The early years of the 20th century found Rochester, Minnesota, to be the center of the world for thyroid surgery. Dr. Charles H. Mayo and Dr. Henry S. Plummer had developed methods for safe thyroidectomy, especially for exophthalmic goiter, that reduced the mortality rate from levels that were as high as 20 percent in some hospitals to below 3 percent. This achievement brought thousands of patients to Mayo Clinic for treatment of thyroid diseases and goiter. In 1908, Drs. Mayo and Plummer reported their experience with 1,000 thyroidectomies, and with 5,000 only three years later. By 1911 thyroidectomy was the most commonly performed operation at Mayo Clinic.

John C. Morris III, M.D., of the Division of Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic's campus in Rochester, Minnesota, explains: “In part because of this great advance in the success of thyroid surgery, there was a great flood of registrations at Mayo. The institution was growing rapidly with patients, physicians, facilities and in reputation. The clinical laboratory also grew rapidly during this period. A decision to add research facilities was considered, including adding what we would now call basic scientists to the staff. Against some opposition, Drs. Mayo, Plummer and Louis B. Wilson argued that ‘pure research’ was vital to the future success of the group and would prevent falling into routine based solely on present knowledge. Their efforts were chronicled in The Doctors Mayo in 1969.”

An opportunity arose when in late 1913 a letter arrived from a young New York chemist interested in isolating the active ingredient of the thyroid gland and seeking a position. Edward C. Kendall received a Ph.D. in chemistry from Columbia University in 1908. During his oral defense, he was asked about iodine metabolism and did not know that it was concentrated within the thyroid gland. He worked briefly in Detroit for Parke-Davis, the pharmaceutical company, but returned to New York after only a few months. There, at Columbia and St. Luke’s Hospital, he became intrigued by the thyroid, in part because of the question he was unable to answer as a doctoral candidate.

It was known by this time that thyroidectomy led to myxedema, and that an extract from the thyroid could be utilized to reverse the symptoms. But the active ingredient responsible for this action was unknown. Kendall became determined to isolate and characterize this substance, but because the salary and research support he was receiving were insufficient, he proposed to complete the project at Mayo Clinic.

Dr. Morris highlights: “After corresponding with Dr. Wilson, head of the Mayo Clinic laboratories, Dr. Kendall came to Rochester for an interview (Figure 1). He brought with him a small vial of his most pure thyroid extract...”
to date, which reproduced the biological effects of the thyroid substance. He was hired in short order, specifically to pursue the project of isolating the active ingredient of the thyroid. He started work in Rochester in February 1914, in a laboratory on the fourth floor of a newly constructed Mayo Clinic building, later known as the 1914 Building."

Dr. Morris recounts: "By December 1914 he had made considerable progress and had a powder that was 40 percent by weight iodine, but its volume was quite small. He decided, rather than risk losing more of his product through another round of barium hydroxide purification, to attempt to crystallize a pure substance from the current and already highly enriched mixture by alcohol extraction. After several rounds of heating in a water bath to evaporate the ethanol and discarding the byproducts, he found that the extract was now 60 percent iodine, much more pure than his previous best. On Christmas morning 1914, he dissolved the extract in ethanol and then added acid, and observed crystals of pure thyroid hormone falling out of the solution. He named the extract ‘thyroxin.’ Later, when it was recognized that the extract was an amino acid derivative, the name was changed to ‘thyroxine.’"

The work was presented to the scientific community with considerable fanfare at the Federation of American Societies for Experimental Biology meeting in New York in 1916, in a paper entitled “Isolation in Crystalline Form of the Iodine-Containing Compound of the Thyroid Gland.” Kendall would work for only a few more years on the thyroid, and later turn his interests toward the adrenal gland and its unknown hormone(s). For this later work he would, in 1950, receive the Nobel Prize for the synthesis and clinical use of cortisone (Figure 2). Dr. Kendall’s research was chronicled in The Quest for Cortisone in 2012.

Dr. Morris concludes: “According to IMS Health and its annual drug survey, Kendall’s product, pharmaceutically named ‘levothyroxine’, is the most highly prescribed drug in the United States, with more than 23 million prescriptions written per year. In December 2014 we celebrate this discovery, which occurred on our campus at a time when a young, growing and vibrant medical institution wishing to expand its research effort sought out a young, hardworking and inspired scientist to come to Minnesota with his lofty plans. As I write a prescription for thyroid hormone, it is fun to think of what must have been in Kendall’s mind that Christmas morning, when he saw crystals falling like the Minnesota snow inside his test tube.”

