



EDITORIAL

DIABETES MELLITUS FROM MYSTERY TO MANAGEABLE DISEASE & INSULIN TRANSITION FROM ANTIQUITY TO MODERN ERA

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Nearly 2000 years ago, Aretaeus of Cappadocia called it a “mysterious disease”. For Morgagni, the father of pathology, it was “morbus insede incerta locatus”- a disease located in an unknown site.

MEN AND MILESTONES

A better understanding of the contemporary sphere of diabetes mellitus may be aided by a historical summary. The study of both the remote and recent literature requires substantial knowledge of medicine and the basic sciences underlying the pathology of the disease. The historical perspective of diabetes mellitus guides us for better understanding of the disease and the care of patients. The evolution in understanding of diabetes is divided into four eras as follows: (1-4)

- **Ancient Period**
- **Diagnostic Period**
- **Period of Empiric Treatment**
- **Experimental Period**

ANCIENT PERIOD (upto 675 AD)

The name diabetes is coined from the Greek word meaning "siphon". It was named by Aretaeus of Cappadocia (AD 81-138) but it was described much earlier in the Egyptian Papyrus Ebers, a copy of Egyptian medical journal of 1500 BC. It described diabetes-such as like polyuric syndrome and identified dietary remedies bones, wheat, grit, green leaf and earth for those passing abundant urine.

Hindu physicians (1500 BC) described syndromes and interpreted two types of diabetes: The first type was related with dehydration, emaciation, lassitude, polyuria and the

second type was associated to gluttony, stout build, sleepiness and obesity. (5)

A good clinical description of diabetes was given by Celsus (30 BC-50 AD) a Roman physician as a disease with "polyuria without pain but with emaciation and danger."

Aretaeus of Cappadocia (AD 81-138) (6), another Roman physician documented: "Diabetes is an enchanting cordiality, less common in males, starting with draining of the muscles and limbs into urine. It is caused due to humid and cold nature, like swelling. Usually the Path is mainly the bladder and kidney of the people, starts uninterrupted production of water with continuous flow, like drainage from a channel. The disease is of chronic nature and it develops in a long time, however the patient life is of short time, if the disease is fully established; the draining is rapid, death is quick."

Galaeus (131-201 AD), a great intellect of his day was the founder of experimental medicine. Galen described diabetes as "diarrhoea urinosa" a disease of kidneys, which were unable to retain back water. The afforesaid and other Galenic theories were accepted without question for centuries. (7)

Tehang Tehong (200 AD), a Chinese physician, described diabetes as "malady of thirst." He observed that a diabetic patient might drink ten liters of liquid per day, with an equal amount excreted as urine. Further Chinese medical writings of about 600 AD mention polyphagia, polydipsia and polyuria.

Ibn Sina or Avicenna (980-1027), prince of physicians, was the great Arab physician of his days and the book "Kanon" written by him was influential among the medicine practitioner for many decades. (5) He put forwarded complete description of the disorder, including some of its complications. He observed that patients with diabetes suffered from great thirst, irregular appetite, loss of sexual function, inability to work and nervous exhaustion.

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Avicenna was of opinion that in diabetes, liver was compromised and the kidneys attracted humor from the liver in huge volume, more than they could hold back, and the urine left a deposit like honey. He observed that carbuncles and phthisis were common problems. He explained furunculosis and diabetic gangrene. (7)

Paracelsus (1493-1541) observed that diabetic urine contained an abnormal substance. He evaporated a liter of diabetic urine and recovered four ounces of 'salt' which, according to him, made the kidney thirsty and caused polyuria. (8)

DIAGNOSTIC PERIOD (1674-1796)

In 1674, Thomas Willis, a professor of natural philosophy, anatomist and physician at Oxford, learned by tasting that the urine of the patient was "pleasingly sweet as if saturated with sugar or honey". He stated that diabetes was mainly a blood disease and that the sweet substance first appeared in the blood, later appeared in the urine. Willis became the author of first carbohydrate "under-nutrition cure" in diabetic patients.

