As highlighted in the prior issue of *Endocrinology Update*, 2017 marks the 50th anniversary of the formal founding of the Division of Endocrinology at Mayo Clinic. *Endocrinology Update* will recognize this milestone in several ways over the year. The publication will highlight some past staff members who had major impacts on the development of the division. This issue honors three of the founders of endocrine research at Mayo Clinic.

**Dr. Leonard G. Rowntree**

Dr. Leonard G. Rowntree trained with Dr. John J. Abel, a pharmacologist at Johns Hopkins University. In an article published in *JAMA* in 1911, Dr. Rowntree was the first to describe the use of phthalein compounds to determine renal function; the “Rowntree test” became a standard test in medicine for the next three decades. In 1913, Drs. Abel and Rowntree developed the first animal model of an artificial kidney and then developed the first successful method for plasmapheresis in dogs. Results of their work were published in *Transactions of the Association of American Physicians* that year.

In 1915, Dr. Rowntree became chair of Medicine at the University of Minnesota. Dr. William J. Mayo at Mayo Clinic saved Dr. Rowntree’s life in 1918 by operating on a perforated ulcer. Also in 1918, Dr. Rowntree entered the U.S. Army, where he served as lieutenant colonel in the Army Medical Corps for the duration of World War I. After the war, Dr. Rowntree accepted a position offered to him by Dr. William J. Mayo at Mayo Clinic in Rochester, Minnesota — an appointment that prompted Dr. William Osler to comment that the Mayos were wise men to make the clinic as important in medicine as it was in surgery.

Dr. Rowntree supervised six hospital services at Mayo Clinic, with a focus on clinical research. He commented: “Each section of our department became productive almost immediately ... almost overnight, everyone in the clinic seemed to become interested in clinical investigation, and output of publications shortly became enormous.”

Dr. Rowntree encouraged Dr. Edward C. Kendall at Mayo Clinic to produce adrenal extracts, and Dr. Rowntree became one of the first physicians to use adrenal extracts effectively to treat patients with Addison’s disease. In an article published in *JAMA* in 1923, Dr. Rowntree and colleagues reported using sodium iodide intravenously to visualize the genitourinary tract — the basis for intravenous pyelograms still in use today. In 1925, Dr. Rowntree reported, again in *JAMA*, on the role for lumbar sympathectomy in the management of severe hypertension — a procedure that became a standard treatment for malignant hypertension for three decades.

Dr. Rowntree left Mayo Clinic in 1932 to continue his research career as director of the Philadelphia Institute for Medical Research. During
Mayo Clinic Doctor Edward C. Kendall (circa 1950)

In 1934, Dr. Kendall joined the Mayo staff on Feb. 1, 1914. On Christmas day in 1914, he succeeded in isolating pure crystalline thyroxine. Although widely recognized for this achievement, Dr. Kendall did not correctly describe the chemical structure of thyroxine and did not win a Nobel Prize.

Dr. Rowntree asked Dr. Kendall to help in the treatment of patients with Addison’s disease by preparing an effective adrenal cortical extract. Dr. Kendall took on this challenge, but with a greater purpose in mind: to isolate and identify the hormone of the adrenal cortex. This research became a major undertaking, with Dr. Kendall’s laboratory processing 900 pounds of beef adrenal glands weekly for more than five years.

Adrenal cortical extract was supplied to Mayo clinicians to treat their patients with Addison’s disease, but Dr. Kendall continued his hunt for “the adrenal hormone.” In 1934, Dr. Kendall recognized that the adrenal cortex produced more than one hormone. Over the next year his group isolated five crystalline compounds — compound E was found to be biologically active. Compounds were labeled by letters based on the order in which they eluted from the columns. Compound E proved to be cortisone; compound F was hydrocortisone. However, the first large-scale synthesis of compound E was not completed until 1948.

