Hyperthyroidism was first described by Caleb Hillier Parry (1825), Robert Graves (1835), and Karl von Basedow (1840). At the beginning of the 20th century, the causes were poorly understood and treatment was limited to surgery because antithyroid drugs and radioactive iodine (RAI) were unavailable until the early 1940s. Because of high surgical mortality, treatment was often delayed until the condition was advanced, and a multistage procedure might be required. Initially, hot water was injected into the thyroid, then a thyroid artery was ligated, and subsequently one or both thyroid lobes were resected. Furthermore, critically ill patients who survived surgery risked postoperative death from thyroid storm.

Understanding of the etiology, pathology, physiology, clinical manifestations, and management of hyperthyroidism has evolved over the past 100 years, and new insights continue to emerge. Mayo Clinic physicians and scientists, working across disciplines, have contributed importantly to understanding this illness. This review of the Mayo Clinic experience will highlight these achievements, including pathologic clarification of the most common forms of hyperthyroidism, isolation of a crystalline product of thyroid hormone, development of a basal metabolism laboratory, discovery of a method to reduce postoperative mortality, investigation of the kinetics of thyroid hormones using radioisotopes, development and/or establishing the clinical utility of laboratory tests to diagnose and monitor therapy for hyperthyroidism, clinical characterization of extrathyroidal manifestations of Graves disease, surgical management of severe Graves ophthalmopathy, the role of orbital radiotherapy, and the pathogenesis of Graves ophthalmopathy.

THE EARLY DAYS (1901-1937)
Charles H. Mayo (1865-1939) developed an early interest in thyroid surgery when he and his brother resected a massive goiter in 1890, and by 1904 reported his experience with thyroidectomy on 40 patients with exophthalmic goiter. Performing thousands of thyroidectomies, he was known as the Father of American Thyroid Surgery. He and his brother William J. Mayo (1861-1939) hired Henry Plummer (1874-1936) in 1901 as one of the early members of Mayo Clinic. As a boy, Plummer had known the first goiter patient of the Mayo brothers, and he too developed an early interest in the thyroid. A superb diagnostician, Plummer classified 4 types of goiters on the basis of his clinical observations: hyperplastic/exophthalmic (toxic and nontoxic) and nonhyperplastic/adenomatous (toxic and nontoxic). In 1905, Plummer and the Mayo brothers hired a pathologist Dr Louis B. Wilson (1866-1943) to develop the clinic’s laboratories (Figure 1). Wilson confirmed Plummer’s clinical findings by correlating with surgical pathology, noting that 99% of hyperplastic goiters but only 23% of adenomatous goiters were toxic. Wilson is best remembered for introducing the frozen section technique to Mayo Clinic surgeons. Of note, his second wife was Maud Mellish (1862-1933). Mellish, a nurse, was hired in 1907 at the recommendation of Dr Albert Ochsner to organize and expand the medical library, and it is said that she rescued physicians’ medical writings from a basement coalbin. From 1909 to 1933 she reviewed all manuscripts as Mayo Clinic’s first medical editor and edited the Collected Papers of the Mayo Clinic. She was, therefore, an integral contributor to the successful dissemination of the early articles on hyperthyroidism, and became an honorary member of Mayo Clinic faculty. Upon her death, Mayo Clinic closed during her funeral. Louis Wilson later died of amyotrophic lateral sclerosis.

On February 1, 1914, Dr Edward C. Kendall (1886-1972), a research chemist with a PhD from Columbia University, began his appointment to the Mayo Clinic faculty to head the biochemistry section (Figure 1).
He was working on identifying the active substance of the thyroid gland, and on Christmas day (11 months after his arrival) isolated a crystalline iodine-containing structure, which he called “thyroxin.” Kendall was unable to identify the chemical structure of thyroxine, but later identified cortisone, and for that shared the Nobel Prize with Dr Philip Hench, a Mayo rheumatologist, and Thaddeus Reichstein from Switzerland.

Mayo Clinic consultants established an early relationship with premier hospitals in Boston, with Dr William Mayo first visiting Massachusetts General Hospital in 1898. In 1916, Plummer recruited Dr Walter Boothby (1880-1953). Boothby received his MD at Harvard and headed the respiration laboratory at Peter Bent Brigham Hospital in Boston where he delivered ether anesthesia for neurosurgical patients of his chief, Dr Harvey Cushing (Figure 2). Joining Boothby at Mayo Clinic was his assistant Miss Irene Sandiford (1889-1978), a recent Radcliffe College graduate who received her PhD at Mayo Foundation in 1919. They established a metabolic laboratory (with Boothby as the head of the section of metabolism), measured the basal metabolic rate (BMR) in thousands of patients, and showed that elevated BMR decreased to normal soon after thyroidectomy. Around that time, Plummer speculated that exophthalmic goiter was caused by “intensive stimulation of unknown source” (eg, thyroid-stimulating immunoglobulin) and also “the possibility of an incompletely iodized thyroxin molecule” (eg, T3). Presumably with this theory in mind, in 1922 Plummer began giving Lugol’s iodine to patients with exophthalmic goiter. Symptoms improved dramatically within days, surgical mortality decreased, and staged thyroid operations were no longer needed. Plummer presided over a popular weekly “goiter lunch” in which internists, surgeons, pathologists, and chemists gathered to discuss cases. These meetings, as well as the mandatory weekly staff meetings wherein presentations were followed by discussions and were published in the Staff Meetings of the Mayo Clinic, promoted collegial interactions contributing to the multidisciplinary approach to patient care. The Mayo brothers also visited Johns Hopkins in the 1890s and, according to Clapcott, liked the “congenial, gay, cooperative group...of internist (Osler), surgeon (Halsted), gynecologist (Kelly) and pathologist (Welch) and their assistants.”

These early Mayo Clinic pioneers made important contributions outside their primary responsibilities as Mayo Clinic clinicians. Plummer helped design and oversee the construction of 2 clinic buildings, the 1914 Building and the 1928 Building (later renamed the Plummer Building) (Figure 1), and the processes within to provide efficient patient flow for a rapidly expanding practice. He also replaced the original patient ledgers kept by each physician with a centralized medical record that permitted reviews of the many patients, both for quality improvement and for publication. Wilson became dedicated to medical education at the clinic and nationally (as President of the American Association of Medical Colleges and a member of the National Board of Medical Examiners) and developed an interest in ballistics research for the US Army. Charles Mayo was elected...
President of the American Medical Association, among many national honors. Boothby, with his background in respiratory physiology, subsequently developed, with colleagues, the Boothby-Lovelace-Bubulion oxygen mask used in high-altitude aviation. For this invention they received the Collier Trophy from President Franklin D. Roosevelt in 1939. Boothby headed the section of Aviation Medicine (1942) and assisted Colonel Charles Lindbergh (Figure 2) in the development of oxygen supplementation for high-altitude flight during World War II.

Two other early consultants had a particular interest in the thyroid. One was Dr Samuel Haines (1892-1993) (Figures 1 and 3). Haines wanted to become a physician after being treated for typhoid fever at age 3 years by Dr Charles H. Mayo. Dr William Worrall Mayo (the father of William and Charles) was his godfather, and Haines met Kendall while working in the laboratory as a college student. Haines received his MD at Harvard in 1919, interned at Massachusetts General Hospital (MGH), then returned to Mayo Clinic and joined Plummer’s section of thyroid disease in 1922, becoming its head in 1932. The second physician, Dr John de J. Pemberton (1887-1967), received his MD in 1911 from the University of Pennsylvania, became a Mayo Clinic surgical fellow in 1913, and was head of a section of surgery from 1918 to 1952 (Figure 1). He worked with Wilson in the laboratory of surgical pathology and in the operating room with Dr Charles Mayo. Pemberton published on surgical aspects of thyroid disease, including hyperthyroidism.11 He and others including Drs Edwin Kepler (1894-1947), Harold Dunlap (1895-1947), and colleagues characterized the hepatic, cardiac, and psychic features of patients with severe, often lethal, thyroid disease. Dunlap and Kepler also identified cases of periodic paralysis in patients with exophthalmic goiter.

