Significant advancements in medicine have prolonged the human life span in developed countries, leading to a dramatic increase in the older adult population. James L. Kirkland, M.D., Ph.D., with General Internal Medicine and Endocrinology, Diabetes, Metabolism, & Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “This increased longevity, however, has contributed to the rise in incidence of age-associated diseases. Therefore, aging itself has been receiving more attention as the single greatest risk factor for the world’s most prevalent chronic diseases.

“To combat this challenge, the geroscience research community has focused on extending health span — without necessarily altering life span — by identifying interventions that promote healthy aging with the long-term goal of postponing the onset of chronic diseases, thereby reducing economic burden and improving quality of life.”

Joshua N. Farr, Ph.D., with Endocrinology, Diabetes, Metabolism, & Nutrition at Mayo Clinic in Minnesota, explains: “Because the onset of several chronic diseases and comorbidities, such as cardiovascular disease, diabetes, sarcopenia and osteoporosis, tends to occur concurrently in older adults, it has been hypothesized that aging is largely controlled by genetic pathways and fundamental mechanisms conserved in evolution. Therefore, it is crucial to define the specific biochemical and molecular processes that drive natural mammalian aging, so that these threats can be targeted to defend against age-related tissue dysfunction. Until recently, however, these processes have remained largely elusive, which has impeded the development of novel approaches to extend health span and delay or prevent multiple age-related diseases as a group.”

Although several hallmarks that represent common denominators of aging have been identified, cellular senescence, a cell fate that involves an essentially irreversible state of replicative arrest induced by various types of stress, has emerged as a promising fundamental aging mechanism that could be targeted to treat multiple diseases of aging simultaneously.

Indeed, as highlighted in an article published in 2017 in *EBioMedicine*, mounting evidence demonstrates that senescent cells accumulate in various tissues with aging, where they commonly develop a unique secretome of chemokines, cytokines and extracellular matrix degrading...
proteins, termed the senescence-associated secretory phenotype (SASP), that can actively damage the tissues in which senescent cells reside, causing natural aging phenotypes.

Dr. Kirkland highlights: “In addition, senescent cells are characterized by profound phenotypic alterations, including upregulation of the cell cycle inhibitors, p16ink4a (Cdkn2a) and p21 (Cdkn1a), increased metabolic activity, resistance to apoptosis, telomere shortening and decondensation of pericentromeric satellite DNA. There is now strong evidence in rodents that selective elimination of senescent cells or blocking the detrimental effects of the SASP improves cardiovascular function, enhances insulin sensitivity and reduces frailty.”

“In articles published in the 2016 Journal of Bone and Mineral Research and in 2017 in Nature Medicine, we reported that senescent cells accumulate with aging in the bone microenvironment, where they play a causal role in age-related bone loss. Osteoporosis, which is responsible for 2 million fractures and $19 billion in related costs every year, is characterized by decreased bone formation relative to resorption, resulting in compromised bone microarchitecture and increased risk of skeletal fractures.

“In recent studies in young versus old mice, we isolated various cell populations from the bone microenvironment, such as B cells, T cells, myeloid cells, osteoblast progenitors, osteoblasts and osteocytes. We then demonstrated that a subset of cells within each of these lineages becomes senescent with aging — although senescent osteocytes and senescent myeloid cells are the predominant culprits that produce the SASP.

“In subsequent studies in old mice, two different senolytic strategies were used to selectively kill senescent cells without affecting nonsenescent cells. These strategies included both a genetic and pharmacological approach, as well as a senomorphic approach, which blocked the pro-inflammatory effects of senescent cells using a JAK1/2 inhibitor. The studies have demonstrated that targeting senescent cells with each of these interventions for two to four months improved bone mass, microarchitecture and strength.

“Importantly, none of these interventions had any effect on bone parameters in young mice, demonstrating specificity of these approaches to aging. Comprehensive in vivo bone histomorphometry analyses revealed that targeting senescent cells led to reduced bone resorption with either maintained (within the trabecular skeletal compartment) or enhanced (along the endocortical bone surface) bone formation, demonstrating an overall anabolic effect. These findings were complemented by detailed mechanistic studies demonstrating specific factors in the SASP-impaired osteoblast mineralization, while simultaneously enhancing osteoclast progenitor survival.

“Intriguingly, elimination of senescent cells alleviated the osteoporosis-associated accumulation of fat in bone marrow, which in combination with the observed increase in osteoblasts, suggests that senescent cell elimination causes a lineage switch whereby bone marrow mesenchymal stem cells preferentially develop into osteoblasts as opposed to adipocytes. Therefore, with aging, senescent cells accumulate in the bone microenvironment where they promote osteoclastogenesis and inhibit osteoblastogenesis. Senolytic therapy eliminates senescent cells, which subsequently reduces bone resorption and either maintains (trabecular sites) or enhances (cortical sites) bone formation due to uncoupling between osteoclasts and osteoblasts (Figure, page 1). Collectively, these data establish a causal role for senescent cells in bone loss with aging, and reveal a novel therapeutic strategy to treat osteoporosis.”