For more information


Figure 2. Edward C. Kendall, Ph.D., received the Nobel Prize in 1950 for the synthesis and use of cortisone.
Retroperitoneoscopic Adrenalectomy: A Useful Surgical Approach in Select Patients

The first description and subsequent adoption of transperitoneal laparoscopic adrenalectomy revolutionized the surgical management of small benign adrenal neoplasms. Laparoscopy resulted in reduced postoperative pain, less morbidity, shorter hospital stay and an earlier return to normal activity compared with open adrenalectomy.

Travis J. McKenzie, M.D., of the Department of Surgery at Mayo Clinic’s campus in Rochester, Minnesota, says: “It is now readily accepted that laparoscopic adrenalectomy is the gold standard surgical approach, with open adrenalectomy being reserved for very large or malignant neoplasms. However, the traditional transperitoneal laparoscopic approach has notable limitations. The transperitoneal procedure involves approaching the adrenal glands from anterior, necessitating substantial organ mobilization to obtain access to the retroperitoneum. For example, laparoscopic left adrenalectomy requires mobilization of the left colon, spleen and pancreatic tail. This dissection can be complicated in the setting of intra-abdominal adhesions from previous operations.”

Dr. McKenzie explains: “The retroperitoneoscopic adrenalectomy (RPA) approach involves placing the patient in the facedown prone position with the adrenal gland being approached posteriorly beneath the 12th rib (Figure). This approach allows direct access to the retroperitoneum and adrenal gland without the need for intra-abdominal organ mobilization. Furthermore, CO₂ insufflation pressures in the retroperitoneum can be kept significantly higher than with traditional laparoscopy without limiting cardiac filling pressures. High insufflation pressures in the retroperitoneal space can limit troublesome bleeding that often occurs with the transperitoneal approach in which pressures are limited to 15 to 20 mm Hg.”

There are currently no large prospective studies comparing laparoscopic transperitoneal and RPA approaches. Multiple retrospective series have demonstrated safety and efficacy of RPA. Martin K. Walz, M.D., Kliniken Essen-Mitte, Germany, and colleagues published results of 560 retroperitoneoscopic adrenalectomies in 520 patients for neoplasms ranging from 0.5 to 10 cm in Surgery in 2006. Results were equivalent to contemporary series of transperitoneal laparoscopic adrenalectomies, including a minor morbidity of 14.4 percent and mortality of 0 percent with conversion to an open or laparoscopic approach in 1.7 percent of patients.

Dr. McKenzie highlights that: “All types of benign adrenal neoplasms may be accessible with the retroperitoneal approach, including both biochemically active and silent neoplasms. Relative contraindications to RPA include tumors larger than 7 cm, and patients with BMI > 40 kg/m². The working space is considerably smaller with the RPA approach, and therefore neoplasms larger than 7 cm are difficult to dissect safely. In addition, creation of the retroperitoneal working space can be limited by posterior compression secondary to a large pannus in an obese patient. RPA provides an excellent surgical option for select patients with benign adrenal neoplasms in the setting of previous abdominal operations where the traditional transperitoneal laparoscopic approach may be difficult. Furthermore, this approach may be utilized as a primary option with equivalent results to transperitoneal laparoscopy.”

For more information


Figure. CT scan from patient with a left adrenal mass. The CT image on the left panel shows the angle of approach (yellow arrow) with transperitoneal laparoscopic adrenalectomy. The CT image on the right panel shows the retroperitoneoscopic approach (yellow arrow) to adrenalectomy.
The triad of hypertension, hypokalemia and an aldosterone-producing adenoma (APA) of the adrenal gland was first reported by Jerome W. Conn, M.D., in 1955. The hypertension and hypokalemia in Dr. Conn’s first patient were cured by removal of an adrenal adenoma.

William F. Young Jr., M.D., of the Division of Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “Over the past 60 years, three facts have become clear. First, primary aldosteronism (PA) is more common than previously thought, and it affects between 5 and 10 percent of all patients with hypertension. Second, most patients with PA are normokalemic. Third, PA has more than one cause, and most patients with PA have bilateral idiopathic hyperaldosteronism (IHA).

“Unilateral adrenalectomy in patients with APA results in normalization of hypokalemia in all patients, normalization of blood pressure in at least a third of patients and improvement of hypertension in the remaining patients. Whereas, in patients with IHA, unilateral or bilateral adrenalectomy seldom corrects hypertension. Patients with IHA should be treated not surgically but medically with a mineralocorticoid-receptor antagonist. Therefore, determining the subtype of PA (APA versus IHA) is critical in directing treatment.”

