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## SUPER -SIZED Youth



As childhood obesity reaches epidemic proportions, ailments once confined to adults are being diagnosed in younger patients. New studies show that childhood adversities and PFC exposure are contributing factors to this growing scourge.

**Double Dosing:**  
TREATING CANCER  
& DIABETES

**Stay or Go?**  
THE INS & OUTS OF  
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# CLINICAL ENDOCRINOLOGY UPDATE



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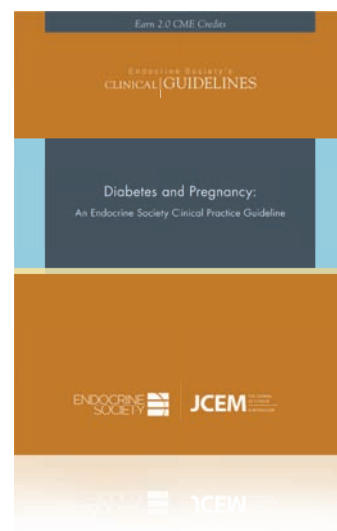
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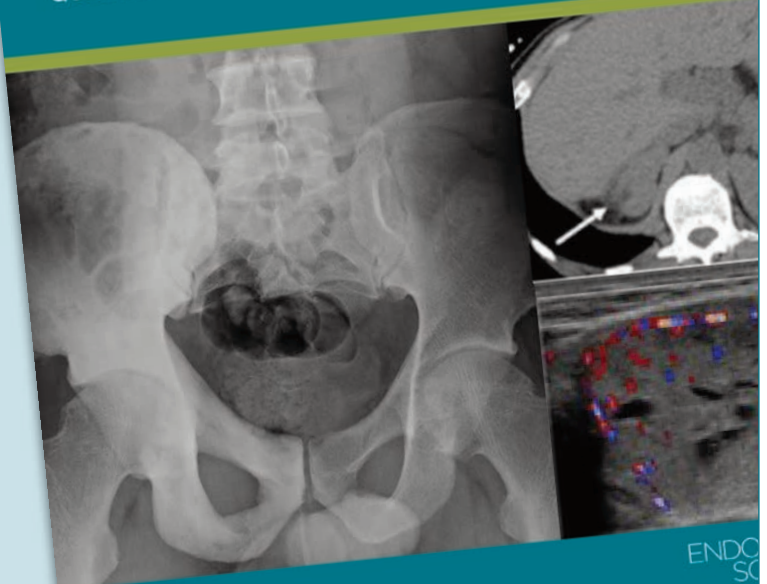
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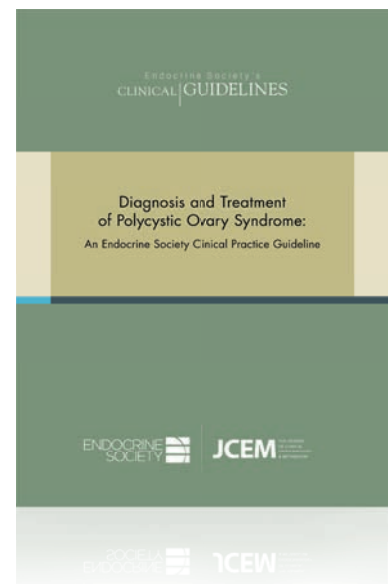
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# GAIN NEW INSIGHT INTO TREATING COMPLEX ENDOCRINE EMERGENCIES

Editor, Glenn Matfin, MSc (Oxon)

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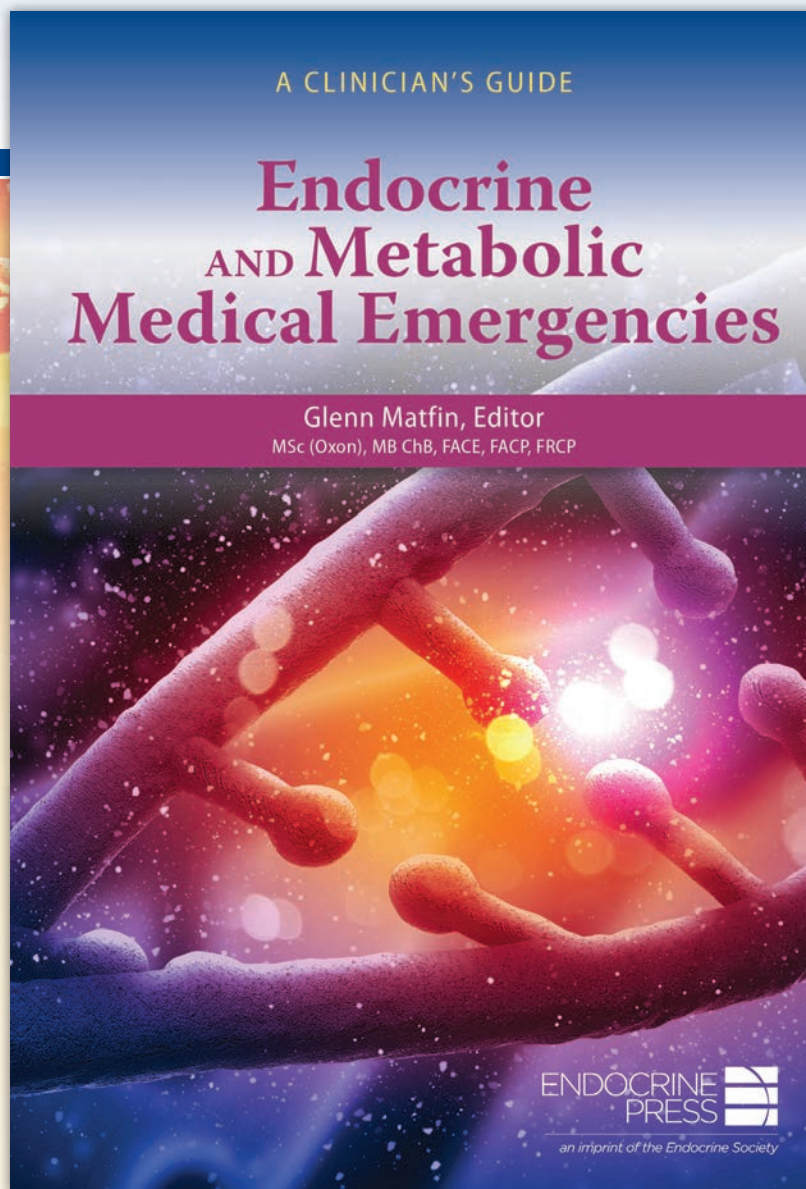
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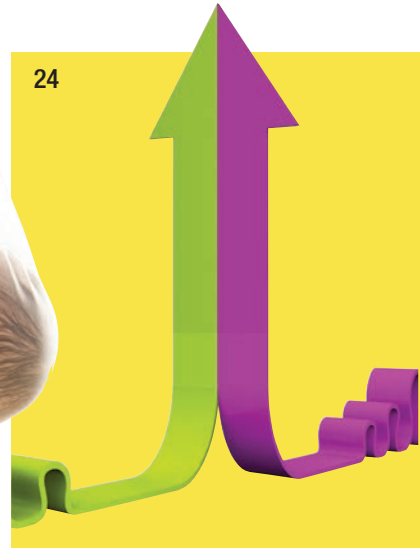
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**14 COVER STORY**  
**Super-Sized Youth**  
*By Kelly Horvath*

As childhood obesity reaches epidemic proportions, ailments once confined to adults are being diagnosed in younger patients. New studies show that childhood adversities and perfluorinated compounds exposure are contributing factors to this growing scourge.

**18 Tri-Point Series:**  
**The First 1,000 Days:**  
**Early Life Determinants of Chronic Disease**

*By Cyrus Cooper, FMedSci, Elizabeth Cottrell, PhD, Elsie M. Taveras, MD, MPH, and Maynika V. Rastogi, MBBS*  
An epidemiologist, a basic researcher, a clinical researcher, and a clinician in practice weigh in on the complex relationship between genetics and environmental factors from conception through a child's second birthday.

**24 Double Jeopardy**  
*By Terri D'Arrigo*

Diabetes is already a complex chronic disease that requires a diligent treatment regimen. When cancer is added, diabetes management may require a Herculean effort both for the patient and the endocrinologists who treat them.

**26 Stuck in the Middle: Non-Compete Agreements**  
*By Kurt Ullman*

Non-compete agreements are a routine way of life for many practitioners. Knowing the ins and outs of these documents can be helpful if your practice situation changes.

**DEPARTMENTS**

**8 President's Viewpoint**  
Introducing Richard J. Santen

**9 Editor's Page**  
July issue highlights

**10 Trends & Insights**  
A look at the latest research

**32 Advocacy**  
Clinician Hill Day

**35 Hormone Health Network**  
Fact Sheet:  
The High Costs of Junk Food

**37 InTouch**  
Saying goodbye to Scott Herman

**40 Classifieds**  
Career opportunities

**43 Research Roundup**  
Society journal studies



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*Hormone Science to Health*

## Introducing the New President: **Richard J. Santen**



Richard J. Santen, MD

The Endocrine Society is pleased to welcome its president for 2014 – 2015, Richard J. Santen, MD, who took office June 25. A professor of internal medicine at the University of Virginia Health Sciences Center, Santen is a renowned expert on aromatase inhibitor development for the treatment of breast cancer, mechanisms whereby estrogens induce breast cancer and estrogen metabolomics as a means to

predict who will develop breast cancer, the effects of menopausal therapy on breast cancer, and menopause management.

Santen succeeds Teresa K. Woodruff, PhD, as the Society continues its rotation of presidents who represent its core constituencies: basic researchers, clinical researchers, and clinical practitioners. Santen's career has spanned each of these areas, as he has spent his time as an endocrinologist both at the bench and by the bedside. Because of this varied experience, he considers the Endocrine Society to be his scientific home.

Santen first joined the Society more than 40 years ago, when he was a clinical fellow at the University of Washington in Seattle. Since joining the Society, he has been very active serving as a member, chair, or liaison to various committees, including Finance and Audit, Minority Affairs, and the Council. "A particular interest of mine was the establishment of the International Scholars Program, now in its 11th year," he says.

Santen has also been a member of several of the Endocrine Society's task forces, helping to write educational materials for the Hormone Health Network on issues related to menopause, as well as participating in writing groups for clinical practice guidelines. "The participation on these committees and task forces has allowed me to meet and work with stellar colleagues and to form warm relationships with many of them," he says. "In addition, I have worked closely with many of the staff of the Endocrine Society and found this to provide wonderful working relationships."

Santen envisions facilitating collaboration among the Endocrine Society's constituencies by exploring a unique type of educational program in conjunction with the Trainee and Career Development Core Committee. "This will provide a comprehensive review of existing information on a specific topic directed toward basic, translational, and clinical researchers, as well as clinicians in practice," he says.

In addition to his clinical and research specialties, Santen has a keen interest in mentoring the younger generation of endocrinologists, something he wants to expand upon as president of the Endocrine Society. "In

my opinion, Santen says, "the Endocrine Society needs to nurture and develop the future Society leaders so that it will remain a vibrant and creative society." To do that, we must recognize that the next generation of endocrinologists has some hurdles to clear along the way. For one, National Institutes of Health funding has been declining "in real dollars" over the past decade, and the more experienced investigators are outcompeting the younger researchers for the available funding dollars.

Another problem is that practicing clinicians will almost exclusively be found in the hospital setting within the next 10 years. "This will create pressures for efficiency and reduce the time available for scholarly activities," Santen says. "Unless we as a Society address these issues, the Society will not be able to retain its vibrant, scholarly character over the next decade."

Santen envisions an initiative to "provide major benefit to the Nex Gen members." This initiative will provide these Nex Gen members with the ability to obtain advice from world leaders. Nex Gen members will submit clinical cases and questions, and the Endocrine Society will forward these to two experts to give their opinion within a specified time frame and provide references in the literature to back up their opinions. "This will be particularly useful for our international members," Santen says. "The idea is to harness the intellectual power of our senior members to enhance the careers of young members."

Santen's next generation initiative emphasizes the need to create innovative programs that enhance the recruitment, retention, and empowerment of early career endocrinologists beyond their training completion. Santen has commissioned an intercommittee task force with two goals in mind: to examine in detail the issues affecting the next generation of endocrinologists and determine future directions for the Society in expanding opportunities for early career endocrinologists; and to develop a road map for enhancement of their career advancement and workforce development.

"If young endocrinologists cannot capture sufficient funding to carry out their innovative ideas, those ideas are lost," he continues. "Consider if James Watson had come up with the idea of the double helix of DNA today, he would not be taken seriously and he certainly could not have obtained funding to support his idea. We need to give considerable thought to the development of means to allow young investigators to pursue their ideas."

