Why would Mayo Clinic, which was founded more than 150 years ago in Rochester, Minnesota, have a division in the Department of Internal Medicine celebrating its 50th anniversary in 2017?

Mayo Clinic has always been different from other medical organizations. Before 1967, Mayo medical services were divided into work groups called sections. Dr. Henry S. Plummer devised the section concept in the early 1900s. In an article published by R.C. Roesler in Mayo Clinic Proceedings in 1968, a medical section was defined as a small group of staff members with common interests working closely together in a specific area. The size of each section was kept small (six to 10 physicians) and the sections became both working and social units.

The section concept was at the core of group practice at Mayo Clinic. The corridors in the outpatient buildings, such as the 1914 Building, the Plummer Building (built in 1928) and the Mayo Building (built in 1955), at Mayo Clinic were designed in size and shape to house the section concept. A senior clinician was made head of a section in either medicine or surgery, and each section was named after its chief, rather than the area of medical specialization.

In 1966, there were three Mayo sections devoted to endocrinology: The Randall G. Sprague Section, Laurentius O. Underdahl Section and F. Raymond Keating Section. Compared with the hierarchical system of a typical university center, the section concept was more horizontally organized. Each section would independently manage clinic assignments, hospital rotations and vacation days. However, this organizational structure became less practical as Mayo Clinic grew — there were 15 medical sections in 1930 and 22 medical sections in 1965.

With the growth of Mayo Clinic and increasing emphasis on balanced programs in residency and fellowship training, in 1967 the board of governors decided it was time to change the organizational structure to something more similar to that used by university centers. As highlighted in a book by John L. Graner in 2002, the Department of Internal Medicine at Mayo Clinic was formed in 1967, and within it, the subspecialty divisions of medicine.

William M. McConahey Jr., M.D., became the first chair of the newly formed Division of Endocrinology, Diabetes, Metabolism & Nutrition. To enhance the training experience in endocrinology, teaching clinics were formed. However, a legacy section and corridor concept persisted (with section heads Raymond V. Randall, M.D., Robert M. Salassa, M.D., and Clifford F. Gastineau, M.D., Ph.D.)within the newly formed division until 1974, when B. Lawrence Riggs Jr., M.D., became chair and the sections within the division...
were formally dissolved. The sections were replaced with core groups or interest groups to facilitate clinical practice and research.

Currently, staff members in the Division of Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic belong to one or more core groups: Bone, Diabetes, Hospital, Nutrition (Hospital), Nutrition (Outpatient), Pituitary-Gonad-Adrenal (PGA), Thyroid, Transplant, and Transgender and Intersex.

So, 2017 marks the 50th anniversary of the formal founding of the Division of Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic. This milestone will be recognized in several ways over the year.

For more information


Metformin Revisited

Metformin (Figure 1) is the most extensively used oral therapeutic agent for type 2 diabetes mellitus (T2DM). The American Diabetes Association recommends metformin as the first line treatment for T2DM in conjunction with rigorous physical activity and dietary restriction.

K Sreekumaran Nair, M.D., Ph.D., with Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “With the rapidly expanding prevalence of T2DM, many novel oral therapeutic agents are emerging, but metformin continues to dominate, both as monotherapy as well as in combination with other medications, including insulin. Metformin can also prevent or delay the onset of T2DM in susceptible populations, such as those with prediabetes, fasting hyperglycemia or impaired glucose tolerance, and it is a safe treatment for pregnant women with gestational diabetes. In women with polycystic ovarian syndrome, metformin is effective not only at improving insulin sensitivity, but also in enhancing their potential for fertility. Currently, over 150 million people worldwide are using metformin.”

Metformin is a highly desirable therapy for T2DM for a number of reasons. Haleigh A. James, M.D., an endocrine trainee in Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic’s campus in Minnesota, notes: “One of its major advantages is that metformin does not cause significant hypoglycemia. Another advantage is that, unlike hypoglycemic agents such as sulfonylureas or insulin, metformin treatment is not associated with weight gain, but may cause modest weight loss.

“Some reports indicate that metformin is associated with preferential fat loss, and it may impart mild anorexic effects via its hypothalamic actions. Although there are conflicting reports, metformin may reduce the risk of cardiovascular events, especially in patients with T2DM who are overweight. This beneficial effect may be in part due to a modest effect of metformin on reducing blood pressure (unrelated to weight loss), improving lipid profiles (especially triglycerides) and endothelial function, reducing fibrinogen levels, and possibly increasing fibrinolysis.”