In 1967, selective adrenal venous sampling (AVS) for aldosterone was first proposed as a test to distinguish between APA and IHA. However, it is an invasive and difficult technique. The right adrenal vein is small and may be difficult to identify, to cannulate and to withdraw blood from. Both adrenal veins must be sampled for meaningful comparison.

When body computerized tomography (CT) became available in the late 1970s, it was thought to be a good test to distinguish among the subtypes of PA. Dr. Young notes: “However, because of the prevalence of nonfunctioning cortical adenomas, hormonal hyperfunction cannot be inferred from simply the presence of an adrenal nodule. A patient with IHA may be thought to have an APA because an adrenal nodule was detected on CT — a finding that may be due to the age-related occurrence of nonfunctioning adrenal cortical nodules. Yet, APAs that are 3 or 4 mm in diameter may escape detection on CT or a patient with a unilateral APA may have bilateral adrenal nodules on CT — one that is nonfunctional and one that is hypersecreting aldosterone (Figure 1).

William F. Young Jr., M.D., and James C. Andrews, M.D.
"An approach to these clinical dilemmas is shown in the algorithm (Figure 2), which outlines that AVS is not needed in all patients with PA. Because adrenal ‘incidentalomas’ are uncommon in young patients, when a solitary unilateral macronodule (> 1 cm) and a normal contralateral adrenal are found on CT in a patient with PA who is less than 35 years of age, unilateral adrenalectomy is reasonable to consider. In addition, some patients prefer pharmacological therapy over a surgical procedure and therefore AVS is not needed. With this approach, AVS is performed in approximately 25 percent of Mayo Clinic patients with PA.”

Patients with an APA have more severe hypertension, more frequent hypokalemia, and higher plasma (> 25 ng/dL) and urinary (> 30 μg/24 h) levels of aldosterone than do patients with IHA. Patients with these findings are considered to have a “high probability” of APA (Figure 2). However, these findings are not absolute predictors of unilateral versus bilateral adrenal disease.

James C. Andrews, M.D., of the Department of Radiology at Mayo Clinic’s campus in Rochester, Minnesota, says: “We have now performed AVS in more than 700 patients. The adrenal veins are sequentially catheterized through the percutaneous femoral vein approach under fluoroscopic guidance, and correct catheter tip location is confirmed with injection of a small amount of contrast medium (Figure 3). Blood is obtained by gentle aspiration from both adrenal veins. Successful catheterization may require an array of catheter configurations, either available from manufacturers or custom made with steam shaping during the procedure to facilitate access to the

**Figure 2.** An algorithmic approach to subtype evaluation of a patient with primary aldosteronism. Terms in the chart: aldosterone-producing adenoma (APA); adrenal venous sampling (AVS); computerized tomography (CT); glucocorticoid remediable aldosteronism (GRA); idiopathic hyperaldosteronism (IHA); unilateral adrenal hyperplasia (UAH).

**Figure 3.** Images of adrenal venous sampling performed in the patient with primary aldosteronism whose computerized tomographic scan is shown in Figure 1. Radiographs show catheters placed in the right and left adrenal veins.
adrenal veins.

“At centers with experience with AVS, the complication rate is 2.5 percent or less. Complications can include symptomatic groin hematoma, adrenal hemorrhage and dissection of an adrenal vein. Aldosterone and cortisol concentrations are measured in the blood from all three sites: right adrenal vein, left adrenal vein and IVC (Table). All of the blood samples should be assayed at ratios of 1-to-1, 1-to-10 and 1-to-50 dilutions — absolute values are mandatory. Accurate laboratory assays for cortisol and aldosterone are keys to successful interpretation of the AVS data.”

Dr. Young concludes: “For patients with PA who want to pursue the surgical treatment option, AVS is the key diagnostic step.”

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A), ng/dL</th>
<th>Cortisol (C), μg/dL</th>
<th>A:C ratio</th>
<th>Aldosterone ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT adrenal vein</td>
<td>17,300</td>
<td>1,210</td>
<td>14.3</td>
<td>6.2</td>
</tr>
<tr>
<td>LT adrenal vein</td>
<td>952</td>
<td>419</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>48</td>
<td>19</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

