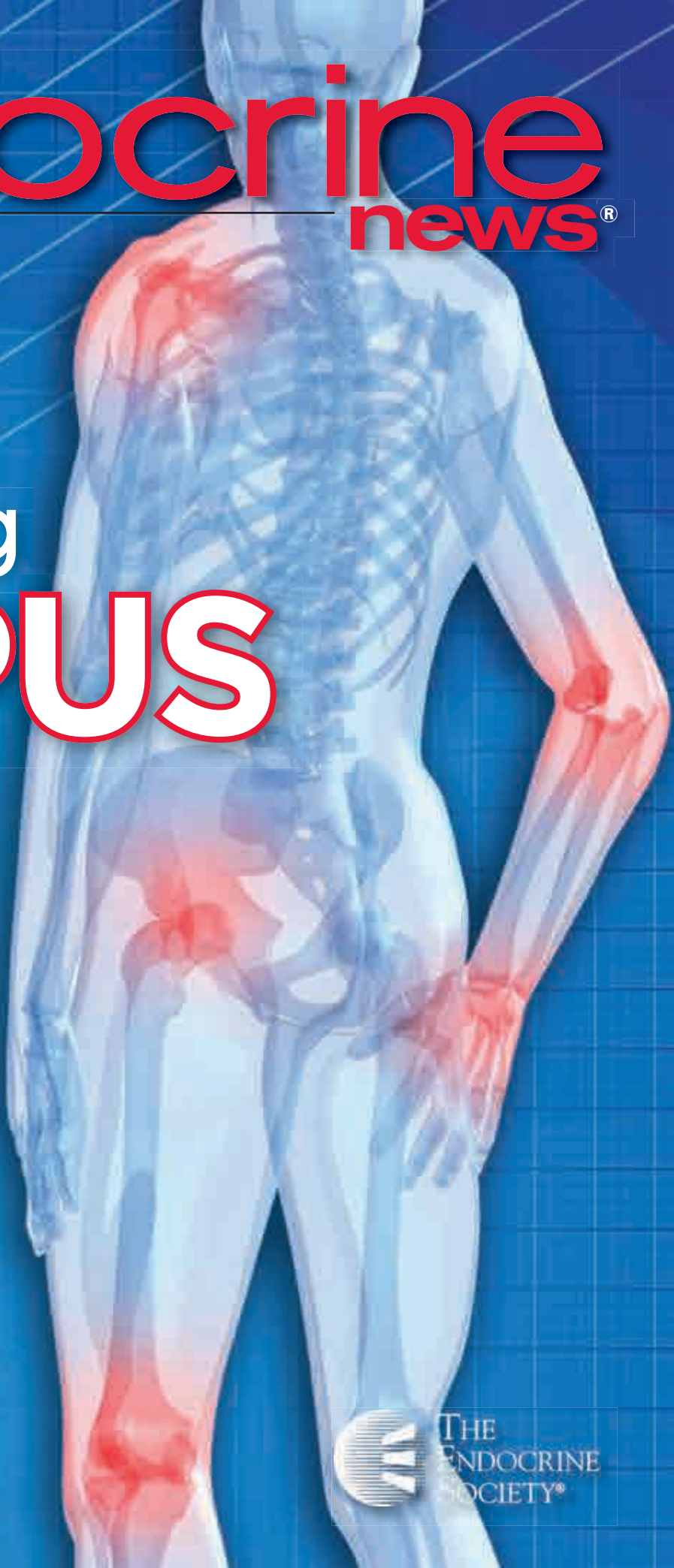
Endocrine news®
DECEMBER 2012

Managing LUPUS



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Counterfeit Drugs

Detecting Sjögren's and Klinefelter

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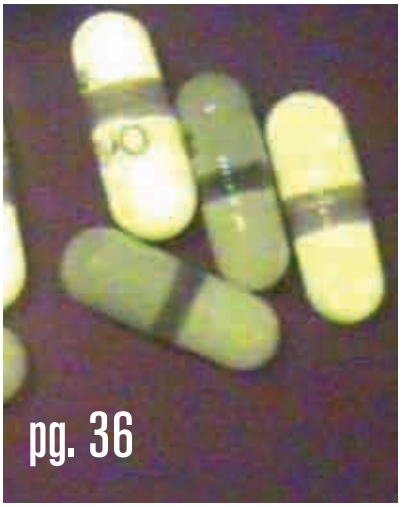

Departments

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Recognizing Excellence in Research, Clinical Practice, Leadership, and Service

Dear Colleagues:

William F. Young, Jr. M.D., M.Sc.

The Endocrine Society's Awards Program is really quite remarkable. Each year at ENDO, the Society presents awards totaling nearly $600,000. These awards recognize U.S. and internationally based clinical researchers, clinical practitioners, and basic scientists. The "Awards Call for Nominations" will launch in early January 2013, and I encourage you to nominate your peers, mentors, trainees, and mentees. In this letter, I highlight some of the unique aspects of the Society's Awards Program.

Laureate Awards

Representing the highest achievement in the field of endocrinology, the Laureate Awards honor endocrinologists whose accomplishments are unmatched in science, leadership, education, clinical practice, and service. In addition to the established 11 Laureate Awards, two new awards will debut in 2013: the International Excellence in Endocrinology Award and the Outstanding Clinical Practitioner Award. Like their predecessors, this year's Laureate Award recipients will be added to the growing list of distinguished endocrinologists who have made significant contributions to improve human health globally. The Laureate Awards Committee encourages all voting members to contribute to the nomination process beginning in January.

Trainee and Early-Career Awards

For trainees and early-career professionals, the Society has invested heavily in awards and grants to recognize their outstanding achievements. In 2012, the Society presented awards to more than 400 trainees. In 2013, the Society will continue to offer a robust portfolio of trainee- and early-career investigator awards aimed at encouraging trainees' continued growth and contributions to the Society and the field. Trainees who are both first and presenting authors of an **ENDO 2013** abstract are eligible for the numerous abstract and travel awards. In addition, trainee authors of the highest-scoring abstracts selected for poster presentation will be invited to participate in the Presidential Poster Competition.

The Society is pleased to offer continued travel grant support to trainees who wish to attend the **ENDO 2013** Early Career Forum (formerly Endocrine Trainee Day). Those who receive the Early Career Forum Travel Award are also provided with complimentary registration to attend ENDO 2013. The Promotion and Tenure Workshop Travel Awards for junior faculty and mid-career professionals will also be offered in 2013. These awards provide travel support for members early in their careers to attend a workshop that focuses on the skills needed to secure promotion and/or tenure. Other awards offered include the Early Investigators Awards for early career investigators, the Future Leaders Advancing Research in Endocrinology Program Awards for leadership development training, the International Endocrine Scholars Awards for international trainees, the Minority Access Program Summer Research Awards for undergraduate students from underrepresented communities, the Medical Student Achievement Awards, the Summer Research Fellowship Awards, the Clinical Research Fellowship Award in Acromegaly, the Endocrine Clinical Research Fellowship Awards, and the ***Endocrinology*** and ***Molecular Endocrinology*** Student Author Awards.

Other Awards

The Delbert A. Fisher Research Scholar Award recipient is recognized for scholarly work on the history of endocrinology. The awardee will deliver the Clark T. Sawin Memorial History of Endocrinology Lecture at **ENDO 2013** and submit an article highlighting the presentation for publication in ***Endocrine News***. Finally, practicing physicians have the opportunity to compete for travel support to ENDO through the Harold Vigersky Practicing Physician Travel Award.

The details and application information for these awards are presented on the Society's Web site and elsewhere in this and other issues of ***Endocrine News***.

2013 Election: Reminder, don't forget to vote!

This is your opportunity to participate in selecting the Society's future leadership.

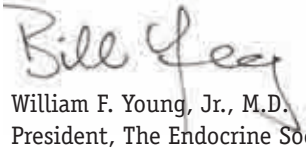
The ballot for the Society's 2013 election of officers and Council will launch in early January 2013. I encourage you to vote and to remind your colleagues to do the same. This is your Society, and your participation is vital.

The positions on the 2013 ballot are: President-Elect (Clinical Scientist), Vice President (Physician-in-Practice), and Council (one Basic Scientist designated seat and two At-Large seats.)

I would like to thank the Nominating Committee members for their thoughtful deliberations in selecting an excellent slate of candidates.

My best wishes for wonderful holidays and a Happy New Year! If you have any comments or questions, please contact me at *president@endo-society.org*. ■

Sincerely,



William F. Young, Jr., M.D.
President, The Endocrine Society

Dear Readers,

Our bodies' immune system usually protects us from invaders like bacteria and viruses, but sometimes the system goes haywire and attacks the very organs it should be protecting. Autoimmune diseases are frequently hard to diagnose and treatment may require a team of specialists, among them endocrinologists. In this issue, four specialists discuss strategies for managing systemic lupus, an autoimmune syndrome that affects multiple body organs and systems. The condition afflicts far more women than men (page 16).

Expanding on the problems of autoimmune diseases and perplexing medical conditions, writers Terri D'Arrigo and Glenda Fauntleroy explore two of the most baffling to diagnose, Klinefelter and Sjögren's syndromes. Sjögren's, like most autoimmune diseases, usually afflicts women, but Klinefelter affects only men. Although a sleeper condition for many men, it usually has devastating consequences for their fertility (page 24).

A fascinating story full of warning is Shannon Fischer's investigation of counterfeit drug trafficking. As our global communications via the Internet have increased in the last decades, the pharmaceuticals market has been inundated with fake medicines. In her article, Fischer takes us along as she shops online for medications and details the how-to of the illicit trade and what authorities are doing to stem the tide (page 36).

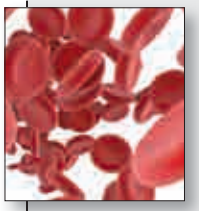
This month's Back Story takes us to the zoo. Dan Kelly's profile of reproductive physiologist Janine Brown tells us how advances in endocrinology are working to increase populations of endangered animals (page 54). ■

Sincerely,

Marian Smith Holmes
Managing Editor
Endocrine News

ENDOCRINE NEWS ONLINE EXCLUSIVES

The following articles are housed online only. See ***Endocrine News*** *Online* to read them and find related links *(www.endo-society.org/endo_news).*



Type O Blood and Tumors
Patients with multiple endocrine neoplasia type 1 develop more tumors if they also have type O blood.

Early Identification of Endometriosis
Physicians may one day use serum microRNAs to diagnose endometriosis.

Sons May Save Mothers from Alzheimer's
Male fetal DNA persists in mothers who gave birth to sons—and may protect them from Alzheimer's.

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Obesity Linked to Taste Sensitivity

Humans have evolved a highly developed sense of taste that steers us away from toxic substances, signaled by bitterness, and toward sweet, sour, savory, salty, and other tastes that we perceive as pleasant. This evolutionary adaptation, however, varies in sensitivity among individuals, and has far-reaching implications for children, who establish lifelong eating patterns based on taste. Studies have shown that those with less taste sensitivity, possibly due to fewer taste buds, need to eat more to feel satiated.

Susanna Wiegand, M.D., at the Charité Children's Hospital, Universitätsmedizin Berlin, in Germany, led a team to find out whether obese children have reduced taste sensitivity. They gave a series of taste strips soaked with varying concentrations of one of the five main tastes to 99 obese and 94 normal-weight subjects ages 6–18 years and asked them to rate each strip from 1 for "no taste" to 5 for "very strong taste." In their paper, recently published online in *Archives of Disease in Childhood*, the researchers report that obese children scored an average of 12.6 out of 20, whereas normal-weight children scored an average of 14.1 out of 20, indicating that the normal-weight children have keener taste perception. Moreover, girls more accurately identified tastes than boys, as did older children; however, the investigators found no significant difference among ethnicities. Importantly, 85 percent of the obese participants had low socioeconomic status.

The researchers conclude that taste sensitivity varies with obesity status, and that endocrine and paracrine levels, which also correlate with obesity status, might influence the taste mechanism. They add that future larger studies should control for socioeconomic factors to confirm the association between obesity and taste sensitivity in view of eventually developing related obesity-prevention strategies. ■

Kelly Horvath

Low Vitamin D Levels May Cause MS Flare-Ups

Patients with multiple sclerosis (MS) experience more active disease when their vitamin D levels drop, according to a study reported in *Annals of Neurology*. Ellen M. Mowry, M.D., M.C.R., now assistant professor of neurology at the Johns Hopkins University School of Medicine, reported the findings. Mowry is principal investigator of a multicenter clinical trial of vitamin D supplementation in patients with MS.

In exploring a possible link between vitamin D deficiency and MS severity, the researchers, based at the University of California, San Francisco, compared vitamin D levels in study participants' blood to magnetic resonance imaging (MRI) results. Their goal was to see if the overall number or the number of active lesions, indicating less-controlled disease, correlated with changes in vitamin D levels.