Dr. Philip S. Hench, a rheumatologist at Mayo Clinic, observed that when patients with rheumatoid arthritis were also jaundiced or pregnant, they may go into remission. He postulated that some humoral substance was formed in the settings of jaundice and pregnancy. Drs. Kendall and Hench discussed this phenomenon on several occasions and in 1941 decided to test compound E for possible effects on rheumatoid arthritis. However, it was not until 1948 when sufficient quantities of compound E became available.

On Sept. 21, 1948, the first patient with rheumatoid arthritis was treated with compound E. The effects were dramatic — a 28-year-old woman who had been bedridden for months was ambulating throughout the hospital within four days. The dramatic results were subsequently documented in many more patients.

In 1949, Drs. Kendall and Hench decided to name compound E “cortisone” and published their work in Mayo Clinic Proceedings. The news of the therapeutic value of cortisone for inflammatory conditions spread like wild fire through the medical community and lay press. On Oct. 26, 1950 (slightly more than two years after the first patient with rheumatoid arthritis was treated with cortisone), it was announced that the Nobel Prize in physiology and medicine would be awarded to Drs. Kendall and Hench at Mayo Clinic and to Dr. Tadeus Reichstein, a Swiss chemist, for their investigations of the adrenal cortex. Dr. Kendall retired from Mayo Clinic in 1951 and took a visiting professor position in the James Forrestal Research Center at Princeton University. He died May 4, 1972, at age 86.

Dr. Alexander Albert

Dr. Albert developed a rapid bioassay for human chorionic gonadotropin by adaptation of the hyperemia reaction — results were expressed for the first time in international units so that values throughout the world could be compared. This work was published in 1948 in the Journal of Clinical Endocrinology & Metabolism and in 1949 in Proceedings of the Staff Meetings of the Mayo Clinic. As an extension of this work, Dr. Albert sought to develop a clinical laboratory method for the determination of gonadotropins in urine as a laboratory test of pituitary function. This was an eight-year project that culminated in a Laurentian Hormone address in 1955 and was published in 1956 in Recent Progress in Hormone Research with discussion.

The Albert method became the method for determination of urinary gonadotropins throughout the world. Until this time, all research at Mayo Clinic was internally funded.
An Emerging Connection Between Circadian Rhythm Disruption and Type 2 Diabetes Mellitus

The incidence of type 2 diabetes mellitus (T2DM) has reached an epidemic proportion of the human population. Recent estimates put worldwide prevalence of T2DM at 415 million. That number is expected to rise to 615 million by year 2040. This widespread emergence of T2DM presents one of the greatest challenges to global human health in this century. For this reason, understanding the molecular and physiological mechanisms underlying increased susceptibility to T2DM is an essential task for development of novel preventive and therapeutic approaches.

Aleksey Matveyenko, Ph.D., with Physiology and Biomedical Engineering at Mayo Clinic’s campus in Rochester, Minnesota, says: “T2DM is a complex polygenic disease the pathophysiology of which involves interactions between genetic, epigenetic and environmental risk factors. Although genetic susceptibilities clearly play an important role in predisposition to T2DM, environmental factors appear to be significantly greater predictors of diabetes onset and progression. Indeed, environmental factors such as caloric intake and physical inactivity have long been appreciated to augment susceptibility to T2DM. More recently, however, circadian rhythm disruption has been gaining greater appreciation as an emerging environmental risk factor for T2DM.”

Circadian disruption is defined as “misalignment between the endogenous circadian system and behavioral circadian cycles” (for example, sleep-wake and fasting-feeding). In today’s 24-hour society, circadian disruption is becoming increasingly commonplace — driven...
primarily by increased exposure to artificial lighting, rotational and night shift work, social jet lag as well as comorbidities such as obesity and sleep disorders. For example, in the United States alone, more than 70 percent of adults report inadequate sleep quality and duration and nearly 20 million people are exposed to daily shift work-like conditions.

