

A History of Diabetes Mellitus or How a Disease of the Kidneys Evolved Into a Kidney Disease

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Diabetes mellitus has a long history during which it was considered to be a disease of the kidneys well into the middle of the 19th century. Recognized in antiquity from its excessive urine output and described as a disease of the urinary tract, its clinical features and fatal outcome were quite accurately recorded by the 1st century AD. Galen (129-200) described it as a disease specific to the kidneys because of a weakness in their retentive faculties. The sweet taste of diabetic urine, which is described in ancient Indian texts and noted by Avicenna (980-1037) and Morgagni (1635-1683), was attributed to the passage of absorbed water and nutrients unchanged into the urine. In 1674, Thomas Willis (1621-1675) first differentiated diabetes from other causes of polyuria by the sweet taste (quasi melle) of diabetic urine and suggested that the sweetness first appears in the blood. A century later, Matthew Dobson (1732-1784) showed that the urine sweetness was because of sugar and was preceded and accompanied by sugar in the blood. Although diabetes then came to be ascribed to increased sugar in the blood, the presence of sugar in the urine continued to be attributed to the decreased retentive properties of the kidneys. The experimental production of diabetes in pancrea-tomized dogs that could be reversed by subcutaneous pancreatic transplantation in 1889, and ultimate isolation of insulin in 1922 clearly established diabetes as an endocrine disease. The stage of diabetes as a disease of the kidneys was now over but that of diabetes as a cause of kidney disease was yet to come. Diabetes as a cause of end stage kidney disease was first described in 1936 and extensively documented shortly thereafter, whereas the evidence of its increasing prevalence as a cause of chronic kidney disease continues to accrue.

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Throughout most of its history, diabetes mellitus was considered classified and promulgated as a disease of the kidneys. It was only in the latter part of the 19th century, when chemistry and physiology moved medicine from an observational to an investigative science, that it first came to be defined as a metabolic and shortly thereafter as an endocrine disease. The present article focuses on the renal aspects of diabetes mellitus whose history otherwise has been recounted in several excellent reviews and texts.¹⁻⁸ For the sake of brevity, diabetes will be used throughout the rest of this article, rather than diabetes mellitus. The history of diabetes is insipidus, and its ultimate differentiation from diabetes mellitus is another story.

Diabetes: A Disease of the Kidneys

Beginning in antiquity, when what constituted the evidence for an illness were the abnormal symptoms with which patients presented, polyuria soon attracted attention and was recorded as a disease. Most extant medi-

cal texts of antiquity devote sections of variable length and detail to its description and treatment. As we know it so well now, polyuria is a symptom of varied etiology, and it is impossible to discriminate clearly what those ancient writings referred to and treatments were directed at. Notwithstanding the more or less justifiable objections of interpreting the past in light of what we know now, the fact remains that features of diabetes were noted in polyuric patients, and several of the descriptions given in ancient texts are arguably consistent with diabetes mellitus. Notable among those are Indian texts, dated to the 5th century BC, that refer to cases of excessive

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urine, coupled with thirst and emaciation, in whom the urine is described as *ksaudra* (sweet) or *madhu* (honey) *meha* (urine), an illness said to affect rich people who consumed large quantities of rice, cereals, and sweets.^{4,6,8,9}

Demetrius of Apameia (1st or 2nd century BC) is credited with introducing the term “diabetes,” which derives from the Ionic meaning to “pass or run through” as in a siphon and its subsequent Latin meaning of “siphon.”^{4,10} It corresponds to the prevailing notion that the large urine volume of these patients was because of the passage of ingested fluids through the body unchanged as if through a tube. It is under the term “diabetes” that Areteus of Cappadocia (early 2nd century AD) wrote what is considered the first accurate clinical description of diabetes. He describes it as “an affliction that is not very frequent. . . being a melting down of the flesh and limbs into the urine. . . life is short, disgusting and painful. . . thirst unquenchable. . . the kidneys and bladder never stop making water. . . it may be something pernicious, derived from other diseases, which attack the bladder and kidneys.”¹¹ Another rare cause Areteus mentions is the bite of a venomous serpent (*dipsas*) that “kindles up an unquenchable thirst.”^{4,6,11}

