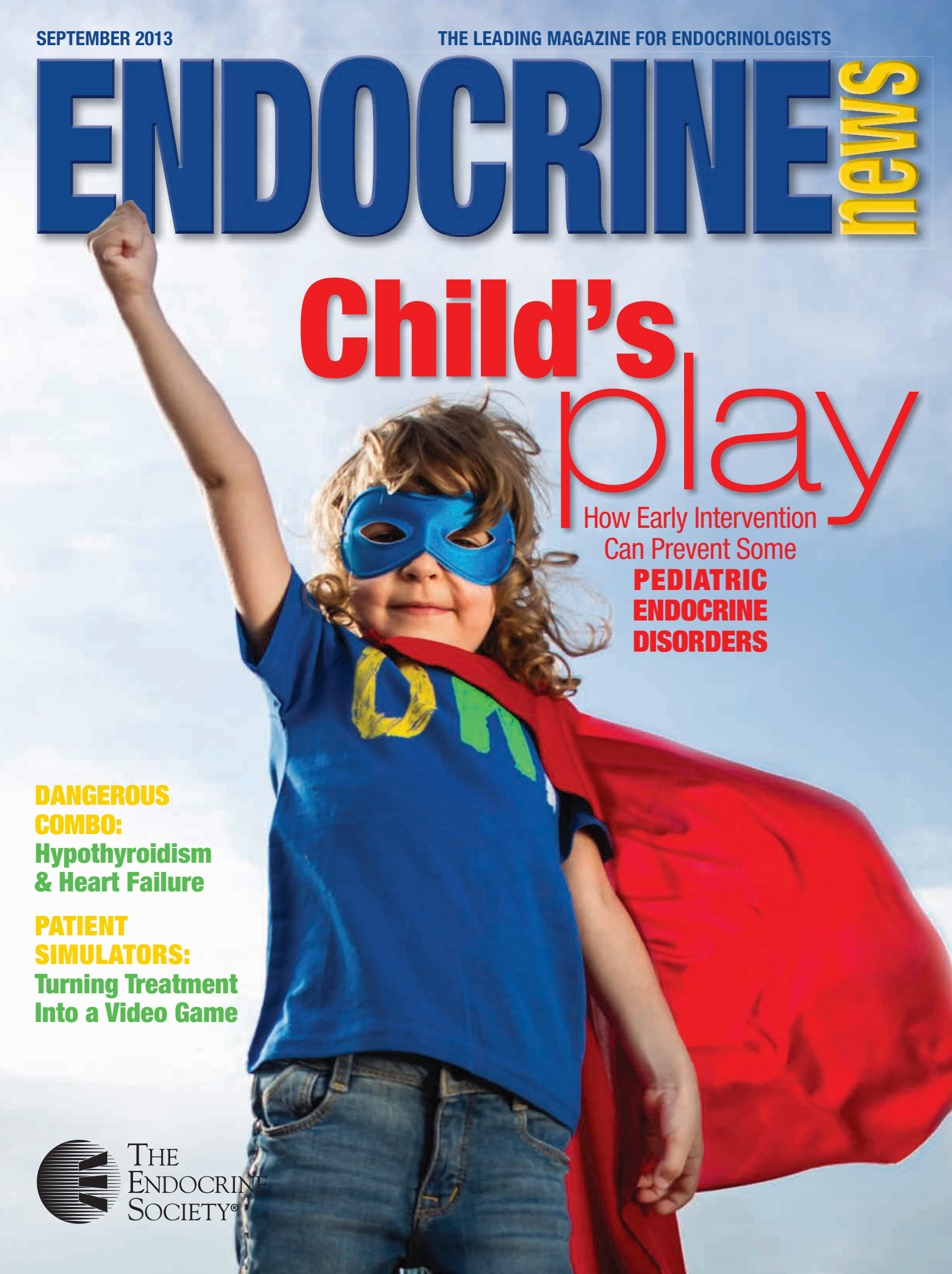
SEPTEMBER 2013

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINE news



Child's play

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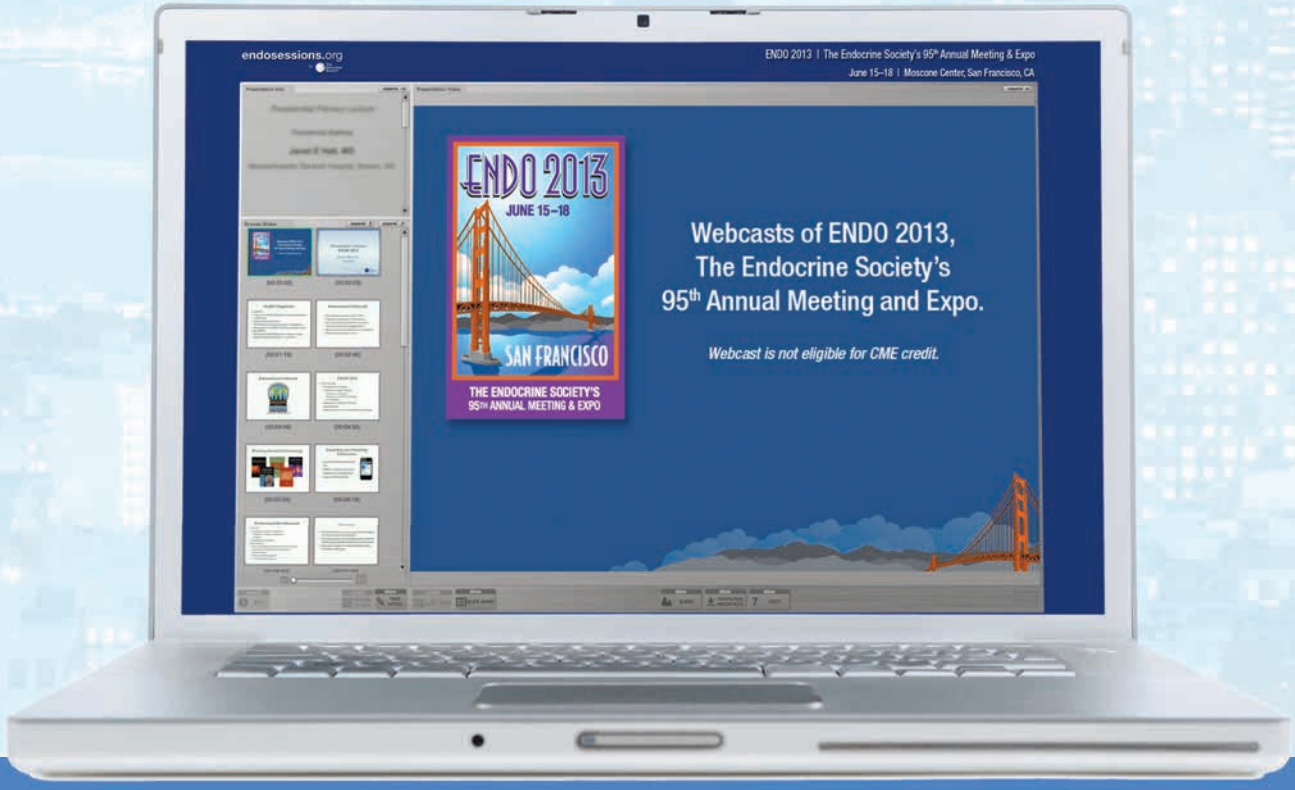

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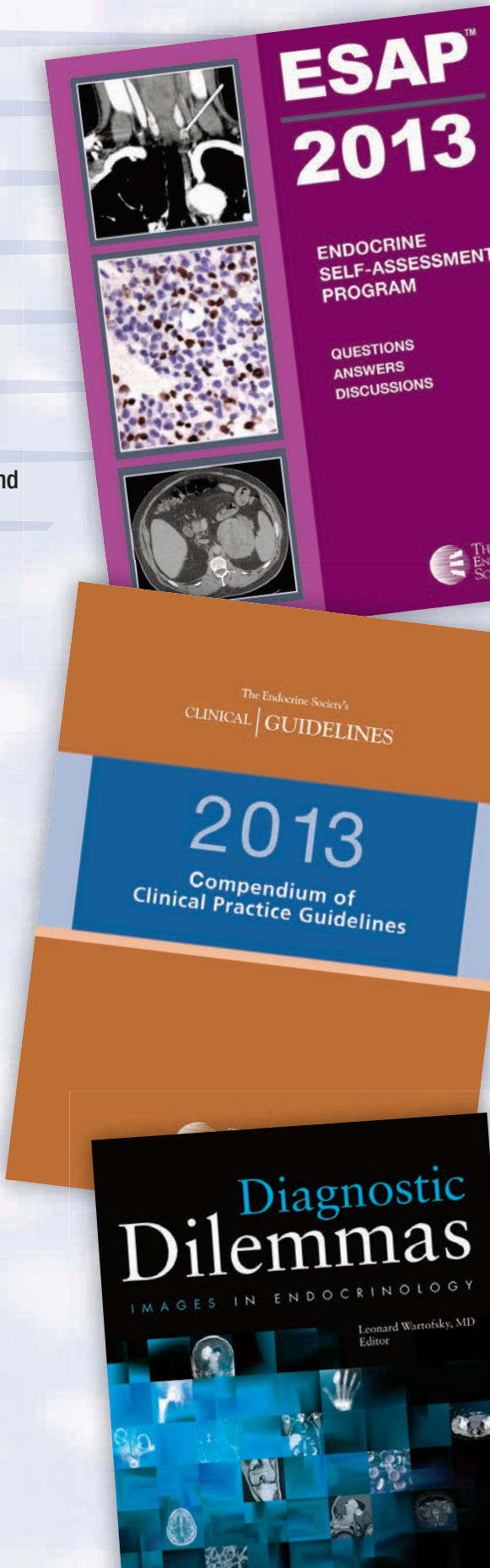

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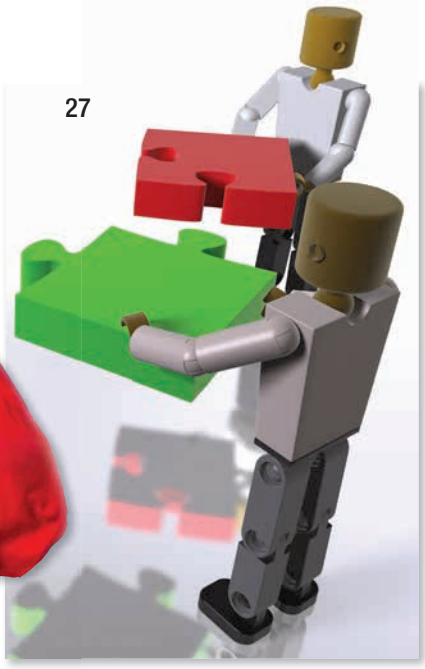

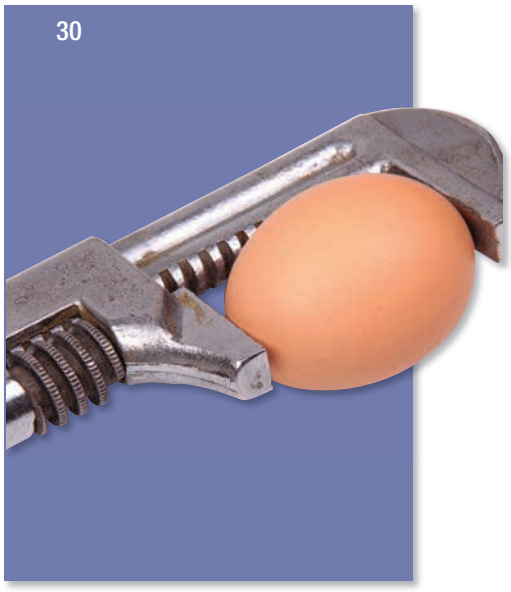

COVER Story

DEPARTMENTS

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ENDO 2013: Breaking Records & Spreading the Word

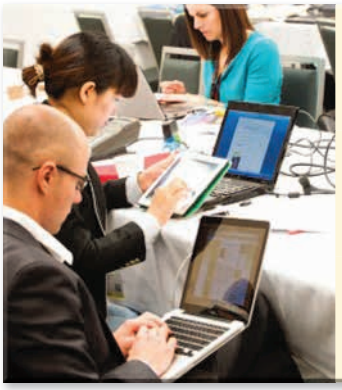
Teresa K. Woodruff, PhD

ENDO 2013 was a landmark meeting for the Society, achieving record attendance. I thoroughly enjoyed taking in the many sessions and symposia, meeting old friends and making new ones. There's really no other event like it, and we're not the only ones who think so. Reporters from around the world know that news will be made at **ENDO,** and they make it a priority to write about the wonderful science being presented. The Society's media relations program is one of our primary conduits to reach the public and promote the value of endocrinology to medicine and science. I'd like to share with you a few highlights regarding media coverage from this year's annual meeting.

Breaking ENDO Records

ENDO 2013: The 95th Annual Meeting & Expo garnered the largest amount of media coverage in the event's history. To date, **ENDO 2013** has generated more than 2,400 articles and reports highlighting the Society and its members' research.

Media outlets covering **ENDO 2013** included *The Boston Globe, Science, Self, WebMD, Huffington Post, Time, Men's Health, Prevention, Fox News,* and *U.S. News & World Report.*



Inside the ENDO '13 NEWS ROOM

"Let's all commit to engaging with the media and ensuring that reporters are accurately informed in order to craft stories that enhance public understanding of the work we do and why it matters."

News Conferences

More than 70 reporters (both on site and online) participated in five news conferences spotlighting some of the most compelling and newsworthy findings presented at the meeting on topics such as diabetes, obesity, endocrine-disrupting chemicals, and adolescent health. The meeting's global reach was evident as reporters from China, Argentina, France, and the United Kingdom were among those in attendance.