Metformin’s most common side effect is gastrointestinal distress, which includes nausea, diarrhea and upper abdominal discomfort.
Dr. Nair explains: “These symptoms are more likely to occur when patients ingest metformin on an empty stomach and may be mitigated by taking metformin in the middle of the meal or using a sustained-release formulation. The exact reasons for the gastrointestinal adverse effects are not fully understood, but there is evidence that local serotonin production may be stimulated by metformin in the gut. Slow-release metformin does not cause a rapid increase in the blood metformin levels, and a similar effect may occur when taking metformin during a meal.

“Another concern about metformin is the potential for lactic acidosis. Metformin use started in France in 1957, but it was not introduced in the United States until 1995, nearly 20 years after the biguanide phenformin was taken off the market because of its risk of lactic acidosis, which was often fatal.”

Metformin has about 24 times less reported incidents of lactic acidosis compared with phenformin. Dr. James highlights: “There are many reasons why metformin causes less lactic acidosis than phenformin. It is a less powerful inhibitor of mitochondrial respiration, which is probably the main reason for its decreased risk of lactic acidosis compared with phenformin’s and buformin’s. Moreover, metformin increases lactate oxidation and does not increase the release of lactate from muscle, unlike phenformin.

“Metformin, however, can cause lactic acidosis in conditions where lactic acid production is high and the disposal of lactic acid is reduced. In conditions such as circulatory failure, sepsis, and anoxia or hypoxia, metformin use may result in lactic acidosis and should be avoided. It should also be avoided in patients who have renal failure with creatinine clearance below 30 mL/min/1.73 m² or hepatic failure. Metformin interacts with some medications, including cimetidine because its metabolism is partially inhibited by metformin, thereby increasing cimetidine concentration.”

Although metformin has been used for almost five decades, its mechanism of action is not fully understood. Dr. Nair highlights: “Human studies indicate the mechanistic hypoglycemic action of metformin is its inhibition of hepatic glucose production, but the underlying mechanism for this inhibition of gluconeogenesis is not fully understood. Preclinical studies in rodents demonstrated that metformin acts by inhibiting endogenous glucose production by limiting the use of glucose precursors for gluconeogenesis. Another preclinical study reported that metformin acts by inhibiting glucagon-induced hepatic glucose production. All of these studies involve rodent models with either suprapharmacological doses of metformin or other biguanides, or injected metformin directly into peritoneum.”

Results of a study performed at Mayo Clinic to determine whether these rodent experiments can be translated into humans was published in Cell Reports in 2016. Dr. Nair explains: “This study was a double-blind, placebo-controlled, randomized crossover design in patients with prediabetes to determine the effect of two weeks of metformin administration. The study confirmed that metformin increases glucose tolerance and insulin sensitivity, but it also increases plasma glucagon levels, not only in the fasted state in some study participants, but also following a meal, which seemed to prevent hypoglycemia.

“This study also indicated that metformin does not inhibit glucagon-stimulated endogenous glucose production, but in fact hyperglucagonemia may mitigate the ability of the metformin to lower endogenous glucose production, thus preventing hypoglycemia in these individuals with prediabetes. During metformin therapy, increased glucagon levels prevented a fall in endogenous glucose production, thus providing a valid explanation for why metformin administration usually is not associated with hypoglycemia. Additionally, we found that gluconeogenesis precursors were reduced by metformin as opposed to reduced utilization of glucose precursors unlike as reported in rodent

Figure 2. Maintenance of normal blood glucose concentrations in individuals with prediabetes during treatment with metformin. Based on Cell Reports.
models. Metformin also counteracted some of glucagon’s catabolic effects, such as increased energy expenditure and protein catabolism.

This study thus offered insight into the effects of metformin in individuals with prediabetes. While extrapolating this information to patients with T2DM may need further clinical studies, it is likely that lack of hypoglycemia in patients with T2DM treated with metformin is explained by enhanced hepatic glucose production due to increased glucagon secretion (Figure 2). The study also shows that metformin reduces insulin secretion, which may reflect lesser need of insulin since insulin sensitivity is enhanced by metformin.”

For more information

Endocrinology Practice and Research at Mayo Clinic’s Florida Campus: 30 Years of Growth

Formally established in 1986, the Division of Endocrinology at Mayo Clinic’s campus in Jacksonville, Florida, began with one endocrinologist, Thomas P. Fox, M.D. Today, under the leadership of Victor Bernet, M.D., division chair, the Florida practice includes six endocrinologists and four advanced registered nurse practitioners who provide endocrine evaluations for referred patients as well as endocrine consultation services to colleagues in the clinic and hospital.