Dr. Matveyenko explains: “Multiple strands of evidence support the causative relationship between circadian disruption and impaired glucose homeostasis. First, individuals engaged in work conditions characterized by circadian disruption, such as rotational shift and night work, exhibit higher prevalence of diabetes, impaired glucose tolerance and metabolic syndrome. In addition, clinical studies performed under controlled laboratory settings show that acute exposure to circadian disruption results in dysregulation of glucose metabolism characterized by impaired insulin secretion and insulin action. Finally, additional support for the role of the circadian system in glucose homeostasis comes from genome-wide association studies showing an association between common genetic variants in key circadian-controlled genes such as CRY2 and MTNR1B and increased prevalence of hyperglycemia and T2DM.

“To gain insights into mechanisms underlying circadian control of glucose metabolism, it is first important to review physiological regulation of the circadian system. The circadian system is organized as a multilevel oscillator network. The master circadian clock (pacemaker) is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN comprises molecular oscillators (also called circadian clocks), operating within individual neurons, governed by a precise transcriptional-translational feedback loop consisting of a set of core clock genes such as CLOCK and BMAL1. Importantly, autonomous circadian clocks are also present in numerous tissues outside of the SCN, including cell types essential for regulation of glucose metabolism, such as pancreatic beta cells, skeletal myocytes and hepatocytes. The SCN integrates and synchronizes peripheral circadian clocks to the solar day by employing a combination of neuronal, behavioral and endocrine outputs.”

Dr. Matveyenko continues: “Recently, an increased emphasis has been placed on understanding how intracellular circadian clocks in metabolic tissues exert physiological control over glucose metabolism, and specifically, insulin secretion and insulin action. Circadian regulation of insulin secretion is particularly critical for normal regulation of beta cell function, given its significance to restrain insulin secretion during the inactive (sleep) phase, and optimize insulin production and release during the active (feeding) phase of the circadian cycle.

“For example, studies show that pancreatic beta cell circadian clocks regulate time-dependent transcription of key genes and transcription factors regulating beta cell glucose metabolism, oxidative stress, proliferation and insulin exocytosis. Subsequently, disruption of circadian clock function in beta cells results in impaired insulin secretory function, altered rate of cell proliferation and survival, and increased susceptibility for development of T2DM.”

In addition to exerting control over insulin secretion, circadian clocks also regulate insulin action (or insulin sensitivity) through molecular control of postprandial glucose disposal and hepatic glucose production. Insulin-stimulated glucose uptake into skeletal muscle accounts for nearly 70 percent of the postprandial glucose clearance. This process is mediated through insulin-stimulated recruitment of GLUT4 glucose transporters to the plasma membrane, thus facilitating skeletal muscle glucose uptake and oxidation.

This process has been recently shown to be controlled by the skeletal muscle circadian clock, which ensures time-dependent expression and translocation of GLUT4 transporters to anticipate meal-induced glucose excursions. In
addition, recent mouse genetic studies demonstrate that ablation of the circadian clock in hepatocytes disrupts hepatic glucose and lipid metabolism and consequently impairs normal regulation of insulin-mediated suppression of hepatic glucose production.

Dr. Matveyenko concludes: “Taken together, circadian rhythms in humans are regulated by a complex multilevel circadian oscillator system that undoubtedly provides an advantage for human health and is essential for maintaining proper metabolic control. However, this system becomes disadvantageous when lifestyle factors impose time constraints that produce circadian disruption — misalignment between internal circadian oscillators and the external environment. In this regard, understanding the molecular and physiological mechanisms responsible for circadian disruption-associated risk of T2DM warrants further research, and holds a potential for contributing to the development of novel therapeutic and preventive strategies for patients with T2DM.”

**Diagnostic Approach to Disorders of Extraskeletal Bone Formation**

Heterotopic ossification (HO) — the formation of bone outside the normal skeleton — can occur in soft tissue and is usually found within muscular, adipose, or nonmuscle fibrous or connective tissue. Ectopic bone formation is the only example of complete recapitulation of an organ system, replete with hard tissue, vascular and marrow elements.