MIDCENTURY (1946-1971)

Within a few years of the deaths of Henry Plummer and Charles H. Mayo, therapy for hyperthyroidism shifted from surgery to radioiodine and antithyroid drugs. Although World War II interrupted academic progress, the underpinnings of a postwar invigoration of thyroid research at Mayo Clinic were established a few years earlier. Dr F. Raymond Keating Jr (1911-1969) became a fellow at Mayo Clinic in 1938, and 4 years later, previous connections with Boston were rekindled. Dr Haines arranged for Keating to spend a 6-month sabbatical in 1942 at the MGH and the Massachusetts Institute of Technology in Boston where...
the exploration of radioiodine for medical research and therapy was in its infancy. In a 1983 letter (on file, Mayo Historical Unit) from Dr Haines to David Becker, MD, at Cornell, Haines said:

[When Ray Keating finished his Fellowship we asked Howard Means to let him go to the M.G.H. for 6 months. We were especially interested in having him see what Means, (Saul) Hertz, and (Rulon) Rawson were doing with radioiodine, a program which, as you know, was carried out with Robley Evans and Wendell Peacock from M.I.T...We also wanted Ray to see as much of Fuller Albright as possible, as we were concerned that he, Fuller, was seeing so much more hyperparathyroidism than we were. Ray’s stay in Boston was very successful in both ways, and when he came back he had arranged with Evans to have small amounts of I-131 sent to him to be used in some studies in chicks.

Keating published several articles with his mentors in Boston. Dr Haines goes on to say:

[As soon as radioiodine could be available from Oak Ridge we applied for it. This was in 1946, and it was sent to the laboratory of Marschelle Power in our chemistry department. From the beginning a series of investigative programs were carried out by several men...I do not remember the exact date we gave the first therapeutic dose, but I remember the patient—a woman with recurrent exophthalmic goiter, mitral stenosis, and cardiac decompensation, in whom the risk of further surgical resection was estimated to be great. She got a good result from I-131.

In 1946, when 131-Iodine became available from Oak Ridge, TN, a lengthy collaboration developed between Drs Keating, Haines, Marschelle Power, and Alexander Albert. Dr Power (1894-1982) received a PhD in organic chemistry in 1923, became a Mayo Clinic consultant in biochemistry in 1930, and was section head from 1947 to 1957. Dr Albert (1911-1997) received his PhD and MD from Harvard and his research fellowship at the MGH where he worked with Means and Rawson in the Thyroid Clinic and where his interest was using radioiodine to study iodine metabolism. He joined Mayo Clinic in 1946 and became head of the endocrine lab and later chair of the Department of Endocrine Research. Other members of the team of Mayo Clinic consultants studying thyroid physiology, biochemistry, diagnostics, and therapeutics included Drs Haines, Pemberton, chemists Harold Mason (1901-1992) and Ralph Ellefson, William McConahey (1916-2004), William Mayberry, Charles M. Blackburn (1920-1979), Alvin Hayles (1915-1988), and Lewis Woolner. In addition, trainees who went on to have distinguished thyroid careers elsewhere included Drs Arnold S. Jackson, Brown Dobyns, J. Edward Rall, and Richard Benua. The studies during this era were impressive, and included radioisotopic studies from human exophthalmic goiter tissue slices, animal studies, and humans with hyperthyroidism that elaborated the changes in iodine kinetics, lipid metabolism, and the effects of antithyroid drugs.12,13 Diagnostic tests were established for clinical use including thyroidal RAI uptake, protein-bound iodine, T4, and T3.14

Dr Rall, in 1996, sent a document titled “A Fellow’s Picture of the Mayo Clinic Half a Century Ago” (on file, Mayo Historical Unit) to Mayo Clinic. His research involved “thyroid hormone, the new technique of paper chromatography and radioactive iodine.” He describes the Mayo Clinic as “remarkably tolerant... never a complaint or request for a progress report,” and he noted that all thyroid surgeries were done on the top floor of the Kahler hotel and “Marden Black (1910-1997) had the record for 21 thyroidectomies in one day.”