Although Areteus attributed diabetes to a disease of the bladder and the kidneys, his contemporary, and the more famous, Galen (129-200 AD.) considered it a disease of the kidneys. In chapter 3 on diseases of the kidneys of his *On Affected Parts* he states: “This condition impresses me as an ailment of the kidneys, whereas other physicians call it ‘dropsy of the chamber pot’, or ‘urinary diarrhea’ others define it as ‘diabetes’; but some call it ‘dipsakos’ (violent thirst). It is a very rare disease, which I observed only twice until now. These patients had an immoderate thirst. For this reason they drank abundantly and passed all the water they consumed after a short time (in the same condition) as they took it.”¹² Making reference to his elegant series of experiments on dogs showing the kidneys as the source of urine,¹³ he continues: “It also has been shown that the kidneys attract the watery substance of the blood, but that the urinary bladder does not attract anything. . . the kidneys send discharged matter to the blad-

der through the ureters. . . Someone could therefore blame the failure to retain the urine for any period of time on a weakness of the kidneys but not the other organs through which the ingested fluid has to pass.”¹²

What is specially interesting and relevant to our current understanding of changes in tonicity and intravascular volume in diabetes, which only began to be elucidated in the 1950s,¹⁴ is his subsequent explanation, speculative but yet so perceptive, that

*diuresis starts slowly, but when it becomes more intense it draws the serum of the blood first from the veins without us being aware of it. When all the serum has been released and the blood in the vein appears to have lost its moisture, the dried up blood vessels will attract new moisture from the liver, and later from the bowels and stomach; but when the veins of the opening of the stomach are dried up, the patient craves fluid, since he becomes aware of this condition. Then, when fluids have been supplied, the parched veins from the liver to the stomach rapidly seize the entire amount which flows from these veins to adjoining vessels until it reaches the kidneys.*¹²

Concluding that:

Diabetes is a disease specific to the kidneys, the thirst analogous to ravenous hunger has its seat in the opening of the gastric cavity, and is combined with a weakness (atonia) of the retentive faculty of the kidneys. . . the lack of a weakened retentive faculty would not allow a rapid elimination of urine.”¹²

Galen had his circulation confused and erroneously placed the site of osmoregulation in the stomach, but his deductive physiological reasoning is impressive. This rational reasoning, coupled with the dogma that Galen’s authority came to be accepted, dominated most of the prevailing concepts of diabetes as a disease of the kidneys over the next 1,500 years.

Over time, additional clinical features of diabetes were described. Avicenna (980-1037), who termed the disease “aldulab” or water wheel and “zalkh el kuliah” or diarrhea of the kidneys, terms that Galen and others had used, added to the complications of the disease those of mental troubles, impotence, gangrene, and furunculosis.^{4,6,15} Avicenna is said to have more clearly differentiated diabetes associated with emaciation from other causes of polyuria and prescribed a treatment that

subsequent clinical trials, at the recommendation of the French director of Tunis, are said to have been effective in 5 cases.¹⁵ With the expanded reference to diabetes in medical texts of the period, one gets a sense of its increasing prevalence. In fact, it is at about this time that the first extant treatise dedicated to diabetes was written by one Abdel Latif el Baghdadi (1162-1231) in 1225.⁶

Diabetes: A Disease of the Kidneys?

The first paradigm shift in the conceptual evolution of diabetes comes from the studies of Paracelsus (1493-1541) who describes it as a constitutional disease that "irritates the kidneys" and provokes excessive urination. Having evaporated the urine from a diabetic patient, Paracelsus reported an excessive residue, which he called "salts," and described diabetes as an affection of the blood "being involved with salt Particles, do run forth through the most open passages of the Reins (kidneys)."^{4,6,8,11} This is a provocative conceptual analysis that Ralph Major (1884-1970) describes as follows: "although couched in somewhat fantastic language, is clear and, if we substitute sugar for salt, has a surprisingly modern ring."¹¹ However, it was the much later report of Thomas Willis (1621-1675) in 1674 that the urine in diabetics, which he evaporated and tasted, was sweet "as if imbued with honey (quasi melle) and sugar" that ultimately directed the attention of the profession to the saccharine character of the urine and differentiated diabetes from other causes of polyuria.^{4,6,8,11}