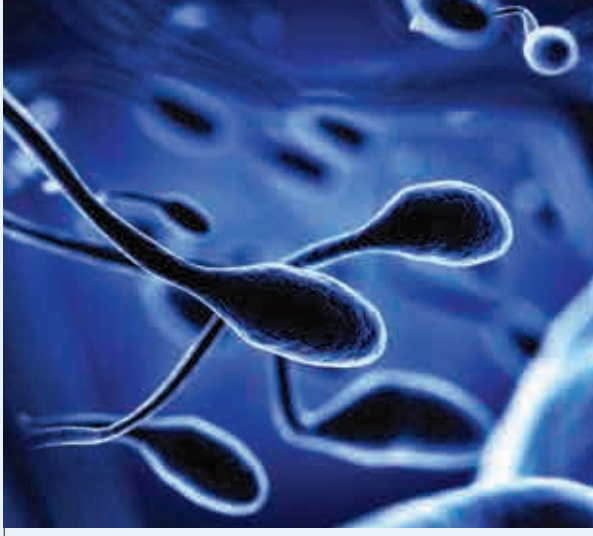
Myelin is a fatty protein that insulates nerves and transmits electrical signals between them. It's instrumental to movement, vision, and speech. With MS, the body's immune system attacks myelin in the brain and spinal cord. Myelin degradation shows up as white spots or lesions on MRIs. In the most common form of MS, called relapsing-remitting MS, the myelin attacks come and go and with them, disease symptoms.

From 2004 to 2009, the researchers drew annual blood samples and performed MRIs with contrast dyes on 469 subjects with relapsing-remitting MS. The researchers found each 10 ng/ml increase in vitamin D levels correlated with a 15 percent lower risk of new lesions and a 32 percent lower risk of active lesions.

Although the research is promising, Mowry cautions it's preliminary and notes that researchers haven't determined whether vitamin D supplements will reduce symptoms or prevent MS altogether. In the ongoing randomized trial, researchers will compare the effects of two vitamin D supplement dosages. ■

Carol Bengle Gilbert

Protein Complex Critical to Fertility



➤ The Scribble/Lgl/Dgl polarity protein complex is crucial to spermatogenesis and may be a potential target for treatment of male infertility, according to a new research study. In their paper soon to be published in ***Endocrinology*** *[endojournals.org]*, researchers studied Sertoli and germ cells from 20-day-old rat testes to investigate the role Scribble/Lgl/Dgl plays during spermatogenesis—the process by which sperm become mature enough to fertilize an egg.

The researchers' findings showed that this protein complex is crucial to spermatogenesis because its disruption perturbs spermatid polarity and cell adhesion in the testis, according to lead researcher C. Yan Cheng, Ph.D., from the Center for Biomedical Research at Population Council in New York City.

Infertility affects about 15 percent of married couples, and the male factor is responsible in about 50 percent of those couples, Cheng said. "These findings suggest that an alteration of the Scribble/Lgl/Dgl protein complex's function, such as might be induced by environmental toxicants, could be the 'cause' of some cases of unexplained male infertility," Cheng added. His study's findings may be of benefit to physicians who specialize in treating reproductive problems. ■

Glenda Fauntleroy

Leptin Homolog Found in Fruit Flies

➤ The humble fruit fly has made key contributions to our understanding of genetics, and now it's poised to affect our knowledge of metabolism. Researchers believe they have found in *Drosophila* a functional homolog of the human hormone leptin, which plays a key role in controlling appetite.

Akhila Rajan, Ph.D., and Norbert Perrimon, Ph.D., of Harvard Medical School in Boston, looked at *Drosophila* fat bodies, the analogs of vertebrate adipose tissue that convey nutrient status to the fly brain. The fat bodies produce a cytokine called unpaired 2 (upd2) in response to dietary fat and sugars. The upd2 in turn leads to the secretion of *Drosophila* insulin-like peptides, which promote systemic growth and fat storage.

Flies that the researchers genetically engineered to lack upd2 function had reduced growth and altered energy metabolism, much as humans who lacked leptin would. The researchers reversed these effects by inserting the human leptin gene into the flies. The human leptin substituted functionally for the upd2, even acting as a ligand in the signaling pathway that regulates insulin secretion. This genetic doppelgänger also led to the secretion of the key *Drosophila* insulin-like peptides.

Differences in human and fly biology had appeared to limit the usefulness of flies in metabolic studies. For example, in humans, pancreatic β-cells secrete the key hormones involved in metabolism. In contrast, the fruit fly cells with insulin-producing function are found in the brain, but the researchers found similarities. Because cytokines play central roles in mammalian nutrition sensing and metabolic homeostasis, the scientists looked for a similar process in flies. Their study illustrates a cytokine-mediated pathway regulating insulin secretion according to nutrient availability.

In an article recently published in *Cell,* Rajan and Perrimon say their finding that the key human hormone leptin is so closely related to *Drosophila* upd2 indicates that the *Drosophila* model can be used to investigate leptin biology. ■

Eric Seaborg

Continued on page 9

NOW AVAILABLE FOR ADULTS WITH TYPE 2 DIABETES WHO REQUIRE INSULIN

WITH THE V-Go™, SHE'S ON THE GO

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Introducing the V-Go, an easy-to-use device providing insulin delivery that mimics the physiologic pattern found in people without diabetes.[*1]

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Important Risk Information: If regular adjustments or modifications to the basal rate of insulin are required in a 24-hour period, or if the amount of insulin used at meals requires adjustments of less than 2-Unit increments, use of the V-Go Disposable Insulin Delivery Device may result in hypoglycemia. The following conditions may occur during insulin therapy with the V-Go: hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose). Other adverse reactions associated with V-Go use include skin irritation from the adhesive pad or infections at the infusion site. The V-Go should be removed before any magnetic resonance imaging (MRI) testing.

*If you follow the V-Go *Instructions for Patient Use.*

Reference: 1. Polonsky KS, et al. *N Engl J Med.* 1988;318:1231-1239.

valeritas

V-GO™ DISPOSABLE INSULIN DELIVERY

FREEDOM TO GO

ART-288 Rev: A 7/2012

Continued from page 7

Hydrogen Sulfide's Role in Diabetes

➤ Hydrogen sulfide not only contributes to that awful odor of rotten eggs, it might also contribute to the pathogenesis of diabetes.

Along with nitric oxide and carbon monoxide, hydrogen sulfide has been classified in the newly identified group called gasotransmitters. These gaseous signaling molecules have multifaceted physiological functions, and hydrogen sulfide appears to negatively affect metabolism. Researchers at Lakehead University in Thunder Bay, Ontario, Canada, led by Rui Wang, M.D., Ph.D., recently found that it inhibits pancreatic insulin secretion from islets and β-cell lines.

Given the key metabolic roles of the pancreas and liver, the researchers followed up these findings by investigating the role of hydrogen sulfide in glucose metabolism and insulin signaling in the $HepG_2$ human hepatoma cell line and in mouse hepatocytes.

They found that hydrogen sulfide down-regulated glucose uptake and glycogen storage, while at the same time enhancing the activity of an enzyme that increased glucose production. This combination of decreasing glucose input and enhancing glucose output contributes to hyperglycemia, which is a major symptom of insulin resistance.

In an article awaiting publication in ***Endocrinology*** *[endo.endojournals.org]*, the researchers say that the interaction of hydrogen sulfide and insulin in the liver plays a pivotal role in regulating insulin sensitivity and glucose metabolism. Hydrogen sulfide contributes to the development of hepatic insulin resistance, a key aspect of the metabolic perturbations leading to diabetes. ■

Eric Seaborg

STATS

U.S. boys are reaching puberty

6 months to 2 years

earlier than previously reported; African American boys are entering Tanner stages 2 to 4 at 9.14 years, white boys at 10.14 years, and Hispanic boys at 10.40 years.

Source: Herman-Giddens ME, Steffes J, Harris D, et al. Secondary sexual characteristics in boys: Data from the pediatric research in office settings network. *Pediatrics*, published online October 20, 2012, doi:10.1542/peds.2011-3291.

Hearing Impairment in Diabetes: A Meta-Analysis

➤ Diabetes patients, listen up: your disease may affect your hearing, according to an upcoming article in ***The Journal of Clinical Endocrinology & Metabolism*** *[jcem.endojournals.org]*. Led by Chika Horikawa, R.D., M.S., at the Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine in Japan, investigators conducted a meta-analysis of the prevalence of adult-onset hearing impairment in patients with and without diabetes.

The researchers searched the MEDLINE (1950 to May 30, 2011) and EMBASE (1974 to May 30, 2011) databases. The group selected studies in which data on both hearing-impaired and non-hearing impaired subjects was presented, in which hearing impairment was assessed by pure-tone audiometry that included at least 2 kHz of frequency range, and in which hearing impairment was categorized as chronic, progressive, sensorineural, or without specified cause. Thirteen eligible studies were identified, for a total of 20,194 participants and 7,377 cases.

People with diabetes were twice as likely to be hard of hearing as non-diabetic individuals. The prevalence was even more pronounced in diabetes patients under 60 years of age: compared to non-diabetic patients, they had 2.5 times the risk of hearing impairment, while those over age 60 had 1.5 times the risk.

The authors hypothesized that diabetes may negatively affect the microenvironment of the ear, leading to the progression of hearing impairment, and that the role of glycemic control in preventing hearing loss in diabetic patients should be studied. ■

Joanne McAndrews, Ph.D.

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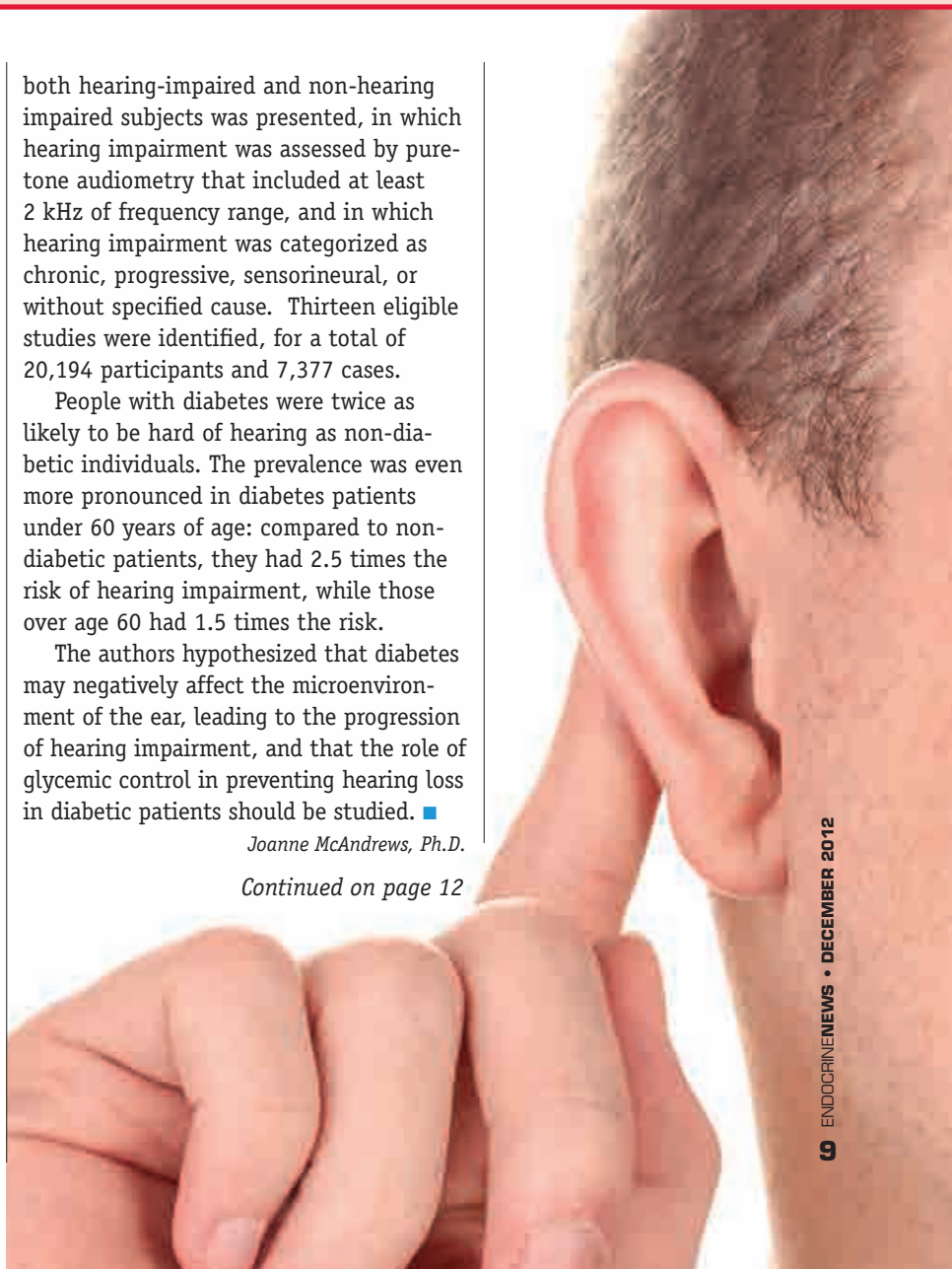


Specific detection of full-length glucagon from blood samples using a chemiluminescent ELISA kit

Why measure glucagon?

