The Heritage of Scholarly Clinician Endocrinologists at Mayo Clinic

As highlighted in the prior issues of Endocrinology Update, 2017 marks the 50th anniversary of the formal founding of the Division of Endocrinology at Mayo Clinic. Endocrinology Update has recognized this milestone in several ways over the year. This issue honors four of the founding scholarly clinician endocrinologists at Mayo Clinic. Drs. Henry S. Plummer and Edward H. Rynearson were also founding scholarly clinicians; their careers were highlighted in prior issues of Endocrinology Update.

Dr. Russell M. Wilder

Dr. Russell M. Wilder was born into a medical family in Cincinnati. His father, Dr. William H. Wilder, was the chair of the Department of Ophthalmology at Rush Medical College, Chicago. Dr. Russell Wilder graduated from Rush Medical College in 1912, where he earned dual degrees in medicine and philosophy and received the Benjamin Rush gold medal. While a medical resident at Presbyterian Hospital in Chicago, he worked with Dr. Rollin Woodyatt on the metabolism of ketones in dogs.

Hired on Oct. 1, 1919, to run Mayo Clinic’s Diabetes Unit, Dr. Wilder cared for about 100 patients with type 1 diabetes each year. Dr. Wilder and Dr. Walter M. Boothby completed extensive metabolic studies, published in The Journal of Biological Chemistry in 1922, on patient Bessie Bakke. Bakke had developed type 1 diabetes in 1918 at 26 years of age. She was prescribed 12 different diets, leading to the discovery that ketoacidosis could be reversed in part with a low-protein and high-fat diet. By adhering strictly to the dietary program, some patients with type 1 diabetes were surviving three to five years after onset.

On the announcement of Dr. Frederick Banting and Charles Best’s discovery of insulin at the American Physiological Society meeting in December 1921, Dr. Wilder wrote in his memoirs: “What a Christmas gift that was — an extract of the pancreas developed at Toronto, which effectively controls the symptoms of diabetes! We learned still more about it at the meeting of the Association of American Physicians in the spring of 1922. Excitement prevailed.” The Toronto group turned to a small group of top clinical researchers for help in determining the appropriate dosages of insulin, and one of those experts was Dr. Wilder at Mayo Clinic.

Dr. Wilder wrote: “Samples of insulin were first received at Mayo Clinic in the early spring of 1922. They were for experimental trials... but an adequate amount of insulin to insure everyone getting it who needed it was not available until the autumn of 1922, and Oct. 1 of that year is the date which divides for us the insulin era from the pre-insulin era.” Dr. Wilder continued: “We had 32 children with diabetes in Mayo Clinic between Oct. 1, 1919, and Oct. 1, 1922, a three-year period. One was moribund on arrival, 28 received satisfactory training and a dietary regimen. Nine survived long enough to benefit from insulin. The others died before it came.”

After treating 40 patients, Dr. Wilder and others published a seminal paper in 1923 in The Journal of Metabolic Research that indicated that a range of 10 to 30 insulin units was needed to transition a patient to a normal diet. They dosed before breakfast and kept patients to a strict eating schedule, with meals at 8 a.m., noon and 5:30 p.m.
They presented detailed charts on patients of varying ages, offered first aid (epinephrine and orange juice) for patients slipping into lethargy. They concluded that physicians needed to treat patients qualitatively, watching them closely to establish the right dose for the individual.

Dr. Wilder also wrote a patient handbook, A Primer for Diabetic Patients, which was first published in 1921 and then in nine subsequent editions, the last published in 1950.

In 1927, Dr. Wilder and colleagues were the first to describe an insulinoma in an article published in *The Journal of the American Medical Association*. Dr. Wilder wrote, "We have recently studied, both clinically and at necropsy, a case of severe spontaneous hypoglycemia. This is attributed to a tumor of the islands of Langerhans with metastasis in the liver and lymph nodes. The condition has not been described heretofore and in this sense it represents a new disease."

