100 Years of Insulin: The Evolutionary Journey from Ants to Analogs in Diabetic Care

DR. SWARUP JENA

Clinical Research Manager, Auxein Medical Pvt. Ltd. Delhi

Abstract- In the ancient time, one of the earliest documented clinical evidence for diabetes was as 'a mysterious diseases causing thirst, enormous urine output and the patient's urine attract flies and Ants. The discovery of INSULIN by Banting and Best was one of the greatest discoveries of the 20th Century in the field of medical innovations, a serendipitous intervention that shapes the future of diabetic care. Following the successful discovery, a bovine crude pancreatic insulin extract was injected into a 14-year-old boy named 'Leonard Thompson' at Toronto General Hospital in January 1922. This was also one of the earliest interventional Human Clinical Trials globally. Insulin also opens up a new avenue for industry-academic linkages in diabetes research. This article is an attempt to capture one of the finest story in the history of medical innovation.

Indexed Terms- World Diabetes Day (WDD), History of Diabetes Care, Evolution of Insulin

I. INTRODUCTION

In India, 14thNovember is celebrated as Children's Day, a day to educate, aware and advocates the rights and welfare of children. In the field of medicine, the day is celebrated as '*World Diabetes Day*. In the contemporary world, Diabetes is a global epidemic. WDD is a flagship programme of International Diabetes Federation (IDF). The Primary Goal of WDD is global diabetetes awareness campaign focusing on Diabetes Mellitus. The Theme for WDD 2024-26 campaign is *"Diabetes and Well-being"* focuses on the physical, mental and societal well-being of people with diabetes. In the contemporaty scenario diabetes education is key to the overall well-being. need for better access to quality diabetes 2022 is also the Centenary celebration of the discovery of INSULIN by Banting and Best, one of the greatest discoveries of the 20th Century in the field of medical innovations, a serendipitous intervention that shapes the future of diabetic care. Every year WDD was celebrated on 14th November to commemorate the birthday of Sir Frederick Banting.This article is an attempt to spread awareness about the disease and share the journey of diagnostic and treatment methods in diabetic care.

- *The silent killer*

In the contemporary world, Diabetes is recognized as a major lifestyle disease. Globally, 537 million adults (1 in 10 people) are living with diabetes; 541 million adults have impaired glucose tolerance (IGT), a medical condition called *Pre-diabetes* where blood glucose levels are higher than normal, but not high enough to qualify as diabetes. Pre-diabetic people are at higher risk of developing diabetes in the future. Diabetes claimed 6.7 million deaths in 2021 (1 in every five seconds). More than 1.2 million children and adolescents are living with type-1 diabetes. Half (1 in 2 people) have undiagnosed diabetes (individuals who did not know about their diabetes status but had high random or fasting blood glucose levels). The global health expenditure on diabetes is estimated at USD 966 billion in 2021 a 316% increase over the last 15 yearsDiabetes is no longer a rich man's disease. Every 3 in 4 adults with diabetes live in low and middle-income countries. *India has an estimation of 77 million people formally diagnosed with diabetes, the second most affected country in the world, after China*. One in seven people with diabetes in the world is from India. In addition to that 25.2 million people have pre-diabetic conditions. 57% of adults with diabetes are undiagnosed in India. (IDF, 2021)

- *About World Diabetes Day*

Diabetes starts as a silent disease, advances painlessly, almost imperceptibly, affects almost all the organs, and leads to partial or permanent disability and premature death, hence often defamed as the '*Mother of all Diseases*'.World Diabetes Day (WDD) was created in 1991 jointly by the International Diabetes Federation and the World Health Organization in response to growing concerns about the escalating health threat posed by diabetes. With the passage of United Nations General Assembly Resolution 61/225, WDD became an official United Nations Day in 2006. The UNGA resolution recognizes diabetes as a chronic, debilitating, and costly disease associated with severe complications that pose severe risks for families, Member States, and the entire world. The disease poses a serious challenge to global development agendas such as Millennium Development Goals (MDG) and Sustainable Development Goals (SDG). UN advocates the urgent need to pursue multilateral efforts to promote and improve human health and encourages Member States to develop national policies for the prevention, and treatment and provide access to treatment and healthcare education. WDD is the world's largest diabetes awareness campaign celebrated in more than 160 countries. The campaign is represented by a blue circular logo, similar to the red ribbon symbol for AIDS awareness and the pink ribbon for the breast cancer awareness campaign. The blue circle is the global symbol that signifies the unity of the global diabetes community in response to the diabetes epidemic. Every year, the WDD campaign focuses on a dedicated theme that runs for one or more years. The theme for WDD 2021-23 is *'Access to Care*. The fundamental components of diabetes care and prevention include; access to insulin, access to oral medicines, access to diagnostic equipment, access to self-blood glucose monitoring devices, access to healthy food and a safe place to exercise, and access to education & psychological support.

