A History of Diabetes Insipidus: Paving the Road to Internal Water Balance

Garabed Eknoyan, MD

Diabetes insipidus is an ancient disease considered under the rubric of diabetes, the Greek descriptive term for polyuria, which was unrecognized even after the sweetness of urine was reported as a characteristic of diabetes mellitus in the 17th century. It would be another century before diabetes insipidus was identified from the insipid rather than saccharine taste of urine in cases of polyuria. After its increased recognition, pathologic observations and experimental studies connected diabetes insipidus to the pituitary gland in the opening decades of the 20th century. Simultaneously, posterior pituitary lobe extracts were shown to be vasoconstrictive (vasopressin) and antidiuretic (antidiuretic hormone). As vasopressin was purified and synthesized and its assay became available, it was shown to be released in response to both osmotic and volume stimuli that are integrated in the hypothalamus, and vasopressin thereby was essential to maintaining internal water balance. The antidiuretic properties of vasopressin to treat the rare cases of diabetes insipidus were of limited clinical utility until its vasoconstrictive effects were resuscitated in the 1970s, with the consequent increasing wider use of vasopressin for the treatment of compromised hemodynamic states. In addition, the discovery of antidiuretic hormone receptor blockers has led to their increasing use in managing hypo-osmolar states.


Shrouded in the origins of creation mythology, water has been considered a vital element since time immemorial. By the time Greek rational medicine emerged, water was incorporated into medical thought as a component of the 4 humors of Hippocratic medicine. Although water was recognized as being essential to life, the regulation of its internal balance remained a mystery well into the early 20th century, when insight into water homeostasis was provided from studies of diabetes insipidus, an ancient disease that had been unexplained before. In antiquity, it was a patient’s presenting symptom of external glaring manifestations that defined an illness, and polyuria soon attracted attention and was recorded as a disease. As we know it today, polyuria is a manifestation of varied causes and it is difficult to discriminate to exactly which of these diseases the ancient authors were referring. Nevertheless, it generally is accepted that most clinical descriptions of polyuria given in ancient texts are consistent with diabetes mellitus, which together with the then other unknown causes of polyuria, such as diabetes insipidus, were classified under the generic term of diabetes.1-3

BEGINNINGS: POLYURIA

Demetrius of Apameia (1st-2nd century BCE) is credited with introducing the term “diabetes,” derived from the Ionic, meaning “to pass or run through,” as in a siphon.4 This descriptive term reflects the prevailing notion at the time that polyuria was caused by the passage of ingested fluids through the body unchanged, as if flowing through a tube or siphon, much as water does in the landmark Manneken-Pis statue in Brussels (Fig 1). It is...
under the term “diabetes” that Aretaeus of Cappadocia (2nd century CE) then recorded what is considered the first clinical description of diabetes mellitus:

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."

The subsequent story of diabetes mellitus has been told many times.\textsuperscript{1-3,6} The less well-known story of diabetes insipidus is the subject of this article.

With a license to interpret, diabetes insipidus also may be traced to Aretaeus, who in his comments mentions another rarer cause of diabetes due to the bite of a venomous snake, \textit{dipsas}, which “kindles up an unquenchable thirst.”\textsuperscript{5} The story of this fabled serpent is told by several early Greek authors and in subsequent literature, came to be used as the name of enchanters, sibyls, and witches who inflicted various cravings in their victims. For our purposes, \textit{dipsas} is the origin of the medical term “polydipsia,” for excessive thirst.

Whatever Aretaeus may have meant in his reference to \textit{dipsas} as another cause of diabetes will forever be a mystery. For all practical purposes, reports of diabetes in the medical literature thereafter likely included cases of diabetes insipidus that were unrecognized well into the 17th century.\textsuperscript{7}

Throughout the rest of this article, the term diabetes, as defined by Demetrius, will be used interchangeably with diabetes mellitus to mean copious volumes of urine and qualified by its characteristics (saccharine, insipid, etc) in the specific diseases that came to be identified as a cause of polyuria.

