Diabetes Detectives

By Lee A. Witters, M.D., Marcus Luciano, Carla Williams, and Jessica Yang

Sometimes illumination comes from looking to the future—teasing out new knowledge at the lab bench or in a clinical trial. But sometimes it comes from delving into the past.

A professor of endocrinology and three undergraduates pursued 19th-century documents for clues to the changing understanding of one of today’s most common chronic conditions.

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he handwritten embellishments with the caricatures of a bygone era, James Goodwin recorded his professor’s lectures about diabetes in the fall of 1813. Goodwin had entered Dartmouth College from South Berwick, Maine, in 1807; earned his undergraduate degree in 1811; and by the fall of 1813 was less than a year away from earning his M.D. He and his classmates were learning about dia-

betes from no less a luminary than Dartmouth Medical School’s founder, Dr. Nathan Smith.

“Diabetes,” Smith told the students—according to Goodwin’s notebook, which today resides in the Dartmouth College archives—is a condition “in which the urine is discharged in great quantities and of a peculiar quality. The quantity depends upon the circumstances of the system. The quality depends upon hystera.”

This disease—now referred to by physicians as diabetes mellitus, to distinguish it from diabetes insipidus, which has similar symptoms but a different origin—was well represented in medical teaching as far back as the early 19th century. But it was as poorly understood then as it had been over the pri-

or two millennia.

Hipocrates, in 400 B.C., recognized diabetes but termed it very rare. Six hundred years later, another famous Greek physician, Galen, admitted to seeing two cases during his lifetime.

Today, however, over 246 million individuals worldwide—more people than live in the United Kingdom and France combined—have diabetes mellitus. In the United States, nearly 25 million indi-

viduals—8.3% of the population—suffer from the disease, and almost 25% of those over the age of 60 have been diagnosed with it. Its incidence is dis-

proportionately high among Native Americans, Hispanics, and African-Americans. It is the na-

tion’s seventh-leading cause of death; it rose to that rank over the course of the 19th century, in close mea-

sure to the concurrent rise in the preva-

lence of obesity.

The disease’s effects are serious. It is a major con-

tributor to atherosclerosis, known popularly as “hardening of the arteries,” which is the leading cause of death in the U.S. It is also the leading cause

of blindness in individuals aged 20 to 74, of renal failure, and of nontraumatic lower-limb ampu-

tations. And it is a major risk factor among pregnant women for fetal death and for birth defects.

The earliest medical texts, and Smith’s lectures, contained descriptions of the disease as far back as the early 19th century. But the understanding of its pathology and pathophysiology required the emergence of the discipli-

nes of chemistry, histology, and cellular pathol-

ogy in the 20th century. These science-sd mini-

sions, in turn, the birth of endocrinology—the branch of medicine dealing with glands such as the thyroid and pituitary. This journey of understand-

ing can be revealed by looking into the notebooks and theses of Dartmouth medical students through the course of the 19th century—the period during which the study of the disease became a fixture in medical school curriculums.

Another Dartmouth medical student, William Pratt, wrote in his 1825 thesis: “Perhaps future ex-

periments may discover the real nature of the prox-

imate cause of diabetes and establish a different mode of treatment from what has hitheric been tried. But until such a discovery is made, the physi-

cian must be guided by the symptoms that appear in the disease in the treatment of it.”

Indeed, it was the symptoms and signs of dia-

betes that dominated its story from ancient times to the late 19th century. The Ebers Papyrus, a document that dates from 1500 B.C., tells of a disease in Egypt characterized by the “passing of too much urine” and even suggests a remedy: “Mix cakes, wheat grains, fresh figs, green lead, earth, and water. Let stand moist, then strain, then take for four days.”

Sushruta—in 500 B.C. India, an early exponent of Ayurvedic medicine—observed that the urine of such patients tasted like honey, was sticky to the touch, and attracted flies. He even described two forms of the disease—one occurring in older, obese individuals and the other in young individuals who did not live long after the diagnosis. This exactly parallels the modern conception of, respectively, type 2 and type 1 diabetes mellitus. Ancient Ara-

bic texts—such as those of the great Islamic physi-

cian Avicenna, who practiced and wrote about medicine 1,000 years ago—also referred to a disease characterized by excessive and sweet-

tasting urine. Diabetes bore many names over the centuries—Galen called it “dropsy of the chamber pot.”

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pointment as a professor of biological sciences at Dartmouth Col-

lege. Luciano and Williams, both ’09s, and Song, a ’10, are Dart-

mouth undergraduates; all have an interest in both medicine and

Dartmouth medical students of the era represented here—except for the skinny guy holding the sign—were required to write a thesis before graduating. Students wrote on many subjects, from variola (smallpox) to diphtheria and fracture repair to diabetes mellitus. The latter was very uncommon then but is today a leading cause of death.

