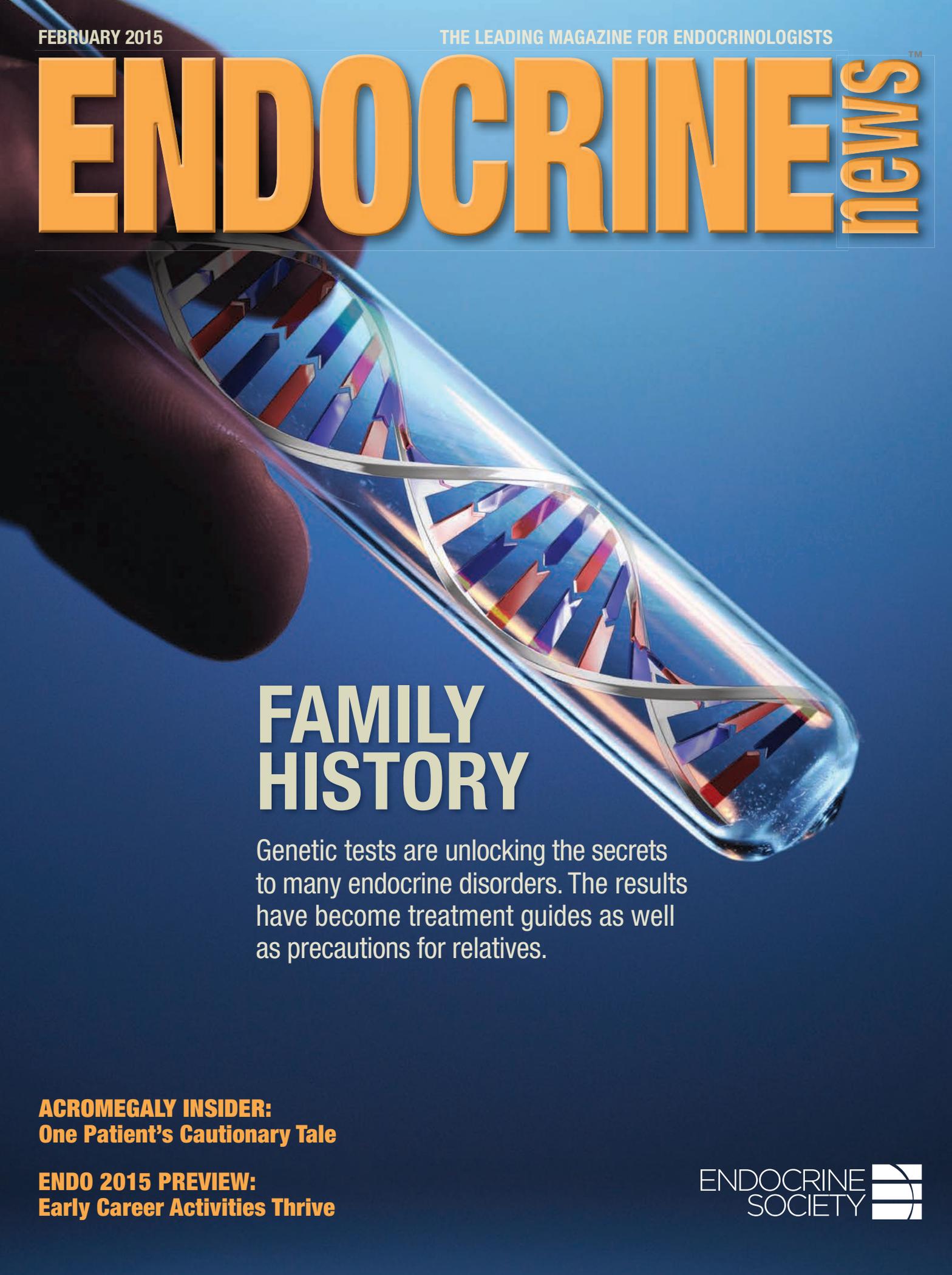


FEBRUARY 2015

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINETMnews



FAMILY HISTORY

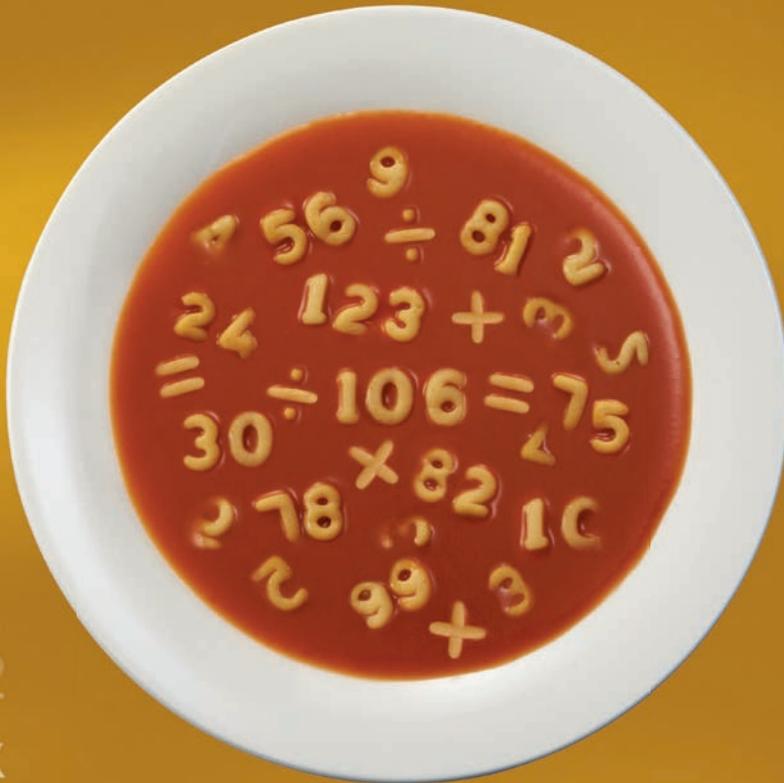
Genetic tests are unlocking the secrets to many endocrine disorders. The results have become treatment guides as well as precautions for relatives.

ACROMEGALY INSIDER:
One Patient's Cautionary Tale

ENDO 2015 PREVIEW:
Early Career Activities Thrive

ENDOCRINE
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Advances in genetic testing have been crucial to discovering the underlying causes of many endocrine disorders. These tests not only act as a guide to treatment but also as a precaution for family members.

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When radio personality Froggy was diagnosed with acromegaly 10 years ago, he made it his personal mission to educate the public — as well as primary care physicians — on this rare and unexpected disease.

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By Robin L. Davisson, PhD, Jenny L. Sones, DVM, PhD, Ravi I. Thadhani, MD, MPH, and Ellen W. Seely, MD

Two basic science researchers, a clinical researcher, and a physician-in-practice shed light on this poorly understood condition that poses great health risks for both pregnant mothers and their unborn children.

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The decision to go from your own practice to working for a group or a hospital requires thought and planning...and preparing for the worst.

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The Endocrine Society Spent the Past Year Spanning the World



Richard J. Santen, MD

Over the past few years the Endocrine Society has gradually expanded its influence and profile worldwide. We have been engaged in a number of international activities and outreach programs and collaborated with several organizations around the world. From my perspective, this has truly been a banner year. To highlight this, I will briefly review some of this year's activities and collaborations.

Ambassador Exchange Program: Year 3

This is the third year of the Ambassador Exchange Program initiative conceived by Past President William Young. In this year's exchange, the participating organizations are the University Medical Center HCMC in Ho Chi Minh City, Vietnam, and the University of California — San Francisco (UCSF). This exchange, as with the previous ones, will prove to be an invaluable experience for the trainees and their mentors to observe how national, ethnic, economic, and cultural factors shape endocrine care.

Highlights of ENDO

There were three Highlights of ENDO programs this year: the first one in Seoul, South Korea, held in May in conjunction with the Korean Endocrine Society's national meeting; the second in Curitiba, Brazil, in September at the Brazilian Society of Endocrinology and Metabolism Congress; and the third one in Cordoba, Argentina, in October during the Congress of the Argentinean Federation of Endocrine Societies. These meetings attracted a large number of attendees who expressed how much they benefitted from the information presented. Importantly, we recruited new members from the host countries to the Endocrine Society and created new interest and awareness of the Society's programs and services. The interpersonal relationships established between our speakers and the leaders of these organizations should yield many benefits over the years.

International Collaborations

We have established several collaborations with international societies, all resulting in very productive and well-attended activities. The Endo-Bridge program, hosted by the Society of Endocrinology and Metabolism of Turkey (SEMT) in conjunction with the European Society of Endocrinology (ESE) and the Endocrine Society, was held for the second year in October. The third Endo-Bridge is already scheduled for October 15–18, 2015 in Antalya, Turkey.

The International Clinical Update program in

Endocrinology (ICUE) in India was organized as a collaborative effort between the Endocrine Society of India (ESI), the International Society of Endocrinology (ISE), the Society for Endocrinology (UK) and the Endocrine Society (USA). This collaboration brought together four of the world's most dynamic endocrine societies, to share evidence and experience, and to improve the science of endocrinology in India.

The Society has participated at other international societies' meetings such as the Chinese Society of Endocrinology in August, the Peruvian Society of Endocrinology in October; the 19th Annual Scientific Conference of the Egyptian Association of Endocrinology, Diabetes, and Atherosclerosis (EAEDA) that was held in Alexandria, Egypt, in November; and the Mexican Society of Nutrition and Endocrinology in December.

In 2015, the Endocrine Society will be participating in several international meetings in Greece, Mexico, Spain, and Brazil, to name a few of the locations that have been confirmed.

Leadership Role in EDCs

Although this topic deserves its own President's Viewpoint to cover all the work that has been done in this area, I would be remiss if I didn't mention the Endocrine Society's leadership role in the endocrine-disrupting chemicals (EDCs) area, which started with the development of a Scientific Statement in 2009. Since then, the Society has participated in European Union Commission meetings on EDCs and has been fully engaged in advocacy and policy work related to EDCs in the U.S. and Europe. This is an area that will require further attention and action from the international endocrine community and the Endocrine Society will continue to lead the way in this area.

Throughout the past several years, our progress on the international scene has been a major success for the Society. As Thomas Friedman articulated so well in his book, *The World is Flat*, technology has opened up our ability to extend our reach worldwide, and we as a Society have recognized that. From the long-term perspective, this should result in improving endocrine science and patient care worldwide. Feel free to contact me at president@endocrine.org if you have any questions or comments. **EN**

Richard J. Santen, MD
President, Endocrine Society

FEBRUARY 2015

ENDOCRINE news

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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Endocrine News informs and engages the global endocrine community by delivering timely, accurate, and trusted content covering the practice, research, and profession of endocrinology.

The mission of the *Endocrine Society* is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

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www.cadmus.com

Endocrine News is published 12 times a year by the Endocrine Society, 2055 L Street, NW, Suite 600, Washington, DC 20036
Phone 202-971-3636 • Fax 202-736-9708
www.endocrine.org

Print ISSN 2157-2089 Online ISSN 2157-2097
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Family truly is the tie that binds in so many ways. And nowhere is that adage more relevant than in the discussion of family history, genetics, inherited traits, and so on. In this month's cover story, "Family History" (p. 9), Eric Seaborg takes a look at how advances in genetic testing have been vital in discovering some of the underlying causes of a variety of endocrine disorders. Seaborg writes that genetic tests can reveal the "inheritable component of a patient's condition and can change the approach to treatment.

The patient's family can also benefit from this knowledge — or in some cases provide important information about a mutation's actual effects."

Associate editor Derek Bagley has authored an interesting and personal account of one man's battle with the exceedingly rare disorder acromegaly. In "Straight Talk" on page 12, Bagley details radio personality Froggy's ordeal with this disorder and how he's using his name recognition to raise awareness. The Society's Hormone Health Network has partnered with Froggy and Novartis for the Straight Talk Acromegaly campaign to help spread the word about this condition. "Once you've come so far," Froggy tells Bagley, "the key is to be your own advocate. No one knows your body better than you do." By the way, this feature is somewhat of a departure from the typical *Endocrine News* article, but prepare to see more of these in the future. It's important to understand what patients go through in dealing with their endocrine disorders so that there can be "learning moments" gleaned from their — and their doctors' — experiences.

According to Kurt Ullman's article, "Team Spirit" (page 26), the business of medicine is something that a lot of physicians really don't want to worry about. That's why some doctors are giving up their private practices and joining a larger group or even a hospital. While there are a lot of pros and cons to both practice settings, Mary Witt, senior vice president for the Camden Group, a consulting firm in El Segundo, Calif., sums it up: "The complexities of running a medical practice have increased while reimbursements are going down and expenses trending up. Many doctors are wondering if it wouldn't be best just to become an employee and focus on taking care of patients."

Hopefully, by the time you receive this issue you've already made your travel plans for **ENDO 2015** in San Diego March 5 – 8. Go to www.endo2015.com to register now if you haven't already. See you in sunny San Diego! **EN**

Mark A. Newman,
Editor, *Endocrine News*



Mark A. Newman

By Derek Bagley

New Drug Approved to Treat **GEP-NETs**

The U.S. Food and Drug Administration recently approved a drug called Somatuline® Depot® (lanreotide) Injection 120mg for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adult patients with unresectable, well- or moderately differentiated, locally advanced, or metastatic disease to improve progression-free survival.

GEP-NETs are a rare type of cancer, affecting about five in 100,000 people in the U.S., but the prevalence of GEP-NETs has increased four- to six-fold in the last 30 years. Compounding the problem is the fact that it takes at least five years to accurately diagnose GEP-NETs (the cancer is often misdiagnosed as irritable bowel syndrome or Crohn's disease), meaning the disease is already in the

advances stages, leading to poor prognoses.

The approval of Somatuline was based on a 96-week registrational Phase III, double-blind, placebo-controlled study (CLARINET®) of 204 GEP-NETs patients enrolled in 48 centers across 14 countries.

Researchers led by Alexandria Phan, MD, director of GI Medical Oncology at Houston Methodist, found that the drug reduced the risk of disease progression or death by 53% versus placebo and published their findings in the *New England Journal of Medicine*.

“Somatuline is the first somatostatin analog to demonstrate a statistically significant improvement in progression-free survival, a clinically significant endpoint in oncology that measures how long the patient continues to live with the disease without it getting any worse,” says Phan. “Somatuline offers a new weapon in our fight against this deadly disease.”



Novel Drug “Tricks” **Body Into Weight Loss**

Researchers at the Salk Institute for Biological Studies have developed a novel drug that “tricks” the body into thinking it has consumed calories, causing the body to begin browning white fat and lose weight, according to a study recently published in *Nature Medicine*.

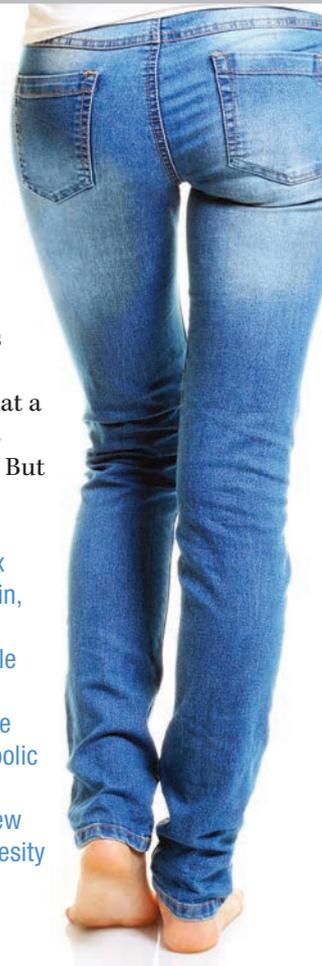
The team, led by Michael Downes, PhD, and Ronald M. Evans, PhD, noted that bile acid released during a meal selectively activates the intestinal farnesoid X receptor (FXR) and that by “mimicking this tissue-selective effect, the gut-restricted FXR agonist fexaramine (Fex) robustly induces enteric fibroblast growth factor 15 (FGF15), leading to alterations in bile acid composition, but does so without activating FXR target genes in the liver.”

Fex was tested in 200 obese mice that were given the drug in solution form daily for five weeks. The team observed that the mice stopped gaining weight, lost fat, and lowered their blood sugar and cholesterol levels more than untreated mice. And since the pill is taken orally,

it only works in the gut, never entering the bloodstream.

“This pill is like an imaginary meal,” Evans said in an Institute statement. “It sends out the same signals that normally happen when you eat a lot of food, so the body starts clearing out space to store it. But there are no calories and no change in appetite.”

The authors concluded that “Fex reduces diet-induced weight gain, body-wide inflammation, and hepatic glucose production, while enhancing thermogenesis and browning of white adipose tissue (WAT). These pronounced metabolic improvements suggest tissue-restricted FXR activation as a new approach in the treatment of obesity and metabolic syndrome.”



Early-Pregnancy Hyperthyroidism and High-Normal FT4 Linked to Hypertensive Disorders

Biochemical hyperthyroidism and high-normal levels of free T4 (FT4) during early pregnancy are associated with an increased risk of hypertensive disorders, according to research recently published in *The Journal of Clinical Endocrinology & Metabolism*.

Hypertensive disorders can cause a wide range of maternal and fetal complications, including renal failure, disseminated intravascular coagulation, cerebrovascular bleeding, intrauterine growth retardation, abruptio placentae, premature delivery, and stillbirths. The disorders affect 2% – 8% of expecting mothers, but few risk factors are known.

So the authors of the study, led by Marco Medici, MD, PhD, and Tim Korevaar, a PhD student, both of the Erasmus Medical Center in Rotterdam, The Netherlands, looked at the

associations between thyroid function within the normal range, thyroid dysfunction, thyroid autoimmunity, and blood pressure (BP) as well as the risk of hypertensive disorders during pregnancy. They analyzed 5,153 Dutch women in early pregnancy with a delivery date between April 2002 and January 2006. The team measured serum TSH, FT4, and thyroperoxidase antibody (TPOAb) levels, as well as mean blood pressures and hypertensive disorders, including pregnancy-induced hypertension (n = 209) and preeclampsia (n = 136).

The scientists found that hyperthyroid mothers had a higher risk of hypertensive disorders [odds ratio (OR) 3.40 [95% confidence interval (CI) 1.46–7.91], p = .005], which was mainly due to an increased risk of

pregnancy-induced hypertension [OR 4.18 (95% CI 1.57–11.1), p = .004]. Within the normal range, high-normal FT4 levels were also associated with an increased risk of hypertensive disorders [OR 1.62 (95% CI 1.06–2.47), p = .03], which was mainly due to an increased risk of preeclampsia [OR 2.06 (95% CI 1.04–4.08), p = .04].

The authors concluded that “hyperthyroidism and also high-normal FT4 levels during the early pregnancy are risk factors for the development of hypertensive disorders. These data demonstrate that even mild variation in thyroid function within the normal range can have such effects.” However, they noted that since there are only a few large studies with data on potential confounders, their results should be “replicated in an independent population.”



GLP-1 May Benefit Heart After Myocardial Infarction

The metabolic hormone glucagon-like peptide 1 (GLP-1) may help the heart heal after a myocardial infarction, according to research published in *Endocrinology* last month.

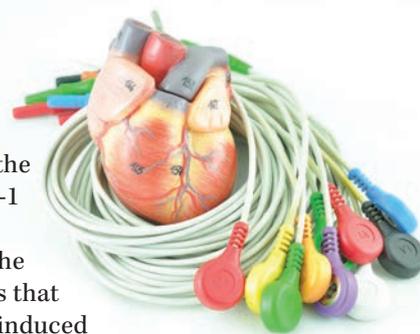
Investigators led by Aleksander Hinek, MD, PhD, DSc, of the Hospital for Sick Children in Ontario, Canada, noted that GLP-1 has been shown to have some “cardioprotective effects and facilitates functional recovery after myocardial infarction through GLP-1 receptor-mediated signaling in cardiomyocytes.” The antidiabetic hormone has also been demonstrated to produce long-term, sustained improvements in cardiac function. However, the reasons for these remain unclear.

Hinek and his team hypothesized that there is a possible interaction among GLP-1 and cardiac fibroblasts, which remodel the heart after a myocardial infarction, because they are less susceptible to ischemia than cardiomyocytes. “[The cardiac fibroblasts’] proliferation and production of a new extracellularmatrix (ECM) are crucial steps in the functional adaptation of the damaged myocardium,” the authors write.

The researchers treated cultures of human cardiac fibroblasts in vitro with GLP-1 peptides and found that those cultures “display a selective up-regulation in elastin gene expression and a consequent increase in elastic fibers production,

in the absence of the classic GLP-1 receptor.” Moreover, the study shows that this GLP-1-induced elastogenesis is triggered through the cross-activation of the IGF-1 receptor, rather than the GLP-1 receptor.

“Because GLP-1 does not stimulate deposition of collagen I,” the authors conclude, “nor promote the proliferation or apoptosis of cultured cardiac fibroblasts, we speculate that its elastogenic effect may also contribute to the beneficial remodeling of the human heart after myocardial infarction.”



BPA Exposure during Pregnancy Linked to Oxidative Damage in Infants



Exposure to bisphenol A (BPA) during pregnancy can cause oxidative damage that may put the baby at risk of developing diabetes or heart disease later in life, according to a new study published in *Endocrinology*.

Researchers led by Vasantha Padmanabhan, MS, PhD, of the University of Michigan, analyzed blood samples from 24 mother and infant pairs to examine the effects of BPA exposure. The women had blood drawn during the first trimester of pregnancy to measure their BPA levels. The women were divided into two groups — those who had lower levels of BPA in their blood and those who had higher levels. The investigators also took blood samples

from the umbilical cords after the babies were delivered and measured the amount of chemical byproducts created by oxidative stress.

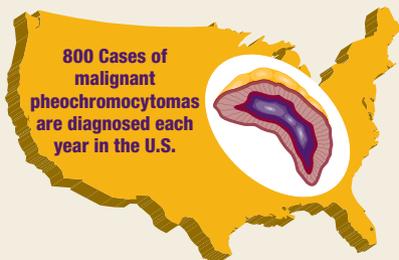
The blood analysis revealed that the mothers exposed to higher levels of BPA and their infants showed signs of oxidative stress caused by overexposure to nitric oxide-derived free radicals. The study participants had larger amounts of byproducts caused by this type of oxidative damage in their blood.

In addition to the human subjects, the researchers studied the effects of BPA on pregnancy in sheep, rats, and mice. The scientists fed the animals diets containing either high or low doses of BPA. They then measured the resulting oxidative stress on the mothers and their offspring using blood samples. The results corroborated the results in the human study.

“Whether or not BPA is harmful to human health has been vigorously debated,” Padmanabhan says. “These findings demonstrate that more studies like this one are needed to determine the disease risk of exposure to BPA. In the interim, these results indicate that pregnant women should minimize their exposure to BPA to safeguard their babies and themselves from oxidant injury.”

Fast FACTS

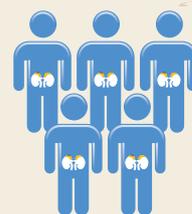
About Inherited Endocrine Disorders



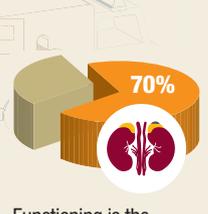
Resistance to thyroid hormone is found in one case per 40,000 births.



Familial occurrence of resistance to thyroid hormone has been documented in 75% of cases.



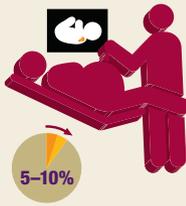
Adrenocortical cancer affects about 300 to 500 people each year in the U.S.



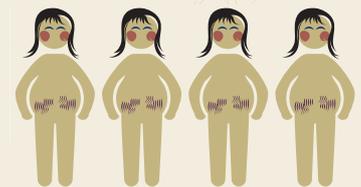
Functioning is the most common type of adrenocortical cancer, accounting for 70% of adrenal cancers



Genetic testing is available for more than 2,000 rare and common conditions.

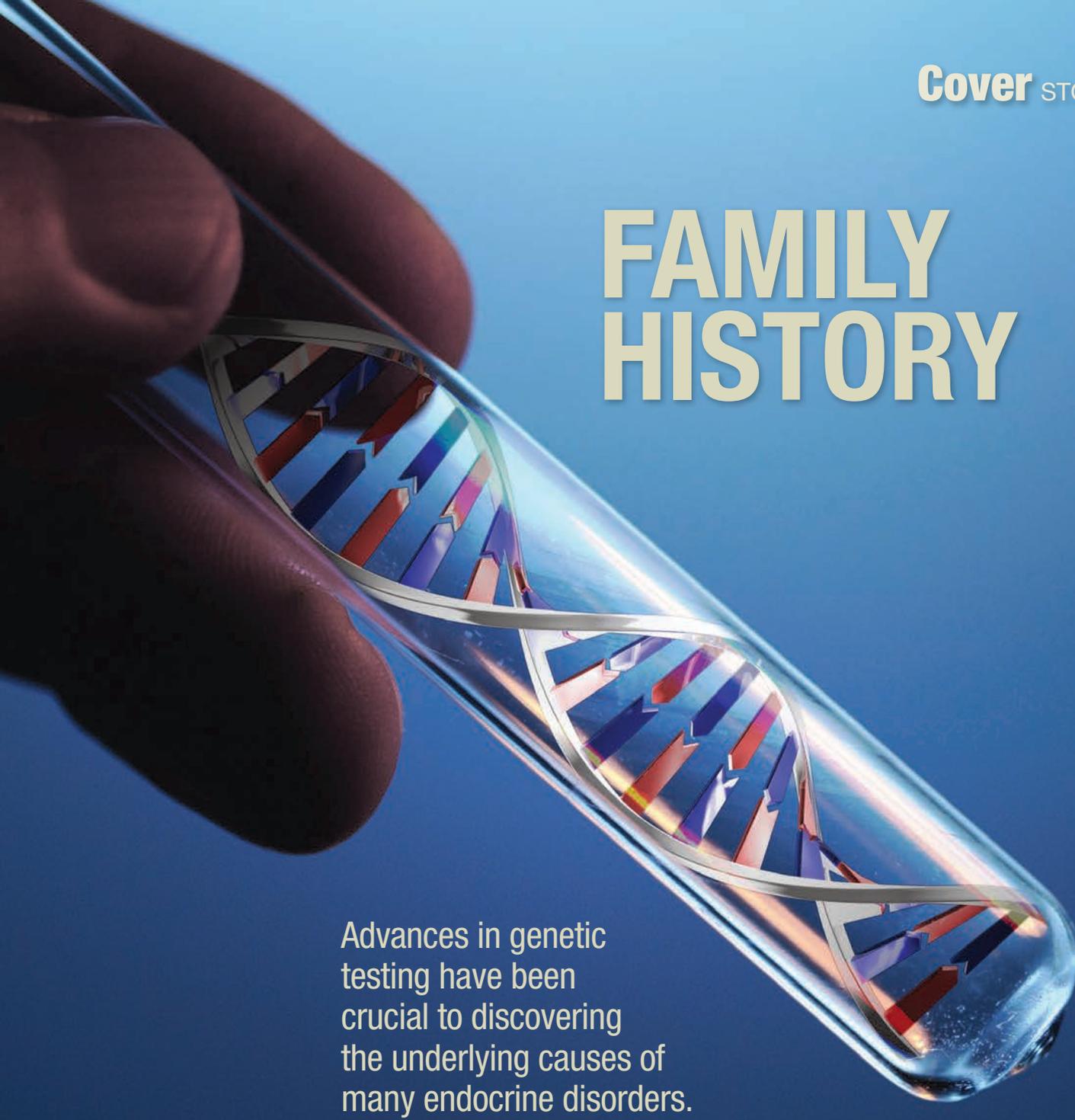


Overall, inherited mutations play a role in about 5% to 10% of all cancers.



Cushing's syndrome affects about two to four people per one million in the U.S. each year.

FAMILY HISTORY

A hand is shown holding a clear glass test tube. Inside the test tube, a glowing DNA double helix structure is visible, with the base pairs represented by colorful blocks (red, blue, green, orange) and the sugar-phosphate backbones as silver ribbons. The background is a solid blue color.

Advances in genetic testing have been crucial to discovering the underlying causes of many endocrine disorders. They not only act as a guide to treatment but also as a precaution for family members.

By **Eric Seaborg**

AT-A-GLANCE

- Genetic tests are becoming more common as options for discovering underlying causes of endocrine disorders.
- The tests provide a tool beyond traditional tests such as hormone levels.
- Physicians cannot change a patient's DNA, but an understanding of a condition's mechanisms can guide treatment decisions.

As genome sequencing continues to reveal the functions — and dysfunctions — of particular genes, genetic tests are gaining currency, particularly when hormone tests give ambiguous results.

From common conditions like thyroid disease to rare adrenal tumors, these tests can reveal the inheritable component of a patient's condition and can change the approach to treatment. The patient's family can also benefit from this knowledge — or in some cases provide important information about a mutation's actual effects.

"Generally speaking in endocrine diseases, we find abnormalities in a particular hormone level, and then we make a diagnosis and recommend a treatment," says Roy E. Weiss, MD, PhD, chair of the department of medicine at the University of Miami Miller School of Medicine and co-editor of the text, "Genetic Diagnosis of Endocrine Disorders." "Certain times, however, based on the history and physical examination, you can measure the hormone levels, and there may be ambiguity about what the diagnosis is. Therefore, you need to understand at a deeper level what the genetic cause is for the abnormal hormone level. Once you understand better the mechanism for the abnormality, you can provide specific treatment."

Weiss says that there are several thyroid conditions caused by mutations that can be pinned down by genetic testing, citing the examples of syndromes of impaired sensitivity to thyroid hormone. These patients' test results can be confusing. A patient might present with hyperactivity and a goiter but discordant blood tests: Although the patient's thyroid hormone levels are elevated, the thyroid-stimulating hormone (TSH) level is normal, rather than being suppressed. There are several potential diagnoses in this case — calling for different treatments — but no single clinical test will nail down the diagnosis.

The problem could be a pituitary gland tumor that is making TSH, and the treatment would be removal of the tumor. The problem could be that the patient has an antibody interfering with the test making his TSH appear normal when it is really low. That patient may need to be treated for hyperthyroidism.

Resistance to Thyroid Hormone Syndrome

Or the problem could be the syndrome of resistance to thyroid hormone, an inherited condition caused by mutations in the thyroid receptor beta gene that is characterized by reduced responsiveness of target tissues to thyroid hormone. "If you send a blood sample and the laboratory reports a mutation in the thyroid hormone receptor that affects function of the receptor, you have made the diagnosis," Weiss says. And that knowledge puts the clinician

on track for the correct treatment.

Of course, no treatment can correct the mutation, but in many patients the thyroid compensates for the lack of sensitivity of tissues to thyroid hormone by increasing its secretion of thyroxine (T4) and generation of triiodothyronine (T3), and treatment may not be needed. "Recognizing that no treatment is needed is very valuable because reduction of thyroid hormone levels would be incorrect in such a patient," Weiss says.

A family history can help in deciding whether treatment is necessary. "Perhaps there is a sibling or parent who also has this mutation and is living perfectly well without any treatment whatsoever and still has the abnormal blood test. That would tell the clinician," that treatment is not needed because the thyroid is compensating for the defect, Weiss says. "In other instances, when the patient is very symptomatic, knowing that the symptoms are due to decreased sensitivity to thyroid hormone, there are specific treatments that can be given. One example would be administration of thyroid hormone analogues or high doses of thyroid hormone at different intervals to reduce the goiter."

Other conditions involving impaired sensitivity to thyroid hormone that can be detected



"...You need to understand at a deeper level what the genetic cause is for the abnormal hormone level.

Once you understand better the mechanism for the abnormality, you can provide specific treatment."

— Roy E. Weiss, MD, PhD, chair, Department of Medicine, University of Miami Miller School of Medicine, Miami, Fla., and co-editor of the text, "Genetic Diagnosis of Endocrine Disorders"

by genetic tests include a syndrome of impaired conversion of T3 from T4 (deiodinase defects) and defects that impair the transport of thyroid hormone into cells.

Rare Adrenal Tumors

Thyroid cases are among the most common conditions that endocrinologists see, but genetic testing can be helpful in the rare adrenal tumors — pheochromocytomas and paragangliomas. These tumors produce large amounts of the catecholamines — epinephrine and norepinephrine — and lead to symptoms including high blood pressure, episodic severe headaches, excess sweating, racing heart, feelings of anxiety, and trembling. Some 0.1% to 0.6% of hypertensive patients have pheochromocytomas, but the condition is notoriously slow to be diagnosed because of its rarity and the nonspecific and paroxysmal nature of symptoms like headaches.

“The average delay in diagnosis is still about three years,” says Jacques W.M. Lenders, MD, PhD, of Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. Lenders chaired the committee that wrote “Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline.”

The diagnosis is important because “in addition to the strain these tumors put on the cardiovascular system, between 10% and 17% of the tumors can become malignant,” Lenders says. “This is one of the rare instances when a pathologist cannot tell us definitely with 100% certainty in an individual patient that this is malignant or benign disease.”

More Definitive Information

Blood and urine tests for the catecholamine metabolites (metanephrines) in conjunction with functional imaging techniques are reliable for identifying and locating tumors, but genetic testing can provide information about an underlying hereditary condition. “About 30% to 40% of these patients have an underlying mutation in some of the genes that are involved in the development of the pheochromocytoma and paraganglioma. Some of these genetic mutations are associated with a very high risk of malignancy,” Lenders says.

“If you have a young patient and you know that the patient has a mutation that is associated with a very high risk of developing malignant disease, you can monitor the patient much more closely,” Lenders says. But there are also mutations that are not related to an increased risk of malignancy. “If you know the mutation, you can check the relatives to see if they have the mutation, and if they have an occult or hidden tumor. Early detection can benefit family members who may be at risk.”

The genetic testing can lead to other avenues as well. For example, a patient who presents with a pheochromocytoma could turn out to have the mutation for Von Hippel-Lindau syndrome. “Then you will look for other manifestations of the syndrome like cerebral hemangioblastomas and renal cell carcinoma. The clinical follow up of such patients is completely different,” Lenders says.

Genetic tests generally involve the classic questions about what to do with the information. The Endocrine Society guideline recommends counseling pheochromocytoma patients about the value of genetic testing — for example, a mutation does not guarantee that the patient will have cancer but raises the risk considerably.

Tests of the Future?

Most of these tests are performed at specialized centers, but the spread of “next generation sequencing” technology will make these tests more widely available, Lenders says.

“Measuring the hormones alone may not be sufficient to give the clinician a clue as to what is really going on,” Weiss concludes. The genetic diagnoses are becoming more definitive and useful for more conditions, “whether it’s gene abnormalities in aspirates of thyroid nodules to aid in the diagnosis of thyroid cancer, or genetic analysis to determine the cause and best treatment of diabetes, or analysis of the genes responsible for thyroid hormone function abnormalities, such genetic tests will direct the physician to a more specific treatment.” **EN**

— Horvath is a freelance writer based in Baltimore, Md. She wrote about erectile dysfunction in the December issue.

OnPOINT from
the Endocrine Society

“Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline” is available at www.endocrine.org/education-and-practice-management/clinical-practice-guidelines.



“If you know the mutation, you can check the relatives to see if they have the mutation, and if they have an occult or hidden tumor.

Early detection can benefit family members who may be at risk.”

— Jacques W.M. Lenders, MD, PhD,
Radboud University Nijmegen Medical Center,
Nijmegen, The Netherlands

Straight Talk

When radio personality Froggy was diagnosed with acromegaly 10 years ago, he made it his personal mission to educate the public — as well as primary care physicians — on this rare and unexpected disease.

By Derek Bagley

Late last year, the Endocrine Society published its clinical practice guideline (CPG) on acromegaly in the *Journal of Clinical Endocrinology & Metabolism*, laying out recommendations and suggestions for diagnosing and treating this chronic condition that causes the hands, feet, and facial features to grow, and if left unchecked, can cause serious health problems and increased mortality. It's a rare disease, affecting three people out of a million each year, and it's tricky to deal with, since each patient presents with different symptoms.

But while this CPG is a valuable resource for creating a treatment plan, it's often just as valuable to hear straight from those who suffer from acromegaly, especially when the nuances of this disease may be lost on the public and the primary care physicians they first go to when something's wrong. And it's even better when an acromegaly patient has a unique platform to make his voice heard.

Froggy is a radio personality on one of the most popular nationally syndicated radio shows in the country, *Elvis Duran and the Morning Show*. And by all accounts, Froggy has it all: a great life with a wonderful family in sunny south Florida and a job that allows him to use his radio-perfect voice (he got the name "Froggy" because his voice is so deep) to make people laugh and grin during their morning routines. But it hasn't always been sunshine and smiles for Froggy.

Froggy has had acromegaly for 10 years, maybe longer, since the disorder is so slow-moving that it can make it difficult to diagnose or even detect. Now, on the heels of the Society's CPG, the Hormone Health Network has partnered with Novartis and Froggy's Straight Talk Acromegaly program, so that Froggy can share his story.

"The Network has joined forces with Froggy and Novartis to help support their Straight Talk Acromegaly disease awareness campaign by participating in a live Twitter chat and sharing the Network's acromegaly online resources to help empower patients and their loved ones who may feel that something isn't quite right," says Cheretta Clerkley, director of the Hormone Health Network. "By hearing Froggy's story, patients may be able to identify and seek medical treatment. It's important that the Network supports this awareness campaign because there are 117 new cases a year and if we can help patients to seek treatment with their healthcare provider and start a dialogue about the symptoms they may be experiencing they can begin the necessary treatment."

"[Straight Talk Acromegaly is] giving me a broader reach to be able to talk

"My goal is to try to [talk to] not only people like me and people who think they're experiencing odd side effects, but at the same time, to get doctors to know more about acromegaly."



AT-A-GLANCE

- Froggy, a radio personality on one of the country's most popular morning programs, has had acromegaly for 10 years.
- One of Froggy's doctors details the advances made in treating this uncommon disease.
- Froggy wants to bring awareness to acromegaly, and support to those who have it, since it can be a long and difficult journey.

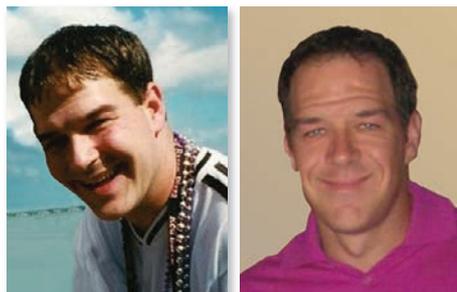
to people who didn't know about the disease," Froggy says, "and I've been saying from the beginning, if I can help one person — if one person hears me talk about the symptoms that I had or the things that I was experiencing, and they're experiencing the same thing, then that's exactly why we started doing this program."

Growing Pains

When the disease first started, or when Froggy first noticed something was wrong, he was tired constantly, suffered from intense headaches, and he sweat profusely. But all these things he attributed to one thing or another, whether it was work-related (a radio personality has odd hours to keep) or simply getting older. Even the sweating could have been explained by living in Florida. After all, in medicine, common things happen commonly. "It happens over such a long period of time that you don't realize it," Froggy says, "and you write it off to aging."

But Froggy had a difficult time continuing to write the symptoms off. The tiredness, the headaches, everything began to "take a toll" on him, so he did what any modern-day patient would do. He went online. "For the first time in my life I saw the word acromegaly," he says. He also saw that the best — really the only — treatment for acromegaly is brain surgery. The Endocrine Society recommends surgery as the first course of action as well, since successful surgery can immediately lower growth hormone levels. But that can be hard for some patients to digest. "I remember seeing 'brain surgery,' closing the browser, closing the keyboard tray, and getting up and walking away from the computer," Froggy says.

Froggy went on with his life, continuing to feel awful. He gained a lot of weight. His hands grew so much that he had to have his wedding ring resized four times. His feet grew from a size 10 to a size 14. His jaw grew so much that he was almost unrecognizable to his friends. His protruding jaw made it difficult to eat or even speak, which is pretty devastating to a guy who talks for a living. But all of this was an extremely slow process, not some sort of Kafkaesque transformation, so people who saw Froggy every day, like his wife, didn't notice the changes much. (He also admits that he became adept at hiding his symptoms because he was afraid to face the fact that something was wrong.) Froggy himself didn't even realize his speech had changed until he listened to



Froggy before (left) and then after (right) acromegaly caused his jaw to grow.

old tapes of himself.

All of this, and he still didn't know why. As it happens, it was a *Jeopardy* clue that gave him the answer. His mother had been watching the game show and seen the clue: "A disease that causes enlargement of the hands, feet, forehead, and lower jaw." The answer: "What is acromegaly?"

When his mother called and told him about what she'd seen,

Froggy knew he had to do something. "When she said that word," he says, "it was like chills went over me."

Getting a Diagnosis

Froggy made an appointment with his primary care physician the week after that phone call from his mother and told the doctor that he thought he had acromegaly, armed with the knowledge he gained from his own research, especially from the Novartis site, acromegalyinfo.com. "It was so informative that it gave me something to lean on," Froggy says, "and when I went to the doctor, I could at least speak somewhat intelligently about what I thought I had."

But his doctor wasn't so sure. "She said, 'No, I don't think that's what you have,'" he says, "and I said 'Well, why?'" The reason was that the primary care physician had never seen an actual case of acromegaly in 20 years.

Convinced he had acromegaly, Froggy persisted and asked his physician to send him for additional testing. He had a MRI that showed nothing wrong, but then he went for insulin-like growth factor-1 (IGF-1) testing with an endocrinologist, and he finally got his answer. "I knew my numbers were supposed to be around 200, 250," Froggy says. "When we got my numbers back I was over 1,200. That was the day I was diagnosed with acromegaly."

A scary diagnosis, to be sure, but Froggy says he was relieved. When he peeked at the chart the nurse had left in the exam room and saw that eye-popping number, he looked at his wife and said, "Well, I got it." "I felt like there was a weight lifted off my shoulders," he says. "There were so many [things] that were answered by that number, by that test, that when we walked out of that office, I went to play golf."

The next step was surgery, the brain surgery that had scared Froggy from even looking at the word "acromegaly" before. Froggy underwent his brain surgery in 2010 at the University of Florida to have the pituitary adenoma

OnPOINT from the Endocrine Society

The Endocrine Society published a **Clinical Practice Guideline** for the diagnosis and treatment of acromegaly in the November 2014 issue of the *Journal of Clinical Endocrinology & Metabolism*. Entitled “Acromegaly: An Endocrine Society Clinical Practice Guideline,” the CPG was co-sponsored by the European Society of Endocrinology.

The Hormone Health Network offers resources on acromegaly at <http://www.hormone.org/questions-and-answers/2012/acromegaly>.

removed, then had to have colon surgery to remove the polyps caused by acromegaly, then had reconstructive surgery on his jaw in 2011. Three separate surgeries, all from a tiny tumor.

After This Break

There is no cure for acromegaly, even with surgery. Patients have a chance for remission, but according to Laurence Kennedy, MD, chairman of the endocrinology department at the Cleveland Clinic and Froggy’s endocrinologist, the likelihood of that happening is only about 50%, so a lifelong regimen of drugs is needed to control the growth hormone (GH) and IGF levels. The Society’s CPG also recommends radiation therapy in patients with persistent tumor tissue after surgery or in cases in which medication is ineffective.

Patients also have to relearn to do some things, as Froggy found out. After the surgery to correct his jaw, he had to almost relearn himself how to eat without biting his tongue and form particular sounds when he was speaking, so that he could talk at a quick pace. “My mouth muscles in my face and my jaw were trained to move a different way,” Froggy says, “so then after surgery, now everything’s in a different place.”

“It was a complete readjustment period,” he continues, “that probably went on for a couple months after that.”

Simple things made difficult. And because of that and the fact that acromegaly is a chronic condition, it can be daunting for patients who have to live with it. But Froggy found comfort from his family, who made sure he takes his medications regularly; his work family, who threw him a party in New York; and online support groups like Acromegaly Community, which provides information and offers tips for living with acromegaly, as well as friendly support through peer-to-peer networks and message boards.

And Froggy says that while a support group is great for the mental battle with acromegaly, the most important thing to do is stay on top of it by taking medications and visiting the endocrinologist regularly to get tested. “If I don’t stay up on my numbers now and stay up with my endocrinologist,” he says, “I could end up back where I was again. I’d have to start all over again.”

Froggy now wears the original wedding ring his wife

gave him in 2002, the size shoes he wore “years ago,” the same size clothes he wore in high school.

“Once you’ve come so far,” Froggy continues, “the key is to be your own advocate. No one knows your body better than you do.”

Up Next

Acromegaly is still considered a rare disease, especially to the public and maybe even primary care physicians. Froggy’s primary care physician had never seen a case in her entire medical career, after all.

Froggy’s goal with Straight Talk Acromegaly is to spread awareness of the disease to patients and doctors alike. “I remember how lost I felt when I didn’t know what to do,” he says. “I didn’t know what was wrong.”

He says that he wants even dentists and oral surgeons to be aware of the disease, since his own acromegaly is what caused him to have to have braces as a young man. “Just to be aware of it and to have that as one of your checklist points and say ‘Does this person have acromegaly?’ and send them for the right test,” he says, “It’s easy to find if you go get the right test.”

But Kennedy says the disease is more “uncommon” than “rare” to endocrinologists. “It’s actually quite common to those with interest in pituitary gland disorders,” he says.

“[Kennedy] told me if he had passed me on the street, he would have known I had it,” Froggy says.

Kennedy has been treating acromegaly for 38 years, and in that time he has seen some major advancements in the diagnosis and treatment of the disorder, such as the ability to image the pituitary gland and the “rediscovery” of microsurgery on the pituitary gland. Drugs that reduce GH and IGF-1 levels have been developed. “We have more arrows in our quiver, so to speak,” Kennedy says.

“Some doctors are so well versed in it that I think they do know,” Froggy says. “But that’s what I’m trying to do. My goal is to try to [talk to] not only people like me and people who think they’re experiencing odd side effects, but at the same time, to get doctors to know more about acromegaly.”

And he’s already seeing results. Froggy says someone reached out to him through Facebook after she heard his story on the radio. She told her best friend about it, and soon after, he was officially diagnosed. “That is why I’m doing this,” he says. “That’s one life that is changed, that’s one person who doesn’t have to go through ‘What the hell is going on with me?’ That’s the whole driving process behind this.” **EN**

— Bagley is the associate editor of *Endocrine News*. He wrote about exercise and diabetes in the November issue.

For more information, resources, and patient support materials on acromegaly, visit hormone.org and acromegalyinfo.com.



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PEARLS OF WISDOM: Experts Lead Career Activities at

ENDO 2015

Early Career Activities at ENDO 2015 will highlight the ins and outs of getting published, finding a mentor, and so much more that you probably weren't taught in medical school.

By Melissa Mapes



Like many young scientists and physicians, Stephen R. Hammes, MD, PhD, professor of medicine and chief of the Division of Endocrinology and Metabolism at the University of Rochester in New York, felt uncertain about his next steps after completing his education at Duke University, Durham, N. C. "I was disenchanted with medicine and wanted to forgo residency and go straight into a postdoc position," he explains.

Fortunately, a mentor intervened. Warner Greene, an MD and PhD himself, reassured Hammes that residency would be a completely different experience from medical school. "I took his advice," Hammes went on, "and, in fact, he was right on." Now a clinical director, he says he cannot imagine life without both a research and a clinical practice.

The advice of experienced mentors, such as Greene, has proven critical to the success of up-and-coming researchers and practitioners time and time again. To help the next generation of endocrinologists navigate the complexities of their chosen vocation, the Endocrine Society is hosting a number of early-career activities at the **98th Annual Meeting & Expo (ENDO)** in San Diego, Calif., from March 4–8, 2015.

Each day includes **Career Development Workshops** on topics ranging from "Setting Up and Managing Your Lab" to "Promotion and Tenure." The sessions are moderated and led by experts in each area, who can share tips and lessons from their professional lives.

Putting the "Me" in Mentor

Alice Chang, assistant professor in the Division of Endocrinology, Metabolism, Diabetes, and Nutrition at the Mayo Clinic in Rochester, Minn., will provide her insight during a "Mentorship" workshop, co-sponsored by the Women in Endocrinology. She has learned from personal experience that aspiring endocrinologists need to take an active role in establishing and maintaining meaningful mentorships.

"If I could talk to myself in the past when I was first starting out as a trainee, I would tell myself to get involved with career development programs and workshops early on," Chang says. Although she regrets waiting until her last year of training to take advantage of such activities, she still managed to assemble an impressive roster of mentors.

One of the most formative bits of advice she received came from Milton Packer, chair of the Department of Clinical Sciences at UT Southwestern. He taught Chang that, "We are the CEO of our own career." She felt empowered by this notion, which inspired her to put less emphasis on finding a singular "super mentor" and instead focus on finding the people that could help build her "company."

“If I could talk to myself in the past when I was first starting out as a trainee, I would tell myself to get involved with career development programs and workshops early on.”

— Alice Chang, assistant professor, Division of Endocrinology, Metabolism, Diabetes, and Nutrition, Mayo Clinic, Rochester, Minn

One of Chang’s first research mentors, Richard Auchus, MD, PhD, now a professor at the University of Michigan, introduced her to networking at poster sessions at **ENDO** back in her fellowship days. “There was no question too big or too small, and he is my favorite person to edit papers and grants,” Chang says. Even though they are at different institutions today, he continues to provide guidance for her work. “Each time, I learn something new about writing.”

She also emphasizes the value of the bonds she has formed through the Women in Endocrinology group. “They have not only offered important advice on transitions during my career but are certainly responsible for nominating me for positions and opportunities through the Endocrine Society,” Chang explains.

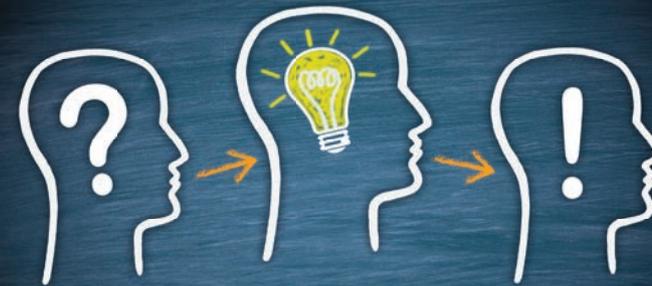
During the workshop, she will be moderating a panel of senior mentors within Women in Endocrinology. The featured speakers come from a wide range of backgrounds. Chang is the most junior participant, providing her with a unique perspective on the subject.

“We give panelists a few minutes to describe their own experiences as mentee and mentor, focusing on key elements of mentorship, including: how to choose a mentor, types of mentors, spheres of mentorship, mentoring networks, how to structure the mentoring relationship to optimize trainee success, gaining independence from your mentor, mentorship through career transitions, and the value of mentors at every stage of your career,” Chang expounds.

She believes that the workshop will answer the many questions that trainees and junior faculty frequently have and worry about when it comes to finding the right mentors. “We focus on the important goal of providing a roadmap of what they need during their career from a mentor or team of mentors.”

Award-Winning Tips

Joy Wu, assistant professor at Stanford University in California, and the director of the Stanford Osteoporosis and Metabolic Bone Disease Clinic, has defined her career path largely through the encouragement and wisdom of mentors. “The best advice I ever received was to select a



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Career Development Workshop Schedule

March 5	11:15 AM – 12:15 PM	Setting Up and Managing Your Lab
March 5	12:30 – 1:30 PM	Setting Up and Negotiating Your Clinical Practice
March 6	11:45 AM – 1:15 PM	Careers in Industry
March 6	1:30 – 3:00 PM	Promotion and Tenure Workshop
March 7	11:15 AM – 12:15 PM	Negotiations: Basic and Clinical Research
March 7	2:15 – 3:00 PM	Opportunities for International Early-Career Professionals
March 7	7:00 – 9:00 PM	How to Write a Successful Career Development Award Application
March 7	7:00 – 9:00 PM	Writing a Successful R01 or Other Independent Research Grant Application
March 8	9:30 – 10:30 AM	Mentorship Co-Sponsored by Women in Endocrinology
March 8	10:45 – 11:15 AM	NIH Early-Career Reviewer Program

Other Career Development:

Endocrine Innovators Oral Competitions – 1:30 – 3:00 PM Thursday, March 5 – Saturday, March 7

Health Disparities Community Forum:

11:30 AM – 1:00 PM Saturday, March 7

lab based on the mentor rather than a project,” she claims.

According to Wu, a great mentor teaches his or her trainees to craft a research proposal that addresses impactful questions. Mentored awards offer great opportunity to augment professional relationships while pursuing one’s scientific interests.

Experienced researchers like Wu know the best practices for winning such awards and will be sharing them at the **Career Development Workshop** titled, “How to Write a Successful Career Development Award Application” on March 7th from 7:00 to 9:00 pm.

Among other accomplishments, Wu has received the NIH Director’s New Innovator Award from the National Institutes of Health (NIH), the Clinical Scientist Program Instructor Development Award from the Harvard Stem Cell Institute, the Claffin Distinguished Scholar Award from Massachusetts General Hospital, and the Merck Senior Fellow Award and the Endocrine Scholars Award from the Endocrine Society.

“The forum as a whole is just a terrific opportunity for trainees to **learn the ins and outs of starting a career in basic or clinical research...**”

— Steve Hammes, MD, PhD, professor of medicine,
chief of the Division of Endocrinology and Metabolism,
University of Rochester, N.Y.

Along with other professors who have either been awarded or mentored a career development award, Wu will share her personal knowledge with research and clinical fellows who intend to apply for similar honors. The lecturers will provide a large amount of information on the steps of preparation. The focus is on K grants from the NIH, but the general advice may be applied to many types of mentored awards.

“In particular, my talk will discuss the steps in planning and applying for basic science K grants (K01, K08, and K99/R00), while a separate session is designed for those with an interest in patient-oriented research,” Wu explains. She will help provide a comprehensive overview of the qualities of a successful career development award. “We will guide potential applicants through the process of identifying the right award, then review how to design a research proposal, and finally emphasize the importance of a clear career development plan to transition to independence.”

Wu claims that the first critical step requires identifying a mentor who can provide rigorous research training, has a strong track record of launching the careers of junior faculty, and has sufficient resources to support the tutelage.

“Start planning early,” Wu says, “as a successful application depends upon evidence of productivity.” In cooperation with one’s mentor, she recommends developing a research plan that provides a gradual independent direction for one’s own research interests. “Begin writing early in order to leave enough time for critical feedback and plenty of rewriting,” she advises.

Wu warns applicants to avoid underestimating the importance of the career development plan. “Unlike investigator-initiated research grants that are predominantly focused on the quality of the research proposal, mentored career development awards place strong emphasis on outlining a clear training plan with a path to independence,” she explains.

Held simultaneously with the presentations by Wu and her contemporaries, a workshop on “Writing a Successful R01 or Other Independent Research Grant Application” is also available at this year’s meeting.

All That’s Fit to Print

Central among the career development activities at **ENDO 2015** is the all-day **Early Career Forum** on Wednesday, March 4 from 8:00 am to 5:30 pm. Endocrinologists from scientific, clinical, and industry backgrounds will converge at the convention center to bring clarity on

a breadth of topics, from “Careers in Government and Science Policy” to “Developing Clinical Teaching Skills.” The forum, which costs \$125, includes speakers such as Hammes, who will host a session titled “Tips for Getting Your Work Published.”

“The forum as a whole is just a terrific opportunity for trainees to learn the ins and outs of starting a career in basic or clinical research, whether it be in academics or industry,” Hammes says. Young endocrinologists will have the opportunity to learn from experienced mentors who all have a strong interest in career development and in teaching and mentoring trainees.

The **Early Career Forum** divides into audiences interested in basic science or clinical practice for most of the day to allow trainees to interact with peers on a similar career path. Additionally, this arrangement consolidates leaders in each field into lectures and discussions that illuminate the important distinctions between research and clinical tracks.

“For my presentation, I just hope that I can clear up some of the mystique of publishing papers and offer the trainees some advice from somebody who has experience from all sides — as an author, as a reviewer, and editor,” Hammes explains.

He does not intend to make a formal presentation but instead lead a discussion. “I use the time to create a forum whereby young investigators can ask me any questions regarding publications, from timing to content to target journals,” Hammes went on. He will also field questions about grant writing and other related aspects.

Hammes offers a few major tips as a preview of the talk. The first theme is timing. “When to publish is very important,” he says. “Some people publish too early when the story is incomplete. However, most people err on the other side — waiting too long into their careers before getting out their publications.” Whether a trainee or junior faculty, he believes that knowing when to publish is essential.

Once ready to submit, the next important question is where to go. “There are so many journals and so many issues, such as impact factor or journal focus,” Hammes adds.

After acceptance, it is equally important to respond appropriately to criticism. Manuscripts are rarely perfect on the first go-around, and humility must be exercised when facing constructive criticism.

This skill should be exercised outside of papers as well. “Learning to deal with people, especially conflict, is never formally taught but is perhaps the most

“Get names, get cards,
and then
**follow up with emails
after the meeting.**”

— Steve Hammes, MD, PhD,
professor of medicine,
chief of the Division
of Endocrinology and Metabolism,
University of Rochester, N.Y.

“The best advice I ever received was to
**select a lab based on
the mentor rather than a project.”**

— Joy Wu, assistant professor, Stanford University,
director, Stanford Osteoporosis and Metabolic
Bone Disease Clinic, Calif.

important skill for any job,” Hammes says. “Some institutions now offer lectures or courses that address this, and I wish that I had learned more as a trainee.”

Maximizing the Meeting

Being personable will especially benefit early-career endocrinologists at the **98th Annual Meeting & Expo**. “Swallowing one’s nervousness and getting out to meet people is really important,” Hammes says. He knows that most senior scientists love talking to trainees, but the trainees need to make the first step to initiate a conversation. “Get names, get cards, and then follow up with emails after the meeting” he advises.

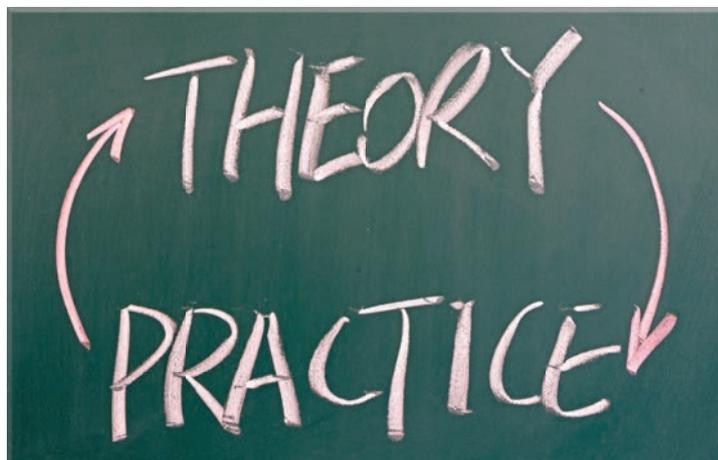
Wu agrees. “Take the opportunity to advance your own clinical or research interests — identify posters from research groups in your field, and then stop by to chat with the presenters.” This allows one to meet peers who are performing exciting research. “You can learn a lot about research methods, novel research directions, and potential research labs this way,” she went on.

Chang thinks that there is no better place to find mentors, peers, and valuable career guidance than **ENDO**. “For many of us, the Endocrine Society is our scientific and career home,” she says. “No matter what your focus or what type of career you would like to develop, this meeting is a tremendous opportunity to meet people who can help you with your science, your clinical interests, and advancement in your career.”

Each year, she comes up with a plan for how to get the most out of the meeting — focusing on which sessions to attend and where she can meet people. This usually includes poster sessions and mingling after oral presentations. “Discuss with your mentors and colleagues who might be helpful for you to meet,” Chang says. As a part of this exercise, one should prepare an “elevator pitch” so that he or she can describe their interests and background in a couple sentences.

ENDO 2015 offers numerous additional career-building and networking activities that are detailed on the conference website (www.endocrine.org/meetings). Even individuals who are unsure of where to focus their professional ambitions should immerse themselves in these events. Uncertainty, and even change, is a normal part of medical and scientific occupations.

“A career in science and medicine is ever evolving,” Chang explains. “Although we emphasize trying to grow a career and learn as much as possible as early as possible, it should not be an intimidating process, but an enjoyable journey.” She encourages trainees to know that no decision or career path has to be permanent. She was a primary care physician, a hospitalist, and a writer for a consumer medical website before she



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Career Development Workshop Schedule
Wednesday, March 4, 2015 from 7:30 AM to 5:30 PM

7:30 AM – 8:00 AM	Registration and breakfast
8:00 AM – 8:15 AM	Welcome and overview
8:15 AM – 9:00 AM	Plenary lecture: Bench to Bedside and Back Again
	Morning breakout sessions for Basic Science and Clinical tracks begin
9:00 AM – 10:00 AM	Careers Symposium
10:00 AM – 12:00 PM	Morning career breakout sessions
	Basic Science and Clinical tracks rejoin
12:00 PM – 1:30 PM	Lunch and career/life balance discussion groups
1:30 PM – 2:30 PM	Plenary lecture: Panel discussion on obesity
	Afternoon breakout sessions for Basic Science and Clinical tracks begin
2:30 PM – 4:40 PM	Skills breakout sessions 1 & 2
4:40 PM – 5:20 PM	Endocrine Society Networking and Service Opportunities
5:20 PM – 5:30 PM	ENDO A to Z: How to Get the Most Learning Possible from Attending the Annual Meeting

pursued an endocrinology fellowship, a master’s in science in clinical science, and finally a research career.

“It is also important to be persistent and realize that the trajectory of your career does not have to be a straight line and no change is permanent,” Chang says. Whether seeking a new path or just starting out, the career development activities at this year’s meeting are formulated to assist endocrinologists in maneuvering the topography of this diverse specialty. **EN**

— Mapes is a Washington, D.C. – based freelance writer and a frequent contributor to Endocrine News. She wrote about the “Plan B” pill and overweight women in the August issue.

PREECLAMPSIA

A Multi-Faceted Look at This Puzzling Condition



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Preeclampsia is a severe disorder of pregnancy, characterized by hypertension and proteinuria, affecting approximately 5% of all pregnancies. In addition to causing intrauterine growth retardation, perinatal mortality, and preterm birth, preeclampsia is a leading cause of maternal death. Despite the severity of preeclampsia, its etiology is poorly understood and its onset difficult to predict. Therefore, a major research focus has been aimed at achieving reliable and early diagnosis using serum markers and placental blood flow measurements. Basic science research has made strides in understanding structure-function relations between serum molecules and pathology, and has been facilitated by the development of mouse models to investigate this disorder in tractable *in vivo* systems. The concerted efforts of practitioners and researchers have enabled development of management protocols for preeclampsia. In this TriPoint, two basic science researchers elucidate our current understanding of the molecular mechanisms of preeclampsia and a model system used to study them; a clinical researcher sheds light on expression analyses to identify therapeutic targets; and a physician-in-practice discusses the health risks in and clinical recommendations for women with a history of preeclampsia.

HIGHLIGHTS

- **Preeclampsia is a hypertensive disease of pregnancy** that resolves only upon delivery of the baby and placenta. Although it has been described for centuries, the cause of preeclampsia is still unknown.
- **Abnormal placental development is a hallmark of preeclampsia.** However, the key events in placenta formation occur at the onset of pregnancy and thus cannot be thoroughly investigated in humans.
- Animal models of preeclampsia are **valuable tools for investigating key early pregnancy events**, including implantation.
- **The BPH/5 murine strain** spontaneously develops the cardinal signs of preeclampsia along with placental pathologies reminiscent of the human disease. BPH/5 mice also exhibit profound periimplantation defects at the maternal-fetal interface.
- Investigating the very earliest stages of pregnancy using animal models provides the **opportunities to gain insight into dysregulated maternal and fetal interactions** that may lead to preeclampsia.
- Recent advances suggest that biomarkers may be used to **predict the onset of preeclampsia.**
- There is evidence that **circulating factors that mark the onset of preeclampsia** also play an important role in the pathophysiology.
- The **consequences of preeclampsia**, including cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, and dyslipidemia require both screening and intervention.
- Studies of long-term outcomes of cardiovascular risk intervention are needed in **women with a history of preeclampsia.**

BASIC RESEARCHERS PERSPECTIVE — *Robin L. Davisson, PhD, and Jenny L. Sones, DVM, PhD*

Preeclampsia affects up to 10% of all pregnancies in the U.S., is responsible for 42% of maternal deaths worldwide, and significantly contributes to neonatal/infant morbidity and mortality. This devastating disease of pregnancy is characterized by a sudden late-gestational rise in maternal blood pressure and urinary protein levels. Even though the maternal signs of preeclampsia have been observed and described for centuries, the exact cause and cure remain elusive.

Understanding Preeclampsia

Because maternal signs only resolve upon delivery of the fetus and the placenta, it is widely accepted that the developing fetoplacental unit plays a causal role in the pathogenesis of preeclampsia. Biopsies of preeclamptic placentae have shown inadequate invasion of trophoblasts into the maternal decidua arterioles, resulting in reduced uteroplacental perfusion. A two-stage disease model has been proposed to link these placental pathologies with the clinical presentation of preeclampsia. The first stage is thought to involve abnormal placentation characterized by poor trophoblast invasion, incomplete vascular remodeling, and placental hypoxia. The second stage manifests as the maternal syndrome of hypertension and proteinuria. The transition between the two stages is thought to be due to the release of factors from the abnormally developed placenta into the maternal

circulation. Recent evidence strongly suggests placentally derived angiogenic factors play a central role in the progression of preeclampsia.

Animal Models of Preeclampsia

The initiation of fetoplacental pathologies has been extraordinarily difficult to study in humans due to logistical and ethical challenges associated with examining the first trimester. Therefore, animal models of preeclampsia are critically important for longitudinal investigation of early events. We have gleaned much insight into the pathophysiology surrounding the maternal syndrome from rodent models of preeclampsia. The RUPP (reduced uteroplacental perfusion) model surgically mimics impaired placental blood flow in late gestation pregnant rats. Another important rodent model involves infusion of an anti-angiogenic factor, sFlt. Although these models recapitulate aspects of the maternal syndrome and the angiogenic imbalances observed in humans, they cannot be used for studying key early pregnancy events that may initiate the disease process. Recently, several mouse strains with single gene mutations have been developed that phenocopy key features of preeclampsia. While these models allow the opportunity to investigate early pregnancy events, preeclampsia is a multifactorial disease that is unlikely to be monogenic.

Our laboratory discovered the first strain of mice to spontaneously develop a preeclampsia-like syndrome, BPH/5. Non-pregnant BPH/5 mice exhibit modest elevations in blood pressure, a



known risk factor for preeclampsia. Similar to humans, BPH/5 mice exhibit late-gestational proteinuria and a significant rise in mean arterial pressure during the second half of gestation that returns to baseline after delivery of the pups and placentae. In keeping with perinatal and neonatal morbidity/mortality observed in human preeclampsia, BPH/5 mice have small litter sizes due to in utero fetal demise and low-birthweight pups. Importantly, BPH/5 mice develop placental pathologies that precede the maternal syndrome, including inadequate remodeling of uterine spiral arteries with decreased trophoblast invasion. Hence, the spontaneous BPH/5 mouse model provides a valuable opportunity to interrogate early pregnancy events prior to the onset of the maternal syndrome.

Unraveling the Mystery of Preeclampsia

There is a growing body of evidence, both mouse and human, that supports the concept that early pregnancy events, such as uterine receptivity, implantation, and decidualization, have “ripple effects” that impact downstream pregnancy outcomes.

These periimplantation events rely on appropriate ovarian hormone signaling as well as vasoactive agents, cytokines, growth factors, transcription factors, and



morphogens that act in an autocrine, paracrine, and juxtacrine fashion. Dysregulations in any of these pathways have been linked to adverse pregnancy outcomes, such as placental insufficiency, intrauterine growth restriction, and preeclampsia. Interestingly, our recent data reveal that the BPH/5 mouse develops profound periimplantation defects, including embryo clustering, deferred implantation, defective decidualization, and altered ovarian hormone profiles that are associated with an abnormal molecular signature of embryo-uterine interactions. These early pregnancy changes of the maternal-fetal interface occur prior to the observed angiogenic imbalance seen during BPH/5 pregnancy. Indeed, inadequate uterine angiogenesis/vascularity at the time of implantation has been suggested.

Summary

Preeclampsia is a multifactorial disease of pregnancy whose onset is sudden and without warning. Although the diagnosis of preeclampsia is made by the clinical presentation of the maternal syndrome, the origins of preeclampsia begin much earlier in pregnancy. The use of certain animal models affords researchers the opportunity to investigate these key early pregnancy events, such as implantation, that may cause preeclampsia but cannot be thoroughly examined in humans. **EN**

CLINICAL RESEARCHER PERSPECTIVE — *Ravi I. Thadhani, MD, MPH*

Maternal and Fetal Health

Preeclampsia classically presents as hypertension and proteinuria at > 20 weeks of gestation and/or < 48 hours after delivery. Its severity is classified based on the degree of hypertension and proteinuria and the presence of concomitant symptoms that occur secondary to kidney, brain, liver, and cardiovascular system involvement. There is currently no acceptable treatment, except for termination of the pregnancy and removal of the placenta. Although this benefits the mother, this solution is highly detrimental to the fetus, primarily when preeclampsia occurs very early in gestation.

Women with a history of preeclampsia have a higher risk for a recurrence and are more likely to have adverse pregnancy outcomes (preterm delivery, fetal growth restriction, abruptio placentae, and fetal death) in subsequent pregnancies. Neonatal mortality in hypertensive women is related to the infant's birthweight and gestational age of delivery, therefore, prolongation of gestational age is of significant benefit for the preterm neonate. However, since delivery is the only definitive treatment for preeclampsia, delaying delivery of the fetus leaves the mother in a vulnerable, hypertensive state that increases the risk of adverse maternal outcomes.

Risk Factors

Known risk factors associated with preeclampsia include the presence of antiphospholipid antibody syndrome, chronic hypertension, chronic renal disease, elevated body mass index, maternal age older than 40 years, multiple gestation, nulliparity, and pregestational or gestational diabetes mellitus. Urinary tract infection and periodontal disease during pregnancy have also been associated with an increased risk of preeclampsia, although evidence of relationships with other maternal infections such as HIV, chlamydia, CMV, or mycoplasma is lacking. Unfortunately, known risk factors, with the exception of first pregnancy, explain less than 25% of all women who develop preeclampsia.

Although the etiology of preeclampsia is not completely understood, numerous factors have been proposed to contribute to the development of preeclampsia, including lipoproteins, proinflammatory cytokines, chemokines and adhesion molecules, procoagulant molecules, and homocysteine, but the evidence to support the association with many of these factors remains weak.

Expression Analysis and Therapeutic Targets

By gene-expression profiling of placenta derived from women with and without preeclampsia, researchers

have identified that messenger RNA encoding for Fms-like tyrosine kinase 1 (sFlt-1) is upregulated in preeclamptic placentas. sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor Flt-1, and in the circulation, acts as a potent VEGF and placental growth factor (PlGF) antagonist. The sFlt-1 molecule prevents angiogenesis, which is the primary physiologic function of VEGF. VEGF is also important in blood pressure regulation and for maintenance of normal glomerular filtration. The presence of excess circulating sFlt-1, via antagonism of VEGF and PlGF, is believed to lead to endothelial dysfunction, hypertension, and proteinuria and is sufficient to explain critical alterations that characterize preeclampsia.

In fact, administration of sFlt-1 to pregnant rats produces the classic lesion of preeclampsia, namely: hypertension, proteinuria, and glomerular endotheliosis. Endothelial function and renal microvascular reactivity in vitro is restored by exposure to exogenous VEGF and PlGF. Reduction of circulating sFlt-1 in mice by neutralization with adenoviral constructs of sFlt-1 and VEGF has been shown to mitigate preeclampsia-like symptoms.

We demonstrated that highly elevated plasma levels of sFlt-1 and decreased levels of PlGF are present in pregnant women well before and during preeclampsia compared to normotensive controls. The increase in sFlt-1 was observed to occur early in the third trimester and precedes the clinical onset of preeclampsia by approximately three to five weeks. Levels of sFlt-1

together with PlGF can be used to predict subsequent development of preeclampsia and with very high sensitivity and specificity. Recently, others identified a threshold, based on a ratio of sFlt-1/PlGF above 85, that is highly predictive of imminent onset of preterm preeclampsia in pregnant women <36 weeks gestational age. The sensitivity and specificity of this threshold is 82% and 95%, respectively. First trimester screening for women at risk for preeclampsia is also premised on alterations of this pathway, as evidenced by our study on the early trimester changes in PlGF.

Summary

Taken together, these data suggest that such factors can help predict preeclampsia onset and that sFlt-1, by binding to and antagonizing the effects of VEGF and PlGF, may have a role in the pathogenesis of preeclampsia. Along these lines, we have been conducting proof-of-concept clinical studies to determine whether excess sFlt-1 can be removed from the circulation of women with preterm preeclampsia. The intervention to remove sFlt-1 employs short-term apheresis using dextran sulfate adsorption columns and exploits the inherent elevated isoelectric point of the protein. We hope to demonstrate that this intervention (i.e., removal of sFlt-1 by apheresis) mitigates the hypertensive and proteinuria symptoms of preeclampsia and that, ultimately, pregnancies in women with very preterm preeclampsia can be prolonged via such intervention. **EN**

CLINICAL PRACTITIONER PERSPECTIVE — *Ellen W. Seely, MD*

Future Risks in Women with a History of Preeclampsia

The only known cure for preeclampsia is delivery of the pregnancy and although preeclampsia resolves with delivery, it has increasingly been recognized to predict increased risk for cardiometabolic diseases later in life of the affected patient. Therefore, a pregnancy complicated by preeclampsia serves as a “window” to the future, offering the potential to identify women of increased cardiometabolic risk and to intervene to decrease such risk.

History of Preeclampsia and Future Cardiovascular Disease

Over the past decade, there has been an increased focus on the link between a history of preeclampsia and cardiovascular disease (CVD). Several meta-analyses have consistently demonstrated that women with a history of preeclampsia have increased risk for CVD and cerebrovascular disease. According to the most recent meta-analysis, the odds ratio for an

association between a history of preeclampsia and subsequent CVD was 2.28 (95% confidence interval, [CI], 1.87 to 2.77) and subsequent cerebrovascular disease was 1.77 (95% CI, 1.43 to 2.21). These results were similar to prior meta-analyses. Of note, some but not all, of the meta-analyses suggest that women with preterm (less than 37 weeks gestation) preeclampsia have the highest risk for CVD. In addition, in a survival analysis, women with a history of preeclampsia had increased risk of CVD death (hazard ratio 2.14 [95% CI, 1.29 to 3.57]). The risk of CVD death was magnified in women with preterm (less than 34 weeks gestation) preeclampsia (hazard ratio 9.54 [95% CI, 4.50 to 20.26]).

History of Preeclampsia and Cardiometabolic Disease Risk Factors

Women with a history of preeclampsia have increased relative risk (3.13, 95% CI, 2.51 to 3.89) for the development of chronic hypertension, a major risk factor for both CVD and stroke. Some data suggest that women with prior



preeclampsia are also at increased risk for Type 2 diabetes mellitus, another important risk factor for CVD. Dyslipidemia, with high triglyceride and low HDL cholesterol levels, has been reported in women with a prior preeclampsia.

A major limitation of current data is that studies are not controlled for many risk factors for CVD that may have developed subsequent to the pregnancy complicated by preeclampsia. This is important as some of these factors are risk factors for both the development of preeclampsia and for the development of CVD, such as obesity. In addition, lack of agreement upon and changes in the definitions of preeclampsia over time make the study populations heterogeneous and not directly comparable.

Link between a History of Preeclampsia and Future CVD

Since preeclampsia and cardiovascular disease share common risk factors (e.g., obesity), it remains unclear whether preeclampsia unmasks CVD risk predisposition or whether it actually causes cardiovascular injury leading to CVD or a combination of these two. Given these issues, more research is needed to better understand the pathophysiologic link between a history of preeclampsia and future CVD. Such an understanding may lead to more targeted interventions to decrease CVD in women with this history.

Clinical Recommendations for Women with a History of Preeclampsia

Given the strength of the association of prior preeclampsia with CVD, the American Heart Association (AHA) and the American College of Obstetrics and Gynecology (ACOG) have recently recommended that all women be asked about a history of preeclampsia when assessing CVD risk. When present, this history should be considered as a CVD risk factor. The AHA recommends that women with a history of preeclampsia be advised to stop smoking, follow a “Dietary Approaches to Stop Hypertension”-like diet, lose



weight if overweight or obese, and engage in physical activity. Studies are needed to determine whether these lifestyle measures will decrease CVD events in women with a history of preeclampsia or whether more targeted therapies are needed.

The ACOG has provided screening recommendations for women with preterm (less than 37 weeks gestation) and recurrent preeclampsia as these women appear to be at the highest risk for future CVD. The ACOG recommendations include follow up of blood pressure and weight as well as laboratory determination of fasting glucose and lipids. The interval at which these should be determined is not specified. Determining whether these screening recommendations will allow for interventions that will decrease CVD risk is not known and requires further study. Furthermore, whether women with preeclampsia at term would also benefit from this monitoring is unknown.

Summary

In summary, a clinical history of preeclampsia is associated with increased risk for CVD. Whether this risk is mediated solely through traditional CVD risk factors or through factors unique to prior preeclampsia requires further study. Given the strength of this link, women should be asked about a history of preeclampsia as a risk factor for CVD similar to the recommendation that a history of gestational diabetes be obtained as a risk factor for Type 2 diabetes. If a history of preeclampsia is obtained, attention should be focused on identifying and treating traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes). Studies are needed to determine whether treatment of these risk factors is sufficient to decrease CVD in women with prior preeclampsia or whether more targeted treatment is required in this population. We are currently studying whether lifestyle modification can decrease progression to hypertension in women with recent preeclampsia. **EN**

ACKNOWLEDGEMENTS

Abir Mukherjee, MSc, PhD, Royal Veterinary College, University of London, is the Research Affairs Core Committee member who suggested this topic and participated in the review.

Research Affairs Core Committee Co-Chairs: Corrine K. Welt, MD, University of Utah, and Daniel J. Bernard, PhD, McGill University

The following studies, among others, will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals at www.endocrine.org.

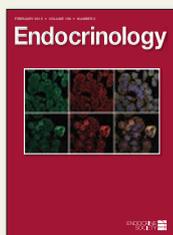


Why Does Rate of Bone Density Loss Not Predict Fracture Risk? • William D. Leslie, Sumit R. Majumdar, Suzanne N. Morin, and Lisa M. Lix • *The low correlation between past and future BMD loss helps explain why the rate of BMD loss is unlikely to be helpful for refining fracture risk.*

A Novel Insulin Resistance Index to Monitor Changes in Insulin Sensitivity and Glucose Tolerance: The ACT NOW Study • Devjit Tripathy, Jeff E. Cobb, Walter Gall, Klaus-Peter Adam, Tabitha George, Dawn C. Schwenke, MaryAnn Banerji, George A. Bray, Thomas A. Buchanan, Stephen C. Clement, Robert R. Henry, Abbas E. Kitabchi, Sunder Mudaliar, Robert E. Ratner, Frankie B. Stentz, Peter D. Reaven, Nicolas Musi, Ele Ferrannini, and Ralph A. DeFronzo • *In IGT subjects, Quantose MQ parallels changes in insulin sensitivity and glucose tolerance with pioglitazone therapy. Due to its strong correlation with improved insulin sensitivity and its ease of use, Quantose MQ may serve as a useful clinical test to identify and monitor therapy in insulin-resistant patients.*

Combined Training Enhances Skeletal Muscle Mitochondrial Oxidative Capacity Independent of Age • Brian A. Irving, Ian R. Lanza, Gregory C. Henderson, Rajesh R. Rao, Bruce M. Spiegelman, and K. Sreekumaran Nair • *Combined training provides a robust exercise regimen to improve muscle mitochondrial outcomes and physical characteristics independent of age.*

Iron Deficiency, an Independent Risk Factor for Isolated Hypothyroxinemia in Pregnant and Non-pregnant Women of Childbearing age in China • Xiaohui Yu, Zhongyan Shan, Chenyan Li, Jinyuan Mao, Weiwei Wang, Xiaochen Xie, Aihua Liu, Xiaochun Teng, Weiwei Zhou, Chenyang Li, Bin Xu, Lihua Bi, Tao Meng, Jianling Du, Shaowei Zhang, Zhengnan Gao, Xiaomei Zhang, Liu Yang, Chenling Fan, and Weiping Teng • *An association between ID and isolated hypothyroxinemia was found in both pregnant and childbearing-aged women independent of the effects of iodine and thyroid autoimmunity. We speculate that ID may be a pathogenic factor for hypothyroxinemia, even in pregnant women during the first trimester.*

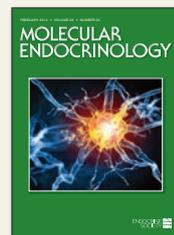


Sim1 Inhibits Bone Formation by Enhancing the Sympathetic Tone in Male Mice • Xunde Wang, Wei Wei, Andrew R. Zinn, and Yihong Wan • *These findings reveal Sim1 as a critical yet previously unrecognized modulator of skeletal homeostasis that functions through a central relay.*

Nedd4 Haploinsufficient Mice Display Moderate Insulin Resistance, Enhanced Lipolysis, and Protection against High-Fat Diet Induced Obesity • Jing Jing Li, Robert J. Ferry Jr., Shiyong Diao, Bingzhong Xue, Suleiman W. Bahouth, and Francesca-Fang Liao • *Combined, these data support novel complex roles for Nedd4 in metabolic regulation involving altered insulin and β -adrenergic signaling pathways.*

Impact of Gestational Bisphenol A on Oxidative Stress and Free Fatty Acids: Human Association and Interspecies Animal Testing Studies • Almudena Veiga-Lopez, Subramaniam Pennathur, Kurunthachalam Kannan, Heather B. Patisaul, Dana C. Dolinoy, Lixia Zeng, and Vasantha Padmanabhan • *This study provides evidence of the induction of nitrosative stress by prenatal BPA in both the mother and fetus at time of birth and is thus supportive of the use of maternal NY as a biomarker for offspring health.*

Maternal Adiponectin Controls Milk Composition to Prevent Neonatal Inflammation • Zixue Jin, Yang Du, Adam G. Schwaid, Ingrid W. Asterholm, Philipp E. Scherer, Alan Saghatelian, and Yihong Wan • *The authors' findings reveal adiponectin as a dosage-dependent regulator of lactation homeostasis and milk quality that critically control inflammation in the nursing neonates. Furthermore, these results suggest that inflammatory infantile disorders may result from maternal adiponectin dysregulation that can be treated by TLR2/4 inhibition.*



Sustained Reprogramming of the Estrogen Response Following Chronic Exposure to Endocrine Disruptors • Andrea R. Patterson, Xiaokui Mo, Ali Shapiro, Karen E. Wernke, Trevor K. Archer, and Craig J. Burd • *Taken together, these data demonstrate that chronic exposure to endocrine-disrupting compounds can permanently alter physiological hormone signaling.*

Mitochondrial Malic Enzyme 3 Is Important for Insulin Secretion in Pancreatic Beta Cells • Noaman M. Hasan, Melissa J. Longacre, Scott W. Stoker, Mindy A. Kendrick, and Michael J. MacDonald • *The data suggest that ME3, far more than ME1 or ME2, is necessary for insulin release. As ME3 enzyme activity is low in beta cells, its role in insulin secretion may involve a function other than its ME catalytic activity.*

Actions of the Small-Molecule Ligands SW106 and AH-3960 on the Type-1 Parathyroid Hormone Receptor • Percy H. Carter, Thomas Dean, Brijesh Bhayana, Ashok Khatri, Raj Rajur, and Thomas J. Gardella • *The study helps to elucidate potential mechanisms of small-molecule binding at the PTH1R.*

Team Spirit



The decision to go from your own practice to working for a group or a hospital requires thought and planning...and preparing for the worst.

By Kurt Ullman

Between an aging physician population, the high capital requirements of new technologies, and the lowering of physician payments, the number of doctors entertaining employment offers from hospitals or practice groups is increasing. A 2011 MedSynergies study found that 70% of responding health systems and hospitals planned to increase their employed physician numbers over the next 36 months.

“Physicians are wondering more and more if they really want to worry about the business aspects of medicine,” says Mary Witt, senior vice president for the Camden Group, a consulting firm in El Segundo, Calif. “The complexities of running a medical practice have increased while reimbursements are going down and expenses trending up. Many doctors are wondering if it wouldn’t be best just to become an employee and focus on taking care of patients.”

What Do I Want?

There are many considerations in making the switch from self-employed to working for a hospital or large group. Most flow from you sitting down and fully answering the question “What do I want?”

“I talk about the Big Three of practice change,” says Nick Fabrizio, principal consultant with the Medical Group Management Association Healthcare Consulting

Group headquartered in Englewood, Calif. “It is about compensation, control of your practice, and your fit with the potential partners. Once you peel away the onion around those issues, there are around 100 other things that will fall in line.”

He suggests a number of questions you should ask yourself. In many ways, compensation may be both the easiest and more challenging part of the discussions. You have to not only look at and understand what you will be paid but also how. Are there any performance standards that might impact the size of your check? What is the amount of your salary, and exactly what are you expected to do for the paycheck?

You will probably have the equivalent of a job interview with the people you will be sharing your office with. You should also interview them as if they were coming to work for you.

Control Issues

The issue of control is another one that a physician should sit down and think long and hard about. Will you still be able to practice the way you are now, or will there be constraints put on you by the policies of the employer? How many patients will you be expected to see? Can you stay in the same office, or will you have to move? What is the status of your staff, and will they be

able to come along? Can you tolerate no longer being the captain of your own ship?

The importance of addressing these questions and making sure you are comfortable with the answers is reinforced by another concern. If you enter an employment situation and are not happy, it is much more difficult to go from employed back to self-employed.

Hard To Go Back

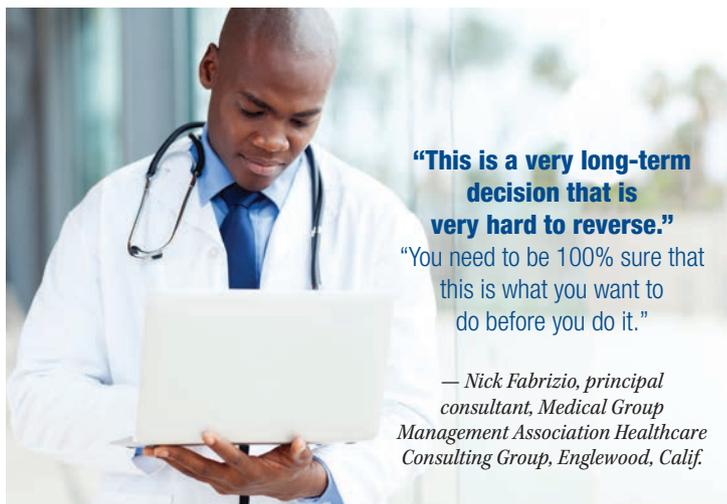
“One of the biggest barriers to transition back is getting the capital required to start a new practice,” Witt says. “You have to cover renting and equipping an office, hiring staff, and covering cash flow needs while you build up the practice.”

A part of the change that may not be immediately recognized when doing your planning is that most of the infrastructure you rely on will disappear. You will have to work out new referral patterns and negotiate payer contracts. With the rise of narrow networks, there is a chance that you will not be able to retain all of your patients. In addition, you no longer have the clout of a group when negotiating with insurance companies.

“Another consideration is ownership of the medical records,” Witt says. “In most cases, they will belong to the group, and you won’t be able to automatically take them with you when you leave.”

Many physicians do not take into consideration non-compete agreements. Depending on the contract and local law, you may not be able to practice within a 30-mile or more radius of the group for up to two years. This gives the twin concerns of how do you make a living for that time and how many of your patients will want to find you when the agreement has expired.

Extricating yourself from a bad situation may be



“This is a very long-term decision that is very hard to reverse.”

“You need to be 100% sure that this is what you want to do before you do it.”

— Nick Fabrizio, principal consultant, Medical Group Management Association Healthcare Consulting Group, Englewood, Calif.

easier if you are going from one group to another. You may get a better environment while still retaining the infrastructure and capital clout that isn’t available among the self-employed.

Exit Strategies

Although it may seem as though you are preparing to fail, experts agree that it is often in your best interests to include exit strategy considerations in all phases of the change.

“This is a very long-term decision that is very hard to reverse,” Fabrizio says. “You need to be 100% sure that this is what you want to do before you do it.” **EN**

— Ullman, RN, MHA, is an Indiana-based freelance writer with nearly 30 years of experience. He wrote about enhancing nurses’ job satisfaction in the January issue.

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ENDOCRINE SOCIETY

LAB EQUIPMENT: BUY, LEASE, or RENT?

Whether you should buy or rent your equipment depends on the type of research you're doing, how often the equipment will be used, and a variety of other considerations.

By Melissa Mapes

The lightning-fast pace of technology has one big downside: the rate of obsolescence. Replacing out-of-date equipment every couple of years requires a big investment, and sometimes the cost is prohibitive. Depending on a number of variables, it makes more sense to lease or rent equipment for some labs — especially for short-term research projects and startups.

Laboratory managers and researchers have to consider several factors when deciding whether to buy their equipment or not. Credit history, the anticipated project lifespan, and tax implications are a few of the factors that must be taken into account when choosing a “procurement model.” Each of these three models offers different benefits and downsides, and, often, the best choice depends on the piece of equipment itself.

Buy

A scenario analysis by *Lab Manager* magazine shows that purchasing laboratory equipment outright only makes sense if it is built to last for at least three years. If the machinery will be operated frequently and can sustain a long life with a consistent level of performance, buying is worth the investment. Equipment “used every day or every week continuously in the research and development

process” falls into this category, according to *Lab Manager*.

Smart shoppers give their business to manufacturers that provide a warranty and repair services. Inevitably, large and complex equipment needs maintenance to survive the day-to-day wear and tear over the course of many years. Research projects that require customization of lab equipment also necessitate a deal that includes such alterations by the experts that built the machine. Trying to make the alterations oneself could result in broken machinery that is no longer covered under warranty after tinkering by the new owner — a potentially expensive error.

With alteration and maintenance services built-in, finding affordable equipment — new or used — becomes a real challenge. Organizations may need to pay top dollar to ensure a high degree of quality and customer care. For this reason, *Lab Manager* explains, “major pharmaceutical and life science companies, contract research organizations, and government research institutes” are the primary buyers of equipment. They tend to have the necessary cash and use expensive tools frequently enough to justify the cost.

Banks do offer loans for purchasing lab equipment for those willing to take on debt in order to own.

However, the added cost of interest combined with the depreciating value of the devices often make this option less appealing than leasing or renting. Generally, medium- to low-end equipment is the best to buy, rather than invest a large amount of funds in a high-end piece of equipment that may not be used frequently.

Lease

Researchers often procure high-end equipment through a lease rather than buying. Companies with small budgets, universities, research and development labs, and companies from chemical, agricultural, and other industries rely heavily on leases, according to *Lab Manager*.

Leasing offers more flexibility and comes in two forms: capital leases and operating leases. A capital lease, sometimes referred to as “rent-to-own,” means that the lessor transfers ownership to the lessee at the end of the lease period. Interest rates are often higher than operational leases because the lab will eventually own the equipment — a similar situation to taking out a loan to purchase.

Lessees need to make sure that the lease includes the same services as the warranty that would come with an outright purchase. Maintenance and customizations are generally included in the package, and any capital lease without these stipulations should be avoided. Because the lessee eventually takes ownership, they want to know that the equipment has been well cared for and has a lifespan of more than three years. A capital lease also only makes sense for machinery that is not subject to frequent upgrades, as it could otherwise become obsolete.

Operating leases work well in the case of shorter lifespan equipment that needs to be replaced in three years or less. Lessees do not own the equipment at the end of the term but are also not responsible for buying newer versions of the devices. Instead, they can usually opt to upgrade if a new version is released during the term of the lease.

For projects that require customized equipment, an operating lease is not an option. The equipment is rented to other labs after the end of term, so it needs to stay in its original condition. Research that requires alterations to the machinery will need to find a capital lease or the funds to purchase the device outright. Only maintenance and other standard services are included in an operating lease.

Rent

Similarly, alterations cannot be made to rented equipment. Renting fits best with short-term projects that need the machinery for less than a year. *Lab Manager* claims that the best type of equipment to rent is that which is only occasionally used, generally on an ad-hoc basis, such as gas chambers. Rental contracts are available for low-end equipment as well.

Renting is more expensive in terms of price for the amount of time the equipment is in a laboratory, so it is not advisable to pursue renting as a long-term solution.



Procurement Models **BREAKDOWN**

High-end equipment

- Lease if it will be used daily or weekly and last >3 years
- Get a capital lease if it needs customization
- Rent if it will be used infrequently or for a short period of time

Mid-range equipment

- Buy if it will be used frequently, last >3 years, and the funds are available
- Get an operational lease if it is an equipment type that involves frequent upgrades
- Get a capital lease if it needs customization but is out of budget to buy
- Rent if you only need it for a brief time period

Low-end equipment

- Buy or get a capital lease if it will be used frequently and last >3 years
- Buy or get a capital lease if it needs customization
- Get an operational lease if it is an equipment type that involves frequent upgrades
- Rent if you only need it for a brief time period

But, it is far more convenient and sensible when a tool is only needed for a matter of days or weeks. “Acquiring equipment for temporary usage through buying or leasing incurs more cost and less return,” says *Lab Manager*.

Private organizations and universities are the largest renting demographic. They mostly go through equipment distributors for their short-term device needs. Often, rental equipment has been put to use in many labs by many different individuals, so the best type of equipment to rent is durable machinery with a relatively long shelf life.

Rent, lease, or buy — each procurement model serves a valuable purpose. The tough part is picking the best choice for each device. Laboratory managers and researchers can save serious money and reduce liability by selecting the right equipment plans for their projects. By keeping in mind the frequency of use, cost, and nature of the machine, the best option should quickly come to light. **EN**

— *Mapes is a Washington, D.C. - based freelance writer and a frequent contributor to Endocrine News. She wrote about the “Plan B” pill and overweight women in the August issue.*



Endocrine Society Increases Global Recognition in EDC Field

The Endocrine Society is committed to improving awareness and understanding of endocrine-disrupting chemicals (EDCs) in the U.S. and globally. Since the 2009 release of its Scientific Statement on EDCs, the Society has advocated for more research on EDCs and for the endocrine perspective to be incorporated into chemical risk assessment paradigms. Because of the Society's scientific expertise, it has been able to influence policy decisions and it has become recognized as a leading scientific organization in this area. In recent months, the Society has advanced its global agenda on EDCs through participation in the Strategic Approach to International Chemicals Management (SAICM), a global policy framework to protect people and the environment from hazardous chemicals. The Society also worked to ensure that the European Parliament takes the latest endocrine science into account as the European Union seeks to regulate EDCs.

Brussels Events Build Society's Reputation as Thought Leader in EDC Field

On November 11, 2014, the Society hosted a special event for members of the European Parliament in Brussels, Belgium. More than 30 people attended the Society's presentation, including four members of the European Parliament (MEPs) as well as other policy makers, journalists, and representatives from environmental health non-governmental organizations.

MEPs Sirpa Pietikainen (Finland) and Pavel Poc (Czech Republic) sponsored the event and framed the conversation about the threat posed by EDCs. The presentations prompted spirited discussion about the best way to regulate EDCs. The event helped establish the Society as a key resource and advisor for policy makers seeking to understand and address this issue.

In conjunction with the Parliament event, the Society held its first-ever media event in the EU. The Science Writers Conference on Endocrine-Disrupting Chemicals took place at the International Press Centre in Brussels on November 12. The *Daily Mail* wrote an in-depth article previewing the conference. The event also generated attention from CNBC. Seven journalists and public

information officers attended the event, including representatives from *Le Monde* and *New Scientist* magazine. Featured presenters from the Society's EU EDC Task Force were: R. Thomas Zoeller, PhD, Jean-Pierre Bourguignon, MD, PhD, Barbara Demeneix, PhD, DSc, Remy Slama, PhD, and Richard Ivell, PhD.



The event laid the foundation for the Society to serve as a key source for European journalists covering EDCs and the regulatory process.

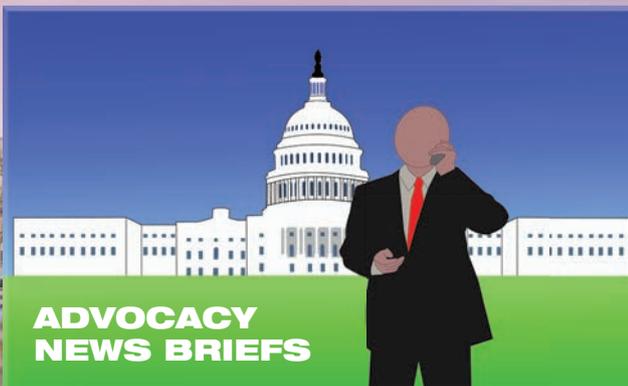
Highlights from the Science Writers Conference are available on the Society's YouTube channel as a valuable resource for other journalists.

On December 15 through 17, the Endocrine Society discussed key endocrine concepts and principles that should be incorporated into the SAICM. Endocrine Society experts from the Global EDC Task Force, Thomas Zoeller, PhD, Jean-Pierre Bourguignon, MD, PhD, and Riana Bornman, MBChB, delivered comments at the second meeting of the SAICM Open-ended Working Group in Geneva, Switzerland.

The Society's public comments emphasized the

Society Members Bring Endocrine Perspective to Global Meeting on Chemical Management

The Society's public comments emphasized the



importance of considering several key characteristics of EDCs in chemicals management approaches. The Society noted that a single hormone will have changing effects at different times and places in the body during development and with different sensitivity; therefore, sensitive endpoints with predictive ability must be prioritized to identify endocrine disruptors. Additionally, hormones act at very low concentrations so the effects of very small amounts of endocrine disruptors need to be taken into account systematically. Finally, chemical interference with hormone actions during early development can have long-lasting, even permanent, consequences that might manifest years later, and endocrine disruptors can set up the body for mis-adaptation.

The Society also recommended a number of activities for SAICM to consider implementing toward the SAICM goal of “sound management of chemicals throughout their life cycle so that, by 2020, chemicals are produced and used in ways that minimize significant adverse impacts on human health and the environment.” The Society recommended that SAICM:

- Assemble a list of EDCs and sources of exposure from the UNEP/WHO State of the Science report and make it publically available and regularly updated on the UNEP website by 2015;
- Conduct substantial monitoring studies of EDCs by 2018 in countries selected in the four UN regions based on stakeholder proposals;
- Gather and disseminate examples of best available practices in reducing the use of 20 EDCs, including safer substitution, non-chemical alternatives, and risk-management by 2018;
- By 2020, derive strong public health and environmental protection policies from understanding of how chemicals disrupt normal physiology;
- Finally, prepare and conduct robust awareness-raising beginning in 2015 and continuing until 2020, involving healthcare and medical professionals and including outreach to vulnerable groups.

ADVOCACY NEWS BRIEFS

Inside Washington: What to Expect from the New Congress

The 114th Congress officially opened January 5 in Washington, D.C., with Republicans in the majority in both the House of Representatives and the Senate setting up one agenda while Democrat Barack Obama has the authority of the presidential veto in the White House. The Endocrine Society will continue to advocate on issues of importance to our members including: federal funding of biomedical research, physician payment, diabetes, obesity, endocrine-disrupting chemicals, hormones and aging, and quality improvement. Below is a summary of the major issues that loom large on the congressional agenda this year and what to expect:

Affordable Care Act

The issue: Republicans have been trying to repeal the healthcare law since its enactment in March 2010. Although they continue to campaign on repeal, GOP lawmakers have acknowledged that it is essentially impossible as long as President Obama is in the White House.

What to expect: Republicans may symbolically pursue legislation to repeal the overhaul through both the budget and appropriations process by targeting provisions some Democrats have opposed, such as the excise tax on medical devices, the Independent Payment Advisory Board (IPAB), and the 30-hour definition of full-time work. While they may talk about proposals to replace the law, there is skepticism that they could be able to coalesce behind legislation.

Doc Fix

The issue: Congress passed a one-year patch to temporarily protect Medicare physicians from scheduled cuts after lawmakers were unable to agree on a way to pay for a permanent policy compromise. It expires at the end of March.

What to expect: The Endocrine Society and others in the physician community will fiercely lobby for Congress to pass a permanent fix ahead of the March expiration date. Although lawmakers came to a policy agreement in early 2014, finding a way to pay for its significant price tag — estimated to



be about \$138 billion over 11 years — will continue to be no easy lift and could result in Congress passing its 18th patch since 2003 to avert a Medicare physician payment cut.

21st-Century Cures

The issue: Last spring, House Energy and Commerce Committee Chairman Fred Upton (R-MI) announced the launch of 21st-Century Cures, a new initiative that aims to accelerate the pace of cures and medical breakthroughs in the U.S. Chairman Upton, along with committee member Representative Diana DeGette (D-CO) led the committee in taking a comprehensive look at the full arc of this process — from discovery to development to delivery — to determine what steps Congress could take to ensure we are taking full advantage of the advances this country has made in science and technology and use these resources to keep America as the innovation capital of the world. During 2014, the committee received input from the National Institutes of Health (NIH), Food and Drug Administration (FDA), and other agencies, as well as the Endocrine Society and other leaders in academia and industry. Now, the committee has announced it plans to introduce legislation early in the Congress with the aim of passing by Memorial Day.

What to expect: Because support of medical research is one of the truly bipartisan issues within Congress and the committee has engaged all stakeholders, many Congress watchers believe this is one of the pieces of legislation that has “legs.” The Endocrine Society has weighed in on several issues related to reducing burdens on scientists, recruiting and retaining the next generation of scientists, and recognizing sex as a critical biological variable in pre-clinical and clinical research. We will continue to advocate on these issues and keep members apprised of developments.

Budget Process

The issue: The Republican leadership wants to show that it can use its newfound control of Congress to make progress on fiscal and economic issues. It is almost a sure thing that the House and Senate Budget committees will employ a filibuster-proof process known as reconciliation, which can be used to make changes in mandatory spending programs, taxes, and the debt limit. Behind the scenes, Republicans are debating whether to use the reconciliation process to pass more modest changes in policies that have a chance of being signed by the president, or to send President Obama a more sweeping product. One of the most pressing questions is how the budget plans will treat discretionary spending in the upcoming fiscal year, which begins October 1. Under

the current debt limit law, the defense cap will rise by \$1.7 billion while the non-defense cap will fall by about \$1 billion. Many Republicans contend that defense is underfunded, but not all of them are willing to break the budget caps unless Democrats agree to offset spending cuts elsewhere.

What to expect: Like a budget resolution, a reconciliation bill only needs 51 votes to pass in the Senate, not the 60 needed to end debate. But unlike a budget resolution, it is regular legislation, which means it must be signed by the president to become law. In the House of Representatives, it is likely Republicans will craft a plan that shows a balanced budget and the deficit disappearing in 10 years, if not less. The House Democrats are also likely to offer an alternative budget. In the Senate, it is also clear that Democrats will fight any attempts to cut Social Security and other mandatory programs.

Appropriations

The issue: Republican leaders are eager to show voters that they can govern in full control of Congress. But other political factors — mainly the push for higher defense spending and the desire to challenge the president on immigration, healthcare, the environment, and Wall Street regulations — will significantly complicate any efforts to pass spending bills in the 114th Congress.

What to expect: A big factor that could determine whether appropriators can complete their work will be what defense and non-defense top-line spending levels the Budget committees set for fiscal year 2016, which will guide the work for the appropriations panels. There is pressure from many Republicans to increase defense spending for FY 2016 above the level in the current deficit law. Democrats, whose votes would be needed to get spending measures through the Senate, will insist on equal boosts for non-defense spending. Any budget deal that does not include such a compromise would likely draw a veto threat from the White House. If Republicans pass a budget resolution that boosts defense spending at the expense of domestic programs, like funding for the National Institutes of Health, it could imperil action on non-defense bills. The Republican desire to fight the Obama administration’s signature domestic policy pieces could also make some sort of spending agreement tough to secure this year. But, any provisions that too severely challenge the president would cause Democrats to fight and would likely draw a veto from the president, which could put appropriations work in jeopardy and threaten another government shut-down. **EN**

FIVE MEMBERS ELECTED TO GOVERNING COUNCIL

Endocrine Society members have elected five new officers and council members to lead the Society. These new officers will have a lasting impact on the Society and will help to determine its future direction in the coming years.

The new officers and council members are:

- Henry M. Kronenberg, MD: president-elect
- Richard S. Legro, MD: secretary treasurer-elect
- Anthony L. McCall, MD, PhD: vice president, clinical scientist
- Alan C. Dalkin, MD: council member, physician-in-practice seat
- Beverly M. K. Biller, MD: council member, at-large seat



Kronenberg

Kronenberg will serve as president-elect in 2015 – 2016 and then as president in 2016 – 2017. He is chief of the Endocrine Unit at Massachusetts General Hospital, and is also a professor of medicine at Harvard

Medical School, Boston, Mass. An active Society volunteer for more than two decades, he has served as vice president, basic science, and as a member of the Society's Leadership Council. He also served on a number of Society committees, including the Laureate Awards Committee and Research Affairs Core Committee. He received his MD from Columbia University.



Legro

Legro will serve as secretary treasurer-elect for one year and then begin a three-year term as secretary treasurer (2016 – 2019). He is professor of obstetrics and gynecology and public health sciences at Penn State College

of Medicine in Hershey, Pa. An active Society member for nearly 17 years, he serves on the Finance and Audit Committee and previously served on the Research Affairs Core Committee. He also has served on the editorial boards for *The Journal of Clinical Endocrinology & Metabolism* and *Endocrine Reviews*. He received his MD from Mount Sinai Medical School.



McCall

McCall will serve a three-year term as vice president, clinical scientist (2015 – 2018). He is the James M. Moss Professor of Diabetes at the University of Virginia School of Medicine, Charlottesville, Va., and a member and investigator at UVA Medical Center's Center for Diabetes Technology. He also is medical director for the Virginia Center for Diabetes Professional Education. An active Society member for more than three decades, he has served as clinical science chair for the Society's annual meeting and a member of the Annual Meeting Steering Committee. He received his MD from Medical College of Wisconsin and his PhD from Massachusetts Institute of Technology.



Dalkin

Dalkin will serve a three-year term in the physician-in-practice designated seat on the Council (2015 – 2018). He is professor of medicine in the University of Virginia's Department of Medicine. A Society member for more than 25 years, he is the self-assessment chair for the Society's Scientific and Educational Programs Core Committee and chairs the Self-Assessment Committee. He previously served on the Membership Committee and Journals Managing Subcommittee. He received his MD from the University of Michigan.



Biller

Biller will serve a three-year term as an at-large member of the Council (2015 – 2018). She is a physician at Massachusetts General Hospital and professor of medicine at Harvard Medical School. A Society member for 25 years, she chaired the Scientific and Educational Programs Core Committee and served on numerous committees, including the Laureate Awards Committee and Nominating Committee. A past editor of the *Journal of Clinical Endocrinology & Metabolism*, she also has served as clinical science chair for the Society's Annual Meeting Steering Committee. She received her MD from the University of Oklahoma College of Medicine.

The new officers and council members will begin serving their terms following **ENDO 2015**, which will take place in San Diego, Calif., March 5 – 8, 2015.

The Best of JCEM 2014 Is Now Available

The Best of JCEM 2014 captures the outstanding progress of scientific research made in the field of endocrinology in 2014. A compilation of the most highly rated peer-reviewed articles, this collection highlights a year's worth of important advances and noteworthy developments. These previously published works all appeared on the pages of the *Journal of Clinical Endocrinology & Metabolism* throughout 2014. Each article presents research findings in a different subspecialty of clinical endocrinology. Subspecialties covered include:

- Lipids
- Diabetes
- Obesity
- Thyroid
- Bone/Calcium/Vitamin D
- Female Reproduction
- Male Reproduction
- Genetics
- Adrenal/Pituitary
- Best Clinical Trial

The Best of JCEM 2014 highlights an outstanding quality of research from internationally recognized clinical researchers and scientists. Curated by *JCEM* Editor in Chief, Paul Robertson, this edition will quickly get you up to date on a full range of new research in endocrine science and medicine.

Visit press.endocrine.org/jcem/bestof2014 to view the complete collection online.

Attending **ENDO 2015**? Make sure you schedule time to hear from *The Best of JCEM 2014* authors as they present their research and new updates during a special scientific session at ENDO, Sunday, March 8, 9:30 AM – 12:30 PM. This is an ideal opportunity to celebrate the quality of work published in *JCEM* and to catch up on outstanding progress in all areas of clinical endocrinology. Pick up a free printed copy of *The Best of JCEM 2014* at the Endocrine Society booth in the *ENDOExpo*.



See the Latest and Greatest at ENDOExpo

ENDOExpo 2015
Thursday, March 5 – Saturday, March 7
10:30 AM – 3:30 PM

Poster presentations, the latest innovations in endocrinology, networking opportunities, and great prizes can only mean one thing — time for *ENDOExpo*!

What You Can Expect at the Expo

More than 200 exhibitors will take the floor at *ENDOExpo*—eager to help you advance your practice and research with the most cutting-edge advances in the field. Visit the *ENDOExpo* Theater daily for an even closer look at the next generation of endocrinology products, hosted by exhibiting companies. Seating is limited for these hour-long, non-Continuing Medical Education sessions, so be sure to arrive early.

Stop by the Endocrine Society booth to pick up our popular free pins and learn more about the Hormone Health Network, our journals, and career development opportunities. Don't forget to visit the official ENDO store for gifts and discounted pricing on the Society's best-selling publications.

Get the most from your time at *ENDOExpo*.
Check out our Attendee Dos and Don'ts on endo2015.org
to make sure your experience is efficient
and complies with industry regulations.

There's Always Something New at the Expo

ENDOExpo's new life sciences Pavilion brings clinical scientists and researchers together with today's leading life science companies. This year, we're offering even more presentations and the best in endocrinology imaging.

First up: the *ENDOExpo Lab*, where you can stay current with the most innovative technologies hitting the market during daily presentations by Life Science companies. Also discover the art in science with the first-ever EndoScapes imaging competition, highlighting the creativity, complexity, and beauty of endocrine research. Be sure to vote for your favorites images during *Expo* hours. We'll feature the winning images in the official 2016 Endocrine Society calendar.

Don't Forget to Make Plans to Play

Participate in the third annual *ENDOExpo* Play every day for the most chances to win. One scan of your badge barcode by an exhibitor earns you one entry into *Expo* Play, where you could win an iPad mini, Apple gift card, and other great prizes.

And everyone's favorite ENDO Prize Wheels are back! Give them a spin for a chance to go home with gadgets, gift certificates, T-shirts, and other great prizes.

Society Publishes Clinical Practice Guideline on OBESITY MEDS

The Endocrine Society has issued a Clinical Practice Guideline (CPG) on strategies for prescribing drugs to manage obesity and promote weight loss.

The CPG, entitled “Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline,” was published online and in the February 2015 print issue of the *Journal of Clinical Endocrinology & Metabolism (JCEM)*.

Obesity is a worsening public health problem. According to the 2012 National Health and Nutrition Examination Survey, about 33.9% of adults ages 19 – 79 were overweight, 35.1% were obese, and 6.4% were extremely obese.

The Food and Drug Administration has approved three new anti-obesity drugs — lorcaserin, phentermine/topiramate, and naltrexone/bupropion — in the past two years. Medications like these can be used in combination with diet and exercise to help people lose weight.

“Lifestyle changes should always be a central part of any weight loss strategy,” says Caroline M. Apovian, MD, of Boston University School of Medicine and Boston Medical Center, and chair of the task force that authored the guideline. “Medications do not work by themselves, but they can help people maintain a healthy diet by reducing the appetite. Adding a medication to a lifestyle modification program is likely to result in greater weight loss.”

In the CPG, the Society recommends that diet, exercise, and behavioral modifications be part of all obesity management approaches. Other tools such as weight loss medications and bariatric surgery can be combined with behavioral changes to reduce food intake and increase physical activity. Patients who have been unable to successfully lose weight and maintain a goal weight

may be candidates for prescription medication if they meet the criteria on the drug’s label.

Other recommendations from the CPG include:

- If a patient responds well to a weight loss medication and loses 5% or more of their body weight after three months, the medication should be continued. If the medication is ineffective or the patient experiences side effects, the prescription should be stopped and an alternative medication or approach considered.
- Since some diabetes medications are associated with weight gain, people with diabetes who are obese or overweight should be given medications that promote weight loss or have no effect on weight as first- and second-line treatments. Doctors should discuss medications’ potential effects on weight with patients.
- Certain types of medication — angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers — should be used as a first-line treatment for high blood pressure in obese people with Type 2 diabetes. These are effective blood pressure treatments that are less likely to contribute to weight gain than the alternative medication, beta-adrenergic blockers.
- When patients need medications that can have an impact on weight such as antidepressants, antipsychotic drugs, and medications for treating epilepsy, they should be fully informed and provided with estimates of each option’s anticipated effect on weight. Doctors and patients should engage in a shared decision-making process to evaluate the options.
- In patients with uncontrolled high blood pressure or a history of

SIMINERIO Named Chair of National Diabetes Education Program



Linda Siminerio, RN, PhD, has been named the new chair of the National Diabetes Education Program (NDEP), a joint program of the National Institutes of Health and the Centers for Disease Control and Prevention.

