History of Diabetes: From Ants to Analog

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Abstract
The earliest description of diabetes was documented in the writings of Hindu scholars as long as in 1500 BC. In 1921 the Canadian scientists Fredrick G. Banting, Charles H. Best, J.J.R. Macleod and James B. Collip discovered insulin, a peptide (small protein hormone) which lowers blood sugar. They extracted insulin from the islets of animal pancreases. A year later, in January 1922, bovine insulin was first given to humans by injection. The co-discoverers, in particular James Collip, continued their work to purify the insulin extract to make it safer and more effective. In 1936, protamine, a low-weight protein, was used to develop a suspension. In 1951 the amorphous 'lente' insulins– semilente, lente and ultralente were developed. After several years of laboratory work during the years 1963–1966 human insulin was chemically synthesized. In 1975, fully synthetic insulin was synthesized. Since 1996, different insulin analogues have been introduced worldwide. Insulin therapy is undergoing a paradigm shift now a days and at this hour we need to focus on the cardinal principles of initiating, optimizing, and intensifying the treatment for achieving adequate control.

A Brief History of Time...

The earliest description of diabetes was documented in the writings of Hindu scholars as long as in 1500 BC. They had already described “a mysterious disease causing thirst, enormous urine output, and wasting away of the body with flies and ants attracted to the urine of people.” The term diabetes was probably coined by Apollonius of Memphis around 250 BC, which literally meant “to go through” or siphon as the disease drained more fluid than a person could consume. Later on, the Latin word “mellitus” was added because it made the urine sweet.¹

Sushruta, Aretaeus, and Thomas Willis were the early pioneers of the treatment of diabetes. Greek physicians prescribed exercise, preferably on horseback, to “employ moderate friction” and alleviate excess urination. Wine, overfeeding to compensate for loss of fluid weight, starvation diet, potato therapy, and oat cure were some of the other curious forms of remedy suggested for the therapy of diabetes in olden days. ¹ Sir William Osler, in the year 1915, is said to have even recommended opium! Early research linked diabetes to glycogen metabolism, and the islet cells of pancreases were discovered by Paul Langerhans, a young German medical student. In 1916, Sharpey-Shafer of Edinburgh suggested that a single chemical was missing from the pancreas and proposed its name as “insulin.” The term insulin originates from the word Insel, which is German for an islet or island.

Researchers like E.L. Scott and Nikolaes Paulesco were successful in extracting insulin from the pancreas of experimental dogs. The key breakthrough, though, came from the Toronto University with the discovery of insulin in 1921. FG Banting and JIR Macleod were awarded the Nobel Prize for Physiology or Medicine in 1923. ² They shared their prize money with CH Best and JB Collip who were “left out” by the prize committee. Banting and Best injected the crude pancreatic extract “thick brown muck” into a 14-year-old boy named “Leonard” in January 1922. His blood sugar levels dropped significantly, but an abscess developed at the injection site making him acutely ill. A refined extract was again administered after 6 weeks, causing drop in blood sugar levels from 520 mg/dl to 120 mg/dl within 24 h. Leonard lived for 13 years before dying of pneumonia (another disease for which no cure was available in those days).²³

Evolution of Insulin

On May 1922, Eli Lilly signed an agreement to pay royalties to the Toronto University to increase the production of insulin. In 1923, August Krogh and Hans Christian Hagedorn began the mass production of insulin extracted from porcine pancreas in Denmark. The Nordisk Insulin Laboratorium (now Novo Nordisk) was thus established. In 1955, Sir Frederick Sanger characterized the amino acid sequence of human insulin, making it the first protein to whose sequence was determined. He was awarded the 1958 Nobel Prize in Chemistry for this work. Subsequently, Hans Christian Hagedorn discovered the prolonged effect of insulin by adding protamine to the insulin molecule. Various intermediate acting preparations were formulated to provide 24-h control of blood glucose. Purified versions of animal insulin were developed in 1974 by chromatographic techniques (less than 1 pmol/l of protein impurities) known as “monocomponent MC” “single peak” insulin in order to reduce the allergic reactions and lipodystrophy.

In 1978, recombinant DNA technology was used to produce synthetic human insulin in E. coli. In early 1980s, mass production of rDNA human insulin was commenced. By the mid of nineties, the structure of human insulin was modified by altering the amino acid sequence (addition, deletion, or exchange of amino acids) to produce insulins with better pharmacokinetic properties, which came to be known as a “modern insulin” or “designer insulin.”

Insulin is a natural hormone and as essential as air, water, and light. Amongst all the antidiabetic medications, it is the most potent agent that reduces blood glucose levels. Its benefits exceed

Table 1: Insulin Changes at a Glance

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<tr>
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beyond the realms of glycemic control. It reduces glucotoxicity and lipotoxicity, reverses insulin resistance, preserves beta cell function, and it improves lipid profile, endothelial dysfunction, anti-inflammatory effects, and anti-platelet effects as well as the quality of life. In spite of all these benefits, there is an inherent clinical inertia before initiating insulin therapy, especially for patients with type 2 diabetes mellitus. Some of the main barriers to insulin therapy, either patient- or prescriber-related are summarized in Table 2.

### The Insulin Dream

Although the accomplishments look glorious, we still have lots to achieve. An estimated 250,000 children in developing countries under the age of 14 years have type 1 diabetes. Some 38,000 of these children are in Africa. Jean-Claude Mbanya, the President of the International Diabetes Federation (IDF), has observed that “Lots of children in the developing world are dying of diabetes when we have had a life-saving drug for 85 years.” We have a dream, “the insulin dream” to achieve.

Insulin therapy is undergoing a paradigm shift and at this hour we need to focus on the cardinal principles of initiating, optimizing, and intensifying the treatment for achieving adequate control. This will involve initiation at an appropriate time by casting aside the inertia and overcoming all barriers; optimization by treating the target by taking the advantage of all insulin formulations available and intelligent drug administration; and intensifying the use of a patient-tailored and customized regimen that aims for a fuller, better, and normal life.

We have come a long way from certain death to the discovery of insulin, from impure to purified human insulin, from once-daily long-acting insulin to continuous subcutaneous insulin infusion pumps, and from urine glucose testing to real-time continuous glucose sensors. Different delivery systems have also been invented to enable injection profile similar to the normal insulin secretion of the human body. The journey from “ants to analogs” has been a truly fascinating one in the world of medical science.

### References