Glucagon is the most important counter-regulatory hormone to insulin in blood glucose homeostasis. It elevates blood glucose levels by stimulating gluconeogenesis and glycogenolysis while inhibiting glycogenesis and glycolysis mainly in the liver. Normal glucagon levels are very low in healthy individuals (< 200 pg/mL) compared to glucagon levels in severe pathophysiological states, such as Type I diabetes (Table 1). As a result, glucagon and its receptors have recently been actively pursued as therapeutic targets. Therefore, it is crucial to have available an assay for accurately, precisely and rapidly quantifying glucagon in blood samples.

A new ELISA meets the glucagon challenge

The development of an effective glucagon ELISA has been long delayed because of the difficulty in raising specific antibodies to mature glucagon. Mature glucagon is a peptide of 29 amino acids and its amino acid sequence highly conserved across the animal kingdom. Glucagon is synthesized from preproglucagon gene in pancreatic α-cells, processed and then secreted into the bloodstream. However, many immunoreactive glucagon forms have been identified in blood. EMD Millipore has developed a new, highly specific glucagon chemiluminescent ELISA kit (Catalogue No. EZGLU-30K) with no cross-reactivity to miniglucagon or glucagon 1–18 and < 5% cross-reactivity to oxyntomodulin.

Another challenge of measuring glucagon in blood samples is interference from serum or plasma matrix components. Therefore, samples need to be extracted prior to glucagon immunoassay. Solid phase extraction (SPE) is a common method of removing matrix components from blood samples; however, this method can be costly (over $300 per 96-well plate). We present a rapid, inexpensive method for extracting serum or plasma samples that enriches the sample for glucagon at a fraction of the cost of solid phase extraction, in only 4-5 hours.

Rapid, cost-effective sample extraction alternative to SPE

To evaluate our rapid extraction method, we collected plasma and serum samples with 500 kU/mL aprotinin and extracted in parallel using our rapid extraction method and SPE (Figure 1). Briefly, acetonitrile (ACN) was added to a final concentration of 60% in each sample. For human and rat samples, for example, 300 µL sample was mixed with 450 µL acetonitrile. Samples were vortexed immediately and centrifuged at 17,000 x g for 5 min. Supernatants were removed and samples were dried. Dried samples were rehydrated in 60 µL assay buffer to achieve 4-fold concentration over initial concentration. 20 µL was used for evaluation using the glucagon chemiluminescent ELISA kit, which showed good correlation between the two extraction methods (Figure 1).

Method	Sample	Population Studied	No. of Subjects	Measured Glucagon (pg/mL)
RIA	Fasting Plasma	Type I Diabetic	12	118 ± 9 (70 ~ 200)
		Diabetic (with Severe Ketoacidosis)	8	587 ± 195 (230 ~ 2,000)
		Diabetic (with Mild Ketoacidosis)	4	185 ± 13 (165 ~ 225)
		None Obese Normal	28	108 ± 10 (50 ~ 210)
RIA	Plasma	Obese Not Fasted	15	73 ± 4.7
		Obese Fasted for 3 Days		144 ± 15.7
RIA	Plasma	Normal	12	102 ± 25
RIA	Fasting Plasma	Healthy Volunteers	30	87.9 ± 23.8
RIA	Serum	Aorto-coronary By-pass Patients	78	72.6 ± 50.8
RIA	Plasma	Normal Male	15	130 ± 30
Unknown	Plasma	Basal (Male)	9	20.9
		After Insulin Infusion		83.6
RIA	Plasma	Normal Male	6	156.6 ± 17.3
RIA	Plasma	False Positive Case Report	1	23 ~ 197
				320 ~ 430 (Glucagon + OXM)
Unknown	Plasma	Case Report, Confirmed Glucagonoma (Male)	1	1,280 (Cited Nomal Range < 60)
Unknown	Plasma	Case Report, Confirmed Glucagonoma (Female)	1	271 (Cited Normal Range 40 ~ 140)
RIA	Serum	10 Female + 9 Male (Bioreclamation Donors)	19	65.1 ~ 189.4

Table 1: **Glucagon levels in various states, as reported throughout the literature.** Highlighted glucagon levels represent the most severe pathophysiological states.

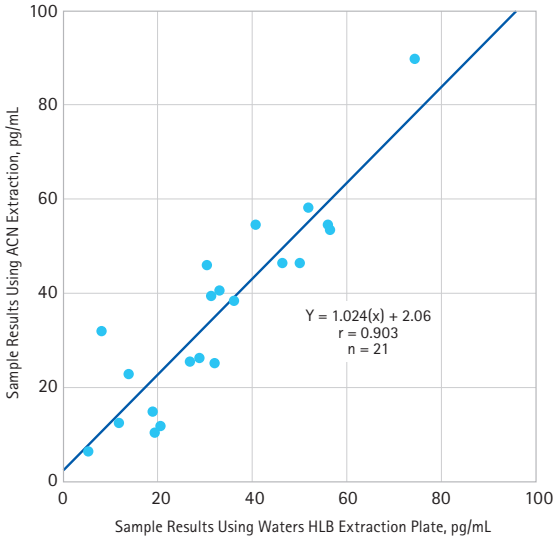


Figure 1: Correlation of glucagon measurements following sample extraction using rapid acetonitrile extraction (y-axis) with measurements following SPE (x-axis). 21 paired human plasma samples were extracted using the rapid extraction procedure (above) and the Waters Oasis® HLB Plate. Both sets of samples were dried and reconstituted in assay buffer. 20 µL was used for measurement of glucagon by ELISA using the chemiluminescent substrate.

Advancing metabolism and endocrine research with EMD Millipore's Glucagon ELISA Kit

Starting with 300 µL serum/plasma sample, this assay, including sample extraction, can be completed within a working day. With slight modifications and longer incubation time (24 - 48 hours), the same kit can be used to measure glucagon in mouse serum/plasma. The levels of glucagon in plasma samples from normal human subjects as measured using the EMD Millipore ELISA kit, in contrast to ELISA kits from competing suppliers, agree well with published glucagon levels derived from RIA, the long-held gold standard method for glucagon assay. Compared to RIA, however, this ELISA enables glucagon quantitation with far greater convenience and throughput. Therefore, this ELISA kit should be easily incorporated into new and ongoing research, preclinical and clinical studies of metabolism and endocrinology.

New ELISA Kits

Glucagon Human/Rat/Mouse (Catalogue No. EZGLU-30K)

GLP-1 HS (Active) Multi-species (Catalogue No. EZGLPHS-35K)

Along with glucagon, glucagon-like peptide 1 (GLP-1) plays a key role in metabolism. Among other functions, it sends satiety signals, increases insulin production and upregulates insulin sensitivity. Compounds that inhibit GLP-1 degradation are attractive therapeutic candidates for diabetes.

With these new ELISAs, measure full-length glucagon and GLP-1 with superior specificity, sensitivity, validated quality and cost efficiency.

Continued from page 9

Pubertal Changes in Hormones May Contribute to Mood Disorders

➤ As sex hormones rise during puberty and transform young bodies and minds, girls suffer from stress-related mood disorders at a higher rate than their male counterparts. The effects of sex hormones on the hypothalamic-pituitary-adrenal (HPA) axis may contribute to important differences in the sexes.

One stress-response hormone, corticotropin-releasing factor (CRF), may be a key player, because its receptors are concentrated in sensitive areas of the forebrain such as the amygdala, which regulates arousal, mood, and the HPA axis. Evidence indicates that one of these receptors, CRF_1, initiates neuroendocrine and behavioral responses to stress, but CRF_2 decreases these responses. For example, CRF_1 agonists increase anxiety-like behavior in rats, and CRF_2 agonists decrease this behavior. CRF_1 knockout mice are less anxious, and CRF_2 knockout mice are more anxious.

To see how the binding properties of these receptors change with age and sex, Jill M. Weathington, M.S., and Bradley M. Cooke, Ph.D., of the Neuroscience Institute at Georgia State University in Atlanta, measured them in the amygdala of prepubertal and adult rats.

Before puberty, the binding densities of the receptors were indistinguishable between the sexes in four subregions of the amygdala. After puberty, a clear difference emerged between the sexes in every subregion. CRF_1 binding was greater in adult females than in males, but CRF_2 binding was greater in adult males than in females. In a paper accepted for publication in ***Endocrinology*** *[endo.endojournals.org]*, the researchers say their study demonstrates that CRF receptors undergo maturational changes consistent with a divergence of the stress response system in males and females during puberty. This sex difference could play a role in predisposing women to stress-related mood disorders. ■

Eric Seaborg

Gastric Bypass and Ovulation

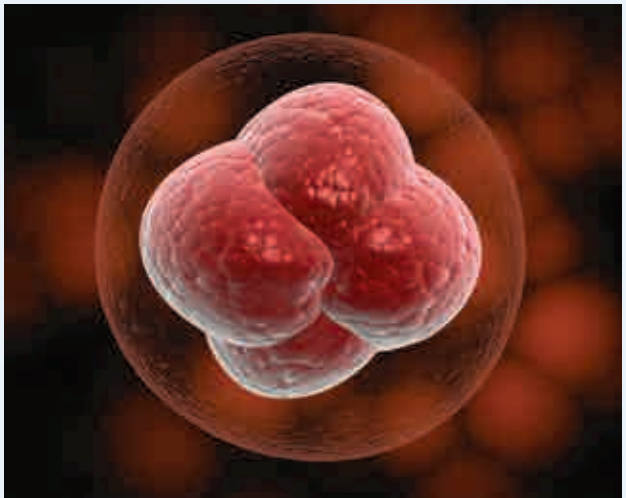
➤ Infertility is one complication of obesity that has perplexed researchers. For example, does it affect ovulation and sexual function? Gastric bypass surgery offers a novel perspective on this poorly understood relationship.

Richard S. Legro, M.D., at the Pennsylvania State University College of Medicine, Hershey, Pennsylvania, led a team to find out whether Roux-en-Y gastric bypass, the most frequently performed gastric bypass in the United States, would improve the frequency and quality of ovulation and sexual function in 29 formerly morbidly obese women ages 18–40 years.

In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism*** *[jcem.endojournals.com]*, the researchers report that post-surgical weight loss resulted in shorter menstrual cycles though of normal duration, specifically the follicular phase shortened while the luteal phase remained constant, and increased sexual desire and arousal. Other measurements, such as bone mineral density and level of facial sebum, an indication of clinical hyperandrogenism, did not change significantly. Notably, and despite the researchers' hypothesis to the contrary, ovulatory function and frequency did not improve significantly.

The researchers conclude that morbid obesity and body composition do not significantly affect ovulation. ■

Kelly Horvath



Low IGF-I Linked to Alzheimer's in Men

➤ It is widely accepted that the endocrine hormone, insulin-like growth factor (IGF-I), contributes to the body's aging process. New research suggests it might also play a role in Alzheimer's disease in elderly men.

In a study, appearing in ***The Journal of Clinical Endocrinology & Metabolism*** *[jcem.endojournals.org]*, a team of French researchers led by Emmanuelle Duron, M.D., Ph.D., Olivier Hanon, M.D., Ph.D., of Broca Hospital and Jacques Epelbaum, M.D., of Centre for Psychiatry and Neuroscience UMR 894 Inserm, Paris Descartes University in Paris, investigated whether a link exists between IGF-I and insulin-like growth factor binding protein (IGFBP-3) serum levels and cognitive impairment, including Alzheimer's disease.

The study included 694 participants older than 65 years (218 men and 476 women), of whom 481 had memory complaints. Those participants were given cognitive tests and were diagnosed with either Alzheimer's disease or mild cognitive impairment. The remaining 213, without memory loss complaints, comprised the control group. The researchers found a significant link between low serum levels of IGF-I and IGFBP-3 and Alzheimer's disease in men but not in women. For instance, in men, IGF-I was 137 ± 69 ng/ml in Alzheimer's disease, but 172 ± 91 ng/ml in the controls. IGFBP-3 was 3,675 ± 1,542 ng/ml in the Alzheimer's disease group, compared to 4,488 ± 1,893 ng/ml in the controls.

The investigators write that these results "justify a longitudinal study to evaluate whether circulating IGF-I/IGFBP-3 are determinants of cognitive decline according to gender." ■

Glenda Fauntleroy

Potassium Bicarbonate Counteracts Effects of High-Salt Diet

➤ Potassium bicarbonate supplements can counteract some of the negative effects of high sodium chloride intake, a new study asserts.