*Right adrenal vein A:C ratio divided by left adrenal vein A:C ratio

**Table.** Results of bilateral adrenal venous sampling performed in the patient with primary aldosteronism whose computerized tomographic scan is shown in Figure 1 and AVS radiographs in Figure 3. The cortisol concentrations from the adrenal veins and inferior vena cava are used to confirm successful catheterization; the adrenal vein cortisol-to-inferior vena cava cortisol ratio is typically more than 10-to-1 when the protocol for continuous cosyntropin infusion is followed (minimum cutoff is > a ratio of 5-to-1). Dividing the plasma aldosterone concentrations (PACs) of the right and left adrenal veins by the respective cortisol concentrations corrects for the dilutional effect of blood from the inferior phrenic vein flowing into the left adrenal vein; these quotients are termed cortisol-corrected aldosterone ratios. In patients with aldosterone-producing adenoma (APA), the mean cortisol-corrected aldosterone ratio (APA-side PAC/cortisol concentration-to-normal adrenal PAC/cortisol concentration ratio) is 18-to-1. A cutoff for the cortisol-corrected aldosterone ratio from high side to low side of more than 4-to-1 is used to indicate unilateral aldosterone excess. The lateralization ratio in this patient is 6.2-to-1 and is consistent with a right adrenal APA.

---

**New Staff in Endocrinology**

Three endocrinologists joined the Division of Endocrinology, Diabetes, Metabolism & Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, in 2014. They and their areas of interest are:

- Irina Bancos, M.D., adrenal, pituitary and gonadal disorders
- Caroline J. Davidge-Pitts, M.B., Ch.B., community endocrinology, medical education, transgender endocrinology
- Meera Shah, M.B., Ch.B., obesity, bariatric surgery, medical nutrition therapy and diabetes
2014 Graduating Clinical Endocrinology Fellows

Left to right, followed by the upcoming appointment:

• Juan P. Brito Campana, MBBS, Mayo Scholar Program at Memorial Sloan Kettering Cancer Center, New York
• Meera Shah, M.B., Ch.B., Division of Endocrinology, Diabetes, Metabolism & Nutrition, Mayo Clinic, Rochester, Minnesota
• Kurt A. Kennel, M.D., Program Director, Clinical Fellowship in Endocrinology, Diabetes, Metabolism & Nutrition, Mayo Clinic, Rochester, Minnesota
• Caroline J. Davidge-Pitts, M.B., Ch.B., Division of Endocrinology, Diabetes, Metabolism & Nutrition, Mayo Clinic, Rochester, Minnesota
• Marcio Longhi Griebeler, M.D., Sanford Diabetes and Thyroid Clinic, Sioux Falls, South Dakota

Education Opportunities

18th Annual Mayo Clinic Endocrine Update
Feb. 16-20, 2015, Fairmont Mayakoba, Riviera Maya, Cancun, Mexico
Designed for endocrinologists and interested internists and surgeons, this course will address gaps in medical knowledge and barriers in clinical practice and explore the role of new tools in the diagnosis and management of patients with endocrine and metabolic disorders. It will span the full range of endocrinology, through lectures, debates, panel discussions, informal breakfast round-table discussions and small-group discussions with experts. Attendees will have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen.

Additional offerings
Thyroid Ultrasound Workshop
Sunday, Feb. 15, 2015, 8 a.m.-5 p.m. Fee: $250.
This workshop is perfect for participants interested in learning ultrasound imaging and ultrasound-guided techniques for fine-needle aspiration of the thyroid.

ABIM Maintenance of Certification (MOC) Shared Learning Session
Monday, Feb. 16, 2015, 1 p.m.-5 p.m. Fee: $250.
Participation will provide 10 points of ABIM MOC requirements.

Accommodations and lodging
The course will be held at the Fairmont Mayakoba in Quintana Roo, Mexico. To ensure accommodations at the discounted rate, please make your reservations directly with the hotel by calling 800-441-1414 (toll-free) or booking online at https://resweb.passkey.com/go/mceh2015. Identify yourself as a participant of the Mayo Clinic Endocrine Update Course. Lodging arrangements are the sole responsibility of the individual registrant.

For detailed information about this course, please visit www.mayo.edu/cme/endocrinology-2015r845 or call 800-323-2688 (toll-free).
Education Opportunities (continued)

15th Annual Mayo Clinic Nutrition and Wellness in Health and Disease
Sept. 25-26, 2015, Washington, D.C.
Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — will provide a full-spectrum, in-depth overview of situations and topics that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, obesity-associated medical conditions, the role of healthy diets, bariatric surgery and pre- and post-surgery medical management, prevention of common medical conditions through healthy lifestyles, effective ways to provide coaching, nutrition for selected groups, nutrition topics in the news, behavior modification, resilience, in addition to physical activity and wellness. A culinary demonstration will highlight cooking techniques to prepare healthy, great tasting food. Current clinical topics will be highlighted through presentations that offer practical clinical management pearls, interactive case studies and panel discussions.

The course will be held at The Mayflower Renaissance Washington, D.C., Hotel.

For more information about this course, please visit www.Mayo.edu/cme/endocrinology or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME