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Diabetes mellitus: a complete ancient and modern historical perspective

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Abstract

Diabetes mellitus is one of medical conditions that have been extensively investigated. Despite these enormous developments cure for diabetes still remains virtual. The history is backdated to the Egyptian antiquity. As the history became unravelled with regard to the pathophysiological and biochemical bases, medical and surgical treatments and other management strategies, roadmap towards achieving success in curbing the menace of diabetes is promising. It is only in the 21st century that diabetes has been considered a chronic and heterogenous endocrine disorder which requires interdisciplinary and multidisciplinary approaches in its management, with the role of genetics looking exciting. However, there are lots of lessons to be learnt from the past. This review aims to explore the timeline of diabetes journey, and correct the inconsistencies in the historical perspectives of diabetes with intent to project the future.

Introduction

Diabetes mellitus (DM) has been described as a 'silent' epidemic. Its presentation can either be a slow onset and asymptomatic progression leading to secondary complications, or rapidly emerging symptoms leading to complications and/or coma. The projection is that by year 2030, an estimated 366-438 million (i.e., 7.8% of the world population) people will have diabetes, an increase of 54% compared to that predicted in 2010 (Wild *et al.* 2004, Whiting *et al.* 2011). After the recognition of diabetes by the Egyptians, various attempts were made to understand the heterogenous nature of the disease, pathophysiological mechanisms, appropriate therapies and prevention strategies. As part of seeking for answers to intriguing questions in diabetes, some authors were more descriptive, analytic or pessimistic rather than scientific in their search. Developmental milestones in diabetes reflect improvements in the understanding and management of the condition. The overview of the history of diabetes, starting from the ancient time to the present millennium helps to showcase the advances that have been made in

diabetes medicine and health. An attempt is made in this study to produce a chronologically organised, engrossing and multi-dimensional account of diverse documented work in diabetes. An in-depth review of the historical timeline of diabetes shows that diabetes has evolved over six era: era of recognition of disease, description of causes, clinical diagnosis, biochemical development and advancement and millennium developments.

Discussions

Ancient time (era of recognition of disease)

The first recognition of what came to be known as DM was documented in the Egyptian ancient papyrus, discovered by Georg Ebers in 1862, dating back to 1550 BC which highlighted the first documented cases of DM over 3500 years ago as stated by Ebbell, in 1937 and Tattersall in 2010. In this chronological and hieroglyphically written document of compendium of medical literature from 3000 BC, was noted '*to regulate………excessive urine*' in 1552 BC by Hesy-Ra, an Egyptian physician. Although this may as well represent the first recognition of diabetes, medical historians believe that the first attempt at describing the symptoms of diabetes was made by Aulus Cornelius Celsus (30 BC-50 AD) of Greece (Medvei 1993, Southgate 1999, Zajac *et al.* 2010). Celsus had described an ailment which presented with excessive urination in frequency and volume, and painless emaciations. Apollonius Memphites, an Egyptian physician at around 230 BC had used the prefix 'diabetes' for the first time to denote an excessive passage of urine and ascribed its aetiology to the kidney (Papaspyros 1964). At that time, due to lack of evidence, treatment had involved dehydration and phlebotomy (bloodletting) as a method of treatment (Papaspyros 1964, Zajac *et al.* 2010). In about 500 BC, two Hindu-Indian physicians (Chakrat & Sushrut) recognised that DM was not a single disorder, and they made observations of the sweetness of urine from observing ants congregating around the urine of patients (Tattersall 2010). Although relatively uncommon, as time went on, the recognition and identification of diabetes became apparent. The concept of nature showed varying and intriguing debates and revisions.

1st century (era of description of causes)

Diabetes, a Greek word was the term used to denote '*run through or siphon*' in the description of incessant urination (Adams 1856), a word originally ascribed to Demetrios of Apamaia in the 200-250 BC. However, at a time, medical historians believed that Aretaeus of Cappadocia (81-138 AD), a Greek physician re-introduced the prefix 'diabetes' to describe the wasting disease from excessive urination (Leopold, 1930). In his manuscript, Aretaeus narrated what his knowledge of origin of diabetes was:

"The disease appears to me to have got the name of diabetes, as if from the Greek word διαβητης *(which signifies a wine-pourer or siphon) because the fluid does not remain in the body, but uses the man's body as a ladder (*διαβαθρη*) whereby to leave it"* (Adams 1856).

Aretaeus went further to describe the features of diabetes as

"*a dreadful affliction being a melting down of the flesh and limbs into urine. The patients never stop making water but the flow is incessant as if from the opening of adequeducts....and patient is short lived"* (Tattersall, 2010, p.3 citing Papaspyros, 1952)*.

This describes the clinical picture of type 1 DM (T1DM). Aretaeus also distinguished polyuria of DM from diabetes inspidus, a disease in which the kidneys are unable to conserve water. A Greek physician, Claudius Galenus, referred to as Galen (129-200 AD) supported the work of Apollonius of Memphis, by attributing the pathology to the kidneys because of the diuretic effect (Eknoyan & Nagy 2005) and called it '*diarrhoea of urine'* [diarrhoea urinosa] (Zajac *et al.* 2010). From China in 200 AD, Tchang Tchong-King described the excessive eating symptoms seen in these people with diabetes. The triad of polydipsia, polyphagia and polyuria was noted in the literature as the characteristic features of the diabetes (Lehrer 2006).

Medical historians rarely mentioned the contributions of Aëtius of Amida, a Byzantine physician, in the important diabetes history. He was a follower of Galen, and his medical expertise reinforced the use of phlebotomy, emetics and use of narcotics in the treatment of diabetes. An approach used by many clinicians for many years in the first half of the 6th century (Withington 1894, Nutton 1984). In medieval Persia, Avicenna (980-1037), an Arabian physician, was the first to emphasise the clinical features and some complications of DM, describing in his book '*Canon of Medicine'* sexual dysfunction, polyphagia and sweet taste of urine (Sina 1593, Sina 2004,

Avicenna 1991). He had suggested that diabetes was a disorder of the nervous system in concert with interplay of liver dysfunction. In a quest for treatment, Avicenna prescribed the use of emetics and exercises to alleviate the symptoms, and discouraged the use of diuretics (Savona-Ventura 2002). The first documented evidence of diabetes in English literature was the use of the word '*diabete*', purported to be written around 1425. Following these early records no further progress was seen until the sixteenth century.

16th-18th century (era of clinical diagnosis)

As different researchers in Egypt, Persia, China, India, Greece, Japan and Korea searched for appropriate treatments of the strange and poorly understood disease, European medical literature showed no evidence of any documentation of the disease. In the middle part of the 16th century, Paracelsus (1493-1541), a Swiss German physician, was pragmatic in his experimental search for the pathogenesis of diabetes. He was the first to depart from the Galenic approach to medical conditions. Paracelsus had evaporated urine samples from people with diabetes with resultant production of solutes (Schadewaldt 1977). However, he did not taste it but called it 'salts'. In his conclusion, he stated that diabetes was as a result of the deposition of salts in the kidneys. The findings made him and other researchers believed that salts were the cause of excessive urination and thirst seen in these people. During the period of recognition of sweetness of urine from people with diabetes, Thomas Sydenham (1624-1689) proposed that 'chyle' from food was not completely digested with excretion of the non-absorbable residue. He concluded that this diabetes was a systemic disease as a consequence of this process (Farmer 1952). In 1674, Thomas Willis, an Oxford-trained British physician (1621-1675), re-echoed the presence of sweet substance in the urine of diabetic patients in his book *Pharmaceutice Rationalis* (Willis 1684, Tattersall 2010, McGrew 1985), although the actual substance was still unknown. However, his work triggered a new interest in diabetes research in the United Kingdom (UK). In 1682, Johann Brunner (1653-1727), aged 29 years had carried out partial pancreatectomy in a dog, and observed that the dog had extreme thirst, polydipsia and polyuria. This was the first step in the recognition of the role of pancreas in the pathogenesis of diabetes. However, Brunner did not identify the particular organ (Willis 1684, Farmer 1952, Mann 1971).Theophile de Bordeu, a French physician (1722-1776) and a pioneer in Endocrinology, in his teachings presented the conceptual theoretical framework for glands and

hormones. He inferred that each gland or organ of the body produced a specific secretion which passes into the blood and maintained the functions of the body (Medvei 1982). In his treatise, published in 1775, entitled *Recherches Sur les maladies chroniques*, de Bordeu stated

"what I believe with certainty is that every organ occupying its own nook…and living its own life…diffuses about itself, into its environment and its particular system, exhalation or certain emanations, which have taken on its characteristics, are integral parts of itself. I do not regard these emanations as useless, or of purely physical necessity. I believe them useful and necessary to the existence of the organism as a whole. I conclude that the blood bear within itself extracts of all organic parts, each of which component, I repeat again, are necessary to the wellbeing of the whole, possessing specific qualities and properties beyond the reach of the chemist's experiments…each (of the organs) serves also a factory and laboratory for a specific humor, which it returns to the blood after having prepared it within itself and imparted to it its own specific character" (Bordeu 1775).