Over the past three decades, the scope and size of the Florida endocrine practice has broadened considerably. The clinical practice currently provides evaluation and treatment for the following disorders:

- Thyroid cancer and nodules
- Pituitary disorders
- Adrenal issues
- Hyperparathyroidism
- Diabetes and lipid disorders

Led by Dr. Bernet, the endocrine team performs approximately 300 thyroid nodule and thyroid cancer-related cervical lymph node fine-needle aspiration biopsies each year.
Spotlight on thyroid cancer clinical services

The diagnosis and treatment of thyroid cancer has evolved into an area of focus for clinicians and researchers within the Florida endocrine group. Robert C. Smallridge, M.D., has played an integral role in the development of the thyroid program on the Florida campus. In addition to extensive clinical efforts, the program has significant educational and research endeavors. In the last five years, the group as a whole has authored 45 thyroid-related peer-reviewed publications. Phase I and II clinical trials are focused on exploring improved thyroid cancer treatment regimens for patients with various forms of advanced thyroid cancer (Figure).

Like their colleagues practicing at Mayo Clinic’s campuses in Rochester, Minnesota, and Phoenix/Scottsdale, Arizona, endocrinologists on the Florida campus have established a long history as active participants and leaders in academic and professional organizations that serve the field of endocrinology. Several Mayo endocrinologists have or had leadership roles in the American Thyroid Association (ATA), a medical society founded in 1923 that currently has more than 1,700 members from 43 countries:

- Dr. Smallridge served as ATA chair and first author on the 2012 anaplastic thyroid cancer treatment guidelines. He also served as ATA president from 2014 through 2015.
- Dr. Bernet serves as ATA secretary and chief operating officer from 2015 through 2019.

Mayo endocrinologists and research staff in Florida also maintain memberships in the International Thyroid Oncology Group.

Related research efforts

Over the past two decades, endocrine division faculty in Florida has increased its engagement in basic and translational research related to endocrine disorders. Interdisciplinary collaboration between clinicians and researchers at Mayo Clinic’s campuses leverages the impact of the organization’s thyroid cancer research efforts. Ana-Maria Chindris, M.D., and Dr. Smallridge currently have funded research time. In addition, Drs. Chindris and Smallridge are members of the cancer biology research team and make significant contributions to the Florida campus thyroid cancer research efforts.

Two recently published thyroid cancer research projects involving Florida researchers explored cell cycle M phase genes in anaplastic thyroid carcinoma and MEN1 mutations in Hürthle cell (oncocytic) thyroid carcinoma.

Cell cycle M phase genes in ATC

Although anaplastic thyroid carcinoma (ATC) accounts for only 3 percent of thyroid cancers, it is associated with almost 40 percent of thyroid cancer deaths, and no effective treatment options exist.

In a study published in *Thyroid* in 2016, Dr. Smallridge and others analyzed global gene expression data from multiple studies in the National Center for Biotechnology Information Gene Expression Omnibus database to identify ATC-specific dysregulated genes in an effort to identify therapeutic targets specific to anaplastic thyroid carcinoma. Focusing on globally altered genes, the researchers identified a set of consistently altered biological processes and pathways in ATC. The data yielded in this process suggest M phase cell cycle genes play an important role in ATC. Mayo researchers are hopeful that these findings may provide direction for future studies to identify novel therapeutic targets for this disease.

MEN1 mutations in Hürthle cell (oncocytic) thyroid carcinoma

Oncocytic thyroid carcinoma, also known as Hürthle cell thyroid carcinoma, is another diagnosis that accounts for only a small percentage of thyroid cancers. No effective treatment options currently exist.
A 28-year-old man was referred for further evaluation of a right adrenal mass and a right pleural mass. He was in overall good health until 1.5 years ago, when he was noted to have a blood pressure reading of greater than 170/90 mm Hg on more than two occasions at his occupational health facility. He was started on antihypertensive medications. Two months later, screening laboratory studies showed an elevated hemoglobin A1C (7.5 percent) and he was diagnosed with type 2 diabetes mellitus and treated with metformin. Medications were titrated to achieve optimal blood pressure, blood glucose and lipid control. He was on six new medications, including two antihypertensives.

As part of his occupational screen, a chest X-ray was performed one year ago, which showed a right pleural mass measuring 4 cm by 3 cm. A three-month follow-up chest X-ray showed growth of the mass to 5.3 cm by 3.1 cm. Due to the concern for malignancy, a fluorodeoxyglucose positron emission tomography (FDG-PET) scan was performed and this detected minimal fluorodeoxyglucose uptake in a right adrenal mass measuring 7.3 cm in largest diameter, a hypermetabolic pleural mass, a presacral mass and multiple soft tissue masses that were not hypermetabolic. Subsequent biopsy of the pleural mass confirmed this to be a peripheral nerve sheath tumor.

On referral to Mayo Clinic, he was asymptomatic. He denied paroxysms, palpitations, presyncope or syncopal events. He did not smoke, use illicit drugs or drink alcohol. Physical examination was significant for diffuse freckling over his shoulders, chest, axillary and inguinal areas. He had four café au lait spots on his trunk and several cutaneous and subcutaneous soft tissue lesions over his forehead, neck and extremities. His father had a history of hypertension diagnosed in his 50s.

