

INSIDE THIS ISSUE

- 3 Endocrine Surgery Training at Mayo Clinic
- 4 The Thyroid Nodule Clinic
- 6 Graves' Ophthalmopathy

Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant inherited disorder that affects tumorigenesis in at least 8 types of endocrine and nonendocrine tissues (Figures 1 and 2). Geoffrey B. Thompson, MD, of the Department of Surgery at Mayo Clinic in Rochester, Minnesota, says: "The true prevalence of MEN 1 is likely underestimated but varies from 0.2 to 2.0 per 100,000 people. The major clinical manifestations in MEN 1 include the 3 P's: primary hyperparathyroidism (HPT), pancreatic and duodenal neuroendocrine tumors, and pituitary tumors. Expression of the disease rarely occurs before age 10 years, and most often, the syndrome presents between the ages of 20 and

40 years. Two of the 3 major lesions must be present for the clinical diagnosis in a proband. However, in family members of a known MEN 1 kindred, the presence of 1 major lesion is diagnostic. Clinical diagnosis is confirmed with genetic testing."

Noralane M. Lindor, of the Department of Medical Genetics at Mayo Clinic in Rochester, Minnesota, says: "The gene responsible for MEN 1 (*MEN1*) was identified in 1997 and is located on chromosome 11q13. *MEN1* encodes a nuclear protein referred to as *menin*. Menin acts as a tumor suppressor

gene to influence gene transcription, cell proliferation, apoptosis, and genomic instability. More than 400 different mutations have been reported to date, with no clinically useful genotype-phenotype correlations confirmed. Of these mutations, 90% are inherited and 10% arise *de novo*. *MEN1* mutational analysis is clinically available and has about a 90% detection rate. In kindreds with undetectable mutations, linkage analysis may still be utilized to track the disease alleles through the family."

Pituitary Tumors

Pituitary tumors in MEN 1 family members are less frequent than primary HPT or pancreatic and duodenal neuroendocrine tumors. William F. Young Jr, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, explains: "Pituitary neoplasms may develop in up to 60% of MEN 1 patients. The mean age at diagnosis of the pituitary tumor is 38 years, with a range from 12 to 83 years. In the majority of MEN 1 patients, the pituitary tumors are macroadenomas, most (60%) of which are prolactinomas. Monitoring for pituitary tumor development in MEN 1 should include measurement of serum prolactin and insulinlike growth factor 1 concentrations yearly and imaging the pituitary with magnetic resonance imaging every 2 to 3 years."

Primary HPT

Most MEN 1 patients will have hypercalcemia and primary HPT by the fourth decade of life. In screened patients, the mean age at detection of HPT has been reported to be as low as 19 years. Dr Thompson notes: "Primary HPT is the initial