He further reported that the 'organs of the body with several of their functions are federated with and dependent upon each other'.

In Liverpool (UK) in 1776, Matthew Dobson (1735-1784) confirmed the presence of sugar in blood as well as urine of these patients. Therefore, he surmised that the kidney only acted as an excretory system for the sugar (saccharine). It was William Buchan who, in 1785, described the clinical presentations of these patients stressing the persistent thirst, dehydration and frothy saliva, as well as elevation in body temperature. He added that the patients lacked energy and had poor appetite which resulted in emaciation and wasting. Efforts aimed at elucidating the pathogenesis of DM were spearheaded by various pathologists including Richard Bright (1789-1858) and Thomas Cowley in the 18th century (Eknoyan & Nagy 2005). In addition, Cowley performed the first autopsy in diabetes and published his findings in the '*London Journal of Medicine'* in 1788, suggesting a relationship between diabetes and pancreatic disease. In same year, Cowley isolated the sugar moiety from urine in those with diabetes. In 1798, an Edinburgh-trained surgeon of the British Army, John Rollo (1749-1809) added the suffix '*mellitus*' meaning honey, to describe the sweetness of urine in the later part of 18th century (Rollo 1797, 1798). At this stage, clinicians and researchers had no evidence of the pathogenesis of diabetes. Inadvertently, Rollo had felt that the gastrointestinal tract was responsible for the excess sugar in blood and urine, as observed by Dobson. Following Rollo's finding on the effects of various food substances on urinary sugar with high carbohydrate meals producing higher urinary glucose, whereas proteinaeous foods caused a lower urinary sugar levels. He treated his patients with 'animal diets' (Rollo 1798), and this became the gold standard for the treatment of this rare disease in the early part of the 19th century.

In the late1800s, chemical methods were developed to test the presence of glucose in urine. Prior to this, urine tasters were used to differentiate sweet urine from tasteless and limpid ones. In order to differentiate the two forms of disease in which urine was sweet from the other in which it was not, Johann Frank (1745-1821) classified diabetes into, *diabetes vera* (sweet urine) and *diabetes insipidus* (tasteless urine). The classification was therefore based on Avicenna's initial observations in patients' who passed excessive urine (Frank 1794).

18th-19th century (era of biochemical and pathological differentiations)

It was between the 18th and 19th century that type 2 DM (T2DM) became known, to differentiate it from the widely documented acutely symptomatic T1DM (McGrew 1985). The concept of protein, fat and carbohydrate metabolism in the body was introduced by Justus Baron von Liebig (1803-1873), a German chemist, who described how the body utilises compounds for tissue growth and energy production respectively (Barnett & Krall 2005). It was not until Liebig's classification of food substances, that the physiological basis of Rollo's experimental findings became obvious.

In 1815, a French-born Chemist, Michael Chevreul [1786-1889] (as cited in Barnett & Krall 2005, p.3), revealed that the actual sugar present in the urine of people with diabetes was glucose, as it behaved like "grape" sugar. He proposed that glucose was not produced in the kidneys, as was originally thought, but was due to the failure of blood to utilise it correctly. This raised the question of the actual site of production of glucose and its role in the body (Chevreul 1815). The findings by Chevreul and Liebig heralded the explosion of intense experiments in biochemistry and clinical chemistry in order to assay and measure the serum glucose levels. Interestingly, Richard Bright (1789-1858), an English physician researched extensively on nephritis, and in his treatise 'Reports on medical cases selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy' reported on nephropathy. In 1828, he pioneered the research into nephropathy seen in

diabetes and Bright's disease (Bright 1831). His findings did not incriminate the kidney as the source of diabetes, rather a complication of it.

William Prout (1785-1850) a renowned endocrinologist believed that diabetes suggested a disease of the stomach and that exposure to cold or cold drinks or rheumatism, as well as mental anxiety and distress were the most exciting causes of diabetes (Prout 1848). However, Prout, later described the clinical features of what came to be known as '*diabetic ketoacidosis*'. John Elliotson, in 1839 attributed diabetes as a disease of the kidney, and was published in his textbook entitled '*Principles and Practice of Medicine*'.

One of the pioneers of modern day endocrinology was Claude Bernard (1813-1878). A physiologist, Bernard achieved this invaluable experimental breakthrough in 1840, after he ligated the pancreatic duct of a dog which was followed by degeneration of the pancreas, and resultant diabetes (Bernard 1849). He was the first to describe the role of pancreas in glucose production, thereafter followed inconclusive reports in England in the mid-1800 on the 'glycogenic theory' i.e., formation of glycogen from glucose in the liver, hence clarifying the understanding of glucose metabolism (Olmsted 1953). Bernard had thought that the liver was the site of the problems in diabetes but not diseased in itself, and that pancreas was not the cause of diabetes (Bernard 1853, 1857). However, he was unable to identify the actual pancreatic substance involved but his experimental techniques paved way for later researchers' discoveries. Landmark laboratory quantitative test for estimation of urinary glucose (Fehling's solution) was developed by a German chemist, Hermann von Fehling, in 1948 (Fehling 1949). At this stage, the diagnosis of diabetes was based on the clinical features and laboratory diagnosis of glucosuria. A decade later, Wilhelm Petters in Germany in 1857, confirmed that urine of diabetes contains acetone alongside glucose (Tattersall 2010). However, it was Adolph Kussmaul (1822-1902) who suggested that the cause of diabetic ketoacidotic coma (DKA) was due to the presence of acetone in the blood in these patients. Thereafter, Bernard Naunyn (1840-1914) described the term 'acidosis' in T1DM, and had treated them with bicarbonate, in his diabetic clinic. He was the first to set up such a clinic for people with diabetes (Naunyn 1898). By 1855, Friedrich Theodor von Frerichs (1819-1885), a famous German experimental pathologist, reported that in people with diabetes, 20% had severe pathological changes in their pancreas (Frerichs 1884). George Harley, in 1866, formulated theories to explain the

pathophysiologies of diabetes, based on the initial discoveries of Bernard. However, he was unable to add much to the knowledge of diabetes at that time. Vehemently, Frederick Pavy had disagreed with the validity in the fundamental research by Bernard on glycogenolytic theory, and went further to argue that glycogenolysis had no part in diabetes (Pavy, 1869). Little did he know that Bernard's theory was going to drive others to identify the enzymes responsible for such metabolic pathway (Cori & Cori 1946). This discovery won a Nobel Prize in Medicine. These formed the bases for the introduction of experimental, investigative and laboratory medicine in clinical practice. The associations of diabetes with the complication of the eye, retinitis and retinopathy, was first documented by Henry Noyes in 1869. However, even though Armand Trousseau in 1865 made a report on people with diabetes with bronze pigmentations of their skin, he did not suggest a correlation. It was Friedrick von Recklinghausen in 1890 that recognised that in those patients with haemochromatosis suffered from diabetes. On the contrary, an English scientist, William Dickinson in 1875, postulated that diabetes was a 'disease of the nervous system, characterised by the secretion of saccharine urine'.

Paul Langerhans, a German pathologist, in his thesis in 1869, had described new 'heaps of cells' in the pancreas histology, called 'islet cells' within the acini of the pancreas, as an endocrine gland. However, the role of the islet cells in diabetes was not immediately known, as he was not able to postulate their functions (Sakula 1988). Several researchers reported on the outcomes of experimental tests on the pancreas in the aetiogenesis of diabetes between 1869 and 1889, amongst whom were Oscar Minkowski (1858-1931), Joseph von Mering (1849-1908) and Gustave-Edouard Laguesse (1861-1927). Minkowski and Mering in 1889 reported that following removal of the pancreas in dogs, the clinical picture resembled 'real permanent diabetes mellitus', which corresponds in every detail to the most severe form of this disease in man (Minkowski 1929, von Mering & Minkowski 1890).

In 1886, a German pathologist, Julius Dreschfeld described in details the clinical features of DKA. In his lecture presented to the Royal College of Physicians in London, he described the chemical determinations of acetoacetic acid, ketones and beta-hydroxybutyric acid and their roles in DKA.