As important as Willis' observation was, it was not a new one. As mentioned earlier, the sweetness of the urine was described in Indian texts. Moreover, tasting the urine was part of its regular examination. Both Avicenna and Paracelsus advise tasting the urine, and Paracelsus refers to its sweetness in other contexts.⁶ Also pertinent in this regard is the description by Morgagni (1635-1683) of diabetes as "what is drunk should be discharged by the urinary passages, without the least change whatever, preserving the same colour, consistence, taste (sic) and smell as when take in."¹⁶ In fact, Avicenna in the first book of the Canon states that "when the urine of diabetics is left

to stand in ambient air, it leaves a residue that is particularly sticky and tastes sweet as honey."¹⁵ It would have been unusual for Paracelsus, a man known for his rough and crude habits, not to have tasted the residue of the diabetic urine that he analyzed. It is fair to conclude then that sweetness of the urine was observed in the past but had been attributed to the fact that ingested nutrients, including sweet ones, passed without change into the urine along with the water that had been drunk.

On the other hand, Willis not only described the sweetness of the urine in diabetes, or the "Pissing Evil" as he calls it, but also considered the disease to be an affliction of the blood arguing that the sweetness appears first in the blood and then in the urine. What makes his report important is his frontal attack of Galen, following the fashion of the times, and strengthened by the discovery of the circulation in 1628 by William Harvey, (1578-1657) in his dogmatic statement that

It in no way pleases us that some do assign for the cause of Diabetes the attracting force of the Reins: because the Blood is not drawn to the Reins but driven thither by the motion of the Heart. Further neither doth Serum seem to be drawn or emulged from Blood washing through them, but to be separated (as we have already more clearly shewed) partly by straining, and partly by fusion or a certain kind of precipitation: wherefore we believe the Diabetes to be rather and more immediately an affection of the Blood than the Reins.¹¹

Nevertheless, it was the simple observation of Willis that gave the disease its new name "diabetes mellitus," but it was more than a century later that his argument was substantiated by the demonstration of sugar in the blood and urine of diabetics by Robert Wyatt in 1774 and subsequently by the more thorough studies of Matthew Dobson (1732-1784), who had a fairly good of knowledge of chemistry.⁴ In 1776, Dobson¹⁷ showed that the sweetness of urine is caused by sugar, which he quantified and showed to be subject to alcohol and acetate fermentation, and that its appearance in the urine is preceded and accompanied by a similar sweetness and sugar in the blood, albeit not as much as that detected in the urine.¹¹ Diabetes now came to be viewed as a disorder of nutrition in which

sugar accumulates in the blood and is excreted in the urine. This was to launch a whole new approach for the dietary treatment of diabetics and with it a shift to the digestive organs as the site of the disease and more specifically to the absorption of "saccharine matter" in the stomach. The series of studies on the dietary treatment of diabetics that followed are best exemplified in the early and pioneering work of John Rollo (d. 1809). As much of this early work was done in England, the disease came to be dubbed facetiously "diabetes anglicus." Much of the subsequent clinical and basic research, however, was done in France and Germany.

The sugar in the blood and urine was identified as glucose in 1815 by Michel Eugene Chevreuil (1786-1889). Efforts to quantify glucose in the urine continued to be refined, and by the second half of the 19th century the disease could be diagnosed from the examination of the urine. Although diabetes was now thought of as a disease of blood composition, it continued to be considered a disease of the kidneys whose decreased retentive powers resulted in the passage of sugar with water, rather than the mere passage of water in the urine as the original Greek texts had implied.⁴⁻¹¹ The source of increased glucose absorption in the gastrointestinal tract continued to be the focus of much debate and investigation until 1855, when Claude Bernard (1813-1878) showed the glycogenic properties of the liver and established glucose as the first internal secretion. It was this observation that, over the next 50 years, was to evolve into the discipline of endocrinology¹⁸ and thereby pave the way to the discovery of the role of the pancreas as the source of insulin.