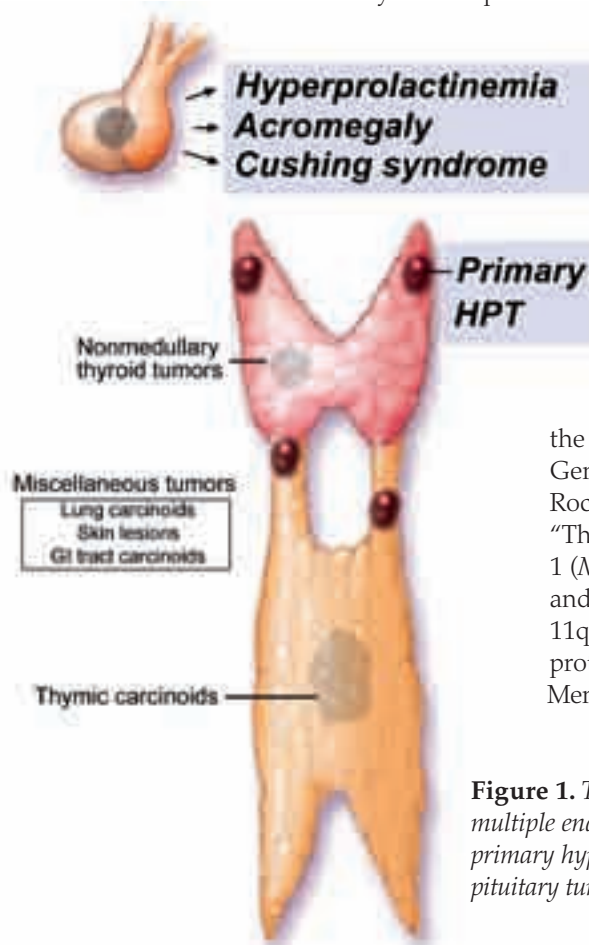


Figure 1. The clinical manifestations of multiple endocrine neoplasia type 1 include primary hyperparathyroidism (HPT) and pituitary tumors. GI indicates gastrointestinal.



William F. Young Jr, MD, and Geoffrey B. Thompson, MD

clinical and biochemical manifestation of MEN 1 in 60% to 90% of patients. In MEN 1 patients, the pathologic features are that of asymmetrical hyperplasia or multiple adenomas involving all parathyroid glands. The timing of parathyroidectomy is an important issue. MEN 1-related primary HPT involves all parathyroid tissue, and thus any treatment we provide is considered palliative at best. Attempts at eradicating all parathyroid tissue can result in a treatment that is far worse than the disease (resulting in permanent hypoparathyroidism). In patients with mild disease, it is appropriate to delay surgery until the serum calcium level is 1 mg/dL or more above the upper limit of the reference range. The preferred surgical approach for a MEN 1 patient with primary HPT is a subtotal parathyroidectomy with transcervical thymectomy. Although recurrence rates are somewhat higher than for total parathyroidectomy with immediate autotransplantation, the risk of permanent hypoparathyroidism is markedly reduced (1% to 2% versus 20% to 30%)."

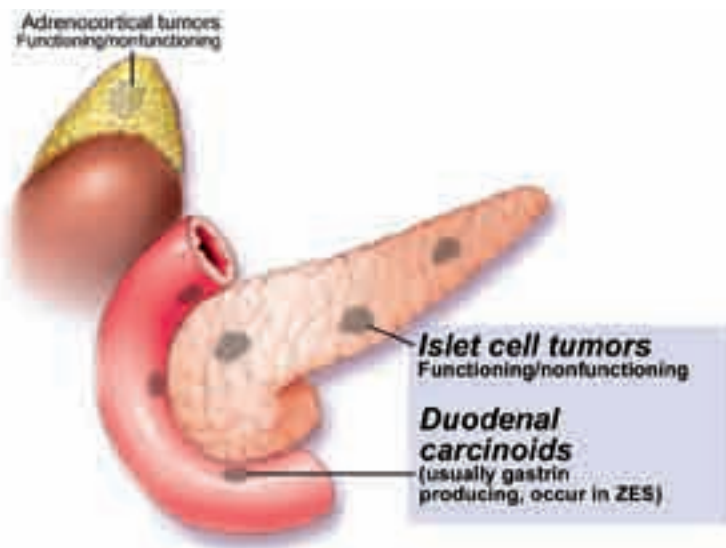


Figure 2. The main clinical manifestations of multiple endocrine neoplasia type 1 also include pancreatic and duodenal neuroendocrine tumors. ZES indicates Zollinger-Ellison syndrome.