Matthew Dobson (Liverpool physician) in 1776 exhibited that diabetic patients excreted "sugar" in their urine. (9) He boiled the urine and found that the remaining deposits consisted of crystals which tasted and looked like brown sugar. Crucially, he also found that the blood of the patients tasted sweet and concluded with foresight, that sugar in diabetic urine was not produced in the kidneys but was present in blood serum.

Cawley in 1788 observed a shriveled pancreas with destruction of pancreatic tissue and kidney stones in a diabetic patient postmortem. This may be the first documented reference of relationship between the pancreas and diabetes.

Cullen (1709-1790) added the word "*mellitus*" to the disease in order to differentiate from diabetes insipidus. (Mellitus is derived from the Greek 'mell-honey'.)

Francis Home isolated sugar from the urine and observed that by the addition of yeast, the sweetness of the urine was lost, because of the fermentation process of the sugar. (3)

PERIOD OF EMPIRIC TREATMENT (1796-1850)

John Rollo (1796), Surgeon General, of the Royal Army developed the first balanced methodology of treatment of diabetes by diet. Rollo studied an adult patient having diabetes with severe symptoms of glycosuria. He maintained a daily chart of quantity and type of the patient's diet and calculated the sugar extracted by evaporating the urine excreted every day. He established that the glycosuria was secondary to the "sacchrification" of vegetables in the stomach. He concluded that the stomach was the main

organ involved in diabetes rather than kidney. Excretion of sugar by the kidneys was a secondary process caused by hyperglycemia. He restricted the diet of diabetics to animal food and small amount of green vegetables of low caloric value, occasionally permitting some milk and bread. Simultaneously, drugs were given to decrease the appetite. Rollo was also the first to observe the significance of diabetic cataracts. (6,7)

Chevreul in 1815 found that the sugar present in the urine of diabetic patients was identical to glucose. (3)

EXPERIMENTAL PERIOD (1850—1921)

The Discovery of Insulin (8-10)

Cawley is credited as the first physician to associate diabetes with pancreas, while von Mering and Minkowski established that total pancreatectomy in dogs caused diabetes. (2)

Trommer described qualitative test for sugar in the urine in 1841, and Fehling discovered a quantitative test in 1850.

Claude Bernard (1855) discovered glycogen and according to his theory, he postulated that the increased blood sugar concentration was an overproduction of sugar by "Liver".

Bouchardat (1806-1886) revived the Rollo's dietary treatment but modified it by substituting fat and alcohol for carbohydrates. He advocated small meals and encouraged occasional days of fasting. He described the importance of exercise in the treatment of diabetics and recommended daily testing of urine for sugar. He classified diabetes in to two different types: first one is the severe type in younger patients which was not improved with dietary measures and the second type was present in obese and old people it improved with dietary measures and exercise.

Lancereaux came to identical conclusion about clinical variations of diabetes and introduced the word diabetes gras (diabetes of the fat) and diabete maigre (diabetes of the thin).

Wilhelm Peters (1857) was the first to demonstrate acetone in urine obtained from a patient in diabetic coma, but it was Kussmaul in 1874 who gave the first detailed clinical description of diabetic coma and the characteristic breathing of "air hunger".

Kutz (1845-1895) discovered oxybutyric acid in the urine of diabetics and documented the importance of exercise for the patients having mild diabetes.

In 1869, Paul Langerhans, a medical student in Berlin, published a paper on pancreatic histology in which he described previously unknown cells. These cells, occurring in small islands were situated between the acini and did not communicate directly with the secretory ducts. Langerhans could not discover any particular function of these cells.

In 1889, Von Mering and Minkowski concluded with experiments that diabetes was of pancreatic origin and this was a turning point in the diabetes history. They discovered that the complete removal of pancreas in dogs lead to glycosuria, hyperglycemia and ultimately death due to coma and ketosis. Minkowski reported that “total removal of pancreas in dogs resulted in the picture of real permanent diabetes, which was similar to the most severe form of this disease in man.” They speculated that a mysterious substance produced by pancreas is responsible for metabolic control. When they ligated the pancreatic duct of another dog, this caused mal-absorption of food but not diabetes. When the first depancreatized dog was passing large amounts of urine, it was Minkowski who tested for sugar and rightly connected the cause of diabetes with the removal of pancreas. He also demonstrated that pancreas was an internal secretory gland and appearance of hyperglycemia was prevented by grafting a fresh small piece of pancreas subdermal in depancreatized dog.

Gustave Laguese between 1891 and 1894 reemphasized the findings of Langerhans and illustrated the collections of interacinar cells which he designated “Islets of Langerhans” as an internal secretory glands in the pancreas.

The experiments of Schulze and Sobolev independently in 1902 and Lydia Dewitt in 1906 brought evidence that the obstruction of pancreatic duct by surgical means caused atrophy of the acini. The animal, however, did not become diabetic because the islets were left intact. In 1904 the concept of hormones was introduced by Ernest Starling. (10)

Bernhard Naunyn (1848-1914) (8,9), was the head of the Strasbourg institute where Von Mering and Minkowski carried out their experiments. He was great authority on the dietary treatment of diabetes and did many studies and observations on ketosis. His famous diet was fat-rich, protein-poor and almost carbohydrate-free. In 1922 before insulin usage, the only method available to reduce the incidence and severity of diabetic ketoacidosis in patients of IDDM was periodic short term fasting low-calorie diets, and exercise. Such therapy could be helpful for a short time, but death due to diabetic coma or starvation was the inevitable outcome. Diabetic ketoacidosis became curable and preventable when insulin therapy was introduced.

Bernard Naunyn had a clinic for diabetics in Strasbourg. He recommended carbohydrate restricted diets and fasting days, even “locking” patients in their rooms to achieve this.

In 1903 Naunyn advocated the following:

1. Use dietary method by Omega and Alpha nutrients for treatment of diabetes, and avoid pharmacological management.
2. With passage of time glycosuria due to diabetes

increases and the tolerance of the patient decreases.

3. If the patient has normal blood sugar level, his tolerance is increased. Therefore, physician should try to maintain normal sugar level of the patient.
4. Limitations of the total daily diet, leading to changes in the metabolism, brings favorable results.
5. Reductions of proteins and carbohydrates intake to decrease glycosuria.
6. Sugar is produced by proteins and carbohydrates food.
7. Qualitative and quantitative diet for every diabetic should be determined.
8. Patients should be asked to consume 30-35 calories per kilo weight.
9. Fats does not produce any notable sugar and therefore does not influence diabetic glycosuria.
10. Due to more calories, fat is the most important substance for patients.

In United States, Fredrick Allen was another advocate of undernutrition as a therapeutic measure. The Joslin Clinic (USA) reported that the ketoacidosis was the most common cause of death (until 1914 it was 63.8% and till 1921 it was 41.5%). The progress from 1914 to 1921, in the pre-insulin era was probably due to the initiation of Friedreck's “semi starvation therapy” (irregular fasts following a high-fat diet). (8) The only methods available to reduce the severity of ketoacidosis were periodic short term fasting, low-calorie diets and exercise. Although, they were unacceptable to the patients. The Friedreck's nutrition plan improved the expectancy of life from 18 months to more than 5 years of patients with insulin-dependency.(9)

In Charles H Best era (8), the average life expectancy after the diagnosis of diabetes was 15.6 years (1950-55) and 18.2 years (1956-57). The figures were even more impressive when attention was given to the groups with onset of diabetes early in life (Table 1). In comparison, the average duration of life after diagnosis of diabetes in Naunyn era was 4.9 years (1897-1914) and 6.1 years in Allen era (1914-1922).

During 1895 and 1921 research was done in two dimensions: Histological study of the islets and search for insulin itself. Numerous attempts were made to prepare extracts from the atrophied pancreas. Zuelzer and E.L.Scott came very near to the isolation of the active principle. Kleiner and Paulesco certainly had small amounts of insulin in their extracts but they had difficulties in accurate estimation of blood sugar and were not successful in its usage in diabetic patients. The name “Insulin” was invented by deMeyer in 1909 and

various unsuccessful efforts were made to extract it. Hormone was studied in literature in nine different studies using different methodologies, however no one was successful in preparing it in its purest state or in large volumes or its safe usage. (11)

In 1920, F.G.Banting independently developed the hypothesis that the active principle produced by the islets might be destroyed by the acinar secretions of the pancreas. If the pancreatic duct was ligated, and the acini was allowed degeneration over several weeks, then undamaged islets could be obtained, from which the 'internal secretion' could be extracted.

Banting in 1921 wrote in his notebook "Diabetes-Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretions of these to relieve glycosuria." In the spring of 1921 at the age of twenty-nine, Banting returned to the University of Toronto to follow the clue which led to the invention of insulin. (11) He was helped by Professor J.J.R.Macleod. Banting was assisted by Charles H Best, a medical student. In seventy-five consecutive tests in dogs, they demonstrated lowering of urine and blood sugar by pancreatic extracts. The extracts

were made by methods to avoid the action of proteolytic enzymes while using acid, alkali and cold. They called the pancreatic extract "isletin". (12) Rigorous experiments started in May 1921, which generated favorable results. (13)

Fredrick, J.J.R.Macleod, biochemist James Collip and Charles, fruitfully devised and organized the production and distribution of insulin and were awarded with the Noble prize. Banting named the extract "insulin" from the Latin word meaning island.

Leonard Thompson, was young boy of 14 years who was treated with insulin for first time in 1922 in Toronto, Canada. (13)

The extraction of insulin was an important incident in the research and treatment of patients. The advancement of methods for modifying and purifying insulin was done in almost next 30 years. Table 1 charts these and other developments from the initial discovery of insulin to the early 1980s. (6,14,15,16)

Insulin analogs are altered form of the hormone which are effective for controlling blood glucose in diabetes. They are genetically engineered and have different pharmacokinetics

Table 1: Insulin Timetable: 1921 through the Present (21-23)

Year	History and Discovery of Insulin (24, 25)
1921	Pancreatic extracts demonstrated to lower blood sugar levels in experimental dogs.
1922	Insulin first used in human.
1923	Commercial production of insulin from animal sources.
1925	First international insulin unit defined (1 unit= 0.25 mg of standard material).
1926	Crystallized amorphous insulin adds to insulin stability.
1936	Addition of zinc to protamine insulin (PZI) to create a prolonged duration of the hormone.
1939	Globin insulin with a shorter duration of action than PZI developed.
1950	NPH (Neutral Protamine Hagedorn) insulin developed.
1951	Lente Insulins developed.
1955	Structure of insulin delineated.
1960	Radioimmunoassay of insulin becomes available.
1967	Proinsulin discovered.
1971	Insulin receptor defined.
1972	U-100 insulin introduced.
1976	C-peptide becomes clinical tool.
1977	Insulin gene cloned.
1981	Insulin receptor kinase activity described.
1982	Recombinant DNA insulin becomes available.
1996	Onwards-Insulin Analogs

from human insulin. They include insulins which have either rapid onset of action or slow prolonged effect, suitable to be used as basal insulin. (17-21)

Examples are:

- i) Insulin Lispro 1996 rapid acting insulin analog
- ii) Insulin Aspart 2000 rapid acting insulin analog
- iii) Insulin Glargine 2000 basal insulin
- iv) Insulin Detemir 2004 basal insulin

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