Diabetes: A Disease of the Pancreas

Ever since its recognition, the pancreas (pan = all, creas = flesh) had been considered as merely a supportive fleshy cushion on which the surrounding visceral organs rested. With the advent of anatomic dissection, its ducts were identified, and, as studies in digestion progressed, its role in the digestive process came to be recognized. In 1683, Johann Conrad Brunner (1653-1727), of Brunner's gland fame, removed the pancreas in dogs, which

survived. For the subsequent 200 years, the pancreas came to be considered a nonvital organ of external secretion, with its principal function being to digest fatty matter and to convert starch into sugar.^{3,6,11,19}

In the interim, pathological studies begun to question this dogma. Postmortem examination of patients with bulky and oily stools (steatorrhea) who had a diseased pancreas reported on its vital role in absorption. Among those reports is a series of 8 cases reported in 1832 by Richard Bright (1789-1858).⁵ The first case he describes had initially presented with diabetes mellitus but succumbed to his pancreatic ailment. In his discussion of the case, Bright considers a possible link but dismisses it because "I have seen a great number of diabetic cases, in which this symptom (fatty stools) did not occur" and "because diabetes was not detected, nor even suspected, in the other cases of this evacuation (fatty stools) which I have related." To the chagrin of any present-day nephrologist, he concludes "that there is no essential connection between the two diseased actions."²⁰ Although not referenced, Bright may have been refuting earlier observations by Thomas Cawley (18th century), who in 1788 had described a case of pancreatic calcification and calculi that was associated with diabetes.⁵

Cawley was the first to suggest a relationship between the pancreas and diabetes, an association subsequently confirmed in various other diseases of the pancreas. These initial clinical observations were confirmed in 1889, when Oscar Minkowski (1858-1931) and Joseph Mering (1849-1908) showed that pancreatectomized dogs developed diabetes, which could be reversed by the subcutaneous implantation of pancreatic fragments.^{4-8,11} The specific role of the pancreas was further refined after Paul Langerhans (1849-1888) described in 1869 the unique morphologic features of the pancreatic islands that were subsequently named after him.³⁻⁵ In 1909, Eugene L. Opie (1873-1971) reported hyaline degeneration of the islands in diabetic patients,²¹ a finding subsequently confirmed in a series of experimental studies that led Edward Sharpey-Schafer to suggest in 1916 that the islands of Langerhans produced a glucose-regulating hormone that he termed insulin.

The race for isolating the hypothesized hormone was now on. Frederick Banting (1891-1941) and Charles Best (1892-1978) finally did so in 1922. They wanted to call it isletin, but J.J.R Macleod (1876-1935), in whose laboratory their work was done, insisted on using insulin.^{2-8,22} The endocrine nature of diabetes was now clearly established. The stage of diabetes as a disease of the kidneys was over. The stage of diabetes as a cause of kidney disease was yet to come.

Diabetic Kidney Disease

For a disease long considered as one of the kidneys, attempts to find an explanatory pathological abnormality in the kidneys had been futile. The resulting frustration is best expressed in an 1847 text on medicine.

Examination of the dead body throws little or no light upon the pathology of diabetes. We naturally look with interest to the kidneys. But we find nothing there to explain the symptoms noticed during life. I have noticed the deep purplish colour of kidneys which were veined and vascular, but not otherwise altered in texture. Others tell us that the kidneys are found hypertrophied in diabetes. But hypertrophy, and unnatural vascularity, are circumstances which we are not surprised at when we reflect upon the vastly increased quantity of work which the glands (sic) have been performing. They are the consequences rather than the cause of the morbid flow of urine.²³

The larger size and increased vascularity of the kidneys is recorded in several other texts of the period in which the kidneys are described as being “rather fuller of blood than usual” and to “exhibit increased vascularity, often enlarged, soft” (Fig 1).^{24,25}