Dr. Wilder left Mayo Clinic in May 1929 to become head of the Department of Medicine at the University of Chicago, but resigned from that position to return to Mayo Clinic in October 1931. Dr. Wilder served as president of the American Diabetes Association from 1946 through 1947. He retired from Mayo Clinic in 1950.

In January 1951, Dr. Wilder took on the directorship of the National Institute of Arthritis and Metabolic Diseases of the U.S. Public Health Service — a position he had to give up in July 1953 due to ill health. In his last address at the American Dietetic Association in 1959, Dr. Wilder said, "I can lay no claim to any great discovery, but I was a member of the crew on several of the ships engaged in exploration of the islands of Langerhans and I must admit to a degree of pleasure in recalling these adventures."

"His comments were published in the *Journal of the American Dietetic Association* in 1960. Dr. Wilder died on Dec. 16, 1959, due to a stroke.

**Dr. Samuel F. Haines**

Dr. Samuel F. Haines was born in Mantorville, Minnesota, a small town 18 miles west of Rochester, in 1892. Like the Mayo brothers, Dr. Haines’ ancestors were among those early settlers of southeastern Minnesota. Dr. Haines’ godfather was Dr. William Worrall Mayo, the father of the Mayo brothers. Dr. Haines’ interest in medicine developed early: At 3 years of age, he received medical care from Dr. Charles H. Mayo because of typhoid fever. Thereafter, he wanted to be a physician.

After attending Dartmouth College from 1911 to 1912, Dr. Haines entered Harvard University, where he earned his B.S. degree in 1915 and his M.D. degree, cum laude, in 1919. During his collegiate years, Dr. Haines spent summers at Mayo Clinic, where he cleaned pathology specimen jars at Saint Marys Hospital and worked at the new Mayo Clinic Group Practice of Medicine building.

Dr. Haines met Dr. Edward C. Kendall, a Nobel Prize winner in physiology or medicine in 1950, while paraffining the countertops in Dr. Kendall’s laboratory. Like Dr. Kendall, Dr. Haines enjoyed canoeing, and during their free weekends, the pair explored the nearby Zumbro River and other area streams. As a result, a lasting professional and social friendship was formed.

Dr. Haines completed his internship at Massachusetts General Hospital in Boston from 1919 to 1921. He entered the Mayo School of Graduate Medical Education in 1921 and was appointed first assistant in Dr. Henry S. Plummer’s section on medicine and thyroid diseases.

Dr. Haines was appointed a Mayo Clinic consultant in medicine in 1924. He assisted Dr. Plummer with several administrative duties in the thyroid section before he became head of that section in 1932. During the next 25 years, he was a leader at Mayo Clinic in the diagnosis and treatment of thyroid diseases.

Dr. Haines was associated with some of the early Mayo Clinic investigations to optimize the care of patients with thyroid disorders. Study findings were published in *The Journal of Clinical Endocrinology & Metabolism* by Dr. Brown M. Dobyns and others in 1946 and by Dr. Haines and others in 1948. In 1948, Dr. Haines was chair of two sections of medicine dedicated to metabolic disorders.

Dr. Haines was a member and chair of Mayo Clinic’s board of governors from 1945 through 1956 and board of trustees from 1951 through 1957. He was also president of the American Goiter Association, now known as the American Thyroid Association, from 1950 through 1951.

Dr. Haines retired from Mayo Clinic in December 1957 and died on Oct. 7, 1993. Each year a visiting professor lectureship in thyroid disorders is held in his honor.

**Dr. Randall G. Sprague**

Dr. Randall G. Sprague was born in Chicago in 1906. He earned his B.S., M.S. (1934) and M.D. (1935) degrees from Northwestern University. Dr. Sprague completed his internship at Presbyterian Hospital in Chicago and in 1936 entered the Mayo Clinic in Rochester, Minnesota, a small town 18 miles west of Rochester, in 1892. Like the Mayo brothers, Dr. Haines’ ancestors were among those early settlers of southeastern Minnesota. Dr. Haines’ godfather was Dr. William Worrall Mayo, the father of the Mayo brothers. Dr. Haines’ interest in medicine developed early: At 3 years of age, he received medical care from Dr. Charles H. Mayo because of typhoid fever. Thereafter, he wanted to be a physician.