Robert J. Pignolo, M.D., Ph.D., with Geriatric Medicine and Gerontology and Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “Genetic forms of HO, such as fibrodysplasia ossificans progressiva (FOP), primary osteoma cutis (OC), progressive osseous heteroplasia (POH), pseudohypoparathyroidism (PHP) and Albright’s hereditary osteodystrophy (AHO)-pseudopseudohypoparathyroidism (PPHP) can be progressive soon after birth and throughout life. In contrast, nonhereditary heterotopic ossification (NHO) occurs as a clinically severe complication in as many as approximately 20 percent of all individuals following major hip surgery, and in as many as approximately 11 percent of those following traumatic brain injury. Bone formation limited to ligaments may occur with seronegative spondyloarthropathies or diffuse idiopathic skeletal hyperostosis.

“NHO may be found in age-related conditions, particularly in the context of common vascular pathology, as well as after total hip arthroplasty for age-onset degenerative joint disease. End-stage calcific valvular heart disease is prevalent in advanced age, and HO occurs in up to 13 percent of patients with this diagnosis. Age-related HO can occur in a variety of other conditions associated with immobilization, such as neuromuscular disorders, or in the context of clinical factors common in the geriatric population, such as pressure sores, urinary tract infection or trauma.”

In a patient presenting with HO, nonhereditary forms can usually be excluded on the basis of prior trauma or surgery, age, and known history or suspicion of arthropathy. Dr. Pignolo explains: “Among genetic forms of HO, FOP is distinguished by the cardinal features of congenital malformation of the first toes and pre-osseous tumorlike inflammation or flare-ups.”

PHP and related disorders (POC, POH, AHO-PPHP) can be distinguished on the basis of three characteristics:

- Extent of HO (superficial or deep; predominantly intramembranous ossification)
- AHO features (more than two features, especially brachydactyly, but also short stature, obesity, round face and neurobehavioral abnormalities)
- Hormone resistance, especially elevated parathyroid hormone (+/- hypocalcemia and hyperphosphatemia), but also elevated thyroid-stimulating hormone and hypothyroidism, hypogonadism, elevated calcitonin
A 33-year-old woman presented to an outside facility with increasing shortness of breath, orthopnea, paroxysmal nocturnal dyspnea and increasing lower limb edema — findings suggestive of biventricular heart failure. Further questioning revealed a two- to three-month history of unintentional weight loss, heat intolerance, diarrhea, abdominal pain and palpitations. The symptoms started about six months after her most recent delivery of a healthy child. Her past medical history was significant for obesity, mild asthma requiring occasional albuterol use and third trimester gestational hypertension during her recent pregnancy (managed without pharmacotherapy).

On presentation, the patient showed signs of tachycardia (118 beats per minute) and tachypnea (22 breaths per minute) and had lower extremity pitting edema. Laboratory testing was significant for hyperthyroidism:

- Thyroid-stimulating hormone (TSH) < 0.1 mIU/L (normal, 0.49 to 4.67 mIU/L)
- Free thyroxine (FT4) 2.6 ng/dL (normal, 0.7 to 1.8 ng/dL)

The serum brain natriuretic peptide was markedly increased at 2,819 pg/mL (normal < 100 pg/mL). Chest X-ray demonstrated cardiomegaly. The patient was diuresed and started on beta-adrenergic blockade and 10 mg of methimazole three times a day. An echocardiogram demonstrated a severely dilated left ventricle and an ejection fraction of 10 to 15 percent.

Despite treatment, shortness of breath and hypotension necessitated intra-aortic balloon pump placement and intubation, and she was transferred to Mayo Clinic in Rochester, Minnesota. On arrival, she was sedated, intubated and hypotensive on inotropic support. A repeat echocardiogram revealed an ejection fraction of 9 percent. Due to severe cardiogenic shock, venoarterial extracorporeal membrane oxygenation was initiated.