The quest to attain complete insulin independence has resulted in trials of pancreatic or part-islet cell transplants for people with T1DM. The first trial was in 1891, by a French scientist, Edouard Hedon, when a

dog's pancreatic tissue, was auto-transplanted under the skin which prevented it from developing diabetes even after the pancreas was excised. This experience proved invaluable when in 1893, in London, the first xeno-transplant was performed in a boy of 15 years.

In 1893, a French scientist, Laguesse confirmed the initial observations of Cowley (relationship of diabetes and pancreatic disease) and named the little *'heaps of cells'* seen in the pancreatic tissue as '*islets of Langerhans'*. Despite the identification of the cells responsible for the secretions of pancreatic substance that regulates glucose, the actual hormone secreted by the islets cells of Langerhans was not known or identified. These experiments changed the entire understanding of the disease and catapulted to an important milestone in the history of diabetes.

Further insight into the role of sugar in the pathogenesis of DM was highlighted by Apollinaire Bouchardat and Moritz Traube in 1870 who observed that consumption of carbohydrate diets increased the sugar content of urine, while low carbohydrate diets had the opposite effect. They began to use personalised dietary modifications as diabetes treatment. Bouchardat and Étienne Lancereaux in 1880, supported the earlier work of Bernard, and implicated the pancreas in the patho-aetiology of diabetes (Bouchardat 1852, 1875, Lancereaux 1877). The pair had carried out a prospective study on these patients, using the earlier findings of Rollo's dietary experiment and found that vegetable rich diets did not cause elevations in urinary glucose. In furtherance, they later described the two different clinical presentations in patients with diabetes; obese [*diabetes gras*] and lean [*diabetes maigre*] (Tattersall, 2010). In continuity with the dietary treatment, Arnoldo Cantani (1837-1893), an Italian physician followed the work of Bouchardat. He, however, made some restrictive dietary modifications of Bouchardat's starvation diet, to allow patients the number of calories that would not produce glucosuria. Cantani observed that fatty liver was seen in people with diabetes than in those without diabetes. These impacts of these findings were not immediately apparent until some years later (Lehrer 2006).

As the quest for definitive treatment heightened, Elliot Joslin (1869-1962), from the Massachusetts General Hospital, Boston pioneered the use of dietary modifications, exercise and patient's education as tools in the improvement of glycaemic control in T2DM (Joslin, 1915, 1921, Allen 1953) based on the observations of Rollo on the effect of different food substances on urinary glucose. In his publication, The *Treatment of Diabetes Mellitus*, Joslin described in

details the effects of diets and exercise in the treatment of diabetes (Joslin 1917). Frederick Allen (1879-1964) supported the role of dietary restrictions (starvation diets). He had used diets very low in calorie, as low as 450 calorie/day in his patients. This improved their diabetes symptoms and prolonged their lives, although was associated with high mortality especially in T1DM. These approaches are still components of present day management of T2DM, and have been shown to improve the quality of life in these patients.

With advancements in knowledge of research, physiology, biochemistry, medicine and surgery of pancreas and the role of its secretions in glycaemic control, many researchers began to narrow down their studies on the pancreatic gland. These changed the concepts and treatment of diabetes as time went on.

By the end of the 19th century, accurate and reliable scientific methods of assessment of both blood and urinary glucose were still not available.

19th-20th century (era of insulin development and advancement)

Up to the 19th and early part of the 20th century, diabetes was still considered a rarity outside Europe due to lack of epidemiological evidence. Following the discovery of the role of pancreas in the pathogenesis of diabetes, clinical researchers and clinicians began treating the patients with pancreatic extracts. In 1901, L. W. Ssobolew (1876-1919) evidence from experimental ligature of the pancreatic ducts showed that even though the pancreatic ducts became atrophic with destruction of enzyme secreting acinar cells, the islet cells remained viable for weeks without any resultant diabetes (Ssobolew 1902). In 1902, in Aberdeen, Scotland, John Rennie and Thomas Fraser extracted the pancreatic substance from Codfish. They had injected the extract into a dog, which died soon thereafter. The death of the dog may have resulted from either severe hypoglycaemia or anaphylactic shock or a combination of them. Developments in the pancreatic extracts were undertaken by other researchers that led to improved purities. George Ludwig Zeulzer, a German physician, in 1908, had treated his dying diabetic patients with pancreatic extracts he termed 'acomatrol' which improved their clinical conditions (Tripathy *et al*. 2012). He patented his 'acomatrol' in the USA and used it to revive a comatose diabetic patient. However, his subsequent extracts were noticed to produce severe reactions and complications with high mortality. Following this outcome, Schering Pharmaceutical withdrew their funding. Regardless of this drawback, Zeulzer continued to work on the extracts and later on

modified it for Hoffman-La Roche Pharmaceuticals. Unfortunately, the newer extracts had unwanted side effects of seizure-like attacks and consequent deaths, presumably from severe hypoglycaemic and/or anaphylactic shocks (Zuelzer 1908). Zeulzer's failure to purify his extracts and its consequent complications led to his discontinuation of his attempts at achieving the goal-to isolate the active substance from the pancreatic extract (Murray 1969). It is worthwhile noting here that knowledge of insulin was described earlier by the Belgian physician, Jean De Meyer in 1909, as internal secretions of the islets of Langerhans (De Meyer 1909 cited in Tattersall 2010). However, it was in 1901 that Eugene Opie established a clear link between the islets of Langerhans with the aetiology of diabetes. He had documented evidence of hyalinisation and sclerosis of islets of Langerhans in some patients with diabetes. This assertion was supported by an English physiologist, Edward Sharpey-Schafer in 1910, through the outcome of his experiments on dogs whose pancreases were surgically removed. Without any experimental evidence, John Homans in 1913 suggested that insulin was produced by the β-cells of the islets of Langerhans (Homans 1913, Papasyros 1952).

Stanley Benedict in 1911 and other researchers' years later developed methods of detection and estimation of urinary glucose (using Benedict's solution), which helped in the prognosticating effects of treatment on these patients (Benedict 1911). Urinary ketone bodies were also tested using the methods of sodium nitroprusside by Cecil Rothera in 1910 (Rothera 1908, Fearson 1921).

As research was going on in an attempt to isolate the active hormone responsible for glucose utilisation present in the pancreas, the concept of islets cell transplantation had been documented when the English surgeon, Charles Pybus in 1916, attempted to graft pancreatic tissue in order to cure diabetes (Pybus & Durh 1924). As a result of high mortality recorded in his surgical approach he surmised:

"although transplants represented the most rational form of therapy, they would continue to fail as long as science did not understand the principles involved" (Schlich 2010, p.74).

In 1919, a young American biochemist and researcher Israel Kleiner (1885-1966) published an article in the *Journal of Biological Chemistry*, describing a procedure for pancreatic extract that reduced the blood sugar level in those with diabetes, at the Laboratories of Rockefeller Institute for Medical research (Kleiner 1919). However, Kleiner, working together with his colleague, an inventive physiologist,

Samuel Meltzer (1851-1920) slowly infused pancreatic extracts into pancreatectomised dogs and analysed their blood glucose levels prior and after the infusions at different time intervals (Kleiner & Melzer 1915, Kleiner 1919). Unfortunately, the original work started by Kleiner was not concluded after he left Rockefeller Institute.

Despite this, in 1920, Moses Barron reiterated the relationship between islets of Langerhans and diabetes pathogenesis from his experimental findings. His findings published in a paper entitled, '*the relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis'* concluded that obstruction of the pancreatic acinar, however, did not affect the islets of Langerhans, as there were complete preservation of the islets and no resultant diabetes. Prior to the successful discovery of insulin by Banting and colleagues in 1921, Nicolae Paulescu, a Romanian physiologist in the same year had extracted pancreatic preparations from animals (*pancreine*), but the World war 1 prevented him from publishing his work early until the 21st of August 1921, when the *Archives of Internationale de Physiologie* in Liège, Belgium published his summaries: *Research on the Role of the Pancreas in Food Assimilation*. In his conclusion he was to continue the experiments and unfortunately, as he had patented his original work in Romania, the saline extract was not used in humans (Bliss 1993, Rosenfeld 2002, Paulesco 1921).

