

A Historical Perspective of the Diagnosis of Diabetes

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Diabetes is a disease whose symptoms have been recorded in the annals of history ever since the earliest reports of polyuria in 1500 BC. However, it was only in the last hundred years that adequate treatment methods have been developed, initiated by Banting and Best's discovery of insulin. Tracing the historical methods used to diagnose diabetes provides a perspective for current diagnostic and treatment strategies. Diagnostic tests have become increasingly quantitative evolving from the earliest diagnostic tests where urine was tasted to modern methods assaying the percentage of glycosylated hemoglobin. The basis of future diagnostic tools for diabetes will most certainly be based on past research findings and experiences.

The signs and symptoms of diabetes have been observed and recorded since the beginnings of civilization. The earliest descriptions were limited to changes in urine output and the fatal outcome of those inflicted with diabetes. Polyuria, as we now know, has many different etiologies, thus it is impossible to discern today whether the symptoms and treatments were correctly directed at diabetes mellitus. However, the early recognition of diabetes began with the examination of urine.

While the term "diabetes" was first introduced in the 1st or 2nd century BC by Demetrius of Apameia,¹ descriptions of abnormal polyuria were recorded as early as 1500 BC in the Egyptian Papyrus Ebers, an ancient written document of medical knowledge.¹⁻³ The term "diabetes" was based from the Ionic and Latin terms that meant to pass through or to siphon.¹ It was coined by Areteus of Cappadocia (AD 30-90) "because the fluid does not remain in the body but uses the man's body as a ladder whereby to leave it".³ It was the prevailing belief that diabetics had large volumes of urine due to large volumes of ingested fluids, unchanged as it passes through the body, as if the patient was a siphon.¹ In addition to coining the term diabetes, Areteus is credited with the first accurate clinical description of diabetes, likening it to "an affliction... melting down of the flesh and limbs into the urine".¹

The first test for diabetes was the urine taste test. While the Greek physician Claudius Galen (AD 129-200) believed diabetics' urine was "unchanged drink" which may have accounted for a different aroma, early Egyptians, Indians, and Asians noted the sweet taste of urine.³ Chang Chung-Ching (AD 229) noted that the urine was so sweet that that dogs liked it.³ Indeed, animals and insects alike were attracted to the sweet urine.^{3,4} The Hindu medical textbooks from the 5th century described sweet, honey and sugarcane urine amongst 20 varieties of diseased flow of urine.^{1,3} Both Avicenna (AD 980-1037) and Paracelsus (AD 1493-1541) later recommended tasting the urine of diabetics.^{1,3}

The source, however, of the sweet taste of diabetics' urine remained unknown. Avicenna noted a sticky residue as sweet as honey remained after urine was left to stand in ambient air.¹ Theophilus Protospatharios (630 AD) was the first to mention applying heat to urine as a diagnostic test.³ Paracelsus reported that boiling diabetic urine recovered "4 ounces of salt".³ However, it was Thomas Willis (1621-1675) that first described the saccharine nature of urine, describing the sweet taste after evaporation "as if imbued with honey (quasi melle) and sugar".¹

In 1776, Matthew Dobson performed a diagnostics experiment that led to the belief that diabetes was not just a disease of the kidneys, but rather a system disorder.^{1,5} Dobson evaporated the urine of diabetic patients to

discover the presence of a substance like brown sugar in taste and appearance, he also went on to observe that diabetic patients had the sweetish taste of sugar in their blood.^{1,5} This confirmed the relationship between the sugars present in the blood and those excreted in the urine.

John Rollo established the link between the food consumed by diabetics and the amount of sugar in the urine.⁶ Rollo recorded the amount and kind of food eaten by his diabetic patients, and then weighed the "sugar cake" which remained after evaporating their urine.⁶ He observed that carbohydrates increased sugar levels, and animal product consumption resulted in less sugar.^{1,5,6} He promoted the idea that the treatment for diabetes should be a diet low in carbohydrates and high in fat and protein. This modification of diet became the recommended treatment for diabetes until the discovery of insulin.⁷

The first clinical tests for glycosuria were developed in the nineteenth century. In 1841, Karl Trommer, developed a qualitative test for sugar which involves treating a urine sample with a strong acid which results in the acid hydrolysis of disaccharides into monosaccharides.^{5,6} The solution is then neutralized and a solution of copper sulphate is added, then excess of alkali, followed by boiling, a brick-red cuprous oxide precipitate forms if glucose is present.^{5,6} In 1850, Hermann von Fehling developed a quantitative test based on Trommer's work to measure sugar content.⁶ Frederick Pavy (1829-1911) established a quantitative relationship between the degree of hyperglycemia and glycosuria based on Fehling's test.⁵ Pavy also improved upon the Fehling's test for quantitative sugar urinalysis by substituting ammonia for caustic potash and thereby facilitating production of the first urinalysis tablets.⁵

