to me". Therefore let's do not forget Banting's altruism and make every effort to provide equal access of insulin for all diabetic patients around the globe. That's the best way we can salute these gentleman as we celebrate centennial anniversary of the discovery of insulin.

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