The news conferences, which were moderated by members of the Society's Advocacy and Public Outreach Core Committee (APOCC), can be viewed in their entirety online at ***www.endowebcasting.com***.

Hot Topics

The Annual Meeting Steering Committee and APOCC worked with Society staff to identify newsworthy presentations at **ENDO** that were suitable for media promotion. These presentations were highlighted for media in the form of news releases, news conferences, and the Research Summaries Book, a resource for reporters that showcases the most newsworthy research presented at **ENDO**.

Some of the most covered studies from this year's meeting include Dr. Peter Y. Liu's (Los Angeles Biomedical Research) research into the effect sleeping in on weekends has on insulin resistance; Dr. Elizabeth Thomas' (University of Colorado Denver) research on the impact skipping breakfast has on insulin resistance in obese women; and Dr. Gail Prins' (University of Illinois at Chicago) study showing exposure to low doses of BPA is linked to increased risk of prostate cancer in human stem cells.

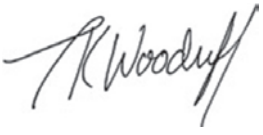
Educating the Public

While at **ENDO**, I was interviewed by Fox News about research from my lab at Northwestern University showing how the drug imatinib can help prevent chemotherapy-induced damage to ovarian eggs. While visiting the **ENDO** newsroom, I saw other presenters taking part in similar media interviews, and I was reminded how **ENDO** is a unique opportunity to help educate reporters and the public about the importance of the work being done in the field of endocrinology.

Today, news is more accessible than ever, and scientists and clinicians have to be aware of the need to inform the public in an authoritative manner. Our issues are complicated, and we've seen many stories in print and online that miss the mark. It is important to communicate endocrinology in a way that is understood by the public — it is in their best interest! Let's all commit to engaging with the media and ensuring that reporters are accurately informed in order to craft stories that enhance public understanding of the work we do and why it matters.

In this regard, **ENDO 2013** was a success, and I'm looking forward to next year's larger stage when **ENDO 2014** will be held jointly with the 16th International Congress of Endocrinology in my backyard here in Chicago. I hope to see you there.

If you have any questions or comments, feel free to contact me at ***president@endo-society.org***. EN



Teresa K. Woodruff, PhD
President, The Endocrine Society

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SEPTEMBER 2013

ENDOCRINE news

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Mark A. Newman, Managing Editor

While the September issue's cover story deals exclusively with pediatric endocrinology, two of this month's features are plumbed from deep within recent research studies from The Endocrine Society's own *Journal of Clinical Endocrinology & Metabolism (JCEM).* The research literature is where much of the latest advances are presented, so we felt a certain sense of obligation to herald that research here on our pages.

The cover story, "The Kids Aren't Alright" (page 22), discusses three very different studies from *JCEM.* Second-hand smoke, a lack of iodine, and a lack of exercise can — not surprisingly — have very adverse effects on the youngest of all endocrine patients, even before they are born. Kelly Horvath delves deep into these studies, all of which demonstrate the truth behind the old adage about a "pound of prevention" since "childhood morbidity can cause adult mortality, these problems are important public health priorities," according to Horvath.

A new way to treat diabetic patients is detailed in "Virtual Reality" (page 27) by Melissa Mapes, who discusses using patient simulator technology. Not only do these simulators give the patients a unique and fun way to manage their diabetes, but it also aids overworked physicians by effectively training students as well as colleagues.

Glenda Fauntleroy examines a study from the June *JCEM* that deals with hypothyroidism and cardiac patients, whose heart problems are easily exacerbated by thyroid disorders. According to the research findings, thyroid disorders and heart disease may also be a deadly combination. The study — detailed on page 30 — revealed that among patients with heart failure, even having mild hypothyroidism significantly increases the risk of death compared to patients with a normally functioning thyroid.

If you haven't had the chance to dive into recent issues of *JCEM,* we hope we've given you an idea of what's waiting for you when you do. Since research is such a vital component of the practice of endocrinology, *Endocrine News* wanted to use this issue to share this data with you. We hope it inspires you as much as it has inspired us.

If you have any story ideas or topics you'd like to see covered in *Endocrine News,* don't hesitate to drop me a line at ***mnewman@endocrine.org.*** I look forward to hearing from you. EN

Mark A. Newman
Managing Editor, Endocrine News

Correction:
In our July cover story on statins and their side effects, we included a list of statins that are available in the U.S., but we left pitavastatin off the list. We regret that omission.

PREGNANCY COMPLICATIONS
Associated With Thyroid Disease

Women with thyroid diseases are at a greater risk for developing complications during pregnancy, labor, or delivery, a recent study published in the *Journal of Clinical Endocrinology and Metabolism* shows.

Thyroid conditions affect up to 4% of all pregnancies, with primary hypothyroidism being the most prevalent disease, according to researchers led by Tuija Männistö, MD, PhD, at the National Institute of Health's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Using thyroid disease and outcome data derived from electronic medical records of 223,512 singleton pregnancies from the U.S. Consortium on Safe Labor, the scientists were able to make the connections between the thyroid conditions and obstetrical complications.

Women suffering from both hypothyroidism and hyperthyroidism had increased odds of complications such as preeclampsia, preterm birth, induction, and ICU admission, to name a few. The authors concluded that the results indicate that thyroid diseases are associated with significant increases in morbidity during pregnancy, but acknowledged that given the lack of information on treatment during pregnancy, they were unable to explore whether inadequate treatment was the cause or whether some of the risk is due to thyroid disease itself.

— Derek Bagley

PREORDERING SCHOOL LUNCH
Fosters Good Choices

Elementary school students who have the option of preordering their lunch are more likely to choose healthier options than those who order on lunch-lines, say researchers at Cornell University in a research letter appearing in the May 3 issue of *JAMA Pediatrics.*

Over a period of four weeks, 272 students in 14 classrooms were randomly assigned to different procedures. In the first week, all students preordered lunch as usual. In the third week, students in four classrooms discontinued preordering, but resumed preordering in the final week. In the fourth week, students in five classrooms discontinued preordering. Students in five classrooms continued to preorder throughout the entire study. After analyzing sales records and entrée choice, the researchers, led by Brian Wansink, found that 29% of the students chose healthier meals when they preordered, but only 15% chose healthier meals when they ordered on lunch lines. When purchasing lunch in the lunch line, 48% fewer students selected a healthy entrée and 21% additional students selected a less healthy entrée. In their letter, the researchers attribute this phenomenon to "hunger-based, spontaneous selection" as affected by the sight and smell of tasty, but ultimately less healthy, foods.

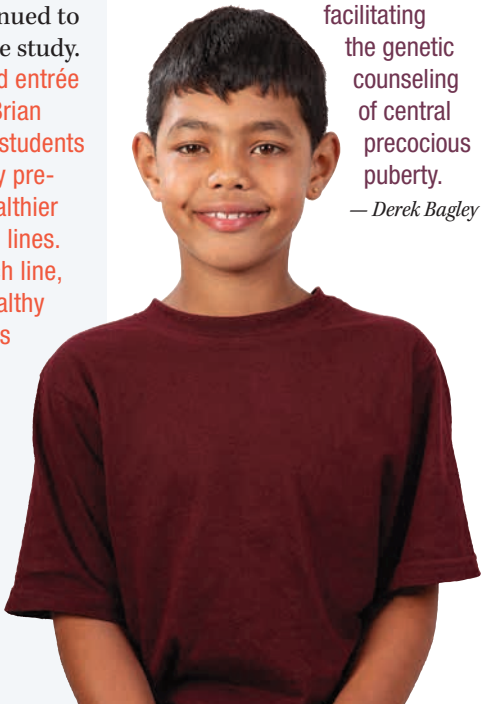
— Terri D'Arrigo

PRECOCIOUS PUBERTY
Caused by Gene Mutation

Central precocious puberty, which causes children to undergo puberty earlier than they normally would, can be caused by a gene that scientists have recently identified in familial cases, according to a study recently published in the *New England Journal of Medicine* and presented at The Endocrine Society's annual meeting in San Francisco.

Girls usually begin puberty between ages 8 and 13, and boys from 9 to 14, but researchers, led by Ursula B. Kaiser, MD, found that loss-of-function mutations of the gene *MKRN3* cause girls and boys to start puberty before ages 8 and 9, respectively. These mutations cause disease when inherited exclusively from the father and seem to release the brake that inhibits the secretion of the reproductive hormones in childhood. Early puberty can result in a number of problems, such as short stature, behavioral disorders during adolescence, and increased risk of cardiovascular disease. The scientists concluded that testing for the *MKRN3* mutation could be useful, leading to a better understanding of what controls puberty and facilitating the genetic counseling of central precocious puberty.

— Derek Bagley



AIR POLLUTION
and Atherosclerosis

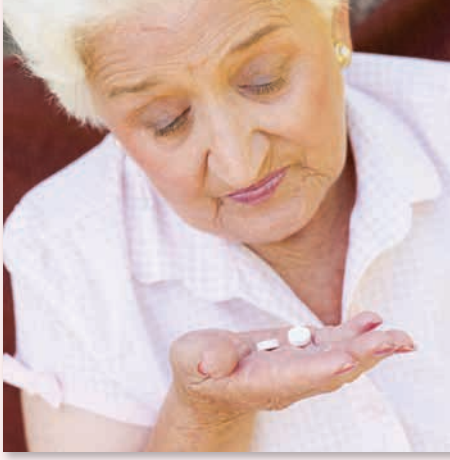
Air pollution from cars, power plants, and other sources of combustion may raise the risk of cardiovascular disease and stroke by promoting atherosclerosis, say researchers at the multicenter Multi-Ethnic Study of Atherosclerosis.

In a study published in the April issue of *PLOS Medicine,* a team led by the University of Michigan's Sara Adar, ScD, MHS, and the University of Washington's Joel Kaufman, MD, MPH, examined changes in the thickness of the right carotid arteries of 5,362 men and women older than 45 in six metropolitan areas — Baltimore, Chicago, Los Angeles, New York, St. Paul, and Winston-Salem — using neck ultrasounds collected roughly 2.5 years apart. In the year leading up to the first ultrasound and for the years between the first and second ultrasounds, the researchers used air samples collected outside the homes and in the communities of the study participants to determine local concentrations of fine-particulate air pollution — air pollution containing particles with a diameter of 1/30 the width of a human hair.

At follow-up, the researchers found that the walls of the participants' carotid arteries increased 14 micrometers per year on average, and that thickening progressed faster among participants who lived in areas with the highest levels of air pollution. In their conclusion, the researchers write that their results support the theory that fine-particulate air pollution may be associated with the progression of atherosclerosis.

— Terri D'Arrigo

TWO OSTEOPOROSIS DRUGS
Are Better Than One



Combining two osteoporosis drugs helps maintain bone density in postmenopausal women better than either drug alone, say researchers at Massachusetts General Hospital in Boston.

In a study appearing online in the May 15 issue of *The Lancet,* a team led by Benjamin Leder, MD, compared the effects of two injectable drugs, denosumab (Prolia) and teriparatide (Forteo), taken separately or together, in 94 post-menopausal women with osteoporosis. Denosumab inhibits osteoclasts, cells that remove bone tissue, and teriparatide stimulates osteoblasts, cells responsible for bone formation.

The team divided 94 study participants into three groups. One group received 60 mg of denosumab every six months, one group received 20 mcg of teriparatide daily, and one group received both treatments. The team measured the women's bone density at three months, six months, and the study's end, and found that women who received combined drug therapy experienced a 9.1% increase in bone density in their lumbar spines (lower backs), compared to a 6.2% increase among those who received teriparatide only, and a 5.5% increase among those who received only denosumab.

Although the researchers call for further study to assess reductions in fracture risk and explore the effects of different doses, they note that their findings suggest that combining these two drugs may be a useful option for women with osteoporosis.

— Terri D'Arrigo

FATTY LIVER and Incidence of Diabetes

Change in an individual's fatty liver status over time leads to "markedly variable" risks of incident diabetes, according to a recent Korean study published in the *Journal of Clinical Endocrinology and Metabolism*.

Non-alcoholic fatty liver disease (NAFLD) occurs often in obese people and is one of the most common chronic liver diseases in the world. Fatty liver is associated with metabolic syndrome and type 2 diabetes.

Scientists, led by Ki-Chul Sung, MD, PhD, of Sungkyunkwan University in South Korea, studied a Korean occupational cohort comprising 13,218 people with no diabetes at baseline. Fatty liver status was measured using an ultrasound at baseline and then again after a five-year follow-up. The assessments placed the fatty liver statuses in three categories: absent, mild, and moderate/severe.

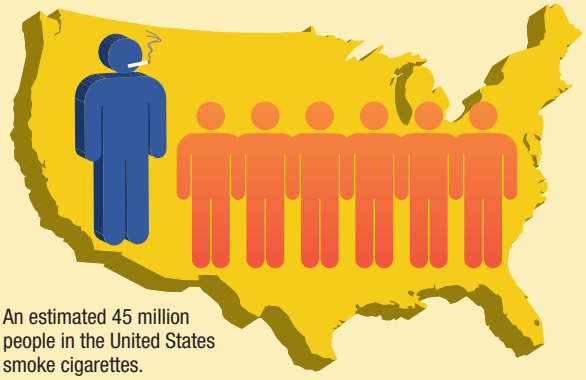
Over the course of five years, NAFLD resolved in 828 people, developed in 1,640, and progressed from mild to moderate or severe in 324. Out of the 828 whose fatty liver disappeared, 12 developed incident diabetes, suggesting that there is no correlation between resolution of fatty liver and risk of development of incident diabetes. In fact, after correcting for BMI, age, sex, physical activity, and other factors, the researchers noted, "In these individuals, there was no increase in risk of incident diabetes over that period, and risk of incident diabetes was similar to that observed in people who did not have fatty liver (at either baseline or follow-up examination)."

However, the subjects who developed new NAFLD at follow-up showed an increase in risk for incident diabetes, while patients whose fatty liver progressed from mild to moderate or severe exhibited a "marked" increase in risk for incident diabetes, most likely due to "changes in visceral adiposity, lifestyle (physical activity, alcohol, smoking), insulin sensitivity, or lipids," or even a liver-specific effect such as the secretion of inflammatory cytokines.

The scientists concluded, "With the caveat that this study design cannot address causal relationships, these data strongly suggest that NAFLD severity is associated with a greater risk of diabetes, and attenuation of fatty liver status decreases risk of developing diabetes."

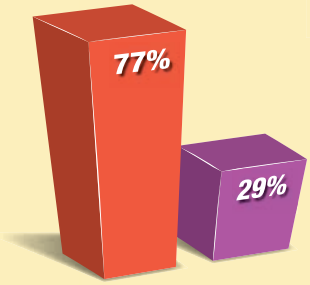
— Derek Bagley

Fast FACTS About Pediatric Endocrine Disorders

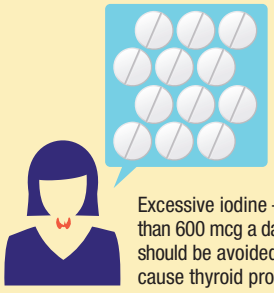


An estimated 45 million people in the United States smoke cigarettes.

Physical activity tends to decline as children and adolescents age. 77% of children aged 9–13 reported participating in physical activity during the previous 7 days. Only 29% of high school students participated in physical activity on each of the 7 days before the study.



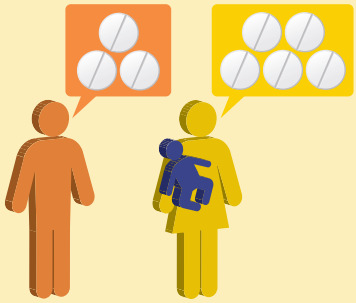
Common sources of iodine include cheese, cow's milk, eggs, yogurt, ice cream, iodized table salt, saltwater fish, and soy sauce.



Excessive iodine — more than 600 mcg a day — should be avoided, as it can cause thyroid problems.

Regular physical activity builds and maintains healthy bones and muscles, reduces depression and anxiety, and improves academic performance.

Adults should consume 150 mcg of iodine a day, while pregnant and breastfeeding women should get 250 mcg a day.

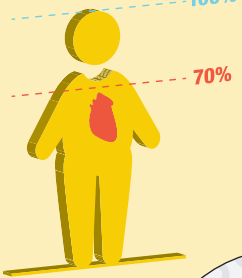


Obese adolescents are immediately at higher risk for a host of diseases and disorders, from diabetes to cardiovascular disease to bone and joint problems.

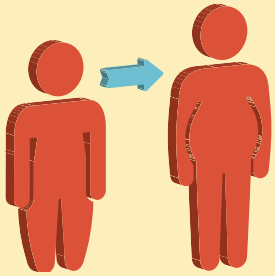
Toddlers and preschoolers should have TV exposure limited to less than two hours a day, and infants should have no TV exposure at all.

Despite advances in tobacco control, millions of Americans are still exposed to secondhand smoke on a daily basis, whether at home or in the workplace.

A 2007 study showed that 70% of obese children aged 5–17 were at risk for cardiovascular disease.



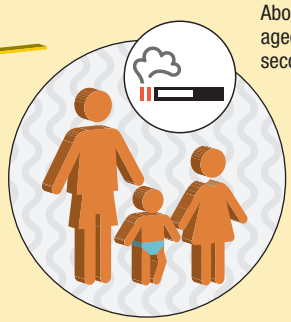
Preschool children should make time for physical activities like running or dancing every day.

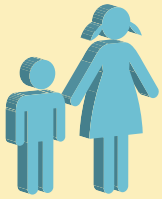


Obese adolescents are far more likely to develop into obese adults, which means they are at much higher risk for type 2 diabetes, heart disease, stroke, and several different types of cancer.

Young people ages 6–17 should participate in physical activity for at least an hour every day.

About 60% of U.S. children aged 3–11 are exposed to secondhand smoke.





Sources: CDC, *The British Dietetic Association, American Thyroid Association, World Health Organization, American Academy of Pediatrics, US Department of Health and Human Services, American Cancer Society*

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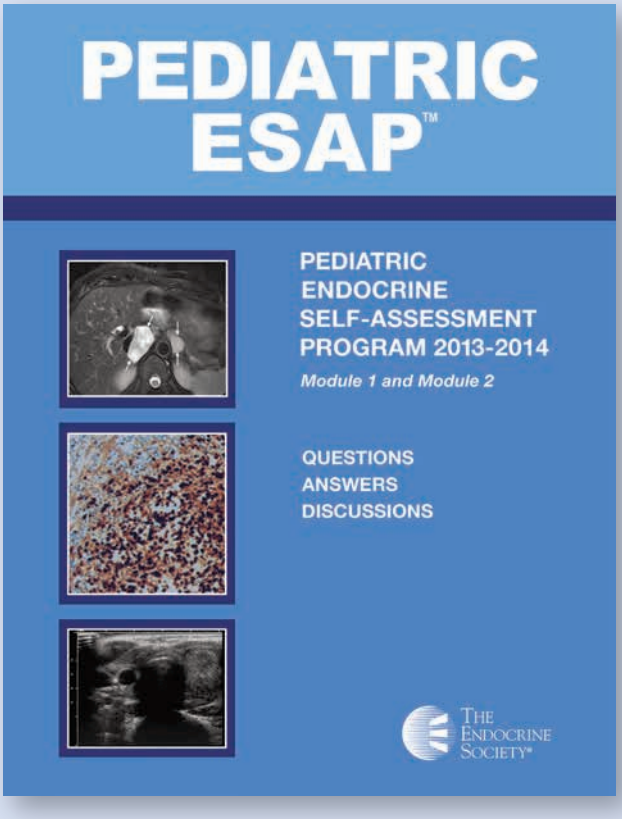

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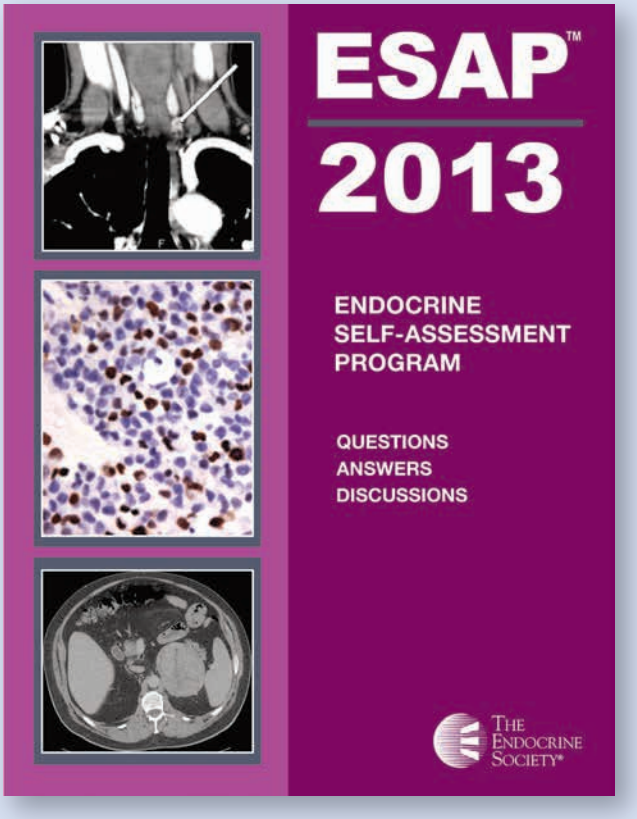

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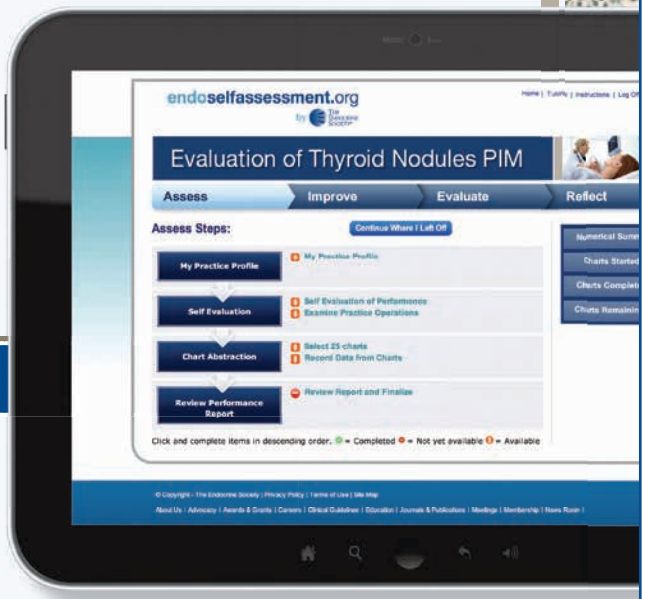

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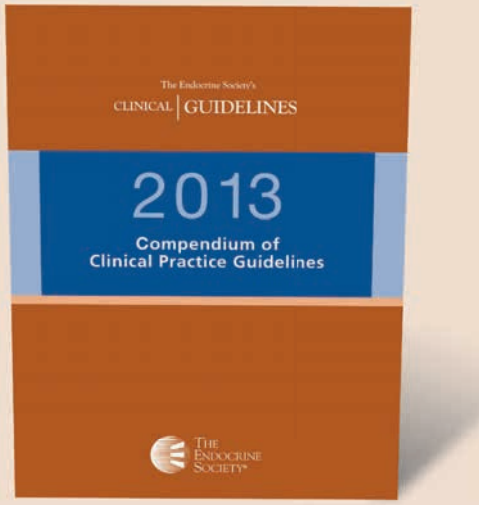

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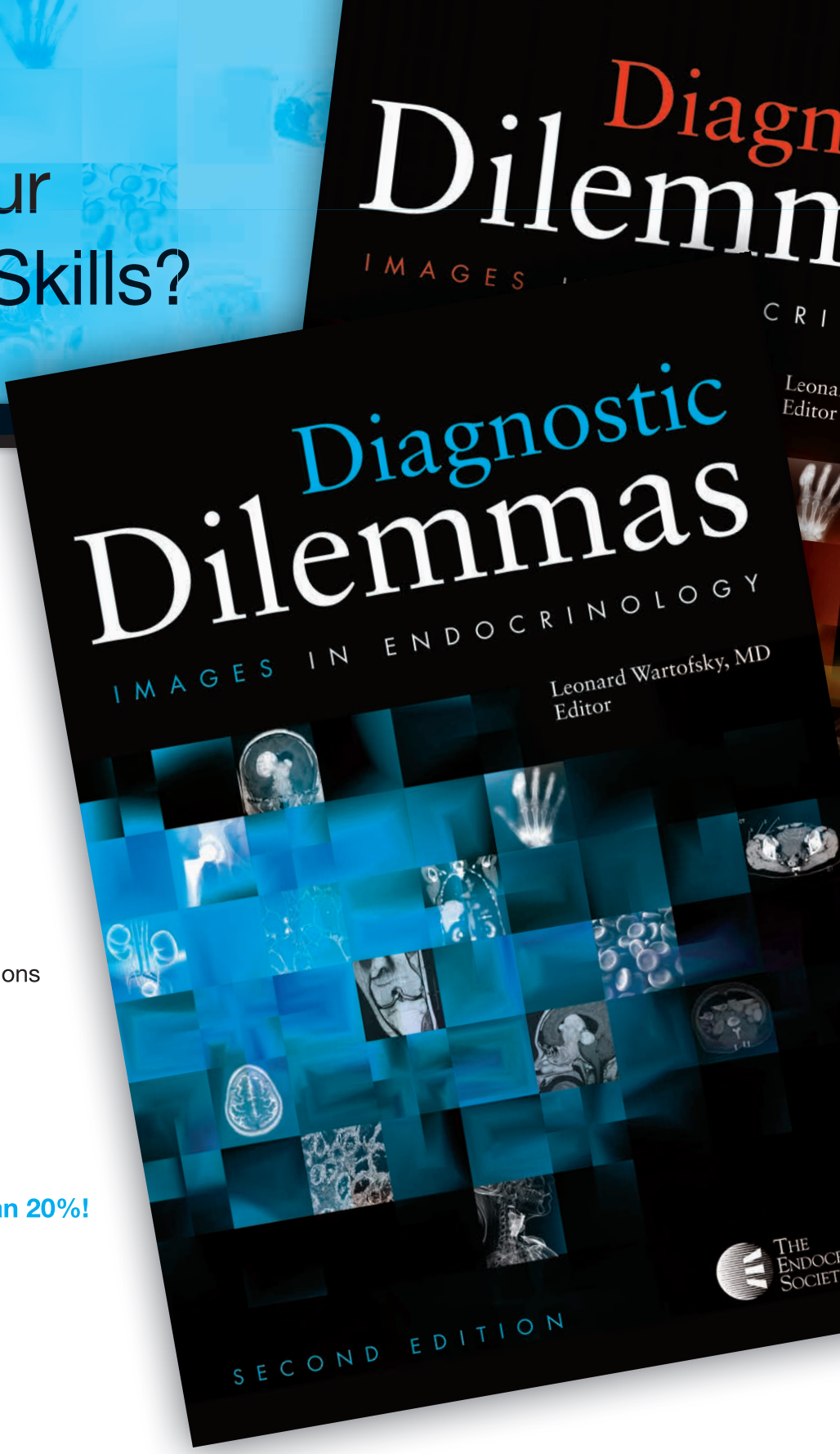

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The Kids Aren't ALRIGHT

By Kelly Horvath

From too little iodine and not enough exercise to too much secondhand smoke, three very different pediatric endocrinology studies indicate the importance of early intervention…sometimes even prenatally.