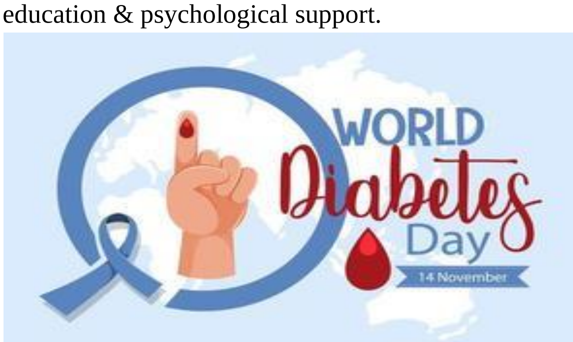

Figure 1: World Diabetes Day: Blue Circular Logo

- *History of Diabetes*

One of the earliest pieces of evidence of documentation of the disease was dated back to1500 BC in an Egyptian manuscript as *a mysterious disease causing thirst and enormous urine output'.* The ancient Indian text termed it *Madhumeha*(Sweet Urine), *a key diagnosis technique involving the urine of the patient attracting flies and ants.* Indian physicians Acharya Sushruta and Acharya Charaka (400–600 BC) were able to identify the two types of diabetes, later to be named Type I and Type II diabetes.The term diabetes was probably coined by *Apollonius of Memphis* (250 BC); however, some texts also give credit to *Demetrius of Apamea* and *Aretaeus of Cappadocian* (1st century AD), which meant (Greek-Siphon) 'to go through, as the disease, drained more fluid than a person could consume.Persian physician, *Avicenna* (980–1037 AD) first observed diabetic gangrene and concocted a mixture of seeds as a panacea. *The earlier account often referred to diabetes as a disease of the Kidney, until Sir Thomas Wills (1674) suggested diabetes may be a disease of the blood.* The Latin term *Mellitus* (Sweet) was added by Sir John Rollo (1798) to distinguish diabetes mellitus from another form of diabetes (*Insipidus*), in which urine was tasteless. Hitherto, various forms of diabetes are identified such as *Diabetes Mellitus* (further categorised into Type 1 DM and Type 2 DM, earlier known as IDDM (insulin-dependent DM) and NIDDM (Non-insulin dependent DM),Gestational Diabetes (during pregnancy), MODY (Maturity onset diabetes of the young), LADA (Latent Autoimmune diabetes in Adults). There are also diabetes-related complications to various body parts such as DFU (Diabetic Foot Ulcer), diabetic retinopathy (eye), diabetic nephropathy (kidney), diabetic neuropathy (nerve damage), periodontal (gum & mouth), brain strokes, and CVD (heart). Diabetes-related complications lead to partial or permanent disability and premature death.

- *Diabetes treatment and evolution of Insulin therapy*

In the pre-insulin era, with a limited understanding of pathophysiology, early remedies for diabetes had diverse and interesting prescriptions. A Greek physician prescribed exercise on horseback to employ moderate friction and alleviate excess urination. Other prescriptions such as wine overfeeding to compensate for the loss of body fluid, starvation diet, opium (syrup of poppies), potato therapy, oat cure, oil of roses, jelly of viper's flesh, broken red coral were some curious forms of remedy resonates the beliefs and practices of the times. However, diet and exercise advocacy by Joslin and Fitz during 19th-century physicians remains an important component of modern-day diabetic management.