Santen's plans to focus on the career enhancement of endocrinologists during the first two decades after completion of their training reflects the Society's commitment to serving its members as described in the Society's strategic plan. **EN**



JULY 2014

# ENDOCRINE<sup>news</sup>

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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

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

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As the incidence of diabetes continues to grow, more endocrinologists will be faced with patients who are managing the disease alongside other ailments. Terri D'Arrigo discusses the challenges of treating diabetic patients who are undergoing cancer treatment in "Double Jeopardy," (p. 24). The article stresses the importance of working with the patient's oncologist to get a heads up on treatments, dosages, therapy changes, etc. "On a fundamental level, I think we need oncologists to give us a reasonable impression of what the goals of care are and the likelihood of success," says Robert Sargis, MD, PhD, assistant professor of medicine in endocrinology at the University of Chicago School of Medicine. "It can be very sad and hard, but it's helpful to us to target therapeutic interventions to the prognosis. If it's poor, I think we can feel more comfortable liberalizing goals and not burdening the patient with undue expectations."

In our effort to continually report on new findings as they relate to the burgeoning epidemic of obesity, Kelly Horvath has gone behind the data of some recent studies that affect the youngest among us ("Super-Sized Youth," p. 14). Diabetes, high blood pressure, and even depression are finding their way into the younger generations. Even more alarming is that one study even shows that these youths are seeing a shortened lifespan due to their weight. While it's easy to point to a lack of exercise and a diet rich in fat as causes for this trend — and those factors certainly play a role — new studies show that adversity early in life can also be a contributing factor.

Whether a physician is in private practice or working as a hospitalist, among the scores of paperwork he or she might have to contend with is a non-compete agreement. It is essentially the "ground rules" when you take a new job, basically controlling the "whens" and "wheres" if you leave. Kurt Ullman's "Stuck in the Middle" (p. 26) gives a basic overview of what to expect from these agreements, but, of course, consult a lawyer before signing on the dotted line.

Also in this issue we introduce you to the Endocrine Society's new president, Richard Santen, MD, (President's Viewpoint, p. 8), who visited the Society staff in May at our Washington, D.C., headquarters and filled us in on what his goals are for the next nine months. We also have the sad task of saying goodbye to Scott Herman, longtime group managing editor of *Endocrinology* and the *Journal of Endocrinology & Metabolism*, who lost his battle with cancer in May (p. 37). He will truly be missed. **EN**

*Mark A. Newman*  
Managing Editor, *Endocrine News*



Mark A. Newman



By Derek Bagley

## MOLECULE IDENTIFIED FOR BLOCKING INSULIN BREAKDOWN

Researchers at Harvard have discovered a molecule that inhibits the breakdown of insulin in mice, according to a study recently published in the journal *Nature*.

The identification of the insulin-degrading enzyme (IDE) as a diabetes susceptibility gene could have a sizable impact on the treatment of diabetes, since it could help maintain a person's insulin levels to lower blood sugar, say the study's lead authors David R. Liu, PhD, and Alan Saghatelian, PhD, both of Harvard University.

The authors wrote that they discovered the physiologically active IDE inhibitor identified from a DNA-templated macrocycle library. "An X-ray structure of the macrocycle bound to IDE reveals that it engages a binding pocket away from the catalytic site," they continued, "which explains its remarkable selectivity." They then treated lean and obese mice with the IDE inhibitor, which showed that the inhibitor regulates the abundance and signaling of glucagon and amylin, in addition to that of insulin.

The scientists concluded that their findings demonstrate the feasibility of modulating IDE activity as a new therapeutic strategy to treat type 2 diabetes and expand an understanding of the roles of IDE in glucose and hormone regulation. "This work validates a new potential target for the treatment of diabetes," Liu said in a university release. "What we show is that inhibiting IDE in an animal can improve glucose tolerance under conditions that mimic the intake of a meal if you administer this compound beforehand."

## ANDROGEN RESPONSE ELEMENT LINKED TO PROSTATE CANCER



Researchers in the United Kingdom may have discovered a novel approach to identifying components that affect development of prostate cancer,

according to a paper recently published in *Hormones and Cancer*.

The authors, led by Iain J. McEwan, of the University of Aberdeen, point out that the androgen receptor (AR) is a widely expressed protein, that plays a role in development of normal prostate tissue as well as prostate cancer (PCa), and mediates androgen signaling by binding to androgen response elements (AREs).

Despite the AR being "widely expressed," that expression is poorly understood. McEwan and his team

used the commonly available human prostate carcinoma cell lines LNCaP, VCaP, and DU145 to study the hormone-dependent repression of the AR gene. The scientists found that there was a primate-specific ARE in the human AR gene five prime untranslated region (5'UTR).

The authors concluded that "ARE represses transcription upon binding of activated AR, and this down-regulation is relieved by disruption of the regulatory element through mutation." However, they noted that this ARE is specific to primates and care must be exercised "when elucidating the operation of the human AR in PCa based upon rodent promoter studies."

## THE ENDOCRINE SOCIETY'S GUIDELINES FOR ADRENAL TUMORS

The Endocrine Society has issued a Clinical Practice Guideline (CPG) for the diagnosis and treatment of pheochromocytomas and paragangliomas, rare adrenal tumors that produce epinephrine and norepinephrine and can raise the risk of cardiovascular disease and even death if left untreated. The guideline was published in the *Journal of Clinical Endocrinology & Metabolism*.

The Society's task force, chaired by Jacques W.M. Lenders, MD, PhD, FRCP, of Radboud University in Nijmegen, the Netherlands, laid out recommendations that include testing the blood and urine for metanephrines, since these are byproducts left over when the body metabolizes epinephrine and norepinephrine. The CPG also recommends:

- People who are diagnosed with pheochromocytomas or paragangliomas should be involved in a shared decision-making process with their physicians to evaluate the need for genetic testing;
- A diagnostic algorithm that takes into account risk factors such as age at tumor presentation and family history should be used to establish which patients would benefit most from genetic testing and which specific gene mutations to test for;
- People with paragangliomas and those diagnosed with metastatic tumors should be tested for specific gene mutations associated with those conditions;
- Computed tomography can be used as the first choice imaging technology for determining the location of pheochromocytomas or paragangliomas for surgical treatment;
- MRI technology is to be used in specific situations, including for patients who have metastatic tumors, for detecting head and neck paragangliomas, and for patients in whom radiation exposure should be limited; and
- Another imaging technology, 18F-fluorodeoxyglucose-positron emission tomography/computed tomography, can be used in patients with metastatic tumors.

**“Correctly diagnosing pheochromocytomas and paragangliomas is extremely important,” Lenders said. “In addition to the strain these tumors put on the cardiovascular system, between 10% and 17% of the tumors can become malignant. Researchers have discovered that at least a third of people with these conditions have a disease-causing genetic mutation, so early detection can benefit family members who may be at risk.”**



## BARIATRIC SURGERY SHOWN TO BE EFFECTIVE TREATMENT FOR T2D

A three-year-long study has shown that more than 90% of the patients who underwent bariatric surgery were able to lose 25% of their body weight and control their diabetes without the use of insulin and multiple diabetes drugs.

The article published in the *New England Journal of Medicine* details the results of the three-year data of the STAMPEDE trial, the largest randomized trial with one of the longest follow-ups comparing medical therapy with bariatric surgery.

Researchers led by Sangeeta Kashyap, MD, and Philip R. Schauer, MD, of the Cleveland Clinic, evaluated outcomes of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. “The primary end point was a glycated hemoglobin level of 6.0% or less,” the authors wrote.

The researchers found that at “three years, the criterion for the primary end point was met by 5% of the patients in the medical therapy group, as compared with 38% of those in the gastric bypass group ( $p < 0.001$ ) and 24% of those in the sleeve gastrectomy group ( $p = 0.01$ ).”

Schauer and his team concluded that three-year data show that bariatric surgery is a highly effective and durable treatment for type 2 diabetes in obese patients, enabling nearly all surgical patients to be free of insulin and many to be free of all diabetic medications three years after surgery. The study also shows that bariatric surgery patients experienced an improvement in quality of life and a reduction in the need for cardiovascular medications to control blood pressure and cholesterol compared to those receiving medical therapy.



# Fast FACTS About Childhood Obesity



Excess weight in childhood has been linked to shorter lifespans.



In 2012, more than 30% of children and adolescents were overweight or obese.

If both parents are obese, the child has an 80% chance of being obese as well.



Only 2% of children eat a healthy diet.



Children typically spend four to five hours a day watching TV or playing video games.



Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years.



80% of obese children ages 10 – 15 years will remain obese by age 25.

Sources: *Journal of the American Medical Association*, U.S. Department of Agriculture, Blank Children's Hospital, Loyola University, Centers for Disease Control and Prevention, American Heart Association

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# Integrated Cross-Disciplinary Approaches to the Management of Diabetic Eye Diseases

**Chicago**

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October 8

Each regional dinner symposium will be hosted by one endocrinologist and one retina specialist, and will consist of didactic lectures, an interactive case study evaluation session, and live question-and-answer periods after each lecture and case study.

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Delineate an integrated cross-disciplinary referral pattern that yields the quickest patient journey with greatest improvement in quality of life.

Assess the clinical implications of the growing diabetes epidemic, including impact on the eye care practice.

Review the AAO guidelines for screening, treatment, and management of patients with diabetic eye diseases.

Survey the range of available and emerging treatment options for patients with diabetic eye diseases, including safety and efficacy from clinical trials and real-world experience.

Analyze the unique roles of ocular imaging modalities in the diagnosis and management of diabetic eye diseases.

Determine treatment and management strategies that minimize burden on diabetic eye disease patients and their caregivers.

## PARTICIPATING FACULTY

**COURSE DIRECTOR Seenu M. Hariprasad**, MD, University of Chicago Professor of Ophthalmology and Visual Science, Chief of Vitreoretinal Service, Director of Clinical Research, Director of Fellowship in the Diseases and Surgery of the Retina, Macula and Vitreous.

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**Carl D. Regillo**, MD, FACS, Director, Retina Service, Professor of Ophthalmology, Wills Eye Hospital, Thomas Jefferson University.

**Thomas A. Albini**, MD, Associate Professor of Clinical Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine.

**David S. Boyer**, MD, Clinical Professor of Ophthalmology, University of Southern California/Keck School of Medicine, Los Angeles, CA, Senior Partner, Retina-Vitreous Associates Medical Group, Los Angeles, CA.

**Darius M. Moshfeghi**, MD, Associate Professor of Ophthalmology, Director of Vitreoretinal Surgery Fellowship and Telemedicine, Byers Eye Institute, Horngren Family Vitreoretinal Center, Dept of Ophthalmology, Stanford University School of Medicine.

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# SUPER-SIZED Youth

As childhood obesity reaches epidemic proportions, ailments once confined to adults are being diagnosed in younger patients. New studies show that childhood adversities and PFC exposure are contributing factors to this growing scourge.

By Kelly Horvath





## AT-A-GLANCE

- Increased exposure to perfluorinated compounds (PFCs) found in many consumer products is associated with detrimental changes in serum concentrations of insulin and triglycerides in overweight children that could represent an early stage of metabolic syndrome.
- Despite overall life expectancy markedly increasing globally, no significant improvement in survival occurred in those who were overweight/obese adolescents — mortality rates associated with adolescent obesity recorded between the years 2000 – 2011 were as high as the rates observed during the 1960s and the 1970s.
- Early-life adversity is associated with central obesity and metabolic syndrome as well as elevated levels of circulating leptin and irisin and decreased levels of adiponectin in midlife adults.



The devastating physical and emotional effects of childhood obesity have been increasingly well documented as the rate of overweight and obesity skyrocketed in the last half of the 20th century on into the first half of the 21st century. At its peak, one in three children, ages two to 19 years, were considered overweight or obese, based on body mass index (BMI) at the 95th percentile or higher of the Centers for Disease Control and Prevention growth charts. “Childhood obesity has reached epidemic proportions,” says Steven J. Czinn, MD, professor and chair of the University of Maryland School of Medicine’s Department of Pediatrics. “The culture of many of today’s youth is not centered on physical activity or eating healthy foods.”

With childhood obesity increasing, serious medical conditions once considered the provenance of adulthood, such as diabetes, elevated blood pressure and cholesterol levels, and depression, as well as insidious effects such as low self-esteem and body dysmorphia began to comorbidly affect children and adolescents, and childhood obesity captured the clinical research world’s attention. Although rates have come down slightly in the last couple of years, especially in the very young, the problem paradoxically continues to grow as more and more complications come to light. Now hovering at about 17% of U.S. children and adolescents, childhood obesity causes a disproportionate share of immediate and long-term adverse health effects.

### Truncated Lifespan

Although morbidity and comorbidities of obesity are common research avenues, obesity’s effects on life expectancy have been unclear. To examine the relationship between BMI at adolescence and mortality rate, a team of researchers headed by Amir Tirosh, MD, PhD, of the Brigham and Women’s Hospital and Harvard School of Public Health, Boston, launched a prospective nationwide longitudinal cohort study of 2,159,327 Israeli adolescents between 1967 and 2011. The largest analysis ever conducted on the impact of childhood and adolescent obesity on all-cause mortality rates in midlife, the study comprised 43 million person-years of follow-up, by linking with Ministry of Interior mortality records.

Their chilling findings, which were published in *The Journal of Clinical Endocrinology & Metabolism*, show that although, overall, people across the globe live longer today than they did 50 years ago, those who were overweight and obese as teenagers did not similarly gain in life expectancy — early mortality rates in 2011 stayed the same as those in the 1960s. For men, the prognosis is even worse. Across all BMI ranges, including what is currently considered normal, men are three

**“Childhood obesity has reached epidemic proportions.**

The culture of many of today’s youth is not centered on physical activity or eating healthy foods.”