**EMERGENCE OF DIABETES INSIPIDUS**

The foundation for differentiating the 2 principal forms of diabetes (mellitus and insipidus) was laid in the 1670s when Thomas Willis (1621-1675), professor of Natural Philosophy at Oxford, reported his observation that the residue of evaporated diabetic (polyuric) urine was “wonderfully sweet and tasted like honey (\textit{quasi melle}).”\textsuperscript{1,6,8} As important as this observation was, it was not a new one. Sweetness of the urine had been reported in the past, but attributed to the “siphoning” of ingested saccharine matter passed without change into the urine along with the water that had been drunk. This concept is vividly illustrated by the Manneken-Pis of Brussels, whose “urine” taste, color, and composition depends on the fluid pumped into its circulating system (Fig 1). The true importance of Wil-
lis's report was the argument that diabetes is not a disease of the kidneys, as it was considered before, but of the blood in which sweetness appears. In his writings, Willis merely highlighted the difference in taste of urine from polyuric compared with healthy individuals. He used the term diabetes in the generic sense, meaning polyuria, and did not comment on the occurrence of nonsaccharine-tasting urine in polyuric individuals. Nevertheless, it was his observation that led to the differentiation of diabetes mellitus from the rarer entity of diabetes insipidus a century later.

In 1769, the Scottish physician and famed chemist William Cullen (1710-1790) of Glasgow and Edinburgh first called attention to diabetic (polyuric) urine that is insipid in taste and added the descriptive adjective “mellitus” to the disease described by Willis. Relevant are the contemporary studies of Matthew Dobson (1732-1784) of Liverpool of diabetes mellitus, who proved the postulates of Willis by showing that the sweetness of urine in diabetes mellitus is caused by sugar, which was preceded and accompanied by the same sweet residue in blood. Dobson had consulted Cullen before reporting his observations of diabetes mellitus. In his response, Cullen, after commending Dobson for his studies, states . . . I have only to add that I wish you would examine both by taste and evaporation what might be called the Urina Potus or that copious limpid urine which runs in some people after drinking largely of water or watery liquors.

The urina potus to which Cullen refers is a medieval remnant of uroscopy in which the urine to be “looked at” was classified as that after eating (urina cibis), after sleep (urina sanguinis), and after drinking (urina potus). The reference to the Latin potus is to the vessels in which drinks were imbibed. The use of urina potus interchangeably with that of excessive urination (polyuria and diabetes) remained in use well into the 1930s, even after chemical analysis and osmometry of urine to diagnose diabetes insipidus had come into use. Potus also is the origin of the clinical entity termed beer potomania that was to be described much later.

In the report of his cases, Dobson recognizes Cullen’s warning:

On the other hand, a learned and justly celebrated professor, the very ingenious Dr. Cullen, assures me, that he has met some cases of the diabetes, in which the urine was not sweet, agreeable to what has been observed by foreign writers. The latter statement is in reference to the challenge on the Continent to the series of reports on diabetes mellitus from the British Isles, notably by Francois Boissier de Sauvages (1706-1767) of Montpellier, who termed diabetes mellitus a British disease (diabetes Anglicus) and declared that all cases of diabetes (polyuria) described in the past must have been cases of diabetes insipidus because the urine was tasted routinely as part of its examination, but its sweetness was not recorded; whereas all cases of diabetes being described from England had sweet-tasting urine. Geopolitical objections notwithstanding, there followed in the literature an increasing number of clinical reports, mostly of individual cases, of diabetes insipidus, for which the definition was expanded and clarified in 1794 by Johann Peter Frank (1745-1821), while at the University of Pavia, as a “long continued abnormally increased secretion of non-saccharine urine which is not caused by a disease of the kidneys.” The latter part of the statement was to differentiate diabetes insipidus from diabetes mellitus, which then was considered a disease of the kidneys. Frank, who further characterized diabetes insipidus as a rare entity, was at a loss as to its cause or treatment, and in deference to diabetes mellitus (verus, or true) called it spurious. Other than diabetes spurious, synonymous terms of diabetes insipidus used over the years include hydriuria, hyduresis, paruria, incontinens aquosa, hyperuresis aquosa, hydrops ad matulum, uorrhea, polyuresis, and diarrhea urinosa.