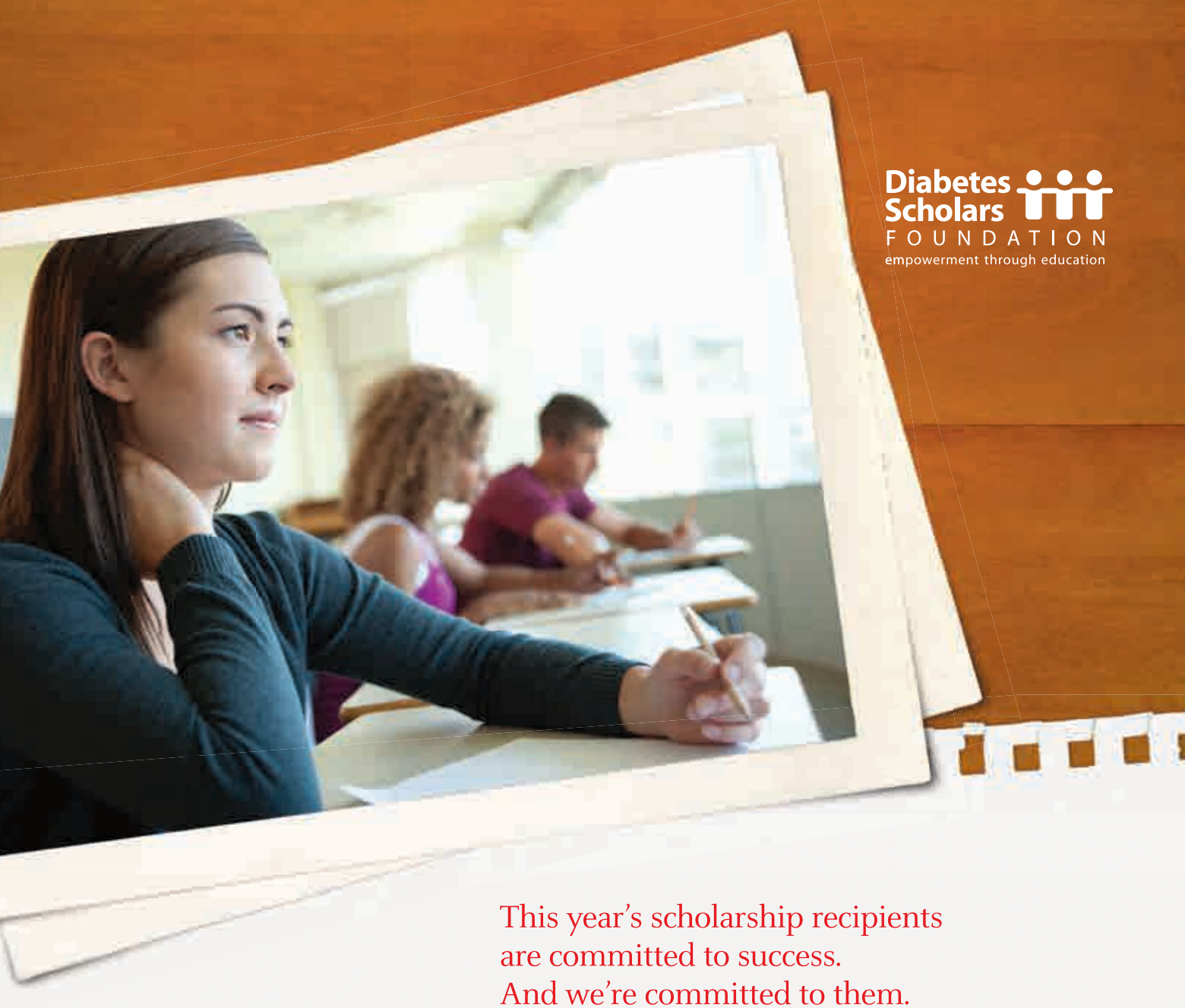
The dangers of too much salt in the diet are well known, and one of them is the induction of a low-grade metabolic acidosis associated with bone resorption and protein loss. To test whether alkaline mineral salts can counter this effect, researchers led by Judith Buehlmeier, Ph.D., of the German Aerospace Center in Cologne, conducted a randomized, crossover study of eight healthy males. During a control period, the subjects were checked for the effects of eating a diet very high in sodium chloride. They then ate the same diet along with potassium bicarbonate supplements.

During the potassium bicarbonate period, the subjects' urinary excretion of potentially bioactive free glucocorticoids and free cortisone dropped 14 percent. Their urinary excretion of calcium declined 12 percent, and excretion of the bone resorption marker, *N*-terminal telopeptide of type I collagen, dropped 8 percent. The researchers measured phenylalanine hydroxylation as a marker of net protein catabolism and found that the supplements led to a decrease just below the level of statistical significance. The bone-preserving properties of the potassium bicarbonate did not compensate for the full metabolic consequences of the high-sodium diet, perhaps because acidosis is just one of several factors contributing to bone catabolism when sodium intake is high. Other processes, such as hormonal or osteoimmunological effects and ion-exchange could also be contributing in ways that the acid-base balance would not affect.

In an article to be published in ***The Journal of Clinical Endocrinology & Metabolism*** *[jcem.endojournals.org]*, the researchers conclude that in the face of high dietary salt intake, potassium bicarbonate can induce a post-prandrial shift to a more alkaline state that reduces metabolic stress. This shift leads to an anti-catabolic state featuring decreased bone resorption and protein wasting, which could have long-term benefits for the musculoskeletal system. ■

Eric Seaborg

Continued on page 15



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Continued from page 13

Smoking Exacerbates Effects of Dietary Fat on Liver

➤ Accumulating evidence suggests that smoking also contributes to fatty liver disease, adding liver pathology to the long list of cardiac, pulmonary, and metabolic disorders smoking is already known to affect. Moreover, a high rate of hepatic steatosis occurs in obese individuals. A new study examines whether fats and smoking are connected in developing fatty liver, which typically leads to more serious liver disease.

Led by Amiya P. Sinha-Hikim, Ph.D., at the Charles R. Drew University of Medicine and Science, Los Angeles, scientists fed mice a high-fat diet (HFD) comprised of 60 percent fat, causing common obesity complications, including visceral fat, hyperglycemia, insulin and leptin resistance, and fatty liver. Control mice ate normal chow. The team injected either nicotine or saline twice daily into mice from both groups. A separate pair of groups was additionally given the lipolysis inhibitor acipimox plus water or drinking water alone. In their paper, to be published soon in ***Endocrinology*** [*endo.endojournals.org*], the researchers report that HFD mice injected with nicotine showed increased oxidative stress, hepatic triglycerides, and hepatocellular apoptosis, with disruption of the adenosine monophosphate kinase signaling pathway, causing increased lipolysis and hepatic lipogenesis.

The researchers conclude that a high-fat diet and smoking synergistically lead to fatty liver disease. Their model can be used to develop an effective treatment at the molecular level, they add. ■

Kelly Horvath

Prostate Cancer Treatment Could Target Estrogen Receptor β2

➤ As prostate cancer advances, it can morph into forms that stymie effective therapies. Increased knowledge of the variants can provide fresh approaches to treatment. Androgen ablation, the frontline adjuvant treatment, loses effectiveness when the disease advances into an androgen-independent state. Once in that state, the disease often metastasizes to bone. In a search for ways to counteract this dangerous progression, researchers are looking at the role of estrogen receptors.

The estrogen receptor, ERβ, has several variants, and the main one, ERβ1, acts as a tumor suppressor with anti-metastatic properties in the prostate. However, the expression of ERβ1 drops during cancer progression, whereas expression of the variant ERβ2 grows. A team of researchers led by Anders Ström, Ph.D., of the University of Houston, Texas, studied the actions of these variants in the prostate cancer cell line PC3, which is often used as a model to study bone metastasis.

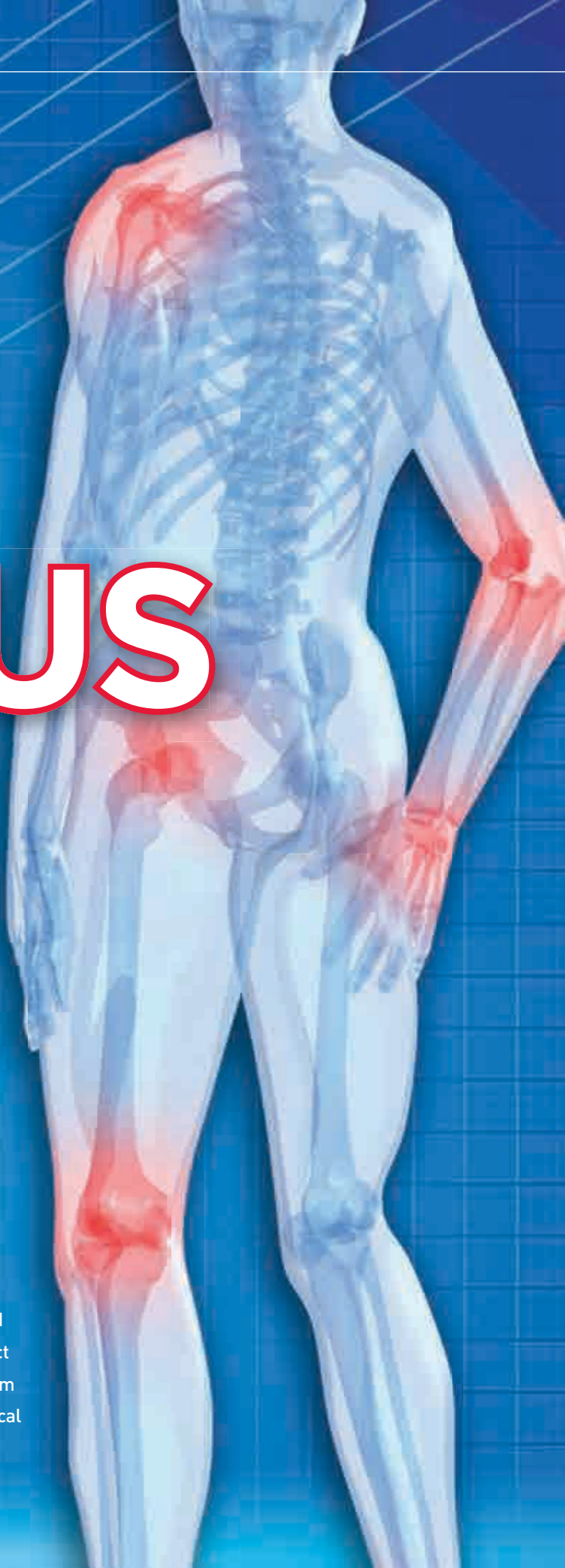
In their study of the effects of ERβ1, the most prominent findings were its simultaneous repression of cell proliferation and bone metastasis genes. It affected multiple cell-cycle genes at both the mRNA and protein levels. It strongly down-regulated *RUNX2,* an important gene in bone formation and bone metastasis.

In contrast, ERβ2 up-regulated RUNX2 at the mRNA level. ERβ2 also increased the expression of Twist1, a factor whose expression strongly correlates with high Gleason scores in prostate carcinoma. ERβ1 inhibited a large number of proliferation markers, and ERβ2 had opposite effects.

These results led the researchers to the conclusion that in PC3 cells, ERβ1 acts as a tumor suppressor, whereas ERβ2 increases proliferation and up-regulates factors involved in bone metastasis. Writing in ***Molecular Endocrinology*** *[mend.endojournals.org]*, the authors say that ERβ2 deserves more study as a possible new target for prostate cancer treatment. ■

Eric Seaborg

Managing LUPUS



Introduction

Systemic lupus erythematosus (SLE) is a syndrome characterized by dysregulation of the immune system and widespread inflammation that can involve multiple organs and body systems. Skin and joints are most frequently affected. SLE afflicts women up to nine times more frequently than men and usually manifests during the childbearing years. SLE is identified serologically by autoantibodies to DNA, RNA, other nuclear antigens, and cytoplasmic/cell surface molecules. Numerous studies (human and animal models) provide evidence for bi-directional communication between the immune and endocrine systems and disruptions in communication that contribute to susceptibility and severity of disease. This article will discuss the impact of hormones and hormone-related factors in SLE from the perspectives of researchers in basic science, clinical science, and clinical practice.

Clinical Practitioner Perspective

By Ida Dzifa Dey, M.B. Ch.B., M.W.A.C.P. and David A. Isenberg, M.D., F.R.C.P., F.A.M.S.

Dey is a clinical research fellow and Isenberg is a professor at the Centre for Rheumatology, Department of Medicine, University College London Hospitals, London.

Highlights

- SLE is a multisystem autoimmune rheumatic disease (ARD) with a wide spectrum of clinical manifestations.
- Pathogenic factors include genetic, environmental, ethnic, hormonal, and immunological factors.
- Prevalence of the disease is influenced by ethnicity, gender, age of onset, and geographical location.
- Diagnosis is based on combination of clinical features and laboratory tests.
- Morbidity and mortality have improved in the past 50 years due to optimizing treatment modalities—notably steroids and immunosuppressives, and supporting therapies such as anti-hypertensives, dialysis, and transplantation—but more needs to be done.

Systemic lupus erythematosus (SLE) is a highly variable multisystem autoimmune rheumatic disease (ARD). It is clearly not a homogenous disease entity but a variable syndrome with some patients manifesting mild clinical signs (e.g., skin rash), whereas others present with potentially fatal disease (e.g., nephritis, cerebral involvement).

Classification and Diagnosis

In 1971, the American College of Rheumatology published preliminary criteria for the classification of SLE for clinical trials and studies and revised these criteria in 1982 and 1997. These classification criteria are often used as the basis for diagnosis, although strictly speaking, they have not been formally validated for that purpose. They consist of four cutaneous, four systemic, and three laboratory components.[1] These criteria show about 90 percent sensitivity and specificity but have weaknesses (e.g., patients with cutaneous lupus can be diagnosed as having SLE without any systemic features). The Systemic Lupus International Collaborating Clinics (SLICC) group has recently re-examined the criteria—incorporating new knowledge of autoantibodies, neuropsychiatric lupus, and advances in imaging—recognizing the importance of low complement and the need for biopsy-proven lupus nephritis to be a "stand alone" criterion. At least four of these criteria need to have been present at some time, not necessarily simultaneously, for lupus to be diagnosed.[2] The diagnosis should be based on clinical signs and symptoms in general, and supported by laboratory evidence.

Epidemiology

Lupus is the third most common ARD. Its incidence rates vary with a worldwide annual incidence from 1.8 to 7.6 cases per 100,000. Current studies suggest the incidence may be increasing.

Differences in prevalence rates occur among people of the same race in different geographical locations. African Americans/African Caribbean women have a higher rate of SLE, followed by Asians, then Caucasians.[3] One in 10,000 white males, one in 1,000 white females, and one in 250 African American females have SLE in the United States. Previous studies reported low rates of SLE in Africa,[4] but paradoxically high rates among black women in the Americas, the Caribbean, and Europe, suggesting the importance of environmental influences. However that may not necessarily be the case and the apparent lower rate in Africa may be due to under-reporting.

Ninety percent of persons with SLE are female. The disease frequently starts in women of childbearing age. The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease.[5] The female-to-male ratio varies from 4.3 to 13.6:1 during the childbearing years, but the pre-puberty and post-menopause sex ratios are almost identical between females and males (2.3:1 and 2.2:1), implicating a correlation of maximal female sex hormone production with the onset of SLE.[6] Of interest, SLE seems to be common in men with Klinefelter syndrome (genotype XXY) [see story, page 24], also suggesting a strong hormonal influence.[7]

Clinical Features

There is a wide spectrum of clinical features and patients are highly variable in their disease manifestations. Almost every organ in the body can be affected, from the skin to the central nervous system. It is important to recognize differences between active ongoing disease activity and organ damage. Approximately one-third of patients develop other autoimmune diseases, notably autoimmune thyroid disease, Sjögren's syndrome [see story, page 24], and antiphospholipid syndrome.[8]

Management

The social and psychological effects of both the chronic disease and its therapy, combined with its effects on fertility and pregnancy, must be recognized and dealt with by physicians and patients. Some general advice needs to be given to patients, such as appropriate rest and avoiding excess stress. Avoidance of ultraviolet light exposure is recommended, because this may cause disease flares and a photosensitive rash. A diet low in saturated

fats and high in fish oils and avoidance of both smoking and estrogen-containing contraceptive pills are advised. Because fatigue is common, a careful exploration of causes of fatigue (including anemia, hypothyroidism, and fibromyalgia) by the physician is important. Vitamin D supplementation may have benefits in the treatment of patients who are deficient.

Pharmacological therapy is directed at organ- and non–organ-threatening disease, organ-specific measures, and adjuvant therapies (e.g., bone and renal protection). Patients with SLE are treated with four main groups of drugs, often in combination: non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, corticosteroids, and cytotoxic drugs.

Complications of therapy include osteoporosis, hypertension, and metabolic syndrome.

Biological therapies directed at immune processes implicated in the pathogenesis of the disease are being developed and show promise for the future.

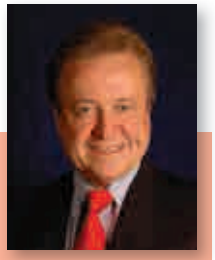
Future

Morbidity and mortality have improved but the advent and development of newer targeted therapies offer further potential for increased survival. However challenges such as the increased risk of atherosclerosis and possibly malignancy remain.

Clinical Researcher Perspective

By Robert G. Lahita, M.D., Ph.D.

Chairman of Medicine, Newark Beth Israel Medical Center; Professor of Medicine, University of Medicine and Dentistry of New Jersey, Newark.



Highlights

- Lupus has a major endocrine component.
- Estrogens modulate disease activity.
- Androgens may be protective.
- Hyperprolactinemia can cause a lupus-like syndrome.
- Male hormones are not an adequate treatment.

Systemic Lupus Erythematosus is the prototypic autoimmune disease. The disease is associated with many T cell and B cell abnormalities and the hallmark of the disease is the synthesis of autoantibodies which are directed at self antigens. There is no genetic basis for this illness, other than association with immune response genes on chromosome 6. There are facets of the disease that are clearly endocrine in nature including the significant effect that sex steroid hormones have on the illness, and the role of prolactin.

Murine Work

An extensive body of work has been done with murine models of lupus, some of which have significant endocrine aspects to the presentation of the murine disease.[1] The *NZB/NZW* F1 hybrid mouse that develops SLE because of genetic influence predominates in the females of the strain, as with the human illness. Males who are gonadectomized have worse disease whereas females who are ovariectomized have quiescent disease, revealing the importance of estradiol in the exacerbation of the illness and the protective nature of androgens.[2] There is also a strain of mouse, the *BXSB*, with SLE that is not mediated by hormones, wherein males succumb to the disease rather than females.

Estrogen and SLE

Studies in humans have examined the metabolism of estrogen in both females and males with SLE. Hydroxylation of estrone toward feminizing 16 hydroxy metabolites was the predominant route in patients with SLE (male and female). Catechol estrogens were depleted in patients with SLE.[3]

Androgens and SLE

In the absence of corticosteroids that decrease levels of free testosterone, oxidation of testosterone at C-19 was increased in female patients with SLE.[4] Males did not show this metabolic aberration. For many years, the occasional observation of autoimmune disease in hypogonadal males with Klinefelter syndrome or acquired hypogonadism has reinforced the putative link between the absence of androgens and worsened disease in humans. The observation that hormones such as dehydroepiandrosterone (DHEA) could ameliorate the murine illness suggested that this might be useful as a therapy in humans.[5] Unfortunately, this was not the case. DHEA therapy of SLE patients did not meet end points in early studies and was abandoned. Use of 19-nortestosterone to treat the disease and avoid aromatization of estrogens was also unsuccessful. Curiously, males who were treated with this steroid had worsened disease, possibly because of feedback inhibition of endogenous testosterone.

Klinefelter Syndrome

Males with Klinefelter Syndrome also get SLE and other autoimmune diseases, suggesting that the epigenetic effects of one X chromosome might ultimately be behind the manifestations of the illness. Hypogonadotrophic Klinefelter patients show no increase of the disease. Autoimmune disease in Klinefelter males is the same as in the general male population.[6] It may be either the higher levels of estrogen or the lower levels of androgen that further the illness in the Klinefelter male.

Hyperprolactinemia

Hyperprolactinemia from a micro- or a macro-adenoma of the pituitary can be associated with SLE.[7] In such cases, the disease is clinically identical to the typical idiopathic

'Factors in the microenvironment can enhance or limit immune system activity and lead to immunopathology.'

form. The disease remits when bromocriptine analogs are given or the adenoma is removed. Lupus flares during pregnancy are well known, but patients are likely to have a flare of the disease any time postpartum. Nevertheless, the relationship of the hyperprolactinemia of pregnancy to flares of lupus is not known.

Use of Sex Steroids to Control SLE

Use of sex steroids like DHEA and 19-nortestosterone to treat lupus have not been successful due to their many side effects and overall lack of efficacy.[8]

Oral Contraceptives and Hormone Therapy

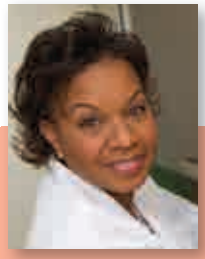
For many years, oral contraceptives were incriminated as a cause of heightened lupus activity. These observations might relate to the total amounts of ethinyl estradiol in early preparations. Further research has indicated, however, that oral contraceptives can be used safely in patients with lupus.[9] The same was true of hormonal replacement therapy in postmenopausal women with the disease. However, a secondary manifestation of procoagulant activity, antiphospholipid syndrome, may coexist with systemic lupus in certain patients and is a definite contraindication to any estrogen use, pre- or postmenopausal.

Pregnancy

Fetal wastage occurs in 50 percent of all pregnancies in lupus patients, and still births, miscarriage, and prematurity are common.[10] Hypertension, antiphospholipid antibodies, and hypocomplementemia may be at the root of most of these problems. These fetal problems might be related to local vasculitis, anti-trophoblastic antibodies, or the procoagulant state resulting from antiphospholipid antibodies. The health of the mother is also at issue, and it is unclear whether women with quiescent SLE worsen during pregnancy or whether disease activity is worse when the mother's disease is serologically and clinically active during conception. The immunosuppression or immunomodulating effects of various steroids like estriol and progesterone during pregnancy are unknown, but must play a role. This entire subject is appropriate for further investigation in lupus and other rheumatic diseases.

Basic Researcher Perspective

By Cherie Butts, Ph.D.



Associate director of immunology research at Biogen Idec, Inc., in Cambridge, Massachusetts.

Highlights

- Immune cells involved in innate and adaptive responses express steroid hormone receptors.
- Changes in expression of subtypes of steroid hormone receptors by immune cells could increase susceptibility to SLE.
- Glucocorticoids are generally immunosuppressive, but can also shift immunity toward responses involved in SLE.
- Resistance to steroid hormones could play a role in disease development.
- Sex hormones affect immunity and could contribute to gender differences in disease incidence.

Impact of Steroid Hormones on Immunity

The immune system provides a strong defense against internal and external threats. However, factors produced in the microenvironment can either enhance or limit its activity and lead to immunopathology. Steroid hormones alter both innate and adaptive immune processes and steroid hormone receptors (e.g., glucocorticoid receptor [GR], estrogen receptor [ER], and progesterone receptor [PR]) are expressed by a variety of immune cell populations, including granulocytes, natural killer (NK) cells, monocytes, dendritic cells (DCs), and B and T lymphocytes, which can affect disease outcome.[1] Many autoimmune/inflammatory conditions, such as systemic lupus erythematosus (SLE), exhibit gender differences in incidence. This suggests a role for sex hormones in disease development.[2] Numerous studies (human and animal model) provide evidence for bi-directional communication between the immune and endocrine systems and disruptions in communication that contribute to susceptibility and severity of disease.

Glucocorticoids (both endogenous-cortisol [or corticosterone in rodents] and synthetic dexamethasone) modulate immunity, and their overall effects depend on dose—pharmacologic or physiologic—and temporal sequence of release in relation to antigenic or pro-inflammatory challenges.[3] Stress levels of glucocorticoids result in rapid involution of the thymus and lymphocyte apoptosis. Glucocorticoids also orchestrate redistribution of circulating white blood cells with neutrophilic leukocytosis, eosinopenia, monocyteopenia, and altered ratios of T-lymphocyte subtypes, resulting in decreased peripheral blood $CD4^+$ and increased $CD8^+$ cells and decreased infiltration of neutrophils and monocytes into tissues.

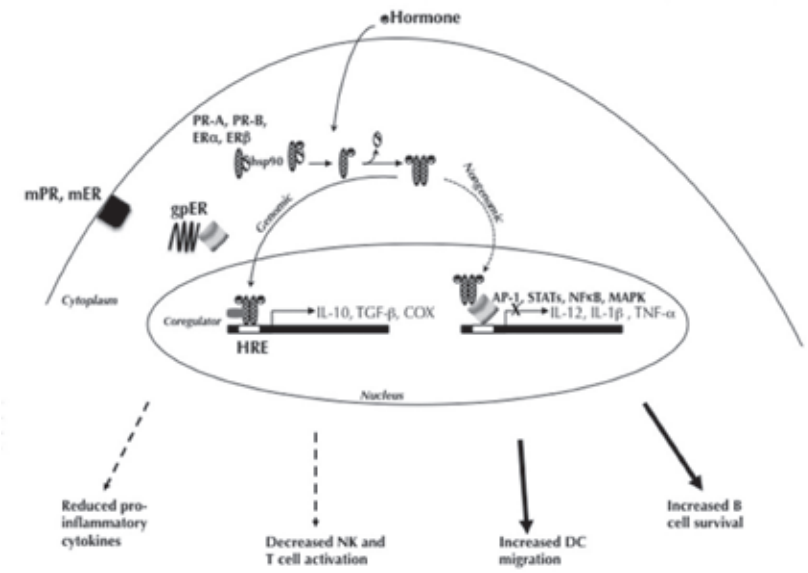


Figure 1. Sex hormone actions on immune cell function. Binding of sex hormones to intracellular receptors leads to recruitment of coactivators and corepressors that facilitate transcriptional activation or suppression of target genes involved in inflammation. Ligand-receptor complexes can also serve a non-genomic role by interacting with other intracellular proteins. As a result, sex hormones are able to modify immunity to enhance pro-inflammatory cytokine production by monocytes and dendritic cells, stimulating NK and T-cell activation, increasing B-cell survival, and also influencing leukocyte trafficking–all important events in SLE. In addition, membrane-bound forms of steroid hormone receptors are able to act quickly to modify cell activity by interfering with activity of intracellular proteins.