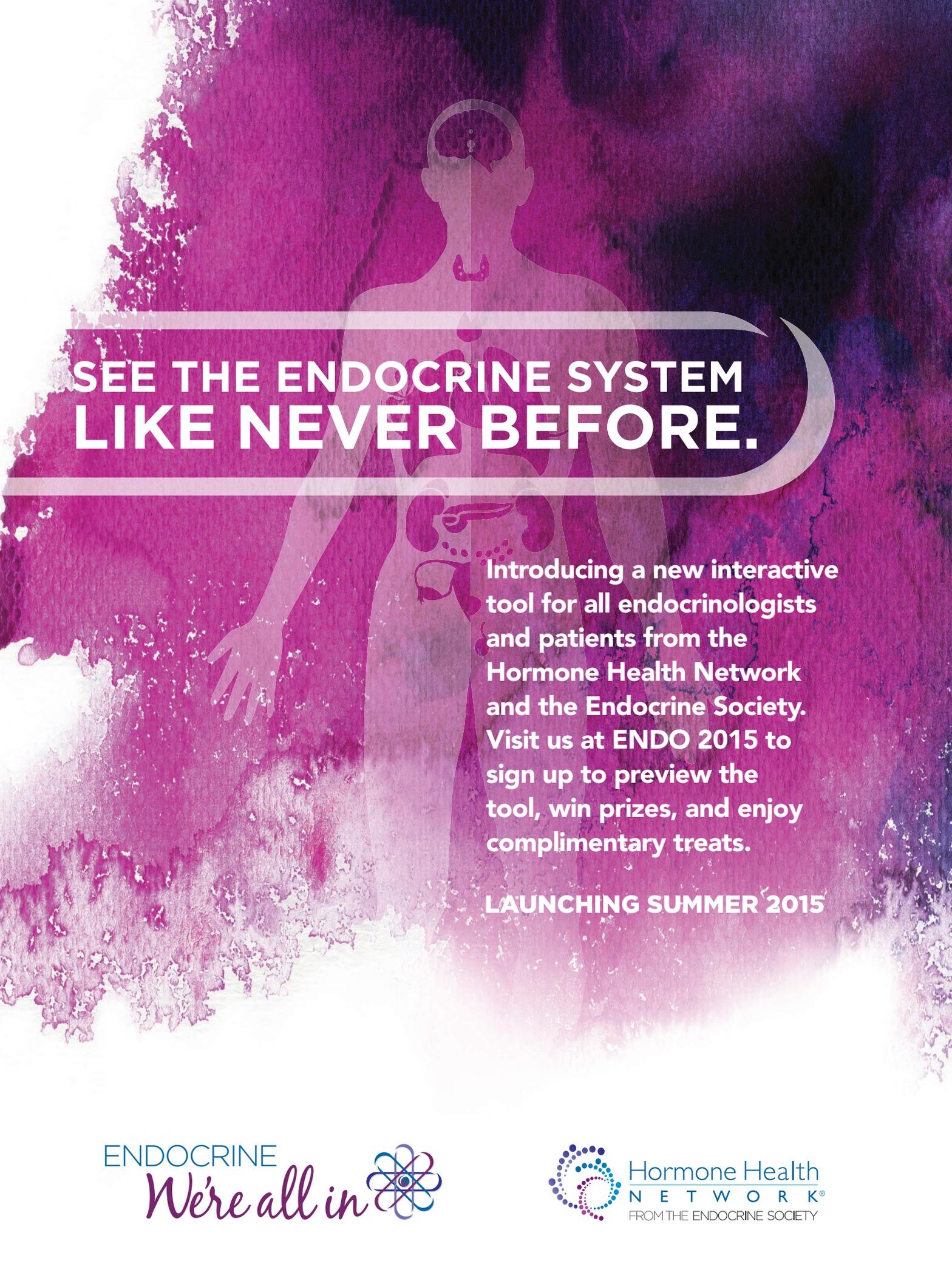
As chair of the NDEP, Siminerio will facilitate the adoption of proven approaches to prevent or delay the onset of diabetes and its complications. Siminerio, who served as executive director of the Diabetes Institute at the University of Pittsburgh, brings more than 40 years of nursing and diabetes-related experience to this position. The Society, which is actively involved in a number of NDEP activities and serves on its strategic directions group, looks forward to working with Siminerio on future endeavors.

For more information, go to <http://ndep.nih.gov>.

heart disease, the medications phentermine and diethylpropion should not be used.

Other members of the Endocrine Society task force that developed this CPG include: Louis J. Aronne, Weill-Cornell Medical College, New York, N.Y.; Daniel H. Bessesen, Denver Health Medical Center, Denver, Colo.; Marie E. McDonnell, Brigham and Women’s Hospital, Boston, Mass.; Mohammad Hassan Murad, Mayo Clinic, Rochester, Minn.; Umberto Pagotto, Alma Mater University, Bologna, Bologna, Italy; Donna H. Ryan, Pennington Biomedical Research Center, Baton Rouge, La.; and Christopher D. Still, Geisinger Health Care System, Danville, Pa.

The CPG was co-sponsored by the European Society of Endocrinology and The Obesity Society. **EN**



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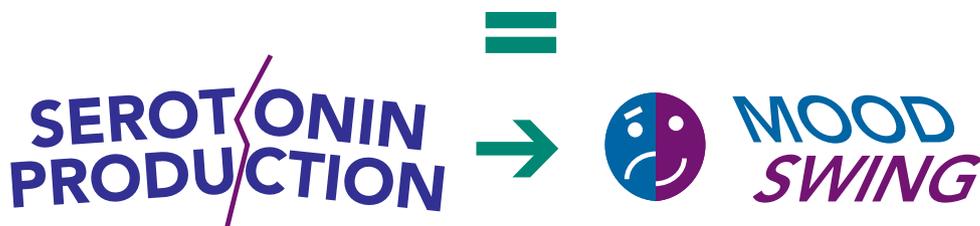
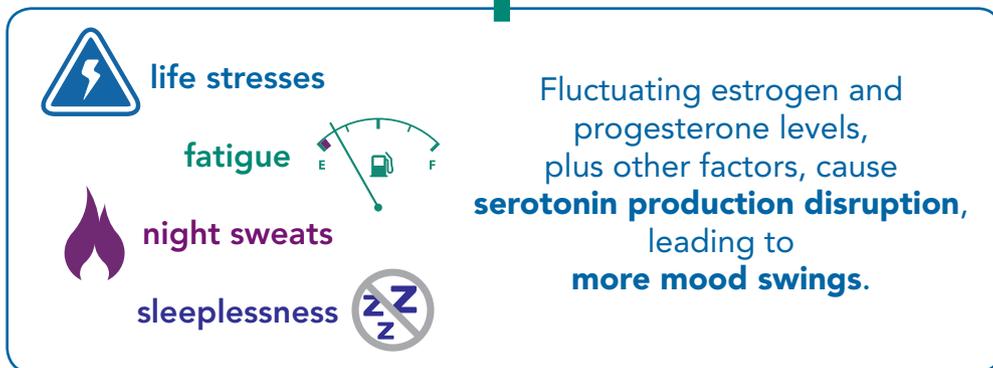
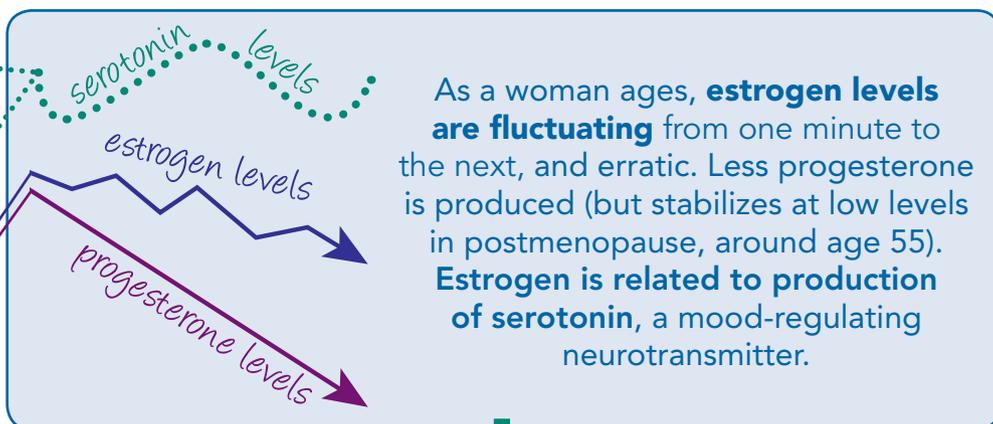
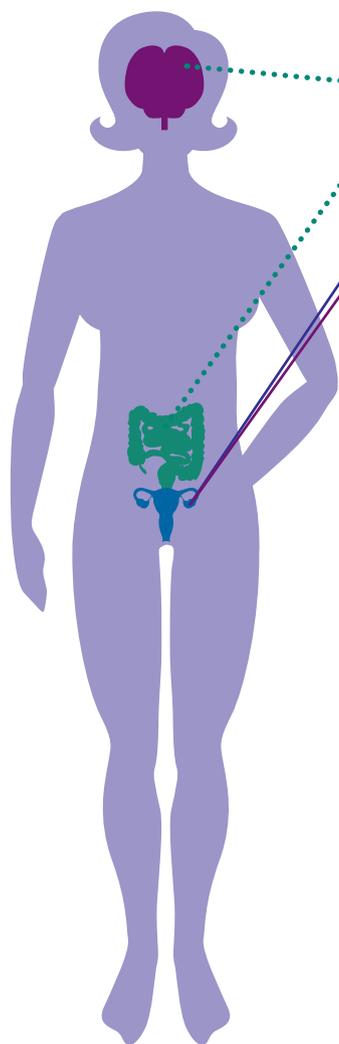
THE ANATOMY OF A MOOD SWING



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You're laughing with your friends one minute and close to tears a few moments later. You feel tired, overwhelmed, and out of control. You're not crazy—it's one of the common symptoms of perimenopause (the first stage of menopause, usually in the early 40s): **mood swings**. And there are ways to cope. Visit hormone.org and menopausemap.org for more information.

What causes mood swings?

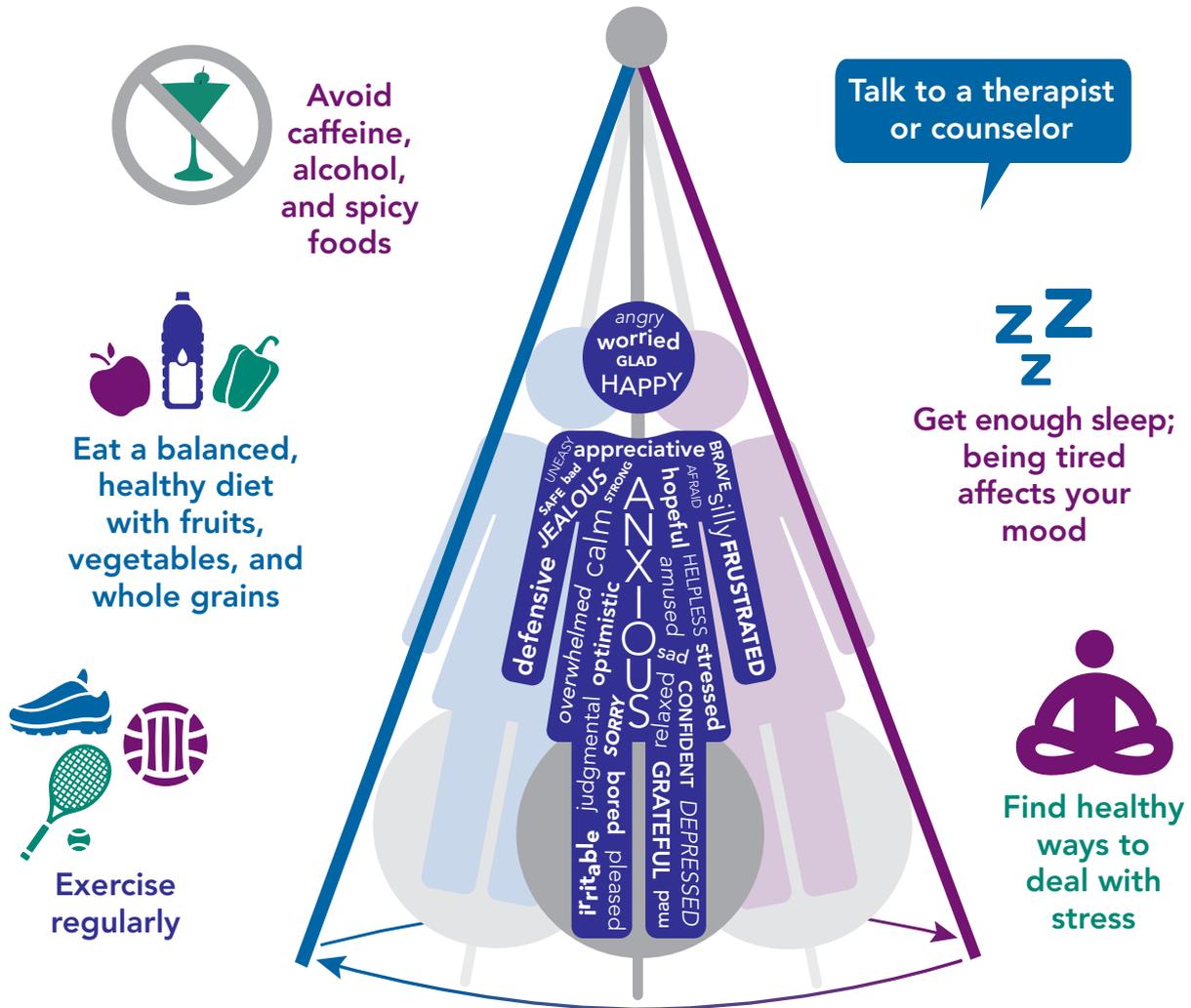


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in the
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Dealing with symptoms of mood swings



- **Hormone therapy:** May help severe mood swings; usually lowest dose for shortest amount of time prescribed (there is no increased risk of breast cancer until after three years of therapy; very few women use therapy for any longer)
- **SSRIs (selective serotonin reuptake inhibitors):** Can be effective in treating mood swings and other symptoms, such as hot flashes and sleep issues, but have side effects; some doctors suggest effectiveness is increased when a woman is first treated with estrogen
- **Complementary alternative medicines (CAM)** such as black cohosh, deep breathing, and soy in some cases; includes treatments such as acupuncture and mind-body therapies such as yoga, tai chi and meditation
- **Low dose birth control pills:** Shuts down the ovarian fluctuation that takes place during perimenopause; offers a fixed dose of estrogen and progesterin every day

Always talk with your health care provider about medications, hormone therapy, and before using CAM supplements.

You have questions. We have answers.

The Hormone Health Network is your trusted source for endocrine patient education. Our free, online resources are available at hormone.org.

Additional editing by Mary Jane Minkin, MD, Yale Medical School

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HMG-CoA
reductase is part
of the LDL-C
metabolism story¹

But PCSK9
also plays an
important role in
LDL-C regulation²

New pathway discoveries are uniting the cholesterol conversation.

By inhibiting HMG-CoA reductase and reducing cholesterol biosynthesis, statins help lower LDL-C.¹ PCSK9, another important protein involved in cholesterol metabolism, promotes degradation of the LDL receptor, thereby increasing LDL-C levels.² **In discussions of cholesterol metabolism, the roles of HMG-CoA reductase and PCSK9 should go hand in hand.**

Join the conversation at DiscoverPCSK9.com.

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **LDL-C** = low-density lipoprotein cholesterol.

References: **1.** Toth PP. *Drugs*. 2010;70:1363-1379. **2.** Zhang D, Lagace TA, Garuti R, et al. *J Biol Chem*. 2007;282:18602-18612.

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