The 19th and 20th centuries heralded galloping advances in diabetes-related diagnosis, treatment, and technology with numerous scientific and medical inventions. In 1869, Paul Langerhans discovered islet cells of the pancreas, one of the earliest researchers linking diabetes to glycogen metabolism. The cells were named after him as *'islets of Langerhans'*. In 1889, Von Mering and Minkowski, when experimenting on dogs, found that removal of the pancreas led to diabetes. Further studies confirmed that a single missing chemical from the pancreas is responsible for lowering blood glucose levels. The term insulin (secretion from insula/island) was coined by de Mayer and Schaefer in 1909 and 1910 respectively, but the key breakthrough came from the University of Toronto in 1921. Frederick Banting, Charles Best, and James B Collip in JJR Macleod's laboratory, in a classic animal experiment, were able to reverse induced diabetes by using canine insulin extracts; thus conclusively established insulin deficiency is the prime reason for diabetes. Following the successful experiment, a bovine crude pancreatic extract was injected into a 14-year-old boy named *'Leonard Thompson'* at Toronto General Hospital in January 1922, another pioneering event in the history of an interventional clinical trial for diabetes on humans. The *Discovery of Insulin is one of the greatest inventions of the 20th Century in medical history. The miracle molecule was decorated with three noble prizes for path-breaking medical innovations: the discovery of insulin (1923), amino acid sequence (Frederick Sanger, 1958), and radioimmunoassay (Rosalyn Yalow & Solomon Berson, 1977).* Insulin also opens up a new avenue for industry-academic linkages in diabetes research. Eli Lilly signed a royalty agreement with Toronto University for the mass production of insulin at the industrial level in 1922. The following year, Nordisk Insulin Laboratorium (now Novo Nordisk) was established; one of the top firms in this insulin segment.

In the last 100 years, Insulin therapy went through a series of changes. The first decade of insulin *(the mid-1920s to mid-1930s)* was considered a period of slow-acting insulin. Insulin in this period was derived from animal proteins in impure form causing irritation and other complications. The search for a purified protein leads to the discovery of Protamine, a protein isolated from fish sperm by Hans Christian Hagedorn, the founder of Nordisk Insulin Laboratorium (Novo Nordisk) in the year 1936. The addition of protamine leads to the formation of clumps that delays insulin release. The mid-1930s -1940s was a period of Intermediate-acting insulin such as NPH (Neutral Protamine Hagedorn) and PZI (Protamine Zinc Insulin). This discovery of partition chromatography techniques in the mid-1940s by Archer Martin and Richard Laurence Millington Synge changes the method of separation and purification. This breakthrough technique leads to a decade of purified insulin (the 1960s) known as 'Monocomponent-MC/single peak' insulin that significantly reduced allergic reactions. Martin and Synge were awarded the Nobel for partition chromatography in chemistry in 1952.

From the 1970s onwards biomedical research took a giant step with enormous development in the fields of molecular biology, immunology, human genetics, genetic engineering, and biotechnology with series of scientific inventions in the following era have changed the courses of technological development for insulin. Paul Berg's 1971 landmark gene-splicing experiment is the earliest step toward the development of Recombinant DNA technology. Paul Berg received Nobel Prize for this outstanding contribution in 1980 along with Walter Gilbert and Frederick Sanger. The first successful experimentation of rDNA in a living organism was achieved by Herbert Boyer and Stanley Cohen in 1973. rDNA technique became instrumental in the formation of a biotechnology firm in the coming year. At the forefront was Genentech, founded in 1976 by Boyer and Robert Swanson. *Synthetic insulin became the first biotechnology-based product.* Later, synthetic insulin was renamed as 'human insulin' whichis less allergic than insulin from animal sources. *'Humalin'* was the first biotechnology-based product launched in the market in 1982. The success of Genentech is considered the birth of the biotech industry.

Modern insulin can be classified into various categories; however major categories are based on the source of insulin (porcine, bovine & human), the strength of insulin, and the time characteristics of their activities. Timecharacteristics are measured through three components as Onset (the length of time before insulin reaches the bloodstream and lowers blood sugar), Peaktime (the time during which insulin is at maximum strength), and Durations (how long insulin continues to lower blood glucose). *The modern day's designer insulin or analog insulin was based on the structural altercation of human insulin sequences with better pharmacokinetic properties.* These Insulin are tweaked to adjust physiological insulin secretion e.g. Rapid-acting insulin is having onset time of fewer than 10 minutes while long-acting or ultra-long-acting insulin lasts for 24-48 hrs, even a week. Insulin therapy undergoes a paradigm shift in the last centuryand is considered the gold standard for diabetes treatment.