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The next significant discovery, about 22 years later, was the work of Dr. William Cruickshank—an artillery surgeon, chemist, a physiologist, Dr. J.J.R. Macleod, who with Banting, Fredrick Banting; a medical student, Charles Best; Minkowski and Joseph von Mering, associated diabetes mellitus and diabetes insipidus (“insipidus” meaning “tasteless”). The latter is now recognized as a totally distinct disease, arising from a failure of the pituitary gland to secrete a hormone called arginine vasopressin (also called antidiuretic hormone, or ADH). The saccharine nature of the urine of people with diabetes mellitus appears to have first been probed experimentally by Dr. Matthew Rollo, an English physician of the late 18th century who was also the first to deliver the delusions of the urine to his patients. The abovementioned sugar, in the blood, as well as glycosuria (an elevation of glucose in the urine). In his 1717 text Medical Observations and Inquiries, Rollo—evidently relying at least in part on gustatory analysis—wrote: “It appears—the saccharine matter inurges by the kidneys, in this case of diabetes, and probably does so in every instance of this disease, where the urine has a sweet taste. . . . It further appears that this saccharine matter is not formed in the secretory organ but previously existed in the serum of the blood.” Rollo’s observation proved to be an important turning point in the understanding of diabetes mellitus.

The nature of the disease then is chronic, and it takes a long period to be completely established, for the melting is rapid, the death speedy. “Diabeates” [sic] was the subject of Nathan Smith’s “Lecture 18” during 1811-12, according to Calvin Gorham’s student notebook. Gorham wrote that Smith, citing Rollo by name, recommended several of his therapies: low liquid intake, warm clothes, and frequent movements of the limbs. The latter is now recognized as a totally distinct disease, arising from a failure of the pituitary gland to secrete a hormone called arginine vasopressin (also called antidiuretic hormone, or ADH). The Saccharine nature of the urine of people with diabetes mellitus appears to have first been probed experimentally by Dr. Matthew Rollo, an English physician of the late 18th century who was also the first to deliver the delusions of the urine to his patients. The abovementioned sugar, in the blood, as well as glycosuria (an elevation of glucose in the urine). In his 1717 text Medical Observations and Inquiries, Rollo—evidently relying at least in part on gustatory analysis—wrote: “It appears—that this saccharine matter is not formed in the secretory organ but previously existed in the serum of the blood.” Rollo’s observation proved to be an important turning point in the understanding of diabetes mellitus.

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n the nineteenth century, about 22 years later, was the work of Dr. William Cruickshank—an artillery surgeon, chemist, and apothecary—Rollo undertook a longitudinal study of one Captain Meredith, who weighed 232 pounds and suffered from intense polyuria and polydipsia. While adhering to a diet, the two doctors recorded the quantity and nature of the sugar in his urine and blood, relying in part on taste and in part on the degree of effervescence produced by Meridith. It was shown that after a diet rich in protein and low in carbohydrates—together with the administration of several medications. T

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Artistic flourishes and marginal digressions

By Marcus Luciano, Carla Williams, and Jessica Yang

In 1810, Jonathan Brown, in his 1828 thesis “On Diabetes Mellitus,” wrote a student in his dissertation on some medical subject—a nearly perfect model of copperplate elegance. Note, however, that he appears to have gotten a little too carried away with his swashes and flourishes—and as a result he ran out of space and was forced to insert the final two letters of his last name in the upper right-hand corner of the page.

The art of doodling in class was apparently well developed, as indicated by these 1858 notes by George Goss.

The “cure” for diabetes, wrote a student in his thesis, lay in perfecting a regimen of “strict diet control”—an idea in line with modern thinking. He appears to be the only one of the six thesis-writers who had actually seen a case of diabetes. He lamented not having used a purgative—a drug that cleans out the bowels—to deal with this patient’s “morbid irritation,” as he put it. “My remarks in relation to purgatives in diabetes were suggested by a case which came under my inspection, where my neglect of the bowels was followed by a sudden increase in the quantity of urine. And were another case presented to me from the impression of this fact, I should be led to the efficiency of regular purging.”

In 1835, William Brown titled his thesis simply “Diabetes.” He made a conceptual leap, suggesting that the body itself produces the glucose present in diabetics’ urine, bypassing our current-day recognition of the impact of gluconeogenesis (the production of new glucose) in hyperglycemia. “The blood contains plenty of Carbon, Hydrogen, and Oxygen,” he wrote, “and why may not they be combined in the proportions to form sugar in preference to the combination which constitutes the composition of urea?”