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the Mayo School of Graduate Medical Education. He received his Ph.D. in medicine from the University of Minnesota in 1942. Dr. Sprague was appointed to the Mayo Clinic staff in 1940.

Dr. Sprague was an internationally recognized authority on metabolic and endocrine disorders. His clinical research focus was the intersection of carbohydrate metabolism and adrenal cortical hormones. Dr. Sprague and Dr. Edward C. Kendall completed and published studies on the proteolytic and glycogenic properties of the early adrenal cortical extracts. In 1947, Dr. Sprague and colleagues also completed the initial studies with cortisone treatment for patients with primary adrenal failure, which were published in The Journal of Clinical Investigation in 1947 and in Proceedings of the Staff Meetings, Mayo Clinic in 1950.

Dr. Sprague and colleagues also described the diabetogenic impact of Cushing syndrome in an article published in Journal of Laboratory and Clinical Medicine in 1948.

In 1948 with Dr. Harold L. Mason, Dr. Sprague identified cortisol in the urine of a patient with Cushing syndrome. Their research was published in The Journal of Biological Chemistry.

With Dr. A. Albert and Dr. Ashton B. Taylor, Dr. Sprague was the first to identify high blood corticotropin levels in patients with Addison’s disease. Results of their study were published in Endocrinology in 1949.

Dr. Sprague had a remarkable personal endocrine story: He was diagnosed with type 1 diabetes at age 15, one year before insulin became available. Dr. Sprague was a patient of Dr. Rollin T. Woodyatt, a renowned diabetes expert in Chicago. Dr. Sprague received the standard treatment at that time — a starvation diet. His weight dropped to 78 pounds.

Before insulin could arrive from Toronto, Dr. Woodyatt prepared a partially effective pancreatic extract that saved many lives, including Dr. Sprague’s. In his presidential address to the American Diabetes Association, titled "Education in Diabetes" and also published in Diabetes in 1954, Dr. Sprague said, “There are many things the diabetic must know if he is to keep out of trouble. He must study his disease, learn its pitfalls, and at all times be responsible for his personal care.”

Dr. Sprague served as president of the American Diabetes Association from 1953 to 1954 and as president of the Mayo Clinic staff in 1960. Dr. Sprague once said: “The joy that comes from medical discovery and its application in the care of the ill is not duplicated, I am sure, in either research or practice by themselves, nor, indeed, in any other calling of man.” Dr. Sprague retired from Mayo Clinic in October 1971 and died on Dec. 28, 1990.

It was the remarkable combination of a uniquely scholarly and compassionate clinician with a strong clinical investigative and academic nature that led the Division of Endocrinology in 1981 to establish an annual award in his honor, The Randall G. Sprague Award in Endocrinology. The award is given to one senior endocrine fellow each year based on excellence in patient care, education, and research.

**Dr. Robert M. Salassa**

Dr. Robert M. Salassa was an endocrinologist on staff at Mayo Clinic from 1949 to 1984. He was born in Lynchburg, Virginia, in 1914, and attended prep school at Staunton Military Academy. Dr. Salassa went on to earn both his B.S. (1936) and M.D. (1939) degrees from Indiana University. Dr. Salassa completed his internship and medicine residency at Indiana University Hospitals in Indianapolis.

After serving as a captain in World War II, Dr. Salassa was appointed a fellow in medicine at the Mayo Foundation in 1948 and appointed to the staff as a consultant at Mayo Clinic in 1949. His clinical areas of focus were adrenal and pituitary disorders. Most of his published work related to Cushing syndrome.

A clinician’s clinician, Dr. Salassa made keen clinical observations:

- In 1970, he was one of the first to report, in an article published in The New England Journal of Medicine, on the cure of tumor-induced osteomalacia by removing small benign sclerosing hemangioma.

- Shortly after the reports on the use of cortisone to treat rheumatoid arthritis, Dr. Salassa and others reported on the suppression of the hypothalamic-pituitary-adrenal axis and important clinical consequences in articles published in The Journal of the American Medical Association and Proceedings of the Staff Meetings, Mayo Clinic in 1953.