In the therapeutic segment, besides insulin, Oral Anti Diabetes (OADs) drugs are effective mode of interventions. OADs used as first line of treatment for type 2 diabetes, comparatively cheapers than insulin and easy to administered. The effect of sodium salicylate on urinary glucose by Muller in 1877 and the blood sugar lowering influence of guanidine in 1918, are some earliest reports on OADs. *Biguanides –Metformin*, world's most widely prescribed antidiabetic medication was first described in the scientific literature in 1922. The success of insulin ceases the OAD research between 1920s- 50s. *Sulphonyurea* (SU) - *Carbutamide* was patented in 1953, approved for medical use 1956. Till 1990s only two pharmacological classes of OADs were available namely *Sulphonyurea* and *Biguanides*, later other OAD drugs classes were discovered.

- *Evolution in diagnostic technology:*

The first clinical evidence of diabetes was the attraction of ants to the sugar in diabetic patients' urine. During the medieval period, Uroscopy (a practice that studies urine to diagnose medical conditions) is a prominent method of diagnosis. The Urine FlavourWheels describe the sight, smell, and taste of urine. Diabetes was diagnosed through the wheel due to the presence of glucose in urine which gives a different texture, colour, and taste. The first clinical test for sugar in urine was developed in 1841 by Karl Trommer, which involved subjecting a urine sample to acid hydrolysis. The self-testing of urine using benedict's reagent requires heat for colourdevelopment, however, as the test involves a liquid reagent it was difficult to transport. This problem leads to the invention of dry reagent strips. The early 19thcentury became the period of development in Dry-Reagent Chemistry. The first ever dry reagent test strip developed in this period was the litmus paper. Clinitest (a modified copper reagent tablet) introduced by Ames Company, (a division of Miles Laboratory) in 1941 was the first convenient tablet test for measurement of urine glucose followed by Clinistix (Diastix) a 'dip and read' urine reagent strip introduced by Miles-Ames Laboratory in 1956. Urine glucose testing is clinically inaccurate as it can measure only the urine output rather than the glucose presence inside the body. The correlation between urine and plasma glucose was inconsistent. The clinical problem leads to the invention of blood glucose dry-reagent test strips (visually monitored blood glucose test strips) in 1964.

Figure 2: Urine Flavour Wheels, Clinitest (1941), Clinistix (1956)

- *SMBG (Self Monitoring of Blood Glucose)*

The concept of SMBG faces stiff resistance during the period 1955 to 1970s from big diagnostic firms. During the 1970s, diabetes became a major health issue in the developed world, and clinical trial data necessitate mass screening and testing, leading to gain in the concept of self-monitoring of blood glucose (SMBG).

1st generation blood glucose meter: Ames Reflectance Meter (ARM) was the first blood glucose meter developed by Anton Clemens at Ames- Miles Laboratory in 1970 to produce quantitative blood glucose results followed by *Reflomat* (StatTek) in 1974, a reflectance meter using a modified reagent strip produced by Boehringer Mannheim requiring a comparatively smaller volume of blood. *Dextrometer* was the first meter with a digital display and could be operated by battery/power was coming to the market in 1980. A series of blood glucose meters were introduced by Lifescan in the following years under the brand Glucochek, Glucoscan. However, 1st generations of glucometers are bulky, expensive, have narrow hematocrit ranges, and take a longer period for calibration, testing, and analysis.

During the second and third generations, the technology at various platforms evolved to address the 1st generation problems. The benefits are becoming evident asa real-time recognitionof blood samples, simplifyingthe procedure by eliminating the blood removal step, separation of plasma from RBCs, correcting for blood colour in colorimetric devices, improvement in electrochemical reactions, and incorporation of checks to identify defects and user error in the procedure (software development). All these improvements lead to simplifyingthe procedure and improvingthe accuracy ofthe result. OneTouch Meter by Lifescan is a ‘second-generation’ blood glucose monitoring system (BGMS). The use of biosensor technology in diagnostics leads to the birth of third-generation BGMS. The enzyme-based electrode strip improves accuracy, precision reduces error. The ExacTech System, by MediSense, is the first blood glucose biosensor system. From the 1990s onwards smaller glucose meters became available. 3rd generation glucose meter focuses on *continuous glucose monitoring*. New technological development occurs in this period on *minimally invasive techniques* (intravenous sensors, micropores, and microneedles) and *non-invasive* techniques such as transdermal. 4th generation glucometers are focused on the alternate mode of delivery or diagnosis, non-invasive methods such as (optical detection methods, thermal detection, etc.) Chronologically, each developmental stage brought improvement in developing capillary methods for blood sampling, improving the error detection routines, decreasing the test time from minutes to seconds, decreasing the sample volume required to 1µl or less, addressing pO2 effects in electrochemical sensors with a change to GDH enzyme, improving dynamic range, improving haematocrit range