This was to remain the general state of knowledge for another century, as summed in 1892 by William Osler (1869-1939) in the first edition of his textbook:

The nature of the disease is unknown. It is doubtless of nervous
Osler’s reference to diabetes insipidus as a disease of nervous origin derives from its reported occurrence in hysteria and individuals of “nervous temperament,” reports of experimental “neurogenic polyuria” induced by needle injury to the brain, and the increasing number of reports that pathologic lesions at the base of the brain (tumors, syphilis, tuberculosis, and trauma) were associated with systemic (endocrine) abnormalities, including diabetes insipidus. His reference to the kidney is from reports of polyuria due to urina atonica, presumably caused by lower tone of the renal vasculature induced by renal denervation.

The prevailing notion of a “nervous origin” of diabetes insipidus remained rather vague until a specific link to the pituitary was documented in 1912 by Alfred Eric Frank (1884-1957), then working on diabetes mellitus in the department of Oskar Minkowski (1858-1931) in Breslau. He reported on the onset of polyuria and polydipsia in a man who had survived after shooting himself in the temple, on whom radiography of the head revealed the bullet lodged in the posterior part of the sella turcica. Shortly thereafter, Morris Simmonds (1885-1925) of Hamburg reported the case of a woman with metastatic cancer of the breast with onset of diabetes insipidus, whose autopsy showed that the posterior lobe and infundibulum of the pituitary were destroyed by metastatic infiltrates, whereas the anterior lobe was intact.

**A DIMINUTIVE ORGAN IN SEARCH OF A ROLE**

The pituitary had been described by Galen of Pergamum (129-199). In the rather complex physiology of Galen, the “animal spirits” were said to be added in the brain to the circulating “vital spirits” generated in the heart, with the waste products of this reaction flowing to the base of the brain, down the pituitary stalk to the pituitary gland, which in turn discharged them through the cribiform plate of the ethmoid bone into the nasopharynx as nasal mucus, phlegm, or pituita; hence the names of pituitary (Latin for phlegmatic) gland and ethmoid (Greek for sieve) bone. This waste disposal function has been taken to belittle Galen’s glandula pituitaria, but can be interpreted to the contrary as a herald of its greater importance documented in coming years, recalling that in the physiology of Galen the pituitary gland dealt with the control of 1 (phlegm) of the 4 (blood, yellow bile, black bile, and phlegm) body humors and therefore served a conceptually essential function in the maintenance of humoral balance vital to good health.

This speculative functional interpretation of the role of the pituitary based on its anatomic position was held for the next 15 centuries after Galen and perpetuated by Andreas Vesalius (1514-1564) of Brussels, who in his *De Humani Corporis Fabrica* provides the first illustrations of the hypothalamic-pituitary structural and circulatory relationships. Although Leonardo da Vinci (1452-1519) made a drawing of the base of the brain showing the rete mirabiliis surrounding the pituitary sometime between 1508 and 1509, the drawing was in his personal notebook and was unpublished for several centuries thereafter. Thus, it is the work of Vesalius, published in 1543 and publicly available, that affected medical thought in general and the pituitary function in particular. In the second half of the 17th century, the structural basis of presumed pituitary function was eroded by the anatomic studies of Conrad Victor Schneider (1614-1680) of Wittenburg in 1655 and the injection studies of Richard Lower (1631-1691) of Oxford in 1670, which failed to show a connection of the sella turcica to the nasopharynx. In 1778, the German anatomist Samuel Thomas Sömmering (1755-1830) of Mainz labeled the pituitary by its anatomic position as hypophysis cerebri to replace that of glandula pituitaria of Galen, now deprived of its phlegmatic function and degraded to the pituitary “body.” The abbreviated term hypophysis entered the medical lexicon thereafter and came to be used interchangeably with pituitary.