Sundeep Khosla, M.D., with Endocrinology, Diabetes, Metabolism, & Nutrition at Mayo Clinic in Minnesota, concludes: “Although senolytic and senomorphic therapies are now being tested in human clinical studies and although they are effective when given intermittently in rodents, there are several challenges that remain. These challenges include the theoretical concern that eliminating senescent cells could interfere with the beneficial effects of these cells. Indeed, cellular senescence is not universally detrimental, but rather can have beneficial biological functions in certain contexts. For example, senescent cells through their SASP can attract immune cells to sites in need of tissue regeneration and wound healing. Therefore, because targeting senescent cells is a potentially transformational strategy to extend health span, future work is needed to establish the long-term efficacy and safety of this therapeutic paradigm.”
For more information


Thyroid Eye Disease Clinic — The Mayo Clinic Model

Graves’ orbitopathy (GO) — also known as Graves’ ophthalmopathy, thyroid-associated orbitopathy and thyroid eye disease — is an entity that requires multispecialty evaluation with involvement of endocrinologists, ophthalmologists and ENT surgeons for optimal management.

Marius N. Stan, M.D., with Endocrinology, Diabetes, Metabolism, & Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, explains: “Timing these evaluations closely together can be a challenge, as patients typically call in to schedule with only one provider. Given the expected fluctuations in the disease, having the evaluations scattered over weeks to months does not allow for a seamless collaboration between these physicians. This issue has been tackled by the European Group on Graves’ Orbitopathy (EUGOGO) and led to the establishment of multispecialty clinics dedicated to GO, where the patients are seen by both an endocrinologist and an ophthalmologist. A joint assessment is then made and an agreed upon management plan is devised. “We have expanded from that practice here at Mayo Clinic with the inclusion of an ENT surgeon and have created a clinic where the three specialties converge. Their individ-

**Figure 1.** Algorithm for assessing severity of Graves’ orbitopathy and treatment options. Abbreviations used: DON, dysthyroid optic neuropathy; GO, Graves’ orbitopathy; IVGC, intravenous glucocorticoid; and, XRT, external beam radiation therapy.

Marius N. Stan, M.D., Elizabeth A. Bradley, M.D., Janalee K. Stokken, M.D., and Erick D. Bothun, M.D.
ual evaluations are combined into one summary assessment and management plan. The patients are seen in the morning in individual consultations by each of the three physicians involved. They are then discussed at a noon conference where patients’ photographs and laboratory data are reviewed. We assess disease activity, severity and modifiable risk factors (Figure 1). A common plan of action is agreed upon and that is presented to the patient in a brief follow-up visit that same afternoon by the ophthalmologist and the endocrinologist.”

Elizabeth A. Bradley, M.D., an ophthalmologist at Mayo Clinic’s Minnesota campus, notes: “The ophthalmologic evaluation includes an assessment of the visual acuity, color vision, visual field and ocular motility. Patients also undergo a comprehensive examination of the eye, including the conjunctiva, cornea, optic nerve and retina. The external examination includes quantitative assessment of upper and lower eyelid position and exophthalmometry.”

Janalee K. Stokken, M.D., an otorhinolaryngologist at Mayo Clinic’s Minnesota campus, says: “I focus on discussing and performing endoscopic medial wall orbital decompressions when deemed necessary (Figure 2). This is a surgical procedure that can be performed in isolation or in combination with a lateral orbital decompression in conjunction with ophthalmology for moderate and severe disease. The main goal is to address significant proptosis or corneal exposure, optic neuropathy and, occasionally, persistent retro-orbital pain despite other therapies.

“The medial wall decompression is performed in a minimally invasive fashion utilizing endoscopic techniques similar to sinus surgery that avoids incisions in the mouth or on the face. Another benefit of the endoscopic approach is the ability to open the sinus cavities that can become obstructed from the decompression.”

Erick D. Bothun, M.D., a surgical ophthalmologist at Mayo Clinic’s Minnesota campus, shares: “Throughout patients’ disease course, they are evaluated by both an orbital surgeon and a strabismus (eye muscle) surgeon. The surgical teams discuss and tailor the approach for each individual patient to minimize or eliminate postoperative eye misalignment and double vision.”

Dr. Stan adds: “From the endocrine perspective, we assess the patients’ thyroid status, risk factors for GO progression, and the activity and severity of GO itself. We aim to restore euthyroidism expeditiously and, when needed, engage the support of our nicotine dependence counseling team. We classify GO activity using the clinical activity score and the severity based on EUGOGO guidelines with the categories of mild, moderate to severe, and sight threatening. If active GO is identified, anti-inflammatory and immunomodulatory therapy are discussed and the risks and benefits of such therapies are outlined.”