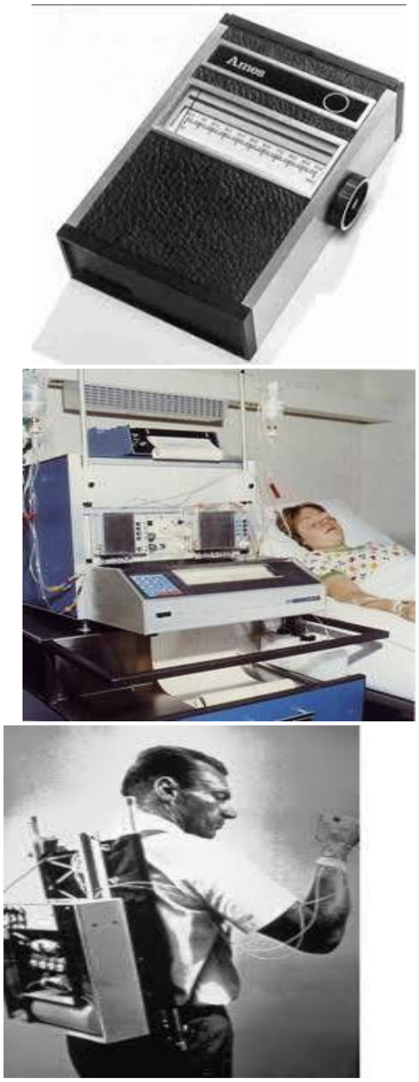

Figure 3:Ames Reflectance Meter (ARM)-(1970), Biostator (1st Generation Insulin Pump)

An insulin pump is a device used for continuous subcutaneous insulin therapy. This device is generally applicable to Type 1 diabetic patients where a daily dose of insulin is required. Compared to the SMBG device insulin pump is a relatively new technological innovation as the 1st prototype of the insulin pump was developed in 1963 by Dr. Arnold Kadish. The first bedside, a computer-controlled closed-loop insulin pump (Biostator) was developed by Miles Laboratory Inc in 1974. Biostator is an important technological innovation that is instrumental inthe development of artificial pancreas or bionic pancreas. Bionic pancrease is the most recent invention in this field is a cellphone-sized wearable device that monitors blood sugar 24/7 and releases the hormones insulin or glucagon to keep levels steady, just like a healthy pancreas would.The evolution and progression of blood glucose monitoring devices is a combination of many scientific and technological progressions and the assimilation of different technologies. They are Test strips techniques, SIP-IN technology; Cartilage based multi-strip systems, Lancet devices, No Coding technology, and biosensor technology in the Point of Care device manufacturing.Contemporary research on blood glucose monitoring devices has focused on data management through cloud-based technologies.

- *The way forward*

Thediagnostic and therapeutic journey of diabetes managementhas so far been fascinating. From Ants, Urine flavor wheel, to Continuous blood glucose monitoring and cloud-based data management in diagnostics; from medieval Opium therapy to the discovery of insulin and its progression to the designer or analog insulin, progress in oral anti-diabetes drugs, and surgical innovation such as pancreatic transplantation we have come a long way forward. However, in the meantime diabetes became a major epidemic that engulfed both developing and developing countries. The issues of availability, accessibility, and affordability remain critical to diabetes care globally. Scientific innovation can be impactful only when translates to the real world. This article is an attempt towards diabetes education and awareness in this world diabetes day.

REFERENCES

[1] Tipton MC. Susruta of India, an unrecognized contributor to the history of exercise physiology. *J Appl Physiol* 2008; 108:1553–6.

[2] Ahmed AM. History of diabetes mellitus. *Saudi Med J* 2002; 23:373–8.

[3] International Diabetes Federation, IDF Diabetes Atlas, 10th edn. Brussels, Belgium: *International Diabetes Federation*, 2021.

[4] Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. *Diabetes* 2011; 60:2672–2682

[5] Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus:

The main contributors. *World J Diabetes.* 2016 Jan 10;7(1):1-7.