Deprived of a role in maintaining humoral balance, the pituitary gland then was relegated to near obscurity. Of the sundry speculative roles attributed to the pituitary during...
the ensuing years (ganglion, lymph node, cerebellar replica, etc), one that stands out for its vision is that of the Swedish polymath, mystic, and theologian Emanuel Swedenborg (1688-1772). In his quest for the seat of the soul, Swedenborg studied brain function, and in his notes published posthumously, wrote the following:

The pituitary is the last of the organs of the chymical laboratory of the brain. It is their complement and crown . . . and even carries out here some sublime and grand work which concerns the whole kingdom, and on which its whole welfare depends. On this account the pituitary gland may deservedly be styled the gland of life, or the arch gland, which receives the whole spirit of the brain and communicates it to the blood.28

This prescient declaration had to wait 2 centuries before it could be made as an evidence-based statement in 1935 by Walter Langdon-Brown (1870-1946) of Cambridge that the pituitary is “the leader of the endocrine orchestra.”29

What follows is the story of one lead player in Langdon-Brown’s orchestra, vasopressin, the hormone essential to maintaining internal water balance and by extension fundamental to maintaining the “internal milieu” of Claude Bernard (1813-1878). However, these future developments were yet to come. In 1890, the pituitary was flatly declared as being “probably the rudiment of an archaic sense organ” by Alexander Macalister (1844-1919), Professor of Anatomy at Cambridge,27 and in 1909 was defined by Harvey Cushing (1869-1939) as “a small bilobed body of unknown function attached to the infundibulum at the base of the brain.”30

It was just about this time that interest in pituitary function, stimulated by the steady accumulation of cases of diabetes insipidus associated with pituitary lesions, prompted experimental studies of pituitary function in various medical disciplines, progressing in parallel but independently of each other, which were to unravel the importance of the pituitary. To recognize individually the contributors who made this possible is beyond the scope of this article, which will mention only pioneering lead investigators, whose steadfast work provided the breakthroughs that allowed for others to expand the field.

ENDOCRINE STUDIES OF PITUITARY FUNCTION

Prompted by the studies of Claude Bernard’s successor to the Chair of Experimental Medicine at the Collège de France, Charles-Édouard Brown-Séquard (1817-1894), on the adrenals and testicles, organotherapy was in full swing in the 1890s.24,25 In 1895, George Oliver (1841-1915) and Edward Albert Schafer (1850-1935) from University College London first reported experiments on the endocrine functions of the pituitary.31 Oliver, a Harrogate practitioner who had invented a “haemodynameter, intended to read variations in blood pressure,” and an “arteriometer, for measuring with exactness the lumen of the radial artery,” convinced Schafer to let him use them in his laboratories to study adrenal function. Following their successful demonstration of vasoconstriction caused by injection of adrenal extracts, they were the first to report that injecting a water extract of the pituitary also results in vasoconstriction.3,25,27,32 In subsequent studies, Schafer and Herring reported that the increase in blood pressure was associated by diuresis, whereas the adrenal extract caused a mark diminution of the kidney and complete stoppage of the secretion of urine, extract of pituitary generally produces after a short period of latency, a remarkable and long-continued expansion of the organ, accompanied by a decided and often prolonged diuresis.32

The effect of the extract was shortly located to the posterior pituitary, but its reported diuretic effect was challenged.3,25,27

There followed a series of conflicting reports of differing results caused by: (1) variation in pituitary extraction methods, dose used, and route of administration; (2) the experimental animals studied, their state of hydration, and method of anesthesia; (3) duration of the experimental observation; and (4) sterile techniques used. In a summary statement of the confusion in the field, Homer Smith (1895-1962) stated that “the subject got off to a bad start and has been marked by many contradictory results.”33

To explain the divergent results (diuretic, antidiuretic) being reported, Schafer argued for the presence of 2 pituitary substances: one that stimulates...
and the other that suppresses urine secretion. The prevailing rather chaotic state that ensued is reflected in the 1912 classic work of Cushing, in which he admits his quandary to explain his own observations at variance with the diuretic effect reported by Schafer:

In all probability the polyuria is due to the excessive elaboration of the hormone contained in the pars nervosa secretion which activates renal secretion. Confessedly, however, there is some difficulty in satisfactorily explaining the diuresis which may accompany hypopituitarism, for one would suppose that individuals in stages of glandular insufficiency would show, more consistently than they do, a lowered urinary output.34

It would be 2 decades before there was general agreement that the diuresis reported by Schafer and his associates was due to increased pressure and blood flow to the kidney and the natriuretic effect of the large doses of the extract used, but that the actual action of the posterior pituitary extract was an antidiuresis that was documented best in unanesthetized animals undergoing water diuresis and given a small dose of the extract subcutaneously.35 Subsequent studies showed that extracts of the posterior lobe, known commercially as Pituitrin, had effects on the vascular system, urine secretion, and skin color.2,3 The substance exerting an effect on the vascular system was shown to also have an effect in decreasing urine excretion by a direct action on the renal tubular reabsorption of water. These experimental findings were substantiated by clinical evidence from the successful use of pituitary extracts in reducing the massive polyuria of individuals with diabetes insipidus.3,21,33 The term antidiuretic hormone (ADH) then entered the medical lexicon and was used interchangeably with vasopressin, Pitresin, and Pituitrin. A purified extract of the posterior pituitary was marketed in 1927 by Parke, Davis & Company under the brand name Vasopressin.

In summary, the available evidence in the 1920s was conclusive enough to define diabetes insipidus as a disorder of the pituitary and label it a hypopituitary syndrome.35-37 However, experimental studies continued to cast doubt about the strict hypophyseal origin of diabetes insipidus. The answer was provided by surgical ablation and morphologic studies in the expanding discipline of neurophysiology that had been launched by Harvey Cushing.34,38

THE PITUITARY-HYPothALAMUS LINK

Needle stimulation of the brain had been used in the 18th century to study nervous action and muscular contractility. After his demonstration of renal denervation diuresis and having just introduced the term “internal secretion,” Claude Bernard undertook experiments in the mid-1850s to produce discrete lesions in the base of the fourth ventricle of rabbit and dog brains, some of which provoked a polyuria that was “independent of glycosuria.”27,39 Bernard’s *piqûre* method of tiny needle lacera-

tions was one of the first to suggest a hypothalamic effect on the kidney, but it was not until the second decade of the 20th century that the physiologic and pathologic characteristics of these lesions were investigated, when Jean Camus (1872-1924) and Gustave Roussy (1874-1948) of the Faculté de Médecine de Paris produced polyuria in dogs by puncturing the hypothalamus while leaving the pituitary intact. In contrast, removing the pituitary while leaving the hypothalamic intact resulted in no polyuria.40 This was one of the first studies of the regulatory functions of a newly identified distinct anatomic brain region described in 1893 by Wilhelm His (1831-1949), who termed it hypothalamus.41 Subsequent ablation and stimulation studies substantiated these early observations of the integrative functions of the hypothalamus and gradually were refined in the 1930s by the introduction of increasingly improved stereotaxic instruments that provided precision in inducing brain lesions. Notable are the reports of Percival Bailey (1892-1973) and his associates at the University of Chicago42 and the substantial studies of Stephen Walter Ranson (1880-1942) and his associates at Northwestern University, who showed that the hypothalamic supraoptic nuclei give rise to nerve fibers terminating in the posterior pituitary, and that injury to the nuclei or supraoptico-hypophyseal tract invariably produced diabetes insipidus in experimental animals.43,44
A potential neurosecretory function of the pituitary was suspected in the 1890s from histologic studies showing colloidal staining of the anterior, but not the posterior, part of the gland or "pars nervosa" that develops from the nervous system. As evidence of posterior pituitary hormonal function accrued, it justifiably was asked how the neuroglial cells or "pituicytes" of the pars nervosa could secrete a hormone.\(^4^5\) This was elucidated in the 1930s by the demonstration of neurosecretion and axonal flow by Ernst Scharrer (1905-1965) and his wife Berta (1906-1995) of Albert Einstein University.\(^4^6\) Their studies were spurred by Wolfgang Bargmann (1906-1978) of Frankfurt, who had used a modified Gomori stain in his studies of pancreatic function in alloxan diabetes and now applied them to the hypothalamic-hypophyseal axis.\(^4^7\) Working in cooperation, the Scharrers and Bargmann proved conclusively that the neurohypophysis is innervated by the supraoptico-hypophyseal tract and that section of the pituitary stalk results in the accumulation of neurosecretory material on the proximal side of the section.\(^4^5\)-\(^4^7\)

