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Willey Glover Denis (1879–1929), Pioneer Woman of Clinical Chemistry[1]

When Dr. Willey Glover Denis joined Professor Otto Folin, in 1910, as a research assistant in his biochemical laboratory at the Harvard Medical School, she became one of the first women to enter the field of American biochemistry (Figure 1). She was apparently the first woman to specialize in the area that Folin had nurtured—clinical biochemistry. From 1901 to 1907, Folin introduced widely adopted quantitative methods for analysis of urine, but their transfer to blood became a longstanding project for Denis, and much of it in the milieu of a hospital laboratory that resembled the modern clinical study or research center.

Folin's studies on protein metabolism with his new methods had provided, *inter alia*, facts about the non-protein nitrogen (NPN), sulfur, and phosphorus content of urine, the concept of endogenous and exogenous catabolism, and the constancy of creatinine output, and had posed stimulating questions about the origins of creatine and urea. Would not blood reveal more intimately than urine the products of protein catabolism?

Until she moved to the Massachusetts General Hospital more than two years later, Dr. Denis worked in one or both of the two unfinished laboratory rooms that were just outside of Folin's office (Figure 2). Here, she launched her dynamic, prolific career, and shared with Folin in some of the most rewarding findings of this gravid period in modern clinical chemistry.

During the near-decade that Denis was associated with Folin (1910–1920), she authored and collaborated in 73 scientific papers, of which 63 were published in the *Journal of Biological Chemistry*.

How had she come to Folin's attention? Folin was well known at the Bureau of Chemistry, U.S. Department of Agriculture, where Denis had worked during 1907–1909 as a research associate. More than likely he met her during a visit he made to see her boss, Dr. H. Wiley. At any rate, in 1909, Denis quit the Bureau and returned to her home town, New Orleans. Perhaps this reflected the difficult life a professional woman then had. After all, it was a time of flagrant male chauvinism, particularly in the scientific and medical profession.[2] Also possible is that her work assignments at the Bureau were insufficiently challenging or rewarding.

Willey Denis probably wrote Folin late in 1909 of her wishes to work in medical biochemistry. He would have learned more about her doctoral training in chemistry with the brilliant organic chemist, John Ulric Nef, at the University of Chicago (1905–1907). Nothing could have attracted her more to Folin than this background. Not only was he himself a product of Nef's department (via Prof. Julius Stieglitz), but he knew the thorough preparation demanded there for the doctoral degree. Nef had seemingly been unimpressed by Folin in his graduate-student days, but Folin was deeply grateful for the European-style preparation in all phases of chemistry that he had received (1892–1896).

Another outstanding feature of Denis' background was her first publication based on a physiological study she had made at the University of Chicago, under the aegis of Anton J. Carlson (*1*). She found greater diffusion rates of NaCl and KCl as compared with $CaCl_2$ and $MgCl_2$ in various non-electrolyte media. This supported Carlson's idea that the cessation of impulse transmission by *Limulus* (horseshoe crab) heart ganglia in isotonic solutions of non-electrolytes was probably influenced in part by the greater relative concentration of "depressor" calcium and magnesium salts in cells and intercellular spaces than by the "stimulatory" sodium and potassium salts.

As had once been the case for Folin, Denis was now

Fig. 1. Willey Glover Denis (1879–1929)
This photograph of her, apparently the only one available, was taken about 1912

[1] This biographical sketch is the eighth in a series that is being prepared by or at the request of the Subcommittee on Archives of the Committee on Professional Affairs, AACC. The last such article appeared in the September 1984 issue (pp 1575–1578).

[2] Dr. Arthur O. Kastler, Denis' sole doctoral student in later years, stated in his notes on the history of the department of biochemistry at Tulane that she was a medical-school student twice, once in 1909 and again in 1910, but dropped out both times because of harassment, particulary by one "vulgar" professor of medical chemistry.

interested in establishing herself in the newly emerging field of biochemistry. Just as he had been grounded in biochemistry by serving as a postdoctoral research fellow with the eminent Swedish physiological chemist, Olof Hammarsten, at the University of Uppsala, she now offered her considerable talents toward the same purpose with Folin. As a woman, however, her opportunities for academic work in this area would be remote. Medical schools were just awakening to their deficiencies in basic sciences (*2*). For practically all, a college degree was not an entrance requirement. Few medical students had had even rudimentary courses in chemistry.

The Harvard Medical School was an all-male institution until 1945, though women from Radcliffe could take some coursework there after 1917. Where a couple of years' experience should have sufficed to prepare Denis for academia, 10 years passed before a solid opportunity came.

Willey Denis was married to science. At age 31, in 1910, she was long past the conjugal age of that era. She was euphemistically referred to as "stout," and this perhaps relates to the apparent lack of pictures of her. Figure 1 is the sole "portrait" known to be available. A cropped version hangs in Antoines Restaurant, New Orleans, in the galaxy of queens of the Mardi Gras, for Denis was Queen of the Proteus in the Mardi Gras of February 1902—an eminence based on family history and other standards set by the "Krewe." According to A. O. Kastler, "She was a very timid girl and she hated the social world. She had to grin and bear it, to be carried around through the French Opera House on the night of the Proteus Ball, which was very cold; and she after told how she wore long underwear both upstairs and downstairs, had a set smile on her face, and hoped to God it would soon be over."

Mrs. Teresa Rhoads, daughter of Otto Folin, remembers Dr. Denis as a cheerful, always pleasant woman, quiet and unobtrusive. She was perhaps 5′3″ to 5′4″ (1.60 to 1.62 m) tall. She always dressed in a severely tailored woman's suit. Her features were "neat": a small to medium-sized nose, petite mouth, fair complexion, perhaps hazel eyes, short dark-brown hair. She spoke with a modified New Orleans accent.

Denis, the oldest of three children, was born on February 26, 1879, of an old, respected New Orleans family. Her father was a banker. She had at least one "strikingly handsome" sister. The family once lived in a house on St. Charles Avenue that has since given way to the Latter Library. Little is known of her childhood except that she attended a private school for girls that was more attuned to teaching the social graces than to education. Miss Denis obtained an A.B. degree in 1899 at the H. Sophie Newcomb College for Young Women (of Tulane University). There were only 10 in her class. She majored in modern languages, and though she took some courses in science, she showed no aptitude for chemistry. Her interest in chemistry (and geology) matured, however, in two years at Bryn Mawr College (1899–1901), culminating in a master of arts degree at Tulane University in 1902.

Fig. 2. Otto Folin in his office in Building C-3, Harvard Medical School, *circa* 1920

She continued undefined graduate work at Tulane University until 1905, when, as mentioned, she entered the doctoral program at the fledgling University of Chicago. She minored in physiology. In August 1907, she received a Ph.D., *cum laude*. Her thesis was "On the Behavior of Various Aldehydes, Ketones and Alcohols Toward Oxidizing Agents." Before joining the Bureau of Chemistry, U.S.D.A., at the end of 1907, she taught one term of analytical chemistry as an instructor at Grinnell College, Iowa.

In 1910, Denis spent perhaps six months in the Harvard biochemical laboratory, to October. During that time she completed research work for three publications. The first—with her mentor, Folin—was on the preparation of quantitative yields of creatinine by autoclaving purified creatine containing only water of crystallization, a method differing from the one that Victor Myers had proposed in that it did not require the use of dilute mineral acid. This was followed by two solo papers, one a modification of Benedict's suggested oxidizing agent for determining sulfur as sulfate in urine—a topic of lifelong interest to Denis—and a second paper on improving the conditions for assaying amide nitrogen in protein hydrolysates.

Having gained experience with Folin, Denis then returned to New Orleans in the autumn, and stayed until the summer of 1911. She continued research in the physiology department of the school of medicine at Tulane University. In December, 1910, she was voted membership in the American Society of Biological Chemists. She had been nominated by the physiologist at Tulane, Gustav Mann, and seconded by Otto Folin.

From Tulane she published four papers. She found no evidence for the presence of iodine in human pituitary; and in two papers challenging her skill as an organic chemist, she studied the alkaline permanganate oxidation of four amino acids: glycine, cystine, alanine, and tyrosine. Then, together with Ralph Hopkins, she found an apparent interrelationship between CO_2 and NH_3 in the blood of dogs. There is no evidence that Dr. Denis either held any recognized academic position or received any pay for her work.

Denis spent the summer of 1911 at the University of Chicago. She took two courses in physiology: pharmacodynamics and research. In the autumn, she returned to the Harvard laboratory as a research assistant, and began a series of grand research projects with the master innovator, Folin, that would prove momentous for the birth of clinical chemistry in the U.S., and certainly the most scientifically rewarding of her productive though unsung career.

Throughout Denis' sojourn at Harvard and at the Massachusetts General Hospital, she was not forced into a woman's subordinate role, except in title; her collaboration with Folin was a matter of choice and mutual esteem. As time passed, Denis increasingly initiated her own projects. From 1917 until her departure in 1920, she was entirely independent.