**RECENT EVENTS (1982-2014)**

More recently, the focus at Mayo Clinic has been on extrathyroidal manifestations of Graves disease. Surgeons Drs James Garrity and George Bartley provided outcomes on orbital decompression for severe ophthalmopathy and collaborated in a series of studies with endocrinologist Dr Colum Gorman who, in a randomized trial, showed minimal benefit of orbital radiotherapy.15,16 Dr Rebecca Bahn has focused on the pathogenesis of Graves eye disease in the laboratory and has carried her work into clinical trials.17 Dr Vahab Fatourechi
provided outcomes of a large cohort of patients with Graves dermopathy (pretibial myxedema) and with acropathy.18

Many faculty members have contributed to other aspects of hyperthyroidism including inappropriate thyroid-stimulating hormone disorders (Drs Hossein Gharib and William Young), amiodarone-induced thyrotoxicosis, thyrotoxic periodic paralysis (Gharib), body composition before and after therapy of hyperthyroidism (Dr Michael Brennan), and laboratory diagnosis of thyroid dysfunction (Drs McConahey, Ian Hay, John Morris, and George Klee). Recent and current surgeons (Drs Clive Grant, Geoffrey Thompson, David Farley, and Melanie Richards) have shown that surgery is still the preferred method of treating toxic multinodular goiter (Plummer disease) at Mayo Clinic,19 while Grant, Thompson, Jon van Heerden, and pediatric endocrinologist Donald Zimmerman showed the continued value of surgery for Graves disease in childhood and adolescence.

The 20th century saw numerous advances in the diagnosis and treatment of hyperthyroidism. Its causes were initially ill-defined, its therapy limited to thyroidectomy, and related mortality was high (from cardiac complications or postoperative thyroid storm). Contributions from Mayo Clinic staff, spanning more than 100 years, have advanced our understanding of hyperthyroidism and greatly improved its treatment. The first notable achievement was that broad collaboration including surgeon (C.H. Mayo), internist (Plummer), pathologist (Wilson), chemist (Kendall), and laboratory physiologist (Boothby); the causes and severity of hyperthyroidism could be gauged, thus guiding therapy. Second, the discovery that Lugol’s iodine improved hyperthyroidism clinically and reduced postoperative mortality was practice-changing and life-saving. Third, the value of radioisotopes for studying thyroid pathophysiology and as diagnostic and therapeutic tools was established. Fourth, clinicians and laboratory colleagues documented a series of increasingly specific diagnostic tests for hyperthyroidism, beginning with the BMR, then RAI uptake, PBI, T4, and T3. Fifth, extrathyroidal manifestations of Graves disease were characterized clinically, orbital decompression was shown to improve visual acuity and reduce proptosis, and more severe ophthalmopathy correlated with dermopathy and acropathy. Investigations into the immunologic underpinnings and clinical trials for treatment of Graves ophthalmopathy are ongoing. Finally, various other causes of thyrotoxicosis have been the subject of clinical research.

Mayo Clinic and its faculty have been leaders in thyroid research and practice for more than a century. Beginning with Henry Plummer in 1933, 11 staff members (Drs Plummer, Pemberton, Haines, Albert, Keating, McConahey, Hayles, Gorman, Bahn, Gharib, and Smallridge) and 4 trainees (Drs Jackson, Dobyns, Rall, and Bryan Haugen [Mayo Medical School]) have been president of the American Thyroid Association. Four staff members were president of the Endocrine Society (Drs Kendall, Mason, Albert, and William Young), and 2 (Drs Mason and Albert) also received the Fred Conrad Koch Lifetime Achievement Award. The 21st century promises to continue this legacy and bring, through innovations in clinical care and research, new insights into the evaluation and management of patients with hyperthyroidism.

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ABBREVIATIONS AND ACRONYMS: BMR = basal metabolic rate; MGH = Massachusetts General Hospital; RAI = radioactive iodine

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