— Steven J. Czinn, MD,  
professor and chair,  
University of Maryland School  
of Medicine, Department  
of Pediatrics, Baltimore





times more likely to die than women before age 50. “If such a trend continues, the high rates of childhood and adolescence overweight and obesity are likely to adversely affect life expectancy,” Tirosh says.

### New Complications Emerge

Such far-reaching consequences are shocking enough; Add to them a new finding that environmental health hazards pose particular risks for overweight and obese children, and the picture grows bleaker for this acutely at-risk population. As part of the 1997 European Youth Heart Study, researchers led by Clara Amalie G. Timmermann, M.Sc., from the Syddansk Universitet Odense, in Denmark, sampled plasma from 499 eight- to 10-year-old Danish children to conduct perfluorinated/polyfluorinated compound (PFC) analysis, using high-performance liquid chromatography and mass spectrometry. Recently, the endocrine disruption and resultant health risks caused by PFCs, industrial chemicals used in a variety of consumer products, have led to decreased commercial use, but, thanks to their long half-lives, PFCs accumulate in air, dust, and water.

**“Primary care doctors and endocrinologists should keep early-life adversity in mind as a potential risk factor for the development of central obesity and metabolic syndrome later in life and intensify, as appropriate, lifestyle modification or other prevention measures in this segment of the population.”**

— Christos S. Mantzoros, MD, DSc, PhD, Harvard Medical School, Cambridge, Mass.

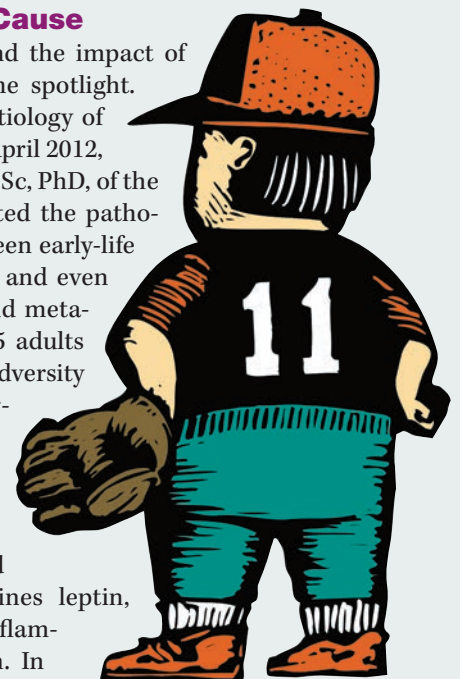
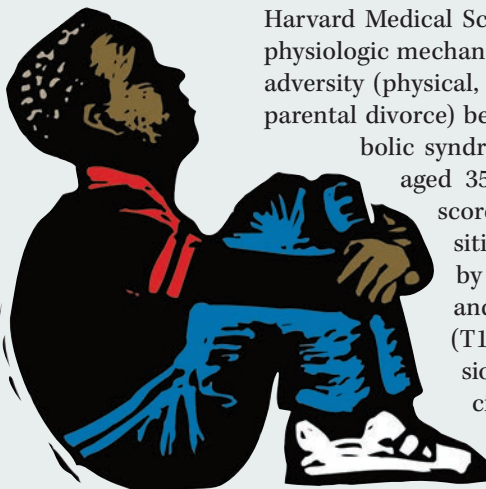
Children tend to have higher serum concentrations of PFCs, likely due to hand-to-mouth transfer.

The researchers’ study, published in *The Journal of Clinical Endocrinology & Metabolism*, is the first to focus specifically on metabolic changes in children exposed to PFCs and shows that they exhibit early stages of metabolic syndrome, consistent with recent findings in American adults. Using the homeostasis model assessment (HOMA), levels of plasma glucose, insulin, triglycerides, adiponectin, and leptin were used to estimate insulin resistance and pancreatic  $\beta$ -cell function.

“Our study shows that increased exposure to these chemicals is associated with changes in serum concentrations of insulin and triglyceride in overweight children,” Timmermann says. “The results suggest that these highly persistent chemicals could represent an important health hazard, which needs to be addressed in further studies,” she continues. Because no link was found between PFCs and glycemic control indices among normal-weight children, the implication is additionally that overweight and obese children may be uniquely vulnerable to endocrine-disrupting substances and their associated complications.

### Adversity-Obesity Link: A Troubling New Cause

With rates of childhood obesity so persistently high and the impact of the condition so catastrophic, prevention has taken the spotlight. However, as researchers and clinicians well know, the etiology of obesity is nothing if not complex. From October 2009 to April 2012, a team of researchers led by Christos S. Mantzoros, MD, DSc, PhD, of the Harvard Medical School in Cambridge, Mass., investigated the pathophysiologic mechanism underlying the association between early-life adversity (physical, emotional, or sexual abuse; neglect; and even parental divorce) before age 18 and obesity, diabetes, and metabolic syndrome in a cross-sectional study of 95 adults aged 35–56. The researchers created an adversity score by multiplying the number of adversities by the overall severity of adversity by the overall chronicity of adversity and grouped participants into tertiles (T1–T3). Using multiple linear regression analysis, researchers measured circulating levels of the adipomyokines leptin, adiponectin, and irisin and the inflammatory marker C-reactive protein. In



their paper, published in *The Journal of Clinical Endocrinology & Metabolism*, researchers report that T3, the severest adversity group, demonstrated elevated leptin, involved in satiety regulation, and irisin, involved in energy metabolism, even after adjusting for potential confounders such as gender and race. Decreased levels of the glucose and lipid metabolism modulator adiponectin were additionally reported.

“These effects of early-life adversity occurred above and beyond any effects of nutrition or exercise on obesity,” Mantzoros says, suggesting that leptin and irisin possibly directly mediate the link between early-life adversity and the pathogenesis of obesity perhaps via threefold disruption of the hypothalamic–pituitary–adrenal axis, the immune system, and metabolic regulation systems. “Primary care doctors and endocrinologists should keep early-life adversity in mind as a potential risk factor for the development of central obesity and metabolic syndrome later in life and intensify, as appropriate, lifestyle modification or other prevention measures in this segment of the population,” Mantzoros says.

Czinn agrees that lifestyle modification is the key to thwarting the obesity epidemic and all of its associated complexities: “Through many national and local initiatives, pediatricians and parents alike are working together to change how children and families view exercise and a healthy diet, which will, in turn, dramatically improve the health of an entire generation.” **EN**

— Horvath is a freelance writer based in Baltimore.  
She wrote about the health disparities in thyroid cancer in the March issue.



**“Through many national and local initiatives, pediatricians and parents alike are working together to change how children and families view exercise and a healthy diet, which will in turn dramatically improve the health of an entire generation.”**

— Steven J. Czinn, MD  
professor and chair,  
University of Maryland  
School of Medicine,  
Department of Pediatrics,  
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# The First 1,000 Days:

EARLY LIFE DETERMINANTS OF CHRONIC DISEASE



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**A** complex interaction takes place between genetic and environmental factors during the first 1,000 days after conception, up to a child's second birthday. This is a plastic period during which events and exposures can have significant effects on a child's development and his or her risk of many chronic non-communicable diseases later in life, including obesity, hypertension, and type 2 diabetes. The right and wrong influences can have a tremendous impact not only on the child but the society in which he or she resides. In this Tri (Tetra)-Point article, epidemiologists discuss the findings of the Hertfordshire Cohort, which provided the first evidence supporting a relationship between early-life influences and chronic endocrine disorders; a basic scientist describes potential mechanisms through which early-life experiences may increase the risk of obesity, diabetes, and other metabolic disorders; a clinical researcher provides an overview of the role of modifiable early-life influences on obesity (a precursor to most chronic non-communicable diseases); and a clinician in practice discusses how emerging evidence should influence pediatric care in the first two years of life and describes guidelines to promote healthy growth and reduce the risk of childhood obesity and other chronic endocrine diseases.

### HIGHLIGHTS

- The link between fetal development and chronic disease was recognized by Professor David Barker when he noted a **significant correlation between early-life conditions and later cardiovascular mortality**.
- Data from the **Hertfordshire Cohort** has provided evidence for the relationship between low birth weight and cardiovascular disease, impaired glucose tolerance/type 2 diabetes, hypertension, obesity, body fat distribution, and bone mineral density.
- Further **exploration of the mechanisms** for these relationships is currently being undertaken in this cohort.

### History of the Hertfordshire Cohort

Over the last quarter century, intrauterine environment and health in early childhood have become increasingly recognized as important factors in the programming of metabolic function across the life course and subsequent propensity to disease. Physician and epidemiologist, Professor David Barker, was the first to advocate the theory that environmental stimuli act at critical periods during early fetal development and lead to persistent structural and functional changes. His hypothesis originated from the observation of a positive geographical correlation between deaths from cardiovascular disease during 1968-1978 and infant mortality rates 60 years previously. These initial observations triggered a cascade of further studies confirming that adverse environmental influences acting in utero and early life increased the risk of later-life cardiovascular disease and additionally various metabolic, endocrine, and musculoskeletal disorders. A number of these associations were identified in the Hertfordshire Cohort Study, which was made possible by the discovery of ledgers containing birth and infancy records from the early 20th century (1911 – 1948). Specifically, the Hertfordshire Cohort Study has contributed to a wealth of research exploring interactions between the genome, intrauterine and early postnatal environment, and adult lifestyle in the etiology of chronic disorders in later life.

### Early-Life Influences and Glucose Regulation

Early work confirmed the relationship between low birth weight and cardiovascular disease. This was thought to result from impaired glucose tolerance and hypertension, which lead to increased plaque deposition within the arteries. The other contributor to the link between birth weight and heart disease was insulin resistance, which was assessed using oral glucose tolerance tests. Participants with low birth weight were more likely to suffer impaired glucose tolerance. Body composition in later life also impacted this association. A quarter of men with birth weights below the median value, who also had a body mass index (BMI) above the median in later life, suffered impaired glucose tolerance. Whereas, only 5% of men above median for birth weight with low BMI in adulthood had impaired glucose tolerance.

Nutritional and growth factors that determine fetal

and infant growth may also influence the size and function of adult pancreatic  $\beta$ -cells. Therefore, a single adverse prenatal influence, such as gestational malnutrition, might be expected to reduce both infant growth and islets of Langerhans development; the latter predisposing to diabetes. Further studies in Hertfordshire have established relationships with diabetes through the measurement of plasma concentrations of insulin and its precursors, such as proinsulin and 33-32 proinsulin.

### Early-Life Influences on Bone Health

The influence of environmental factors during intrauterine and early postnatal life on the risk of metabolic bone diseases, such as osteoporosis, has also been investigated, and low birth weight was associated with lower bone mineral content in late adult life. Growth hormone (GH) activation of Jak-Stat signalling pathways stimulates liver production of insulin-like growth factor 1 (IGF-1), leading to growth stimulatory effects on a variety of tissues including osteoblasts and chondrocytes. This can promote chondrogenesis and increased bone formation. Consequently, this pathway has been investigated as a potential mediator of the developmental origin of bone health. Cohort women had their circulating GH profiles examined over a 24-hour period with blood samples taken every 20 minutes. Analyses showed a positive association between circulating GH concentrations and bone mass at lumbar spine sites. Furthermore, women of higher birth weight tended to have higher basal GH concentrations. These data support a role for the GH/IGF-1 axis in the determination of bone health.

### Early-Life Influences, Musculoskeletal Disorders, and Body Composition

In recent years, the Hertfordshire Cohort Study has permitted a more comprehensive evaluation of the life course determinants of musculoskeletal aging. Thus, in addition to enhancing our characterization of risk factor profiles that might be used in the prediction of osteoporotic fractures among patients, the program has extended to understanding the definition, prevalence, and determinants of sarcopenia and osteoarthritis.

### Summary

In summary, from Professor Barker's initial ecological observations, epidemiological research has grown in the



Hertfordshire Cohort Study to demonstrate additional diseases influenced by early-life experiences and to delineate the potential endocrine mechanisms that may underlie them. **EN**

— Charlotte Moss, MA, research assistant;  
Mark Edwards, MRCP, clinical research fellow;  
and Elaine Dennison, PhD, FRCP, professor of rheumatic  
disease epidemiology, all of the Southampton General  
Hospital, UK, contributed to this section.

## BASIC RESEARCHER PERSPECTIVE — Elizabeth Cottrell, PhD

### HIGHLIGHTS

- The **maternal environment**, and particularly maternal nutrition, plays a key role in determining (programming) both short- and long-term offspring health.
- Research over the past two decades has focused on understanding how the perinatal environment interacts with the developing genome to bring about **permanent changes in gene expression and tissue structure and function**.
- Future research may enable the **development of interventions** that prevent or ameliorate adverse programming outcomes.

### Early-Life Determinants of Chronic Disease

It is now clear that early-life experiences shape our physiology and can permanently modify long-term susceptibility to disease. The maternal environment — influenced by factors such as nutrition, psychological stressors, or disease — affects not only pregnancy outcome, but also the long-term health of the offspring. In recent years, significant progress has been made in understanding the mechanisms by which these perturbations in early environment can lead to later metabolic disease risk.