The relatively greater sensitivity to glucocorticoid suppression of components of cellular versus humoral immunity tends to shift immune responses from a cellular to a humoral pattern, which is important in SLE.[4] Physiological glucocorticoids can also activate the mineralocorticoid receptor (MR). The primary receptor in immune cells is GR, which is consistent with the physiologic role of glucocorticoid regulation of the immune system by stress levels of these hormones. Recent studies have shown a role for the MR, acting as a receptor for cortisol/corticosterone, in the monocyte/macrophage lineage and potentially in other immune cells. In SLE, glucocorticoids can increase expression of the IL-6 receptor—supporting B cell growth. Because SLE is characterized by excessive or inappropriate antibody production, it is important to delineate whether glucocorticoids contribute to or exacerbate this shift. These findings indicate that in addition to their suppressive role, glucocorticoids can stimulate some aspects of the immune or inflammatory response to initiate or aggravate SLE.

Impaired glucocorticoid control of inflammation could result from a lack of responsiveness in cells and tissues that normally respond to circulating glucocorticoids due to impaired receptor function.[5] The contribution of the glucocorticoid receptor to glucocorticoid resistance has been explored in studies examining binding number and affinity characteristics of GR in SLE. Patients who exhibit hormone resistance had abnormally high levels of GRb (a dominant-negative isoform of the GR) or defective, mutated GR. A decrease in GR number in mononuclear cells was also identified in some lupus patients, and patients had a higher percentage of lymphocytes with high P-glycoprotein activity—a molecule responsible for transporting steroids outside the cell. In addition, patients with SLE often require large doses of glucocorticoids before a therapeutic effect is seen. Furthermore, a relatively recent study examining GR in SLE patients showed not only reduced GR expression in, but also lower binding affinity for glucocorticoids.[6]

In addition to glucocorticoids, sex hormones modulate immune responses. This has been especially demonstrated by studies examining immune function during pregnancy. Sex hormones can act indirectly on immunity by inducing epithelial and other cells to secrete factors that modify immune cell activity or directly by binding sex hormone receptors expressed by immune cells (Figure 1). They alter both innate and adaptive immune responses. Different isoforms of receptors for estrogen (ER) and progesterone (PR) are expressed by a variety of immune cell populations (e.g., dendritic cells, monocyte/macrophage populations, B lymphocytes, T lymphocytes) involved in SLE. Immune cells of the myeloid lineage express ERb, which is thought to uniquely facilitate binding to plant-derived and synthetic estrogens. In addition, PR-A:PR-B ratios change during an inflammatory response. This is due, in part, to the increase in PR-A gene expression initiated by NF-kB. Sex hormones indirectly alter immunity by modifying secretion of factors such as transforming growth factor b (TGF-b), interleukin 10 (IL-10), and prostaglandins, by epithelial, endothelial, and other cells.[7] Low-to-moderate concentrations of estrogen have been shown to increase severity of a variety of autoimmune diseases driven by B and T cells and to increase antibody production by B cells. Therefore, estrogen has been implicated in improper regulation of B-cell development and aggravation of SLE and is thought to be a primary contributor to gender differences in incidence of disease.[8] ■

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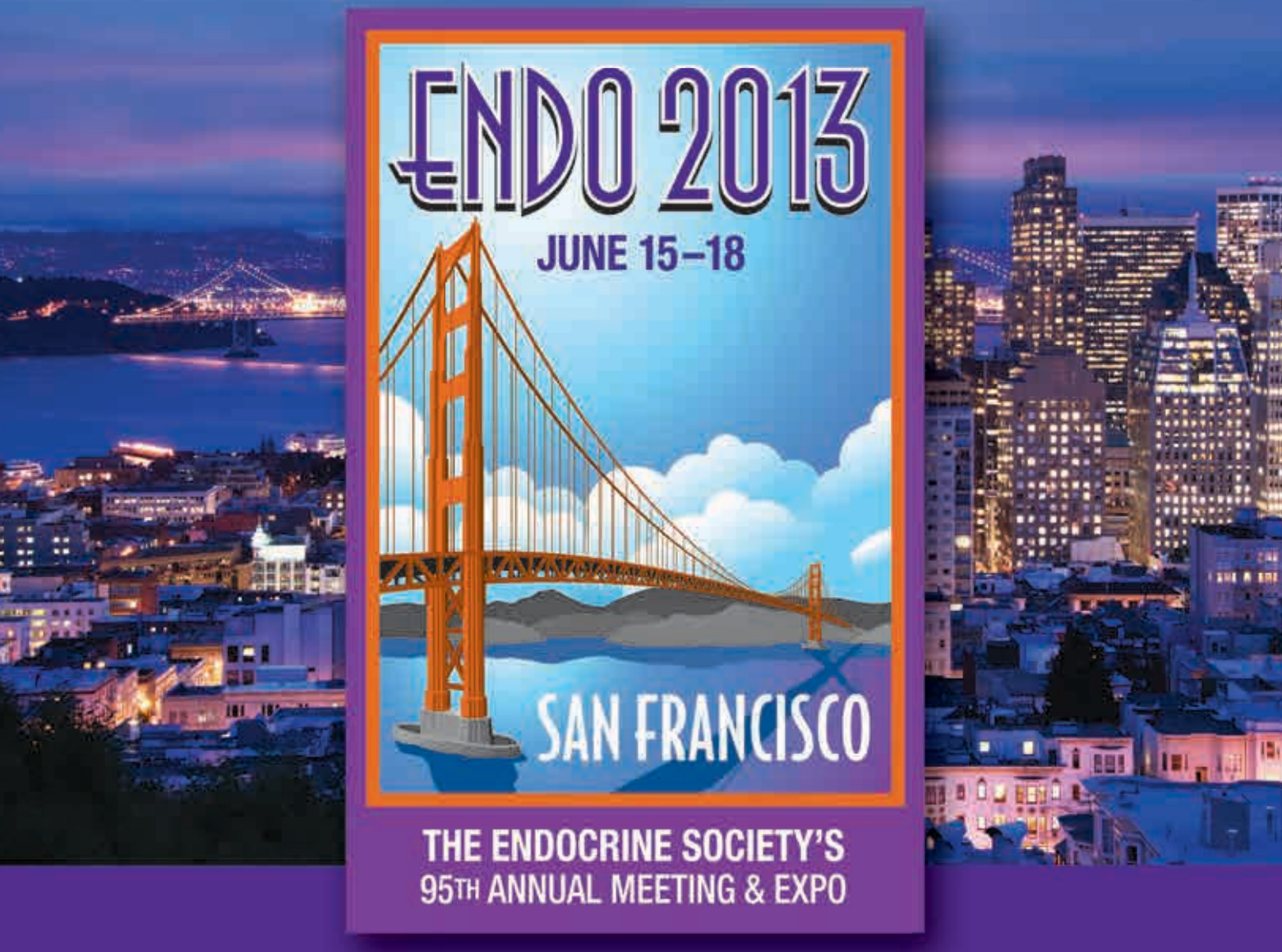

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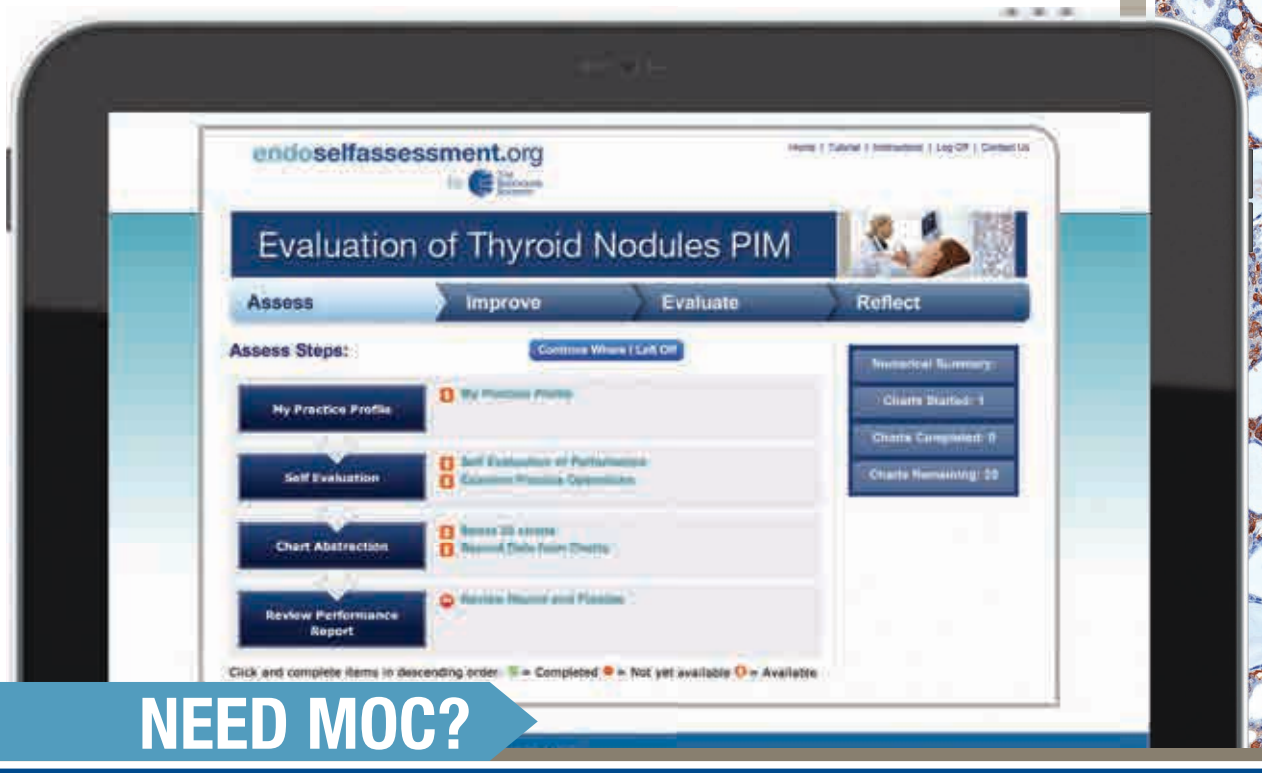

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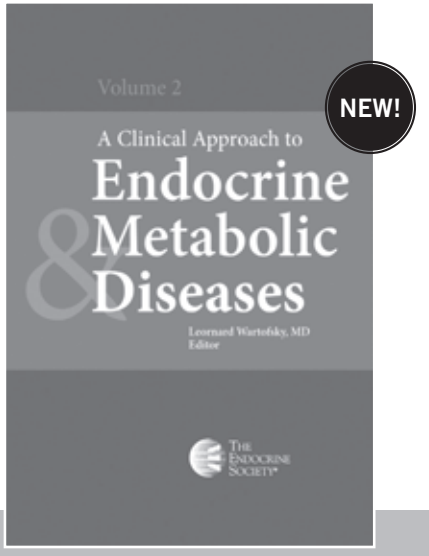

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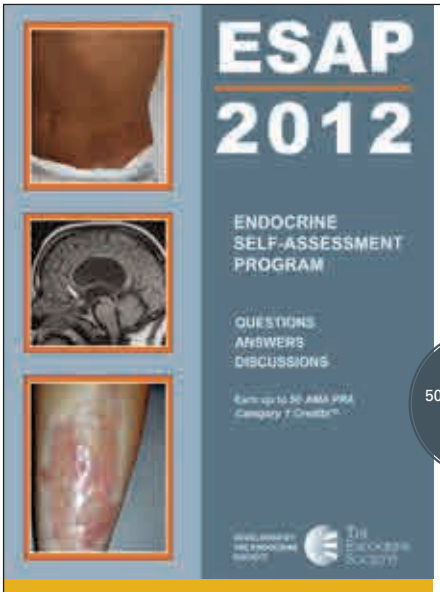

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Two Conditions that Challenge Diagnosis

Sjögren's Syndrome

By Terri D'Arrigo

When pro tennis star Venus Williams dropped out of the 2011 U.S. Open, she called national attention to Sjögren's syndrome, an autoimmune disease in which the immune system attacks the body's own moisture-producing glands. Williams revealed that she had been diagnosed with Sjögren's earlier that summer and had been coping with symptoms—dry eyes, dry mouth, joint pain, and profound fatigue—that left her feeling unable to compete.

At the time, Williams told the press that she had been suffering from symptoms for several years, but didn't know the cause until she was diagnosed. According to Denise L. Faustman, M.D., Ph.D., director of the Immunobiology Laboratory at Massachusetts General Hospital and associate professor of medicine at Harvard Medical School in Boston, Williams' case is typical. "Reports say that it takes roughly seven years from the time patients initially experience symptoms to the time they're diagnosed."

The reason for this delay is the broad range of symptoms, she said. "Dry mouth gives you a problem with cavities, so the dentist will say you need to brush your teeth more. Dry eyes give you a problem with contact lenses, so the eye doctor will tell you to switch to glasses. Fatigue can be from anything. Sjögren's is a cryptic disease."

Indeed, diagnosis is a three-specialty process, said Alan Baer, M.D., director of the Jerome L. Greene Sjögren's Syndrome Center and associate professor of medicine at the Johns Hopkins Division of Rheumatology in Baltimore. "It's a coordinated evaluation by rheumatologists, ophthalmologists, and oral surgeons or oral pathologists."

Because the symptoms are so broad, it's difficult to know when to suspect Sjögren's. 'The same antibodies are also seen in lupus and rheumatoid arthritis,' Baer said.