Story Goss wrote a thesis in 1856 on “Diabetes Mellitus.” He drew in part on an important text in the Dartmouth library, William Prout’s Inquiry Into The Nature and Treatment of Diabetes, Calculus, and Other Affections of the Urinary Organs, published in 1826. Goss’s paper indicates that he had knowledge of two important developments in the emerging science of metabolism. First, he was clearly aware of the important observations of Dr. Claude Bernard, a French physiologist who in 1848 demonstrated the important observations of Dr. Claude Bernard, a French physiologist who in 1848 demonstrated the liver was the organ that metabolized glucose into the bloodstream. He went on to suggest that hyperglycemia arises because the lungs are limited in the amount of glucose they can metabolize, so they dump unmetabolized glucose into the bloodstream.
Diabetes Detectives
continued from page 41
acts by inhibiting polysaccharide metabolism in the intestine. But despite Gries’s insightful leaps, and his comprehensive review of all the then-current therapies, he listed none beyond those pointed out by Rolls 60 years earlier.

The final two student theses on diabetes date from 1880—Fred Spafford’s “History, Pathology and Treatment of Diabetes Mellitus” and Howell Tyler’s “Pathology of Diabetes Mellitus.” Their papers present most of the then-known thoughts about diabetes and glucose metabolism.

Spafford leaned heavily on the French physiologist Bernard, citing his important observation that diabetes could be induced by making lesions in the floor of the brain’s fourth ventricle, indicating a neural contribution. This understanding presaged observations by Dr. Bernardo Houssay about the role of pituitary hormones in the onset of diabetes—work that won him the 1947 Nobel Prize. Spafford even sought a genetic role in the disease—despite the fact that human genetics did not yet exist as a discipline—in his mention of twin boys with diabetes mellitus and of a sister who died of diabetes. This, too, presaged later knowledge: the modern recognition of an inherited form of the disease.

Tyler’s 1880 thesis contained references to both the past and the future. He reached back to the first century in citing descriptions of diabetes by the Roman encyclopedist Celsus. But he also correctly theorized that a contributing factor in the development of hyperglycemia was “increased introduction of [glucose], decreased destruction, or both.” This is consistent with modern understanding of the enzymes involved in the elevation of blood glucose.

From William Ellsworth’s 1806 notes to these two 1880 theses, the documents in Dartmouth’s archives show an evolving comprehension of the nature of diabetes. Interestingly, however, the conceptual leaps that occurred during this period did not lead to a parallel evolution in treatments. As late as 1880, Spafford and Tyler still listed near the same remedies that Nathan Smith, borrowing from John Rolle, had taught in the first decade of the century. Furthermore, all these remedies were entirely empirical, reflecting the ignorance that then prevailed regarding the genesis of diabetes mellitus.

But less than a decade after Spafford and Tyler penned their theses, Minkowski and von Mering’s 1889 observation regarding the role of the pancreas finally pierced the cloud of ignorance around the disease’s metabolic derangements. And that led to the discovery of insulin just three decades later. Yet, as is the case with all advancements in medical science, the discovery of insulin was hard due to the work and imagination of just a few investigators. Louis Pasteur once said, “If the fruit has appeared, there must have been some cultivation of the tree.” This cultivation, in the case of diabetes mellitus, occurred over the course of many centuries—but especially during the period encompassed by the Dartmouth documents. These medical students of the 19th century bore witness to a dramatic unraveling of the mysteries of “dropsy of the chamber pot.”

Jonathan Brown concluded his 1828 thesis with this qualification: “These desultory remarks, which I . . . called on, are extant in mangled form, possess perhaps more imperfections than would be pondeorable even in a juvenile debut. . . . With truth I assert that nothing short of a law of this institution induced me to attempt the discussion of this medical subject which would come to the inspection of my elders in the sciences.” (Let it be noted that though Brown deemed his thesis a “mangled” effort, he went on to a career of some distinction. He later studied with Dr. Walter Channing—Boston’s leading obstetrician, the dean from 1826 to 1847 of Harvard Medical School—and a founding editor of the New England Journal of Medicine. Brown also—after living in Santo Domingo, now Haiti, in 1833-34—wrote one of the important early histories of that nation, from its French colonization to its independence.)

Brown went on to end with these words: “With a lively sense of gratitude; I express my acknowledgments to the learned professors of this school and with them and the institution that prosperity and more of which learning joined to virtue so much deserves.”

Similarly, it is “with a lively sense of gratitude” that today’s medical detectives reflect on the hope that inspired Hugh and Adele to establish a charitable gift annuity with DHMC, designating that their gift advance neurological research. Funded with stock that had grown in value over many years, their gift provided Adele with a charitable income tax deduction and a fixed, guaranteed income for the rest of her life. “It seems like the perfect solution,” says Adele.

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