### Thrifty Phenotype — Lessons from Human Studies

Initial epidemiological studies linking poor early development with later disease identified that being born small for gestational age significantly increased the risk of developing both hypertension and type 2 diabetes in later life. These studies formed the basis of the “thrifty phenotype hypothesis,” which proposed that in response to a poor intrauterine environment, the fetus is able to adapt its physiology to promote survival in the short term, by maximizing metabolic efficiency. However, this “thriftness” becomes maladaptive if nutrients in the postnatal period are plentiful, resulting

in an increased risk of metabolic disease. A wealth of data from animal models has since corroborated this hypothesis and has also provided key mechanistic insight into the pathways that may be disrupted and lead

to the development of obesity and associated metabolic dysfunction in the offspring.

### Mechanistic Insight from Animal Models

A range of animal models have been developed to study pregnancy complications that reduce fetal growth and result in low birth weight (LBW) offspring. Interestingly, despite the variety of manipulations used — from altered maternal nutrition, surgical interventions that restrict blood flow to the fetus, or glucocorticoid treatment (to name a few) — the long-term phenotypic outcomes are often remarkably similar. Amongst these models, those that manipulate maternal nutrition are most commonly used. Global nutrient restriction (i.e., a reduction in the overall number of calories) or the feeding of a low protein diet during pregnancy leads to LBW in animals. These LBW offspring display alterations in structure and function of a diverse range of tissues, and crucially these alterations often precede the onset of overt disease.

Within the pancreas, the development of insulin secreting  $\beta$ -cells is compromised in LBW offspring. This is characterized by a decrease in  $\beta$ -cell number, reduced insulin secretory capacity and, as a result, impaired regulation of blood glucose. In the adipose tissue, LBW offspring appear to be programmed to store fat more efficiently, as a result of both enhanced insulin sensitivity as well as a persistent up-regulation of key adipogenic signaling pathways. In addition to this tendency for more efficient storage, offspring are often also hyperphagic, due to alterations in central nervous system (CNS) pathways controlling food intake. Leptin, secreted by peripheral fat stores, is one of the key feedback signals that regulates food intake, and CNS leptin resistance is a common feature of many programming models. Combined, these perturbations in multiple tissues generate a phenotype that favors the development of obesity and metabolic syndrome, particularly in the face of excessive nutrient availability postnatally.



## The Additional Risk of Catch-Up Growth

In addition to being born small, the rate of growth in early life contributes to later metabolic disease risk. LBW combined with rapid “catch-up” growth during the early postnatal period is associated with increased adipose tissue mass both in childhood and later adult life. This preferential accumulation of adipose tissue not only increases storage in fat depots, but can also lead to the ectopic deposition of lipids in other metabolic tissues including pancreas and skeletal muscle, ultimately impairing insulin secretion and action. Furthermore, LBW individuals attain a lower lean mass in later life, potentially compounding impairments in whole-body insulin sensitivity.

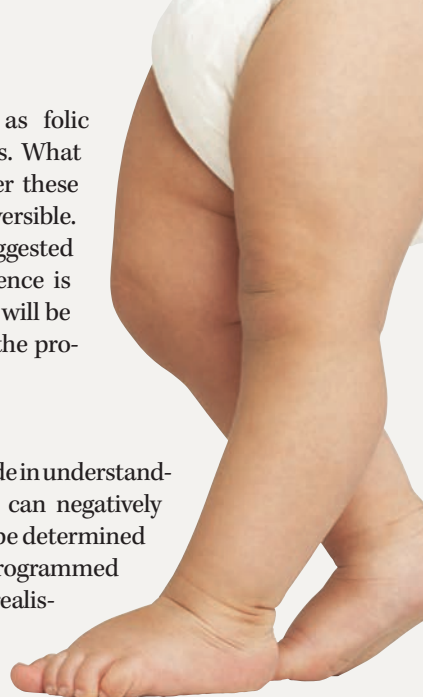
## Epigenetic Programming

Determining how these permanent alterations in cell and tissue function occur is currently a highly active area of investigation. Epigenetic mechanisms clearly play a role, as altered chromatin structure and DNA methylation status influence target gene expression in a number of different tissues, contributing to the observed metabolic dysfunction. There is now abundant evidence demonstrating that supplementation with

specific micronutrients, such as folic acid, can alter epigenetic status. What is currently less clear is whether these epigenetic modifications are reversible. Although some studies have suggested that this is possible, more evidence is required, and it is likely that this will be a key area of future research in the programming field.

## Summary

Significant progress has been made in understanding how the early environment can negatively affect adult health. It remains to be determined just how permanent these programmed changes are, and whether it is realistically possible to intervene to reduce the risks of subsequent ill health. Ultimately, strategies to optimize maternal nutrition during pregnancy and infant nutrition during critical developmental periods may well allow us to improve the health of future generations. **EN**



## CLINICAL RESEARCHER PERSPECTIVE — *Elsie M. Taveras, MD, MPH*

### HIGHLIGHTS

- **Childhood obesity is of increasing concern worldwide** and threatens to undo the health gains made in the last century.
- Women's health during pregnancy as well as the role of the father and his health during this period may be a potential new area for exploration in **reducing disparities in obesity and preventing this disease and its complications**.
- Multi-level, multi-sector strategies, especially those that invoke change at the individual, family, social environment, and systems levels are needed to **address the global obesity epidemic**.

## The Chronic Non-Communicable Disease Epidemic

Obesity rates among adults and children have substantially increased worldwide over the past three decades with all but the poorest countries now struggling with a growing obesity problem. Obesity represents a major threat to public health and results in significant excess burden of non-communicable diseases (NCD) and societal costs. In adults, a body mass index (BMI) as low as 23 kg/m<sup>2</sup> is associated with dramatically high rates of type 2 diabetes and cardiovascular disease. In children, obesity is associated with both short- and long-term adverse outcomes including hyperlipidemia, diabetes, and hypertension, and with higher morbidity and mortality in adulthood. If current worldwide trends continue, the number of overweight people is projected to increase from 1.3 billion in 2005 to nearly 2.0 billion by 2030. The underlying causes of obesity and NCDs are modifiable risk factors throughout the life course. These

risk factors represent major causes of health inequalities worldwide. Thus, prevention of obesity and NCDs is a global health priority.

## A Life-Course Approach to Addressing the Chronic Disease Epidemic

The life-course approach to chronic disease prevention posits that factors may act in the prenatal period and extend into infancy, childhood, and beyond to determine risk of chronic disease. Today we recognize that the First 1,000 Days — conception through 24 months — is a crucial period for the development, and thus prevention of obesity and its consequences.

During pregnancy, greater postpartum weight retention (PPWR) predicts long-term weight gain, risk of obesity, and altered metabolic state among women. PPWR, estimated as the difference between weight after delivery, usually six or 18 months, and pre-pregnancy weight, averages a seemingly modest ~1.5 kg but 13% – 20% of



women experience weight retention >5 kg, especially those who were overweight or obese before pregnancy. Women who retain excess weight after pregnancy also have a higher risk of gestational diabetes and having a large-for-gestational-age infant in their subsequent pregnancies, disadvantaging future offspring.

Epigenetic research is increasingly demonstrating the important role of the father's diet and obesity on offspring health. Evidence is also demonstrating that the father's involvement can have a substantial impact on pregnancy and infant outcomes. When fathers are involved during pregnancy, maternal negative health behaviors diminish and risk of preterm birth, low birth weight, and fetal growth restriction is significantly reduced. The father's involvement has also been associated with infant mortality up to one year after birth. Strengthening the father's involvement in pregnancy and parenting has been recommended as a potential strategy for reducing health disparities particularly among racial/ethnic minority families.

In children, early obesity and excess weight gain in infancy not only predicts later obesity and cardio-metabolic risk, but also serious morbidity within childhood, including asthma, orthopedic problems, psychosocial adversity, and increasingly, type 2 diabetes. Epidemiologic studies from our group and others suggest that adverse exposures in the intrauterine and infancy periods can "program" trajectories of adiposity and metabolic function throughout life and may increase short- and long-term risks for obesity and its sequelae.

### Summary

Preventing obesity in the First 1,000 Days can be achieved by developing multi-level, multi-sector strategies, especially those that invoke change at the individual, family, social environment, and systems levels. Such interventions should draw lessons from an understanding of the etiology of obesity, sources of resistance to change, and effective levers of sustainable change. Preventing the pernicious, inter-generational cycle of obesity will also require interrupting the effects of "obesogenic systems" early in life. Such system-level interventions promise new and sustainable approaches for entraining healthful lifelong weight trajectories. **EN**

## CLINICIAN IN PRACTICE PERSPECTIVE — *Maynika V. Rastogi, MBBS*

### HIGHLIGHTS

- **Obesity and the metabolic syndrome** can be abated through health supervision even before the age of two years.
- Examples of **modifiable contributors** include: feeding, sleep training, and screen time.
- **Parents exert a huge influence** on the formation of healthy habits and, given guidance, can be proactive in nurturing a healthy home.

Chronic diseases are becoming more common in childhood. There is a documented prevalence of childhood obesity of 16.9% among children two to 19 years with 12.1% of these in the two- to five-year-old age group. This rises to 18.4% during adolescence. Obesity is associated with metabolic abnormalities that result in type 2 diabetes, hypertension, and hyperlipidemia. Pediatricians are now faced with the care of chronic diseases in our children, an area of increasing research focus. This commentary highlights areas of health supervision where general practitioners can make an impact in the prevention of obesity and slow the rise in prevalence of chronic diseases.

### Screening

There are several parental indicators associated with a future risk of obesity or chronic disease from the first clinic visit. For example, it is worth noting whether one or both parents are overweight. Maternal smoking and a history of maternal diabetes during pregnancy

provide additional clues. Obesity is also more frequent in families with lower household incomes, single-parent homes, and families of African or Hispanic heritage. Families that practice unhealthy eating habits also have a higher risk. The birth history is important as children with birth weights over 4 kg or under 2.5 kg can develop the metabolic phenotype.

### Feeding Practices

Early childhood feeding practices exert a great influence on the future risk of obesity and metabolic disease. During infancy, exclusive breastfeeding may lead to lower rates of obesity with lower rates of weight gain in the first year of life. Promotion of exclusive breastfeeding, avoidance of overfeeding, and an introduction of solid foods at six months of age as recommended by the American Academy of Pediatrics (AAP) should be encouraged. Parents should also be warned about excessive weight gain seen on a growth chart by plotted points climbing



rapidly above the given centile lines.

The transition from infancy to toddlerhood provides further opportunities to be proactive. Many, when faced with the challenge of the “picky eater,” resort to giving unhealthy food and snacks; some moral support from their pediatrician can be invaluable to promote healthier choices. Other important practices include limiting fruit juices to 4 – 6 oz. daily, the avoidance of sweetened beverages, and providing a calcium-rich diet with liberal servings of fruits and vegetables. Toddlers should be left to eat as they choose rather than encouraged to “finish the plate” and portion sizes should follow the FDA food pyramid. Practitioners should also be aware of cultural norms that promote “chubby babies” and traditional foods that may be high in calories but low in nutrients. In the Caribbean, for example, a “flour porridge” paste made with baking flour or arrowroot is often used in early infancy as a “fattening” agent.

### Other Factors

Sleep, screen time, physical activity, and parental issues are also modifiable factors. Children with a healthy sleep schedule (more than 10 hours) have lower tendencies to obesity later in life. Thus, parents should be encouraged to prioritize an early bedtime. While screen time and physical activity may seem to be issues for older children, younger children are also affected. The advent of tablet computers and YouTube has turned many of our toddlers into technology addicts. Parents should be warned of these trends and introduce scheduled playtime without a TV screen so that physical activity becomes the norm rather than the exception. Families should be encouraged to themselves adopt healthy diets and increase physical activity. Timed family meals away from the TV with an emphasis on a variety of home cooked foods is also essential. Additional advice includes giving small portions, allowing children to participate in meal preparation, positive feedback for healthy food choices, and discouraging snacking.

Clinicians should adopt a sensitive approach. Obesity may be a source of depression or viewed as a personal failure by the parents involved. The AAP, therefore, recommends motivational interviewing techniques centered on listening without judgment, giving support, and empathy. Further guidelines can be found in the 2007 Policy Statement on Obesity Prevention.

### Summary

Obesity and the metabolic syndrome are now common pediatric problems. Modifiable factors include diet, sleeping habits, TV time, and physical activity. Parental influences are strong factors; thus, early encouragement to adopt a healthy family diet, increase exercise, and smaller portion meals can lead to good health habits that decrease risk for obesity and chronic disease in their offspring. Clinicians should employ non-judgmental approaches, emphasizing listening and motivational techniques to address this health problem. Table 1 highlights tips for obesity prevention incorporated into the well-child visit. **EN**

**Table 1: Tips for the prevention of childhood obesity at the health supervision visit**

Age at visit	Tips*
Newborn/ 2 weeks	Ask questions pertaining to maternal risk factors, parental diets, and lifestyle. Note birth weight, encourage breastfeeding.
6 weeks/ 2 months	Follow up on breastfeeding, ask about formula introduction, monitor weight gain**, warn against overfeeding.
4 months	Re-emphasize exclusive breastfeeding for the first six months. Discuss solid food introduction especially early introduction of vegetables and other healthy foods. Encourage homemade baby food with no added sugars and scheduled meals.
6 – 8 months	Monitor solid food introduction, weight gain, and discuss sleep training.
10 – 12 months	Discuss feeding habits and types of foods. Discourage snacking, encourage playtime away from the TV. Ask about scheduled family mealtimes. Limit intake of juices to 4 – 6 oz. per day.
12 – 15 months	Warn about picky eating, offer support to continue healthy diets. Discourage snacking and overuse of juice. Follow up on sleep habits. Minimize screen time.
2 years	Reinforce the above discussions starting from the 10-12 month visit.

\* All tips can be repeated at each visit or introduced earlier at the clinician's discretion

\*\* Should be done at every visit

**For a complete list of references, go to: [endocrinepress.org](http://endocrinepress.org).**



# DOUBLE JEOPARDY

Diabetes management can be trying in the best of situations for both patient and doctor. When the patient is also being treated for cancer, the challenges are abundant.

By Terri D'Arrigo

**D**iabetes is one of the more complex chronic diseases, requiring treatment through not only lifestyle and dietary measures, but a finely tuned medication regimen that may include insulin and one or more oral agents.

But add cancer on top of it, and diabetes management may require what feels like a Herculean effort both for patients and the endocrinologists who treat them. Chemotherapy and pain drugs can affect glucose homeostasis and insulin sensitivity, drug-drug interactions can interfere with the patient's tolerance for diabetes drugs, and the decreased appetite, nausea, vomiting, and consequent weight loss of both illness and cancer treatment can wreak havoc with a patient's blood glucose.

## Corticosteroids

When it comes to cancer drugs, corticosteroids are the 800-pound gorilla in the room, says Victor Lavis, MD, professor in the Department of Endocrine Neoplasia and Hormonal Disorders at the University of Texas MD Anderson Cancer Center in Houston. "They're a major part of chemotherapy and widely used for amelioration of nausea and vomiting associated with chemotherapy, as well as to suppress neurological symptoms when cancer has metastasized to the spine or brain. And they induce hyperglycemia."

An observational study appearing in the December 2013 *Current Oncology* found that blood glucose rose significantly in the hours following administration of corticosteroids in cancer patients with diabetes, as detected by blood glucose checks taken six hours after the patients received the drugs. The researchers found that the patients were still hyperglycemic 20 hours after administration.

This kind of spike is to be expected, but it can pose problems if the patient is receiving cyclic chemotherapy, says Catherine M. Edwards, MD, FACE, program director and associate professor of endocrinology in the Division of Endocrinology, Diabetes, and Metabolism at the University of Florida College of Medicine, in Gainesville, Fla.

"Within the first 24 hours, blood glucose will go way up, and then come down slowly after the last steroid dose, generally not coming back to baseline for about four days," she says. "So patients who get chemotherapy every

two weeks will have a fairly significant portion of time where blood glucose is very high."

The simple answer, then, is insulin, she says. "Insulin is by far the most flexible and powerful way to address that. Patients with type 1 will need to adjust their dose. Patients with type 2 who are already taking oral agents at baseline will need to add insulin, but only during that period when their blood glucose is high."

However, "simple" doesn't necessarily mean "easy," especially for patients with type 2 who have never taken insulin before, she adds. "They will need to learn how to take shots, and they are already dealing with a host of issues because of their cancer. That's where we come in as physicians and make sure they have the right education and motivation to treat themselves."

Joel Zonszein, MD, director of the Clinical Diabetes Center at Montefiore Medical Center in New York, treats patients with type 2 with basal insulin. "I like insulin for the simple fact that it's anabolic," he says. "While the patient is losing weight from the cancer and cancer treatment, the insulin will strengthen muscles and increase caloric reserve in fat cells."

He adds that bolus insulin requires checking blood glucose more frequently than patients who are already grappling with multiple treatments and therapies may be willing to accept.

"Checking blood glucose can be painful, so I try to keep the insulin to one shot a day and the blood glucose check to one a day at the peak of insulin so I know whether there needs to be an adjustment," Zonszein explains. He notes that some patients may focus on their diabetes care as a distraction from the stress of coping with cancer.

"I've seen patients get compulsive about their blood sugars. They want to get better, so they focus on their diabetes because they can control that better than their cancer," he says. Keeping insulin shots and blood glucose checks to one per day each may help avoid such a preoccupation.

"It comes down to taking an individual approach with a high degree of flexibility based on what patients need and can handle," Edwards says. "One day may be very different from the next. The patient should be instructed to



monitor his or her blood glucose and stay in close contact with the physician who is managing the diabetes.”

## How Much Control?

Given hyperglycemia's deleterious effects on the body, it's natural to want to control blood glucose in patients with diabetes as much as possible. But when cancer is added to the mix, there is more at stake. Several studies of cancers as disparate as small cell lung cancer and breast cancer note an association between hyperglycemia and poor outcomes in patients with diabetes and cancer. Hyperglycemia raises the risk of infection as well.

“If your sugar is high, there is a lot of food for cells, whether it's bacteria or cancer cells, to help them grow,” says Kristi Silver, MD, associate professor of medicine in the Division of Endocrinology at the University of Maryland School of Medicine in Baltimore. “Now consider someone who might be neutropenic from the cancer treatment.”

Lavis agrees. “If there is a risk of infection or the patient is neutropenic, I'd be keen to get the blood glucose down to below 180 mg/dl in short order because blood glucose that high diminishes host resistance to infection.”

However, there can be such a thing as too much control, depending on the cocktail of medications the patient is taking, says Robert Sargis, MD, PhD, assistant professor of medicine in endocrinology at the University of Chicago School of Medicine.

“Pain medications can cause constipation that affects patients two-fold. It can make them not want to eat, but also, by slowing intestinal motility, it's possible that narcotics can delay absorption of nutrients. This can lead to a mismatch in insulin delivery and glucose absorption. Then the patient will run the risk of hypoglycemia,” Sargis says.

“The key is to avoid extremes, with no hypoglycemia and minimal hyperglycemia,” he adds. “In the context of active cancer treatment, avoidance of risk [of hypoglycemia] significantly trumps tight glycemic control. That said, I think it's reasonable to shoot for keeping the blood sugars below the renal threshold of glucose during treatment, with intensification of therapy once the patient is on the road to recovery.”

## Prognosis and Comfort

Prognosis, longevity, and quality of life are important considerations in determining glycemic goals, says Otis Brawley, MD, chief medical officer of the American Cancer Society in Atlanta.

“The point of very tight blood glucose control is to try to prevent complications 10, 15, 20 years down the road. But in someone with a poor prognosis or an expected longevity of just a few years, we might be more concerned with comfort and quality of life in the years they have left,” Brawley says.

Lavis agrees. “If the life span of the patient is shorter than the time it takes to get complications like renal disease, we're less likely to fuss over getting the A1c down to below 7 mg/dl.” The goal then would be to avoid the effects of acute

## AT-A-GLANCE

- Corticosteroids are often part of cancer treatment and will cause a rapid spike in blood glucose that takes days to resolve after the last dose.
- Insulin offers an advantage because it is anabolic and will help preserve muscle mass in patients who are losing weight because of their cancer or cancer treatment.
- Statins are tricky. Because statins, like many chemotherapy drugs, are metabolized in the liver, taking a statin will affect how quickly the body clears the chemotherapy drugs.

hyperglycemia, such as dehydration and ketoacidosis.

Prognosis will affect decisions about other drugs patients may be taking because of their diabetes and risk of diabetes-related complications. Statins in particular can be tricky, says Brawley.

“Statins and chemotherapy drugs are metabolized by the same enzymes in the liver. If the enzymes are all tied up processing a statin, that can create a backup of chemotherapies to be eliminated,” he says. “Some research suggests that it works the other way, too. If you give someone who is on a statin chemotherapy and stop the statin, they will eliminate the chemotherapy drug much more quickly. Consistency is very important.”

This could create a trickle-down effect on blood glucose depending on which chemotherapy drugs the patient is taking and how those drugs affect blood glucose and insulin sensitivity.

“I would be reluctant to begin a statin on someone who is just beginning chemotherapy,” Lavis says. “If they are already on a statin, be aware of what the effects are and watch carefully. But if not, I wouldn't want to risk some deleterious effect or a drug interaction in the liver.”

“It comes back to general prognosis,” Silver says. “If you have a good prognosis, you may back off on statins for a short period when the patient is in acute therapy, but you don't want to ignore their cardiovascular risk from diabetes over the long term.”

Overall, the endocrinologist should find out what the oncologist's plans are for the patient's chemotherapy, Sargis says. “It's important for us to know what the planned doses and durations of treatment are, and any changes in therapy.”

“On a fundamental level, I think we need oncologists to give us a reasonable impression of what the goals of care are and the likelihood of success,” Sargis adds. “It can be very sad and hard, but it's helpful to us to target therapeutic interventions to the prognosis. If it's poor, I think we can feel more comfortable liberalizing goals and not burdening the patient with undue expectations.” **EN**

— D'Arrigo is a health and science writer based in Holbrook, N.Y., and a regular contributor to Endocrine News. She wrote about the debate over using insulin pens versus syringes in the April issue.

**“If the life span of the patient is shorter than the time it takes to get complications like renal disease, we're less likely to fuss over getting the A1c down to below 7 mg/dl.”**

— Victor Lavis, MD, professor, Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston

# STUCK IN THE MIDDLE: NON-COMPETE AGREEMENTS

Non-compete agreements can limit a doctor's ability to leave a practice and even stay in town. Make sure you know the ins and outs before you sign on the dotted line.

By Kurt Ullman

**N**on-compete agreements (NCA) have long been used by both independent and hospital-based integrated practices to keep physicians who leave on the sidelines for a prescribed period of time. Negotiating these agreements can be a problem for doctors of all ages.

An NCA, also known as a restrictive covenant, has two major elements. The first is as a provision in contracts giving an employer a reasonable amount of time to find, recruit, and hire a replacement for a departing physician. The other protects an employer from "raising their competition" by not allowing the ex-employee to compete against them for a period of time.

## Reasonable Geographic Scope & Duration

"The non-compete agreement has to be reasonable as to geographic scope and duration," says Robert Milligan, JD, LL.M, a healthcare attorney with Milligan Lawless, PC in Phoenix. "Reasonableness is decided by balancing the interests of the employer, the employee, and the patients, and it is judged on a case-by-case basis. There is truth in the saying that NCAs do not prohibit competition,





just give the employer a fair opportunity to compete when an employee leaves.”

Unlike other areas where NCAs are used, there is a third group whose interests are included: the patient. Courts will often look at what is reasonable from their viewpoint.

“At least under Arizona law, if an NCA is thought to unreasonably impair the rights of the patient to see their doctor, or worse, any doctor, the courts may say it is unenforceable,” notes Milligan. “The courts in our state can include the interests of the patient in their deliberation.”

## Changes by State

Which brings up another important part of the NCA legal environment: The circumstances under which an agreement will be upheld varies widely from one state to the next. Massachusetts, California, Delaware, and Alabama are states that ban or demand buy-out provisions in restrictive covenants as a matter of law. Most of the states have a bias against their enforceability, but will not interfere with those deemed reasonable as to time and geographic area.

“Most states are loathe to enforce agreements restricting professionals, so they tend to narrowly construct and review those restrictions,” says Ronald L. Vance, JD, managing director and physician strategy team leader for Navigant Consulting in Atlanta. “Many jurisdictions won’t

support anything much over a year and may cut geographic restrictions to something like five to 10 miles around the office where the physician worked.”

Some of the points physicians should make sure they understand completely about restrictive covenants include:

- Time: How many months or years will the restriction last?
- Scope: How many miles around a given office does the restriction encompass? Is it around any office of the practice or just the one(s) you have worked in?
- Type: What type of medical practice is involved? Medicine as a whole or just a specific specialty such as endocrinology?

## See an Attorney

Given the intricacies of both the agreements and their enforceability, it is important for every physician to have an attorney look over the entire contract with attention to the NGA. It is also important to find an attorney who is familiar with the laws in the state of practice. Someone coming out of a residency in California who takes a job in New York should find representation in New York.

“One place to look for an attorney is the American Health Lawyers Association,” Milligan says. “Their website lists members, the states they work in, and their specialty. You probably shouldn’t get a malpractice lawyer to look at contracts.”

Although it sounds very complex, it often isn’t. Many attorneys will not need to see you face-to-face, an important consideration if the position is across the country. Often, the attorney looks at the contract, highlights areas of interest, returns it to the doctor, and arranges for a telephone call to discuss any concerns.

## Hospital Employee vs. Private Practice

There are often differences in the wording of the agreements if you are entering a private practice or will be a hospital employee. The private practice is likely to be more restrictive saying you can’t practice, period.

“If the doctor is in good standing and is still supportive, a hospital may be less inclined to have them leave the community,” Vance says. “As long as another hospital doesn’t get 100% of referrals, they often won’t restrict the physician as an economic, business, and patient access decision.”