Methods for diagnosing Sjögren's include a blood test to determine the presence of certain antibodies, ocular staining in which the surface of the eye is treated with a vegetable dye to reveal damaged cells, and a biopsy of salivary glands from the inner lip to check for injury. In the April 2012 issue of *Arthritis Care & Research*, the American College of Rheumatology published new guidelines recommending that clinicians use these tests as a standard for diagnosis. Another common test involves placing a strip of filter paper in the lower eyelid to measure tear production.

Yet even with these tests, diagnosis is tricky. "The same antibodies are also seen in lupus and rheumatoid arthritis," explained Baer. "Also, clinicians tend to be reluctant to perform lip biopsies, and the results are often interpreted incorrectly by pathologists."

Because the symptoms are so broad, it's difficult to know when to suspect Sjögren's and get tested, Baer added. "Dry eyes and mouth become more common as you get older, and only a small percentage of people with those [symptoms] will actually have Sjögren's. But if the problems increase and there are also systemic symptoms such as joint pain or fatigue, or there is swelling of lacrimal [tear] or salivary glands, that should prompt your doctor to think about Sjögren's."

Faustman notes that autoimmune diseases tend to cluster in both individual patients and in families. "If you have one autoimmune disease, that signals to me to look for others. Or if there is a family history of autoimmune disease—one person has hypothyroidism, another has Crohn's disease, another has rheumatoid arthritis—that will raise a flag."

Gender is also a consideration: 90 percent of the nation's estimated 3 million people with Sjögren's are women.

Currently, there is no cure for Sjögren's. Treatment focuses on alleviating symptoms, said Baer. "We can treat dry eyes with artificial tears and we can use products for dry mouth, but we aren't able to alter the immune process yet."

In an effort to provide their patients with short-term relief, some doctors prescribe drugs approved by the U.S. Food and Drug Administration for other conditions, a strategy known as "off-label" use. These drugs include the corticosteroid prednisone, which suppresses the immune system and helps to bring down inflammation in the joints, and the anti-malarial drug quinine. However, these drugs are not recommended for long-term use because of possible side effects.

Although Sjögren's is incurable, patients can take steps to minimize their symptoms. Baer recommends using a humidifier as necessary and avoiding dry or windy environments. He also notes that certain antidepressants and drugs that treat overactive bladder and gastrointestinal conditions can make symptoms worse, mainly because their side effects include decreased saliva production.

Williams has said that adopting a vegan diet has helped her battle the condition and continue competing. Although a specific "Sjögren's diet" is not known, the Sjögren's Syndrome Foundation recommends an "anti-inflammatory diet" that emphasizes whole fruits and vegetables, healthy fats like omega 3 oils, fiber, and moderate amounts of organic meat. The anti-inflammatory diet also curtails consumption of trans or hydrogenated fats, refined oils, processed foods, red meat, and artificial sweeteners and preservatives; evidence suggests that these foods promote inflammation. ■

D'Arrigo is a health writer in Holbrook, New York.

Symptoms of Sjögren's Syndrome

- Dry eyes, with burning or redness
- Dry mouth, difficulty swallowing
- Decreased sense of taste
- Increased dental cavities
- Enlarged jaw glands
- Excessive fatigue
- Muscle and joint pain

Klinefelter Syndrome

By Glenda Fauntleroy

Although considered the most common chromosomal disorder in humans, the subtle symptoms of Klinefelter syndrome can result in a man living with the condition his entire life without ever being diagnosed.

Klinefelter affects only males. Instead of having the usual XY chromosome pattern of most males, boys are born with an extra X chromosome in most of their cells, causing an XXY pattern. The exact cause of the extra X chromosome is unknown, but an estimated one in 500 males has the extra X, which can come from either parent. The syndrome, however, is a random occurrence and is not inherited.

Also called the XXY condition or 47, XXY, Klinefelter syndrome gets its name from physician Harry Klinefelter, who published a paper in 1942 about several men with enlarged breasts and small testes and an inability to produce sperm. Whether a man will have these traits or others, such as sparse facial and body hair or poor motor skills and weak muscle tone, depends on the number of XXY cells he has and the amount of testosterone he produces. Many men, however, don't have noticeable symptoms.

"The traits are not recognizable unless they are severe," said Ilene Fennoy, M.D., a clinical professor of pediatrics at Columbia University Medical Center in New York, who specializes in treating boys with the disorder.

"About 66 percent of males with Klinefelter syndrome are never diagnosed, and only about 10 percent are diagnosed prior to puberty," she said. The majority of cases detected before a boy reaches puberty are detected during prenatal amniocentesis, according to Fennoy.

Many other cases are diagnosed when men undergo fertility testing. Although XXY males can have normal sex lives, between 95 and 99 percent are infertile because they produce no or minimal sperm. Klinefelter is a leading cause of male infertility.

Young boys with the disorder, however, are likely to have language, social, or physical development problems. Symptoms include delayed speech, ADHD, motor delays, sensitivities to sounds or touch, and learning disabilities.

Symptoms like these led to the diagnosis of Roberta Rappaport's son at age 12. His pediatrician first noticed early language delays and suggested speech therapy. His nursery school teacher was next to point out that the child was "not settling down like he should by his age."

"We kept telling our pediatrician about comments we'd get from teachers or things we noticed. Finally at our son's 12-year check-up, his doctor linked the symptoms together and sent us for genetic testing," recalled Rappaport, who with her husband founded the Chicago-based American Association of Klinefelter Syndrome Information & Support.

XXYs have increased risk for:

- Infertility
- Autoimmune diseases
- Breast cancer
- Osteoporosis

Pediatricians, endocrinologists, geneticists, speech therapists, psychologists, and other medical experts may be involved in assessing a boy for the condition.

Fennoy said she prefers to treat young patients with "psychiatric therapy and behavioral counseling rather than medical interventions." Some physicians, however, suggest starting testosterone replacement at the onset of puberty to allow a boy to undergo the physical changes that usually occur at puberty, such as increasing muscle mass, developing a deeper voice, and growing facial and body hair.

> 'About 66 percent of males with Klinefelter are never diagnosed, and only about 10 percent are diagnosed prior to puberty,' Fennoy said.

Researchers are currently studying the efficacy of testosterone replacement therapy in the pediatric population. A clinical trial at the University of Colorado at Denver is currently enrolling 50 XXY adolescent males, ages 8–18, to determine whether testosterone replacement therapy leads to changes in psychological factors and motor skills. The study will be completed in February 2017.

Another trial at Denmark's Aarhus University will conclude in July 2014. It is investigating the quality of life in adult males with Klinefelter. Participants are being surveyed on their marital status, fatherhood, education, and mental and physical health.

Rappaport says her son, now 44, is a talented handyman, but has poor organizational skills. "Klinefelter is a spectrum disorder, meaning it goes in a bell curve," she said. "I also know many men who function well as doctors and lawyers, so it's not insurmountable." ■

Fauntleroy is a freelance writer in Carmel, Indiana.

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Early Investigators Forum in San Francisco

By Dan Bernard, Ph.D.

The Trainee and Career Development Core Committee, in collaboration with the Research Affairs Core Committee, hosted the 2012 Early Investigators Workshop on September 28 and 29 in San Francisco. Thirty-two postdoctoral and clinical fellows attended this unique two-day program, which offered an in-depth introduction to hypothesis-driven clinical research and/or translational research along with invaluable advice and mentoring on how to establish independent careers in endocrine research. Participants from around the United States and other countries attended this year's workshop.

In its second year, the Early Investigators Workshop provided integrated sessions for basic science and clinical fellows on general topics such as "How to Write a Grant," "Selecting a Mentor and Becoming an Effective Mentor," and "Balancing and Achieving Your Personal and Professional Goals." This year we held a "Mock Study Section," which provided trainees with eye-opening insights into the inner workings of peer review at the National Institutes of Health. The workshop included breakout sessions that covered topics specifically tailored to basic science or clinical careers, such as job opportunities in academia and industry for clinical researchers and negotiating your first academic position and setting up your first lab for basic scientists.

The workshop also provided one-on-one interaction between participants and senior faculty leaders in The Endocrine Society by dividing fellows into small groups for research project critique sessions. Each fellow had an opportunity to present his or her own research and then to receive feedback from faculty moderators. This has been and continues to be a highlight of the meeting; trainees greatly value and benefit from the constructive and personalized advice they receive.

While in San Francisco, the trainees had ample opportunity to network with faculty and each other. Our hope is that many of these fellows will have established long-lasting friendships and professional relationships within and across the clinical and basic science disciplines. Indeed, such interactions, particularly at these early career stages, provide a clear and tangible means to remove barriers to transformative bench to bedside research.

We are looking forward to planning next year's Early Investigators Workshop and offering even more exciting programming in 2013. If you have any questions or comments about the workshop, please email *awards@endosociety.org*. ■

Dan Bernard, Ph.D., Associate Professor of Pharmacology, McGill University, Co-Chair, 2012 Early Investigators Workshop

KEY DATES 2013

FUTURE LEADERS ADVANCING RESEARCH IN ENDOCRINOLOGY (FLARE)
- FLARE Workshop—January 25–26, 2013 San Diego, California

ENDO 2013 ABSTRACT SUBMISSIONS
- Abstract Submission Deadline—January 30, 2013
- Abstract Disposition Notification—March 15, 2013
- Abstract Awards Notification—March 19, 2013

EARLY CAREER FORUM
- Travel Award Application Deadline—January 30, 2013
- Travel Award Notification Date—February 28, 2013
- Early Career Forum Open Registration—March 1, 2013
- Early Career Forum —June 14, 2013

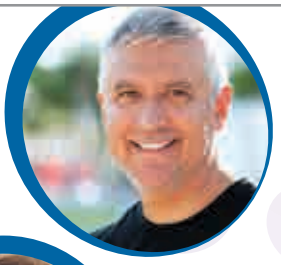
HOW TO SECURE PROMOTION AND TENURE WORKSHOP
- Travel Award Application Deadline—January 30, 2013
- Travel Award Notification Date—February 28, 2013
- Open Registration—December 5, 2012 (Members); January 3, 2013 (Non-Members)
- How to Secure Promotion and Tenure Workshop—June 14, 2013

RESEARCH FELLOWSHIP AWARDS
- Summer Research Fellowships Deadline—January 30, 2013
- Acromegaly Clinical Research Fellowship Award—January 30, 2013
- Research Fellowship Award Notifications—March 20, 2013

EARLY INVESTIGATORS AWARDS
- Application Deadline—January 30, 2013

CLINICAL ENDOCRINOLOGY IN-TRAINING EXAM
- 2013 ESAP-ITE™ available online—April 1–30, 2012
- Registration will be available beginning January 7, 2013

ENDO 2013
- Meeting Dates—June 15–18, 2013



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INDICATIONS AND USAGE

- FORTEO is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture
- High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

FORTEO is administered as a 20-microgram once-daily dose and is available in a 2.4-mL prefilled delivery device for subcutaneous injection over 28 days.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

See the Important Safety Information for Complete Boxed Warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor.**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk.**
- **FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (eg, those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).**

Please see Important Safety Information, including Boxed Warning regarding osteosarcoma, and Brief Summary on following pages. See Full User Manual that accompanies the delivery device.

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INDICATIONS AND USAGE

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IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® (teriparatide [rDNA origin] injection) only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

CONTRAINDICATIONS

Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO: Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Cases of bone tumor and osteosarcoma have been reported rarely in people taking FORTEO in the post-marketing period. The causality to FORTEO use is unclear.

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. The use of FORTEO for more than 2 years during a patient's lifetime is, therefore, not recommended.

Patients with the following conditions also should not receive FORTEO: bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders.

FORTEO may increase serum calcium, urinary calcium, and serum uric acid.

Use with caution in patients with active or recent urolithiasis because of risk of exacerbation. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered.

Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. FORTEO should be administered initially under circumstances where the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Patients receiving digoxin should use FORTEO with caution because FORTEO may transiently increase serum calcium and hypercalcemia may predispose patients to digitalis toxicity.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials include: arthralgia (10.1% FORTEO vs. 8.4% placebo), pain (21.3% FORTEO vs. 20.5% placebo), and nausea (8.5% FORTEO vs. 6.7% placebo). Other adverse reactions include: dizziness, leg cramps, joint aches, and injection site reactions.

USE IN PREGNANCY/NURSING MOTHERS

FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal studies, FORTEO may cause fetal harm.

It is not known whether teriparatide is excreted in human milk. Breastfeeding mothers should discontinue nursing or FORTEO, taking into account the importance of treatment to the mother.

INSTRUCTIONS FOR FORTEO USE

FORTEO is provided as a fixed-dose, prefilled delivery device that can be used for up to 28 days, including the first injection. The delivery device contains 28 daily doses of 20 mcg each. Do not transfer the contents of the delivery device into a syringe. The FORTEO Delivery Device should be stored under refrigeration at 36° to 46° F (2° to 8° C) at all times. Do not use FORTEO if it has been frozen.

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For more safety information, please see Brief Summary of Prescribing Information, including Boxed Warning regarding osteosarcoma, on following pages. See Full User Manual that accompanies the delivery device.