The interval between late 1911 through 1913—when Denis moved to the Massachusetts General Hospital—was

one of the three most intensive and creative periods of Folin's life, and this was unquestionably fortified by Denis' ingenuity and industriousness. In just two years, 1912 and 1913, Folin published a phenomenal 32 papers, including a book chapter. Denis coauthored 18 of these, and contributed to part of another paper. She also published three papers of her own on the nitrogen metabolism of fish, and a fourth with G. G. Scott, on the relation of osmotic pressure to absorption phenomena in the dog fish, as a result of her work at Woods Hole, Massachusetts, where she spent the summers of 1912 and 1913.

The research that Denis performed during that epic two-year stint set the pattern for her career as a clinical chemist. She shared with Folin the magnificent discovery of the phosphotungstate–phosphomolybdate reaction with phenols and its subsequent exploitation for colorimetric analysis (*3*). They fashioned the already-known qualitative color test for uric acid with phosphotungstate into a quantitative method (*4*). They published seven papers on protein metabolism, as they studied the fate of proteins, amino acids, urea, and other substances in the ligatured intestine of the cat. They showed that amino acids were rapidly absorbed and disseminated, and that NH_3 in portal blood was largely derived from bacterial digestion in the large intestine (*5*).

Denis' major contribution, however, was the application and extension of the Folin methods, created for use with urine, to blood (NH_3, NPN, creatinine, creatine, urea), as well as the newly developed procedure for uric acid analysis (*6*). The "phenol" reagent was used for determining tyrosine in protein, vanillin in flavoring extracts, and epinephrine in adrenal gland extracts (*7–9*). Indeed, the birth of modern clinical chemistry can be ascribed to the pioneer work performed by Folin and Denis during this period—although, as mentioned before, the analytical methods had for the most part been introduced by Folin a decade earlier.

Once Dr. Denis was ensconced in the extension of the pathology laboratory into the third floor of the power house at Massachusetts General Hospital, she and Prof. Folin then had readier access to patients, and there was space to house some animals for experimental work. Folin was officially appointed Chemist, and Denis, Assistant Chemist. She was the first woman to be elected a member of the staff at Massachusetts General Hospital. As Dr. Joseph C. Aub recalled, "By 1915 blood chemistry was being done extensively in the very good chemical laboratory that Willey Denis ran, and I remember her feeling of dissatisfaction with the medical House Officers who, she said, did not have enough scientific interest to allow her to accumulate specimens. She said the dermatologists were the ones who really cooperated with her" (*10*).

Most of the research that Denis did in the interval 1914 through 1916 was in collaboration with Folin. There is no record to show how much time Folin spent at the laboratory of the Massachusetts General Hospital (or how much she spent at his laboratory), or whether prolonged phone calls were involved.

With studies on patients now possible, they found that the NPN and urea-nitrogen concentrations in the blood of the nephritic patient could be affected by dietary protein, and they confirmed that the phenolsulfonphthalein excretion test was the best for testing kidney "efficiency." Normal reference values for creatinine and creatine in the blood of humans and various animals were established. It was presciently suggested, after further studies with cats, that creatine was derived from an unstable precursor in muscle, and that creatinine elimination was a clear-cut index of total normal tissue metabolism. Later, however, Denis alone found that the creatine concentration in blood and urine increased after food intake, suggesting its exogenous origin as well. The duo looked at stress as a cause of emotional glycosuria and studied the effect of protein intake on a patient with Bence Jones proteinuria.

Methodology was advanced when they created a turbidimetric measurement of ketone bodies in urine (*11*). They introduced sulfosalicylic acid for assaying urinary protein turbidimetrically, using a stable protein solution as the standard (*12*). Uric acid and NPN were determined in normal persons and in patients with gout, nephritis, and other disorders. Denis found that a high-purine diet did not immediately affect the blood uric acid concentration, hence restriction to a low-purine diet before diagnostic testing was not essential (*13*). A method for quantifying phenols in urine and feces was developed and applied (*14*). Improved modifications of Folin's methods, together with the use of Nessler's reagent, were introduced for NH_3, NPN, and urea-nitrogen determinations. They described a major new blood protein precipitant, metaphosphoric acid (*15*).

On her own from 1917 to the summer of 1920, Denis published 18 papers in the *Journal of Biological Chemistry*, of which only two had Folin as coauthor. She increasingly collaborated with Massachusetts General Hospital staff members, particularly Dr. Fritz B. Talbot of the Children's Medical Service, and with one Radcliffe graduate student, Anna S. Minot. During this period, Folin was busy with Hsien Wu in their classical work on tungstic acid as a protein precipitant, on blood sugar, and on a system of analysis of blood by use of the tungstic acid filtrate.

Denis made an extensive study of cholesterol in whole blood as a diagnostic tool. She found that a 3-h postprandial blood sample was valid for determining cholesterol, even after a meal rich in lipids. Values were below normal in anemia, and in some types of dermatoses, but she did not find the increase reported for certain other diseases.

She published a series of papers demonstrating that creatinuria was increased in children and women, but not in men, by feeding a high protein (low creatine) diet, establishing thereby a dietary cause for creatinuria. She improved Folin's methods for determining blood creatinine and creatine by using metaphosphoric acid to make protein-free filtrates. Values for creatine were markedly lower than Folin had found previously after using picric acid as the protein precipitant.

Denis published seven papers on the composition of milk and her attempts to alter its contents. Her sole paper with Folin in 1918 was on a semiquantitative assay of lactose in milk (cow, human), and her final paper with Folin, in 1919, was on the lactose, fat, and protein content of milk from various animals (*16*).

Denis provided one of the first reliable procedures for quantitatively and qualitatively determining lead in urine, feces, and tissues. She developed a practical clinical method for determining plasma magnesium as magnesium ammonium phosphate, in a trichloroacetic acid filtrate, and assaying the phosphorus nephelometrically with use of a strychnine–molybdate reagent. Her reference range for human plasma was 1.6 to 3.5 mg/dL (0.66 to 1.44 mmol/L), certainly values still acceptable for adults.

In 1920, Denis and Ayer published a paper that is still familar to us in the 1980's, on the quantitative determination of protein in cerebrospinal fluid by use of sulfosalicylic acid and turbidimetry, a modified version of the Folin–Denis method for urinary albumin (*17*). This "first" method required 0.6 mL of CSF, and human serum was used as standard; the standard could be preserved for as long as three months if preserved with chloroform and refrigerated. The normal reference interval was 35 to 100 mg/dL. Abnor-

mally high values were found in CSF from persons with syphilis or meningitis, or with spinal cord compression.

Denis' final paper (with Aldrich) on work done exclusively at the Massachusetts General Hospital was on preserving blood specimens with formaldehyde for blood-sugar determination. One drop of formalin (40% formaldehyde) would preserve 5 mL of oxalated blood for up to 96 h at 20 to 33 °C. Formaldehyde did not interfere with the alkaline copper tartrate method for sugar of Folin and Wu, when their tungstic acid filtrate was used as the sample. Formaldehyde interfered with NPN and urea, but not creatinine and uric acid analysis (*18*).

On June 14, 1920, Dr. Willey Denis, now 41 years old, was appointed an assistant professor in the department of physiology (and physiological chemistry) in the medical school of Tulane University. This was momentous in that it probably represented the first such appointment of a woman by a major medical institution in the U.S. For her it must have been particularly gratifying to return to her hometown. (It was in that same year that women finally won the right to vote.) Prof. Denis' productivity would continue. In 1922 she was promoted to associate professor, and in 1925 to professor and head of the new, autonomous department of biological chemistry. This chairmanship was unique for the times. In 1920, Otto Folin and Walter B. Cannon nominated Denis for membership in the American Physiological Society, to which she was elected.

Denis' research in the years ahead (1921–1927) followed two recurring and overlapping themes, the clinical chemistry of the inorganic constituents and of the sulfur-containing fractions in blood and urine, a persistent study of their analysis and metabolism.

She spent the summer of 1922 working in the Marine Biological Laboratory at Woods Hole. She subsequently published one of her most remarkable papers (*19*). Using improved analytical methods (mostly Folin's) with a few added twists of her own, she re-examined the NPN constituents in the blood of elasmobranch (three species) and teleost (four species) fishes, and added information on blood sugar, amino nitrogen, and NH_3. The blood of elasmobranch fishes showed huge concentrations of NPN and urea nitrogen (1000 and 800 mg/dL, respectively) and much greater values for creatinine and creatine than that of teleost fishes, but the latter had much higher uric acid content. Values for amino nitrogen were alike in the blood of the two classes of fishes, though much above human values, and were close to those of muscle tissue of fishes. NH_3-nitrogen concentrations were much greater in fish than in human blood, but the blood sugar content was similar. Considering that a "summer" at Woods Hole more than likely lasted less than 10 weeks, this paper borders on the classical in the depth of its grasp of comparative biology and in its ingenious application of the latest fruits of clinical chemistry—in the abbreviated period of laboratory work involved.

Denis and her group had the unique opportunity to measure firsthand the changes in pH of human duodenal fluid before and after eating (*20*). A modified hydrogen electrode was placed in a fistulous opening in the duodenum of a man. Values found electrometrically varied between pH 5.90 to 8.23, with an average (n = 182) of 7.02. Meals consisting largely of fat, carbohydrate, or protein caused little change in the reaction.

Turbidimetry replaced nephelometry in determining the concentration of calcium, fats, and inorganic phosphorus in human plasma and in milk (*21*). A year later, however, Denis found that nephelometry, because of its greater sensitivity, was useful in determining plasma inorganic sulfate as a $BaSO_4$ suspension prepared from a protein-free filtrate. Values obtained for 10 samples from normal individuals ranged from 0.5 to 1.1 mg/dL. Increased sulfate was found in individual cases of leukemia, nephritis, intestinal obstruction, and, markedly, in uremia.

Denis and Meysenburg found that the anticoagulants oxalate and citrate interfered with the Bell–Doisy colorimetric method for inorganic phosphorus involving a hydroquinone–molybdic acid reagent. Although serum was preferably used to avoid anticoagulants, the authors modified the reagent to overcome this problem; then Denis applied the method to determine magnesium colorimetrically in a filtrate containing the magnesium as the ammonium phosphate. This original method replaced the nephelometric one (*22*). The newer micromethods made it possible for Denis to perform the first complete analysis for inorganic constituents in a single specimen of serum.

Denis was a key designer of the laboratories of the new Science Building (later, Dinwiddie Hall) that would house the department of biological chemistry, and into which it moved in 1924. Particularly remarkable was the foresight she displayed in providing adequate electrical wiring, moveable laboratory furniture, sinks, and central hoods for proper acid-proof exhaust systems.

In the summer of 1924, Dr. Denis was found to have a breast cancer. It was treated at the Mayo Clinic, and she returned to her duties at Tulane in the autumn. The cancer, however, would prove metastatic.

Although there is no record of how Denis fared as a teacher, unquestionably she patterned her lectures on those of Folin. The departmental teaching staff included, besides herself, two assistant professors, a full-time assistant, and three part-time assistants in the laboratory. The textbooks used were Mathews' *Physiological Chemistry,* Folin's *Laboratory Manual of Biological Chemistry,* and MacLeod's *Physiology and Biochemistry in Modern Medicine.* She was a prodigious reader as well as laboratory worker, and subscribed to 30 journals. Her library, valued in those days at more than $8000, was posthumously donated to the medical school. She was a "remarkable organizer" despite a very low departmental budget. The faculty taught three trimesters of biochemistry to first-year medical students and placed strong emphasis on laboratory work. Evidently Denis paid herself a nominal salary, little more than she paid the assistant.

The last six papers that Denis published (with Lucille Reed), in the interval 1926–1927, were on the unified research theme of the analysis of and factors determining the concentration of non-protein sulfur fractions in blood and urine.

Sometime after the summer of 1927, the research productivity of Willey Glover Denis abruptly halted. She did not take a leave of absence from her duties as head of the department of biochemistry before the autumn of 1928, hence it can be assumed that she was able to fulfill her duties for the 1927 academic year. "... her heroic fortitude with the philosophy of resignation when her affliction came, more than ever added to the admiration already felt by those so closely associated with her in daily life" (*The Tulane News Bulletin,* vol. 9, March 1929, p 103). According to Kaster, "Things got too bad for her—the cancer got out of control—she went blind and had to stay home, but every week she telephoned to find out what was going on in the Department." She died on January 9, 1929, a month short of her fiftieth birthday, and was buried in the Greenwood Cemetery. On March 3, 1943, Miss Aimee C. Denis, Willey's sister, made a bequest of $30,000 to the Tulane University School of Medicine, an endowment to establish the *Willey Glover Denis Fellowships in Biological Chemistry,* and these

remain active to this day.

In all, Denis published some 99 papers, excluding her thesis and abstracts, of which 41 were with Folin, 21 solo, and 37 with other collaborators.[3] Denis was not known to attend meetings of the scientific societies to which she belonged. These included, besides the American Society of Biological Chemists and the American Physiological Society, the Society for Experimental Biology and Medicine and the American Chemical Society.

No honorary awards or research grants were bestowed on her. She stands not only as the greatest pioneer woman in clinical chemistry, but as one of the very few leading American clinical biochemists of her era. Whereas Folin, Benedict, and Van Slyke opened the doors, Denis came with the next great generation that included Bloor, Myers, Peters, Somogyi, and Wu.

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[3] Kastler reported her productivity to be 124 papers.