The studies on the experimental works of Kleiner (at the Rockefeller Institute and New York Medical College in 1919), Baron (in Minneapolis in 1920), and the 'near to the discovery' works of Paulescu (in Bucharest between 1916-1920), and the identification and the description of the morphology of pancreatic cells that produce the hormone insulin by Paul Langerhans in 1869, heralded new research directions leading to the discovery of insulin in 1921 by Frederick Banting (1891-1941) and his colleagues in Canada: John Macleod (1876-1935), James Collip, and Charles Best (1899-1978), in an acid ethanol extract of pancreas from dogs (Bliss 2007, Tattersall 2010). They isolated and purified insulin, which was made more available to people with diabetes. Their first trial was on a 14 year old T1DM, Leonard Thompson in 1922 who later died after 13 years, at age 27 (Mann 1971). It was observed to reduce blood and urinary glucose concentrations, and ketones disappeared in urine (Banting & Best 1922, Banting et al. 1922). Their discovery won Banting and MacLeod a Nobel Prize in 1923.

Following the effects observed by the scientists, in 1922, Eli Lilly and Company signed an agreement with

Banting and Best of the University of Toronto for purification and commercial production of bovine insulin which was used to treat humans. Robert Lawrence, an endocrinologist was diagnosed with diabetes in 1919, and was given 4 years to live. However, he benefitted from early insulin therapy, soon after its discovery. He set up a Diabetes Clinic at King's College Hospital, London in 1923. As the discovery of insulin was still gaining international publicity, in the later part of 1922, a Danish Nobel laureate in Physiology, two years earlier, for the discovery of the mechanism of regulation of the capillaries in skeletal muscle, had visited McLeod in Toronto (Sulek 1967, Larsen 2007). After his return to Denmark, he liaised with Hans Hagedorn to found Nordisk Insulinlaboratorium, in 1922. Later on in 1923, Novo Company and Nordisk merged forming Novo Nordisk, which became a colossum in insulin and pharmaceutical industry. In 1934, he also founded the British Diabetic Association (later became Diabetes UK), with the help of an author of 'Time Machine', H. G. Wells. This was the first of such national organisation in the world. In 1923, Novo Nordisk Insulin Laboratory started the commercial production of insulin. This invention brought about the evolutionary changes in newer insulin manufacture, producing newer insulin formulation; modified slow and fast acting regular insulin. At the John Hopkins University in 1926, John Abel, a biochemist prepared the first crystalline insulin (Murnaghan & Talalay 1967), which Svedberg determined its molecular weight in 1934.

The previously, classified obese (*diabetes gras*) and lean (*diabetes maigre*) was later differentiated in the 1930s, based on the action and sensitivity of newly discovered insulin, by Wilhelm Falta in 1931, and Harold Himsworth in 1936, into *'insulin sensitive'* and *'non-insulin sensitive'* types. However, Himsworth's proposition remained unconfirmed until plasma insulin was bioassayed and measured by Joe Bornstein and Robert Lawrence, and thereafter with the availability of radioimmunoassay for insulin (Bornstein & Lawrence 1951, Yalow & Berson 1961, Berson & Yalow 1963). Invariably, this formed the basis of the present classification of diabetes into T1DM (insulin-dependent) and T2DM (non-insulin dependent) previously, labelled as *'juvenile-onset'* and *'maturity-onset diabetes'* respectively (Tattersall 2010). Falta's publication of his hypothesis of insulin resistance as the cause of T2DM heralded the pathoaetiological factors in T2DM (Falta & Boller 1931), although T2DM does not occur without a corresponding failure of the compensatory insulin secretion (Nolan 2010). The need for longer acting insulin was necessitated by repeated daily injections and its rapid absorption. Hagedorn (Novo Nordisk) in

1936 developed the first protamine insulin (PZI) using zinc salts that crystallised the insulin, and conjugated the insulin with specific proteins. This preparation slowed down the absorption and distribution of insulin injected. As a result of the heterogenous nature of patients with diabetes and the consequent outcomes of treatment modalities, Harold Himsworth in 1936 postulated that insulin resistance as opposed to insulin deficiency was the main aetiopathogenesis. In the disease, especially T2DM, insulin resistance results in impaired β-cell function in the pancreas (Cavaghan *et al.* 2000) and impaired insulin secretion.

The increasing incidence and prevalence with subsequent poor mortality statistics in the USA, resulted in the formation of the American Diabetes Association (ADA) in 1940, aimed at addressing these challenges. Initially formed as a national Diabetes Association but was renamed to accommodate Canadian physicians, who did not have any associations of such even after the discovery of insulin in Toronto.

The ever-evolving contribution of laser surgery in T2DM has paved way for improvements and restoration of vision in modern management strategies. Photocoagulation of retina was first discovered in 1940s by a German ophthalmologist, Meyer-Schwickerath (Meyer-Schwickerath 1989).

Although diabetes is not a disease of the nervous system as envisioned by Dickinson, similar thoughts and eventual experiments by Housay *et al.* (1942) resulted in the discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugars. These findings won Housay a Nobel Prize in Medicine in 1946.

Meyer-Schwickerath further developed a sunlight photocoagulator in 1947, and within 1950-56, he had used a Beck carbon arc photocoagulator for treatment of retinopathy associated with diabetes.

After the stabilisation of people with diabetes with insulin, there was need for an oral medication to replace the repeated injections associated with insulin. Sulfonylureas were the first oral hypoglycaemic agents to be discovered by Marcel Janborn and co-workers at the Montpellier University in France in 1942 while studying on sulphonamide antibiotics (Janborn *et al.* 1942, Patlak 2002). Unexpectedly, they found that the compound caused hypoglycaemia in animals. It was this side effect that was investigated that led to the production of sulfonylureas.

Different Pharmaceutical Laboratories began to source for the possibilities of mimicking the natural patterns of insulin actions in order to improve the quality of life of

the patients. In 1946, Hagedorn produced the first prolonged acting insulin (Neutral Protamine Hagedorn-NPH), or isophane insulin, intermediate acting insulin. Insulin research progressed at various levels of scientific discipline. Rachmiel Levine, in 1949 discovered that insulin transports across the cells are like a key. This finding was in concert with the understanding of glucose metabolism.

Initially, Best in the 1950's had made a strong proposition for an oral insulin within the preceding 10 years after insulin discovery, however, the polypeptide nature of insulin compound meant that it would rapidly be digested by enzymes of the gastrointestinal system. In quest for the discovery of an oral therapy, several trials were conducted, including the use of aspirin and synthalin, without any positive outcome.

Hallas-Muller and Schlichkrull in 1952 developed the series of Lente insulin at the Novo Nordisk Laboratory. This was a great improvement in the production of insulin injections that led in the treatment of diabetes.

However, the concept of blood glucose measurement and the methods available was first utilised in the early 1950s and its principle was based on the reducing properties of glucose. This approach, inadvertently over-estimated the actual concentration of glucose as other reducing sugars exist in blood (King & Wootton 1957). Regardless, chemical pathologists, clinical chemist, biochemists and physicians were able to at least estimate the concentration of glucose in blood in people with diabetes prior and after treatments. In 1953, glucose oxidase tablets or impregnated paper strips was introduced in the measurement of blood glucose (Kohn 1957). At the same time the tablets were used in testing urinary glucose, became available in clinical medicine (Froesch & Renold 1956, Marks 1959). In addition, urine strips were available for clinical use in 1960 which added reliability and compliance to repeated testing (Cormer 1956). The quantitative analysis of blood glucose and the semi-quantitative detection of urinary glucose levels revolutionised the management of people with diabetes and their prognoses (Marks & Dawson 1965).

The evolution and developmental milestone of bariatric surgery in obese T2DM commenced in the early 1950s and have shown dramatic contributions in the management of the disease. In 1954, Arnold Kremen and colleagues performed the first bariatric surgery, which involved intestinal anastomosis (Kremen et al. 1954). They had earlier on observed loss of weight induced by intestinal resection and anastomosis in patients and wandered if such a procedure could be beneficial in obese T2DM.

Thirteen years after the unexpected discovery of hypoglycaemic effects of sulfonamides by 1955, the German duo, Hans Franke and Jürgen Fuchs introduced carbutamide, an oral hypoglycaemic agent in the treatment of diabetes. Since the introduction of carutamide as an oral hypoglycaemic agent, research and experimental work has exponentially increased (Franke & Fuchs 1955, Bertram et al. 1955).

At the end of 1956, Littman, Zeiss and Meyer-Schwickerath used for the first time a xenon arc coagulator to treat retinal vascular diseases and anterior and posterior segment abnormal growths. The photocoagulation produced by light of various spectra (Bessette & Nguyen 1989, Krauss & Puliafito 1995).

Within two years, many more first generation sulfonylureas with different potencies, tissue distributions, duration of action and interactions were introduced into clinical practice. These include tolbutamide and chlorpropamide in 1957. Competition in the pharmaceutical industry for the production of an oral antidiabetic agent that would replace insulin injections or similar to insulin was at its peak, and in 1957, another oral hypoglycaemic agent called biguanides came into clinical use. The first two biguanides to be used were metformin and phenformin, with the former still popular till date.

