A history of diabetes: from antiquity to discovering insulin

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Abstract

This article, the first of a three-part series, gives a historical account of events for diabetes, dating from antiquity and its first recording in the Ebers Papyrus — an Egyptian document circa 1500 BC. This article describes initial thoughts that diabetes was linked to an alimentary complaint, and concludes with the discovery of it being a chronic systemic disease. It highlights the discoveries and also includes details of the failed attempts to locate the cause and identify a solution to the ancient mysterious disease which became known to all as diabetes mellitus. Early remedies and treatments are included. The article tells how for many centuries individuals suffered from the debilitating complaint with very little offered in terms of treatment or relief. Eventually the pancreas was identified as the causative organ and, some time later, animal experimentation resulted in the abstraction of the substance insulin. The article concludes with Frederick Banting and John Macleod being awarded the Nobel Prize in 1923 for their revolutionary discovery of insulin.

Diabetes mellitus was first observed in antiquity. An early reference to diabetes was made by the Egyptians in 1500 BC, who mentioned polyuria as a common symptom of the 'sugar disease' in the Ebers Papyrus (a papyrus said to have been written between 300 and 1500 BC by an Egyptian physician named Hesy-Ra). The papyrus was discovered in the tomb of Thebes and sold in 1872 to George Ebers, a German Egyptologist (Brar, 2001).

It was not until perhaps 1000 years later that a clinical diagnosis of diabetes was described by Susruta of India, although the exact date of this is still a subject of much debate — estimates range from 1000 BC to the 6th century AD (Suleyman, 1998; Bretzel et al, 2001; Pyke, 2001).

The Greeks Aretaeus, Celsus, and Galen gave a description of the symptoms. In 164 AD Galen mistakenly concluded that diabetes was an ailment of the kidney (Vivisection Information Network, 2001). It was Aretaeus of Cappadocia who introduced the name 'diabetes' — the Greek word for 'siphon' and described diabetes as:

> **'...a remarkable disorder, and not very common to man. It consists of a moist and cold wasting of the flesh and limbs into urine, from a cause similar to that of dropsy; the secretion passes in the usual way, the kidney and the bladder. The patients never cease making water, but discharge is as incessant as a sluice to let off. This disease is chronic in character, and is slowly engendered, though the patient does not survive long when it is completely established for the marasmus produced is rapid and death is speedy'**
> (*Aretaeus of Cappadocia [quoted in Roszler, 2001]*).

In ancient times diabetes was considered to be a constitutional disease, characterized by the passing of copious amounts of urine that was light in colour, had an odour resembling sweet hay, and it was suggested that, if tasted, one could detect the presence of sugar. Indeed, outside of Europe, up until the 11th century, diabetes was commonly diagnosed by 'water tasters', who 'sampled' the urine of those individuals suspected of having diabetes (Thompson and Thompson, 1998).

Further, in early times, attention was directed towards an individual when large amounts of wasps and flies were noted to be hovering over his/her chamberpot (Gull, 1886), while ancient Indians noticed that ants were attracted to the urine from a person with diabetes (Pyke, 2001).

The urine of people with diabetes was understood to be sweet, and as a result of this important discovery, the word 'mellitus' (the Latin for honey) which referred to the sweetness of the urine was added to the term diabetes (MacCracken and Hoel, 1997).

THE ANCIENT MYSTERY

Early records describe diabetes as a 'mysterious and savage disease' (MacCracken and

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Hoel, 1997), whereby patients complained not only of passing excessive amounts of urine, but also of very dry skin, being troubled with boils and carbuncles, from having very little perspiration, of dry bowel movements and from basically wasting away. According to MacCracken and Hoel (1997): ‘No one knew how to live with, let alone correct it.’ Children died quickly and older individuals battled with the devastating symptoms.

Remedies at this time included patients being prescribed cooling diets of bear meat, diluted wine, herbs and grains. The use of diuretic preparations was refuted by Paul of Aegina in 230 BC who believed their use would result in dehydration. However, venesection (the cutting of veins) was allowed and thought to be beneficial by reducing the burden on the kidneys, which were initially considered to be the cause of the complaint (Bretzel et al, 2001). The avoidance of sex was encouraged in an attempt to suppress the overabundance of urine (Bliss, 1982; Raman, 2001), while Aetius (45–117 AD) used opiates for those individuals suffering from the final stages of diabetes mellitus, and Avicenna (900–1037 CE) encouraged bareback horse riding as a form of exercise to ‘employ friction and alleviate excess urination’ (Bliss, 1982).