Dr. Stan highlights: “We conduct the clinic on a monthly basis. Patients have orthoptics, thyroid function tests, a TSH receptor antibody test and an orbital CT prescheduled for the same day. The latter is set for the afternoon, in the event surgical intervention is not planned. We also utilize the services of our Infusion Therapy Center; when the treatment is considered necessary, the first dose of intravenous methylprednisolone is administered the same day.

“We see the clinic as an effective way to have a multidisciplinary evaluation for GO patients in a timely manner that allows rapid decision-making and agreement between the specialties involved in the sequence of steps to be followed. We also see the educational benefit both for staff and for

Figure 2. Anatomic relationships of a medial wall orbital decompression, which can be performed in isolation or in combination with a lateral orbital decompression for moderate and severe disease.
A 34-year-old woman was referred for evaluation of ovarian enlargement and a pituitary mass. She had normal childhood development and regular menses until age 33, when her cycles became more frequent. She and her husband had been trying to conceive for approximately five years, but were unsuccessful.

Three months prior to her presentation at Mayo Clinic, the patient developed pelvic pain and evaluation revealed marked enlargement of her right ovary (10 cm) with 12 cysts and a serum estradiol of 1,790 pg/mL (reference range, 15 to 350 pg/mL). She underwent right oophorectomy, but developed recurrent pelvic pain six weeks later, prompting an ultrasound that showed a 4.6-cm cyst on the left ovary. She was treated with leuprolide 3.75 mg and 12 hours later her luteinizing hormone (LH) was 26.7 IU/L (reference range, 1.2 to 12.9 IU/L) and follicle-stimulating hormone (FSH) was 43.9 IU/L (reference range, 1.8 to 8.8 IU/L). Two days after receiving leuprolide, the patient developed a severe headache associated with photophobia and vomiting. Head MRI showed a sellar mass (4.7 by 5.1 by 3.7 cm) extending into the suprasellar cistern, cavernous sinuses, clivus and sphenoid sinus (Figure 1, panels A and B).

On examination at Mayo Clinic, the patient appeared well, but had a palpable mass in her lower abdomen. Laboratory evaluation showed the following: serum estradiol, 3,740 pg/mL; LH, 36 IU/L; FSH, 38.7 IU/L; prolactin, 115 ng/mL (reference range, 4.8 to 23.3 ng/mL); and normal blood concentrations of cortisol, insulin-like growth factor-I, testosterone, thyroid-stimulating hormone (TSH), free T4 and beta-human chorionic gonadotropin (βHCG). Pelvic ultrasound revealed a markedly enlarged left ovary with innumerable hemorrhagic cysts (Figure 2, panel A, see page 6).

The patient underwent transsphenoidal surgical debulking of the pituitary tumor without complications. Immunohistochemistry findings were consistent with a gonadotroph adenoma, staining weakly for LH alpha-subunit, and FSH beta-subunit, and strongly for chromogranin. The Ki-67 labeling index was less than 2 percent. Laboratory studies the day after surgery showed the following: LH, 6.8 IU/L; FSH, 10.5 IU/L; and estradiol, 2,190 pg/mL.

During the first postoperative month, LH and FSH remained normal, but estradiol fluctuated between 2,000 and 4,000 pg/mL as the patient’s left ovary decreased in size. At 1.5 months post-surgery, estradiol normalized to 19 pg/mL with LH equal to 1.9 IU/L and FSH equal

Figure 1. Head MRI scan. A. Coronal image showing pituitary macroadenoma (large arrows) extending into the suprasellar cistern, elevating the optic chiasm (small arrows), and involving sphenoid sinus and both cavernous sinuses. B. Sagittal image showing extension into the clivus (arrow). C. Three-month post-surgery head MRI coronal image shows debulking of the pituitary macroadenoma, visible pituitary stalk (small arrow), and residual tumor in the left cavernous sinus (large arrow). D. Three-month postoperative sagittal MRI shows a secondary empty sella and a normal pituitary stalk (small arrow).
to 2.8 IU/L. Three months after surgery, the patient had return of menses and pelvic ultrasound showed marked reduction in ovarian size (Figure 2, panel B). Head MRI showed debulking of the pituitary macroadenoma with residual tumor in the left cavernous sinus (Figure 1, panels C and D, see page 5).

Because the residual tumor was in close proximity to the left optic nerve, the patient was not a candidate for stereotactic radiotherapy. She received fractionated radiation to prevent future tumor growth; six months later, she became pregnant.