Pancreatic and Duodenal Neuroendocrine Tumors

Pancreatic and duodenal neuroendocrine tumors represent the second most frequent manifestation in MEN



Noralane M. Lindor

1 and continue to be the number 1 cause of tumor-related death. Dr Thompson highlights: "Pancreatic and duodenal neuroendocrine neoplasms become clinically apparent in 50% to 75% of kindred family members, and more than 80% of MEN 1 patients have histologic changes within the pancreas. Insulinoma associated with endogenous hyperinsulinism is the most common functioning pancreatic neuroendocrine tumor in MEN 1 patients younger than 25 years. Although these patients often have multiple pancreatic tumors, typically only 1 or 2 tumors are the source of insulin excess. All pancreatic and duodenal endocrine tumors are capable of malignant transformation, and this capability is especially true for nonfunctioning tumors. MEN 1 patients with glucagonomas, neuroendocrine tumors that hypersecrete vasoactive intestinal polypeptide, and obviously malignant nonfunctioning tumors warrant an aggressive surgical approach that includes an 80% distal pancreatectomy, splenectomy, and lymphadenectomy, along with enucleation of any residual tumors. Isolated liver metastases or a finite number of multiple metastases can be successfully managed with excellent control of hormonal sequelae through a combination of hepatic resection, radiofrequency thermoablation, and hepatic artery embolization. Octreotide and systemic chemotherapy can also be used for palliation of advanced disease."

Gastrinomas represent the most common functioning tumors in MEN 1 patients. Nearly one-third of patients with Zollinger-Ellison syndrome are MEN 1 kindred members and more than 50% of MEN 1 patients have hypergastrinemia. Dr Thompson explains: "Although medical therapy with proton pump inhibitors is effective for managing the hormonal sequelae of gastrin excess, it does nothing to prevent malignant transformation or progression, or both. More than 90% of gastrinomas in MEN 1 patients are duodenal in origin. The surgical approach involves a distal pancreatectomy, lymphadenectomy, enucleation of residual tumors in the head of the pancreas, and an exploratory duodenotomy to excise all visible and palpable duodenal carcinoid tumors."

Endocrine Surgery Training at Mayo Clinic

The Endocrine Surgical Fellowship is in its third year under the auspices of the Department of Surgery and fully funded by Mayo Clinic. Clive S. Grant, MD, of the Department of Surgery at Mayo Clinic in Rochester, Minnesota, says: "Our program is recognized by the American Association of Endocrine Surgery (AAES) as 1 of about a dozen such programs. National standards and accreditation have yet to be established, but the AAES has developed a detailed curriculum. Institutional standards and guidelines are already in place to ensure objective assessment and monitoring not only of the fellow, but also of the fellowship training program."

The goal at completion of the fellowship training is for the surgeon to have both a thorough knowledge of the integrated multidisciplinary approach to the patient with a specific endocrine problem and the advanced surgical expertise to treat these patients whether their problem is common or complicated. Dr Grant explains: "This goal encompasses not only expertise in the operating room but also thoughtful consideration of indications and contraindications preoperatively and excellence in overall perioperative management and postoperative care. Our fellows comprehend controversies in the treatment of these patients and are able to weigh pros and cons in formulating surgical decisions."

All aspects of the 4 major endocrine organ systems—thyroid, parathyroid, adrenal gland, and endocrine pancreas—are explored in depth. Dr Grant says: "We are fortunate to inherit the long-established institutional referral practice of all manner of endocrine conditions. This referral practice covers the spectrum from common problems, such as primary hyperparathyroidism, to rare, challenging situations, such as multiply operated medullary thyroid carcinoma, a pure virilizing adrenal tumor, or endocrine neoplasia involving multiple endocrine organs."

Dr Grant continues: "Our philosophy of delivering the most optimal, high-value care to these patients from a surgical perspective often requires a team approach. To facilitate communication among team members and the patient, the surgeon should have a solid knowledge of other associated medical disciplines involved in their patient's care. We are fortunate to have enthusiastic support from colleagues in the departments of endocrinology, radiology, pathology, medical oncology, and nuclear medicine, who set aside their time and talents to enhance the training of our fellows for 3

months. This training often allows one-on-one mentoring by extraordinary clinical educators. The remaining 9 months of the yearlong fellowship are spent working with different surgical consultants whose principal interest and surgical caseload are endocrine."

He explains: "Clinical experience alone is insufficient for our fellowship training. The fellow participates in regularly scheduled didactic programs and presentations, such as conferences by our general surgery chief residents, mortality and morbidity conferences, morning 'coffee conferences,' noon endocrinology case conferences, and monthly endocrine surgery teleconferences held in conjunction with colleagues at Mayo Clinic in Arizona and Mayo Clinic in Florida. Clinical research is strongly emphasized and integrated early in the educational year. Fellows develop a clinical project with supervision and mentoring from the staff endocrine surgeons and colleagues from other related disciplines."

Dr. Grant highlights: "A process invaluable for the young endocrine surgeon continues to be that of inception of an idea or hypothesis, the many steps of protocol design and approval, data acquisition and analysis, manuscript and presentation preparation, and defense of the scientific work in front of recognized national and international authorities. Even when the employment that follows the fellowship year is not within an academic setting, this type of scholarly effort affords tremendous insight into the time, effort, and rewards, as well as the very definite limitations, of the research process."

Every March, a week is dedicated to technology-based endocrine topics, as well as didactic and case-based discussions, at Endocrine University, cosponsored by Mayo Clinic and the American Association of Clinical Endocrinologists and held at Mayo Clinic. This forum facilitates valuable interaction among medical endocrinology fellows and the other endocrine surgical fellows from around the country.

Innovative surgical techniques and participation in educational opportunities for newer residents are also emphasized. The fellows develop their educational and technical skills not only in the operating room, but also through the use of ultramodern simulation and cadaver laboratories.

Dr Grant concludes: "Ultimately, the success of our endocrine surgery fellowship program resides with the diligence, enthusiasm, dedication, and future success of our fellows."



Clive S. Grant, MD

A very high percentage of general surgery residents pursue fellowship training, which implies keen competition with other specialized surgical disciplines for outstanding fellowship candidates. With the fascinating and stimulating

subject matter (admittedly, we are biased!), the ongoing commitment to the clinical, research, and educational aspects on the part of both staff and fellows, we believe that the future of endocrine surgical training is bright."

The Thyroid Nodule Clinic

Thyroid nodules are common, with palpable nodules found in 4% to 7% of the adult US population and solitary or multiple nodules found at much higher rates during ultrasonographic screening. "Most of these nodules—about 95%—are entirely benign," says Hossein Gharib, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota. "However, identifying the occasional thyroid cancer requires careful evaluation of every nodule we find, using a combination of clinical assessment, neck palpation [Figure 1], ultrasound imaging [Figure 2], and, in many cases, analysis of a biopsy specimen [Figure 3]."

Sometimes, thyroid nodules are noticed by the patient or a family member or are discovered during a routine physical examination. They rarely cause symptoms, unless they are large enough to interfere with swallowing. Thyroid cancer can invade and damage the recurrent laryngeal nerve,



Hossein Gharib, MD, Bryan McIver, MB ChB, PhD, Diana S. Dean, MD, and Melanie L. Richards, MD

causing hoarseness. Such invasion and damage are infrequent, however. "Most nodules are incidental discoveries," notes Diana S. Dean, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, "and now many more such nodules are discovered because of the increased use of imaging performed for other reasons, including carotid ultrasonography, neck or chest computed tomography, magnetic resonance imaging, and even positron emission tomography."

"Diagnosing a thyroid nodule accurately and promptly is important," says Melanie L. Richards, MD, of the Department of Surgery at Mayo Clinic in Rochester, Minnesota, "because early diagnosis improves the likelihood that a cancer can be discovered while still contained within the thyroid gland and amenable to surgery. Once soft tissue invasion has occurred or lymph nodes are extensively involved, the chance of surgical cure drops substantially and there is a much higher incidence of metastatic spread of these late-stage cancers."

Prompt diagnosis is also important for the patient because the finding of a nodule often raises fears about cancer and a delay to diagnosis fuels the concern and anxiety. "The most recent



Figure 1. Palpation of the thyroid gland.

set of guidelines from the American Thyroid Association, published last year, specifies that the evaluation of a thyroid nodule should include clinical assessment to determine the number, size, and location of all nodules within the gland; measurement of serum thyrotropin (TSH) to exclude hyperthyroidism; an ultrasound to assess the nodule for features

of malignancy; and fine-needle aspiration (FNA) of nodules that meet the appropriate size and ultrasound criteria," says Bryan McIver, MB ChB, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota. However, he goes on to say, "not every nodule needs to be biopsied, so the clinical scenario and ultrasound features are important in selecting the appropriate nodule for biopsy."

Typically, these steps involve several appointments for the patient and often take a number of days. "Given the small number of steps involved," says Dr McIver, "it seemed sensible to develop a coordinated approach to meet the needs of these patients so that their entire assessment could be provided at a single visit to the clinic. To streamline the evaluation, we created the Thyroid Nodule Clinic, at which patients with thyroid nodules can have their assessment completed at a single visit."

Opened in July 2009, the Thyroid Nodule Clinic provides a 1-stop thyroid nodule evaluation that includes a focused clinical assessment, ultrasound evaluation, and FNA—all typically performed within a 60-minute appointment. "The ultrasound allows us to select both palpable and impalpable nodules for biopsy and target the most suspicious nodule, which is not always the largest nodule," says Dr Dean. "Using ultrasound guidance for those biopsies, we have improved our diagnostic yield dramatically. We perform more than 600 biopsies per year in this way and can now expect a clear diagnosis in more than 95% of cases at the first attempt."

Furthermore, because of the coordinated assessment provided through the Thyroid Nodule Clinic, FNA results are typically available within 2 hours, so the patient usually receives a definitive result of the entire assessment within 4 hours.

Dr McIver says: "For most patients referred



Figure 2. *Ultrasound-guided fine-needle aspiration of a thyroid nodule.*

with a thyroid nodule, the Thyroid Nodule Clinic provides coordinated care, a thorough assessment, and a definitive result, all in the space of a morning. Patients with a benign nodule can be reassured, and those with a malignant or suspicious nodule can be offered an appropriate surgical referral, often within 24 hours. We believe that the Thyroid Nodule Clinic improves our care of these patients while lowering costs, improving efficiency, and providing a better service to the referring physician."

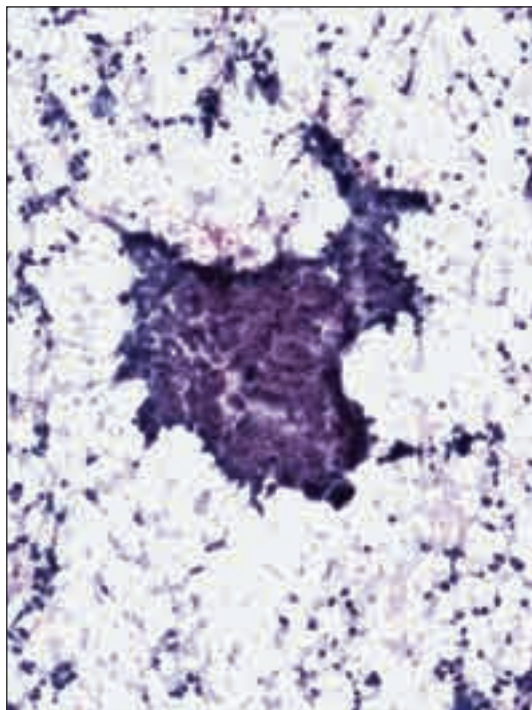


Figure 3. *Thyroid cytology of a specimen of papillary thyroid carcinoma showing papillary architecture and nuclear enlargement with crowding of classic papillary thyroid cancer (Papanicolaou stain, original magnification $\times 100$).*

Graves' Ophthalmopathy

On conservative clinical grounds alone (eyelid signs not included), Graves' ophthalmopathy (GO) can be identified in 25% of unselected patients with Graves' disease. However, with detailed orbit imaging (computed tomography, magnetic resonance imaging, or ultrasonography), up to 90% of patients with Graves' disease have evidence of ocular involvement.