Interestingly, Frederick Sanger in 1955 reported on insulin's molecular structure of the amino acid sequence, and later on Dorothy Hodgkin noted in 1969, its three-dimensional structure. In 1958, Sanger was awarded a Nobel Prize in chemistry for his work in the structure of proteins, especially insulin (Sanger 1958). Hodgkin, had previously developed methods of sequence for determining the structure of vitamin B_{12}, and consequently was awarded a Nobel Prize in chemistry. Rosalyn Yalow and Solomon Berson in 1959, reported on their development of the radioimmunoassay for insulin. Their sensitive radioisotope method led to the observation of antigen-antibody complexes. They demonstrated for the first time that hormones developed antigen-antibody reactions within 3-5 weeks of injection of insulin. This discovery resulted in the award of Nobel Prize to Yalow in 1977, which added new knowledge on measuring serum insulin levels and other serum peptides.

Theodore Maiman in 1960, discovered the first ophthalmic laser photocoagulators, which produce a single wavelength beams (Krauss & Puliafio 1995), that brings about tissue specific burns as opposed to full thickness retinal burns.

In 1961, glucagon, a hormone produced by the alpha

cells (α-cells) of islets of Langerhans, which raises plasma glucose (Samols *et al.* 1965), was introduced by Eli Lilly and Company to treat hypoglycaemia resulting from insulin therapy. The characteristic developmental milestones of insulin were also seen in its delivery apparatuses. Early insulin syringes were initially made of glass in 1961, which were used in multiple numbers of times after sterilisation alongside their needles. Later on in the late 1960s, the glass syringes were replaced by disposable plastic ones by Becton-Dickinson. This discovery greatly reduced the pain, sterilisation time, and infections associated with re-use of the syringes.

Early bariatric surgery as a management approach continued in 1963, as Howard Payne and Loren Dewind performed a jejuno-colonic shunt and further enhanced the procedure by doing a jejuno-ileal bypass. Unfortunately, the latter procedure was not unconnected with extreme intractable diarrhoea.

In 1964, McIntyre and colleagues were able to establish the concept of role of incretins in the glucose regulation (McIntyre *et al.* 1964). Initially, reported in the 1920s, to play a role in glucose regulation. It was suggested that following ingestion of a carbohydrate meal and its arrival in the intestine, the cells in the intestinal wall secrete a substance which stimulate the pancreas to release hormones that will ultimately lead to the regulation of glucose (Creutzfeldt & Ebert 1985, Porte *et al*. 2003). This concept was dismissed as it lacked scientific proof. Marks and Co-workers proposed that glucagon mediated the incretin effect (Marks 2012, Marks & Samols 1968). These brought about the well-established understanding of the hormonal regulations of glucose metabolism.

In the later part of the 20th century, however, the discovery of screening methods revolutionised the diagnosis of diabetes, to include both asymptomatic and symptomatic patients. The World Health Organisation (WHO) formed two decades previously, became interested in the study of diabetes and formed its first Expert Committee Meeting in 1964 (WHO, 1964). Following the great challenges in insulin delivery, Novo Nordisk again in 1964, went further to develop the first premixed insulin preparations which were later made available for commercial purposes.

In 1968, L'Esperance reported the progress made by the use of argon laser, which is still used to date (L'Esperance 1968, Castillejos-Rios *et al.* 1992). Laser photocoagulation has been used to provide restoration of sight in those with retinopathies of various degrees, and has contributed immensely in the management of eye complications associated with diabetes.

Newer technologies improved the availability to monitor glucose more effectively and efficiently. Ames Diagnostics Company introduced a colour-coded plasma glucose testing strips in 1964, whereas the first glucometers were produced in 1969. Glucometers brought innovations in the management of diabetes, as it improved the blood glucose estimations, allowed ambulatory assessments and reduced the frequency of hypoglycaemic episodes experienced by patients prior to its availability (O'Grady *et al.* 2012). It has progressed from urine testing in the emergency room and hospital glucose tests, to home glucometers.

The first successful pancreatic transplant was performed in 1966, by William Kelly and colleagues at the University of Minnesota in a procedure called *'simultaneous pancreas-kidney transplantation'* in T1DM (Demartines *et al.*2005, Kelly *et al.* 1967). Pancreatic transplant was associated with high mortality and failure rates, as it simultaneously involved renal transplant, and this paved the way for islet cell transplant.

Attempts at bringing down the body weights of obese T2DM patients was heightened by Edward Mason and Chikashi Ito in 1967 when they developed gastric bypass procedure which resulted in minimal complications than the earlier intestinal bypass (Mason & Ito 1967, Nguyen *et al.* 2001, Mason 1982). Mason and Henry Buchwald directed the development of improved procedures that yielded substantial weight loss with little complications. Different procedures were practiced to provide limited complications and at the same time provide sustained weight loss in obese T2DM patients (MacDonald *et al.* 1997). However, in the pharmaceutical laboratory, Donald Steiner and Philip Oyer in1967 discovered the pro-active form of insulin, which he called *'pro-insulin'* and further, described the mechanisms of insulin synthesis in the β-cells of islets of Langerhans (Melani *et al.*1971, Melani *et al*. 1970). It was the initial fundamental discoveries by Bernard that propelled, a Novel Prize winner in 1971, Earl Wilbur Sutherland, to go further to discover cyclic adenosine monophosphate (cAMP), and its role in the hormonal action, particularly with counter-regulatory hormones; epinephrine and glucagon (Sutherland 1972). Table 1 provides a synthesised summary of further advancements in diabetes research with the corresponding discoverers.

[Insert Table 1 here]

In 1971, Pierre Freychet discovered insulin receptors on cell membranes (Freychet *et al.* 1971). These discoveries paved the way for unanswered questions on possible genetic variants on insulin receptors which could account for insulin resistance in T2DM. Interests

in the molecular basis of insulin led to the identification, isolation and purification of the insulin receptor proteins by Pedro Cuatrecasas in 1972.

After the discovery of insulin, there were rapid developments in the field of diabetes research, experiments and its treatment as well as in the management of its complications. These brought about a sharp reduction in morbidity and mortality from the disease. After several years of pharmaceutical experiments, following the discovery of insulin, Johannes Meienhofer and colleagues, in Germany, Panayotis Katsoyannis and colleagues in the USA, and Y. T. Kung and colleagues in China, discovered human insulin in the 1960s (Meienhofer *et al.* 1963, Katsoyannis *et al.* 1966, Kung *et al.* 1966).

In the early 1970s, open gastrectomy was done to provide safer outcomes. Scott Dean in 1973, modified the bariatric surgery procedure of bypassing a segment of the small intestine, and yet the complications persisted (Griffen *et al.* 1983).

 By 1974, development of the Glucose-Controlled Insulin Infusion System (Biostator) enhanced continuous glucose monitoring and closed loop insulin infusion (Clemens, Chang & Myers, 1977). In addition, in 1974 Human Leukocyte Antigen (HLA) were found on the surfaces of cell membranes. Some of these HLA were identified to be associated with T1DM. In addition, in 1974, a purified form of animal insulin was produced by chromatographic techniques (Steiner & Oyer 1967). The impurities and allergic reactions of the initially produced insulin led to further work in 1975 that resulted in the production of fully synthetic human insulin in Basel, Switzerland.

The journey through the discovery of insulin, its modifications and refinements of the bovine and porcine extracts cannot be overemphasised. These advancements brought about quality of life, improved life expectancy and reduced mortality indices over the past 100 years.

The first insulin pumps such as the Mill-Hill infusers were invented in 1976. With weights of about 500g, they were uncomfortable. Current pumps are much smaller, portable and comfortable. In 1978, Wilkinson introduced another method, gastric banding, which was modified by Molina. In 1979, the first needle-free insulin delivery system, weighing less than 2 pounds, was produced by Derata, called 'Derma-Ject'.

Variability in blood glucose readings across the globe became a concern among clinicians and practitioners. In order to standardise the blood sugar measurements, glycated haemoglobin (HbA$_{1C}$) test was developed in 1979. It measures blood glucose levels over 2-3 months, which corresponds to the life span of the red blood cells (Rabhar 1968, Day 2012a).

In 1980, the duo at the University of Glasgow, John Ireland and John Paton developed the first insulin administration pen, called 'Penject'. In the same year, the outcome of the second Expert Committee Meeting brought about the diagnosis and classification of diabetes, and endorsement of the USA National Diabetes Data Group (NDDG) Report on diabetes (WHO 1980, NDDG 1979).

The classification systems of diabetes include insulin dependent (type 1 diabetes), non-insulin dependent (type 2 diabetes), gestational diabetes, and diabetes associated with other syndromes or condition (Table 2).

[Insert Table 2 here]

This new categorisation and classification led to disuse of the older terms *'juvenile-onset'* and *'maturity-onset diabetes'*. The NDDG/WHO classification highlighted that the diabetes syndrome is made up of conditions of different heterogeneity which differ in pathogenesis, natural history and treatment and/or preventive strategies. The roles of environmental and genetic influences in its aetiology were also noted (Table 3 and 4). At present there are over 50 genetic variants known to play various roles in T2DM aetiology. Evidence suggests that the people with these genetic variants have between 10-15% increased risk of diabetes. The place of gene therapy is still at its experimental and rudimentary stages.

The defining characteristic of T1DM is its abrupt onset with severe symptoms, dependence on exogenous insulin and tendency towards ketosis. The pathogenesis lies in absolute insulin deficiency from β-cell destruction, although some insulin resistance can be present.

[Insert Table 3 here]

[Insert Table 4 here]

 With improved diagnostic techniques adults have been documented to have T1DM, with 15-30% of T1DM being diagnosed after 30 years of age (Laakso & Pyorala 1985, Scott & Brown 1991, Melton *et al.* 1983) called latent autoimmune diabetes of adult [LADA] (Tuomi *et al.* 1993). Other studies reported 7% of all insulin treated patients at onset at age 30 years or more are T1DM (Melton *et al.*1983, Harris & Robbins 1994).

Advancements in insulin research continued with Graham Bell in 1980 reporting on the sequencing of the human insulin gene (Tattersall 2010, Ulrich *et al.* 1977, Bell *et al.* 1980).

The developmental milestone in pancreatic transplant continued relentlessly, although hampered by a significant degree of mortality. However, improvements in graft and patients' survival were achieved between 1978 and 1998 with newer surgical techniques (Gruessner & Sutherland 2002). The modern day knowledge of islet cell transplantation is credited to Paul Lacy in 1980, but it was Lacy and Camillo Riordi who discovered the present enzyme based method, collagenase-based method used presently in islet cell transplantation (Lacy & Kostianosvsky 1967), which led to the first successful allo-transplantation at the University of Pittsburgh in 1990 (Tzakis *et al.* 1990).

As bovine insulin continued to be made available, there was an unnecessary speculation on the possibility of sudden scarcity of insulin in the next 10 years preceding discovery, if the demand was to become more than the supply. The recently cloned gene for insulin by Ulrich and colleagues was then used to produce human insulin. This recombinant DNA 'human' insulin came into clinical use in 1980 (Keen *et al.* 1980). This success in genetic and molecular engineering in medicine was widely welcomed. In addition, this invention paved way for another milestone discovery in diabetes. In 1981, Jan Markussen and colleagues at the Novo Nordisk produced the first commercially available human insulin using DNA technology (Markussen *et al.* 1987, 1988). This has made insulin easily accessible, acceptable and readily affordable by many. This innovation alleviated fears and scares of possible run short of animal insulin injections.

The production of second generation sulfonylureas commenced at around 1970s and became available for patients use in 1983. The popular ones include glibenclamide, glipizide and gliclazide.

The role of bariatric surgery continued with modifications that produced inflatable balloon resulting in adjustable bands (Sugerman *et al.*1987, Belachew *et al.* 2002, O'Brien *et al.* 2002, Dixon & O'Brien 2002, Ponce *et al.* 2004). The outcomes of bariatric surgery in the 1980s were not only contributory to weight loss but also led to remission of diabetes in over 83% of patients. Consistent with the findings of other researchers, in 1986, Doug Hess reported the outcome of his procedure involving duodenal switch in bariatric surgery (Hess & Hess 1998). This was supposed to improve the outcome of obese T2DM.

By 1990, other sulfonylureas with better profile and relatively longer half -life came into the market, called glimepiride, Furthermore, around the 1990's, there were advancements in the delivery of insulin technology with the discovery of insulin pens, which made its administration easier and precise. In addition, there was a breakthrough in molecular and cellular pathology in the same year, 1990; when a 64K autoantibody protein associated with T1DM called glutamate decarboxylase (GAD) was identified. It was thought that the immune system can be attacked by its effect on GAD and resultant diabetes.

The term '*insulin resistance syndrome*' (syndrome X) was first used by an American endocrinologist, Gerald Reaven in his 1988 Banting lecture. He had purposed that a cluster of symptoms of central obesity, diabetes and hypertension were associated with insulin resistance and impaired glucose tolerance (Reaven 1988). More recently, syndrome X has been called metabolic syndrome, and is it one of most extensively investigated area in diabetes, as Reaven believed that it is a separate entity (Reaven 2005).

As research geared up, and explanations and theories were proposed towards the aetiogenesis and pathophysiologies of diabetes, different scholars continued to emerge to clarify the heterogenous concept of diabetes. However, the total cure continued to elude researchers. Yet the area of bariatric surgery which was demonstrated to yield observable loss of weight, in 1990, Kuzmak and colleagues pioneered the modification of gastrectomy by combining it with gastric banding (Kuzmak *et al.* 1990).

Edmond Fischer and Edwin Krebs won a Nobel Prize in 1992, for their discovery of the role of the reversible protein phosphorylation by protein kinase as biological regulatory mechanisms (Fischer 2010).

A reflection of the achievements in diabetes treatment and management strategies show immense progress, yet the mortality indices continue to deteriorate. These led to a call for research into ways to reducing the risk and rate of progression of complications in diabetes. The National Institute of Diabetes and Digestive and Kidney Diseases, USA accepted and funded the study, called Diabetes Control and Complications Trial (DCCT) and had a full cohort of 1,441 participants (DCCT Trial Research Group, 1993). This study was conducted between 1983 and 1993 and an innovation in the use of HbA_{1c} as the index of blood glucose estimations, which thereafter became the gold standard in the measurement of long term glycaemic control in diabetes. The study compared the effects of intensive glycaemic control ($HbA_{1c} \leq 6\%$) versus standard glycaemic control on the complications of

cardiovascular events, retinopathy, nephropathy and neuropathy in people aged 13-39 with T1DM across 29 medical centres in the USA and Canada. The outcomes of the study demonstrated that intensive glycaemic control reduced the risks of retinopathy, nephropathy and neuropathy by 76%, 50% and 60% respectively (DCCT Trial Research Group 1993). Further analysis of the participants in a follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC) showed that intensive control reduces risks of any cardiovascular disease event by 42% and non-fatal heart attack, stroke or CVS-related mortality by 57% (ADA 2003, DCCT & EDIC 2005). Although there was no evidence of reduction in fatal CVS-related mortality, these outcomes significantly changed the principles and course of future management goals in diabetes.

Hess and Marceau in 1993, modified the original bariatric surgery procedure by adding on duodenal switch proposed by Hess himself, to improve the side effects and produce effectively sustainable weight loss (Hess & Hess 1998, Marceau *et al.* 1998). A year later, Wittgrove and Clark performed the first successful laparoscopic Roux-en-Y, bilio-pancreatic diversion for the management of obese T2DM whose body mass index (BMI) ≥35kg/m^2 (Wittgrove *et al.* 1994, Lugan *et al.* 2004, Podnos *et al.* 2003, Oria 1999).

In this vein, other oral hypoglycaemias were produced which differ from biguanides and sulfonylureas. Incretin hormone (glucagon-like peptides-1, GLP-1) was finally discovered in 1994 and will lead to the production of new antidiabetic agent that acts by increasing insulin secretions in response to glucose. In addition, alpha-glucosidase inhibitors (e.g., acarbose) produced by Bayer Corporation and were made available in 1996. They slow down the digestion of carbohydrate meals therefore delaying the availability of blood glucose.

Curiously, in 1996, Scopinaro and colleagues performed a modified gastric bypass procedure, involving bilio-pancreatic diversion, limited gastrectomy with long limb Roux-en-Y and a short common intestinal segment. Although the procedure was supposed to be safer than jejuno-ileal bypass, it was associated with serious side effects of malabsorption (dumping syndrome) and stomach ulcers (Scopinaro *et al.* 1996).

The improvements in insulin quality and purity continued, in 1996, Eli Lilly and company produced the first commercially available insulin analog called Lispro (Humalog). Further improvements were made in the pharmaceutical industry with the production of more classes of antidiabetic medications.