Even for those doctors currently employed, trends in healthcare suggest they still need to be aware of new non-compete agreements. “When people think about these kinds of restrictive covenants, they should note that more private practices are joining or being bought by health systems,” Vance says. “Even if they have been attentive to the agreements within their group, they should also make sure they understand any changes due to a buy out or merger.” **EN**

— Ullman, RN, MHA, is an Indiana-based freelance writer with nearly 30 years of experience. He wrote about adding advanced practitioners to an endocrinology practice in the May issue.



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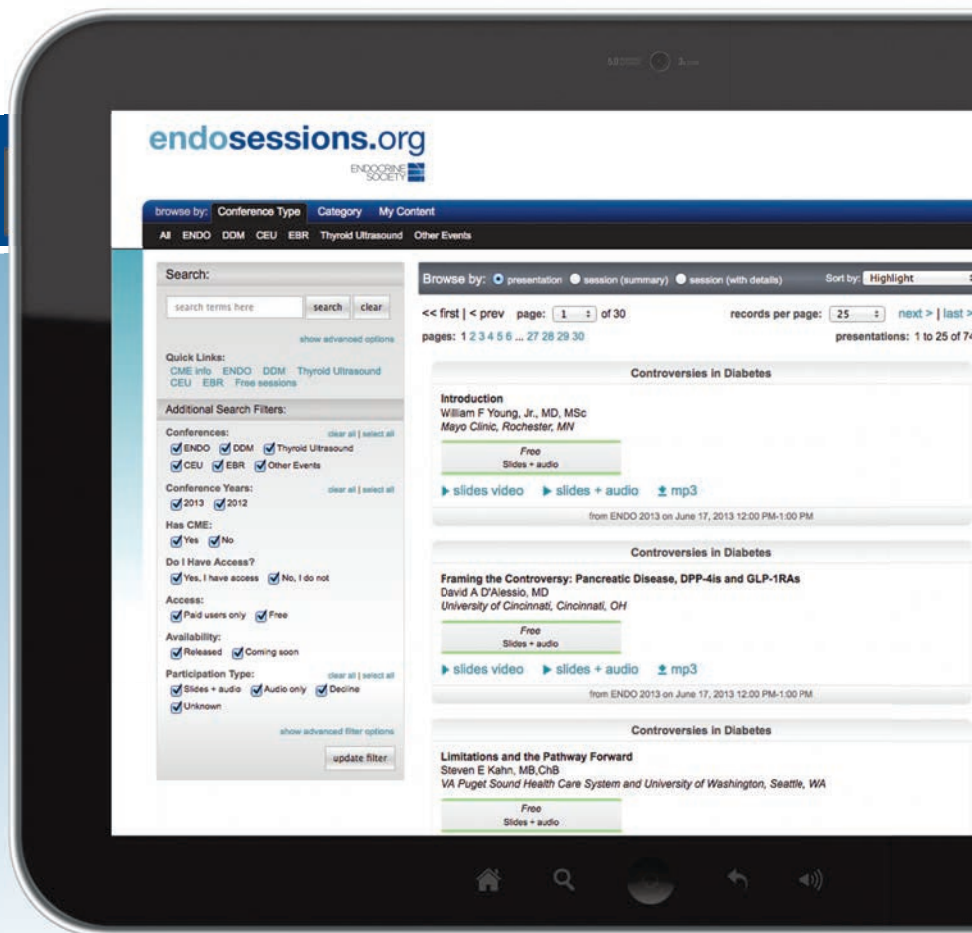


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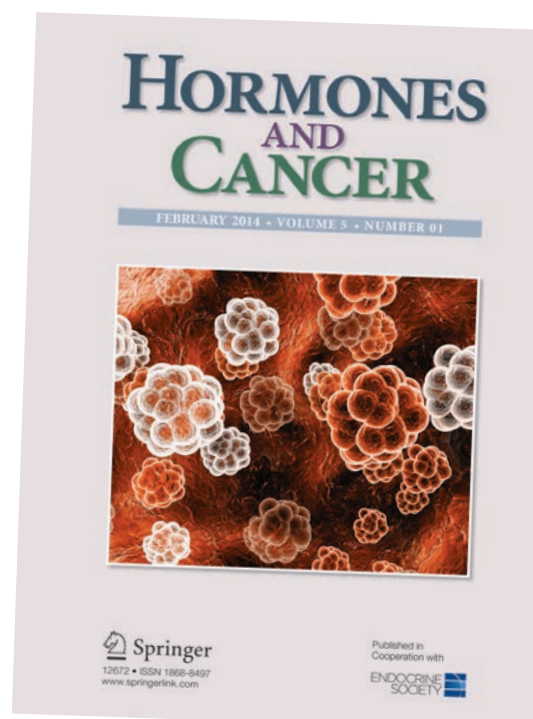
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## Society Members Advocate on Capitol Hill for Expansion of Diabetes, Obesity Coverage

By Meredith Dyer

On May 6, 2014, the Society held a clinician Hill Day to build support for a variety of advocacy issues related to diabetes, obesity, and physician reimbursement. Members of the Advocacy and Public Outreach Core Committee and the Clinical Affairs Core Committee came to Washington, D.C., to meet with congressional offices about the importance of increased funding for the National Diabetes Prevention Program, coverage of lifestyle intervention programs and chronic weight management drugs for seniors with obesity, and a permanent fix to the flawed sustainable growth-rate formula. This successful endeavor followed an equally successful researcher Hill Day in April.



From left to right: Vice President, Physicians-in-Practice, Susan Mandel, MD, MPH, Congresswoman Lois Capps (D-CA), and CACC member, Steven Nagelberg, MD



Congressman Chris Van Hollen (D-MD) and CACC Chair, Jason Wexler, MD

During the clinician visits, Society members urged members of Congress to appropriate \$20 million in FY 2015 for the National Diabetes Prevention Program (NDPP) and to expand coverage of the program to the Medicare population by supporting the Medicare Diabetes Prevention Act. The NDPP has been proven to prevent or delay the onset of type 2 diabetes through lifestyle intervention programs that promote moderate weight loss and regular physical activity.

Society members also educated members of Congress about the importance of addressing the obesity epidemic by supporting the Treat and Reduce Obesity Act, which provides a pathway for Medicare coverage of lifestyle intervention programs and chronic weight management drugs for individuals with at least one comorbidity. These meetings also addressed the critical nature of passing a permanent solution to the flawed

sustainable growth rate formula that threatens physicians with double-digit cuts each year.

By holding separate visits for our constituencies, we make more effective use of our opportunities to talk with policy makers about issues that are important to our members. We look forward to holding future Capitol Hill Days, and we hope you will join us at these events. **EN**

— Dyer is associate director, health policy, of the Endocrine Society.

## Society Guideline Program Offers Valuable Resources for Practicing Physicians

By Stephanie Kutler

The Endocrine Society plays a role in helping endocrinologists improve their quality of care through the development of clinical practice guidelines on various endocrine-related topics. The Society has published 23 guidelines to date, with 16 guidelines in varying stages of development or revision. The newest guideline, “Pheochromocytoma/Paraganglioma,” was published in the June edition of the *Journal of Clinical Endocrinology & Metabolism*. Upcoming topics include a revision of the “Androgens in Women” guideline, and new guidelines on Paget’s disease of the bone, acromegaly, and pharmacologic management of obesity.

Society guidelines are developed by a task force of experts and offer practical, evidence-based recommendations that are developed using the grading of recommendations, assessment, development, and evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The Society’s development process follows the majority of Institute of Medicine recommendations for trustworthy guidelines, and improvements are frequently made by the Clinical Guidelines Subcommittee to ensure that the guidelines are of the highest quality.

All guidelines are available on the Society’s website [www.endocrine.org/cpg](http://www.endocrine.org/cpg) for free download. While research shows that physicians value guidelines that lay out the evidence for a recommendation, there is also an acknowledgement that this does not always fit with the way physicians practice. The Society has developed a number of tools and resources to help physicians integrate the guidelines into their practice, including pocket cards, webinars, and performance improvement modules, and is embarking on an initiative to provide the guideline content in an e-format.

Endocrine Society members are encouraged to help shape the guideline program by emailing suggestions for new topics and tools to [govt-prof@endocrine.org](mailto:govt-prof@endocrine.org). **EN**

— Kutler is director, quality improvement, for the Endocrine Society.

## Endocrine Society Advocates for Equitable Inclusion of Both Females and Males in Biomedical Research; Helps to Fuel Changes at Federal Agencies

By Joseph M. Laakso, PhD

A critical component of the translation of basic science to new therapies is the extent to which females and males are equitably incorporated in research studies in all phases of biomedical research. At the basic research stage, this includes taking into account the sex of cell lines and animals used in preclinical research studies. During downstream clinical research, this means ensuring that women and men participate equally in clinical trials. The investigation of sex-specific effects is considered by the Society to be a significant component of the rigor and completeness in research.

The lack of proper investigation of such effects may create gaps in understanding of fundamental biological processes or discrepancies between basic research and downstream clinical effects. This inconsistency in the biomedical research pipeline can have serious consequences. For example, of the 10 drugs that were withdrawn from January 1, 1997 through 2001, eight posed greater health risks for women. However, despite years of awareness of this issue, women are still inadequately represented in many clinical trials. Additionally, sex differences are still not routinely considered as a critical variable in basic biological studies.

The Endocrine Society has worked to raise awareness of the issue of sex differences in biomedical research and urge that federal agencies specifically incorporate sex as a critical biological variable in research plans. Recent efforts by the Society include:

- Meeting with congressional offices to discuss the need for federal agencies to incorporate sex as a biological variable in research.
- Supporting a recent effort by a bipartisan group of women senators who called for equitable inclusion of women and minorities in clinical research while urging them to consider similar efforts for preclinical research.
- Advocating that the House Energy and Commerce Committee's "21st Century Cures Initiative" encourage the equitable study of both sexes in all stages of the biomedical research pipeline, in an effort to optimize overall research productivity.
- Asking the National Institutes of Health (NIH) to ensure that strategic plans and scientific initiatives include a consideration of sex differences in preclinical research.

In response to concerns articulated by the Society and other stakeholders, federal agencies are developing and implementing new policies to more appropriately balance the reporting and inclusion of sex differences in all phases of the biomedical research pipeline. The NIH and Office of Research on Women's Health (ORWH), for example, recently announced the development of new policies "to balance sex in cell and animal studies" in preclinical research funded by the NIH. The policies will be rolled out in phases beginning in October 2014 and include changes in the grant review process and ongoing engagement with stakeholders.

The FDA's Office of Women's Health has been working to ensure adequate participation of women in clinical trials and encourage analysis of data by sex to determine if sex differences exist in disease therapies. In response to section 907 of the FDA Safety and Innovation Act, the FDA will develop an action plan on the inclusion of demographic subgroups, such as women and underrepresented minorities, in clinical trials. The action plan will include recommendations to "improve the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling."

The Endocrine Society has been a leader on the issue of sex differences in research, for instance by advocating for the appropriate consideration of sex as a critical biological variable, and also through leading by example, establishing journal policies that require reporting of the sex of animals used in research. The Society is encouraged by the development of the new NIH policies and complementary efforts by other federal agencies to achieve equity in all stages of the biomedical research pipeline.

The Society will remain engaged with the NIH, ORWH, FDA, and other critical stakeholders as new policies affecting Society members are developed and rolled out. We encourage members to provide input on the Society's ongoing efforts. To stay on top of new developments, look to new issues of *Endocrine Insider*. To provide comments and suggestions for staff to bring to the attention of federal agencies, please reach out to the Society's Government and Public Affairs Department at [govt-prof@endocrine.org](mailto:govt-prof@endocrine.org). **EN**

— Laakso is the associate director, science policy, for the Endocrine Society.





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Reference: 1. Waters DD, Brotons C, Chiang CW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. *Circulation*. 2009;120:28-34.

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The obesity epidemic now under way in the U.S. is, in part, a result of the junk food we eat. This high-fat, low-nutrient, low-fiber diet exacts a high, hidden cost that makes junk food dangerously expensive—even deadly.

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- The percentage of adolescents aged 12–19 years who were obese increased from 5% to nearly 21% over the same period.
- In 2012, more than one third of children and adolescents were overweight or obese.

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← **HEART DISEASE**



← **OSTEOPOROSIS**



← **DEMENTIA**



← **MORE WORK ABSENCES**



← **MORE DOCTOR VISITS**



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**HEALTHIER HEART** →

**STRONGER BONES** →

**BETTER MENTAL CLARITY + MEMORY** →

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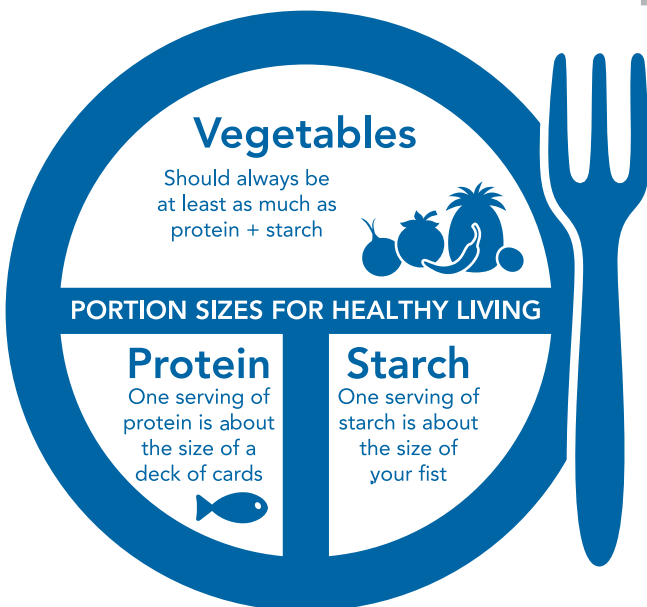
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FROM THE ENDOCRINE SOCIETY

## IN MEMORIAM: SCOTT HERMAN



The Endocrine Society lost one of its own May 5, when Scott Herman, group managing editor of the *Journal of Clinical Endocrinology & Metabolism (JCEM)* and *Endocrinology*, lost a hard-fought battle with cancer. He was 58.