Rebecca S. Bahn, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Fortunately, less than 5% of patients with Graves' disease have severe GO. The natural history of GO is characterized by progression over 3 to 6 months followed by a plateau phase lasting months to years. Active inflammation underscores both of these phases, and as the inflammation resolves, a third phase of gradual, but incomplete, improvement occurs. Overall, 66% of untreated patients with mild-to-moderate GO show spontaneous improvement over a 12-month period, while about 10% of untreated patients have deteriorating GO. Several risk factors for GO have become evident. A striking association between cigarette smoking and GO has been noted consistently in clinical studies, and it applies both to active and passive smoking. In addition, smoking has been shown to be associated with progression of eye disease after radioiodine therapy and to adversely influence the course of GO during treatment with corticosteroids and orbital radiotherapy."

Hyperthyroidism Treatment

Another important factor in prevention of development or progression of GO appears to be early and effective control of thyroid dysfunction. In most cases, the treatment method for hyperthyroidism is of secondary importance to restoring euthyroidism quickly and effectively and maintaining the euthyroid state. Marius N. Stan, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, advises: "In patients with active inflammation and mild GO, sodium iodide I 131 (^{131}I) therapy with or without corticosteroid use, antithyroid drugs, and thyroidectomy are



James A. Garrity, MD, Rebecca S. Bahn, MD, and Marius N. Stan, MD

all acceptable modes of treatment—provided an assessment of the risk-benefit ratio of concurrent corticosteroid therapy is made for those patients choosing radioiodine therapy. In cigarette smokers and other patients at increased risk for GO or ophthalmic deterioration, the risk-benefit ratio would likely favor the use of corticosteroids. Besides smoking, other risk factors to be considered include a high titer of thyrotropin receptor antibodies, recent GO progression, and high triiodothyronine levels. The equivalent of a daily prednisone dose of 0.5 mg/kg beginning the day after radioiodine therapy and tapering over 6 to 12 weeks is generally used for prophylaxis against the development of GO. However, when GO is severe and remains active, it is probably best that ^{131}I therapy be avoided and that antithyroid drugs or thyroidectomy be chosen as the treatment of hyperthyroidism. In all patients with GO or at risk for its development, hypothyroidism is to be avoided, and frequent monitoring of thyroid status (eg, every 2 weeks starting at 6 weeks after the therapeutic dose of ^{131}I) is important in the initial phases of treatment, when changes in thyroid status are expected."

Ophthalmopathy Treatment

Management of GO requires a carefully integrated approach involving endocrinologists and ophthalmologists with expertise in the condition and other experts of particular specialties (eg, otorhinolaryngology, radiation oncology, neurosurgery, dermatology, psychiatry) in consultation, with the goal of preserving the patient's vision and restoring favorable self-perception and quality of life. Determining the appropriate treatment of patients with GO rests on assessing whether the eye disease is active (inflammatory) or



Figure 1. The ophthalmologic findings in this patient with active inflammatory Graves' ophthalmopathy would likely respond to corticosteroid therapy.

inactive (quiescent) and defining the severity of the ocular symptoms.

James A. Garrity, MD, of the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota, explains: "Most patients with GO have a self-limited and mild disease course and require only local measures for symptomatic relief. These patients have modest periorbital and eyelid edema, intermittent diplopia, photophobia, and a sensation of mild ocular irritation or dryness. Symptoms resulting from corneal drying are effectively treated with instillation of artificial tear eye drops during the day and use of artificial tear ointment at night, along with taping the eyelids shut if they do not close completely during sleep. Elevating the head of bed may help improve GO-dependent edema, which can lead to increased soft tissue changes or temporary worsening of diplopia. The use of sunglasses or tinted lenses may assist in decreasing photophobia. In a dusty or windy environment, lateral shields or goggles can be used to avoid corneal irritation. Occasionally, prisms are useful for the correction of mild diplopia."