- In 1951, before the era of modern transsphenoidal surgery, Dr. Salassa and colleagues wrote about the role for subtotal adrenalectomy in an article published in the Annals of Surgery.

By 1958, Dr. Salassa had collected five patients with pituitary-dependent Cushing syndrome who had experienced diffuse hyperpigmentation and aggressive pituitary tumor growth following bilateral adrenalectomy. He wanted to be certain about this association before publishing. It was in July 1958, however, that Dr. Don H. Nelson and colleagues published their single case of this association in The New England Journal of Medicine. Dr. Salassa and colleagues...
published their five cases in *The Journal of Clinical Endocrinology & Metabolism* the following year.

Dr. Salassa wrote in the conclusion, “The observations in this small group of patients are disquieting, since they suggest that adrenalectomy occasionally may enhance the growth of pituitary tumors. Further observation of a larger number of patients with a long follow-up period is needed before the magnitude of the hazard of a progressive pituitary tumor can be accurately evaluated. Similar observations on a group of patients with coexisting Cushing syndrome and pituitary tumor who are treated by pituitary irradiation or surgical removal of the tumor, or both, are needed before the relative merits of treatment directed at the pituitary, on the one hand, and of subtotal or total adrenalectomy, on the other, can be evaluated.”

The disorder became known as Nelson syndrome. However, at Mayo Clinic it has always been referred to as Nelson-Salassa syndrome. Dr. Salassa was president of the Mayo Clinic staff in 1972. He retired from Mayo Clinic in October 1984 and died on March 27, 1992.

**For more information**


Novel Therapeutic Approach for Ectopic Cushing Syndrome: A Case From the Endocrine Teaching Clinics

A 69-year-old woman presented to the endocrine teaching clinic for evaluation of progressive weakness over 1 1/2 years. She had proximal muscle weakness with inability to stand from a sitting position and she required assistance to ambulate.

More recently, her symptoms progressed to the point where she became wheelchair- or bed-bound most of the time. A stair lift had to be installed in her home. In addition, the patient noted easy bruising with minimal trauma, progressive swelling of her face and lower extremities, and a net loss of weight due to decrease in her muscle mass.

The patient was also recently found to be hypokalemic and was prescribed potassium supplements. She had a two-year history of type 2 diabetes mellitus and long-standing hypertension with recent deterioration necessitating additional pharmacotherapy.

On physical examination the patient appeared chronically ill, sitting in her wheelchair. Her skin was very frail with multiple bruises noted in all four extremities but no striation in her abdominal area. There was supraclavicular fullness noted. Her muscular exam revealed severe proximal but only mild distal muscle weakness.

Biochemical evaluation confirmed corticotropin (ACTH)-dependent Cushing syndrome (Table 1). Pituitary-directed MRI demonstrated a normal pituitary gland, and inferior petrosal sinus sampling indicated a nonpituitary source of ACTH hypersecretion (Table 2). In search of an ectopic neuroendocrine tumor, a chest CT scan identified a 7-by-5-mm nodule in the right lower lobe (Figure 1, see page 6). Additional findings included hypertrophied bilateral adrenal glands but no other foci of potential disease. Notably, both 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET-CT) and 111In-DTPA-pentetreotide scintigraphy failed to demonstrate focal activity in the lung lesion or anywhere else.

Based on a multidisciplinary discussion involving endocrine surgery, thoracic surgery, interventional radiology and informed patient decision-making, it was decided to proceed with a minimally invasive procedure targeting the lung lesion using CT-guided cryoablation (Figure 2, see page 6). The procedure was performed using three freezes of three to six minutes each, separated by five minutes of thawing, achieving an ablation zone that encompassed the entire tumor without evidence of residual disease.

The patient tolerated the procedure exceedingly well and was discharged from the hospital the following morning. The morning after the procedure, the patient had developed glucocorticoid withdrawal symptoms indicating resolution of the hypercortisolism. The serum cortisol concentration decreased to 6 mcg/dL and the serum ACTH concentration to 13 pg/mL 24 hours after the cryoablation.