Nor did microscopic examination of the kidneys seem to shed much light on the subject other than to confirm enlarged glomeruli and vessels that were engorged with blood.⁴ In 1881, Wilhelm Ebstein (1831-1912), acknowledging their prior recognition by Armanni in 1875, reported hyalinization of tubular epithelial cells in diabetic kidneys—hence, the acronym Armanni-Ebstein, for these lesions that came to be considered pathognomic of diabetes. In 1883, Paul Ehrlich (1854-1915) determined the glycogenic nature of the tubular epithelial cell changes, which subsequently were shown to be related to the severity of the

glycosuria and, with the advent of insulin therapy, became rare and only occasionally mentioned.^{26,27} Things were to change after 1936, when Paul Kimmelstiel (1900-1970) and Clifford Wilson (1906-1983) reported on the presence of peculiar hyaline masses in the glomerular lobules of 8 diabetic patients, aged 48 to 68 years, none of whom was on insulin therapy, which they termed intercapillary glomerulosclerosis.²⁸ Similar lesions had previously been encountered,²⁹ but as suggested also by Kimmelstiel and Wilson, were attributed to the “aging process of the glomerulus,”

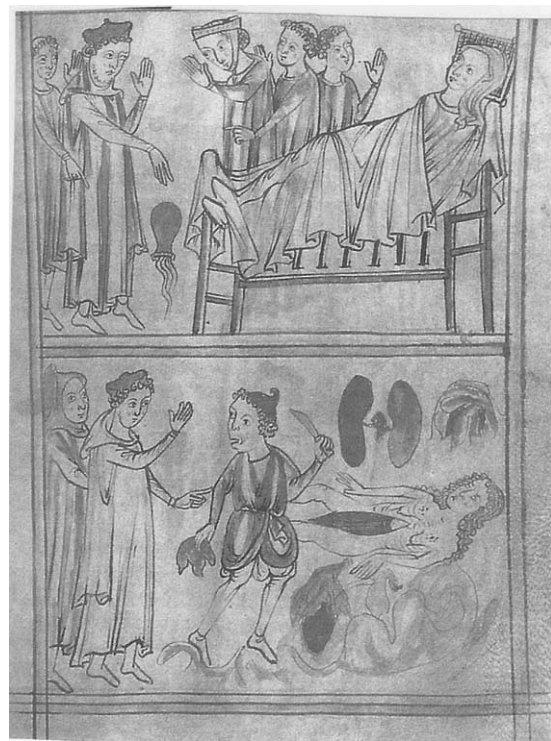


Figure 1. (Top) A sick lady with her physician. The dropped urine flask (matula) indicates that the condition is hopeless. (Bottom) The patient has died, and a postmortem examination is in progress. Note the relative size of the kidneys, in the upper center part of the figure, relative to the size of the liver, in the hand of the prosector, and that of the lungs and heart, next to his left foot. The story told in this 13th century illustration can be taken as an allegory of that of diabetes until the first part of the 20th century when excessive urine that was sweet indicated a poor prognosis, and at autopsy the kidneys were found to be engorged and hypertrophied. Reprinted with permission of the Bodleian Library, University of Oxford, MS. Ashmole 399, folio 34r.

which Kimmelstiel had previously attributed to arteriosclerosis.³⁰

What is critical in their report, however, is the accompanying symptom complex of diabetes, proteinuria, hypertension, nephrotic edema, and impaired kidney function. Proteinuria in diabetics had been described clearly by Pierre Rayer (1793-1867) and reported by others before him. In his classic monograph on diabetes, Bernhard Naunyn (1839-1925) commented on proteinuria, indicating that mild albuminuria in diabetics is insignificant while that of heavy albuminuria was a bad prognostic sign.^{4,5} In his *The Principles and Practice of Medicine*, William Osler (1849-1919) comments on the albuminuria of diabetics as "a tolerably frequent complication. The amount varies greatly, and, when slight, does not seem to be of much moment. It is sometimes associated with arteriosclerosis. It occasionally precedes the development of diabetic coma."³¹ However, the clinical pathologic correlation described by Kimmelstiel and Wilson had not been recognized previously and prompted, within a very short period of time, a series of reports confirming the clinical picture but showing a closer association with another characteristic lesion of diffuse, rather than nodular, glomerulosclerosis, whose severity was increased with the duration of diabetes.³²⁻³⁷ It is this syndrome complex soon termed diabetic nephropathy,^{38,39} which now is a, if not yet the, leading cause of chronic kidney disease and end stage renal disease. The present issue of *Advances in Chronic Kidney Disease* presents the current state of knowledge accrued over the recent past, when diabetes mellitus ceased to be known as a disease of the kidneys and emerged as a leading cause of kidney disease.

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