His presentation and physical examination findings were consistent with neurofibromatosis 1 (NF1). The levels of fractionated metanephrines and catecholamines in a 24-hour urine collection were elevated (Table). Given the multiple masses found on the FDG-PET scan, additional imaging was obtained and included I-123 metaiodobenzylguanidine (MIBG) scintigraphy and MRI of the chest and abdomen (Figure, 6).
Panels A and B. MIBG uptake was limited to the right adrenal mass. The FDG-PET scan showed activity in the pleural mass but not the adrenal mass (Figure, Panel C).

Preoperative adrenergic blockade included phenoxybenzamine, metoprolol and metyrosine. He underwent an open right adrenalectomy without complication. Final pathology showed a 9.8-cm pheochromocytoma encompassing the entire right adrenal gland with negative margins. Genetic analysis was positive for heterozygous splicing mutation in the NF1 gene.

Pheochromocytoma is a rare neoplasm with an estimated annual incidence of 0.8 per 100,000 person-years. It is the cause of hypertension in less than 0.2 percent of patients. Genetic causes of pheochromocytoma account for 30 percent of all cases. Hereditary pheochromocytomas tend to occur at a younger age (for example, younger than 45 years) and are usually inherited in an autosomal dominant fashion.

The three most common hereditary causes of adrenal pheochromocytoma are von Hippel-Lindau disease, multiple endocrine neoplasia, type 2, and NF1. Approximately 3 percent of patients with NF1 will have a catecholamine-secreting tumor, most commonly a unilateral benign adrenal pheochromocytoma or periadrenal paraganglioma.

A Mayo Clinic study published in Clinical Endocrinology in 2017 found that only 58 percent of catecholamine-secreting tumors in patients with NF1 were symptomatic, and of those who were symptomatic, hypertension was the most common symptom (76 percent). Bilateral adrenal pheochromocytoma was found in seven (17 percent) of the 41 patients with NF1; 7.3 percent of patients had recurrent or metastatic disease. In the seven patients with bilateral adrenal pheochromocytoma, four underwent cortical-sparing surgery, negating the need for glucocorticoid and mineralocorticoid replacement.

Asymptomatic pheochromocytoma is quite common in the setting of NF1. It has been suggested that the prevalence of pheochromocytoma in NF1 may be as high as 6.6 percent when case detection testing is routinely performed. It is recommended that biochemical case detection testing for pheochromocytoma be performed every three years in patients with NF1.

**Key message**

NF1 has a high prevalence of asymptomatic pheochromocytoma with hypertension being the most common symptom. Biochemical case detection should be performed every three years in asymptomatic patients with NF1.

**For more information**


<table>
<thead>
<tr>
<th>Test</th>
<th>Preoperative</th>
<th>3 months postoperative</th>
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<tbody>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>168</td>
<td>78</td>
</tr>
<tr>
<td>Metanephrine, mcg</td>
<td>16,933</td>
<td>102</td>
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<tr>
<td>Epinephrine, mcg</td>
<td>1,399</td>
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<td>Normetanephrine, mcg</td>
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<td>Norepinephrine, mcg</td>
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<td>Dopamine, mcg</td>
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<td>258</td>
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</tbody>
</table>

Reference ranges: fasting plasma glucose 70-100 mg/dL; metanephrine < 400 mcg/24hr; epinephrine < 21 mcg/24hr; normetanephrine 900 mcg/24hr; norepinephrine < 80 mcg/24hr

Table. Preoperative and three months postoperative laboratory tests.

Figure. Coronal images of the chest and abdomen with arrows highlighting the right adrenal pheochromocytoma and the pleural-based nerve sheath tumor on MRI (A), 123-I-MIBG scan (B), and FDG-PET scan (C).
Education Opportunities

17th Annual Nutrition and Wellness in Health and Disease 2017
Sept. 25-26, 2017, at Park Central Hotel, San Francisco

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 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 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 http://ce.mayo.edu/nutrition2017 or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME

21st Annual Mayo Clinic Endocrine Update
Feb. 26-March 2, 2018, at Caribe Hilton, San Juan, Puerto Rico

Designed for endocrinologists and interested internists and surgeons, this course addresses gaps in medical knowledge and barriers in clinical practice to improve the outcomes of patients with endocrine and metabolic disorders. Topics span the full range of endocrinology through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees have plenty of opportunity for interaction with the course faculty, who are selected for their expertise and clinical acumen. For more information, visit https://ce.mayo.edu/endocrinology/ or call 800-323-2688 (toll-free).