AT-A-GLANCE:

- Even mild maternal iodine deficiency in pregnancy causes cognitive impairment in children, but this adverse effect is completely preventable with daily iodine supplementation.
- Female children exposed to secondhand smoke in the home are more susceptible to cardiovascular disease due to reduced levels of good cholesterol, but treating this risk factor early (i.e., eliminating secondhand smoke) staves off the detrimental effects.
- Children with low levels of physical activity produce more of the stress hormone cortisol, which can cause depression and a host of other health problems, but increasing the amount of exercise to 60 minutes daily decreases cortisol production.

A guiding maxim among endocrinologists is that pediatric medicine is altogether different from adult medicine. However, it's also true that pre-adult health has direct consequences during adulthood. Three new, very different studies on children published recently in The Endocrine Society's *Journal of Clinical Endocrinology & Metabolism (JCEM)* demonstrate how critical childhood health is, because early insults can cause lifelong impairment. Some pediatric nutritional deficiencies, toxic exposures, and even lifestyle habits are the culprits of some of the most serious adult conditions. As childhood morbidity can cause adult mortality, these problems are important public health priorities.

Iodine Deficiency

Optimal iodine nutrition in pregnant women is essential for full fetal development. Congenital hypothyroidism due to maternal iodine deficiency is the most common preventable cause of intellectual disability worldwide. Some estimates put as many as 2 billion people (~40% of the global population, particularly in developing countries and mountainous and inland areas remote from iodine-containing marine life) at risk for iodine deficiency. A new study published in the May issue of *JCEM* preliminarily shows that even mild iodine deficiency (defined as a maternal urinary concentration less than 150 µg/L) during pregnancy might be associated with cognitive impairment. Initiatives to reduce salt intake, vegan diets, and lack of information (particularly in low socioeconomic status [SES] populations) about iodine as an essential nutrient are contributing to mild iodine deficiency also in the developed world.

Kristen L. Hynes, PhD, of the Menzies Research Institute at the University of Tasmania in Australia and her team of scientists found not only that even mild deficiency during pregnancy can harm the baby's neurological development but also that children experience the adverse effects of insufficient iodine for years after birth, as evidenced by poorer literacy test scores. Unfortunately, providing iodine after birth did not mitigate the gestational insufficiency, as scientists formerly thought, heightening this public health problem. "Although the participants' diet was fortified with iodine during childhood, later supplementation was not enough to reverse the impact of the deficiency during the mother's pregnancy," says Hynes.

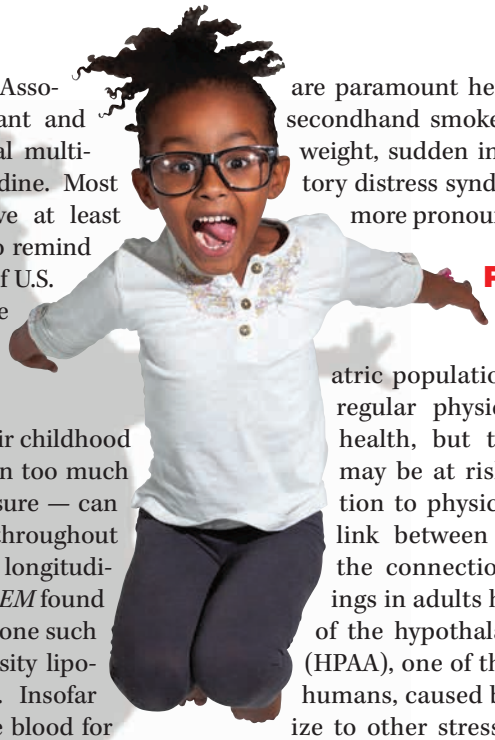
Her team reviewed national and state standardized test scores of the Gestational Iodine Cohort, 228 Tasmanian children born between 1999 and 2001, when the Tasmanian population as a whole experienced iodine deficiency until bread manufacturers began fortifying bread with iodized salt in late 2001. At age nine years, the study participants born to mothers with gestational iodine deficiency had 5.7% lower overall literacy skills, 7.6% lower grammar skills, and 10.0% lower spelling skills than those who did not experience gestational iodine deficiency. Because the deficit in spelling was so pronounced, whereas no deficit was found in math performance, Hynes and colleagues suggest that auditory pathway development and, consequently, auditory working memory are most affected by inadequate iodine.

"Fortunately, iodine deficiency during pregnancy and the resulting neurological impact is preventable," Hynes says. "Pregnant women should follow public health guidelines and take daily dietary supplements containing iodine." In the U.S., the Institute of Medicine puts the current recommended dietary allowance for iodine at 220 µg and 290 µg daily for pregnant and breastfeeding women, respectively (a teaspoon of iodized salt contains ~400 µg iodine). The World Health Organization recommendation is comparable at 250 µg daily for both pregnant and lactating women. Furthermore, says Hynes, "public health supplementation programs also can play a key role in monitoring how much iodine the population is receiving and acting to ensure at-risk groups receive enough iodine in the diet."

"Fortunately, iodine deficiency during pregnancy and the resulting neurological impact is preventable. **Pregnant women should follow public health guidelines and take daily dietary supplements containing iodine."**

— Kristen L. Hynes, PhD, Menzies Research Institute at the University of Tasmania, Australia

Accordingly, the American Thyroid Association recommends that all pregnant and breastfeeding women take a prenatal multivitamin daily containing 150 µg iodine. Most iodine-containing multivitamins have at least 150 µg of iodine, but it's important to remind patients that about half of the types of U.S. multivitamins do not contain iodine and to choose carefully.



Where There's Smoke ...

Just as a lack of a substance can impair childhood health, the opposite is also true when too much of a substance — even indirect exposure — can create adverse effects that persist throughout the lifespan. A large population-based longitudinal study also published in the May *JCEM* found that long-term secondhand smoke is one such substance, interfering with high-density lipoprotein cholesterol (HDL-C) levels. Insofar as HDL-C clears cholesterol from the blood for breakdown by the liver, thereby, preventing the atherosclerosis that results from cholesterol accumulation, it is an important endogenous heart disease combatant.

Chi Le-Ha, MD, of the University of Western Australia in Perth, led a team of researchers to study smoking practices in the homes of 816 adolescents born between 1989 and 1992, from the time their mothers were pregnant to the time the participants were 17 years old, when the researchers measured their HDL-C levels via blood sample. Of the cohort, 48% were exposed to secondhand smoke in utero and/or in the home. Girls exposed to passive smoking showed significantly lower levels of circulating HDL-C compared to unexposed girls, a relationship not replicated in boys.

Thus, girls may be more vulnerable to the detrimental effect of secondhand smoke exposure.

He-La says these findings are very important in the context of preventing heart disease, the leading cause of death in women in the Western world. "Both low levels of HDL-cholesterol and cigarette smoking — active and passive — are major risk factors of cardiovascular disease in adults. We have learned that atherosclerosis begins in childhood, that the lipids are expressed in childhood, and that they track from childhood to adulthood. Hence, starting treatment of risk factors early in life is essential to prevention of heart disease later."

Although smoking in public has largely been eradicated, smokers may consider the home a safe smoking haven. Public health efforts to educate smokers on the lifelong adverse effects of passive smoke on their children — especially girls — are paramount here, adds Le-Ha. Infant exposure to secondhand smoke is also associated with low birth weight, sudden infant death syndrome, and respiratory distress syndrome. The earlier the exposure, the more pronounced the negative impact may be.

Physical Activity

Treating lifestyle risk factors early is also important in the pediatric population. We know that children require regular physical activity for optimal physical health, but those who aren't getting enough may be at risk for mental impairment in addition to physical. Though many studies report a link between mental and physical well-being, the connection is not well understood. "Findings in adults have suggested that the adaptation of the hypothalamic-pituitary-adrenocortical axis (HPAA), one of the main stress response systems in humans, caused by physical exercise might generalize to other stressors as well, such as psychosocial ones," says Silja Martikainen, MA, of the University of Helsinki, Finland, the lead author of a recent paper on the effects of exercise on stress in children that was published in the April issue of *JCEM.*

In their cross-sectional study, the researchers administered the Trier Social Stress Test for Children to 258 Finnish eight-year-olds and then measured their salivary cortisol levels. They report little or no increases in stress hormone levels in those with high levels of activity measured by wrist accelerometers, compared to those with a low level of physical activity, even though diurnal salivary cortisol profiles were similar in both groups.

Thus, the highly active children had lower HPAA reactivity to stress, suggesting that exercise promotes mental health by regulating the stress hormone response to psychosocial stressors. Alternatively, the findings could suggest that a sedentary lifestyle itself causes susceptibility to psychosocial stress, as a result of higher HPAA reactivity. "As these finding are from a cross-sectional study, the causality of the effect cannot be identified," says Martikainen. "These results call for prospective controlled studies, such as interven-

"We have learned that atherosclerosis begins in childhood, that the lipids are expressed in childhood, and that they track from childhood to adulthood. **Hence, starting treatment of risk factors early in life is essential to prevention of heart disease later."**

— Chi Le-Ha, MD, University of Western Australia, Perth

With recent pediatric studies demonstrating time and again that environmental health insults in childhood have ramifications through adulthood, the impact of such insults cannot be overstated.

PERPLEXING CONGENITAL HYPOTHYROIDISM INCIDENT IN A NEWBORN: A Case Study From Pediatric ESAP™

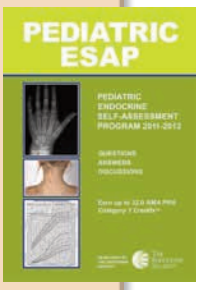
A nine-month-old female infant has congenital hypothyroidism that was initially detected through the state newborn program. On day one of life, her total T^4 concentration (on blood spot analysis) was 5.0 µg/dL (<10th percentile), and her thyroid stimulating hormone (TSH) concentration was 738 mIU/L. On day eight of life, her serum-free T^4 concentration was 0.61 ng/dL (normal range at eight days = 0.9-2.3 ng/dL), and her TSH concentration was 578 mIU/L. She was prescribed levothyroxine, 37.5 mcg daily (12 mcg/kg per day).

Monitoring of thyroid function and levothyroxine dosing shows the following:

AGE	FREE T^4, ng/dL (REFERENCE RANGE FOR AGE: 0.6-1.50 ng/dL)	TSH, mIU/L (0.34-5.60 mIU/L)	LEVOTHYROXINE DOSAGE, mcg DAILY (→ = dosage change)
1 month	1.40	16.8	37.5
3 months	1.24	12.3	37.5 → 50
5 months	1.50	10.5	50
7 months	1.70	12.2	50 → 62.5
9 months	1.95	10.1	62.5

Growth and development have been normal. After the dosage increase at seven months, her mother noted some fussiness and difficulty sleeping.

QUESTION



The Pediatric Endocrine Self-Assessment Program (Pediatric ESAP™) is a self-study curriculum specifically designed for endocrinologists seeking initial certification or recertification in pediatric endocrinology, program directors interested in a training instrument, and clinicians seeking a self-assessment and a broad review of pediatric endocrinology. *Pediatric ESAP* is in both print and online formats with 100 multiple-choice questions in all areas of pediatric endocrinology, diabetes, growth, and metabolism. There is extensive discussion of each correct answer and references. *Pediatric ESAP* is updated biennially with new questions, and now available is the new *Pediatric ESAP 2013–2014*. Learn more at ***www.endoselfassessment.org.***

Which one of the following is the best explanation for these data?

A Pharmacy switching thyroid preparations
B Poor parental adherence to daily dosing regimen
C Mixing levothyroxine pill with soy protein formula
D Pituitary-thyroid hormone resistance from altered feedback axis
E Laboratory artifact due to heterophile TSH antibody

answer on page 26

tion studies, to further investigate whether physically active lifestyle or physical exercise could alleviate hormonal responses to psychosocial stress," she adds.

Given that sustained cortisol exposure disrupts many body systems, leading to everything from heart disease to obesity to depression, the benefits of regulation strategies are clear. Demographics show that low SES kids have the highest inactivity rates. If exercise is the body's built-in regulatory system, funding to promote exercise programs for kids age two years and older is needed. The American Heart Association recommends at least 60 minutes of enjoyable, moderate-intensity physical activities daily that are developmentally appropriate and varied. Inactivity begets inactivity; the earlier interventions can happen, the better.

With recent pediatric studies demonstrating time and again that environmental health insults in childhood have ramifications through adulthood, the impact of such insults cannot be overstated. Public health efforts will be critical in each of these areas (i.e., iodine supplementation, secondhand smoke avoidance, and adequate physical activity) to educate high-risk groups, and physicians are important public health stakeholders to help disseminate that information. The pediatric care opportunity window cannot be squandered — the burden of enjoying a healthy adulthood seems to fall largely on health care in childhood because many negative effects are simply irreversible, even when the environmental condition is reversed. EN

— Horvath is a freelance writer in Baltimore and a regular contributor to Endocrine News.

