JUNE 2013

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINE news

NEW HORMONE Treatments show promise for Metastatic Prostate Cancer

BIG BOYS Face an Uphill Climb

Does INSULIN DRIVE OBESITY?

- The Bionic Pancreas
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- The Latest Research Studies

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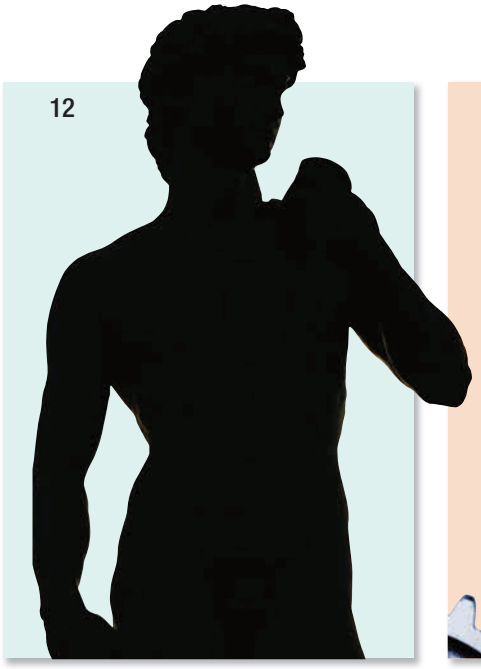

The Endocrine Society®

A Presidential Farewell

As I celebrate the culmination of my presidency at **ENDO** in San Francisco, I look back at the past 12 months with great pride, appreciating the Society's numerous achievements in such a short time. It is remarkable what a group of motivated volunteer members and dedicated staff can accomplish when working together.

William F. Young Jr., MD, MSc

Ambassador Exchange Program and International Activities

The first year of the Ambassador Exchange Program concludes at **ENDO** in San Francisco, where all the program participants will be in attendance. The participants from India and South Africa visited the respective U.S. institutions (University of Michigan and University of Pennsylvania) in early June to complete the second part of the exchange. The four trainee participants will share their experiences at the Early Career Forum at **ENDO** on Friday, June 14. I would like to thank our ambassadors for their enthusiasm, dedication, and energy.

A Highlights of **ENDO** program was held in Russia in May, and planning is underway for similar programs in China (August) and in Mexico (November). These programs significantly expand the Society's international presence while establishing new relationships with international endocrine organizations.

Advocacy and Outreach

The past year has been another strong year for the Society's advocacy program. We have continued to focus on biomedical research funding, physician payment, diabetes, obesity, minority health disparities, and endocrinologist workforce issues, and we have made progress toward achieving our goals in these areas. Meetings on Capitol Hill and with the administration, congressional briefings, and the efforts of the grassroots network have helped to strengthen our relationships with policymakers and establish the Society as a preeminent source of knowledge. I look forward to seeing the future results of our work.

The Society continues to develop tools to support clinicians in their practice. Working with a broad coalition of organizations, the Society led an initiative to develop mealtime insulin decision support tools for primary care physicians and their patients. Tools to smooth the transition from pediatric care to adult care for numerous conditions are also now available.

The Society published two scientific statements, one on health disparities and one on vitamin D, as well as a Statement of Principles on Endocrine-Disrupting Chemicals (EDC). The Society has expanded its EDC advocacy beyond U.S. borders by presenting the statement at the European Union Commission meeting in Brussels and through continued participation in meetings with European policymakers.

Media coverage of **ENDO 2012** was record-breaking, generating more than 2,232 news stories. In 2012, the Society set new records for media coverage of both its journals and the Society itself.

This past year, the Society launched its Media Webinar Series, where reporters learn about "hot topics" or current events associated with high-profile endocrine-related issues. The media webinars have been attended by many leading outlets including *The New York Times, Chicago Tribune, Reuters, Newsweek,* and Bloomberg News.

Education and Trainee Activities

One of the most important and enjoyable activities of my presidential year was planning for **ENDO 2013.** Under the able leadership of its chairs—Didi Robins, Dan Marks, and Mike Tuttle—the Annual Meeting Steering Committee has created a spectacular scientific program designed to meet the highest expectations of our diverse Society membership.

In March, the Society held the first annual Reducing Health Disparities in Type 2 Diabetes Mellitus Summit in Baltimore. The health disparities initiatives were conceived by now immediate Past President Janet Hall, and I would like to thank her for her efforts in this area. I would also like to thank the members of the Minority Affairs Committee and the intercommittee task force who worked diligently to ensure the success of the Summit.

In January 2013, students and fellows attended two days of leadership and professional development programming at the first Future Leaders Advancing Research in Endocrinology (FLARE) Workshop. FLARE is funded by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that supports programs aimed at recruiting and retaining early-career faculty and trainees from underrepresented groups.

Publications

The Society is increasing its journals' online functionality and has developed new forms of content delivery by launching a full-text journals app for iPhone, iPad, and Android

devices. Additionally, the Society is developing Endocrine Press, a platform for delivering authoritative and trusted knowledge to scientists, endocrinologists, primary care physicians, and allied health professionals.

A new publications hosting platform will be launched later this year to allow custom content delivery, advanced search features, book content hosting, enhanced continuing medical education experience, and mobile device support.

Hormone Health Network

The Hormone Health Network's new website, launched in June 2012, offers clear, easy navigation of more than 100 patient education resources. The Network's substantive library of patient education materials is now available through a mobile app developed by the Cleveland Clinic Foundation.

At **ENDO 2013,** the Hormone Health Network and Taking Control of Your Diabetes have teamed up to provide a unique, half-day learning experience for Bay-area patients with type 2 diabetes. This motivational health education event will provide patients with the latest approaches to managing the day-to-day challenges with diabetes. Nearly 300 patients will attend this first-of-its-kind **ENDO** event.

Other Accomplishments

In 2012, the Society membership surpassed 16,000 members. The Society has embarked on major infrastructure enhancements to provide the best services to our members. A new Web site, www.endocrine.org, was launched in late May to deliver a better user experience. Other enhancements that will be launched later this year include a new membership database, a new publications and journals hosting platform, and the implementation of a learning management system.

I would like to recognize the outstanding leadership of the Society, particularly Past President Janet Hall and President-Elect Teresa Woodruff, as well as our colleagues serving on committees. And finally, I want to recognize the support from our entire staff, under the excellent leadership of Scott Hunt. It has been an honor to serve as your president and I look forward to the opportunity to continue to serve our Society in other ways in the years to come. **EN**

William F. Young Jr., MD
President, The Endocrine Society

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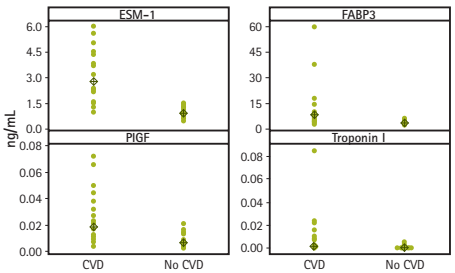

Multiplex analysis of plasma samples using MILLIPLEX® MAP Cardiovascular Disease (CVD) Panels shows significantly elevated CVD biomarkers in CVD patient samples.

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THE ENDOCRINE SOCIETY®

JUNE 2013

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.

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EDITOR'S PAGE

Mark A. Newman, Managing Editor

If it's June, you know what that means: It's time for **ENDO 2013,** this year in the City by the Bay, San Francisco. It should come as no surprise that this meeting – the Society's 95th Annual Meeting & Expo – is on track to becoming the biggest conference in our history. As I write this, more than 6,500 of you have already registered and more than 8,000 scientists and clinicians from around the world are expected to attend.

So far the Society has received nearly 3,000 abstracts for **ENDO 2013,** second only to **ENDO 2006** in Boston, and the meeting's Continuing Medical Education Services events are already sold out. CMES programs are compliant with the Accreditation Council for Continuing Medical Education and American Medical Association guidelines and can focus on the latest research and development, new disease state management guidelines, or new therapies and treatment options.

One of the many highlights of **ENDO 2013** is the **ENDOExpo** where attendees can learn about cutting-edge advances in medicine, science, and technology. The Expo features exhibits, poster presentations, food vendors, and plenty of areas to relax and commiserate with your colleagues. There's also the Expo Theater where you can see some enlightening presentations, and find educational materials, gifts, and apparel in the **ENDO** Store. The ever-popular prize wheel is back and twice the fun: It's going to be in two locations this year.

When you're not darting from session to session, take a breather and check out this month's *Endocrine News.* In "A Battle for Boys" (p. 23), Glenda Fauntleroy discusses how childhood obesity is tough for all kids, but many boys have a tougher time with it. Since boys don't talk about their weight as much, they often internalize their pain, which could lead to another set of problems.

Eric Seaborg's article "New Treatments Offer Hope for Advanced Prostate Cancer" (p. 12) explores how new hormone treatments could offer hope to those men suffering from metastatic castration-resistant prostate cancer. Seaborg further reports on a research study on mice ("Study Calls Insulin a Driver of Obesity," p. 20), where it appears that mice engineered to be genetically incapable of making large amounts of insulin did not gain weight when fed a high-fat diet. No doubt this will be a hot topic pursued by a variety of researchers in the future.

I hope to meet many of you at some point in San Francisco. If you see me, be sure to say hello and let me know what you think of *Endocrine News.* Even if you don't happen to see me at **ENDO 2013,** drop me a line any time at *mnewman@endo-society.org.*

Mark A. Newman
Managing Editor, *Endocrine News*

Obese Children May Lose Pounds With **SELF-HELP**

Self-help guides may offer obese children an opportunity to lose weight on their own, according to a new study.

Recent estimates put the number of overweight or obese children in the U.S. at 12.5 million, but losing the excess pounds is an uphill battle that often requires treatment at weight loss management clinics that are not an option for many families.

In the study published in *Pediatrics*, researchers from the University of California, San Diego, evaluated 50 overweight or obese children (ages 8–12) to see whether a guided self-help treatment program would result in weight loss. The children and their parents were divided into two groups—one receiving a five-month self-help program immediately and the other getting delayed treatment. The program included just 12 visits with a pediatrician over five months and taught healthy lifestyle habits, including healthy eating, exercise, and how parents can set limits on food consumption.

At the end of the study, children in the treatment group significantly decreased their body mass index compared to the second group. The authors concluded, however, that additional efficacy and translational studies are needed to evaluate the guided self-help treatment.

— Glenda Fauntleroy

DIET-SLEEP LINK Investigated

If you have trouble getting out of bed in the morning — or falling asleep at night — your diet might be the culprit. Then again, it could be lack of adequate sleep or excess shut-eye wreaking havoc on your diet.

Scientists have understood for some time that suboptimal sleep patterns are correlated with weight gain. A study published in *Appetite* provides new insight into this link.

Researchers from the Perelman School of Medicine at the University of Pennsylvania divided study participants into four groups based on self-reported nightly sleep patterns: very short sleepers (< 5 hours); short sleepers (5 to 6 hours); standard sleepers (7 to 8 hours); and long sleepers (9 or more hours).

Very short sleepers reported eating the least variety of foods and consumed the third highest calories among the groups. Short sleepers took in the second most variety but topped the calorie scale. Normal sleepers ate the most varied diets, consuming the second highest number of calories, while long sleepers took in the least calories and third greatest variety of foods.

Certain micronutrients contributed to the variance in sleep duration. Theobromine had the greatest effect, followed by vitamin C, tap water, Lutein + zeaxanthin, dodecanoic acid, choline, lycopene, total carbohydrates, selenium, and alcohol. Researchers did not identify the mechanism underlying differential micronutrient intake.

The findings pose a "which came first, chicken or egg" dilemma, since researchers were unable to pinpoint the direction of effect. They did conclude certain nutrients may play an underlying role in short and long sleep duration and that people who report eating a large variety of foods had the healthiest sleep patterns. Future research in the form of a prospective study using objectively measured sleep duration is needed, the Perelman team noted.

— Carol Bengle Gilbert

Antidepressants and Weight Regain in **PRE-DIABETES**

The use of antidepressants pose a threat to weight maintenance in people with impaired glucose tolerance (pre-diabetes) who have shed a few pounds, say researchers in the nationwide, multicenter Diabetes Prevention Program (DPP) and its follow-up study, the Diabetes Prevention Program Outcome Study (DPPOS). A paper in the February issue of *Diabetes Care* describes the research, a collective effort of the Diabetes Prevention Program Research Group.

The team analyzed the medical records of 1,442 participants who had lost at least 3% of their body weight one year into the DPP. Throughout the DPP and DPPOS, researchers recorded participants' weight and antidepressant use every six months, and assessed participants for symptoms of depression once a year, all for an average of 10 years per participant.

Among the participants who had lost weight, 826, or 57%, had regained the weight after an average of 5.1 years. When assessing antidepressant use among the participants, the researchers found that the risk of weight regain was 72% higher in those who took the drugs than those who did not. In their conclusion, the researchers note that the weight regain may be a side effect of the drugs.

—Terri D'Arrigo

Diabetes Ups Risk of **SEVERE OSTEOARTHRITIS**

Osteoarthritis is thought to be caused by wear and tear on joints associated with age and weight. But data from the Bruneck Study, which tracked 927 men and women aged 40–80 in Bruneck, Italy, from 1990 to 2010, suggest that type 2 diabetes may also play a role. The research appears in the February issue of *Diabetes Care*.

In the study, a team led by the University of Erlangen-Nuremberg's Georg Schett, MD, analyzed the medical records of all participants and found that 69 had type 2 diabetes. Thirteen participants in that group, or 17.7%, developed severe osteoarthritis that required either a knee or hip replacement, compared to 73 participants without diabetes, or just 5.3%. Results were similar when the team grouped participants of similar age and body mass index.

The researchers noted previous studies suggesting that high blood glucose may promote the destruction of cartilage and stimulate the expression of pro-inflammatory and pro-degenerative proteins. They also cited evidence that diabetic neuropathy may increase the risk of osteoarthritis by contributing to muscle weakness, which in turn can change the amount of stress placed on the affected joints.

—Terri D'Arrigo

Baldness Linked to Prostate Cancer in **AFRICAN AMERICANS**

African-American men who lose their hair early in life may be at a higher risk of prostate cancer, finds new research.

Researchers from the University of Pennsylvania School of Medicine studied 318 African-American men with prostate cancer and 219 controls (ages 33–93). They were asked about any diagnosis of prostate cancer and the category of their hair loss at age 30.

In most cases, baldness increased the risk of prostate cancer. Men younger than age 60 with any baldness had more than three times the risk of being diagnosed with advanced prostate cancer, and younger men with frontal baldness were six times more likely to have advanced cancer than men without this pattern, according to the study published in *Cancer, Epidemiology, Biomarkers & Prevention*.

Lead author Charnita Zeigler-Johnson, PhD, said although their study found a link between hair loss and prostate cancer, they cannot recommend new screening guidelines at this time. "Our results need to be confirmed by future studies to be certain the associations that we observed are found in other populations," she said.

— Glenda Fauntleroy

MEDITERRANEAN DIET Chops Cardiac Risks

People at high risk for cardiovascular disease can substantially reduce their risk of a major cardiovascular event by consuming a Mediterranean diet, according to a study published in the *New England Journal of Medicine*.

The Prevención con Dieta Mediterránea (PREDIMED) study was a parallel-group, multicenter, randomized, primary prevention trial with a sample of 7,447 participants on similar drug treatment regimens. The subjects were elderly men and women with no cardiovascular disease but either type 2 diabetes or three cardiovascular risk factors. The researchers randomly assigned them to one of three groups, two directed to consume Mediterranean diets, and the control group instructed to minimize dietary fats.

Both experimental groups significantly increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings) in comparison to the control group. Members of one experimental group supplemented their diets with 1 liter of olive oil weekly, while the other group added 30 g of nuts per day to their diets. The Mediterranean dieters avoided red meat while limiting sodas, partially solidified fats, and commercially baked sweets. There were no energy restrictions applied to any of the study population.

Researchers followed the groups for a mean of 4.8 years. Their identified end point was a composite of myocardial infarction, stroke, and death from cardiovascular causes, with secondary end points defined as any of those events individually or death from any cause. Of the 288 primary-outcome events, 96 (3.8%) occurred in the Mediterranean diet with extra-virgin olive oil group, 83 (3.4%) in the Mediterranean diet with nuts group, and 109 (4.4%) in the control group.

Both experimental groups experienced an absolute risk reduction approximating three major cardiovascular events per 1,000 person-years representing a 30% risk reduction. The study was published in the *New England Journal of Medicine*.

— Carol Bengle Gilbert

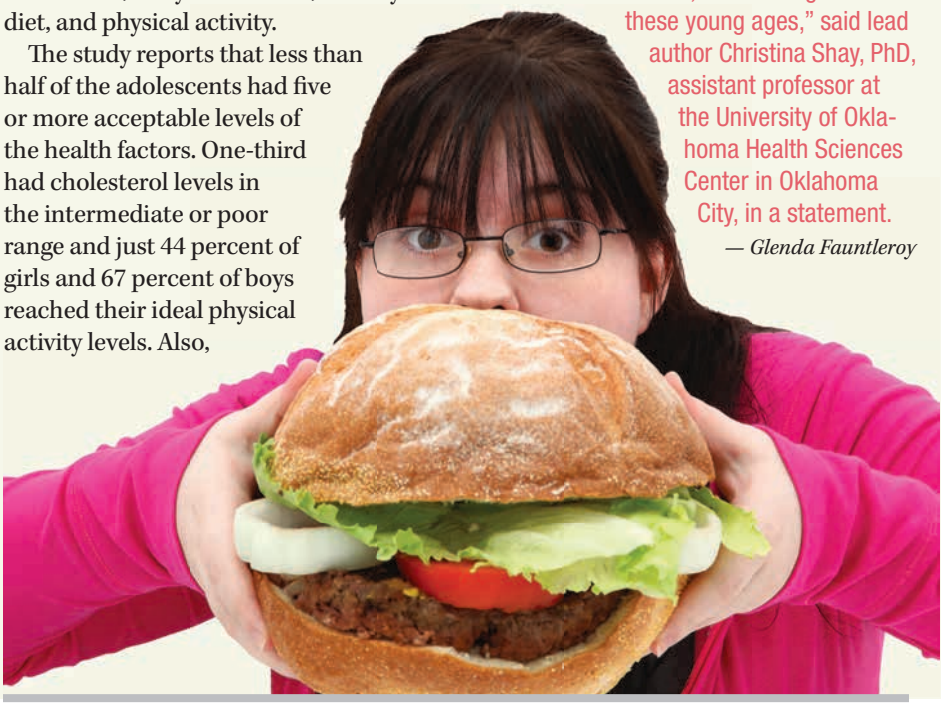
TEENS' POOR HEALTH Raises Heart Disease Risks

In a new study published in *Circulation*, researchers evaluated 4,673 adolescents (ages 12–19) from all major ethnic groups who took part in the National Health and Nutrition Surveys. Adolescents' cardiovascular health was judged based on seven components of the American Heart Association's 2020 impact goals, which include blood pressure, cholesterol, body mass index, healthy diet, and physical activity.

The study reports that less than half of the adolescents had five or more acceptable levels of the health factors. One-third had cholesterol levels in the intermediate or poor range and just 44 percent of girls and 67 percent of boys reached their ideal physical activity levels. Also, more than 80 percent had a poor diet that didn't include recommended levels of fruits and vegetables, fish, and whole-grains.

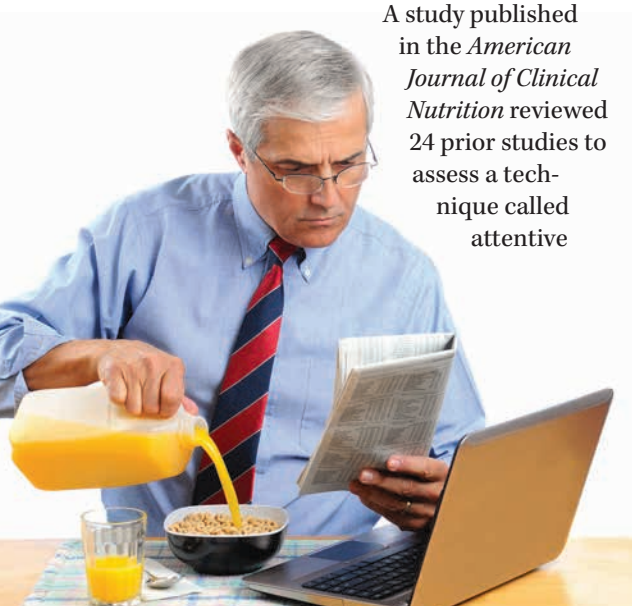
"The far less-than-optimal physical activity levels and dietary intake of current U.S. teenagers is translating into obesity and overweight that, in turn, is likely influencing worsening rates of high blood pressure, high cholesterol, and blood glucose at these young ages," said lead author Christina Shay, PhD, assistant professor at the University of Oklahoma Health Sciences Center in Oklahoma City, in a statement.

— Glenda Fauntleroy



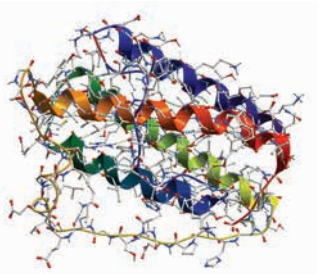
DISTRACTED EATING Bumps Up Later Consumption

The dangers of distracted driving are increasingly in the spotlight, but now researchers are pointing the finger at another deleterious distraction: eating. It seems paying attention to what you eat may help keep you from overeating.



A study published in the *American Journal of Clinical Nutrition* reviewed 24 prior studies to assess a technique called attentive eating. That's when people pay attention to what and how much they're putting in their mouths. The researchers found distracted eating caused moderate overeating on the spot and even greater increases in food intake two hours later. When the research design included prompts to jog subjects' memory of what they'd eaten, their immediate consumption remained stable while their delayed intake declined moderately. These findings could prove helpful in establishing behavioral strategies to discourage overeating. Such strategies may be an effective alternative to calorie counting for dieters. However, the researchers cautioned, most of the studies reviewed involved subjects with body mass indices in the healthy range. Further work is needed to see if the results hold up with overweight subjects.

— Carol Bengle Gilbert



LEPTIN, **OBESITY**, and Hypertension

Obesity is a well-known risk factor for the development of hypertension, but the scientific community is still sorting out the relationship between the two conditions. Now a small study by German researchers, appearing in the March issue of the *Journal of Clinical Endocrinology and Metabolism*, suggests that leptin, a key metabolic hormone often elevated in obese people, may play a role.

In the study, a team led by Felix Machleidt, MD, of the University Hospital of Schleswig-Holstein in Lübeck, observed the effects of high levels of leptin in 12 healthy, normal-weight men. In each of two visits, the men received an intravenous bolus of either leptin or saline (placebo). Using electrodes placed on the men's skin, the team measured the men's vasoconstrictory muscle sympathetic nerve activity (MSNA) 10 minutes before the bolus and 20, 60, and 140 minutes after the bolus. Vasoconstrictory MSNA is thought to play a role in the development of hypertension and, like leptin, is often elevated in the obese.

Although there were no significant changes in the men's blood pressure or heart rate when they received leptin, their MSNA shot up as much as 135%. The researchers concluded that high levels of leptin may account for increased vasoconstrictory MSNA often seen in the obese, and therefore play a role in the development of hypertension in this population.

—Terri D'Arrigo

New CT Angiography Technique Provides **BETTER SCANS**

Rapid kilovolt peak-switching dual-energy cardiac computed tomography (CT) angiography is superior to standard CT scans, according to a study published in *Radiology*. This prospective, diagnostic study funded by GE Healthcare was conducted in four centers in three countries. Thirty-nine patients underwent dual-energy CT scans with a subset of 25 also undergoing single-energy coronary CT angiography. The goal was to compare scanning techniques to determine if the dual-energy scans provided clearer imaging.

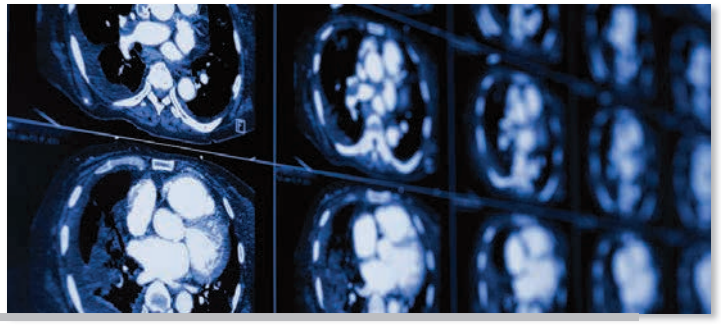
Artifacts, image features not present in the scanned objects, are an inherent pitfall of CT scanning. They can lead to inaccurate diagnosis if not recognized. One type of artifact, the beam-hardening (BH) artifact, occurs because X-ray beams are polychromatic or nonlinear. A previous study evaluating asymptomatic patients without a history, or CT findings, of obstructive coronary artery disease identified BH-related differences between the inferobasal myocardial segment and the remainder of the myocardium, mimicking a perfusion defect, in 72% of patients.

The researchers used paired t tests to evaluate the difference in myocardial attenuation between the dual-energy and single-energy images and compare the BH levels against an ideal scenario of no BH.

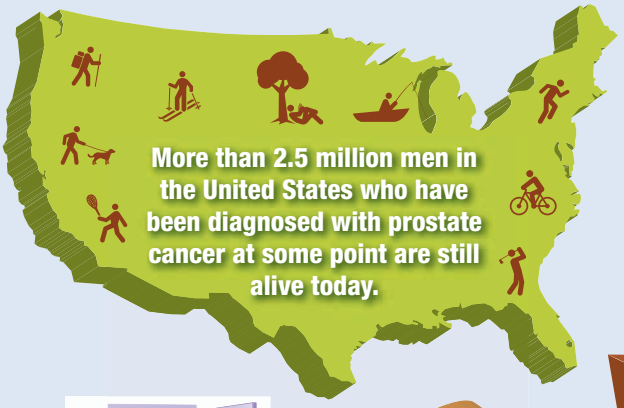
The dual-energy technology significantly reduced myocardial BH artifact, improving signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) in the coronary arteries and the myocardium. CNR is the most important factor in imaging, allowing radiologists to distinguish between healthy and diseased tissue by comparing SNR in adjacent areas.

The researchers recommend reconstruction at 80 kiloelectron volts (keV) for myocardial SNR and CNR optimization, and 65 keV for optimal coronary artery evaluation. They say those parameters will help healthcare providers integrate the new technology into clinical practices. Because of the small study population, future testing is needed to confirm these findings.

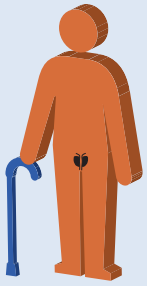
—Carol Bengle Gilbert



Fast FACTS About Prostate Cancer

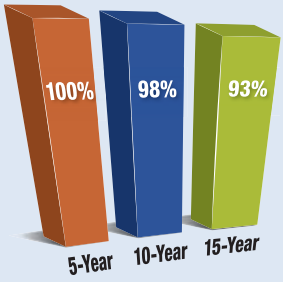


About 1 man in 6 will be diagnosed with prostate cancer during his lifetime.



Prostate cancer occurs mainly in older men. Nearly two thirds are diagnosed in men aged 65 or older, and it is rare before age 40. The average age at the time of diagnosis is about 67.

About 240,000 new cases of prostate cancer will be diagnosed in 2013.



The relative survival rate for all men with prostate cancer, according to the most recent data.

Prostate cancer is the second leading cause of cancer death in American men, behind only lung cancer. About 1 man in 36 will die of prostate cancer.

Sources: cancer.org; National Cancer Institute

NEW Treatments offer hope for Advanced PROSTATE CANCER

By Eric Seaborg

New treatments for metastatic castration-resistant prostate cancer (CRPC) are gaining approval at a dizzying pace, and endocrinologists could play an important role in their use.

The recently approved drugs abiraterone acetate and enzalutamide represent important breakthroughs in androgen deprivation therapy, and more drugs are in clinical trials, promising more sophisticated approaches to the treatment of advanced prostate cancer. "This is something that endocrinologists really should take ownership of," said Alice Levine, MD, professor of medicine, endocrinology, diabetes, and bone disease, and co-director of the Adrenal Center at the Icahn School of Medicine at Mt. Sinai in New York City. "This explosion of new hormonal treatments is rooted in the basic physiology and biochemistry of the adrenal and testicular steroid hormones and their receptors. And although oncologists and urologists are utilizing these therapies in patients, endocrinologists have a deeper understanding of the molecular pharmacology of these agents and the consequences of blocking steroidogenesis and androgen receptor signaling. This is very sophisticated endocrinology."

AT-A-GLANCE:

- **Androgen deprivation therapy (ADT) usually leads to remission in advanced prostate cancer, but the metastatic disease generally recurs.**
- **Abiraterone acetate is a new-generation ADT drug that takes a novel approach to inhibiting adrenal androgens.**
- **Enzalutamide is a second-generation androgen receptor antagonist that also offers new hope for extending the lives of these patients.**

Traditional Treatment

Androgen deprivation therapy (ADT) has been the treatment of choice for advanced prostate cancer since the 1940s, when it was first reported that surgical castration or estrogen administration was effective in knocking back bone-metastatic disease. This approach led to the development of medical castration therapies. Drugs were developed to reduce androgen and action signaling, with ADT typically consisting of a gonadotropin-releasing hormone agonist or antagonist often combined with a first-generation nonsteroidal androgen receptor (AR) antagonist.

More than 80% of patients respond to ADT treatment, but that response lasts on average roughly two years. Although most metastatic lesions regress after ADT, they almost uniformly progress after time. Because prostate specific antigen (PSA) is expressed by most prostate cancers and is regulated by the androgens, a rise in PSA levels in a patient on ADT is the earliest sign of disease recurrence.

"In successful hormone therapy, AR activity is suppressed, PSA goes down, and tumor remission results," said Karen Knudsen, PhD, a professor in the departments of cancer biology, urology, and radiation oncology at Thomas Jefferson University, deputy director of the Kimmel Cancer Center in Philadelphia, and editor of the journal *Molecular Cancer Research*. "When treatment fails, almost invariably PSA rises prior to visualization of a recurrent tumor. Such 'biochemical failure' is evidence that the androgen receptor has been reactivated, and castration-resistant disease is imminent."

Metastatic Castration-Resistant Prostate Cancer

Because the cancer progressed during ADT, clinicians previously referred to this stage as androgen-independent disease. However, as evidence mounted that most of these tumors still express AR and show continued activation of the AR signaling system, they adopted the current term, metastatic castration-resistant prostate cancer, to reflect this new understanding.

Once the disease reaches the CRPC stage, there is no durable cure. The typical treatment has been taxane-based chemotherapy, such as docetaxel, which confers a survival benefit of only a few months.

New Avenues of Attack

The realization that AR is reactivated in CRPC—frequently as a result of restored local androgens—spurred researchers to look for new ways to attack androgen pathways. "When patients have a rising PSA you need to do something to knock androgen receptor activity back down," Knudsen told *Endocrine News*. "So people looked at mechanisms of failure, and one of the main mechanisms was that the tumor flips on genes that induce conversion of weak adrenal androgens into testosterone. Tumors themselves are making androgens. This process of intracrine androgen synthesis or intratumor androgen production requires adrenal androgen synthesis."

> "...Endocrinologists have a deeper understanding of the molecular pharmacology of these agents and the consequences of blocking steroidogenesis and androgen receptor signaling. **This is very sophisticated endocrinology."**
>
> *—Alice Levine, MD, Adrenal Center at the Icahn School of Medicine at Mt. Sinai in New York City*

Researchers looking for a way to interfere with this adrenal process came up with abiraterone acetate (Zytiga), which works by inhibiting the CYP17 pathway. CYP17 is a critical enzyme for androgen production in the normal adrenal gland as well as in CRPC. It catalyzes two steroid reactions through its 17-hydroxylase and 17,20-lyase

Other Promising THERAPIES

In addition to the hormonal therapies, new approaches are addressing other aspects of treatment:

- Cabazitaxel (Jevtana) is a chemotherapy agent as second-line therapy for patients who fail to respond to docetaxel (approved in 2010).
- Sipuleucel-T (Provenge) is an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic CRPC (approved in 2010).
- Radium-223 (Alpharadin) is a first-in-class pharmaceutical that is taken up by bone because of radium's kinship to calcium, where its alpha radiation is showing success in knocking back metastatic tumors (in clinical trials).

INCIDENCE RATES by Race

Race/Ethnicity	Male
All Races	154.8 per 100,000 men
White	146.9 per 100,000 men
Black	236.0 per 100,000 men
Asian/Pacific Islander	85.4 per 100,000 men
American Indian/Alaska Native	78.4 per 100,000 men
Hispanic	125.9 per 100,000 men

Sources: cancer.org; National Cancer Institute

activities, and abiraterone interferes with both these steps. Inhibition of 17-hydroxylase results in a blockade of cortisol synthesis, with a resultant rise in adrenocorticotropic hormone that induces mineralocorticoid excess. Co-administration of a glucocorticoid such as prednisone can prevent this side effect.

Because intracrine androgen synthesis is only one mechanism of AR activation, abiraterone acetate works in only a subset of patients, but it has shown marked antitumor effects in them.

In April 2011, the Food and Drug Administration (FDA) approved it for use in combination with prednisone to treat patients with metastatic CRPC who have received docetaxel chemotherapy. In December 2012, the FDA expanded the indication to include use before chemotherapy, which puts it on par with other anti-androgen treatments.

AR Antagonists: The Next Generation

Enzalutamide (Xtandi) is considered the first of the next generation of AR antagonists. Formerly known as MDV3100, its creators designed it to overcome the limitations of the commonly used AR antagonist bicalutamide by, for example, offering higher binding affinity and inhibiting AR function by blocking nuclear translocation. In addition, it does not share bicalutamide's characteristic of having agonistic effects in prostate cancers in which AR is overexpressed.

In August 2012, the FDA gave the nod to enzalutamide for the treatment of metastatic CRPC patients who have previously received docetaxel. Clinical trials are under way aimed at expanding approval to include use before chemotherapy, matching abiraterone.

The increased survival benefit conferred by these drugs is only about four months, but "these people are very end stage, so four months .... in an advanced cancer, that's significant," Levine said.

"Although the ultimate goal is to provide a cure, an immediate, achievable goal is to delay the time that you have to start chemotherapy," Knudsen said. "Hormone therapies are generally well tolerated," especially compared with chemotherapy. Because prostate cancer is a disease of older men, staving off the need for chemotherapy, and perhaps avoiding it altogether, is a major benefit.

When to Begin ADT

Perhaps with this goal in mind, an increasing number of clinicians have been tempted to use ADT as primary treatment, despite the lack of evidence supporting this approach. "Nobody has ever shown improvement in survival with partial or complete androgen deprivation therapy done early in the disease, except for some trials that combined ADT with external beam radiotherapy," Levine said.

> "It's exciting to me that we can still wring something more out of the androgen signaling system, **that we can still prolong life in these very end-stage patients.**"
>
> *—Alice Levine, MD, Adrenal Center at the Icahn School of Medicine at Mt. Sinai in New York City*

"If you've got an earlier stage prostate cancer, the chances are you are going to live at least 15 to 20 years," she said. "And androgen deprivation therapy, particularly if it is very potent, is associated with a lot of side effects. It can cause metabolic syndrome, osteoporosis, poor quality of life, fatigue, decreased libido, and increased cardiovascular mortality. So it's a balancing game. It hasn't been shown that if you begin it earlier that you improve overall survival except in very specific circumstances."

Because many of the side effects are the direct result of the absence of androgens, it is unlikely that the new agents will lessen them. With other drugs in the pipeline, the new generation will likely be a ripe area for research into the best sequences to give them, best combinations to use, integration with older drugs, and timing of delivery. "Considering that this is a disease for which you really had no new drugs on the market that were useful for decades, it's a very exciting time," Knudsen said.

Levine looked forward to even more advances from an old approach: "It's exciting to me that we can still wring something more out of the androgen signaling system, that we can still prolong life in these very end-stage patients." Cancer cells exhibit great adaptiveness in avoiding efforts to stop them, but a greater understanding of their molecular pathophysiology could allow researchers to stay a step ahead. EN

—Seaborg is a freelance writer in Charlottesville, VA, and a regular contributor to Endocrine News.

Stage Distribution and 5-year Relative Survival

by Stage at Diagnosis for 2002–2008, All Races, Males

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	81	100.0
Regional (spread to regional lymphnodes)	12	100.0
Distant (cancer has metastasized)	4	27.8
Unknown (unstaged)	3	71.1

Sources: cancer.org; National Cancer Institute

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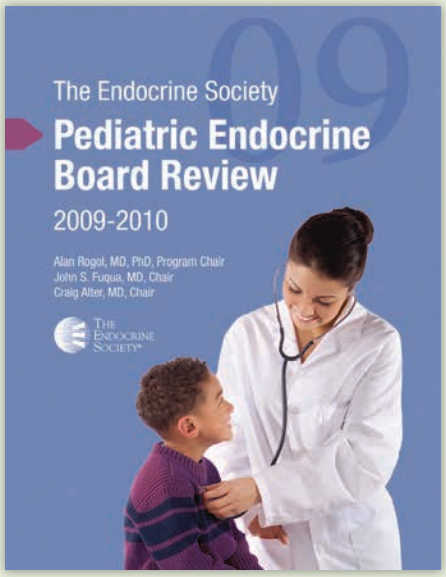

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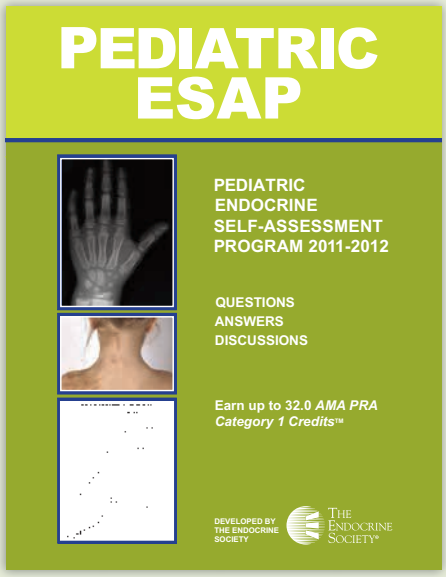

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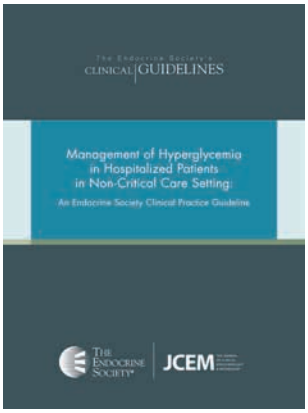

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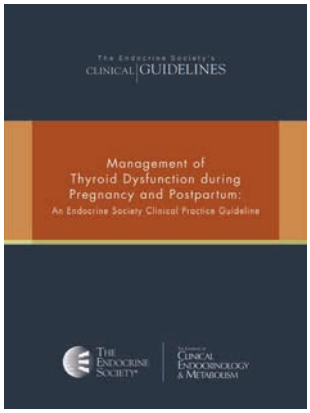

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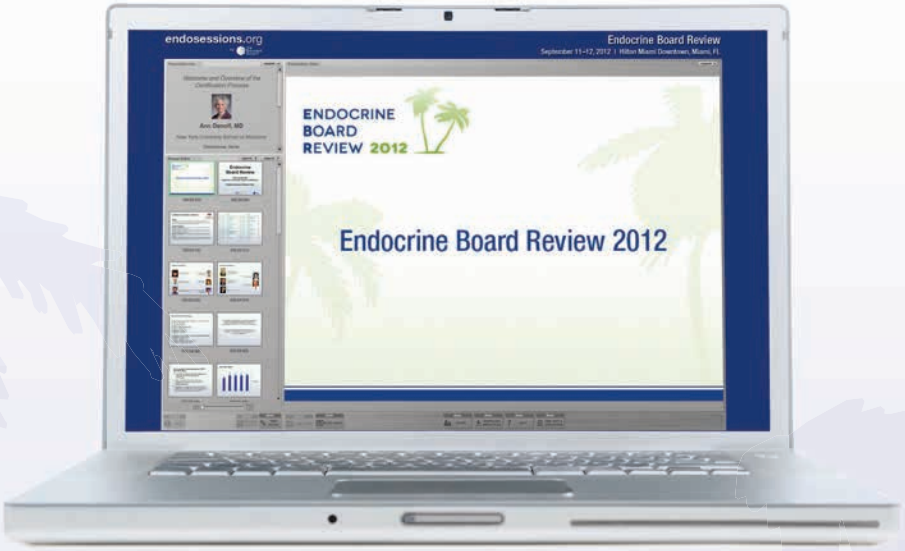

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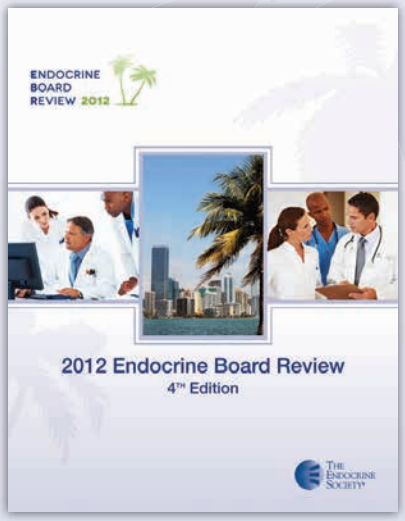

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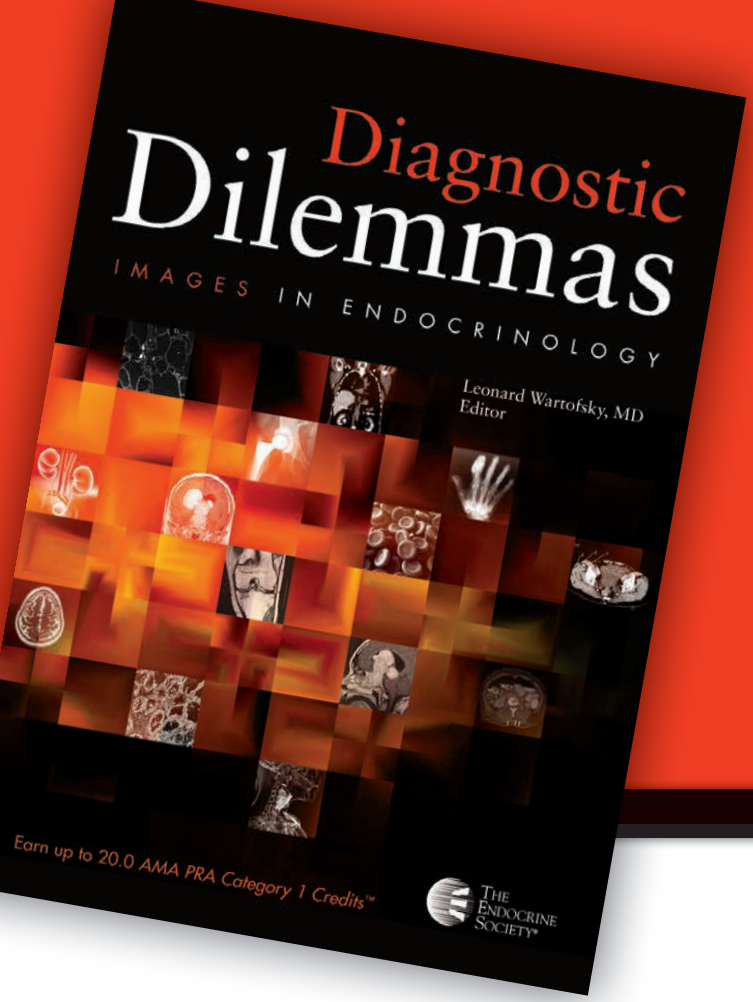

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References: 1. Victoza® [summary of product characteristics]. Bagsværd, Denmark: Novo Nordisk A/S; 2012. **2.** Pratley R, Nauck M, Bailey T, et al; for the 1860-LIRA-DPP-4 Study Group. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *Int J Clin Pract.* 2011;65(4):397-407. doi:10.1111/j.1742-1241.2011.02656.x. **3.** Internal calculations based on IMS Midas Quantum data, May 2012.

Prescribing information

Victoza® ▼ (liraglutide) 6 mg/ml solution for injection in pre-filled pen
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1 ml of solution contains 6 mg of liraglutide.
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MAKING GAINS: DOES INSULIN DRIVE OBESITY?

A new study shows that reduced insulin levels protect mice from metabolic problems

By Eric Seaborg

Far from being an innocent response to insulin resistance, hyperinsulinemia drives weight gain and metabolic disruptions, a new study says. Researchers who manipulated mice genes to limit their ability to make insulin found that low-insulin mice did not become obese on a high-fat diet but actually burned more energy, with their white adipose tissue acting akin to brown fat.

"It's a very clever experiment," said C. Ronald Kahn, MD, a prominent insulin and diabetes researcher at Harvard Medical School who was not involved in the study. "I think it is a significant finding because it does challenge our concepts of what is the role of hyperinsulinemia in metabolic syndrome."

Insulin Genes

Researchers at the University of British Columbia devised an approach to lowering insulin levels that avoids the pitfalls of previous studies that used drugs, with their unavoidable side effects. The researchers exploited the fact that mice have two insulin genes, and therefore four possible alleles. Insulin gene 1 is specific to the pancreas. Insulin gene 2 is like the human insulin gene, present in the pancreas and also in organs such as the brain and thymus.

Mice with both genes knocked out make no insulin and die in infancy, but those with just a single allele function relatively normally. The researchers controlled the amount of insulin their mice could make by knocking out the insulin 2 gene entirely, and then creating a line who were missing one allele of gene 1 and therefore genetically limited in the amount of insulin they could produce. The researchers then compared how the mice with both alleles vs. a single allele of the pancreas-source gene fared when fed a high-fat diet. That diet normally leads to obesity, hyperinsulinemia, diabetes, and other complications, and the mice with two alleles gained weight as expected.

But the mice with only one allele did not. In addition to avoiding obesity despite consuming a similar amount of calories, they had less inflammation and less liver fat than the other mice. "These mice were healthy across the board; they didn't accumulate fat in their livers, or any of their other not normally fat-storing tissues, like the regular high-fat mice do," said lead author James Johnson, PhD, an associate professor of medicine at the University of British Columbia in Vancouver. "Their glucose levels are surprisingly normal given the fact they were missing three of the four insulin genes."

New Finding on Energy Expenditure

The mice ate similar amounts of food, which raised the question of where the extra calories went in the mice that did not gain weight. To explore the molecular mechanisms involved in this phenomenon, the researchers designed a real-time polymerase chain reaction miniarray of 45 key metabolic, inflammatory, and insulin target genes. They were surprised to find that one of the major sets of genes upregulated in the white adi-

AT-A-GLANCE:

- **Mice engineered to be genetically incapable of making large amounts of insulin did not gain weight when fed a high-fat diet.**
- **The low insulin levels in these mice evidently contributed to greater energy expenditure, compared with mice with higher insulin levels.**
- **The white adipose tissue in the low-insulin mice took on energy-burning attributes associated with brown adipose tissue.**

pose tissue of the haploid mice increased the activity of uncoupling proteins—mitochondrial proteins associated with burning energy in brown adipose tissue. This process has been referred to as "browning" of white fat.

"High insulin programs the white fat to really hold onto its nutrients and not burn any of them," Johnson told *Endocrine News*. "If you can reduce the hyperinsulinemia, you have an upregulation of these uncoupling proteins, which will burn energy and increase energy expenditure, with no difference in food intake."

These findings on insulin's effect on energy balance make the study stand out, said Kahn: "I think they are the first people to say it in quite this way. There are other people who have said that the hyperinsulinemia might be bad because it makes more insulin resistance, but this is something different. [The idea] that hyperinsulinemia actually changes energy expenditure is very new. Most people would say that high insulin promotes obesity because it causes more fat storage directly. But [Johnson] is saying it's not causing more fat storage directly, but what it is doing is decreasing energy expenditure, and allowing the energy to be stored."

"[The idea] that hyperinsulinemia actually changes energy expenditure is very new. Most people would say that **high insulin promotes obesity because it causes more fat storage directly."**

— C. Ronald Kahn, MD, Harvard Medical School

Not a New Idea

This idea that insulin is a driver of obesity has had its champions since the 1970s, but this is the most direct evidence and clearest demonstration of a mechanism yet, according to Robert Lustig, MD, a pediatric endocrinologist at the University of California San Francisco and member of the Endocrine Society Obesity Task Force. Lustig has been convinced of high insulin's detrimental role since treating pediatric patients who had obesity caused by hypothalamic tumors. Because the brains of these patients could not sense leptin, their bodies went into a starvation response, and constantly over-released insulin to store energy.

Lustig's team treated the patients with the acromegaly drug ocreotide, which is used to treat pituitary tumors but also reduces pancreatic insulin secretion. "When we were successful in reducing their insulin release, the patients lost weight and started to feel better. But even more importantly, they started exercising spontaneously and their resting energy expenditure went up, suggesting that energy expenditure was tied to energy intake through insulin," said Lustig, who has been in the spotlight recently after release of his popular book on obesity (see sidebar).

Insulin Resistance Paradox

Johnson said that his experience in working with the pituitary leads him to question the generally accepted reasoning about insulin resistance: "We were taught as neuroendocrinologists that if there is too much of a certain hormone or neurotransmitter, the receptor for that hormone or neurotransmitter gets desensitized, which is that hormone's resistance. Diabetes is the only field in endocrinology where they think the opposite, where they think that the resistance happens first."

He cites research in flies and worms, which has shown that when researchers knock out a cluster of genes that control aging and leanness and stimulate insulin, the animals with reduced insulin are lean and live twice as long. "The people who study worms and flies are tuned in to the idea that you can have excess insulin, and if you bring that down it is beneficial for the organism. But clinical endocrinologists are used to thinking of insulin as a good guy because in the complete absence of insulin you have diabetes. It can be very difficult to think of it as both a good guy and potentially a bad guy when there is too much," Johnson said.

The study, which Johnson calls "the first evidence that insulin itself is required for weight gain in vivo," appeared in the December 5 edition of *Cell Metabolism*. EN

—Seaborg is a freelance writer in Charlottesville, VA, and a regular contributor to Endocrine News.

DR. BUZZKILL

Being called "Dr. BuzzKill" by Stephen Colbert on national television for his stance against sugar is all right with Robert Lustig, MD, if it helps him get out the message of his book, *Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease.*

He has been featured on CBS' *60 Minutes* as well as National Public Radio's Diane Rehm Show and Science Friday and interviewed countless other times. A video of his talk, "Sugar: The Bitter Truth," went viral on YouTube and garnered more than 3 million views.

Lustig calls the experience "surreal," but it's given him a megaphone to say that "what we are doing isn't working" to combat the obesity pandemic: "The science and clinical data are pointing in a completely different direction" from most doctors' traditional approach.

"I have had a lot of emails from private practice generalists who have been handed the book by their patients," and their response to the book has been very positive, Lustig said.

In-office A1c Results Improve Diabetes Decision Making, Patient Compliance, and Outcomes

A1c is the "test of choice" says the International Expert Committee

Summary: According to the July 2009 International Expert Committee Report, "The A1c assay is the test of choice for the chronic management of diabetes."[1] Other studies show in-office A1c results improve diabetes decision making, patient compliance, and outcomes.

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Abnormal	11.60	1	84	11.03	2.5%
	11.60	2	83	11.40	3.0%
	11.60	3	84	11.17	2.8%

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[a]National Glycohemoglobin Standardization Program
[b]Diabetes Control and Complications Trial

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A BATTLE FOR BOYS

By Glenda Fauntleroy

Robert Denny's son was just 9 years old when his pediatrician first expressed concern about his weight.

"They were worried about his blood pressure and heart condition," recalls Denny of San Diego, Calif. "He had dark rings around his neck and arms that doctors said were because of his obesity."

At his heaviest, Justin tipped the scale at 250 pounds and was once deemed ineligible to play football at his position due to his weight. After years of visits with doctors and nutritionists, Justin is now battling against his obesity. Now 16 years old and 5'7" tall, his weight is down to 216 and he's committed to lose more, says Denny.

Justin is just one of the country's children who make up the generation's alarming epidemic of obesity. Recent estimates from the Centers for Disease Control and Prevention (CDC) put the number of overweight or obese children between ages 2 and 19 at 12.5 million or 17%. A number almost tripled from 1980.

The Gender Role

A child's weight status is determined using an age- and sex-specific percentile for body mass index (BMI) rather than the BMI categories used for adults. Overweight is considered a BMI greater than the 85th percentile on the growth chart and obesity is greater than the 95th percentile.

Research has shown obese children are at higher risk for a host of serious health complications, including high blood pressure and cholesterol, sleep apnea, asthma, type 2 diabetes, and joint problems. But recent headlines suggest obesity may be impacting boys more significantly

Childhood obesity is at an all-time high, but boys may face tougher challenges

AT-A-GLANCE:

- **About 12.5 million U.S. children are now overweight or obese—triple from 1980—and there's been a significant increase in the prevalence of obesity in young boys.**
- **Recent studies suggest obese boys have higher risks of health and emotional problems than their peers.**
- **Weight management treatment programs focus on changing the habits of the entire family, while many teens turn to bariatric surgery for a solution.**

than their peers.

For starters, the CDC reports that between 1999–2000 and 2009–2010, there was a significant increase in the prevalence of obesity among boys, but not girls. In 2010, 18.6% of all boys were obese compared with 15% of girls.

In the November 2012 issue of *Obesity Review,* a review of six studies including more than 18,000 children found obese boys were significantly more likely than obese girls to develop asthma.

Another study in the *Archives of Pediatric and Adolescent Health* reported that obese boys are also twice as likely as boys of normal weight to have puberty delayed beyond the age of 11½.

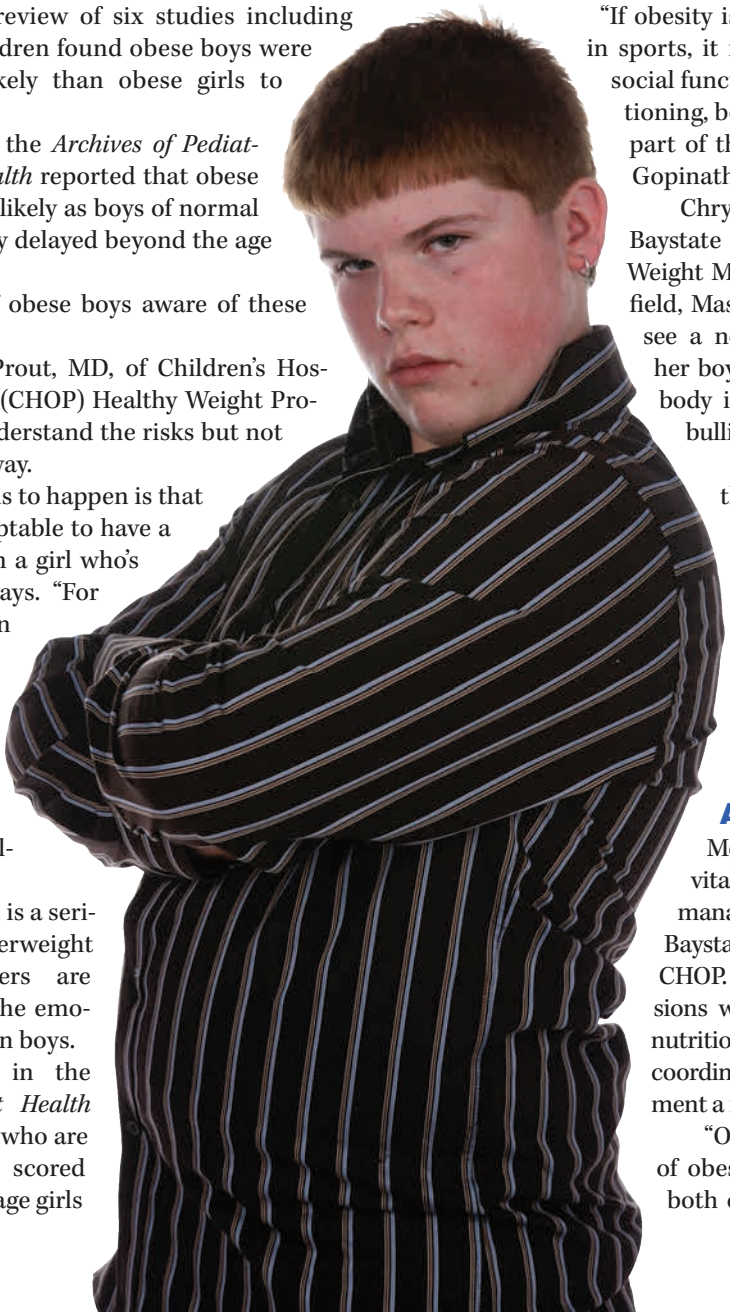
So are parents of obese boys aware of these potential health risks?

Elizabeth Parks Prout, MD, of Children's Hospital of Philadelphia's (CHOP) Healthy Weight Program, says parents understand the risks but not all take action right away.

"I think what tends to happen is that it's more socially acceptable to have a boy who is larger than a girl who's larger," Parks Prout says. "For some boys, there's even some resistance to lose weight because it provides them a sense of safety in terms of being heavier allows them not to be pick on or bullied."

"For some boys, there's even some resistance to lose weight because it provides them a sense of safety in terms of **being heavier allows them not to be picked on or bullied**."

— Elizabeth Parks Prout, MD, Children's Hospital of Philadelphia's Healthy Weight Program



Bullying, however, is a serious issue for many overweight boys, and researchers are beginning to look at the emotional toll it has on teen boys.

A recent study in the *Journal of Adolescent Health* revealed teenage boys who are overweight or obese scored lower than obese teenage girls on quality of life questionnaires about their emotional, social, and school functioning.

Bamini Gopinath, PhD, lead author of the study from University of Sydney, Australia, says the reasons for the difference are unknown, but she speculates it might be because of the importance of sport in boys' social lives.

"If obesity is limiting their participation in sports, it might negatively affect their social functioning and/or physical functioning, both of which are measured as part of the total quality of life score," Gopinath says.

Chrystal Wittcopp, MD, director of Baystate Children's Hospital Pediatric Weight Management Program, Springfield, Mass., says, however, she doesn't see a noticeable difference between her boy and girl patients. Both have body image issues and tend to be bullied about their weight.

"Boys don't talk about their weight as much and may internalize their feelings more than girls," Wittcopp says. "But for all obese adolescents, there is a significant impact on mental health as long as their obesity continues."

An Encompassing Approach

Mental health counseling is a vital component of the weight management programs at both Baystate Children's Hospital and CHOP. Both programs include sessions with physicians, psychologists, nutritionists, and a physical activity coordinator. And both make treatment a family affair.

"One of the biggest risk factors of obese children is having one or both obese parents," explains Bay-

state's Wittcopp. "Some of it has to do with lifestyle within the family so any changes we recommend for young kids involves the parents."

"We want the entire family to get more activity, change their intake, get rid of sugar-sweetened beverages, and drink 1% or skim milk," she adds.

> **"Boys don't talk about their weight as much** and may internalize their feelings more than girls. But for all obese adolescents, there is a significant impact on mental health as long as their obesity continues."
> *— Chrystal Wittcopp, MD, Director, Baystate Children's Hospital Pediatric Weight Management Program, Springfield, Mass.*

Parks Prout agrees. "At CHOP, our program never includes just changes for the child, it's changes for the entire family," she says. "In the initial visits, parents are also asked to track their food intake as well as the child's so they understand they are a partner in the process."

Children treated at Baystate typically spend two years in the program, with the intensive first phase lasting six months. After that, patients attend monthly maintenance group sessions, which they are welcome to attend for the rest of their lives.

"Patients' weight loss goals depend on their starting weight, age, and their motivation," Wittcopp says. "Of course, we'd like everyone to get less than the 95th percentile, but we know that with a 7–10% decline in BMI, they'll have significantly improved health benefits, so that's a good achievement of success."

The Surgical Solution

For some teens with BMIs over 35, bariatric surgery has become a necessary option to treat substantial obesity-related health problems. As the first and largest bariatric surgery program facility for adolescents, Cincinnati Children's Hospital has performed laparoscopic gastric bypasses and sleeve gastrectomies on 205 teens since 2001, according to Thomas Inge, MD, PhD, surgical director of the Surgical Weight Loss Program for Teens.

Sleeve gastrectomy is the latest surgical technique used to treat obesity, in which about 85% of the stomach is removed, leaving just a narrow tubular stomach that becomes full with only a one-half to a cup of food, says Inge.

And while national statistics show obesity rates higher in boys, at Cincinnati's Children's, there is a significant difference in which gender seeks help through surgery. Girls make up 75% of the patients—just 53 of the 205 teens operated on since 2001 have been boys.

Before surgery, there is a six-month program during which teens must adhere to lifestyle modifications such as taking vitamins, controlling calorie intake, and increasing physical activity. And while teens are not instructed to lose weight during the pre-op period, one rule is firm—they cannot gain any weight.

"We look for signs that they can adhere to a different lifestyle and we don't proceed with surgery if the family and child cannot put the basics of the healthy lifestyle into action in the six-month period," says Inge.

The average weight of patients at time of surgery is 382 pounds with an average BMI of 59.5. At three months post-surgery, patients have an average weight loss of 75 pounds. Within 12 months, the average loss is 141 pounds.

Inge says, however, that there is still more to learn about bariatric surgery for teens.

"There are a lot of unanswered questions. For instance, what procedure, bypass, sleeve, or band should we be recommending and why? On balance, is one superior from the standpoint of treating obesity-related health conditions, nutritional risks, weight loss, and durability of weight loss?"

Inge believes that several long-term clinical studies now being conducted will help provide answers to these questions. He is the principal investigator for Teen-LABS (Teen-Longitudinal Assessment of Bariatric Surgery), a study that follows 250 teens for up to five years who had weight loss surgery at five participating hospitals.

On Track

Back in San Diego, Justin Denny is banking on the old adage of "eat less, move more" to achieve his normal weight. He exercises at the gym with his father or personal trainer four days a week and follows a healthy diet suggested by a nutritionist.

"What changed is that Justin became concerned about his own weight," says his father Robert. "It all turned around when he took control and wanted a better lifestyle." EN

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Tri-Point SERIES

Under Pressure: Unlocking the Secrets of Primary Aldosteronism

Primary aldosteronism is a common cause of secondary hypertension, affecting up to 10% of hypertensive patients. Fortunately, we have made progress in the diagnosis and treatment of the disorder, as well as in the elucidation of disease-causing mechanisms. In this Tri-Point article, a clinical practitioner discusses the factors to consider when screening patients for the presence of primary aldosteronism; a clinical researcher provides an overview of diagnostic approaches to determine the subtype of primary aldosteronism, appropriate treatment modalities, and outcome measures; and a basic researcher reviews recent advances in our understanding of genetic and molecular mechanisms underlying unopposed aldosterone secretion by the adrenal gland.

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HIGHLIGHTS

- Experts on every continent have recognized that **primary aldosteronism (PA)** is more common than previously thought—affecting 5% to 10% of all hypertensive patients—and that most patients with PA are not hypokalemic.
- **Hypertension** affects 68 million adults in the United States, and approximately 14 million persons in this population (21%) have treatment-resistant hypertension and should be tested for PA.
- **Case-detection testing** with the aldosterone-to-renin ratio (ARR) may be performed while the patient is taking antihypertensive medications (with some exceptions) and without posture stimulation.

The approach to screening for primary aldosteronism (PA) has evolved over the 58 years since Jerome Conn reported the first case of PA. PA was thought to be a rare cause of hypertension for three decades because of strict rules for case-detection testing (e.g., sodium-balanced diet for two weeks, discontinuing most antihypertensive medications) and the erroneous concept that most patients with PA are hypokalemic. In 1981, Hiramatsu and colleagues showed that case-detection testing could be performed with very few restrictions on dietary sodium intake or blood pressure medications. They demonstrated that screening for PA could be accomplished by measuring the morning ambulatory paired plasma aldosterone concentration (PAC) and plasma renin activity (PRA) for the aldosterone-to-renin ratio (ARR). On the basis of studies completed with the ARR as a case-detection test, experts on every continent have recognized that PA is more common than previously thought—affecting 5% to 10% of all hypertensive patients—and that most patients with PA are not hypokalemic.

Who Should Be Tested for PA?

The Endocrine Society clinical practice guidelines recommend that case-detection testing for PA should be performed in patient groups with a relatively high prevalence of PA:

- Blood pressure >160/100 mm Hg
- Drug-resistant hypertension
- Hypertension and spontaneous or diuretic-induced hypokalemia
- Hypertension with adrenal incidentaloma
- Hypertension and family history of early-onset hypertension or stroke at a young age (<40 years)
- All hypertensive first-degree relatives of patients with PA

Hypertension affects 68 million adults in the United States, and approximately 14 million persons in this population (21%) have treatment-resistant hypertension and should be tested for PA. Thus, case-detection testing should occur commonly in the offices of primary care providers and endocrinologists.

Cutoffs and Accuracy of Case-Detection Testing

The ARR is widely accepted as the screening test of choice for PA. Importantly, the lower limit of detection varies among different PRA assays and can have a dramatic effect on the ARR. Thus, the cutoff for a high ARR is laboratory-dependent and, more specifically, PRA assay–dependent. At Mayo Clinic, a PAC (in ng/dL) to PRA (in ng/mL per hour) ratio greater than 20 (>555 in SI units) and a PAC ≥15 ng/dL (≥416 pmol/L) are found in more than 90% of patients with surgically confirmed aldosterone-producing adenomas. In patients without PA, most of the variation in the ARR occurs within the reference range.

It is important for the clinician to recognize that the ARR is a case-detection tool with a sensitivity and specificity of approximately 75% and that most positive results should be followed by a confirmatory aldosterone suppression test to verify autonomous aldosterone production before subtype evaluation or treatment is initiated.

Some reference laboratories have changed renin measurement methodology from PRA to measurement of plasma renin concentration (PRC). It is reasonable to consider a result from a PAC:PRC case-detection test to be positive when the PAC is 15 ng/dL or greater (≥416 pmol/L) and the PRC is below the lower limit of detection for the assay.

Impact of Antihypertensive Medications

The ARR may be assessed while the patient is taking antihypertensive medications (with some exceptions [see below]) and without posture stimulation. Mineralocorticoid receptor (MR) antagonists (e.g., spironolactone and eplerenone) and high-dosage amiloride are the only medications that absolutely interfere with interpretation of the ARR, and they should be discontinued at least six weeks before testing.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARBs), and diuretics have the potential to falsely elevate PRA. Therefore, in a patient treated with an ACE inhibitor, ARB, or diuretic, the finding of a detectable PRA level or a low ARR does not exclude the diagnosis of PA. However, a very useful clinical point is that when a PRA level is undetectably low in a patient taking an ACE inhibitor, ARB, or a diuretic, PA should be highly suspect. Thus, ACE inhibitors, ARBs, and non–potassium-sparing diuretics do not need to be discontinued. A second important clinical point is that PRA is suppressed (<1.0 ng/mL per hour) in almost all patients with PA. Adrenergic inhibitors (e.g., β-adrenergic blockers and central α_2 agonists) suppress renin secretion, but also in turn suppress aldosterone secretion (although to a lesser degree than renin) in normal individuals; thus, although the ARR may rise in hypertensive patients without PA treated with adrenergic inhibitors, the PAC remains less than 15 ng/dL (<416 pmol/L) and the case-detection test is not affected in a clinically important way. EN

HIGHLIGHTS

- **After a positive screening test,** the diagnosis of PA must be established by confirmatory testing.
- When confirmed, **the subtype of PA** must be determined (lateralized aldosterone secretion versus bilateral aldosterone secretion) with adrenal imaging and/or adrenal venous sampling.
- Surgical or medical treatment targeted appropriately to the PA subtype can **improve morbidity and mortality in these patients.**

The correct diagnosis of primary aldosteronism (PA) and its subtypes is essential for optimal treatment. After a positive screening test, the clinician must proceed by A) establishing the diagnosis of PA with confirmatory testing; and B) performing subtype determination (lateralized aldosterone secretion versus bilateral aldosterone secretion) by adrenal imaging and adrenal venous sampling. This approach allows a targeted treatment which is highly effective in controlling hypokalemia and hypertension, reducing cardiovascular event incidence to that of matched hypertensive patients, and normalizing overall mortality.

Targeted therapy requires correct subtype identification. The great majority of patients (≥98%) have sporadic PA. In these patients unilateral aldosteronism (mostly aldosterone-producing adenoma, APA) has to be distinguished from bilateral adrenal hyperplasia (IHA). The pretest probability for unilateral aldosteronism from an APA is around 70% in spontaneously hypokalemic patients. However, in the much more prevalent normokalemic cases APA is found in approximately 30% of cases. If subtype differentiation is incorrect, the patient will be subjected to inappropriate therapy: adrenalectomy in IHA or mineralocorticoid receptor blockade in APA.

Adrenal imaging by MRI or CT appears to be rather insensitive and nonspecific regarding subtype differentiation. Based on adrenal vein sampling (AVS) as the gold standard, up to 50% of patients may be categorized incorrectly based on imaging. Misleading results are mainly attributable to nonsecreting adrenal tumours (incidentalomas). Furthermore, the majority of hormone-producing adenomas are small (<1.5 cm) and may therefore escape notice even in thin-section images. In bilateral adrenal hyperplasia, imaging frequently shows normal-sized adrenal glands, and only sometimes demonstrates multiple small nodules. Therefore, many institutions, including our own, have adopted AVS as the standard in all patients who are candidates for surgery. There is no universal agreement as to how to perform AVS. Data linking postsurgical outcome with different protocols such as ACTH stimulation during AVS or simultaneous sampling from both adrenal veins are lacking. In the absence of evidence we prefer the simplest protocol: AVS without ACTH stimulation and with sequential sampling from adrenal veins. In our hands rapid cortisol determination is essential to verify correct catheter positioning during AVS. Using rapid cortisol determination routinely in our center has improved technical success rates of AVS to >90%. A standard operational procedure is necessary to avoid protocol violations, and has been in place in our institution since 2008. In addition, a multidisciplinary PA board to discuss AVS results of each patient is important because interpretation of AVS results remains a challenge. In our center, the decision for surgery is based on a lateralization index of ≥4.0. We do not request contralateral suppression for a surgical approach. Based on these criteria patients with suspected APA in Munich subjected to surgery have a 98% chance to enter biochemical remission (normalized serum potassium concentrations, normalized ARR, normalized aldosterone concentrations following sodium loading).

Patients with PA suffer from a multitude of comorbidities. Before targeted therapy is initiated, careful screening for metabolic, psychiatric, and cardiovascular disease is required. Metabolic complications include impaired glucose tolerance or frank diabetes. Patients with PA often have secondary hyperparathyroidism with consequent osteoporosis requiring vitamin D substitution. Longstanding secondary hyperparathyroidism may lead to tertiary hyperparathyroidism requiring parathyroidectomy. PA patients also suffer from increased anxiety and depression levels, which have to be adequately addressed. Prevalent cardiovascular disease such as atrial fibrillation, myocardial infarction, and stroke are more frequent than in matched hypertensive controls. Renal function is often impaired although aldosterone excess may obscure renal insufficiency via increased renal plasma flow.

Subtypes of primary aldosteronism require different therapeutic strategies. In our center, candidates for unilateral adrenalectomy are treated with mineralocorticoid antagonists pre-operatively. The rationale is to block aldosterone action, control hypertension, correct potassium losses, and increase plasma renin concentration to avoid postsurgical zona glomerulosa insufficiency with consecutive hyperkalemia. Evidence from randomized controlled trials supporting this strategy is still lacking.

Unilateral minimally invasive laparoscopic adrenalectomy is the standard in unilateral aldosteronism leading to reduced operating time and hospital stay. Morbidity of this procedure is very low, and mortality close to 0%. Nearly all patients will profit from surgery with regard to their postoperative blood pressure. The rate of remission from hypertension is higher for younger patients, female patients and patients with a short time between hypertension onset and diagnosis of PA (< 5 years). Whereas early studies using less stringent criteria for

normotension reported remission rates of 70% and higher, more recent series reported remission in one-third of patients. The remaining patients have persistent hypertension, which is more easily controlled using fewer drugs. Cases in which surgery is not possible receive life-long long-term mineralocorticoid receptor blockade. Outcome with MR blockers is similar to surgery, and escape from treatment effects have rarely been reported.

Bilateral adrenal hyperplasia is treated medically, as bilateral adrenalectomy in early series did not provide convincing improvement with regard to postoperative blood pressure. In addition, such a strategy requires life-long hormone substitution with inherent risks from adrenal crisis. Medical treatment aims to antagonize aldosterone at the receptor level by the mineralocorticoid antagonists spironolactone, potassium canrenoate or eplerenone, with additional antihypertensives, as needed, to reach target blood pressure levels. Spironolactone is given at a low starting dose of 25 mg and titrated—depending on potassium and blood pressure—to 50 or 75 mg. Higher doses of spironolactone often induce side effects such as gynaecomastia, impotence, and menstrual disturbances, which result from its action on progesterone and androgen receptors. In the RALES study, 10% of male patients receiving 25 mg spironolactone developed gynecomastia/breast pain vs. 1% in the placebo group. Recently, remission from PA has been reported after long-term treatment with spironolactone in IHA. Compared to spironolactone, less adverse effects can be expected from the more selective mineralocorticoid antagonist eplerenone (off-label use for hypertensives in Europe). It has been the experience that eplerenone has to be used in 1.5 to 2 times higher doses than spironolactone to achieve a similar effect on blood pressure. If additional antihypertensive medication is needed, potassium-sparing diuretics such as triamterene or amiloride can be used. Reduction of salt intake supports medical treatment as adverse effects of aldosterone are intensified in a high salt environment.

Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type I) is treated with low-dose dexamethasone (0.125-0.25 mg/day), which usually corrects hypertension, although biochemical alterations may persist. Patients can alternatively be given aldosterone antagonists or potassium-sparing diuretics, the latter especially being an option when treating children. Familial hyperaldosteronism type II is treated in the same way as sporadic cases of primary aldosteronism. Familial hyperaldosteronism type III caused by germ-line mutations in the potassium channel *KCNJ5* often requires bilateral adrenalectomy because of severe intractable hypertension. EN

BASIC RESEARCHER PERSPECTIVE

HIGHLIGHTS

- Primary aldosteronism results from autonomous aldosterone production from the **adrenal cortex**.
- **Early diagnosis of primary aldosteronism** is essential for efficient therapeutic intervention and prevention of the adverse effects of aldosterone excess.
- Recent discoveries have improved our understanding on the genetic causes of **familial and sporadic primary aldosteronism.**

Aldosterone plays a major role in regulating sodium and potassium homeostasis, and blood pressure. Primary aldosteronism (PA) results from autonomous aldosterone production from the adrenal cortex. Studies published in the last two years have uncovered the genetic causes of a subset of PA and highlighted the central role of ionic homeostasis and maintenance of zona glomerulosa cell membrane potential in the pathogenesis of the disease. These discoveries may pave the way toward better diagnostic approaches and new therapeutic opportunities, concerning up to 10% of the hypertensive population.

Mechanisms Controlling Aldosterone Biosynthesis

Aldosterone production from the zona glomerulosa (ZG) is tightly controlled to maintain electrolyte and fluid homeostasis by the kidney. Both angiotensin II (AngII) and potassium, the major regulators of aldosterone biosynthesis, act by increasing intracellular calcium concentrations, thus activating the calcium signaling pathway. This triggers a cascade of events ultimately leading to increased transcription of the CYP11B2 gene coding for aldosterone synthase. The maintenance of an appropriate zona glomerulosa cell membrane potential and intracellular ionic homeostasis is crucial to this mechanism because membrane depolarization leads to opening of voltage-gated calcium channels and an increase in intracellular calcium. In the zona glomerulosa the main ionic conductance is that of K^+, due to the expression of different types of K^+ channels. Thus, the cell membrane potential closely follows the equilibrium potential of K^+ over a large range of extracellular K^+ concentrations. The concentration gradient of K^+ between the intracellular and extracellular space that is required for the establishment of the membrane potential is generated by the activity of the Na^+, K^+-ATPase. Alteration of intracellular ionic homeostasis plays

an important role in the pathogenesis of PA. Mutations affecting proteins involved in the regulation of zona glomerulosa cell membrane potential and ionic homeostasis have recently been identified in familial and sporadic forms of PA.

Familial Forms of PA

While the majority of cases of PA are sporadic, there exist three familial forms of hyperaldosteronism, accounting for 6%–10% of cases. In two of them, genetic diagnosis allows prompt and optimized therapeutic intervention. Familial hyperaldosteronism type I (FH-I), also called glucocorticoid suppressible aldosteronism (GRA), is characterized by early and severe hypertension, most often before the age of 20 years, in subjects with biochemical abnormalities of PA of variable intensity and in some cases adrenal nodules. FH-I is inherited as an autosomal dominant trait and is characterized by significant production of hybrid steroids (18-hydroxycortisol and 18-oxocortisol), and normalization of aldosterone levels and blood pressure with low doses of dexamethasone. The condition is due to formation of a hybrid gene resulting from unequal crossing over between *CYP11B2* and the adjacent highly homologous gene *CYP11B1,* coding for steroid 11β-hydroxylase. Fusion of the promoter region of *CYP11B1* to the coding region of *CYP11B2* produces a chimeric gene, with the activity of aldosterone synthase, but tissue specificity and ACTH regulation of 11ß hydroxylase.

Familial hyperaldosteronism type II (FH-II) is also transmitted as an autosomal dominant trait, but is not associated with hybrid gene formation and, thus, hyperaldosteronism is not suppressible by dexamethasone. FH-II is clinically and biochemically undistinguishable from sporadic PA. The anatomic findings are variable from aldosterone-producing adenomas to bilateral adrenal hyperplasia. FH-II is diagnosed on the basis of two or more affected family members, and phenotypic variability within affected families is typical for the disease. In contrast to the other familial forms of PA, the genetic cause of FH-II has not been resolved so far, although a locus associated with the disease has been mapped to chromosome 7p22.

Potassium Channels and ATPases in the Pathogenesis of Familial and Sporadic PA

Recent work identified germline mutations in the *KCNJ5* gene in a severe familial form of PA, familial hyperaldosteronism type III (FH-III), and similar recurrent somatic *KCNJ5* mutations as cause of sporadic aldosterone producing adenomas. Patients with FH-III displayed early-onset resistant hypertension, profound hypokalemia, and very high levels of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol. The disease was due to massive bilateral adrenal hyperplasia requiring bilateral adrenalectomy during childhood to control blood pressure. Subsequently, additional mutations and phenotypic variability of FH-III have been reported, with some patients presenting with mild PA resembling to FH-II.

KCNJ5 encodes the G protein-activated inward rectifier potassium channel GIRK4. The different mutations identified in aldosterone-producing adenomas and FH-III are all located near or within the selectivity filter of GIRK4 and affect the ion selectivity of the channel, with increased sodium conductance leading to sodium entry into the cell and chronic membrane depolarization. These changes are responsible for increased intracellular calcium leading to constitutive secretion of aldosterone and possibly cell proliferation. Somatic KCNJ5 mutations are present in 34%–47% of aldosterone producing adenoma samples from Western countries, and as high as 65% of patients from Japan. These mutations are associated with female gender, younger age, and a more severe phenotype of the disease. More recently, whole exome sequencing in APA has identified somatic mutations in two members of the P-type ATPase gene family, namely *ATP1A1,* encoding the α1 subunit of the Na^+, K^+-ATPase, and ATP2B3, coding for the plasma membrane calcium-transporting ATPase 3 (PMCA3). Mutations in the α1 subunit of the Na^+, K^+-ATPase led to a complete loss of pump activity and a strongly reduced affinity for K^+, while mutations of PCMA3 were predicted to affect intracellular calcium clearance. ATPase mutations were present in ~7% of a large series of tumors, but in contrast to *KCNJ5* mutations, were more prevalent in males. Once again, mutation carriers had higher preoperative aldosterone levels compared to patients without mutation and lower serum potassium concentrations. Future studies will indicate whether carriers of somatic *KCNJ5, ATP1A1,* or *ATP2B3* mutations may benefit from specific treatment options. Additional genetic investigation in large cohorts of patients will allow unraveling the missing genetics of the remaining 50% of APA, as well as discovering the susceptibility factors leading to bilateral adrenal hyperplasia, the other most common form of PA. EN

Society Advocates GLOBALLY on EDCs; Members Can Get Involved

The Endocrine Society has continued to expand its advocacy program internationally by proactively engaging on several fronts with key policymakers and collaborators. First branching out into the European Union in 2012, the Society has continued its international efforts by becoming active in the debate among global policymaking bodies. By partnering with pivotal international organizations, the Society broadens its reach and amplifies its message that endocrine science is central in the identification, study, and regulation of endocrine-disrupting chemicals (EDCs), which represent a global concern for the environment, wildlife, and human health.

Society members can become involved in these efforts by volunteering to convey the Society's central messages to key policymakers in their countries. Volunteer opportunities are available at The Endocrine Society's booth at **ENDO 2013** or by contacting the government and public affairs department at ***govt-prof@endo-society.org.*** Members who do not wish to volunteer can still contribute to the Society's advocacy efforts by stopping by the booth to sign a letter to global policymakers in support of the Society's positions on EDCs.

In the European Union (EU), the Society has collaborated with the Brussels-based Health and Environment Alliance (HEAL) to meet with Members of the European Parliament (MEPs), Directorates General (DGs) of the European Commission, and World Health Organization (WHO). In these meetings, Society member volunteers have been pivotal in presenting the endocrine perspective to policymakers in the European Union who are grappling with revising and refining the EU's approach to defining and regulating EDCs.

In December 2012, Society representative Jean Pierre Bourguignon, MD, partnered with HEAL to meet with MEP Anne Delvaux (conservative, Belgium) and MEP Frederique Ries (liberal, Belgium). These meetings came during deliberations by the Parliament's Committee on Environment, Public Health, and Food Safety on a report—presented by MEP Asa Westlund—on the protection of public health from endocrine disruptors. The report, which Parliament passed in March by a vote of 489–102,

calls on the Commission to strengthen the science base and regulatory requirements for EDCs. The report references the Society's 2009 Scientific Statement on EDCs, and the report's provisions are strongly aligned with the Society's policies. Some specific actions requested are: application of the precautionary principle; consideration of mixtures, long-term effects, and irreversible effects during critical windows of development; consideration of EDCs as nonthreshold substances; consideration of the entire scientific literature, including academic studies, in the risk assessment of EDCs; and increased research efforts in the field.

The report has no legislative weight but conveys the position of the European Parliament to the European Commission as it prepares to revise the EU's strategy on EDCs and to define the official criteria by which EDCs will be identified and categorized for EU law. The strategy will guide further legislative revisions and adjustments, as well as other efforts, including international cooperation and research support. The criteria will be officially deployed for the pesticides and biocides legislation, and will be applied to other legislation in due course.

In February, R. Thomas Zoeller, PhD, presented the Society's Statement of Principles to the Expert Advisory Group on Endocrine Disruptors during the fifth meeting of commission services, European agencies, and member states in Ispra, Italy. Subsequently, Zoeller and Bourguignon again partnered with HEAL in Brussels to meet with members of the DG Environment, DG Health & Consumer Affairs, and WHO. These combined activities served to expand the Society's efforts to convey its message to those charged with formulating and implementing EU regulations. To reach an even broader audience, meetings were also held with the media and with other European nongovernmental organizations interested in issues of health and the environment.

The Society has recently expanded its international work beyond the EU, partnering with IPEN, a global network of public interest organizations, to advocate for global action on EDCs. IPEN serves as the principal public-interest focal point for over 700 nongovernmental organizations (NGOs) in the Strategic Approach to International Chemicals Management (SAICM), a UN global policy framework that represents a commitment by the world's governments to achieve the sound management of chemicals so that "chemicals are produced and used in ways that minimize significant adverse impacts on human health and the environment." More than 100 governments participate in SAICM and its governing body—the International Conference on Chemicals Management (ICCM)—along with the chemical industry, NGOs, and other key stakeholders. ICCM meets every three years to assess implementation and evaluate additional issues that SAICM needs to address. At its third and most recent meeting, ICCM3 in 2012 in Nairobi, the ICCM officially acknowledged that EDCs are a global issue. ICCM3 recognized by consensus the "…potential adverse effects of endocrine disruptors on human health and the environment" and "…the need to protect humans, and ecosystems and their constituent parts that are especially vulnerable." The decision called for several actions, including "advice on translation of research results into control actions."

In an April 21 letter to key institutions responsible for implementing EDC actions under SAICM, The Endocrine Society and IPEN urged progress on these actions and encouraged the involvement of endocrinologists and the Society as key scientific experts. To strengthen their case, both groups sought signatures from prominent scientists in the field, and a number of scientists in key countries signed the letter. Society members from across the globe with expertise and interest in EDCs were among the signatories, including co-authors of a number of high-profile reports—the Society's Scientific Statement and Statement of Principles, a 2012 *Endocrine Reviews* article on low-dose effects of EDCs, and the recent report on EDCs by WHO and the UN Environment Program (UNEP).

The collaboration with IPEN marks a bold step forward by the Society in disseminating its messages to the global chemicals policy community and holds the potential to put endocrine science right where it needs to be – in the center of the discussion on the effects of EDCs.

By working with pivotal partners such as HEAL and IPEN, the Society has the opportunity to change the tenor of the global EDC discussion so that the endocrinology of endocrine disruptors is considered during important policy and regulatory decisions. Just as the effects of EDCs are not bound by borders, neither are the principles of endocrinology that help delineate and predict those effects. As the preeminent global organization devoted to endocrine research and the clinical practice of endocrinology, The Endocrine Society's membership represents the richest source of expertise in the field of endocrine disruption. The Society is well positioned to effect change in the approach to the study, assessment, and regulation of EDCs. EN

Society Members can become involved
by volunteering to convey the Society's central messages to key policymakers in their countries.

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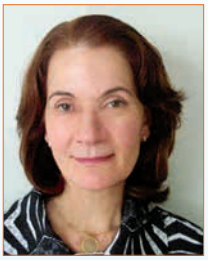

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Maia Corpuz
Chimdi Ego-Osuala

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Vol. 97, No. 3, P. 1020-1031
Corresponding author: Jan Bolinder

"Impaired Incretin-Induced Amplification of Insulin Secretion after Glucose Homeostatic Dysregulation in Healthy Subjects"
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Corresponding author: Katrine B Hansen

"Sclerostin and Its Association with Physical Activity, Age, Gender, Body Composition, and Bone Mineral Content in Healthy Adults"
Vol. 97, No. 1, P. 148-154
Corresponding author: Karin Amrein

"Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome"
Vol. 97, No. 6, P. 2039-2049
Corresponding author: Maria Fleseriu

"Metabolically Healthy Obesity and Risk of All-Cause and Cardiovascular Disease Mortality"
Vol. 97, No. 7, P. 2482-2488
Corresponding author: Mark Hamer

"Combined Effects of the Variants FSHB –211G>T and FSHR 2039A>G on Male Reproductive Parameters"
Vol. 97, No. 10, P. 3639-3647
Corresponding author: Frank Tüttelmann

"Reference Ranges and Determinants of Testosterone, Dihydrotestosterone, and Estradiol Levels Measured using Liquid Chromatography-Tandem Mass Spectrometry in a Population-Based Cohort of Older Men"
Vol. 97, No. 11, P. 4030-4039
Corresponding author: Bu Beng Yeap

"Fractures in Healthy Females Followed from Childhood to Early Adulthood Are Associated with Later Menarcheal Age and with Impaired Bone Microstructure at Peak Bone Mass"
Vol. 97, No. 11, P. 4174-4181
Corresponding author: Thierry Chevalley

"The Timing of Total Thyroidectomy in *RET* Gene Mutation Carriers Could Be Personalized and Safely Planned on the Basis of Serum Calcitonin: 18 Years Experience at One Single Center"
Vol. 97, No. 2, P. 426-435
Corresponding author: Rossella Elisei

"Long-Term Follow-Up for Mortality and Cancer in a Randomized Placebo-Controlled Trial of Vitamin D3 and/or Calcium (RECORD Trial)"
Vol. 97, No. 2, P. 614-622
Corresponding author: Alison Avenell

"Insights into Puberty: The Relationship between Sleep Stages and Pulsatile LH Secretion"
Vol. 97, No. 11, P. E2055-E2062
Corresponding author: Natalie D Shaw

"Somatic Mutations in the *KCNJ5* Gene Raise the Lateralization Index: Implications for the Diagnosis of Primary Aldosteronism by Adrenal Vein Sampling"
Vol. 97, No. 12, P. E2307-E2313
Corresponding author: Gian Paolo Rossi

"Increased Activation of the Alternative "Backdoor" Pathway in Patients with 21-Hydroxylase Deficiency: Evidence from Urinary Steroid Hormone Analysis"
Vol. 97, No. 3, P. E367-E375
Corresponding author: Clemens Kamrath

"Complete Inhibition of rhTSH-, Graves' Disease IgG-, and M22-Induced cAMP Production in Differentiated Orbital Fibroblasts by a Low-Molecular-Weight TSHR Antagonist"
Vol. 97, No. 5, P. E781-E785
Corresponding author: Anita Boelen

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Cintia Bagne Ueta
Mentor: Antonio C Bianco, MD, PhD

Frédéric Picou, PhD
Mentor: Frédéric Flamant, PhD

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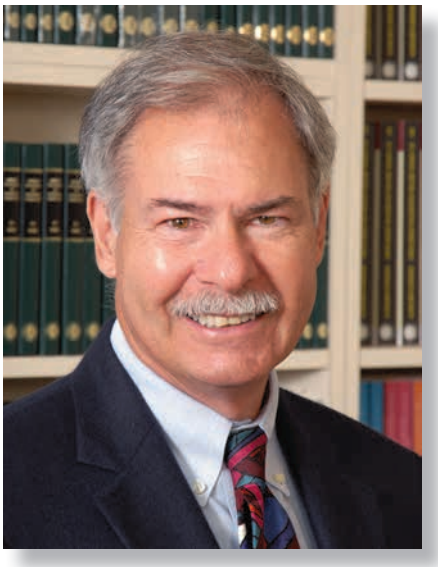


A SILVER CELEBRATION

A remarkable era in the history of The Endocrine Society comes to a close as CEO Scott Hunt steps down after 25 years.

By Mark A. Newman

In 1988, George H.W. Bush was elected president. George Michael's *Faith* was the number one song and moviegoers, meanwhile, were skeptical of Dustin Hoffman's claim that he was a "very good driver" in his Oscar-winning turn in *Rain Man*.

A very good driver of fortunes took place for The Endocrine Society in 1988 when Scott Hunt got behind the wheel as the CEO. And the rest, as they say, is history. During the intervening quarter century, Hunt was intimately involved in shepherding the Society to where it is today. One clear example of his leadership is evidenced by how much the Society's revenue stream has grown during Hunt's time as CEO: When he began, annual revenue was less than $2 million; today the Society takes in over $30 million annually. That's a track record any Fortune 500 CEO would envy.

A Transformative Impact

"Scott Hunt's impact on The Endocrine Society over the past 25 years has been transformative," said Society president William F. Young, Jr., MD. "Scott has a unique way to empower and inspire Society staff and volunteer members. In this way, Scott has transformed the Society from a 'mom and pop' shop with a handful of staff, a limited number of standing committees, and a membership of less than 5,800 to a vibrant Society with 90 staff, 22 standing committees, and a total Society membership of more than 16,000."

Another increase was found in the Society's heart and soul – the headquarters staff. When he began, there were only four full-time employees devoted to carrying out the Society's mission; now the Society boasts over 90 souls hard at work in the Washington DC-area headquarters. This steady growth for an association during a time when the economy was unpredictable at best and downright ornery at worst is clearly a testament to Hunt's abilities as well as his own vision for what the Society could become.

Kelly E. Mayo, professor of molecular biosciences, associate dean for research and graduate studies, Weinberg College of Arts and Sciences at Northwestern University, and a past president of the Society echoes these sentiments and feels that Hunt's most important legacy is in the people he recruited and the culture he instilled within Society staff and the organization. "We are fortunate to have a remarkable staff that drives our many initiatives and supports the initiatives that come from our committees," he says. "Scott has built and led that staff, and he has a tremendous ability to identify good people and provide them with what they need to be successful. It will be awfully hard to replace Scott himself, but I do think that he leaves us in terrific shape as a Society, largely because of the abilities and culture that he has developed within the Society staff."

"When I got here the Society had four employees and the budget was $2 million and essentially the staff had contractors that did everything."

Realizing the Potential

Hunt came to The Endocrine Society after a stint as VP/general manager of the American Association for Clinical Chemistry. Armed with a bachelor's degree from Lafayette College in Easton, Penn., and a Harvard MBA, Hunt was not only aware of the Society's potential but also its myriad challenges.

"When I got here the Society had four employees and the budget was $2 million and essentially the staff had

With Honors

In 2007, The American Medical Association honored Hunt with the Medical Executive Meritorious Achievement Award. The award is given to a medical association executive who has demonstrated exceptional service and contributions to the goals and ideals of the medical profession.

Hunt served as president of the Council of Engineering and Scientific Society Executives from 2007 to 2008, and served on its board from 2003-2009.

contractors that did everything," Hunt explains, adding that maintaining the finances and the annual meeting – now ENDO – as well as publishing the journals were all performed by outside firms. "[The Society office] was more like an executive secretariat, forwarding mail and asking members to make decisions. It was very quiet."

Hunt says that he saw the potential of what the Society could be as soon as he was hired. His first order of business was getting the finances clear followed by taking on the management of the annual meeting. He recounted a story of his first Society Annual Meeting that was so low-key that there was no official signage. "The individual chairs of each session wrote in their own scrawl the names of the speakers and what they were speaking on," he says. "There was no clinical program per se, just a day at the end of the meeting where clinical topics were discussed."

As soon as the meeting operations were well run, Hunt addressed the publishing program. He brought all four journals under Society management, increasing pages and profits from advertising and subscriptions. Today, the journal program is the biggest financial engine for the Society.

As Hunt grew the Society, he always had an eye on the bottom line and finding ways to increase it to better serve the membership. "We had to turn the activities of the society into money-making activities so that we could begin to expand services for the members and add new services," he says. "If we want to serve all the different member groups and not take from one group to give to another group, we had to increase the total available dollars to do that. We had to be growing."

Without inherent growth for the Society, Hunt says that every year one group would get a bigger piece of the available "pie" while another group may be shortchanged. "By increasing the pie, the gross, we were able to add services for each of the constituencies of the Society," he says. "So you had to have a business model that is diverse, that would allow us to get money from many different sources so that any time one source is weak, another may be particularly strong. And that's been our history. There are times when we would have a very poor performance in one area and very strong in another."

The Short List

During Hunt's tenure, the Society's fortunes improved in a number of ways. For example, since 1988:

- Revenue has increased from $1.6 million to $30 million
- Membership has grown from 5,800 to 16,200, in more than 100 countries
- ENDO attendance has grown from 4,100 to 9,100
- Staff has grown from four to 90 employees
- Named a Top 50 Association by the *Washington Business Journal* from 2009 to 2012
- Creation of the Hormone Health Network, a public education program
- The creation of *Endocrine News.*

A Quarter Century of Achievements

After 25 years of unprecedented growth, there have been many milestones in the Society's history where Hunt has played a role in its implementation. "One is hard pressed to think of any of the multiple activities and initiatives of the Society over the years without visualizing Scott's hand in either the conception of the process or actually bringing it to fruition, either overtly or in his typically modest, behind the scenes self-effacing manner," said Leonard Wartofsky, MD, MACP, chairman, Department of Medicine, Washington Hospital Center, in Washington, DC, and a former Society president.

"The Society has changed so much during Scott's long tenure that it is difficult to point to any single thing," Mayo said when asked for one of Hunt's top accomplishments. "We have obviously grown the membership and become more diverse, and have developed many new programs, products, and markets. Clearly, respect for the Society as an impactful organization has grown tremendously, including how we are viewed by the public, our standing as a non-for-profit association, our place in the medical and research communities, and the impact of our advocacy, to name a few significant positive changes."

Hunt was also instrumental in broadening the Society's educational outreach programs such as the Endocrine Self-Assessment Plan (ESAP) instituted in 2004 as well as the Maintenance of Certification (MOC), Performance Improvement Modules (PIM), in-service exams, board reviews, clinical practice guidelines, scientific statements, early investigators workshops, and the list goes on. The CME programs that began in 1996 vastly expanded the content of the annual meetings. "Adding all these morning and evening programs to the annual meeting was very purposeful for us," Hunt says. "They added more to the coffers so we could increase services elsewhere, as well as increasing medical content."

However, all these accomplishments were a part of Hunt's strategic plan for the Society to prepare it for the next steps. "Through all of this we've had tremendous success and we've been managed appropriately on the business side," he says. "We have placeholders ready to move into new services and programs. If there is any business opportunity out there, we have a way to take advantage of it."

Headed for the Future

Despite the remarkable growth the Society has undergone in the last

two and a half decades, there is no time for resting on laurels and the future is always within sight. "We are in the midst of a massive rebuilding of our infrastructure so we're going to be ready for the next ten years by the end of this year," Hunt explains, citing a new association management system that is currently being readied for launch.

Hunt also sees the Society's continued growth hand-in-hand with that of the practice of endocrinology itself. "Primary care is seeing 90% of the endocrinology in this country and yet we have the content to support that," he explains. "But our content is in Greek and primary care needs it in English so we need to change the way we present our content. It's a many orders of magnitude bigger market that we can support. To me, it's so clearly the future of the Society's programming. It will increase our influence dramatically and is a sustainable model."

Hunt explains that this growth doesn't mean that the Society will stop the way it is currently doing things; it just means that Society content must be made accessible in a way that is useful to primary care physicians. "This should generate a huge surplus for the Society over time," he says. "[This surplus will be] even bigger than we have had and that should enable us to increase programming for basic scientists and clinical scientists, as well as for clinical practitioners. The pieces are coming on line to be able to do that."

Regardless of the many successes of the Society under Hunt's leadership, it seems that everyone who has been involved with the Society over the years will really miss Scott Hunt, the man. "What I will always remember about Scott is how he truly cares about the people -- members and staff -- that make up the organization, and how he uses his acumen and professionalism to make everyone else look so good!" said Margaret A. Shupnik, PhD, senior associate dean for research, University of Virginia School of Medicine in Charlottesville. "Everyone who is a part of this organization could not help but feel that he is on their side. I wish other organizations had true creative business individuals working on their behalf the way that Scott works for all of us."

"With the announcement of Scott Hunt's retirement, innumerable colleagues have made comments like 'a hard act to follow' or 'big shoes to fill'. Indeed, the sentiment is so true because for the past two decades Scott has been The Endocrine Society!" Wartofsky said. "We will miss his tact, his respect for confidentiality, his humor, his wisdom, his camaraderie, his boyish enthusiasm, his maturity, and his ever present professionalism. Yes, he will be dearly missed, but leaves behind the legacy of the most dynamic, most vital, most highly reputed and respected, and most productive endocrine society in the world. We say goodbye reluctantly, recognizing that we have been so fortunate to have had his leadership, and now wish him well in this next very personal new phase of his life."

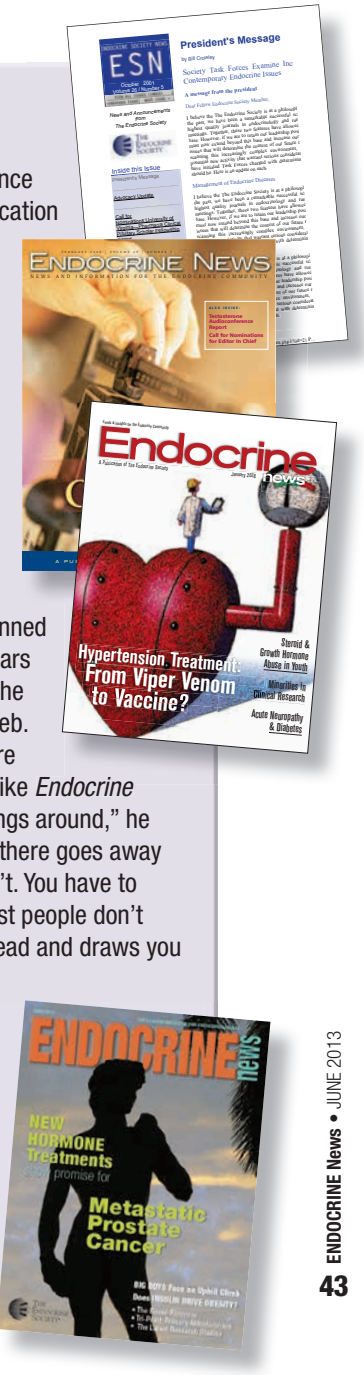
Hunt's post-Society life will be spent traveling with his wife Pamela and, of course, racing his Porsche. But he still plans to do some consulting with not-for-profits who are in the process of setting up their own strategic plans. Future success stories are bound to happen. EN

Upon retirement, Hunt will have plenty of time to race his Porsche. Here he is at Lime Rock Park in Connecticut, leading the "I" class race.

Breaking News

Endocrine News owes its existence to Scott Hunt's vision for a publication that would be easily accessible to the members and appeal to a wider audience as well. "The creation of *Endocrine News* was a big leap forward for the Society's communication," Hunt says. "It is a vehicle for the Society to say what it's doing and what it's programs and activities are, but in a more conversational manner that the journals are not able to do."

Endocrine News was also planned as a channel for advertising dollars that would slowly slip away as the print journals moved onto the web. Hunt proudly proclaims that there is no other medium in the field like *Endocrine News*. "It's sticky because it hangs around," he says. "All of the online stuff out there goes away with a keystroke, but this doesn't. You have to decide to throw it away and most people don't because they like it. It's fun to read and draws you in. There's nothing like it in our market. It's accessible and has the potential for expansion. It's one of the big successes."



Endocrine News through the years, from its earliest incarnation as ESN (top) in 2001 to its current, four-color format.

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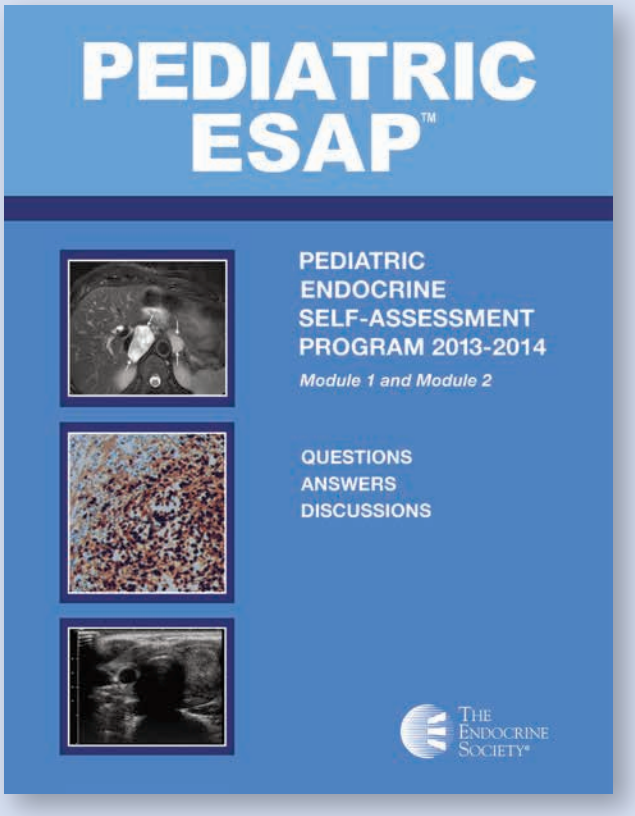

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THE ENDOCRINE SOCIETY®

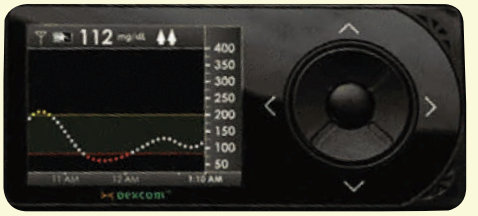
The Building of a BIONIC PANCREAS

By Melissa Mapes

Thirteen years ago, Edward Damiano, PhD, associate professor of biomedical engineering at Boston University, found out his infant son had type 1 diabetes. Since he did not think he had the expertise to develop a cure, he figured he could contribute in another way to the quality of his son's life. "My skill set seemed to lend itself more toward developing devices, technology, gadgets that could help improve blood glucose control rather than finding an actual cure for type 1, so I set my sights on that," he explained.

Damiano's expertise is in applied mathematics, specifically pertaining to physiological systems. He reasoned that a smart algorithm could be used to interpret a glucose signal and dose hormones accordingly, which would take the burden of finger pricks and insulin estimates off patients. He began collaborating with one of his PhD students at the time, Firas El-Khatib, to test mathematical algorithms in diabetic pigs. From the very beginning, Damiano felt it was essential that the artificial pancreas, or the bionic pancreas as he likes to call it, could infuse both insulin and glucagon. The goal was to keep patients' blood glucose as even as possible throughout all daily activities: from big meals to big workouts.

When Edward Damiano discovered that his infant son, David, had type 1 diabetes, he used his expertise in biomedical engineering to help develop a "bionic" pancreas.



BIONIC PANCREAS: How It Works

- Reads blood glucose every five minutes
- Distributes drugs based on readings
- Worn like a traditional insulin pump
- Only needs the patient's weight to get started
- Adjusts to specific glucagon and insulin needs within hours of initiation
- Links to a typical smartphone

The task of finding an accurate and reliable sensor created a major obstacle for the device in the initial stages. "That was actually a tougher nut to crack than any other part of this," Damiano said. The resources needed to develop such medical technology were beyond the scope of his work, so he and his team had to wait for innovations from the medical device industry. Fortunately, they came through. "We now are in a position where we have two sensors out there that are accurate enough to drive the system." Ultimately the DexCom G4 became a part of the bionic pancreas and resolved past concerns – allowing the project to move forward.

There's an App for That

As an academic, the United States Food and Drug Administration (FDA) approval process for clinical trials was alien to Damiano. He was the first academic to obtain an investigational device exemption (IDE) for an artificial pancreas system and has since obtained several others as the bionic pancreas has evolved. The current prototype consists of a mobile system with two tandem pumps – one for insulin and one for glucagon – and a third device that merges an iPhone and a DexCom receiver into a handheld unit that wirelessly controls the pumps.

Damiano claims that the bionic pancreas would not be possible in its current form without the help of a smartphone. "It's amazing what that technology has brought us in five years," he said. Rather than develop a whole new platform, Damiano and his team collaborated with engineers at SweetSpot Diabetes and Egret Technologies to build an app that runs the algorithm and communicates wirelessly with the Bluetooth-enabled pumps and sensor. The rest of the phone is inaccessible to the subject once the app is open, so

"subjects can't get into it to play Angry Birds," he explained.

The bionic pancreas reads blood glucose every five minutes and distributes drugs accordingly. It is worn in a similar manner to a traditional insulin pump, but is significantly more effective at controlling diabetes. The fully automated system requires only the patient's weight to get started. The algorithm learns and adjusts to the specific individual's glucagon and insulin needs within hours of first use. Damiano has tested the artificial pancreas in both adults and children over multiple-day periods with both in-patient and out-patient settings and has seen great success. His team is planning to test the performance of the system in 32 children at a diabetes camp in central Massachusetts over a four-week period this summer. In April the FDA approved the device's IDE for this specific purpose.

The Road Ahead

The last big hurdle for the bionic pancreas is the development of a stable, pumpable glucagon. There is no commercial pathway forward using reconstituted glucagon from rescue kits because current formulations are not chemically stable in solution. Damiano is collaborating with device and pharmaceutical companies to test more stable formulations in animal and human studies, and is so far encouraged by the results.

Naturally, Damiano's team is not the only group developing an artificial pancreas. Several different versions of a closed-loop system are undergoing testing around the United States and the world. The Artificial Pancreas Project was started in 2005 to motivate the creation of algorithms for diabetes care, and the FDA listed the artificial pancreas as a major priority shortly thereafter. Grant funding began to flow in the millions and pancreas projects sprouted up across the globe, according to the May 2012 issue of *Nature.*

The goal was to
keep patients' blood glucose as even as possible
throughout all daily activities:
from big meals to big workouts.

However, most of these studies have limited patients to a hospital setting and required hookups to a laptop computer. They also have often involved only insulin. Damiano's version allows full mobility, thanks to the iPhone, and glucagon control, making it an appealing contender to patients.

Damiano hopes to bring the bionic pancreas to market by the time his son leaves for college. That milestone is four short years away, but his team just might achieve it.

Providers interested in learning more about the bionic pancreas, including those with a patient that may like to participate in a future trial, can find more information at artificialpancreas.org. EN

—Mapes is a freelance writer in Washington, D.C., and a regular contributor to Endocrine News.

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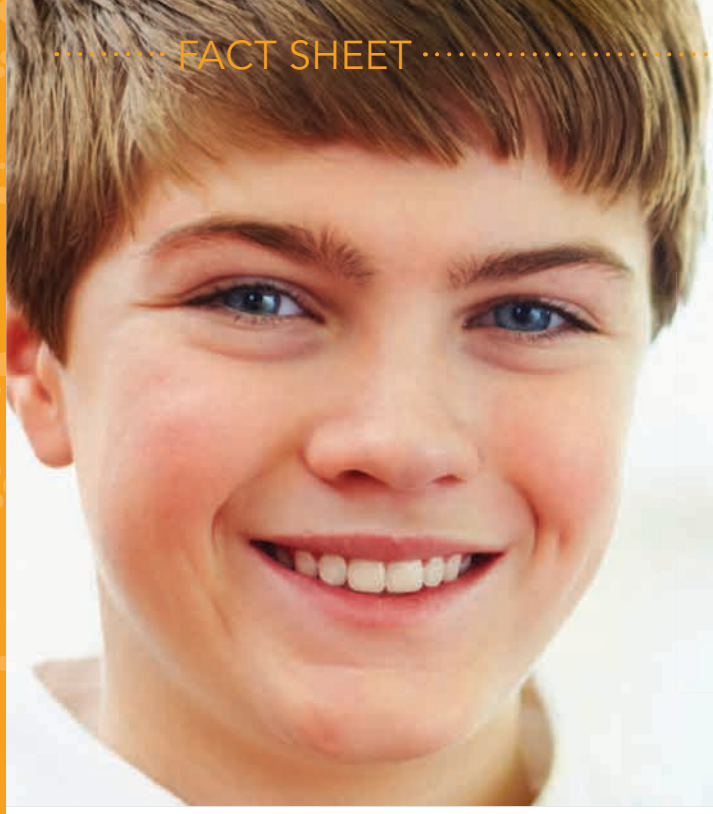

Hormone Health NETWORK
Keep your body in balance

Delayed Puberty

What Parents Need to Know

WHAT IS PUBERTY?

Puberty is the time of life when a child's body matures into an adult's.

- For girls, puberty can start as early as age 7½ years or as late as age 13. Their breasts begin to develop and their hips get wider. Girls start to grow underarm hair and pubic hair, and have a growth spurt. They start having menstrual periods about 2 to 3 years after their breasts start to develop.
- For boys, puberty usually starts between ages 9 and 14 years. The testicles and penis get larger. Boys start to grow underarm hair, pubic hair, and facial hair. Their voices deepen and they have a growth spurt. Boys' shoulders widen and they develop more muscle.

WHAT IS DELAYED PUBERTY?

Delayed puberty is when a teen goes through these body changes later than the usual age range.

- For girls, it means no breast development by age 13 or no menstrual periods by age 16
- For boys, it means no enlargement of the testicles by age 14

DID YOU KNOW?

Delayed puberty can run in families. Many teens who go through puberty late have parents, siblings, aunts, uncles, or cousins who also went through puberty late.

WHAT CAUSES DELAYED PUBERTY?

Some teens are "late bloomers" who just happen to start puberty later than most children their age. Being a late bloomer is the most common cause of delayed puberty. It's not caused by a medical problem and usually doesn't need treatment. Late bloomers will eventually start puberty on their own and catch up to their friends.

LESS COMMON CAUSES OF DELAYED PUBERTY

- Medical conditions that keep the intestines from absorbing nutrients from food, such as celiac disease or inflammatory bowel disease
- Malnutrition (not getting proper nourishment) due to an eating disorder such as anorexia
- Problems with the pituitary or thyroid glands, which make hormones that help children grow and develop
- Problems with the ovaries or testicles, which make sex hormones
- Genetic problems such as Turner syndrome in girls or Klinefelter syndrome in boys
- Some cancer treatments that affect sex hormone production
- Medicines that decrease appetite such as stimulants for attention deficit hyperactivity disorder (ADHD)

Sometimes, girls don't start having periods because their uterus and vagina don't develop properly. Or they may have too much of a hormone called prolactin, or a condition called polycystic ovary syndrome (PCOS).

DOES MY CHILD NEED TO SEE A DOCTOR IF HE/SHE HAS DELAYED PUBERTY?

Most likely, your child's delayed puberty won't need treatment. But if you or your teen are concerned about it, it's wise to see a doctor, especially if your child started to develop but then suddenly stopped. Your family doctor or pediatrician can tell you if your child should be checked for medical problems. Often, the only thing teens need is reassurance that they'll catch up to their peers.

HOW DOES A DOCTOR CHECK FOR DELAYED PUBERTY?

Your doctor will ask about your teen's health and medicines. The doctor will also want to know whether your child has noticed any signs of puberty or if there's a family history of delayed puberty. Your child will have a physical exam and also might have blood tests to check hormone levels. The doctor will check your child's growth by measuring height and weight, and doing an X-ray of the hand to see if his or her bones are developing more slowly than usual. Sometimes, a doctor can see signs of puberty that you or your teen might not have noticed. Some teens need a brain scan (such as an MRI) to check for problems with the pituitary gland. Girls might need a sonogram to see if their uterus and ovaries are developing as they should.

WHAT'S THE TREATMENT FOR DELAYED PUBERTY?

If your doctor doesn't find a medical problem, your teen probably doesn't need any treatment and will eventually start developing on his or her own. Your doctor may want to keep track of your child's progress toward puberty.

If your teen does have a medical problem, your doctor might refer you to a pediatric endocrinologist, an expert in growth and puberty.

Sometimes, doctors will prescribe short-term hormone therapy to help teens start developing. Girls take estrogen pills or use skin patches; boys get testosterone injections. Some teens need long-term hormone therapy if they are not able to make normal amounts of estrogen or testosterone.

WHAT CAN I DO TO HELP MY CHILD COPE WITH DELAYED PUBERTY?

Seeing your child's pediatrician or family doctor to make sure nothing is wrong is the first step. If your child feels worried or depressed, consider counseling for him or her. Some teens need extra help to sort out their feelings.

Questions to ask your doctor

- **Does my child have delayed puberty?**
- **What's causing my child's delayed puberty?**
- **Does my child need treatment for delayed puberty?**
- **What are the options for treatment?**
- **What are the risks and benefits of each treatment option?**
- **How long will my child need treatment?**

RESOURCES

- Find-an-Endocrinologist: *www.hormone.org* or call *1-800-HORMONE (1-800-467-6663)*
- Hormone Health Network information:
  - PCOS: *www.hormone.org/Menopause/upload/polycystic-ovary-syndrome-bilingual-071509.pdf*
  - Klinefelter Syndrome: *www.hormone.org/Resources/upload/FS_MH_Klinefelter_Syndrome_EN-6-12.pdf*
  - Turner Syndrome: *www.hormone.org/Resources/upload/FS_GD_Turner_Syndrome_EN-6-12.pdf*
- MedlinePlus (National Institutes of Health) information about puberty: *www.nlm.nih.gov/medlineplus/puberty.html*
- TeensHealth (Nemours Foundation) information:
  - "Delayed Puberty": *kidshealth.org/teen/sexual_health/changing_body/delayed_puberty.html*
  - "Everything You Wanted to Know About Puberty": *kidshealth.org/teen/sexual_health/changing_body/puberty.html?tracking=T_RelatedArticle*

EDITORS

Luiz Claudio Castro, MD
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February 2013

The Hormone Health Network offers free, online resources based on the most advanced clinical and scientific knowledge from The Endocrine Society (*www.endo-society.org*). The Network's goal is to move patients from educated to engaged, from informed to active partners in their health care. This fact sheet is also available in Spanish at *www.hormone.org/Spanish*.

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- **World of ENDO Map,** Near the Welcome Center
- **Spin to Win! Prize Wheels,** Booths 622 and 2023
- **Scan to Win! ENDOExpo Play,** new twist to exhibitor passport program

Learn more at *www.endo-society.org/endo2013.*

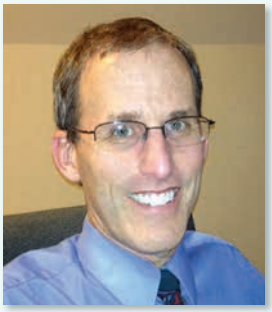
Event CALENDAR

JUNE 15–18: SAN FRANCISCO, CA
ENDO 2013:
The 95th Annual Meeting & Expo
www.endo-society.org/endo2013

JUNE 21–25: CHICAGO, IL
American Diabetes Association (ADA)
www.diabetes.org/

AUGUST 7–10: PHILADELPHIA, PA
American Association of Diabetes Educators (AADE)
www.diabeteseducator.org/

HAMMES NAMED EDITOR IN CHIEF OF *MOLECULAR ENDOCRINOLOGY*



Steven R. Hammes, MD, PhD, has been recently named as the new editor in chief of *Molecular Endocrinology,* published by The Endocrine Society. Hammes is the Louis S. Wolk Distinguished Professor of Medicine and chief of the division of endocrinology and metabolism, department of medicine, at the University of Rochester School of Medicine and Dentistry in Rochester, N.Y.

Molecular Endocrinology publishes research devoted to describing molecular mechanisms by which hormones and related compounds regulate function. It has a reputation as a high-visibility journal with very rapid communication of cutting-edge science in the signaling, metabolism, neuroscience, and tumor biology fields.

"I am thrilled that I was chosen to be the next editor in chief of *Molecular Endocrinology,*" Hammes says. "Not only have I served on the editorial board for many years, but I also publish regularly in *Molecular Endocrinology* and consider it one of the premier journals for basic endocrinologic research. To have the opportunity to give back to the journal and the Society that has done so much for me and my career is truly an honor."

Hammes feels that *Molecular Endocrinology* is a high-impact journal where basic researchers interested in mechanisms of endocrine function and disease can both publish their own work and read about exciting advances from other laboratories. "What separates *Molecular Endocrinology* from some other journals is the rapid and thorough reviews from a very responsive group of editors, meaning that submitted manuscripts are reviewed and published quickly and fairly," he explains. "Also, unlike other journals that focus on basic physiology, *Molecular Endocrinology* is published and supported by The Endocrine Society, meaning that the journal has more of a clinical endocrine focus – something both endocrine researchers and clinicians can appreciate."

Living up to the high standards set by previous editors in chief is one of Hammes' main goals, as he credits his predecessors with doing a tremendous job in making *Molecular Endocrinology* a premier journal. "As we move forward, I am fortunate in that I have eight new associate editors who are a truly remarkable and diverse bunch," he says, adding that they have both basic research expertise as well as clinical acumen. "I hope that, with their help, we can continue to publish manuscripts that demonstrate how basic science can be used to explain both normal human physiology as well as human disease."

Although Hammes has no specific plans to make any immediate changes at this point, he is looking toward the future and that future will include providing content in a manner that takes full advantage of emerging technologies. "As we start our term, the associate editors and I will work closely with The Endocrine Society to see how we can best serve its membership and how we can position *Molecular Endocrinology* to reflect their needs into the next decade."

Hammes' term as editor in chief of *Molecular Endocrinology* will begin on January, 1, 2014. He previously served on the journal's editorial board from 2006 to 2011.

Molecular Endocrinology can be accessed online at: *http://mend.endojournals.org/.*

Hormone Health NETWORK
www.hormone.org

SPECIAL SYMPOSIUM
FOR PATIENTS DEBUTS AT ENDO 2013

The Hormone Health Network and Taking Control of Your Diabetes (TCOYD) are teaming up at **ENDO 2013** to provide a unique, half-day learning experience for Bay-area patients with type 2 diabetes. Entitled "Living Your Best Life with Diabetes," this motivational health education event will provide patients with the latest approaches to managing the day-to-day challenges of and living your best life with diabetes.

VIEW THE ONLINE PROGRAM: *www.hormone.org*

CHECK OUT THE NEW *HORMONE.ORG*

Patients asked. We listened. The Hormone Health Network's new website now offers improved key features that patients and providers want—clear, easy navigation of our more than 100 patient education resources; better organized, visually engaging content; an enhanced experience for Spanish-speaking audiences; and much more. With new expert-reviewed patient education information published each month and over 2 million visitors per year, the Network is your trusted source for endocrine patient education.

Visit *www.hormone.org* to and sign up for Hormone Hotline, our monthly e-update, for the latest news on Hormone Health Network publications and events.

SOFIA VERGARA HELPS RAISE HYPOTHYROID AWARENESS

In order to help hypothyroid patients take control of their disease and to raise awareness about the condition, Abbott Laboratories spinoff, AbbVie, has enlisted the help of actress Sofia Vergara for its "Follow the Script" campaign.

The campaign aims to educate those suffering from hypothyroidism about the importance of being consistent with the treatments their doctor prescribes, thus providing a "script" to ensure they consistently receive their needed medications. AbbVie is the manufacturer of Synthroid, a prescription synthetic thyroid hormone that is used to treat hypothyroidism. "AbbVie is proud to work with Sofia Vergara and support this education campaign," said Maria Rivas, MD, vice president of global medical affairs at AbbVie in a statement. "The hope and aim of this campaign is to increase awareness about hypothyroidism and empower patients to engage in dialogue and work with their healthcare providers throughout their treatment."

Vergara, Emmy-nominated for her role as Gloria on the hit ABC sitcom *Modern Family,* is the ideal advocate for such a campaign. The actress, 40, had thyroid cancer at age 28, which resulted in her thyroid being surgically removed. She has been hypothyroid ever since and dependent upon thyroid medication.

In a statement, Vergara said that she is known in her career to ad-lib or go "off script," but not when it comes to her health, adding that she makes sure to "Follow the Script" to get what her doctor prescribed. The campaign is accompanied by a website—*www.followthescriptcampaign.com*—where Vergara and others share their stories about coping with hypothyroidism. Also on the website are interactive polls, symptom and treatment information, and tips for patients on dealing with their doctors and pharmacists.

REMEMBERING Boris Catz: 1923-2013

The Endocrine Society and its members are remembering the life of Boris Catz, an endocrinologist and thyroid specialist who was a clinical professor emeritus at the University of Southern California School of Medicine.

A pioneer in the field of clinical endocrinology for more than 60 years, Catz was renowned for his innovative treatments of myxedema coma and exophthalmos. He received much acclaim for his pioneering work with Samuel Perzik in developing the total thyroidectomy to treat hyperthyroidism, cancer, multinodular goiter, and chronic thyroiditis not responsive to medical management. In his work with Franz Bauer, Catz first recommended total thyroidectomy and radioactive iodine treatment for exophthalmos and Graves' disease. In addition, he authored two editions of the book *Thyroid Case Studies* and contributed numerous articles on thyroidology to a litany of medical journals.

Former Society President Leonard Wartofsky, MD, MACP, chairman, department of medicine at Washington Hospital Center in Washington, D.C., had the distinct honor of serving as the Boris Catz Lecturer at Cedars Sinai Hospital in Los Angeles. "Boris was an early pioneer in clinical thyroid disease, having trained with Dr. Paul Starr," he says. "He established and supported the Paul Starr Award and Lectureship of the ATA for many decades and was a strong supporter of The Endocrine Society as well, most recently of the Sawin Memorial Library," where he supplied an in-depth oral history in 2010.

According to Wartofsky, Catz and his surgical colleague, Samuel Perzik, postulated that Graves' ophthalmopathy would not remit until all thyroid tissue -- as an antigenic source -- was destroyed. "To this end, he advocated total thyroidectomy followed by radioiodine," he says. "Subsequent studies lent some credence to this theory."

> "He was irascible, bigger than life, and often painfully frank in his wit and criticism. **He will be warmly remembered by all who knew him."**

From Russia to Mexico

Catz's path to an acclaimed career as a thyroid pioneer was, in a word, byzantine. He was born in the Ukraine in 1923 in a little village that no longer exists, called Troyanov, which he once described as coming directly out of *Fiddler on the Roof.* In 1928 his family immigrated to Mexico, where he considered himself lucky to have been since the Great Depression quickly overtook the U.S. shortly thereafter.

After attending Jewish schools in Mexico, Catz enrolled at the National University of Mexico, then the National University of Mexico Medical School because, as he said in a 2010 oral history for the Society, "that was the only university that would take me." After graduation in 1947, he ended up working in a Mexican village near a cigar factory where his patients paid him in cigars...a habit he held onto for the rest of his life.

After being told to leave town or risk getting murdered – he published information in a required report about the town's lackluster living conditions that angered the locals – he continued his studies at the University of Southern California (USC). That same year, 1948, he married his wife Rebecca Schecter, an American involved in the foot and mouth disease campaign who was sent to Mexico. While at USC he was mentored by Starr and Donald Petit and; as a fellow in thyroid he did clinical research with Austrian physician Ernest Geiger.

Pioneering Research

The following years were consumed with research on how best to treat thyroid disorders. Catz and Bauer were, Catz has stated, the first to recommend Iodine-131 treatments for thyroid cancer post-thyroidectomy. He participated on further treatment research such as Itrumil – a seemingly counter-intuitive mixture of iodine and thiouracil. "Who uses iodine and antithyroid drug at the same time?" Catz pondered in his oral history. "It will wash out. But the patients responded."

Catz added that a very important discovery was

made by his team at the time: When some antithyroid drugs were given with barbiturates, the result was often anemia or even death. He said that barbiturates were given in the time before Valium in order to calm patients down but that in some cases patients developed aplastic anemia and died. Catz and his team had their findings on this topic published in the *Journal of Endocrinology.*

Catz's research continued unabated until 1955 when he became an American citizen…and then Uncle Sam called. Newly commissioned Capt. Catz reported for duty in San Juan, Puerto Rico, where he was treating career soldiers as they were heading into civilian life. That tour of duty only lasted until 1957 when he returned to USC as a clinical professor, continuing his research and treating patients as the chief of the Thyroid Clinic at the Los Angeles County Hospital, all the while blazing a trail using experimental thyroid treatments that are still in use today.

Cedars-Sinai Medical Center in Los Angeles honored Catz in 1985 when it established the Boris Catz Thyroid Lectureship, which recognized his devotion to patient care, his role as an educator, and his trailblazing career in pioneering novel treatments for diseases of the thyroid. He was further recognized in 2002 by the American Thyroid Association with the Certificate of Distinguished Service.

Wartofsky fondly remembers his time as the Boris Catz Lecturer. He recalls making rounds with Catz, his trademark unlit Cuban cigar in his mouth, visiting his patients who obviously adored him. "He was irascible, bigger than life, and often painfully frank in his wit and criticism," Wartofsky says, adding that much of his fire dissipated after the death of his wife, whom he adored. "He will be warmly remembered by all who knew him."

Aside from his emeritus status at Cedars-Sinai and USC, Catz continued his part-time private practice until just two weeks prior to his passing at age 90. EN

Much of the information in this article came from an oral history Catz gave for The Endocrine Society's archives in 2010. The complete interview can be found at www.endo-society.org/about/sawin/boris-catz-video.cfm.

Donations in his memory can be sent to the
**Boris Catz Thyroid Leadership Fund,
Cedars-Sinai Medical Center,
8700 Beverly Blvd., #2416,
West Hollywood, CA 90048.**

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

CALL FOR NOMINATIONS AND APPLICATIONS FOR EDITOR-IN-CHIEF OF JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM

The Endocrine Society is seeking candidates for the position of Editor-in-Chief of *Journal of Endocrinology and Metabolism* for a five-year term beginning January 1, 2015. This position requires a dynamic, nationally recognized clinician who has a broad background in the field and is committed to maintaining the journal's reputation for publishing cutting-edge science. *Journal of Clinical Endocrinology and Metabolism* provides an international forum for papers enhancing the understanding, diagnosis, and treatment of endocrine and metabolic disorders. It is the world's leading peer-reviewed journal for endocrine clinical research and cutting edge clinical practice reviews.

RESPONSIBILITIES

The Editor-in-Chief of *Journal of Clinical Endocrinology and Metabolism* receives editorial and administrative support from The Endocrine Society's Managing Editor and editorial office staff in Chevy Chase, MD, as well as an honorarium. The Editor-in-Chief oversees the peer review process and content development:

- Selecting his or her Deputy Editors, Associate Editors (6) and Editorial Board (47)
- Providing direction for the journal and its content features and identifying emerging "hot" areas of importance and soliciting papers for submission
- Participating in meetings of the Publications Core Committee
- Participating in meetings with the editors-in-chief of the Society's other journals

NOMINATIONS

All members of The Endocrine Society are encouraged to suggest the names of potential candidates by contacting Scott Herman, Group Managing Editor – Associate Director, Publications for The Endocrine Society, at sherman@endo-society.org. Please submit your suggestions by **August 30, 2013.**

APPLICATIONS

Applicants for the position of Editor-in-Chief of Journal of Clinical Endocrinology and Metabolism should submit the following materials:

- Description of qualifications
- Statement outlining how the candidate plans to oversee the journal, including goals for content, target readership, acceptance criteria, and editorial policy
- Proposed Associate Editors, areas of expertise, and process for editorial decision-making
- Discussion of the present status of the journal, opportunities for growth and enhancement, and plans to achieve goals
- *Curriculum vitae*

Applications are due by **September 30, 2013,** and should be e-mailed as PDF attachments to Scott Herman (sherman@endo-society.org). Please call 301.951.2615 to ensure that your submission has been received. Selected candidates will be contacted by the search committee chair and asked to provide more details. The Publications Core Committee will interview finalists in person at its March 2014 meeting and choose a candidate to recommend to The Endocrine Society Council.

PUBLICATIONS CORE COMMITTEE

The search process is being undertaken by the Publications Core Committee, and the chair of the search committee is Janet Schlechte, MD. The other members of the committee are: Margaret Shupnik, PhD, Chair; Dennis Baskin, PhD; Joanna Burdette, PhD; Kerri Burnstein, MD; Martin Fassnacht, MD; Sandra Licht, MD; Jeffrey A. Sandler, MD; and Daniel Spratt, MD.

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.endo-society.org.***

Pathogenesis of Prediabetes: Role of the Liver in Isolated Fasting Hyperglycemia and Combined Fasting and Postprandial Hyperglycemia Rita Basu, Cristina Barosa, John Jones, Simmi Dube, Rickey Carter, Ananda Basu, and Robert A. Rizza *Elevated gluconeogenesis in the fasting state in IFG/NGT and impaired insulin-induced suppression of both gluconeogenesis and glycogenolysis in IFG/IGT suggest that alteration in the regulation of these pathways occurs early in the evolution of type 2 diabetes.*

Approach to the Cushing's Disease Patient With Persistent/Recurrent Hypercortisolism After Pituitary Surgery Xavier Bertagna and Laurence Guignat *Although it is the ideal treatment, pituitary surgery is not always successful, and success is not always lasting*

Kinase Inhibitors: Adverse Effects Related to the Endocrine System Maya B. Lodish *The use of kinase inhibitors (KIs) in the treatment of cancer has become increasingly common, and practitioners must be familiar with endocrine-related side effects associated with these agents.*

Low- or High-Dose Radioiodine Remnant Ablation for Differentiated Thyroid Carcinoma: A Meta-Analysis Weiwei Cheng, Chao Ma, Hongliang Fu, Jianing Li, Suyun Chen, Shuqi Wu, and Hui Wang *The low dose of 1100 MBq radioiodine activity is sufficient for thyroid remnant ablation as compared to 3700 MBq radioiodine activity with similar quality of life, less common adverse effects, and a shorter hospital stay.*

Ghrelin Restoration of Function In Vitro in Somatotropes from Male Mice Lacking the Janus Kinase (JAK)-Binding Site of the Leptin Receptor Mohsin Syed, Michael Cozart, Anessa C. Haney, Noor Akhter, Angela K. Odle, Melody Allensworth-James, Christopher Crane, Farhan M. Syed, and Gwen V. Childs *Leptin may optimize somatotrope function by facilitating expression of membrane GHRH receptors and the production or maintenance of GH stores.*

Excess Androgen During Puberty Disrupts Circadian Organization in Female Rats Michael T. Sellix, Zachary C. Murphy, and Michael Menaker *Excess androgen during puberty, a common feature of PCOS, negatively affects internal circadian organization in both the reproductive and metabolic axes.*

The Androgen Metabolite, 5β-Androstane-3β,17β-Diol (3β-Diol), Activates the Oxytocin Promoter Through an Estrogen Receptor-β Pathway Ryoko Hiroi, Anthony F. Lacagnina, Laura R. Hinds, David G. Carbone, Rosalie M. Uht, and Robert J. Handa *3β-diol induces oxytocin promoter activity via ER-β–cHRE interactions.*

Conditional Mutagenesis of Gata6 in SF1-Positive Cells Causes Gonadal-Like Differentiation in the Adrenal Cortex of Mice Marjut Pihlajoki, Elisabeth Gretzinger, Rebecca Cochran, Antti Kyrönlahti, Anja Schrade, Theresa Hiller, Laura Sullivan, Michael Shoykhet, Erica L. Schoeller, Michael D. Brooks, Markku Heikinheimo, and David B. Wilson *GATA6 regulates the differentiation of steroidogenic progenitors into adrenocortical cells.*

Investigating New Therapeutic Strategies Targeting Hyperinsulinemia's Mitogenic Effects in a Female Mouse Breast Cancer Model Ran Rostoker, Keren Bitton-Worms, Avishay Caspi, Zila Shen-Orr, and Derek LeRoith *Targeting (even partially) both IR and IGF-IRs impairs hyperinsulinemia's effects in breast tumor development while simultaneously sparing the metabolic abnormalities observed when targeting IR alone with virtual complete inhibition.*

Androgens Promote Prostate Cancer Cell Growth Through Induction of Autophagy Yan Shi, Jenny J. Han, Jayantha B. Tennakoon, Fabiola F. Mehta, Fatima A. Merchant, Alan R. Burns, Matthew K. Howe, Donald P. McDonnell, and Daniel E. Frigo *Androgens regulate overall cell metabolism and cell growth, in part, by increasing autophagy in prostate cancer cells.*

Mutations in MCT8 in Patients with Allan-Herndon-Dudley-Syndrome Affecting Its Cellular Distribution Simone Kersseboom, Gert-Jan Kremers, Edith C. H. Friesema, W. Edward Visser, Wim Klootwijk, Robin P. Peeters, and Theo J. Visser *MCT8 mutations in AHDS patients may have tissue-specific effects on TH transport probably caused by tissue-specific expression of yet unknown MCT8-interacting proteins.*

Hanne B. Moeller, Søren Rittig, and Robert A. Fenton *Nephrogenic Diabetes Insipidus: Essential Insights into the Molecular Background and Potential Therapies for Treatment*

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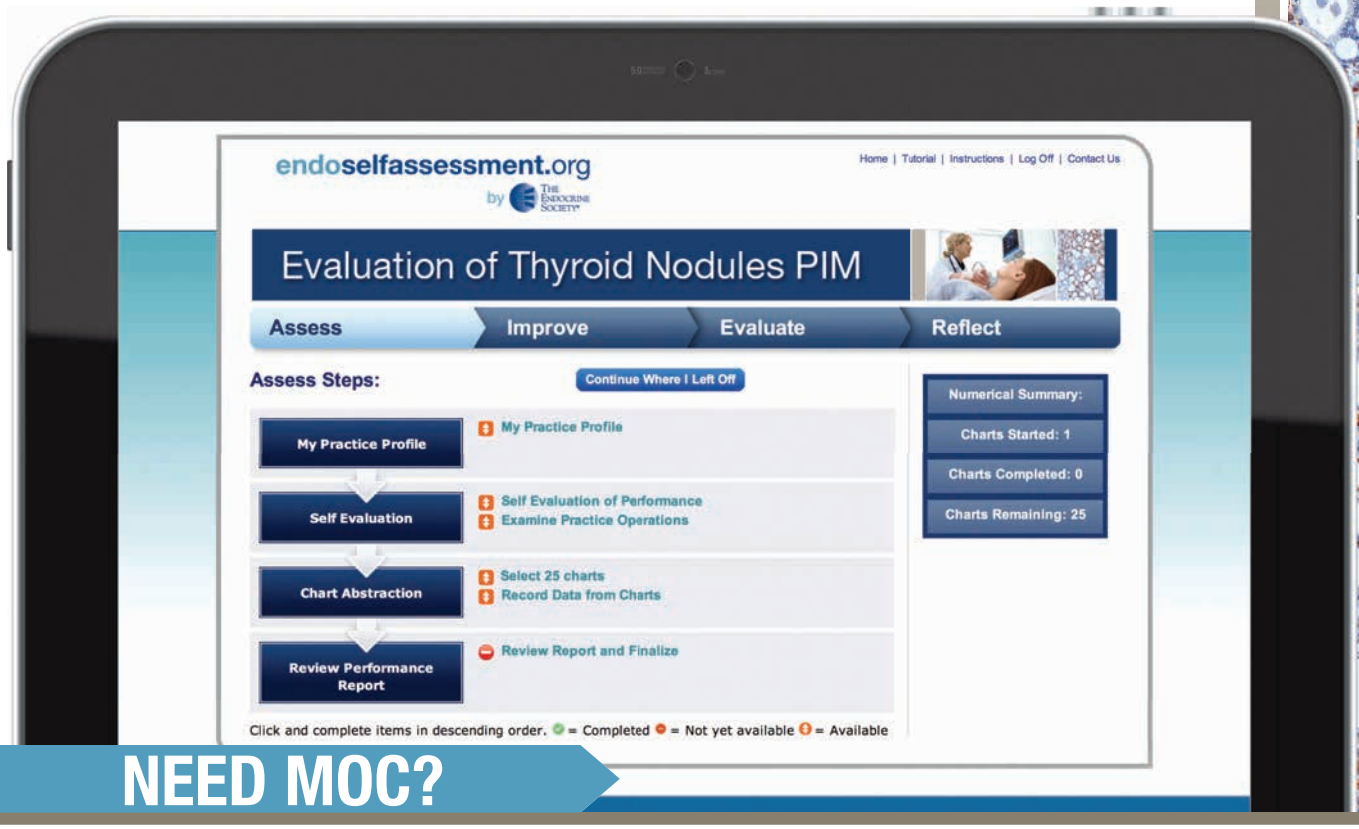

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Evaluation of Thyroid Nodules PIM Task Force
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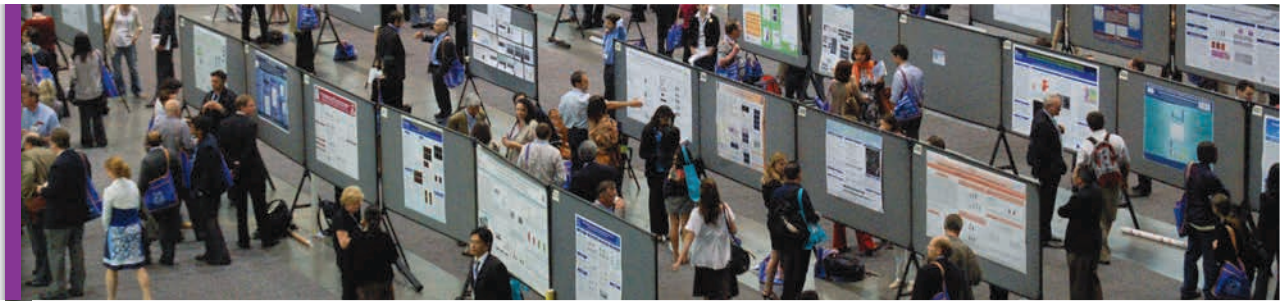

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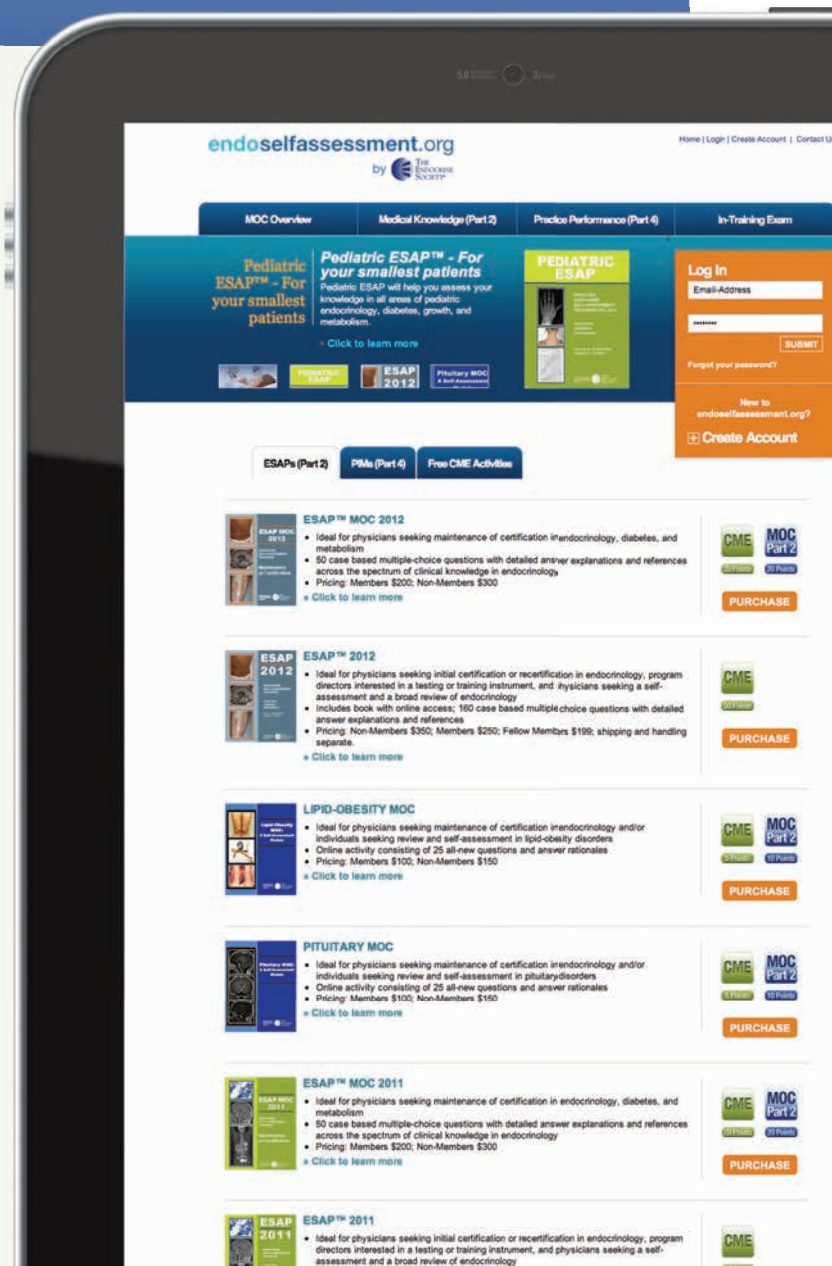

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Vermont:
The Division of Endocrinology, Diabetes and Metabolism at the University of Vermont/Fletcher Allen Health Care invites applications for a board-eligible or board-certified clinician educator endocrinologist at the Assistant/Associate Professor level on the Clinical Scholar Pathway. The selected candidate will be an MD or MD plus PhD with specialty training in diabetes metabolism. Priority will be given to persons who have experience with providing endocrine clinical services in a university setting. The selected candidate will be expert in all aspects of clinical care for diabetes mellitus and endocrine diseases. The selected candidate will join a busy and collegial program that is sole provider of endocrinology and specialty diabetes services to a large geographical area. Opportunities exist to interact with research programs focused on the pathogenesis and therapy of diabetes, obesity, and their complications along with diabetes health care delivery, and osteoporosis and metabolic bone disease. Burlington offers beautiful surroundings and excellent family atmosphere. UVM is an Affirmative Action/Equal Opportunity Employer. Applications from women and people from diverse racial, ethnic and cultural backgrounds are encouraged. The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal. Applicants should send letter, CV and name and address of three references to: Joel J. Schnure, MD, Chairman, Search Committee, Division of Endocrinology, University of Vermont, Colchester Research Facility, Room 110, 208 South Park Drive, ATTN: Linda Del Hagen, Colchester, VT 05446; fax: (802) 656-8031; email: *Joel.schnure@vtmednet.org* or at *http://uvmjobs.com.* Applications will be accepted until the position is filled.

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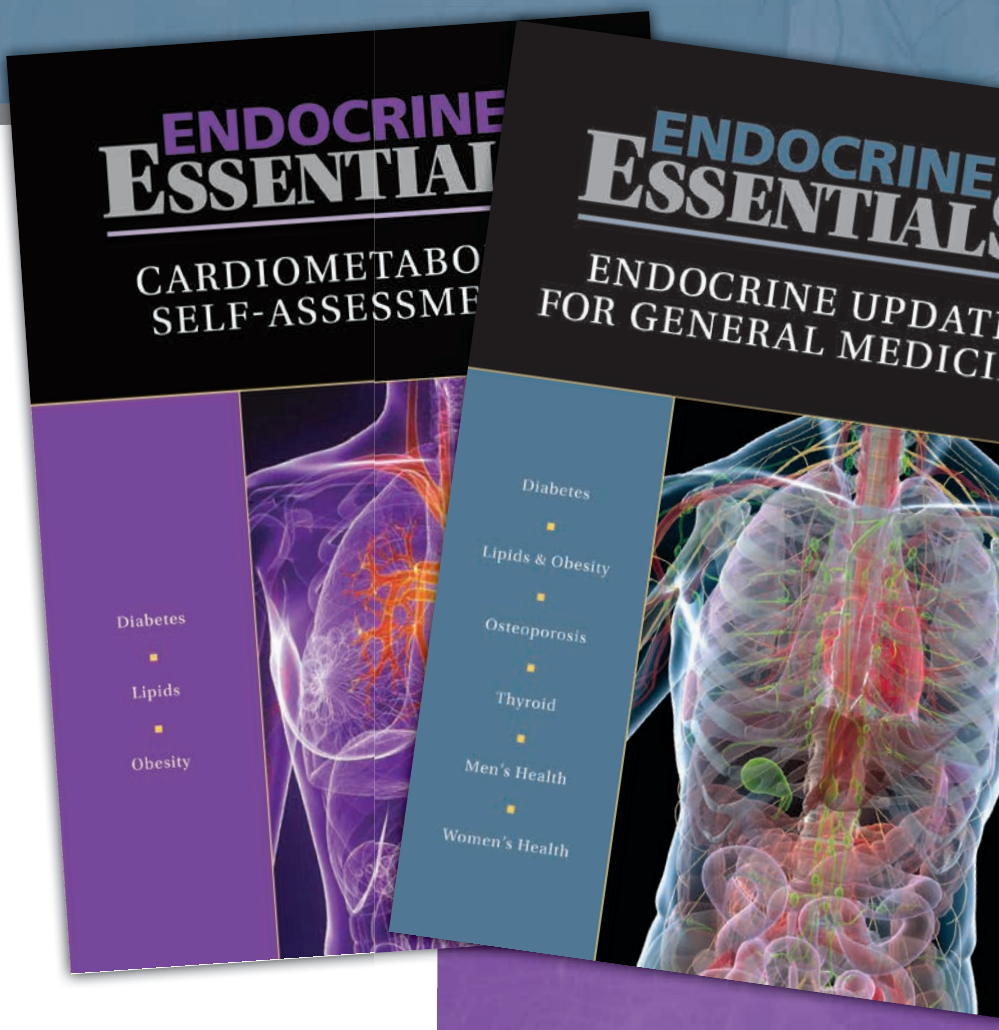

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Tresiba® 100 units/mL - 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device or one cartridge contains 300 units of insulin degludec in 3mL solution. Tresiba® 200 units/mL - 1 mL of solution contains 200 units insulin degludec (equivalent to 7.32 mg). One pre-filled device contains 600 units of insulin degludec in 3mL solution. **Indication:** Treatment of diabetes mellitus in adults. **Posology and administration:** Tresiba® is a basal insulin for once-daily subcutaneous administration, any time of day preferably at the same time of day. On occasions when not administered at the same time of day, a minimum of 8 hours between injections should be ensured. One unit (U) of insulin degludec corresponds to 1 international unit (IU) of human insulin, 1 unit of insulin glargine/insulin detemir. If a dose is forgotten, the dose should be taken on discovery and usual once daily dosing should then be resumed. In patients with type 2 diabetes mellitus Tresiba® can be used alone, in combination with oral antidiabetic medicinal products or with a bolus insulin; the recommended starting dose is 10 units. In type 1 diabetes mellitus, Tresiba® is to be used once-daily and must be combined with short/rapid-acting insulin. Tresiba® is available in 100 units/mL and 200 units/mL. For the 100 units/mL a dose of 1-80 units per injection, in steps of 1 unit can be administered; for the 200 units/mL a dose of 2-160 units per injection, in steps of 2 units can be administered. The dose counter shows the number of units regardless of strength. No dose conversion should be done when transferring to a new strength. During transfer from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component; in type 1 diabetes the same applies as for type 2 diabetes apart from where transferring from twice-daily basal insulin or patients with an HbA1c < 8.0%, the Tresiba® dose needs to be determined on an individual basis with a dose reduction considered. Doses /times of concomitant treatment may require adjustment. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising glycaemic control. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. The safety/efficacy of Tresiba® has not been established in adolescents/children below 18 yrs. of age. Tresiba® must not be administered intravenously, intramuscularly or in insulin infusion pumps. It should be administered subcutaneously in the thigh, upper arm or abdominal wall; injection sites should be rotated. Adjustment of dose may be necessary if patients undertake increased physical activity, change their diet or during concomitant illness. Tresiba® comes in a pre-filled pen, FlexTouch® (2 concentrations) or cartridge, Penfill® designed to be used with NovoFine®/NovoTwist® needles and for Penfill® Novo Nordisk insulin delivery systems. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Too much insulin, omission of a meal or unplanned strenuous exercise may lead to hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. As with any basal insulin, the prolonged effect of Tresiba® may delay recovery from hypoglycaemia. Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Use of inadequate doses or discontinuation of treatment may lead to hyperglycaemia and ketoacidosis which are potentially lethal. Transferring to a new type, brand or manufacturer of insulin should be done under strict medical supervision. Cases of cardiac failure reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure; if the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Intensification of insulin therapy with sudden improvement in glycaemic control may be associated with a temporary worsening of diabetic retinopathy. Patients must be instructed to check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins. Patients who are blind/have poor vision must get assistance from another person with good vision who is trained in using the insulin device. Insulin administration may cause antibodies to form; due to the presence of antibodies in rare cases adjustment of dose may be necessary. Hypoglycaemia may constitute a risk when driving or operating machinery. Patients must be advised to take precautions to avoid hypoglycaemia while driving. Tresiba® must not be mixed with other medicinal products. **Fertility, pregnancy and lactation:** There is no clinical experience with use of Tresiba® in pregnant women and during breast feeding. Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility. **Undesirable effects:** Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reactions may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers:** Tresiba® Penfill® 100U EU/1/12/807/007 Tresiba® FlexTouch® 100U EU/1/12/807/004 Tresiba® FlexTouch® 200U EU/1/12/807/013 **Legal category:** POM. **Basic NHS price:** 5 x 3 ml 100 U/mL Penfill® £72.00 5 x 3 ml 100 U/mL FlexTouch® £72.00 3 x 3 ml 200 U/mL FlexTouch® £86.40 **Full prescribing information can be obtained from:** Novo Nordisk Limited, Broadfield Park, Brighton Road, Crawley, West Sussex, RH11 9RT. **Date created:** January 2013

REFERENCES: 1. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN™ Once Long). *Diabetes Care*. 2012;35(12):2464-2471. **2.** Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Ocampo Francisco AM, Pei H, Bode B. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes. (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1489-1497. **3.** Tresiba® [summary of product characteristics]. Bagsværd, Denmark: Novo Nordisk A/S; 2013.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.

Stated price is specific to the UK. Prices may vary from country to country.

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At Novo Nordisk, we are changing diabetes. In our approach to developing treatments, in our commitment to operate profitably and ethically and in our search for a cure.

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