Thyroid Storm: A Case From the Endocrine Teaching Clinics

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Cannulation (VA ECMO) was initiated (Figure 1).

Endocrinology was consulted. Mild exophthalmos was noted without dermopathy or acropachy. The patient’s presentation with decompensated heart failure, preceding gastrointestinal complaints, and tachycardia was highly suggestive of thyroid storm (Burch and Wartofsky Point Scale 40).

Aggressive therapy was started with 200 mg of propylthiouracil administered every four hours, 100 mg of hydrocortisone administered every eight hours and a saturated solution of potassium iodine administered two hours after propylthiouracil. Repeat biochemical testing revealed a TSH of < 0.01 mIU/L (normal, 0.4 to 4.0 mIU/L), FT4 of 3.4 ng/dL (normal, 0.9 to 1.7 ng/dL) and a total tri-iodothyronine of 308 ng/dL (normal, 80 to 200 ng/dL).

While thyroid receptor antibodies were pending, a bedside ultrasound revealed a hypervascular thyroid gland (Figure 2). The patient’s clinical picture was most consistent with cardiogenic shock in the setting of thyroid storm of autoimmune origin, and possible postpartum cardiomyopathy.

Despite treatment, five days later the patient was still clinically and biochemically hyperthyroid with serum TSH of 0.02 mIU/L and FT4 of 5.4 ng/dL by equilibrium dialysis (employed because of her significantly altered protein status). Given the critical nature of the patient’s condition and the need for rapid normalization of her thyroid status, total thyroidectomy was recommended.

Plasmapheresis was initiated to optimize preoperative thyroid levels. Endocrine and cardiovascular surgeons collaborated to perform a total thyroidectomy during which anticoagulation, necessary for ECMO, was held. Pathology revealed diffuse follicular hyperplasia (Figure 3) consistent with Graves’ disease. As expected, the patient also had an elevated thyroid receptor antibody concentration of 20 IU/L (normal, 0 to 1.75 IU/L). Postoperatively, anticoagulation was restarted without complication.

Following total thyroidectomy, the patient improved and was able to be weaned off vasopressor support and she was extubated. Thyroid replacement therapy was initiated. Unfortunately, her cardiac function remained suboptimal (ejection fraction of 15 percent), and therefore a left ventricular assist device was placed to bridge to cardiac transplantation.

As highlighted in an article in the journal Thyroid in 2012, thyroid storm is a life-threatening condition and early recognition is essential — mortality remains high (11 percent) despite improvements in management. The diagnosis should be considered in an individual with severe symptoms of multiorgan dysfunction and biochemical thyrotoxicosis. Several scoring systems have been devised to assist recognition and early implementation of aggressive treatment. The authors note that a high level of suspicion is important.

In this case, despite aggressive nonsurgical management of hyperthyroidism, additional cardiovascular support was required. ECMO
can be used in such cases, and a growing body of literature supports its use in thyroid storm-induced cardiogenic shock refractory to usual treatment — as highlighted in an article in the journal *Thyroid* in 2011.

Total thyroidectomy for thyroid storm on ECMO, however, has not been reported, but occurred without complication in this case. Close collaboration between endocrinology, endocrine surgery and cardiovascular surgery is vital. Reports suggest that rapid cardiac function recovery with the normalization of thyroid hormone occur following thyroidectomy. In the current case, cardiac function improved, but left ventricular assist device (LVAD) therapy was eventually required to bridge to cardiac transplantation, suggesting an additional underlying cardiomyopathy. The patient was able to be discharged home with an LVAD, awaiting heart transplantation.

**Key points**

- Early recognition and appropriate treatment of thyroid storm — which may include thyroidectomy — is essential to improve outcome.
- Thyroidectomy should be pursued when medical therapy fails to control the thyrotoxicosis.
- ECMO should be considered as a means of cardiac support in patients who are unresponsive to conventional therapy until thyroid hormone normalization can be achieved.

**For more information**