The patient went home on a long-term corticosteroid taper. She was also provided with recommendations for intensive physical therapy and Pneumocystis jiroveci pneumonia and

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 a.m. cortisol, mcg/dL</td>
<td>52</td>
<td>7-25</td>
</tr>
<tr>
<td>Corticotropin, pg/mL</td>
<td>138</td>
<td>10-60</td>
</tr>
<tr>
<td>8 a.m. serum cortisol following 8-mg overnight dexamethasone suppression test, mcg/dL</td>
<td>34</td>
<td>&lt; 1.8</td>
</tr>
<tr>
<td>24-hour urinary-free cortisol, mcg</td>
<td>260</td>
<td>3.5-40</td>
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</tbody>
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Table 1. Biochemical evaluation confirming presence of ACTH-dependent Cushing syndrome.

<table>
<thead>
<tr>
<th>Time before or after CRH* administration</th>
<th>Right IPS ACTH, pg/mL</th>
<th>Left IPS ACTH, pg/mL</th>
<th>Peripheral vein ACTH, pg/mL</th>
<th>Peripheral vein cortisol, mcg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5 min</td>
<td>122</td>
<td>111</td>
<td>94</td>
<td>19</td>
</tr>
<tr>
<td>-1 min</td>
<td>120</td>
<td>117</td>
<td>103</td>
<td>18</td>
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<tr>
<td>2 min</td>
<td>195</td>
<td>106</td>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>5 min</td>
<td>233</td>
<td>111</td>
<td>108</td>
<td>18</td>
</tr>
<tr>
<td>10 min</td>
<td>183</td>
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<td>30 min</td>
<td>108</td>
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<td>45 min</td>
<td>109</td>
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<tr>
<td>60 min</td>
<td>109</td>
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</table>

Table 2. Inferior petrosal sinus (IPS) sampling showing comparable corticotropin (ACTH) concentrations in the left IPS, right IPS and peripheral vein — indicating a nonpituitary source of ACTH hypersecretion.

*Corticotropin-releasing hormone
venous thromboembolism prophylaxis for the duration of the supraphysiological corticosteroid treatment. Within three months she had lost 12 pounds, improved her muscle function and resumed ambulation. She did not require pharmacotherapy to treat her diabetes. Currently, 16 months after her thermal ablation treatment, the patient continues to improve.

Conclusions
Ectopic tumors account for about 20 percent of all cases of ACTH-dependent Cushing syndrome. The vast majority of these are located in the thorax, with bronchial neuroendocrine tumors being the leading cause (up to 54 percent), as noted by Maria Vittoria Davi, M.D., and colleagues in the European Journal of Endocrinology in 2017 and Jaroslaw Aniszewski, M.D., and others in the World Journal of Surgery in 2001. Due to their small size, effective preoperative localization can be problematic. The patient reported here was evaluated before the Food and Drug Administration approval of gallium 68 (68-Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE) for PET-CT. Andrea M. Isidori, M.D., Ph.D., and others reviewed conventional and nuclear medicine imaging in ectopic Cushing syndrome in The Journal of Clinical Endocrinology & Metabolism in 2015. A 68-Ga DOTATATE-PET-CT scan may or may not have localized the ACTH-secreting bronchial neuroendocrine tumor in our patient. In concert with advances in targeted imaging for neuroendocrine tumors, there have been advances in minimally invasive therapy allowing delivery of cryoablation probes to small tumors. Cryoablation induces cancer cell death by activating a number of molecular and cellular processes during the freeze-thaw cycles leading to cancer cell destruction and tissue necrosis, with protection of surrounding normal lung tissue. Subsequent inflammatory and immune reactions continue for hours to days following the procedure to achieve local tumor control — as reported by Thierry de Baere, M.D., and colleagues in the Journal of Thoracic Oncology in 2015 and Masanori Inoue and others in BioMed Research International in 2014.