In the twentieth century, easier methods to determine urine sugar content and tests for blood glucose were developed. In 1907, Stanley Benedict developed a milder test for glycosuria using a copper reagent with a carbonate base rather than the hydroxide base of Fehling's test.⁸ In 1913, Ivar Bang pioneered a method to test

blood glucose levels whereby blood proteins were fixed to filter paper and the filtrate was used to measure glucose using copper sulfate and KCl.⁹ However, the use of glucose-dependent copper reagent reduction reactions became increasingly analytically problematic as they underestimated the amount of glucose present.⁸ In 1941, the Ames company introduced the first "stick" or "strip" tests (Clinitest) which was still based on the old methodology involving copper sulfate reduction.¹⁰ Shortly thereafter, the Ames company produced the far more accurate Clinistix which is based on the enzymatic reaction of glucose oxidase.¹⁰ This enzyme generates hydrogen peroxide as it interacts with glucose, which in turn reacts with horseradish peroxidase to produce oxygen which oxidizes orthotoluidine to produce a blue or purple colour.¹⁰

In more recent times, the diagnosis of diabetes has taken on a more quantified approach. The emphasis over that last forty years has been on measuring blood glucose levels and response to oral glucose challenges. Debate, however, has ensued over the determination of cut-off values for diagnosis, and the accepted values have changed a number of times, reflecting changes in trends and attitudes.

In 1979, the National Diabetes Data Group and the World Health Organization developed diagnostic criteria for the diagnosis of diabetes that involved measuring glucose tolerance using an oral glucose tolerance test (OGTT).¹¹ An OGTT involves giving a patient 75 gm of glucose by mouth and then measuring their blood sugars two hours later. If a patient's blood sugars are elevated more than they would be in a normal individual, then that patient has impaired glucose tolerance. Using this test, the following criterion was established for the diagnosis of diabetes: fasting blood glucose 7.8 mmol/L or higher, or an OGTT two-hour blood glucose value of 11.1 mmol/L or higher.¹¹

These guidelines were updated in 1997 by the American Diabetes Association (ADA), and then revised in 2003. The new guidelines require meeting one of three criteria in order to diagnose diabetes: a) a fasting blood glucose concentration

of 7.0 mmol/L or higher with symptoms of hyperglycemia, which include polydipsia, polyuria, and weight loss; b) a random blood glucose of 11.1 mmol/L or higher; c) a two hour value in an OGTT of 11.1 mmol/L or higher.¹² The diagnosis must then be confirmed on a different day with any of the three criteria.¹² The ADA cautions use of the OGTT as a tool for diagnosis, and stresses the use of fasting blood glucose measurements instead, because the results of the OGTT are not always reproducible and so the test is not reliable.¹³

There has been recent interest in using hemoglobin A1c values to aid in the diagnosis of type 2 diabetes in conjunction with random blood glucose levels.^{14,15} Hemoglobin A1c is the glycosylated form of hemoglobin A, the major adult hemoglobin type. The utility in measuring hemoglobin A1c comes from the fact that its concentration is proportional to blood glucose levels. In non-diabetics, the normal hemoglobin A1c level is less than 5% of the total hemoglobin.¹⁶ In patients with diabetes, chronically elevated blood sugars will lead to a higher than normal percentage of hemoglobin A1c. It has been proposed that to avoid the inconvenience of measuring fasting blood glucose as a means of diagnosis, an abnormal random blood glucose value (11.1 mmol/L or higher) in addition to a hemoglobin A1c value greater than 2 standard deviations above normal could be used.^{14,15} Before the incorporation of hemoglobin A1c measurements into diagnostic criteria, a number of issues need to be addressed including erroneous levels due to diseases that falsely elevate or depress A1c values.¹⁷ Despite these potential sources of error, since 1999 Japan has been using HbA1c levels over 6.5 % as a diagnostic marker for diabetes.^{18,19} It seems clear that there still remains work to be done to standardize the diagnostic tools in the determination of diabetes.

From the initial reports of sweet tasting urine to the biochemical analysis of glycosylated hemoglobin, the tests employed to diagnose diabetes have become more sophisticated over the past centuries as our knowledge of the disease grows. The future promises to have ever

more specific tests to diagnose the different varieties of diabetes, some of which may enter the realm of genetic screening or pharmacogenetics.

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