This case illustrates the clinical course of a functioning gonadotroph adenoma causing ovarian hyperstimulation. As described in a review published in the Journal of Clinical Endocrinology and Metabolism in 2014, functional gonadotroph adenomas are rare pituitary tumors that secrete biologically active gonadotropins and cause distinct clinical manifestations. Premenopausal women may experience menstrual irregularities, infertility, galactorrhea, headaches, visual disturbances from mass effect and ovarian hyperstimulation.

Laboratory findings include hyperestrogenism (which may range from mild to marked), elevated or inappropriately normal FSH, variable LH levels, and hyperprolactinemia due to pituitary stalk compression or elevated estradiol levels. When ovarian hyperstimulation occurs, pelvic ultrasound demonstrates bilateral ovarian enlargement with multiseptated cysts of variable sizes.

Most of the reported functioning gonadotroph adenomas have been macroadenomas, often invading the cavernous sinuses and distorting the optic chiasm due to suprasellar extension. These rare pituitary adenomas have also been reported in men, sometimes causing testicular enlargement, and rarely in children, causing precocious puberty.

Like other nonprolactinoma pituitary adenomas, surgery is the mainstay of therapy for functioning gonadotroph adenomas. If successful, surgery may lead to normalization of gonadotropin secretion and resolution of symptoms, but surgery alone may not be curative for the larger, more-invasive tumors. Residual tumor has been treated with radiotherapy in some cases, but long-term follow-up data evaluating efficacy are lacking.

Several medical therapies, including dopamine agonists, somatostatin analogues, and Gn-RH agonists and antagonists have been used, but none of these has been associated with tumor shrinkage. While dopamine agonists and somatostatin analogues have decreased ovarian volumes and gonadotropin secretion in a limited number of cases, Gn-RH antagonists have been associated with mixed results, and Gn-RH agonists have led to increased gonadotropin secretion and exacerbation of ovarian hyperstimulation syndrome.

While there is little long-term data to guide ongoing management of our patient, we plan on monitoring for tumor regrowth on an annual basis.

For more information
Research Corner: Anaplastic Thyroid Cancer

Anaplastic thyroid cancer is a universally fatal form of advanced thyroid cancer. It is characterized by a rapidly growing neck mass and requires treatment in an emergent fashion. Multimodality treatment that combines surgery when feasible with intensity-modulated radiation therapy and chemotherapy has emerged as the most appropriate treatment for this devastating cancer. Unfortunately, most patients still succumb to the disease, and median survival is around three to six months. Therefore, new treatment options are sorely needed.

In the last few years, immunotherapy with anti-programmed death-1 (PD-1) antibody has emerged as another effective option against many cancers, including melanoma, lung cancer, and head and neck cancers. These agents are more effective in cancers that carry a high burden of mutations or high expression of programmed death-ligand 1 (PD-L1); both have been shown to be present in anaplastic thyroid cancer.

On the basis of these studies, Mayo Clinic has initiated a clinical trial incorporating pembrolizumab, an anti-PD-1 antibody, with multimodal treatment for patients with anaplastic thyroid cancer. This is a phase II trial with a target of 20 patients to be enrolled. All treatments, including surgery, radiation therapy, chemotherapy, and infusions of the study drug pembrolizumab, will be performed at the study center at Mayo Clinic’s campus in Rochester, Minnesota. Patients will need biopsy-proven diagnosis of anaplastic thyroid cancer and should not have undergone complete surgical resection.

Inclusion criteria include:
- Age older than 18 years
- Biopsy-proven diagnosis of anaplastic thyroid cancer (squamous or sarcomatoid differentiation also is acceptable)
- Eastern cooperative group performance status of 0-1
- Willingness to be treated at the study center

Exclusion criteria: Autoimmune diseases including pneumonitis, human immunodeficiency virus infection, hepatitis B or C, brain metastasis, or prior neck radiation precluding curative doses of radiation therapy.

For more information
Clinical trials: Pembrolizumab, Chemotherapy, and Radiation Therapy With or Without Surgery in Treating Patients With Anaplastic Thyroid Cancer. Mayo Clinic.

To refer a patient for this trial, contact a member of the endocrine oncology care team — Ashish V. Chintakuntlawar, M.B.B.S., Ph.D., principal investigator, Keith C. Bible, M.D., Ph.D., John C. Morris III, M.D., or Mabel Ryder, M.D., at 507-293-0552, or email chintakuntlawar.ashish@mayo.edu.
Education Opportunities

18th Annual Nutrition and Wellness in Health and Disease 2018
Sept. 27-28, 2018, at Marriott San Antonio Riverwalk, San Antonio

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 will 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 will 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 https://ce.mayo.edu/ internal-medicine/content/18th-annual-nutrition-and-wellness-health-and-disease-2018 or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME

21st Annual Endocrine Update 2019
Feb. 11-15, 2019, at Fairmont Orchid, Kohala Coast, Big Island, Hawaii

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/internal-medicine/content/21st-annual-endocrine-update-2019 or call 800-323-2688 (toll-free).