For more information

Figure 1. Axial CT image showing a 7-by-5-mm right lower lobe nodule (arrow) that lies immediately adjacent to a vessel and an airway.

Figure 2. CT-guided cryoablation of the 7-by-5-mm lung nodule. Two cryoprobes (arrows) are seen on each side of the nodule.
2017 Graduating Endocrine Fellows

Patricia Cronin, M.B., B.Ch., BAO, 2017 graduating Endocrine Surgery fellow, and Melanie L. Lyden, M.D., Endocrine Surgery Fellowship director. Dr. Cronin’s new appointment is at Mayo Clinic’s campus in Phoenix/Scottsdale, Arizona.

2017 graduating Clinical Endocrinology fellows (left to right): Anu Sharma, M.B.B.S., University of Utah, Salt Lake City; Shrikant U. Tamhane, M.B.B.S., Reid Health, Division of Endocrinology, Richmond, Ind.; Danae A. Delivanis, M.D., Division of Endocrinology, University of Patras Medical School, Patras, Greece; Sina Jasim, M.B., Ch.B., Division of Endocrinology, Metabolism, and Lipid Research, Washington University, St. Louis School of Medicine, St. Louis; Kurt A. Kennel, M.D., Clinical Endocrinology Fellowship director, Mayo Clinic, Rochester, Minn.; and Diane Donegan, M.B., B.Ch., Indiana University, Indianapolis.

Ray A. Kroc and Robert L. Kroc Lecturer

Richard Eastell, M.D., the Ray A. Kroc and Robert L. Kroc Lecturer, professor and head of the Academic Unit of Bone Metabolism and director of the Mellanby Centre for Bone Research, Academic Unit of Bone Metabolism, Metabolic Bone Centre, Northern General Hospital, University of Sheffield, and Mayo Clinic Bone Core Group members and endocrine fellows. Seated, left to right: Ann E. Kearns, M.D., Ph.D., Richard Eastell, M.D., Matthew T. Drake, M.D., Ph.D., and Daniel L. Hurley, M.D. Standing, left to right: Kristen M. Gonzales, M.D., Aolfe M. Egan, M.B., B.Ch., Ph.D., Natalia Genere, M.D., Tiffany M. Cortes, M.D., Peter J. Tebben, M.D., Kurt A. Kennel, M.D., Jad Sfeir, M.D., and Oksana Hamidi, D.O.
Education Opportunities

21st Annual Endocrine Update 2018
Canceled: Feb. 26-March 2, 2018, at Caribe Hilton, San Juan, Puerto Rico
After careful deliberation, the Endocrine Update 2018 scheduled for Feb. 26-March 2, 2018, will be
canceled. We are sorry for the inconvenience and hope you join efforts to help the recovery from natural
disasters that have affected Puerto Rico, Mexico, Florida, Texas and California. We greatly value your trust
in Mayo CME to meet your educational needs and hope to see you at a future Endocrine Update.

18th Annual Nutrition and Wellness in Health and Disease 2018
Sept. 27-28, 2018, at San Antonio Marriott Riverwalk, San Antonio, Texas
This course is designed for physicians, advanced practice clinicians, dietitians, nurses, and health and
wellness staff. Many physicians and other clinicians have had limited training in nutrition, yet nutrition is
key to the management of many endocrine disorders, such as diabetes, obesity and lipid disorders. In
addition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of
health and the treatment of disease. Physicians, bariatric surgeons, psychologists, dietitians, and health
and wellness specialists will discuss situations commonly encountered in the ambulatory setting. Topics
include obesity in adults and children, individual and group-based weight management strategies, and
dietary, behavioral change, activity, pharmacologic and bariatric approaches. Additional topics will include
nutrition and physical activity management of common obesity-associated conditions plus physical activity
and wellness topics for attendees and their patients. Presentations offer practical clinical management
pearls, interactive case studies and panel discussions. For more information, visit https://ce.mayo.edu/
internal-medicine/content/18th-annual-nutrition-and-wellness-health-and-disease-2018 or call
800-323-2688 (toll-free). Course hashtag: #MayoNutrCME