By 1996-1997, the ADA set up an Expert Committee to review the previous NDDG/WHO classification (ADAEC 1997), in order to eliminate treatment based nomenclature, and to make some modifications in the inclusion of pathogenic findings in the diagnostic criteria. Insulin dependent diabetes and non-insulin dependent diabetes were withdrawn, being replaced by aetiological based classification of T1DM and T2DM. In addition, the fasting plasma glucose level was reduced to 7.0mmo/l from 7.8mmol/l (126mg/dl from 140mg/dl).

The first thiazolidinedione class of oral hypoglycaemias approved in 1997 was troglitazone, and it was purported to improve insulin sensitivity in muscles. It was not quite long afterwards it was withdrawn from clinical use because of its adverse liver toxicity. In 1998, the first meglitinides was developed and marketed as repaglinide. This drug stimulates insulin secretion in the presence of glucose. Other newer medications produced included neteglinide.

Presently, with explosions in technology, internet and programming, newer pumps are able to adjust delivery of insulin doses against serum glucose. Insulin pumps have virtually improved glycaemic control and removed the erratic glycaemic variability. Other modifications in insulin delivery include inhaled insulin and oral sprays.

The recognition of the linkages between hyperglycaemia and the development of diabetes complications was revealed in clinical trials, observational studies and animal experimental studies in the last 30 years (Genuth 1995). This work included the pioneering work of the DCCT in T1DM published in 1993, and the series of studies by the UK Prospective Study (UKPDS) in T2DM published in 1998. The DCCT demonstrated that lowering blood glucose as close to normal as possible reduced the risk by 35-75%, and delayed the onset and progression of diabetic retinopathy, nephropathy and neuropathy in T1DM. There was also a reduction in cardiovascular events, although of no statistical significance. The UKPDS was the largest and longest clinical research study ever conducted with over 5000 T2DM patients newly diagnosed between the periods of 1977-1991 in 23 centres in the UK, with a mean follow up period of 10 years. The aims of the study were to ascertain whether intensive glycaemic control had any beneficial cardiovascular effects, the differential benefits of oral hypoglycaemic drugs and insulin or otherwise, and whether 'tight' or 'less tight' blood pressure control in those with hypertension were of any benefits. The study also sought to ascertain if the use of drug

groups, angiotensin converting enzyme inhibitors (ACEI) or beta-blockers were of any differential therapeutic benefits over each other. The outcomes provided robust evidence that the complications of retinopathy and nephropathy in T2DM can be reduced significantly (by 25%) by attaining a median HbA_{1C} of 7%. Findings also supported evidence that elevated blood glucose (hyperglycaemia) in part or in conjunction with other risk factors contributes to the microvascular complications, similar to the findings of the DCCT. There was a significant degree of risk of microvascular complication with glycaemic levels, such that for every 1% decrease in HbA_{1C} there was a corresponding 35% reduction in the risks, 25% reduction in diabetes related deaths, 7% reduction in all-cause mortality and 18% reduction in myocardial infarction deaths. The UKPDS did not show any statistical significant benefit of lowering blood glucose on the macrovascular complications such as cardiovascular mortality however, there was a 16% reduction (p-value=0.052) in the risk of myocardial infarction. Findings on anti-hypertensive agents showed that a reduction of blood pressure (BP) to a mean of 144/82mmHg significantly reduced the occurrence of cerebrovascular disease, microvascular complications (retinopathy) and diabetes-related mortality (with risk reduction ranging from 24-56%). However, in comparisons of treatments types, those on beta-blockers had slightly better controlled BP than those on ACEI, although neither drugs showed any superiority in any of the outcomes measured (UKPDS 1998a, 1998b, Turner, 1998, Turner et al. 1998)

The later part of the 20th century brought about the discovery of home blood glucose monitoring making it possible for 'tighter glycaemic control'. Technological developments include the introduction of insulin pens and the development of the insulin pump (Watkins, 2008, p.vii). Evidence exists that the use of insulin pumps improves the wellbeing and quality of life of patients needing insulin, and reduces the rate of hypoglycaemias (Pickup 2012, Nicolucci et al. 2008, Hammond et al. 2007, Nuboer et al. 2008, Scheidegger et al. 2007).

21st century (era of millennium developments)

The beginning of the millennium was when James Shapiro and colleagues at the University of Alberta, Canada developed an improved steroid free protocol (the Edmonton protocol), in which patients achieved normal glycaemic levels. Since this time, islet cell transplantation became a more practicable and successful procedure and operations are carried out primarily for people with T1DM who have severe uncontrolled diabetes associated with secondary complications (Shapiro et al. 2000). In addition, in the later part of 2000, Novo Nordisk and Aventis Pharmaceuticals produced a rapid acting analog (insulin aspart) and a long acting form (insulin glargine) respectively. The luxury of DNA technology accorded Novo Nordisk an opportunity to produce another long acting insulin analog, determir, in 2003.

The 21st century, heralded the revision of the guidelines for the diagnosis and definitions of various stages of hyperglycaemia by the ADA in 2003 and the WHO in 2006, and of the use of glycosylated haemoglobin (HbA_{1C}) as a diagnostic and prognostic tool in diabetes (ADA 2003, WHO 2006). However, it was not until 2011 that the WHO, International Diabetes Federation (IDF), European Association for the Study of Diabetes (EASD), ADA and Diabetes UK unanimously endorsed the use of HbA_{1C} as a diagnostic tool (WHO 2011). New concepts were introduced into the nomenclature of diabetes. *Prediabetes* was defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The IFG defines FPG of 6.1-6.9 mmol/l (100-125mg/dl) or HbA_{1C} =42-46 mmol/mol (6.0-6.4%), whereas IGT defines FPG < 7.0 mmol/l (< 126mg/dl) or HbA_{1C}= 42-46 mmol/mol (6.0-6.4%). Today, researchers have shown those at high risk of T2DM to include IFG and IGT. Even though they are not clinically diagnosed as T2DM they are subject to some cardiovascular risks.

These new clinical entities brought about the reassessment of those at increased risk of diabetes. Newer medications were found in the 21st century, which brought about options and choices and consequently improved the management of T2DM. Exenatide, a class of incretin mimetic (GLP-1) was introduced in 2005 (Day 2012b). This originally was designed as an oral medication, but later on an injectable form was produced.

Innovations in 2005 brought a new modification of laser therapy in treatment of retinopathy in diabetes, using Pascal photocoagulator which was made available to limit the energy dissipation by producing an accurate and faster semi-automated laser pulses in a rapid pre-determined fashion (Sanghvi et al. 2008).

In 2006, the first dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin was approved and made available for clinical use in T2DM. This medication enhances the body's ability to reduce blood sugar levels by its action on the naturally occurring GLP-1, to increase insulin production.

In 2008, the outcomes of Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and

Veterans Affairs Diabetes Trial (VADT) were made public. Although large scale trials of ACCORD, ADVANCE and VADT have not shown that glycaemic control can reduce CVD mortality in people with high cardiovascular risks, but observational studies continue to demonstrate consistent correlations between CVD risk and glycaemia (Levitan *et al.* 2004, Selvin *et al.* 2004). However, sensitivity analyses from VADT, ACCORD and ADVANCE trials have shown beneficial effects of tight glycaemic control on the CVD risk (Gerstein *et al.* 2008, Patel *et al.* 2008, Duckworth *et al.* 2008), and reduction of all-cause mortality and AMI (Holman *et al.* 2008). The benefits of improved glycaemic control as identified in the UKPDS study therefore appears to contradict the findings of the ACCORD and ADVANCE studies in which there seems to be no benefit from improved glycaemic control in reducing myocardial infarction and improving cardiovascular outcomes, even though there was an approximately 10% reduction in primary endpoint cardiovascular diseases (Patel *et al.* 2008, Gerstein *et al.* 2008). Analyses of these studies showed no benefits or improvement in cardiovascular risk and mortality with tight glycaemia regulation (Dluhy & McMahon 2008, Skyler *et al.* 2009, Duckworth *et al.* 2009), and can worsen cardiovascular disease events (Meier & Hummel 2009). The deductions are that tight glycaemic control, $HbA_{1C} \leq 53$mmol/mol ($\leq 7.0\%$) is beneficial with regard to microvascular and macrovascular disease risk reduction in people with recent onset T2DM with no history of CVD and longer life expectancy. In those with longer duration of diabetes (>15 years), history of known CVD, and shorter life expectancy, tight glycaemic control can be deleterious particularly with CVD risk. The major implications from these three studies were re-shaping the future management of people with T2DM towards a personalised (individualised) therapy for setting treatment and glycaemic targets.