Herman started with the Endocrine Society in 2002 as managing editor of *Endocrinology*, getting promoted to managing editor of both *Endocrinology* and *JCEM* in 2004, and in 2008 he was named group managing editor and associate director of *Endocrinology* and *JCEM*.

Herman made such an impact in his role at the Endocrine Society that he is even credited with expanding the amount of exceptional endocrinology research that was published in the last few years. "For more than a decade, no one more than Scott Herman was responsible for the high quality of published endocrinology research and scholarship," says Paul W. Ladenson, MD, a former editor-in-chief of *JCEM* and professor and director, Division of Endocrinology, Diabetes, & Metabolism, Johns Hopkins University School of Medicine, in Baltimore, Md. "He was a splendid managing editor who worked with legendary efficiency. Everyone who knew Scott soon saw that beneath his gruff demeanor was a man of great warmth and good humor."

Herman had a long and distinguished career in the world of scholarly journal publishing. He came to the Society from the *Journal of Immunology* where he served as the assistant managing editor for eight years. Prior to that, he was the production manager for the *Journal of Immunology*, editor for the *Proceedings of the National Academy of Sciences*, and production editor for the Transportation Research Board. He began his career as a proofreader for the American Council of Life Insurance in 1978, shortly after graduating from Washington University in St. Louis with a BA in English Literature.

Andrea C. Gore, PhD, editor-in-chief of *Endocrinology* and professor at the University of Texas, in Austin, Texas, credits Herman with her involvement at the highest level of the Society's journals. "I would never have considered the position of editor-in-chief of *Endocrinology* had it not been for Scott Herman," she says. "Having worked with him previously as an author, a reviewer, and an editor, I experienced his wisdom and humor. After becoming editor-in-chief and working with Scott daily, I learned how much I had underestimated his abilities and, more importantly, his kindness and dedication."

Leonard Wartofsky, MD, MACP, editor-in-chief of *JCEM* and professor of medicine, Georgetown University School of Medicine; Department of Medicine, Washington Hospital Center in Washington, D.C., has found himself overwhelmed by the flood of notes, remembrances, phone calls, and emails that he has received in response to Herman's passing, a testimony to the warmth and admiration for him by his friends and colleagues. "I had the pleasure and honor of enjoying Scott's collegiality, friendship, and humor for many years, even well before we started working together on *JCEM* almost five years ago," he says. "As his co-worker, I benefited daily from his vast publishing experience, wisdom, insights, candor, delightful sarcasm, and unique joie de vivre."

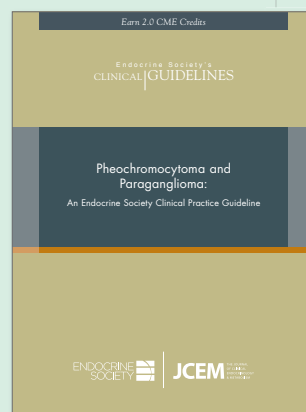
When Herman's prognosis took a downward turn, Wartofsky was inspired by his grace, serenity, equanimity, and even humor in dealing with his terrible illness in such a remarkably gallant and courageous manner. "John Donne wrote that 'any man's death diminishes me because I am involved with mankind...' and certainly Scott's death diminishes me, and all of us, because he was so involved with mankind as a husband, brother, uncle, editor, colleague, and dear friend," he continues. "Death is, of course, inevitable for us all, but still we mourn. Today we mourn Scott's loss even more because his death was so premature and untimely. Yet, there is some palliation for our grief in the celebration of his lifetime of achievement and the memories and legacy that he leaves behind." **EN**

— Mark A. Newman

## NEW CLINICAL PRACTICE GUIDELINE NOW AVAILABLE

"Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline", chaired by Dr. Jacques Lenders, provides actionable recommendations for practicing physicians on biochemical testing for diagnosis, imaging studies, genetic testing, perioperative medical management, and surgery.

Download the Society's latest guideline free at [endocrine.org/education-and-practice-management/clinical-practice-guidelines](http://endocrine.org/education-and-practice-management/clinical-practice-guidelines), or purchase a print copy at [endocrine.org/store/clinical-practice-guidelines](http://endocrine.org/store/clinical-practice-guidelines). Please email questions to: [govt-prof@endocrine.org](mailto:govt-prof@endocrine.org).





## Endocrinology Editor Responds to *Washington Post* Article on EDCs



Andrea C. Gore, PhD, the editor-in-chief of the Endocrine Society journal *Endocrinology*, had a letter to the editor published in the June 6 edition of the *Washington Post*.

Gore, professor of pharmacology and toxicology at the University of Texas, in Austin, responded to an article in the June 2 edition entitled, "Are some antimicrobial soaps harmful? A state's decision to ban renews questions."

In her letter, Gore stated that the original article seemingly downplayed the risks posed by exposure to triclosan and other endocrine disruptors. "A growing body of research shows that triclosan alters levels of thyroid and reproductive hormones in disturbing ways," she wrote. "Triclosan is shaping up to be the new bisphenol-A (BPA)." BPA, of course, is the ubiquitous petroleum derivative found in everything from food containers to children's toys, which has been at the center of the endocrine-disruptor debate for many years.

Gore wrote further that despite the evidence, "triclosan remains widespread in products marketed to people, including pregnant women and infants," adding that any conscientious consumer curious about what is really contained in household products is forced to read tiny labels in order to make sure there are no endocrine-disrupting chemicals.

"People have the right to know what they are buying, and they should be aware that washing with antibacterial soap containing triclosan may do more harm than good," she concluded. **EN**

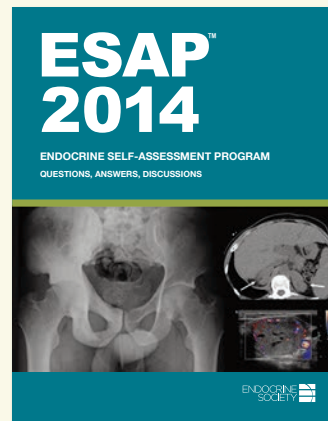
— Mark A. Newman

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Both the *Evaluation of Thyroid Nodules* and the *Androgen Deficiency in Men* PIMs will help you earn your required 20 MOC Practice Performance (Part 4) points from the American Board of Internal Medicine. And the new *Congenital Hypothyroidism* PIM has just been released! Developed in collaboration by the Pediatric Endocrine Society and the Endocrine Society, the PIM provides you with 20 MOC Part 4 points to meet the American Board of Pediatrics MOC requirements.

For more information about PIMs, MOCs, and other self-assessment products from the Endocrine Society visit [www.endoselfassessment.org](http://www.endoselfassessment.org). **EN**



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completed the exam in April. Of those 139 training programs, five new training programs registered their fellows, including three international programs. The addition of SI units to the 2014 exam has increased applicability

to international training programs. Learn more about ITE on [endoselfassessment.org](http://endoselfassessment.org). ESAP-ITE 2015 dates will change. The exam will be available for proctoring January 15, 2015 to February 15, 2015.

# Make Your Plans Now: **ENDO** 2015 Starts Earlier than Ever

The year's largest endocrinology meeting is now also the first, as ENDO 2015 moves to March. Join leading endocrinology practitioners and researchers from around the world in San Diego, California, March 5th – 8th, Thursday through Sunday, for four exhilarating days of discovery, education, and networking.

An earlier ENDO means earlier submission deadlines, so don't forget to adjust your calendars.

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ENDO 2015 brings you all the expert speakers, insightful sessions, and ENDOExpo exhibits you've come to expect — only you won't have to wait as long to explore what's new and exciting in your field. ENDO 2015 will be the first opportunity of the year to present your best science for oral, poster preview, and poster presentation to the world of endocrinology.

You'll find a diverse mix of pre-conference events, expert plenary sessions, renowned international speakers, and well-deserved teaching, science, and service awards. Endocrinology's brightest minds will be on hand to present their latest research and take part in hands-on workshops.

## A Brilliant Setting

What better backdrop to launch an early ENDO 2015 than San Diego, the birthplace of California and second-largest city in the state? The San Diego Convention Center lies in the Marina District on the San Diego Bay — just a skip from the Pacific Ocean. The award-winning venue features the unique Sails Pavilion, a 90,000 square-foot exhibit and special events area.

You may want to consider bringing the family or extending your stay, because San Diego truly offers something for everyone: perfect weather, gorgeous beaches, art museums, the world-famous San Diego Zoo, LEGOLAND — it's easy to see how this place earned the moniker "America's Finest City."

## Register Now for the Earliest ENDO

Don't miss the earliest — and best — ENDO yet: Registration for ENDO 2015 is now open! Visit [ENDO2015.org](http://ENDO2015.org) for more details.

And don't forget: Abstract submission begins in September — three months earlier than previous years. Note the new dates and spread the word. We'll see you there. **EN**

## ENDO 2015 AT A GLANCE

**March 5 – 8, 2015 (Thursday-Sunday)**  
**San Diego Convention Center, San Diego**  
[ENDO2015.org](http://ENDO2015.org)

- **Abstract submission opens:**  
September 17, 2014
- **Abstract submission closes:**  
November 12, 2014
- **Late-breaking abstract submission:**  
December 29, 2014 – January 12, 2015

## Event CALENDAR

### AUGUST 6 – 9, 2014, ORLANDO, FLA.

AADE14 – American Association of Diabetes Educators  
<http://www.diabeteseducator.org/ProfessionalResources/AnnualMeeting/CorporateOpps/>

### SEPTEMBER 2 – 6, 2014, SAN FRANCISCO, CALIF.

Endocrine Board Review and Clinical Endocrinology Update  
[Endocrine.org/SF](http://Endocrine.org/SF)

### SEPTEMBER 5, 2014, CURITABA, BRAZIL

Highlights of ENDO, [www.endocrine.org](http://www.endocrine.org)

### SEPTEMBER 14 – 17, WASHINGTON, D.C.

10th International Meeting of Pediatric Endocrinology  
[www.pedsendo.org](http://www.pedsendo.org)

### SEPTEMBER 15 – 19, 2014, VIENNA, AUSTRIA

50th European Association for the Study of Diabetes Annual Meeting  
[www.easd.org](http://www.easd.org)

If you are interested in submitting classified advertising to *Endocrine News*, please contact Christine Whorton at [endocareers@endocrine.org](mailto:endocareers@endocrine.org) or 800-361-3906.

**PRESBYTERIAN HEALTHCARE SERVICES, Albuquerque, NM:**

Presbyterian Healthcare Services is seeking BE/BC Endocrinology trained physicians to join Presbyterian Medical Group and our well established Endocrinology providers. Our medical group employs more than 600 primary care and specialty providers and is the fastest growing employed physician group in New Mexico. Presbyterian Healthcare Services is a locally owned, not-for-profit organization based in Albuquerque. Our integrated healthcare system includes eight hospitals in seven New Mexico cities, a medical group, multispecialty clinics and a health plan (over 400,000 members). We have been proudly providing care to New Mexicans for 105 years. In addition to a guaranteed base salary we also offer a sign on bonus, incentive bonus, malpractice, relocation, house hunting trip, health, dental, vision, 403(b) w/contribution from PHS 457(b), short & long term disability, CME allowance, etc. Albuquerque thrives as New

Mexico's largest metropolitan center with a population of 700,000. Albuquerque has been listed as one of the best places to live in the United States by Newsweek, U.S. News & World Report, Money and Entrepreneur Magazines! Albuquerque is considered a destination city for most types of outdoor activities with 310 days of sunshine. Albuquerque is recognized as one of the most culturally diverse cities in the country. Its ethnic diversity is carried into its architecture, art, music, dance and cuisine. A truly diverse and multicultural city, Albuquerque offers you and your family a great variety of activities and entertainment including national theater productions, sporting events, golf courses ranked among the best in the country, the largest hot air balloon festival in the US, American Indian Cultural activities and much more. For more information, e-mail *Kelly Herrera at kherrera@phs.org* or call 1-505-923-5662. H1B Opportunity. Visit our website at [www.phs.org](http://www.phs.org) EOE

## Joe DiMaggio Children's Hospital Seeks Medical Director of Pediatric Endocrinology

**About the Opportunity:**

Joe DiMaggio Children's Hospital is seeking a medical leader to lead its dynamic pediatric endocrinology team. The desired candidate must be board-certified in pediatric endocrinology and should have pediatric endocrinology and medical leadership experience. The medical director will lead a successful team of 4 pediatric endocrinologists, 1 nurse practitioner, 2 certified diabetes educators and 1 registered dietitian. This team works collaboratively with our excellent in-house physician teams, including hospitalists, intensivists and neonatologists. Joe DiMaggio Children's Hospital also has the largest and most diverse group of pediatric specialists in the region. You will find a supportive clinical research environment with close interaction and staff support provided through the Office of Clinical Research, an experienced diabetes team with support for patients and families dealing with this chronic illness, and a dynamic general endocrinology practice with a diverse patient population.