OnPOINT from The Endocrine Society

The Endocrine Society has a Clinical Practice Guideline that deals specifically with pediatric endocrinology: *Prevention and Treatment of Pediatric Obesity* (2008); and a *Position Statement on Pediatric Obesity* (2011) at ***www.endocrine.org.*** There are also a series of fact sheets published by the Hormone Health Network accessed at: ***www.hormone.org***.

PERPLEXING CONGENITAL HYPOTHYROIDISM INCIDENT IN A NEWBORN: A Case Study From Pediatric ESAP™

ANSWER

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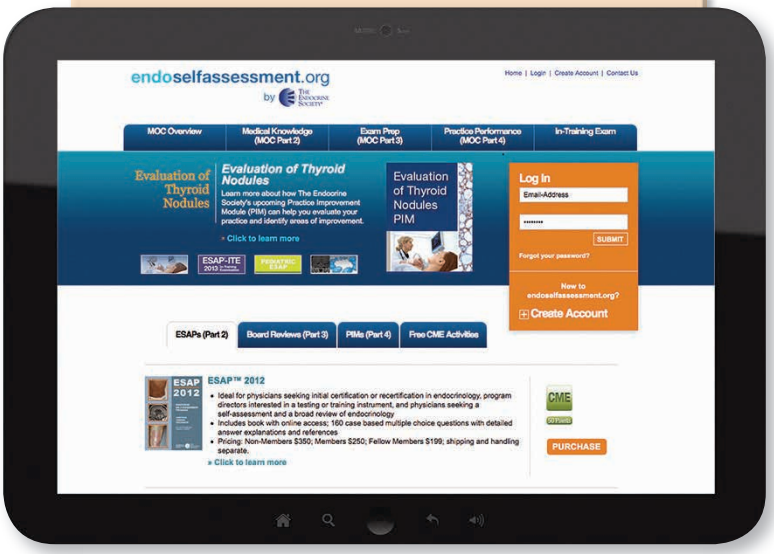


question on page 25

The answer is: D

This infant with congenital hypothyroidism manifests persistent serum TSH elevation despite serum free T^4 levels above the upper reference range and increasing levothyroxine dosing. After the increase in the levothyroxine dosage at five months, testing at seven and nine months of age show a free T^4 concentration above the reference range (note: the free T^4 reference range for age can vary significantly with assay methods; it is important for clinicians to compare patient results with the reference range established for the specific assay used for their patient). In addition, the patient's mother notes fussiness and difficulty sleeping, clinical features consistent with hyperthyroxinemia.

The best explanation for this set of laboratory data and clinical features is pituitary-thyroid hormone resistance from alteration of the negative feedback axis (Answer D). The hallmark of this condition is persistent elevation of serum TSH levels despite the prevailing serum free T^4 concentration. Pituitary-thyroid hormone resistance is relatively common in infants with congenital hypothyroidism. One study reported a prevalence of 43% in infants younger than one year, decreasing to 10% in older children. These findings appear to result from an abnormal set-point for T^4 control of TSH secretion associated with in utero hypothyroidism. It seems to improve with age, as noted by the prevalence numbers quoted above. Increasing the levothyroxine dosage in an attempt to suppress the serum TSH into the reference range often results in elevation of serum total T^4 or free T^4 above the reference range, with clinical features of hyperthyroxinemia, as was the case in this patient. Long-term overtreatment carries the risk of potential adverse effects.

There are several brands of thyroid hormone and several forms of generic levothyroxine. Because the actual dose may vary slightly between the brand name and generic levothyroxine, studies show that switching preparations (Answer A) may result in a higher (or lower) serum TSH level. However, if this was the explanation of the TSH elevation in this case, one would expect the serum free T^4 level to fall, not rise. Parental nonadherence to the treatment regimen (Answer B) also can affect serum thyroid function tests. If several doses have been missed and then quickly made up, for example, just before a blood test to check thyroid function, the serum free T^4 may rise quickly into the normal range, but TSH may take a few weeks to fall into the normal range. However, most such infants will have experienced normalization of serum TSH levels, followed by a rise with missed doses. In addition, test results in this infant show a steady rise in the serum free T^4 level as the dosage increases, evidence in favor of good regimen adherence. Thus, Answer B is unlikely to be correct. Soy protein binds levothyroxine and interferes with absorption. Mixing the pill with soy protein (Answer C) could lead to TSH elevation, but the serum free T^4 level would be appropriately low. Heterophile antibodies, for example "human antimouse antibodies," can produce erroneously high TSH results in some assays. Such antibodies present in early infancy would probably be of maternal origin, so their effect would be expected to disappear by four to six months of age. Thus, although the TSH elevation in this set of thyroid function test results could be explained by heterophile antibodies (Answer E), it is a less likely explanation than altered negative feedback. EN

VIRTUAL REALITY

Patient simulators make diabetes education more like a game and less like treatment.

By Melissa Mapes

Imagine a patient walks into your office with type 2 diabetes mellitus and low motivation for management. He is a 50-year-old white male who suffers from depression and has a body mass index (BMI) of 30. What is your first step?

Ask any large group of providers, and one may receive a smorgasbord of answers. The next move in such a scenario can vary due to philosophy or simply a different sequence of care, yet some treatment choices are inevitably more effective than others. Unlike a broken bone or an infection, there are few, if any, universal fixes. Each patient brings a different set of variables to the table. To reduce any deficits of care that a clinician may have, a new generation of patient simulators has emerged to hone the modus operandi for patients with diabetes.

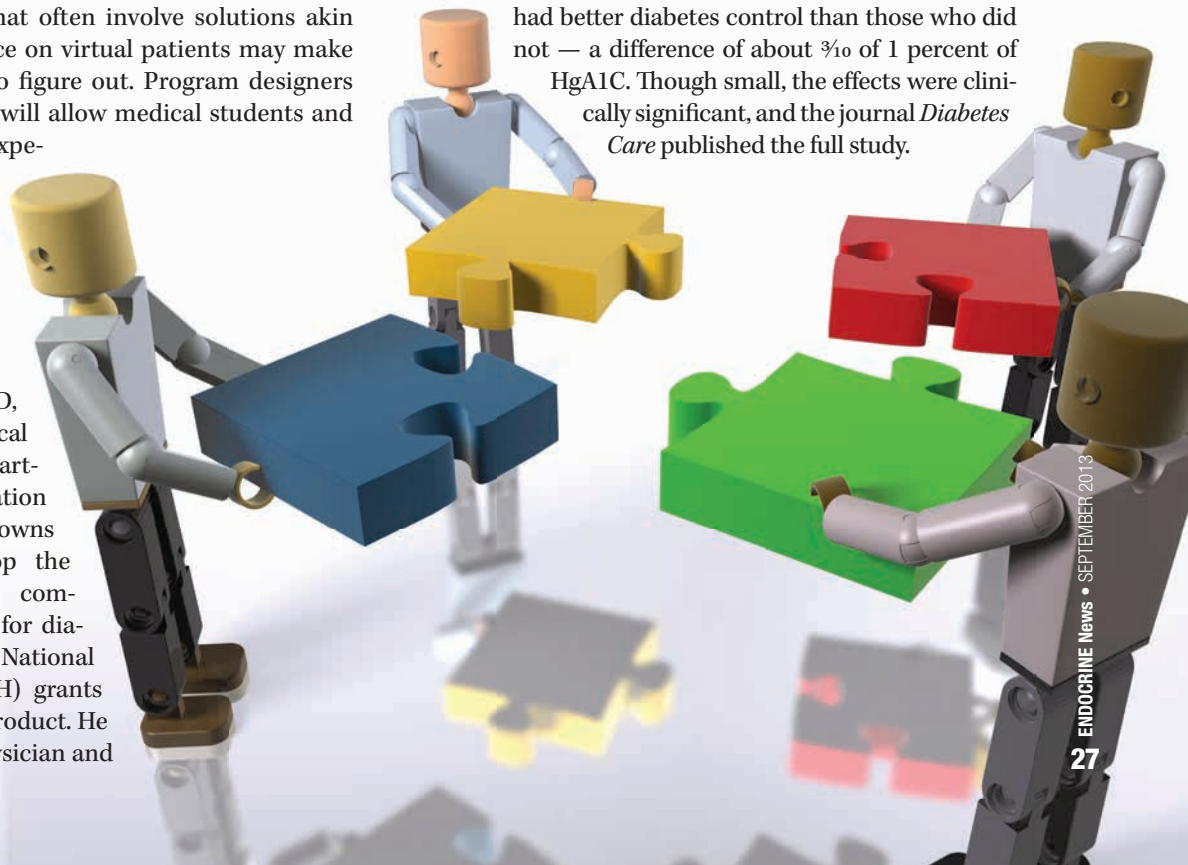
Software programs such as SiMCare Diabetes and the American Diabetes Association (ADA) Simulation Case Program take metadata about patient treatment plans and outcomes and distill them into a user interface almost like a video game that allows practitioners to run through unique patient cases. Because endocrine experts face complex diseases that often involve solutions akin to a Rubik's cube, practice on virtual patients may make treatment plans easier to figure out. Program designers hope that their software will allow medical students and clinicians to gain the experience of hundreds of patient interactions and outcomes in a risk-free virtual environment.

Patterns of Failure

Patrick J. O'Connor, MD, MPH, the senior clinical investigator at HealthPartners Institute for Education and Research, which owns SiMCare, helped develop the original version of the company's patient simulator for diabetes with support from National Institutes of Health (NIH) grants before patenting it as a product. He is also a primary care physician and chronic disease epidemiologist. He says that the eight or nine main factors that a physician must consider for each case of diabetes often create room for error. "We mapped the decision space, and we found that doctors have many different patterns of failure," he says.

He and his colleagues profiled providers across 22 domains of diabetes care, from depression to drug prescriptions, in a study of the simulated learning program's effectiveness. A library of 600 learning cases were compiled, and they then assigned about a dozen to each provider that best matched their weak points. Physicians had six months of simulated time to reach desired outcomes, receiving performance feedback along the way.

The entire process took about three hours per doctor, and they were asked to keep trying at each learning case until attaining treatment goals. The results of the participating physicians' real-life patients were compared to a control group of patients treated by providers that did not use the simulated patient program. Over the next year and a half, the patients treated by doctors who used the software had better diabetes control than those who did not — a difference of about 3/10 of 1 percent of HgA1C. Though small, the effects were clinically significant, and the journal *Diabetes Care* published the full study.



AT-A-GLANCE:

- Because endocrine experts face complex diseases that often involve solutions akin to a Rubik's cube, practice on virtual patients may make treatment plans easier to figure out.
- Such technology helps solve another growing problem: the shortage of expert physicians to train students and colleagues.
- Every single participant agreed that the *Second Life* intervention was effective for diabetes education.

Filling a Gap

Such technology helps solve another growing problem: the shortage of expert physicians to train students and colleagues. Doctors can spend more time treating real patients and less time teaching others if virtual trainers are found to be effective. O'Connor conducted a second study among primary care residents to see how the technology fared as a teacher. "We found major improvements in their knowledge of diabetes and ability to manage cases with this simulated intervention." The research included 19 residency programs and also used a randomized control group for comparison.

The same type of software could be used for patient education as well — informing patients about their best treatment options and how their diet and other health behaviors may result in varying outcomes. E-learning modules can already be found through some organizations, like the Children's Hospital of Philadelphia and its online courses on different patient concerns, like *Taking Care of Ketones* and *Alcohol & Diabetes*. However, these examples lack the cause and effect function of decisions made by the user in a virtual program. The videogame-like reality of simulated patients seems to play an important role in the effectiveness of theses tools.

A study published in the *Journal of Medical Internet Research* used the virtual world *Second Life* to execute continuing medical education (CME) for diabetes. Test cases showed the percent of the participating physicians providing a correct insulin initiation plan increased from 60% (6 of 10) before the program to 90% (9 of 10) afterward, and the amount of participants providing correct initiation of mealtime insulin increased from 40% before to 80% after. Every single participant agreed that the *Second Life* intervention was effective for diabetes education.

These results bode well for the use of highly interactive simulators for teaching both providers and patients about the treatment of diabetes and other diseases. A company called SciMed launched what is perhaps the closest program to *Second Life* for diabetes, called the *Virtual Diabetes Institute*. The institute offers numerous different CME courses that immerse the user in a simulated world comprised of a two-story educational center that contains a library, courtyard, and other features for physicians to use and collaborate within.

More recently, a study published in the *Journal of Diabetes Science & Technology* required patients to watch a 15-minute video each week of an avatar with their physical characteristics, like weight and skin color, performing healthy behaviors such as walking on a treadmill that led to weight-loss. In theory, the virtual reality helped participants actualize diet and exercise habits. They lost 3.5 lbs. over the course of four weeks on average.