Around the globe, use of the '*artificial pancreas'* is still at the trial stages (O'Grady *et al.* 2012). Initially, started in 1970s with intravascular insulin delivery, but was later progressed to subcutaneous route in 1990s because of increased infection risk and cost. It involves an automated electromechanical closed-loop insulin delivery device which mimics physiological insulin release (Hovorka 2011, Kowalski 2009). In the UK, this campaign is spearheaded by the Diabetes UK, aimed at reducing the risks of hypoglycaemia and improves overall glycaemic regulation, entails a technique of continually glucose-responsive insulin pumps with coupling of subcutaneous continuous glucose monitoring in a closed loop system (Pickup 2012, 2011, Hoeks 2011).

In 2010, the controversies and inconsistencies in the clinical laboratories estimation of HbA_{1C} values were resolved by the international agreement of standardisation of values, to the present, mmol/mol from percent (Hanas & John 2010). This rectification and agreement brought about comparable estimations between laboratories.

In 2013, a new class of antidiabetic medications, sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., canagliflozin) was made available for clinical use in people with T2DM. The mechanisms of action involves blockade of the sodium glucose transport proteins in the kidneys thereby reducing glucose re-uptake and increasing secretions of glucose in the urine.

Bariatric surgery has been known to induce disease remission. In the UK, the impact of bariatric surgery on T2DM has necessitated the NHS to reduce the criteria for bariatric surgery in T2DM to include those with BMI greater or equals 30kg/m^2.

Conclusions

In summary, over 3000 years have passed since the first evidence of this chronic, heterogenous endocrine disorder of carbohydrates, fat and protein metabolisms. The historical developments of diabetes and its management and its continued advances have demonstrated emergence and evolution over a long period of time. The DCCT, UKPDS, VADT, ADVANCE, ACCORD and other seminal studies have demonstrated the differential effects of different factors on short-term and long-term outcomes, yet another milestone in the history of diabetes. Regrettably, after 32 years, no new ground breaking discoveries have been made to warrant a Nobel Prize despite evidence of other advancements in diabetes investigations. The introduction of HbA_{1C} revolutionised the unwanted, repeated and regular blood sugar estimations characterising follow-up visits. It brought the management of blood glucose more acceptability and compliance.

As the 21st century grinds through its 'adolescent period' and we approach the centenary of insulin discovery, we do hope to drive the history forward by cruising on the road of finding a cure to diabetes. The future lies on the outcomes and availability of cell-based therapy and immunotherapy alongside the improvements in oral hypoglycaemic agents.

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Illustrations

Illustration 1

Table 1 Short summary of important advancements in diabetes research

Table1. Short summary of important advancements in diabetes research (adapted from: Tattersall, 2011, p.3)

- insulin receptor (Freychet in 1971)

- insulin receptor protein isolation (Cuatrecasas in 1972)

- synthetic insulin in USA (1979)

- recombinant DNA technology insulin production in the UK (1980)

- sulfonylurea oral hypoglycaemic (1956)

- use of photocoagulation therapy for retinopathy (Meyer-Schwickerath)

- the role of blood pressure reduction in slowing the progression of nephropathy (Mogensen & Parving)

- New role, diabetes specialist nurse in the UK (Joan Walker in 1950)

- Role of the charity, Diabetes UK (formerly called British Diabetic Association) by Lawrence and Wells in 1934.

Illustration 2

Table 2 Classification of disorders of glycaemia based on aetiology

Table 2 Classification of disorders of glycaemia based on aetiology (adapted from WHO

1999, Alberti 2010)

Type 1 diabetes (β-cells destruction leading to absolute insulin deficiency)

- Autoimmune

- Idiopathic

Type 2 diabetes (insulin resistance with insulin hyposecretion leading to relative insulin

deficiency)

Other specific types (please see Tables 3 & 4)

Gestational diabetes (include former categories of gestational IGT and gestational diabetes

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NB: IGT, impaired glucose tolerance

Illustration 3

Table 3 Specific conditions associated with T2DM

Table 3 Specific conditions associated with T2DM (Kahn 1996, WHO 1999)

I.   Type 1 diabetes (β-cell destruction, usually leading to absolute insulin
     deficiency)

A.   Immune mediated

B.   Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative
     insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A.   Genetic defects of β-cell function

1.   Chromosome 12, HNF-1α (MODY3)

2.   Chromosome 7, glucokinase (MODY2)

3.   Chromosome 20, HNF-4α (MODY1)

4.   Chromosome 13, insulin promoter factor-1 (IPF-1, MODY4)

5.   Chromosome 17, HNF-1β (MODY5)

6.   Chromosome 2, *NeuroD1* (MODY6)

7.   Mitochondrial DNA

B.   Genetic defects in insulin action

1.   Type A insulin resistance

2.   Leprechaunism

3.   Rabson-Mendenhall syndrome

4.   Lipoatrophic diabetes

5.   Others

Illustration 4

Table 4 Other specific conditions associated with T2DM

Table 4 Other specific conditions associated with T2DM (adapted from Kahn 1996, WHO 999)

A. Diseases of the exocrine pancreas (Pancreatitis, Trauma/pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis, Fibrocalculous pancreatopathy and others)

B. Endocrinopathies (Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma and others)

C. Drug or chemical induced (Vacor, Pentamidine, Nicotinic acid, Glucocorticoids, Thyroid hormone, Diazoxide, β-adrenergic agonists, Thiazides, Dilantin, γ-Interferon and others)

D. Infections (Congenital rubella, Cytomegalovirus, and others)

E. Uncommon forms of immune-mediated diabetes ("Stiff-man" syndrome, Anti-insulin receptor antibodies and others)

F. Other genetic syndromes sometimes associated with diabetes (Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader-Willi syndrome and others)

G. Gestational diabetes mellitus

Reviews

Review 1

Review Title: Diabetes mellitus: a complete ancient and modern historical perspective

Posted by Dr. Mahbubur Rahman on 20 Mar 2015 01:51:06 PM GMT

1	Is the subject of the article within the scope of the subject category?	
2	Are the interpretations / conclusions sound and justified by the data?	
3	Is this a new and original contribution?	
4	Does this paper exemplify an awareness of other research on the topic?	
5	Are structure and length satisfactory?	
6	Can you suggest brief additions or amendments or an introductory statement that will increase the value of this paper for an international audience?	
7	Can you suggest any reductions in the paper, or deletions of parts?	
8	Is the quality of the diction satisfactory?	
9	Are the illustrations and tables necessary and acceptable?	
10	Are the references adequate and are they all necessary?	
11	Are the keywords and abstract or summary informative?	

Rating: 8

Comment:

Need to be more careful in referencing. In some places listing of referencing missing. In some other instances, some inconsistancies seen in referencing;e.g. In page 11: in 1974, a purified form of animal insulin was produced by chromatographic techniques (Steiner & Oyer 1967).

Also, tables should be placed in right position or need to be mentioned correctly within the writeup. Also tables should be better visualized

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:

I have knowledge and experience on Diabetes Mellitus

Publications in the same or a related area of science: Yes

References:

Rahman M, Rahman MA, Flora MS, Rakibuz-Zaman M. Depression and associated factors in diabetic patients attending an urban hospital of Bangladesh. International Journal of Collaborative Research on Internal Medicine & Public Health. 2011; 3:65-7

How to cite: Rahman M.Diabetes mellitus: a complete ancient and modern historical perspective [Review of the article 'Diabetes mellitus: a complete ancient and modern historical perspective ' by Nwaneri C].WebmedCentral Diabetes 1970;6(3):WMCRW003196

Review 2

Review Title: Diabetes mellitus: a complete ancient and modern historical perspective

Posted by Dr. Sze M Ng on 03 Mar 2015 03:54:45 PM GMT

1	Is the subject of the article within the scope of the subject category?	
2	Are the interpretations / conclusions sound and justified by the data?	
3	Is this a new and original contribution?	
4	Does this paper exemplify an awareness of other research on the topic?	
5	Are structure and length satisfactory?	
6	Can you suggest brief additions or amendments or an introductory statement that will increase the value of this paper for an international audience?	
7	Can you suggest any reductions in the paper, or deletions of parts?	
8	Is the quality of the diction satisfactory?	
9	Are the illustrations and tables necessary and acceptable?	
10	Are the references adequate and are they all necessary?	
11	Are the keywords and abstract or summary informative?	

Rating: 5

Comment:
It is certainly a well written paper and interesting aspects of the history of diabetes conveyed

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:
yes

Publications in the same or a related area of science: No

How to cite: Ng S. Diabetes mellitus: a complete ancient and modern historical perspective[Review of the article 'Diabetes mellitus: a complete ancient and modern historical perspective ' by Nwaneri C].WebmedCentral Diabetes 1970;6(3):WMCRW003189