Patients with active and moderate-to-severe GO may have severe periorbital edema, exophthalmos, eye pain, changes in visual acuity or color vision, or severe restriction of ocular motion (Figure 1). Dr Bahn advises: "These patients should be assessed by an ophthalmologist to determine whether they require emergent treatment of compressive optic neuropathy or corneal ulceration. If no early surgical intervention is needed, the patient may benefit from a course of immunosuppressive therapy. Although oral corticosteroids have been shown to be effective in approximately 66% of patients with active GO, evidence is mounting that intravenous corticosteroids may be somewhat more effective in providing relief from pain, conjunctival edema, and swelling and in rendering the disease inactive. Some medical centers use orbital radiotherapy either alone or in combination with corticosteroids, which may be of benefit to patients with active GO, especially those with extraocular muscle dysfunction. Currently, we are recruiting

patients with active, moderate-to-severe GO for a randomized clinical trial to determine the effectiveness of rituximab, an immunosuppressive monoclonal antibody targeting B cells, in these patients. Rituximab has been used successfully in the treatment of rheumatoid arthritis and other autoimmune conditions."

Dr Garrity adds: "Orbital decompression surgery is generally considered for patients with GO who have excessive or disfiguring exophthalmos, orbital congestion, optic neuropathy, or corticosteroid dependency [Figure 2]. Patients with active disease who have shown intolerance or insufficient response to immunosuppressive therapy or have debilitating retrobulbar or periorbital pain may also benefit from decompression surgery. Optic neuropathy is our most common indication for orbital decompression. The orbit is decompressed surgically by removing 1 or more of its bony walls, a procedure that expands the eye socket and increases the potential space for orbital contents. In general, thyroid hormone levels should be restored to reference range before any type of orbital surgery is performed, except when severe GO threatens vision and requires urgent orbital decompression."

Dr Garrity continues: "Typically, eye muscle surgery (strabismus surgery) is performed after decompression surgery if the patient has diplopia postoperatively. In patients not requiring decompression, strabismus surgery may be performed after at least 6 months of stable eye deviation measurements without concurrent corticosteroid therapy. The goal of strabismus surgery is single vision in primary gaze and the reading position; diplopia with deviant gaze may persist after surgery. Eyelid surgery for GO usually follows orbital decompression and strabismus procedures, if either or both are needed. Upper-lid retraction is relieved by weakening (recessing) the muscles; lower-lid retraction is treated with analogous procedures, although since it is an antigravity lid, spacers are often required."



Figure 2. Graves' ophthalmopathy in this patient is inactive and associated with extreme proptosis, lid retraction, and extraocular muscle dysfunction. She would likely benefit from orbital decompression surgery followed by extraocular muscle and eyelid surgery.

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CME Opportunities

13th Mayo Clinic Endocrine Course

July 14-17, 2010, Rochester, Minnesota

This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders.

For more information about this course, please call

800-323-2688 or visit www.mayo.edu/cme

/endocrinology.html.



Mayo Clinic Nutrition and Wellness in Health and Disease

November 4-5, 2010, San Francisco, California

This course—designed for physicians, nurse practitioners, physician assistants, dietitians, and health and wellness staff—will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory setting. An additional course objective is to discuss wellness programs that include nutrition, activity, and other lifestyle behaviors. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

Recognition



2010 Graduating Clinical Endocrinology Fellow

Denise Bargsten education program coordinator, Rachel P. Espiritu, MD, whose upcoming appointment is at Summa Health System, Akron, Ohio, and Neena Natt, MD, Program Director, Clinical Fellowship in Endocrinology, Diabetes, Metabolism, and Nutrition.

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