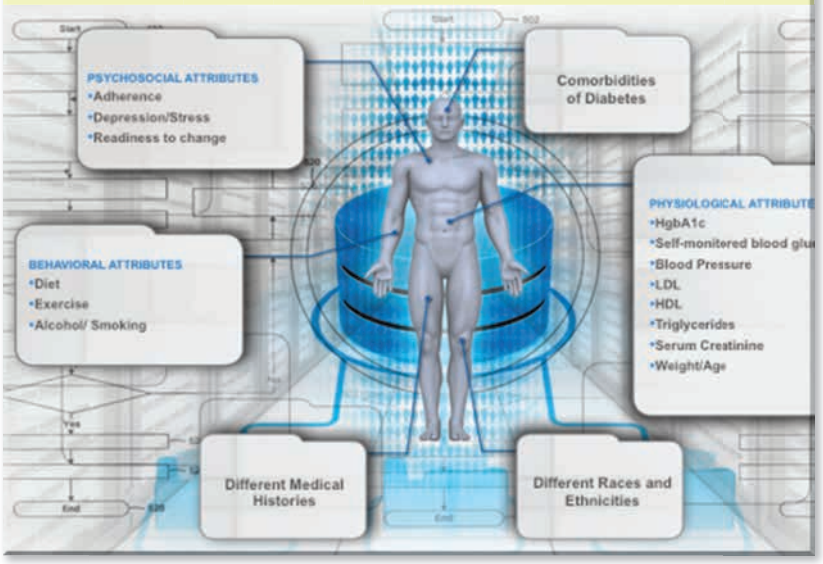
Patient simulators have, of course, been used for ages in the form of mannequins, but digital learning programs may be better suited for nuanced diseases like diabetes. Such programs can often be operated from one's iPad at home or a computer in the office, making education more convenient and efficient. But the largest benefit may be the engaging platform of virtual reality. When learning feels like a game, patients and providers alike seem to be tuned into treatment. EN

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

The ADA Simulation Case Program – A case simulation program developed by the American Diabetes Association and TheraSim to reinforce best practices *professional.diabetes.org/Congress_Display.aspx?CID=84062*

The Virtual Diabetes Institute – A 3-D simulated education campus with CME accreditation *virtualdiabetesinstitute.org/*

SIMCare Diabetes Patient Simulator Engine (below) **–** Real patient data is used, de-identified, and aggregated to represent the current case profiles that most primary care providers experience. This patient simulator takes into consideration psychosocial, behavioral, and physical attributes along with cultures, ethnicities, and other complex co-morbidities for modeling clinical response. *simcarehealth.com/simcare-diabetes/*



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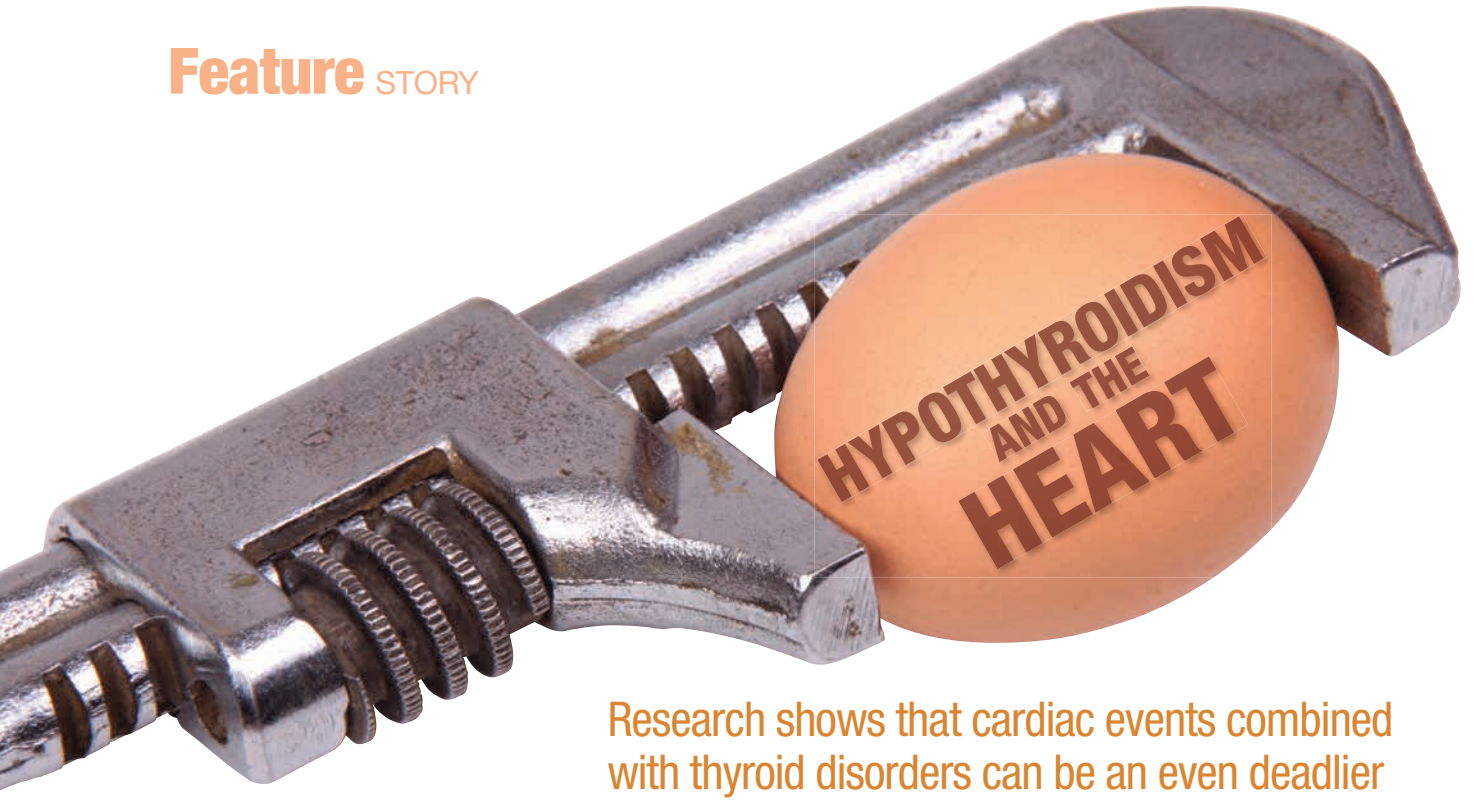

Research shows that cardiac events combined with thyroid disorders can be an even deadlier combination than previously thought.

By Glenda Fauntleroy

For people with almost any type of heart disease, disorders of the thyroid gland can worsen old cardiac symptoms or contribute to new ones. New research now strengthens the evidence that thyroid disorders and heart disease may also be a deadly combination.

In the June issue of the *Journal of Clinical Endocrinology & Metabolism (JCEM),* a large study revealed that among participants with congestive heart failure, having hypothyroidism — even the mild form — significantly increases the risk of death compared to people with normal thyroid function.

"Hypothyroidism has known effects on multiple cardiovascular pathways, including adverse effects on systolic and diastolic function, endothelial function, and lipid levels, and our study suggests that if someone has higher underlying cardiovascular risk, they may be more vulnerable to the effects of mild hypothyroidism," says Connie Rhee, MD, of Brigham and Women's Hospital in Boston, and lead author of the study.

In hypothyroidism, an underperforming thyroid gland makes insufficient thyroid hormone, which may affect nearly every organ in the body, including the heart. According to the NIH's National Institute of Diabetes and Digestive and Kidney Diseases, nearly 5% of the U.S. population over the age of 12 (more than 9.5 million people) has hypothyroidism, which is diagnosed by measuring the levels of thyroid stimulating hormone (TSH) and thyroxine (T4) in the blood.

"Heart failure is the final common pathway of all different kinds of negative events that happen to the cardiovascular system, such as untreated hypertension and diabetes, and **heart failure is the state you end up in when these types of stresses have negatively impacted heart function."**

— Ann Bolger, MD, American Heart Association spokesperson and William Watt Kerr Professor of Medicine at the University of California, San Francisco

In the *JCEM* study, researchers analyzed data from 14,879 participants from the "Third National Health and Nutrition Examination Survey". Almost 750 of the participants had hypothyroidism, and 691 had a mild ("subclinical") form of the condition. Patients were divided into two groups: those with heart failure and those without heart failure. In the group with heart failure, when researchers compared subclinical hypothyroidism to those patients with normal thyroid function, there was an increased death risk for subclinical hypothyroidism patients. But there was no greater risk for those in the non-heart failure group.

"In heart failure patients, we found that both hypothyroidism overall and subclinical hypothyroidism increased the risk of death," Rhee says.

Rhee and her team considered the normal reference ranges for TSH at 0.39 to 4.6 mIU/L and for total T_4 (TT_4) at 4.5 to 13.2 µg/dL. Subclinical hypothyroidism was defined as an elevated TSH (>4.6 mIU/L) and a nor-

AT-A-GLANCE:

- Hypothyroidism, even the mild form, can increase the risk of death for patients with heart failure.
- The disease is a "total body challenge," and heart failure patients can least afford its impact.
- Health care providers should use a more individualized approach in assessing those with hypothyroidism.

mal TT_4 level in the primary analyses, and as a TSH between 0.39–10 mIU/L in the secondary analyses.

The *JCEM* study joins a number of previous studies that have established correlations between thyroid problems and an increased risk of advanced heart disease. A recent study in *Circulation* reported that serious health risks appeared at both ends of the thyroid disorder spectrum. Both higher and lower TSH levels, particularly for TSH ≥10 and <0.10 mIU/L, were found to cause increased heart failure events.

A 2010 *The Journal of the American Medical Association* study of more than 55,000 participants also found subclinical hypothyroidism was linked to an increased risk of heart disease events and death in patients with higher TSH levels, especially those with a TSH of 10 mIU/L or greater.

So, why are heart patients so susceptible to such grave outcomes?

Heart Matters

"Heart failure is the final common pathway of all different kinds of negative events that happen to the cardiovascular system, such as untreated hypertension and diabetes, and heart failure is the state you end up in when these types of stresses have negatively impacted heart function," explains Ann Bolger, MD, American Heart Association spokesperson and William Watt Kerr Professor of Medicine at the University of California, San Francisco.

"And no matter how they got there, this population of patients is very vulnerable."

Hypothyroidism is a disorder that interferes with the efficiency of body functions, such as muscular function and aerobic capacity, and heart patients are the ones who can least afford any additional negative effects, continues Bolger.

"I don't think hypothyroidism would be well-tolerated by almost anyone, but most of us are in the happy circumstance where nature gives us so many different layers of coping mechanisms that we can defend ourselves in other ways," she adds. "Hypothyroidism, however, is a total body challenge. It's not hard to understand how it can have a negative impact on heart patients."

"I think thyroid experts are taking a more personalized approach and are very interested in **defining which patients with mild thyroid failure should, in fact, be treated."**

— E. Chester Ridgway, MD, executive vice chair of medicine, University of Colorado Denver School of Medicine

A Tailored Approach

When treating patients with heart disease, thyroid functioning may not always be a normal part of the health assessment for cardiologists. Bolger says the treatment plan often depends on the patient's actual heart condition.

"Heart patients are not all the same," she says. "We monitor 100% of the patients with arrhythmia, for example, because we know that thyroid levels could be the reason for the heart problems. But with other types of heart problems, such as acute heart attack, thyroid function might not be as tightly correlated, so doctors may not be paying as much attention.

"And when people get into more serious stages of heart disease and then heart failure, we do look for anything that can help them feel better so we look at thyroid function," Bolger continues.

Rhee has also advised a more individualized approach. She says health care providers should not use a blanket approach in assessing people's risk for mild hypothyroidism and determining whether they require treatment.

On the contrary, thyroid expert E. Chester Ridgway, MD, executive vice chair of medicine at the University of Colorado Denver School of Medicine, says a blanket treatment plan for those with mild hypothyroidism is seldom used.

"I think thyroid experts are taking a more personalized approach and are very interested in defining which patients with mild thyroid failure should in fact be treated," he says.

"If the patient with a high TSH has valid hypothyroid symptoms and elevated lipids, most would recommend treatment," Ridgway continues. "In contrast, a person with no symptoms and normal lipids might just be observed over time to see if symptoms develop."

Although the *JCEM* study might suggest that patients with heart failure and high TSH values should be appropriately treated, prospective randomized studies will need to be done to determine whether there is benefit from the treatment, he adds.

Rhee agrees more research is needed. "Our study was an observational study that found an association between mild hypothyroidism and increased death risk in heart failure patients, but it doesn't tell us if it causes it," she says.

Rhee adds that there is a need for more studies that determine the mechanisms that drive the increased death risk in these patients.

Her team has received much interest in their study and is planning follow-up research. EN

— Fauntleroy is a freelance writer in Carmel, Ind., and a regular contributor to Endocrine News.