Later in the course of the illness, tepid baths and the drinking of wine were also recommended (Bretzel et al, 2001). The 1300s saw purgatives, along with astringents, prescribed by physicians, which were thought at that time to relieve the intense polyuria and subsequent strain on the kidneys (On Target, 1999).

The following centuries saw very little change in terms of understanding and treatment of this mysterious disease, with speculation directed towards the kidneys, blood, liver and indeed the stomach as the possible cause of the problem. Paracelsus in the 16th century is reported to have identified diabetes as a serious general disorder (Canadian Diabetes Association, 2002), although uncertainty remained regarding the actual cause of this harrowing affliction.

In terms of remedy, further accounts between the 15th and 17th centuries depict a diet of roast meat dripping in fat, sweet sugar pastries and an abundance of butter and cream, with very few green vegetables; this diet was possibly believed to contribute towards retrieval of weight loss (MacCracken and Hoel, 1997; Raman, 2001; Roszler, 2001).

There is no mention of there being sugar in the urine of people with diabetes in the medical literature of Europe until the 17th century (Bliss, 1982). In 1675, it was Thomas Willis, a British physician, who became the first European to taste the urine of a patient with diabetes and discover it was sweet, and who also subsequently recommended a diet that was high in carbohydrates and low in calories and suggested milk, bread and barley water. Later, in 1697, he commenced the fashion towards a mainly meat, high-fat and high-protein diet that was low in carbohydrates (Raman, 2001).

However, apart from the discovery of urine to be sweet tasting, with some individuals with diabetes apparently benefiting from a diet of low calorific value, very little was known about the disease.

FURTHER MILESTONES

A century later, in 1776, Dr Matthew Dobson of Manchester confirmed the findings of Thomas Willis that urine was sweet, and went on to demonstrate that boiling urine until evaporation eventually left a substance that had not only the sweetness of sugar, but also the same crystalline characteristic (Roszler, 2001). Dobson went on to make the important discovery that sugar was not only present in the urine but also found in the blood of diabetic patients, realizing the condition to be a systemic complaint.

However, it was not until 1788 that Thomas Cawley, a researcher, acknowledged a correlation between a ‘shrivelled pancreas’ and diabetes while performing an autopsy of a diabetic patient. Unfortunately, at the time, this observation went unheeded (Roszler, 2001). In 1796, John Rollo, a surgeon general, dramatically emphasized the alimentary system, suggesting the stomach rather than the kidneys as the focus for attention when he noted that a diet of meat amounted to less sugar production, while bread, fruits and grains led to more.

This remained the school of thought for many years to come, a benefit incidentally also observed by the French physician Apollinaire Bouchardat in 1870 during the Franco-Prussian War, with the rationing of food being attributed to the reduction of glycosuria in

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those soldiers with diabetes (Thompson and Thompson, 1998; Raman, 2001).

EARLY TREATMENT: DIET

Gull (1886) tells us that the first and salient point of treatment over the centuries was the need for stringent attention to diet (*Table 1*). Indeed, the intention was for the individual to withdraw from all types of foods containing sugar and starch, which were to be replaced with meat and some green vegetables. Potatoes, carrots, turnips, peas and beans were to be abandoned as they contain sugar.

Any foods containing starch, e.g. macaroni, vermicelli and bread, were also strongly prohibited and subsequently had to be avoided. For those individuals who complained of being deprived for want of bread, bran cakes were a suggested alternative which could be prepared without too much difficulty in the home, or purchased from most bakers or confectioners in large towns.

Beverages that were considered to be non-stimulating, such as tea, coffee and cocoa were allowed, along with soda and water. Lemonade was forbidden as it contained sugar, as were sweet wines, porter and sweet ales. However, dry sherry, bitter ales and small amounts of whisky or brandy were occasionally allowed. It was generally suggested that in order to alleviate the craving for liquid, all drinks should be taken warm (Gull, 1886).

This close attention to diet based on empirical findings at that time was deemed appropriate, in that it did offer some reduction in blood glucose levels but did little to relieve suffering and extend life with patients surviving for only a few months (Suleyman, 1998).

Today, a diet that is low in fat and high in both unrefined carbohydrates and dietary fibre is recommended, with carbohydrates making up at least 50% of the total intake of energy (MacKinnon, 2002). For obese and overweight individuals, reducing the daily total intake of energy remains the overall objective. In real terms the advice given to patients with diabetes is no different than advice given to the population generally (MacKinnon, 2002).

TREATMENT: DRUGS

Up to and including the 1800s, treatment was often in the form of opium given as compound soap pills three times a day and was considered to be of benefit in reducing the amount of urine passed (Bliss, 1982). Phosphoric acid, bromide of potassium and nitrate of uranium were also thought to be useful in reducing urine and restoring general demeanour.

Extract of ergot was found to be of particular benefit when other treatment failed, and for special cases, skimmed milk treatment was given. This treatment basically amounted to drinking six pints of skimmed milk a day, and was the only form of nourishment allowed for six consecutive weeks. After that time, animal food would be allowed once or twice daily. The skimmed milk treatment was thought to be less invasive than treatment

Table 1. A 19th century diet for people with diabetes mellitus

The diet
Butcher's meat of all kinds (except liver)
Ham, bacon or other smoked, salted, or dried or cured meats
Poultry and game
Fish of all kinds (fresh, salted, cured)
Soup (except vegetable soup)
Beef tea and broths
Bran, gluten or almond substitutes for bread
Eggs dressed in any way
Cheese, cream cheese
Butter and cream
Foods allowed
Watercress, mustard and cress, green lettuce, spinach
Celery, occasionally radishes, spring onions
Jelly (flavoured but not sweetened)
Blancmange made with cream, but not milk
Custard made without sugar
Nuts of any description (but sparingly)
Food that must be avoided
Sugar in any form
Bread, wheaten or otherwise
Rice, arrowroot, sago, tapioca, macaroni
Peas, french beans, cabbage, Brussels sprouts, asparagus
Pastry and puddings of all kinds
Jams, marmalade, fruit of all kinds — fresh or preserved
Drinks that may be allowed
Tea, coffee, cocoa, dry sherry and claret
Brandy and spirits that have not been sweetened
Soda water, water
Bitter ale (sparingly)
Drinks that must be avoided
Milk (except very sparingly)
Sweet ales, mild and old porter and stout
All sweet wines, port wines and champagne
All liqueurs

Adapted from Gull (1886)

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> ...physicians had developed the association that it [diabetes mellitus]...appeared to be more prevalent in urban and industrial areas and appeared to develop as a result of an individual being cold or wet. Indeed, early writings indicated that the cause of diabetes mellitus could be attributed to either drinking cold water when one was hot, or drinking an excess amount of alcohol...

previously described and allowed the individual to continue his/her ordinary occupation. Gradually, bran bread along with other foods chosen from the stringent menu in *Table 1* would be added.

Generally, this was the situation for those unfortunate individuals suffering from diabetes mellitus, with treatment in early times being essentially that of monotonous ritualistic practice and avoidance of excess in any form. Relieving factors included a warm bath once or twice a week which was thought to ease the patient's discomfort, or a Turkish bath which was also thought to be beneficial in terms of circulatory effects (Gull, 1886; Raman, 2001).

Diabetes mellitus was not at this time considered to be hereditary, although physicians had developed the association that it did appear to run in families, appeared to be more prevalent in urban and industrial areas and appeared to develop as a result of an individual being cold or wet. Indeed, early writings indicated that the cause of diabetes mellitus could be attributed to either drinking cold water when one was hot, or drinking an excess amount of alcohol or suffering from an intense amount of anxiety as a result of being a victim of an act of crime such as burglary or a fit of anger, or as a direct result of a physical attack to the body (Gull, 1886).

DIABETES AND THE INVOLVEMENT OF THE PANCREAS

By the early 19th century, an individual presenting with a history of glucosuria resulted in the diagnosis of diabetes mellitus and because of the very limited knowledge of the disease, was subsequently prescribed a life of misery and a very frugal existence.

Possibly the greatest man in the history of diabetes was Claude Bernard who, early in the 19th century, hypothesized that glycogen was stored by the liver and that the liver secreted a substance that was sugary into the blood. It was this overproduction of glucose that he considered the cause of diabetes (Pyke, 2001).

There were no further developments until 1869 when Paul Langerhans, a German medical student, discovered islet cells in the pancreas. Unfortunately, he died in 1888 not having explained them or having discovered their significance (Pyke, 2001). A year after Langerhans' death, two fellow Germans, Joseph von Mering, a pharmacist, and Oscar Minkowski, a diabetologist, discovered that the removal of the pancreas from a dog led to the dog developing diabetes (Bliss, 1982; Pyke, 2001). It was Gustave Laguesse, a French doctor, who, in 1893, finally suggested that the islet cells in the pancreas were involved in a role other than a secretion to aid digestion and named them the islets of Langerhans after their discoverer (Hammonds, 2000).

MAJOR BREAKTHROUGH

Shortly after Joseph von Mering and Oscar Minkowski's historic breakthrough, Moses Barron, an American vivisectionist, while undertaking the autopsy of a patient with diabetes, discovered by chance that the islets of Langerhans were damaged. Barron subsequently suggested that this damage to the islets must be the cause of human diabetes and although it was not obtainable at the time, went further to deduce that the substance from such cells was the anti-diabetic treatment (Vivisection Information Network, 2001).

In 1910, Sir Edward Albert Sharpey-Schafer, an English physiologist, named this substance 'insuline' (Gerritsen, 2001), a recommendation that the Belgian Jean de Meyer had made a year earlier in 1909 after the Latin word insula, meaning island (Catania, 1995). Later, the anti-diabetic treatment became known as insulin (Brar, 2001).

After many failed attempts to extract the substance insulin by other scientists, Moses Barron, following his own in-depth studies, hypothesized that diabetes was indeed caused by damage to the islets of Langerhans. Frederick Banting and Charles Best, in collaboration with John Macleod at the University of Toronto, using Moses Barron's hypothesis, reproduced and further developed the work of Joseph von Mering and Oscar Minkowski by isolating and extracting the substance insulin from 'healthy' dogs, and injecting it into diabetic dogs, thus at least temporarily controlling the diabetes.

Unfortunately, these early experiments using the insulin from dogs were found to be flawed and subsequently criticized as a solution to offer to the unfortunate diabetic human patients who ultimately suffered further and

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developed a fever (Vivisection Information Network, 2001).

Finally, after enlisting the biochemist James Collip, who incidentally had managed to 'extract a reasonably pure form of insulin from the pancreas of cattle' (Brar, 2001), as part of the team, it was Banting and Best from Toronto who eventually won major acclaim. Leonard Thompson, a 14-year-old weighing a mere 64 lb received Banting and Best's 'thick brown mucus' known then as insulin.

Although the solution initially caused some localized inflammation at the injection sites, further purification of the solution by Collip yielded tremendous results, causing Thompson to gain both weight and strength. Thompson subsequently went on to live reasonably well, until he unfortunately developed pneumonia and died at the young age of 27 years (MacCracken and Hoel, 1997). Banting and Macleod received the Nobel Prize in 1923 in physiology/medicine for their work in the discovery of insulin. After some time, Banting split his prize with Best and Macleod shared his with Collip (Lilly, 2002).

The second article in this series of three will explore the production and development of insulin over the last 80 years and its mode of delivery. It will also discuss a major new initiative aimed at patient self-management, together with important scientific advances in insulin therapy. The third and final article of the series will describe the aetiology of diabetes, clarify the new classifications for diabetes and demonstrate that nursing has a key contribution to make in diabetes management. It will conclude with a discussion regarding the Government's important strategic healthcare agenda for diabetes care. BJN

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KEY POINTS

- Diabetes was first reported in approximately 1500 BC.
- The term 'mellitus' is the Latin word for honey and refers to the sweetness of urine.
- Early treatment consisted of high-fat diets and high-protein diets.
- Opium was used to alleviate suffering.
- Gustave Laguesse, a French physician, named the islets of Langerhans.
- Frederick Banting and John Macleod were awarded the Nobel Prize in 1923 for discovering insulin.

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