The final pieces of the hypothalamic-hypophyseal coordination puzzle in controlling internal water balance were provided from studies in physiology and chemistry.\(^5^7\)-\(^5^9\)-\(^6^1\) The physiologic studies of Ernest B. Verney (1894-1967) from London and then Cambridge of the isolated heart, lung, and kidney preparation documented the direct effect of vasopressin on the denervated kidney and subsequently by the intracarotid injection of hypertonic solutions showed the release of ADH in response to stimulated osmoreceptors in the anterior hypothalamus.\(^5^2\),\(^5^3\) For all the anatomists, physiologists, basic scientists, and clinical investigators who resolved the posterior pituitary physiology and determined the cause and treatment of diabetes insipidus, the Nobel Prizes for work on the subject were given only in Chemistry, in 1955 to Vincent du Vigneaud (1901-1978) of Cornell Medical College, for determining the structure and synthesizing oxytocin and vasopressin,\(^5^4\) and in 2003, to Peter Agre (b 1949) of Johns Hopkins for the discovery of aquaporin channels that allow the free flow of water through cell membranes, including that of the action of ADH on renal epithelial cells.\(^5^5\)

**RECOGNITION OF NEW FORMS OF DIABETES**

Much as tasting the urine for sweetness and analyzing its sugar content helped the detection of diabetes insipidus, testing changes in urine osmolality in response to water restriction and ADH administration now helped the identification of new entities that had been unrecognized in the differential diagnosis of polyuria. The first of these was the renal as opposed to central origin of diabetes insipidus, termed "nephrogenic diabetes insipidus" in a 1947 report of its hereditary transmission by women to infants.\(^5^6\) The familial occurrence of diabetes insipidus had been noted in the second half of the 19th century and extensively documented in a German family by Adolf Weil (1848-1916) from Heidelberg in 1884 and subsequently by his son Alfred Weil (1885-1949) in 1908.\(^5^7\) The genetic origin of this rare entity has now been worked out and that of its much more frequent acquired form due to tubulointerstitial nephritis and electrolyte abnormalities has been documented extensively.\(^5^8\)

The second entity, caused by excessive production of ADH, was defined in 1957 when William B. Schwartz (1922-2009) of Tufts University School of Medicine and Frederic C. Barter (1914-1983) of the National Institutes of Health reported their eponymous syndrome of inappropriate secretion of ADH.\(^5^9\) Whereas this first report was of 2 cases of bronchogenic carcinoma, the release of ADH by factors other than serum osmolality has emerged as a more common cause of excess water retention.\(^5^1\) Since then, hyponatremia caused by inappropriate circulating ADH levels has come to be identified as the most common electrolyte disorder in hospitalized patients, whose management has been the subject of considerable debate, but is likely to be facilitated by the recent introduction of vasopressin receptor antagonists.\(^6^0\)

Other causes of diabetes insipidus include gestational diabetes insipidus, caused by increased placental vasopressinase activity,\(^6^1\) and polydipsia, either primary or psychogenic.\(^6^2\)
CONCLUSION

The discovery of diabetes insipidus as a deficiency of pituitary ADH during the past century paved the way to our understanding of internal water balance, when it was shown that receptors of osmolality and of effective volume that elicit responses from the hypothalamo-hypophyseal system are essential for the precise regulation of osmolality and volume of body fluids fundamental to survival. In the process, the original vasopressin that became ADH remained an orphan drug until its vasopressor effects were resuscitated. The pleomorphic effects of vasopressin have found increasing use in clinical practice for the management of a vast number of systemic and cardiovascular disorders that continues to expand as new agonists and antagonists of vasopressin receptors are identified and developed.

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