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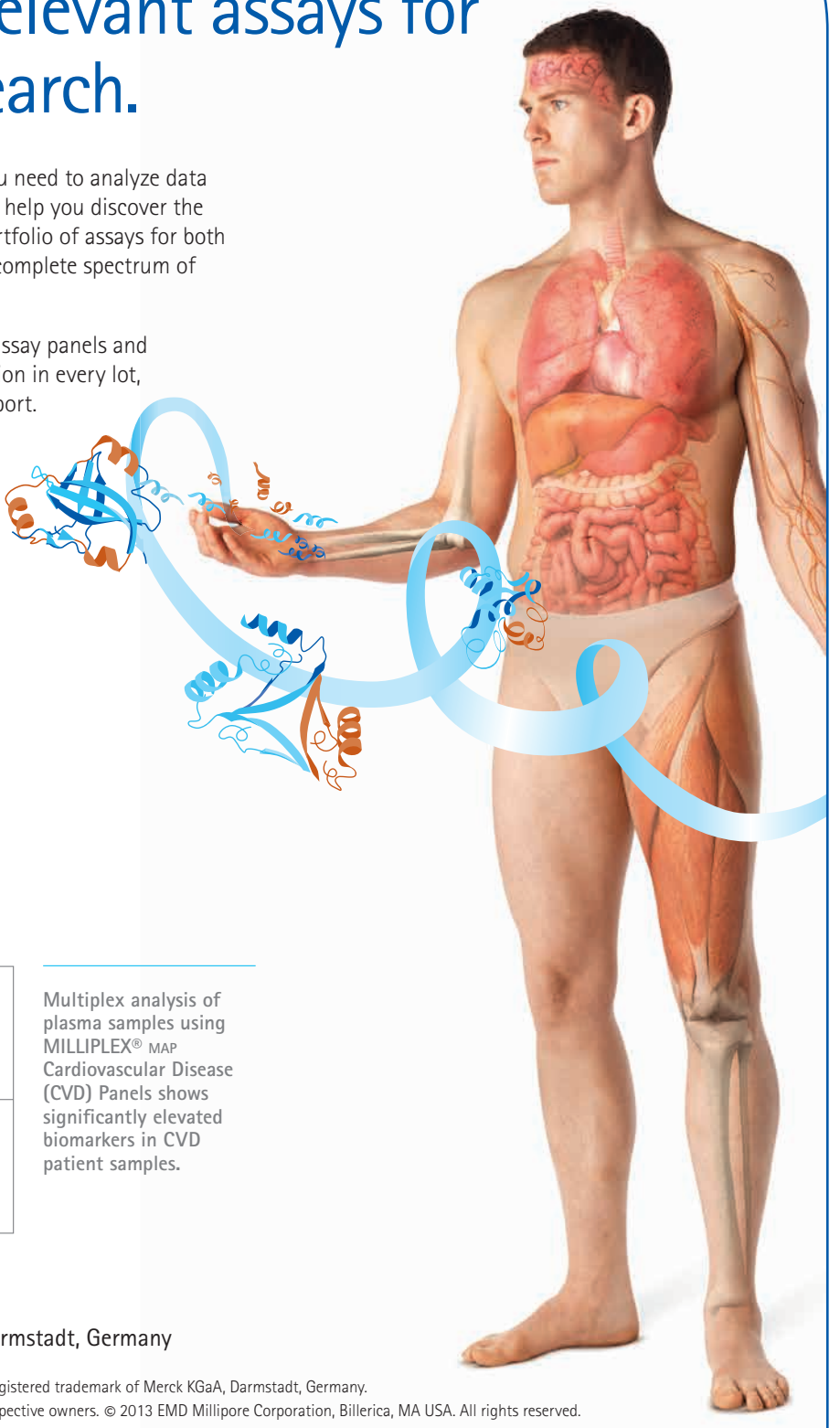

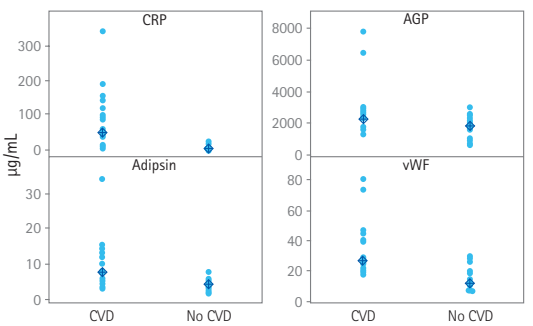

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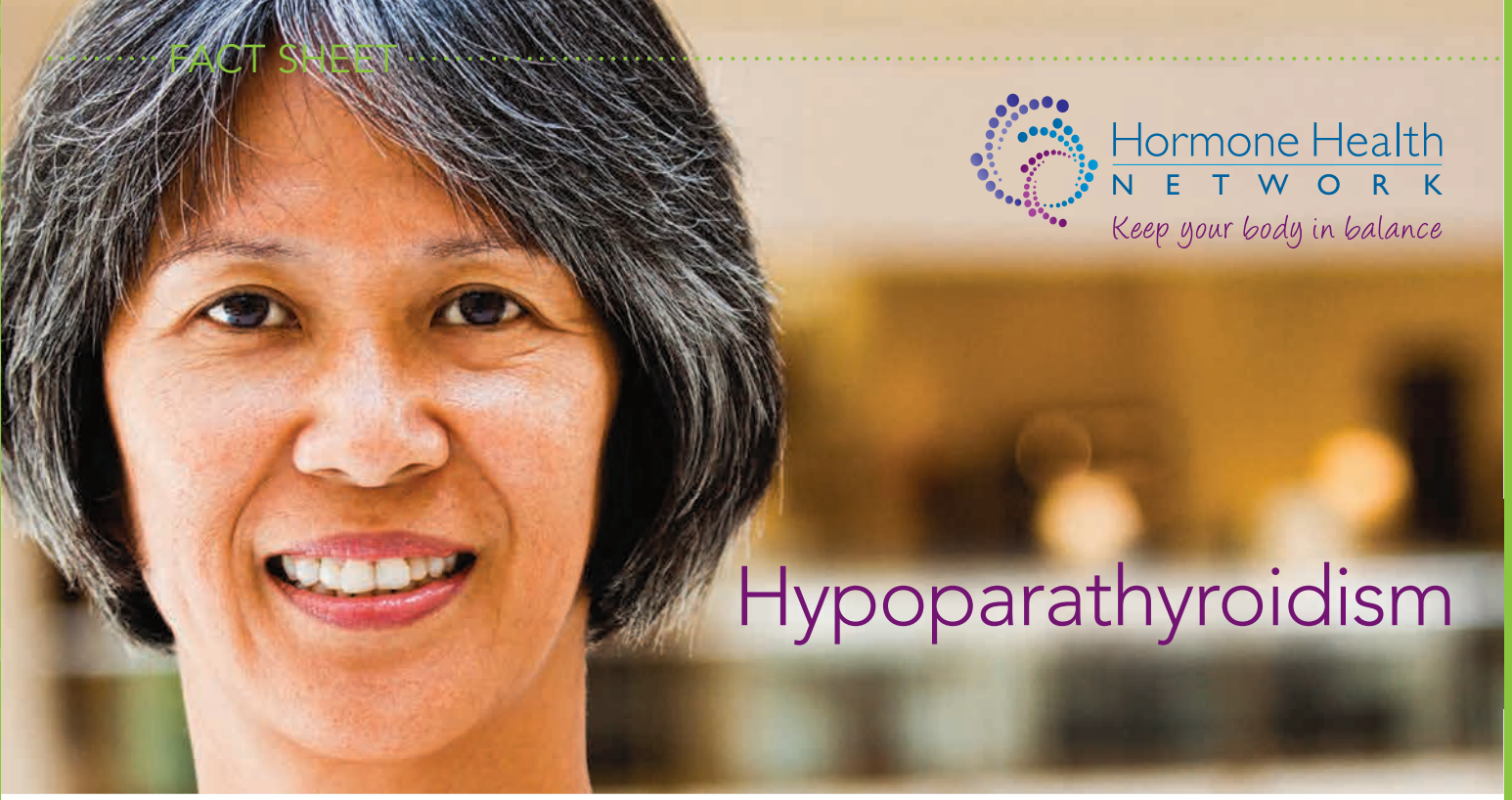

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Hypoparathyroidism

WHAT IS HYPOPARATHYROIDISM?

Hypoparathyroidism is the condition in which you don't have enough parathyroid hormone (PTH). Without enough PTH, the level of calcium in your blood can fall and the level of phosphorus can rise, which could lead to health problems.

DID YOU KNOW?

Your parathyroid glands are four pea-sized glands located in your neck that make parathyroid hormone. They play an important role in bone development.

DEFINITIONS

Parathyroid hormone (PTH): The hormone made by your parathyroid glands. When blood calcium falls too low, PTH brings it back to normal by moving calcium from the bones, kidneys, and intestines into the blood.

Calcium: A mineral stored in your bones where it builds and maintains bone strength. It is also found in every part of the body. It helps muscles contract, helps nerves and the brain work properly, and helps regulate your heart rhythm and blood pressure.

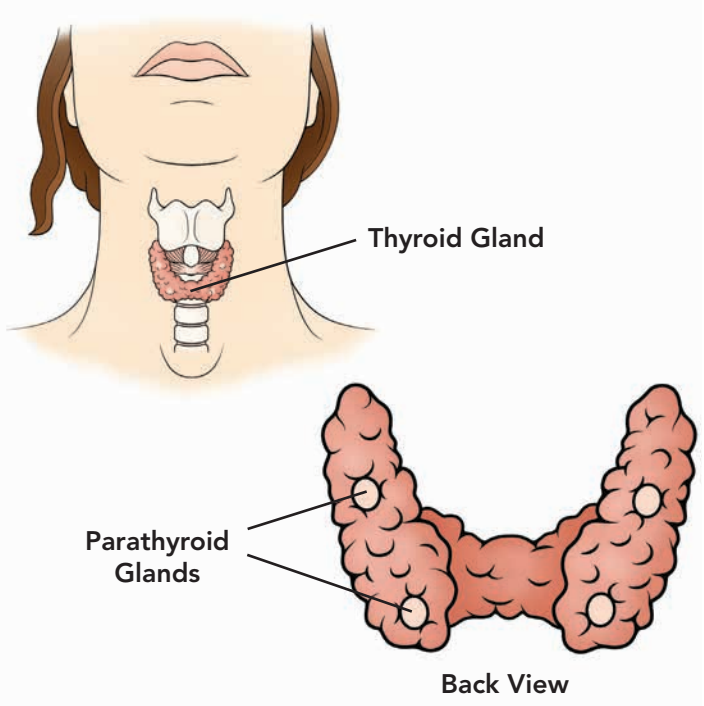
Phosphorus: A mineral found in all cells but stored mostly in your bones. It helps your body use food for energy. It also helps your kidneys, muscles, heart, and nerves work properly.

Vitamin D: A vitamin that helps your body absorb calcium from food and helps keep blood calcium levels in the normal range.

WHAT CAUSES HYPOPARATHYROIDISM?

Your parathyroid glands can be damaged during surgery on your thyroid gland, throat, or neck. Sometimes one or more parathyroid glands are removed if they're making too much PTH. Hypoparathyroidism also can be inherited. Other causes include:

- Autoimmune disease (when your body's defense system attacks your own cells)
- Radiation therapy to your head or neck
- Low levels of magnesium (a mineral) in the blood



WHAT ARE THE SYMPTOMS OF HYPOPARATHYROIDISM?

Common symptoms include

- Muscle spasms, cramps, and/or pain in your legs, feet, stomach, or face
- Weakness
- Hair loss
- Dry hair and dry skin
- Tingling in your fingers, toes, and lips
- Pain with menstrual periods
- Headaches
- Memory problems
- Depression

WHAT HEALTH PROBLEMS CAN HYPOPARATHYROIDISM CAUSE?

When children have hypoparathyroidism, they might grow poorly, have tooth problems such as delayed tooth development or a lot of cavities, and have slow mental development.

In adults, hypoparathyroidism can lead to kidney problems, heart problems, and calcium deposits in the brain. Calcium in the brain can cause tremors, slowed movement, balance problems, and seizures.

Hypoparathyroidism can be linked to other health problems, such as cataracts, Addison's disease (problems with your adrenal glands), and pernicious anemia (a shortage of vitamin B12).

HOW IS HYPOPARATHYROIDISM DIAGNOSED?

Your doctor will do a blood test to check levels of calcium, phosphorus, magnesium, and PTH. You also might have a urine test to show how much calcium you are losing in your urine.

WHAT IS THE TREATMENT FOR HYPOPARATHYROIDISM?

You will take calcium and vitamin D supplements to keep your blood calcium levels normal. Depending on the cause of your hypoparathyroidism, you may need to take the supplements for the rest of your life. Your doctor will check your blood levels regularly.

If your blood calcium level becomes extremely low, it can be dangerous for your health. Then you will be given calcium through a vein (IV) and your heart will be checked to make sure it's OK. Once your calcium level is normal, you can go back to taking oral supplements.

You might need to follow a diet high in calcium and low in phosphorus. A registered dietitian can help you plan a special diet.

Good Sources of Calcium: Milk, yogurt, cheese, collard greens, and foods with added calcium, such as cereal and soy drinks.

Good Sources of Vitamin D: Salmon, shrimp, and milk with vitamin D. Vitamin D is also made in your skin when you spend time in the sun.

Foods High in Phosphorus: Protein foods such as meat, milk, and hard cheeses; also whole grains, dried peas and beans, nuts, and chocolate.

Questions to ask your doctor

- **What caused my hypoparathyroidism?**
- **What tests do I need?**
- **What are my options for treatment?**
- **What are the risks and benefits of each treatment option?**
- **How long will I need treatment?**
- **How often will I need check-ups?**
- **Should I see an endocrinologist?**
- **Should I see a registered dietitian?**

RESOURCES

- Find-an-Endocrinologist: *www.hormone.org* or call *1-800-HORMONE (1-800-467-6663)*
- Find a registered dietitian (a service of the Academy of Nutrition and Dietetics): *www.eatright.org/programs/rdfinder/*
- MedlinePlus (National Institutes of Health) information about hypoparathyroidism: *www.nlm.nih.gov/medlineplus/ency/article/000385.htm*
- Mayo Clinic information about hypoparathyroidism: *www.mayoclinic.com/health/hypoparathyroidism/DS00952*

EDITORS

Jens Bollerslev, MD
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Benjamin Z. Leder, MD

June 2013

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

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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.***

Increased Brain Transport and Metabolism of Acetate in Hypoglycemia Unawareness Barbara I. Gulanski, Henk M. De Feyter, Kathleen A. Page, Renata Belfort de Aguiar, Graeme F. Mason, Douglas L. Rothman, and Robert S. Sherwin • *Increased MCA transport and metabolism among T1DM individuals with hypoglycemia unawareness may be a mechanism to supply the brain with non-glucose fuels during episodes of acute hypoglycemia and may contribute to the syndrome of hypoglycemia unawareness, independent of diabetes.*

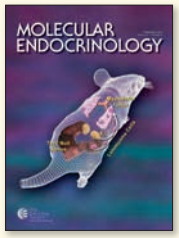
Central Hypothyroidism and Its Replacement Have a Significant Influence on Cardiovascular Risk Factors in Adult Hypopituitary Patients M. Klose, D. Marina, M. L. Hartoft-Nielsen, O. Klefter, V. Gavin, L. Hilsted, Å.K. Rasmussen, and U. Feldtrasmussen • *This single-center study over a 20-year period has strengthened the importance of improved awareness of thyroid status and optimal thyroid replacement of hypopituitary patients in order to reduce cardiovascular risks in hypopituitary patients.*

Insulin Resistance and Impaired Pancreatic Beta-Cell Function in Adult Offspring of Women with Diabetes in Pregnancy Louise Kelstrup, Peter Damm, Elisabeth R. Mathiesen, Torben Hansen, Allan A. Vaag, Oluf Pedersen, and Tine D. Clausen • *Reduced insulin sensitivity as well as impaired pancreatic beta-cell function may contribute to the increased risk of glucose intolerance among adult offspring born to women with diabetes during pregnancy.*

Uncovering Novel Roles of Non-Neuronal Cells in Body Weight Homeostasis and Obesity Julie A. Chowen, Jesús Argente, and Tamas L. Horvath • *This minireview focuses on the recent advances in our understanding of how glial cells participate in the physiological regulation of appetite and systemic metabolism, as well as their role in the pathophysiological response to poor nutrition and secondary complications associated with obesity.*

Chemerin Suppresses Ovarian Follicular Development and Its Potential Involvement in Follicular Arrest in Rats Treated Chronically with Dihydrotestosterone Ji Young Kim, Kai Xue, Mingju Cao, Qi Wang, Jia-yin Liu, Arthur Leader, Jae Yong Han, and Benjamin K. Tsang • *The findings are consistent with authors' hypothesis that antral follicular growth arrest in DHT-treated rats results from increased chemerin expression and action, as well as changes in follicular cell fate and structure, which are a consequence of dysregulated interactions of pro-survival and pro-apoptotic modulators in a cell-specific manner. Their observations suggest that this chronically androgenized rat model may be useful for studies on the long-term effects of androgens on folliculogenesis and may have implications for the female reproductive disorders associated with hyperandrogenism.*

Peripheral Androgen Receptors Sustain the Acrobatics and Fine Motor Skill of Elaborate Male Courtship Matthew J. Fuxjager, Kristy M. Longpre, Jennifer G. Chew, Leonida Fusani, and Barney A. Schlinger • *Together, the findings help differentiate the various effects of peripheral and central AR on the performance of a complex socio-sexual behavioral phenotype, while indicating that peripheral AR can optimize the motor skills necessary for the production of an elaborate animal display.*



Kisspeptin Regulates Gonadotropin Genes via Immediate Early Gene Induction in Pituitary Gonadotropes Emily A. Witham, Jason D. Meadows, Hanne M. Hoffmann, Shadi Shojaei, Djurdjica Coss, Alexander S. Kauffman, and Pamela L. Mellon • *Overall, the findings indicate that kisspeptin regulates gonadotropin gene expression through the activation of Kiss1R signaling through PKC, inducing immediate early genes in vitro, and responds to physiologically relevant cues in vivo, suggesting that kisspeptin affects pituitary gene expression to regulate reproductive function.*

Novel, Gel-Free Proteomics Approach Identifies RNF5 and JAMP as Modulators of GPCR Stability Sébastien J. Roy, Irina Glazkova, Louis Fréchette, Christian Iorio-Morin, Chantal Binda, Darlaine Pétrin, Phan Trieu, Mélanie Robitaille, Stéphane Angers, Terence E. Hébert, and Jean-Luc Parent • *The data suggest that RNF5 regulates the turnover of specific GPCRs by ubiquitinating JAMP and preventing proteasome recruitment.*

New Insights Into the Role of Sequestosome 1/p62 Mutant Proteins in the Pathogenesis of Paget's Disease of Bone Sarah L. Rea, John P. Walsh, Robert Layfield, Thomas Ratajczak, and Jiake Xu • *The purpose of this review is to outline recent advances in understanding of the multiple pathophysiological roles of SQSTM1/p62 protein, with particular emphasis on their relationship to PDB, including challenges associated with translating SQSTM1/p62 research into clinical diagnosis and treatment.*

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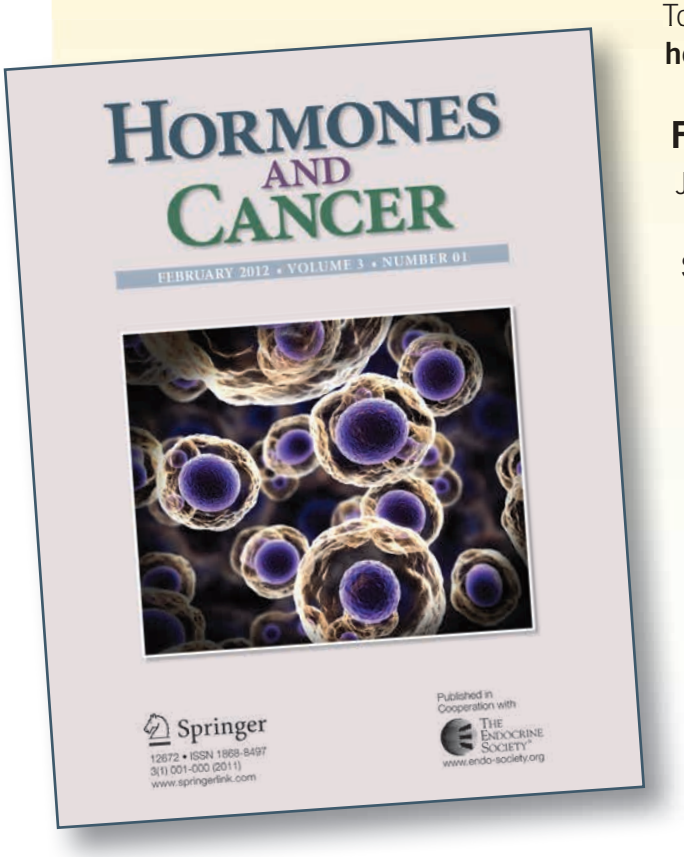

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†Victoza 1.2 mg + metformin (n=155); Victoza 1.8 mg + metformin (n=176); vs sitagliptin 100 mg + metformin (n=166) over 52 weeks.

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

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1 ml of solution contains 6 mg of liraglutide.
Indication: Treatment of adults with type 2 diabetes mellitus in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of metformin or sulphonylurea monotherapy; or in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy. **Dosage:** Victoza® is administered once daily by subcutaneous injection and at any time independent of meals however it is preferable to inject around the same time of day. Victoza® should not be administered intravenously or intramuscularly. Recommended starting dose is 0.6 mg daily, after at least one week, the dose should be increased to a maintenance dose of 1.2 mg. Based on clinical response, after at least one week the dose can be increased to 1.8 mg. Daily doses higher than 1.8 mg are not recommended. When added to existing sulphonylureas or in combination with metformin and sulphonylureas, a reduction in the dose of sulphonylurea may be necessary to reduce the risk of hypoglycaemia. Victoza® can be used in the elderly (>65 years) without dose adjustment but therapeutic experience in patients ≥75 years is limited. No dose adjustment for patients with mild renal impairment (creatinine clearance (CrCl) 60-90 ml/min). Due to lack of therapeutic experience Victoza® is not to be recommended for use in patients with moderate (CrCl of 30-59 ml/min), severe (CrCl < 30 ml/min) and end-stage renal disease or patients with hepatic impairment or children <18 years. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions for use:** Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. The addition of Victoza® in patients already treated with insulin has not been evaluated and is therefore not recommended. Limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Due to limited experience Victoza® is not recommended for patients with inflammatory bowel disease and diabetic gastroparesis. Victoza® is associated with transient gastrointestinal (GI) adverse reactions. GLP-1 analogues have been associated with pancreatitis; patients should be informed of symptoms of acute pancreatitis if pancreatitis suspected, Victoza® and other suspect medicinal products should be discontinued. Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm reported in clinical trials particularly in patients with pre-existing thyroid disease. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. No studies on effects on ability to drive and use machinery. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulphonylureas. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products. **Fertility, pregnancy and lactation:** If a patient wishes to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued; use of insulin is recommended instead. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed. **Undesirable effects:** The most frequently observed adverse reactions which varied according to the combination used (sulphonylurea, metformin or a thiazolidinedione) were: Very common (≥ 1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulphonylureas, headache when used in combination with metformin and vomiting when used in combination with metformin and rosiglitazone; Common (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, gastroenteritis viral, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue and pyrexia. GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of; angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Rates of thyroid adverse events - 33.5, 30.0 and 21.7 events/1000 subject years of exposure for liraglutide, placebo and total comparators; Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently reported thyroid adverse events/1000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers:** Victoza® 2 x 3ml pre-filled pensEU/1/09/529/002. Victoza® 3 x 3ml pre-filled pensEU/1/09/529/003. **Legal Category:** POM. **Basic NHS Price:** Victoza® 2 x 3ml pre-filled pens: £ 78.48. Victoza® 3 x 3ml pre-filled pens: £117.72. **Further prescribing information can be obtained from:** Novo Nordisk Limited, Broadfield Park, Brighton Road, Crawley, West Sussex, RH11 9RT. **Date created:** March 2012.

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

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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 4 hospitals, 43 community practice sites and more than 900 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 Join-Geisinger.org or contact: John W. Kennedy, MD, Endocrinology Department Director, Geisinger Health System c/o Kathy Kardisco, Department of Professional Staffing, at 1-800-845-7112 or kkardisco@geisinger.edu.

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Budget Battle Could Have Devastating Consequences for NIH, Researchers

While the ongoing debate surrounding fiscal policy in the U.S. directly impacts many government programs, recent developments concerning the effect of austerity policies on science funding has pointed the gaze of researchers squarely on Washington, D.C.

Many biomedical researchers rely on federal grants from the National Institutes of Health (NIH) to run their labs. Consequently, government actions surrounding the budget process as it applies to the NIH are of particular importance to researcher members of The Endocrine Society. A decade of flat funding for biomedical research, coupled with cuts in the NIH budget due to sequestration implemented in fiscal year 2013 (FY13), have severely undercut the biomedical research infrastructure in the U.S. and caused considerable financial uncertainty for researchers.

The appropriations subcommittees that set the budget for the NIH are restricted in the amount they can distribute to the programs under their purview by the allocations set forth in the respective budget resolutions passed by the House and Senate. The overall budget resolutions are restricted by caps set by the Budget Control Act of 2011 (BCA). The Senate budget, at $1.058 trillion, matches the overall cap set by the BCA but does not include any cuts due to sequestration. The House budget, at $967 billion, matches the BCA level and also applies all the cuts from sequestration to the non-defense agencies, including the NIH.

In the absence of an alternative to sequestration, discretionary programs such as the NIH seem set for further cuts in the future. However, as the differences between the House and Senate budget make clear, whether those cuts are applied equitably — as happened in FY13 — or are applied in alignment with party priorities — as the House budget seeks to do — remains unclear.

Catastrophic Consequences

If the House budget were to be implemented as it stands at the time this article was written, the consequences for the NIH are potentially catastrophic. The House and Senate allocations for the Labor, Health and Human Services (LHHS) Subcommittee differ by ~$42.5 billion, and the House allocation represents a $28 billion cut from the FY13 level after sequestration. If the LHHS cut were applied evenly to all programs within the subcommittee's jurisdiction, the NIH budget would be a staggeringly low $23.8 billion (~18.75% below the post-sequestration level of $29.3 billion.)

The most likely outcome of the budget process for FY14, given the immense divergence between the House and Senate budget resolutions, would be a Continuing Resolution (CR) for at least part of FY14. A CR usually funds all existing government programs, in the absence of a formal appropriations bill, at prior-year levels with minor changes. NIH policy under a CR, for example, is to fund existing grants at slightly less than prior-year levels. However, even under a CR, the spending distribution could change through special provisions within the CR (called "anomalies"), or as part of a bill that raises the debt ceiling. Therefore, it is extremely important to continue to pressure legislators to make funding for the NIH a national priority.

Exercise Influence

The Endocrine Society, in partnership with coalitions such as the Federation of American Societies for Experimental Biology (FASEB) and United for Medical Research (UMR), has long advocated for steady, sustainable increases in biomedical research funding as a major part of its advocacy efforts. Given the uncertainties surrounding the FY14 budget process, and the potential consequences for biomedical research funding, The Endocrine Society urges individual members to act locally to influence policymakers. Efforts that members can participate in could include writing letters to the editors of local newspapers, inviting members of Congress to tour their labs, participating in town hall meetings, or visiting members of Congress while they are in their home districts.

The Society encourages members to share their stories and increase awareness of the immense value of biomedical research to the U.S. Members can make use of the Society's online resources, for example, to help identify and contact representatives. Other resources can also be found on coalition websites, such as FASEB and UMR. To read regular updates on the budget process, members are also encouraged to read the bi-weekly newsletter, *Endocrine Insider,* which keeps members informed of health and science policy issues affecting endocrinologists.

The Endocrine Society regularly seeks member input and expertise when engaging legislative bodies or funding agencies as part of the Society's advocacy efforts. For more information on how members can become involved in grassroots efforts to increase NIH funding, or to access information to help in advocacy efforts, contact the Society's Government and Public Affairs Department at ***govt-prof@endocrine.org.*** EN

— Joseph M. Laakso, PhD, is the manager of science policy for The Endocrine Society.

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