**About Joe DiMaggio Children's Hospital:**

Joe DiMaggio Children's Hospital, a 204-bed facility, opened in 1992 and is located in Hollywood, Florida. This premier provider of tertiary-level pediatric care has a 64-bed Level II & III NICU, 22-bed PICU and 12-bed intermediate care unit. As South Florida's newest freestanding children's hospital, JDCH is redefining the pediatric healthcare experience. We combine cutting-edge excellence with a commitment to patient- and family-centered care. Thanks to exemplary medical expertise, advanced technology and exclusive pediatric programs, JDCH has earned the distinction of being the leading children's hospital in Broward and Palm Beach counties. JDCH is the only Level I Pediatric Trauma Center in South Broward County and is dedicated to the physical and emotional care of children. We're continuing to pioneer revolutionary programs that define the standard in pediatric care. To learn more, please visit [JDCH.com](http://JDCH.com).

**About South Florida:**

South Florida offers an urban/suburban lifestyle with an abundance of cultural and recreational amenities, miles of beautiful beaches, top-rated golf courses, museums and world-class dining. **Florida has no state income tax.**



Joe DiMaggio  Children's Hospital  
AT MEMORIAL  
1005 Joe DiMaggio Drive / Hollywood, Florida 33021

To learn more about this opportunity visit [memorialphysician.com](http://memorialphysician.com), or send your cv to [jdchdoctor@mhs.net](mailto:jdchdoctor@mhs.net)



## Endocrinologist Opportunities

**Geisinger Health System (GHS) is seeking Endocrinologists for two locations:**

- **Endocrinology at Geisinger Wyoming Valley Medical Center (GWV), Wilkes-Barre, Pa.**
- **The Endocrinology team at Geisinger-Patton Forrest, State College, Pa.**

### **About the Position at GWV**

- Join a team of 3 Endocrinologists, 2 Nurse Practitioners and 3 Certified Diabetes Educators, and is positioned for additional growth
- Work collaboratively with Geisinger's community practice network to enhance diabetes care, as well as to work with multiple subspecialties to enhance inpatient care
- Opportunities for clinical practice include serving as investigator on diabetes clinical trials, US-guided Thyroid Fine Needle Aspiration Biopsies, Continuous Glucose Sensors and Bone Density interpretation
- Engage in clinical mentoring and educational programs for medical students and family medicine residents on the GWV campus, as well as internal medicine residents on rotation at GWV

### **About the Position at Geisinger-Patton Forrest**

- Join a growing endocrinology department in a thriving, multi-specialty group practice, located in a progressive university town
- Provide 100% endocrinology subspecialty outpatient care and inpatient consultations
- Provide consultative care at Mt. Nittany Medical Center, State College, Pa., and Lewistown Hospital, Lewistown, Pa.

**Geisinger Health System** serves nearly 3 million people in Northeastern and Central Pennsylvania and has been nationally recognized for innovative practices and quality care. A mature electronic health record connects a comprehensive network of 5 hospitals, 43 community practice sites and more than 1,000 Geisinger primary and specialty care physicians.

**Discover for yourself why Geisinger has earned national attention as a visionary model of integrated healthcare. For more information, please visit [geisinger.org/careers](http://geisinger.org/careers) or contact: John W. Kennedy, MD, Endocrinology Department Director, Geisinger Health System c/o Kathy Kardisco, Department of Professional Staffing, at 800.845.7112 or [kkardisco@geisinger.edu](mailto:kkardisco@geisinger.edu).**

**GEISINGER**  
HEALTH SYSTEM

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# Discover

life changing work

IPSEN Bioscience, a global specialty-driven pharmaceutical company, seeks a highly experienced scientist to join its Endocrinology Research Department, located in their new facility in the heart of the Kendall Square biotechnology community in Cambridge, Massachusetts.

## Head, In Vitro Endocrinology Group Cambridge, MA

The mission of the Endocrinology Research Department is novel drug discovery, with a focus on peptide-based therapies targeting endocrine diseases with high unmet medical need. In this position, the successful candidate will oversee the molecular and cellular endocrinology functions of the department, including the development and validation of tools and methods to test the cellular responses and mechanisms of action of selected compounds; will supervise, lead and develop Ph.D. level scientists and technical staff; will contribute to internal drug discovery programs, including the proposal of new concepts and projects; will manage collaborative efforts with other internal departments, external academic groups and companies; and, will manage the outsourcing of routine activities to CROs.

A Ph.D. degree in Endocrinology with 10+ years of related research experience in the molecular and cellular aspects of endocrinology research is required. Applicants should have an expert working knowledge of endocrine principles and diseases (focus in neuroendocrinology a plus), and strong research experience in molecular/cellular techniques supported by a solid publication record. Working knowledge of tumor biology, as it applies to endocrine disease, is a plus. Previous supervisory experience is required. Prior experience with the drug discovery process is desirable. The successful candidate will report to the VP, Endocrinology Research, and will contribute to the development of global therapeutic strategies and department priorities. Exact title and compensation will be commensurate with experience. Applicants should submit a letter of interest with curriculum vitae at:

## IpsenEndoCareers.com

*Ipsen is an Equal Opportunity employer committed to a culturally diverse workforce. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, national origin, disability or protected veteran status, or any other characteristics protected by applicable law.*



# HORMONES AND CANCER

## CALL FOR NOMINATIONS AND APPLICATIONS FOR EDITOR-IN-CHIEF OF HORMONES AND CANCER

The Endocrine Society seeks candidates for the position of Editor-in-Chief of *Hormones and Cancer* for a two-year term beginning January 1, 2015. *Hormones and Cancer* is published six times per year by Springer Science+Business Media New York in cooperation with the Endocrine Society, and is a multidisciplinary translational journal, including basic scientific, epidemiological, pre-clinical and clinical research papers in the field of hormones and cancer.

### RESPONSIBILITIES

The Editor-in-Chief receives editorial and administrative support from Springer and the Endocrine Society's editorial office staff, as well as an honorarium. The Editor-in-Chief oversees the peer review process and content development, including the following:

- Selecting Associate Editors (2) and Editorial Board members (27)
- Providing direction for the journal and its content by 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 Nancy Rodnan, Senior Director of Publications for the Endocrine Society, at [nrodnan@endocrine.org](mailto:nrodnan@endocrine.org). Please submit your suggestions by July 31, 2014.

### APPLICATIONS

Applicants for the position 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 **August 29, 2014**, and should be e-mailed to Nancy Rodnan ([nrodnan@endocrine.org](mailto:nrodnan@endocrine.org)). Please call 202-971-3669 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 October 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 is overseen by its chair, Margaret Shupnik, PhD.

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

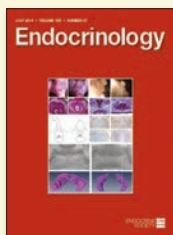


**Effects of Rosiglitazone vs Metformin on Circulating Osteoclast and Osteogenic Precursor Cells in Postmenopausal Women with Type 2 Diabetes Mellitus** • M.R. Rubin, J.S. Manavalan, S. Agarwal, D.J. McMahon, A. Nino, L.A. Fitzpatrick, and J.P. Bilezikian • *In postmenopausal women with T2D, circulating osteoclast precursor cells*

*increase with both RSG and MET, and increase further when switching from RSG to MET. Sub-populations of cells that may be involved in the osteogenic lineage pathway are also altered with RSG. Further work is necessary to elucidate how these changes may relate to fracture risk.*

**Bone Mineral Density in Young Women With Primary Ovarian Insufficiency: Results of a Three-Year Randomized Controlled Trial of Physiological Transdermal Estradiol and Testosterone Replacement** • Vaishali B. Popat, Karim A. Calis, Sophia N. Kalantaridou, Vien H. Vanderhoof, Deloris Koziol, James F. Troendle, James C. Reynolds, and Lawrence M. Nelson • *Long-term physiological transdermal estradiol replacement in combination with oral medroxyprogesterone acetate restores mean femoral neck BMD to normal in young women with spontaneous 46, XX primary ovarian insufficiency. However, the addition of physiological transdermal T replacement did not provide additional benefit.*

**Parathyroid Hormone-Related Peptide (PTHrP) Secretion by Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Clinical Features, Diagnosis, Management, and Follow-Up** • Kimberly Kamp, Richard A. Feelders, Roxanne C. S. van Adrichem, Yolanda B. de Rijke, Francien H. van Nederveen, Dik J. Kwekkeboom, and Wouter W. de Herder • *Hypersecretion of PTHrP by metastatic GEP-NETs is very rare and seems to be exclusively associated with metastatic pancreatic NETs. PTHrP production has major clinical impact because poorly controllable hypercalcemia is associated with increased morbidity and mortality. The most successful treatment options for PTHrP-producing GEP-NETs are SSAs and PRRT using radiolabeled SSAs. Isotonic saline and bisphosphonates can be considered as supportive therapies.*

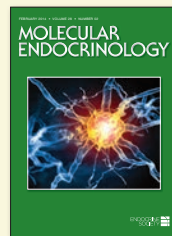


**Maternal Inheritance of an Inactive Type III Deiodinase Gene Allele Affects Mouse Pancreatic  $\beta$ -cells and Disrupts Glucose Homeostasis** • Mayrin C. Medina, Tatiana Foseca, Judith Molina, Alberto Fachado, Melany Castillo, Liping Dong, Renata Soares, Arturo Hernández, Alejandro Caicedo, and Antonio C. Bianco • *The authors conclude that Dio3 gene is*

*preferentially expressed from the maternal allele in pancreatic islets and that inactivation of this allele is sufficient to disrupt glucose homeostasis by reducing pancreatic islet area, insulin2 gene expression and glucose-stimulated insulin secretion.*

**Transgenerational Epigenetic Inheritance: Focus on Endocrine Disrupting Compounds** • Emilie F. Rissman and Mazhar Adli • *The goal of this article is to educate readers about the range of possible epigenetic mechanisms that exist and encourage researchers to think broadly and apply multiple genomic and epigenomic technologies to their work.*

**Estradiol Modulates Translocator Protein (TSPO) and Steroid Acute Regulatory Protein (StAR) via Protein Kinase A (PKA) signaling in Hypothalamic Astrocytes** • Claire Chen, John Kuo, Angela Wong, and Paul Micevych • *The experiments detailed in this paper completed the characterization of how estradiol action at the membrane leads to the augmentation of neuroprogesterone synthesis through increasing cAMP, activation of PKA and the phosphorylation of TSPO and StAR in hypothalamic astrocytes.*



**Naturally Occurring Mutants Inform Sex Hormone-Binding Globulin Structure and Function** • Tsung-Sheng Wu and Geoffrey L. Hammond • *The naturally occurring mutants described in this paper provide insight into SHBG structure and function, and defects in SHBG production or function need to be considered in the context of its utility as a biomarker of diseases.*

**Gut Microbiota: The Neglected Endocrine Organ** • Gerard Clarke, Roman M. Stilling, Paul J Kennedy, Catherine Stanton, John F. Cryan, and Timothy G. Dinan • *The authors conclude that it is tempting to speculate that therapeutic targeting of the gut microbiota may be useful in treating stress-related disorders and metabolic diseases.*

**Human Endometrial DNA Methylome Is Cycle-Dependent and Is Associated with Gene Expression Regulation** • Sahar Houshdaran, Zara Zelenko, Juan C. Irwin, and Linda C. Giudice • *Together, the data support that epigenetic mechanisms are involved in gene expression regulation in human endometrium in different hormonal milieus, adding endometrium to a small number of normal adult tissues exhibiting dynamic DNA methylation. The data also raise the possibility that interplay between steroid hormone and methylome dynamics regulate normal endometrial functions and, if abnormal, may result in endometrial dysfunction and associated disorders.*



REGISTER TODAY FOR THE BEST RATES

# ENDO2015

THE ENDOCRINE SOCIETY'S 97TH ANNUAL MEETING & EXPO



MARCH 5-8, 2015 (THURSDAY-SUNDAY)  
SAN DIEGO, CALIFORNIA

SAN DIEGO CONVENTION CENTER

BEGINNING IN 2015, ENDO, THE LARGEST GATHERING OF  
ENDOCRINE PRACTITIONERS AND RESEARCHERS, WILL TAKE PLACE IN THE SPRING.

## KEY ENDO 2015 DATES

**REGISTRATION OPENS**

JUNE 23, 2014

**ABSTRACT SUBMISSION**

SEPTEMBER 17 – NOVEMBER 12, 2014

**LATE-BREAKING ABSTRACT SUBMISSION**

DECEMBER 29, 2014 – JANUARY 12, 2015

[ENDO2015.ORG](http://ENDO2015.ORG)

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