References: 1. Riggs BL, Parfitt AM. *J Bone Miner Res.* 2005;20:177-184. **2.** FORTEO Prescribing Information. **3.** National Osteoporosis Foundation. Osteoporosis medicines: what you need to know. Available at: http://www.nof.org/aboutosteoporosis/managingandtreating/medicinesneedtoknow. Accessed September 19, 2012.

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Brief Summary Consult the package insert for complete prescribing information.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

INDICATIONS AND USAGE

FORTEO is indicated: for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture. High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

CONTRAINDICATIONS

Do not use FORTEO in patients with Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

Osteosarcoma In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma. These include Paget's disease of bone (unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone); pediatric and young adult patients with open epiphyses; prior external beam or implant radiation therapy involving the skeleton. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org. **Treatment Duration** The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended. **Bone Metastases and Skeletal Malignancies** Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO. **Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO. **Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO. **Urolithiasis or Pre-existing Hypercalciuria** In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition. **Orthostatic Hypotension** FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment. **Drug Interactions** Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. *Treatment of Osteoporosis in Men and Postmenopausal Women* The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day. The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients. **Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality(FORTEO, N=691, Placebo, N=691):** *Body as a Whole:* Pain (21.3%, 20.5%), Headache (7.5%, 7.4%), Asthenia (8.7%, 6.8%), Neck Pain (3.0%, 2.7%); *Cardiovascular:* Hypertension (7.1%, 6.8%), Angina Pectoris (2.5%, 1.6%), Syncope (2.6%, 1.4%); *Digestive System:* Nausea (8.5%, 6.7%), Constipation (5.4%, 4.5%), Diarrhea (5.1%, 4.6%), Dyspepsia (5.2%, 4.1%), Vomiting (3.0%, 2.3%), Gastrointestional disorder (2.3%, 2.0%), Tooth disorder (2.0%, 1.3%); *Musculoskeletal:* Arthralgia (10.1%, 8.4%), Leg cramps (2.6%, 1.3%); *Nervous System:* Dizziness (8.0%, 5.4%), Depression (4.1%, 2.7%) Insomnia (4.3%, 3.6%), Vertigo (3.8%, 2.7%); *Respiratory System:* Rhinitis (9.6%, 8.8%), Cough increased (6.4%, 5.5%), Pharyngitis (5.5%, 4.8%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); *Skin and Appendages:* Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%). Immunogenicity In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response. *Laboratory Findings* **Serum Calcium:** FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men. **Urinary Calcium:** FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo. **Serum Uric Acid:** FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis. **Renal Function:** No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. *Studies in Men and Women with Glucocorticoid-Induced Osteoporosis* The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with $\geq$ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active

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control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Osteosarcoma**: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia**: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: *Allergic Reactions*: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; *Investigations:* Hyperuricemia; *Respiratory System*: Acute dyspnea, chest pain; *Musculoskeletal*: Muscle spasms of the leg or back; *Other*: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C. There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses $\geq$ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses $\geq$120 times the human dose (based on surface area, mcg/m2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively. Exposure multiples were normalized based on body surface area (mcg/m2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **Nursing Mothers:** It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** No studies have been performed in patients with hepatic impairment. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur. In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported. Overdose Management There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION

Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

06/15/2012

PLEASE SEE FULL PRESCRIBING INFORMATION OR WWW.FORTEOHCP.COM FOR ADDITIONAL INFORMATION.

Literature revised: March 21, 2012

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RESEARCH BRIEFS

➤ The following studies 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 via *www.endo-society.org*.

Endocrinology

➤ **GCGL and its receptor, GCGLR, have been identified in chickens and teleosts, indicating a non-identified role in non-mammalian vertebrates and clues to the evolutionary history of these genes in vertebrates.**
Wang Y, Meng F, Zhong Y, Huang G, Li J. *Discovery of a novel glucagon-like peptide (GCGL) and its receptor (GCGLR) in chickens: Evidence for the existence of* GCGL *and* GCGLR *genes in non-mammalian vertebrates.*

➤ ***MCH1R* knockout mice exhibit primary hypothyroidism: High thyrotropin-releasing hormone and thyroid-stimulating hormone, but low circulating iodothyronine levels.**
Chung S, Liao X-H, Di Cosmo C, et al. *Disruption of the melanin-concentrating hormone receptor 1 (MCH1R) affects thyroid function.*

➤ **Autophagy might dampen inflammatory gene expression, thereby limiting excessive inflammation in adipose tissue during obesity.**
van Essen P, Jansen HJ, Koenen T, et al. *Autophagy activity is up-regulated in adipose tissue of obese individuals and modulates pro-inflammatory cytokine expression.*

➤ **Thyromimetics like GC-1 and KB2115 may represent promising cholesterol-lowering therapeutics.**
Lin JZ, Martagon AJ, Hsueh WA, et al. *TR agonists reduce serum cholesterol independent of the LDL receptor.*

The Journal of Clinical Endocrinology & Metabolism

➤ **In heart and liver transplant patients, one 5-mg infusion of zolendronate and weekly alendronate prevent bone loss at the hip.**
Shane E, Cohen A, Stein EM, et al. *Zoledronic acid versus aldendronate for the prevention of bone loss after heart or liver transplantation.*

➤ **EPCs co-expressing osteocalcin are increased at an early stage of diabetes. These cells indicate that vascular calcification occurs early in the disease.**
Flammer AJ, Gossl M, Li J, et al. *Patients with HbA1c in the prediabetic and diabetic range have higher numbers of circulating cells with osteogenic and endothelial progenitor cell markers.*

➤ **High thyroid-stimulating hormone levels and thyroid autoimmunity in early pregnancy increase the risk of gestational diabetes, low birth weight, and spontaneous preterm delivery.**
Karakosta P, Alegakis D, Georgiou V, et al. *Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes.*

➤ **Orchidopexy at 9 months is more beneficial for testicular development than an operation at 3 years of age.**
Kollin C, Stukenborg JB, Nurmio M, et al. *Boys with undescended testes: Endocrine, volumetric, and morphometric studies on testicular function before and after orchidopexy at 9 months or 3 years of age.*

Molecular Endocrinology

➤ **In the mouse fetal testis, both Leydig and Sertoli cells are needed for testosterone synthesis.**
Shima Y, Miyabayashi K, Haraguchi S, et al. *Contribution of Leydig and Sertoli cells to testosterone production in mouse fetal testes.*

➤ **Chronic circadian disruption faced by nightshift workers and age-related sleep disturbances may contribute to breast cancer incidence and spread through the inhibition of glycogen synthase kinase 3β, which drives EMT.**
Mao L, Dauchy RT, Blask DE, et al. *Circadian gating of epithelial-to-mesenchymal transition in breast cancer cells via melatonin-regulation of GSK3β.*

➤ **Hypoxia-inducible factor-1α may play an important role in the initiation of gene regulatory events that lead to cervical ripening and dilation at term.**
Kishore AH, Li X-H, Word RA. *Hypoxia and PGE2 regulate MiTF-CX during cervical ripening.*

➤ **An additional role for calcimimetics has been proposed: increasing calcium-sensing receptor FHH/NSHPT mutant trafficking to the plasma membrane.**
Grant MP, Stepanchick A, Breitwieser GE. *Signaling regulates trafficking of familial hypocalciuric hypercalcemia (FHH) mutants of the calcium sensing receptor.*

December 2012 issue of *Endocrine Reviews*

Chopin LK, Seim I, Walpole CM, Herington AC. *The ghrelin axis—Does it have an appetite for cancer progression?*

Diamanti-Kandarakis E, Dunaif A. *Insulin resistance and polycystic ovary syndrome revisited: An update on mechanisms and implications.*

Di Gialleonardo V, de Vries EFJ, Di Girolamo M, Quintero AM, Dierckx RAJO, Signore A. *Imaging of β-cell mass and insulitis in insulin-dependent (type 1) diabetes mellitus.*

Bonnema S, Hegedus L. *Radioiodine therapy in benign thyroid diseases: Effects, side effects, and factors affecting therapeutic outcome.* ■

IMPOSTERS in the Medicine Cabinet

A wave of counterfeit drugs puts public at risk

By Shannon Fischer

One hundred dollars for 360 tablets of generic Synthroid? Good deal. With a click, I add them to my digital shopping cart, and for good measure, toss in 60 250-mg Zithromax pills, 90 generic Glucophage tablets, and a few months' supply of generic Yasmin before hitting checkout.

I'm shopping at an online pharmacy I found through a Google search. The site looks professional, with customer reviews, a picture of a reassuringly white-coated man with a stethoscope, and plenty of social media–sharing options. What's not present is any requirement to provide a doctor's prescription for the purchase of these drugs. However, a medical questionnaire asks for my age, sex, and medical conditions, in case their in-house doctor wants to check the order over. Good enough?

Caveat emptor. The site is on the National Association of Boards of Pharmacies' (NABP) "Not Recommended" list, meaning it's one of hundreds the organization suspects could be selling counterfeits. If I were to go through with the sale (which I am not), I couldn't be certain about where the products really came from or what they actually contained. They might have drugs inside, but they also might contain cement powder, floor polish, lead, dextrose, rat poison, or some completely different therapeutic altogether—all ingredients that have been identified in counterfeit pharmaceuticals intended for the unwary public.

Right now, fake medicines are a multi-billion-dollar problem, affecting consumers in virtually every country and demographic in the world, and the problem is getting worse. It has been estimated that up to 15 percent of drugs sold worldwide are counterfeit, and in parts of Africa and Asia, that figure can surpass 50 percent. In the United

States, the problem is comparatively less severe thanks to our strictly regulated pharmaceutical system, yet we are still vulnerable.

According to the World Health Organization (WHO) and the NABP, less than 1 percent of the pharmaceuticals in the United States are fraudulent, but in a country that spends $320 billion on 3.7 billion prescription drugs a year, even a fraction of 1 percent is in the millions. In the past 19 years, the U.S. Food and Drug Administration (FDA) has initiated 580 counterfeit drug arrests, and this year alone, it has had to warn consumers and clinicians away from ineffective fakes of the anticancer drug Avastin, useless versions of the ADHD medication Adderall, and ersatz Vicodin.

These modern iterations of snake oil began in the late 1990s with the globalization of pharmaceutical manufacturing, the commercialization of the Internet, and the blockbuster success of Pfizer's erectile dysfunction drug Viagra. The sheer profitability of the drug—it grossed the company more than a billion dollars in its first year—led to counterfeits almost immediately. By 2002, hundreds of thousands of fake Viagra pills flooded the market. Nothing is off limits today: birth control pills, hormone replacements, diabetes treatments, weight-loss aids, cancer and transplant drugs, schizophrenia medicines, and HIV therapies have all been counterfeited. Internet pharma-

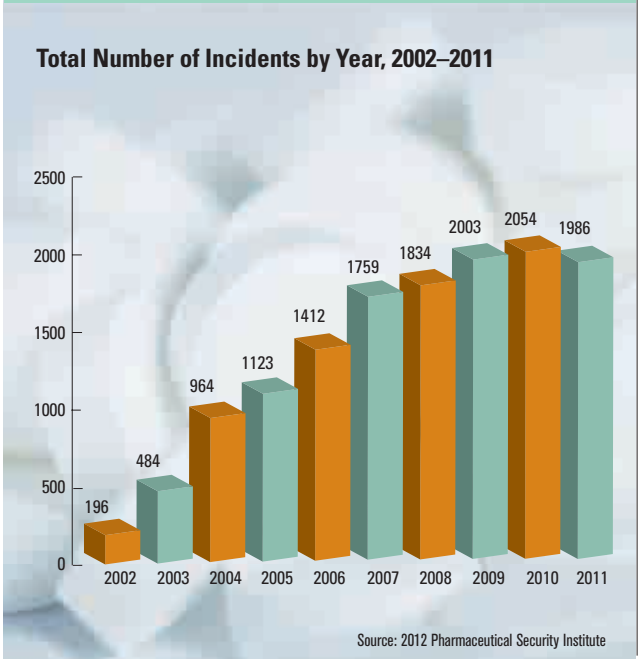
TOP 5 COUNTERFEIT DRUG CATEGORIES IN 2011

1. Genito-urinary
2. Anti-infective
3. Cardiovascular
4. Central nervous system
5. Metabolic

cies hawk pills, injectables, IUDs, even stem cell therapies promising to cure everything from autoimmune disease to autism. Most—but not all—of the manufacturing appears to take place in loosely regulated countries like China and India, but the selling occurs through online pharmacies worldwide.

Because of the obesity epidemic, metabolic and endocrine drugs are particularly appealing to drug forgers. In 2010, the rate of counterfeiting incidents in the metabolic therapeutic category—which includes glucose test strips and blood sugar stabilizers—shot up by 182 percent. Because many endocrine drugs come in the form of injectable biologics like insulin, they can be even easier to counterfeit than tablets, says Marvin Shepherd, president of the Partnership for Safe Medicines.

Increase in Incidence



"You can just use sterile water, or tap water if you want. All you have to do is just copy the container," he says. Biologics also require particular handling, like refrigeration, to maintain their efficacy. This makes even genuine insulin suspect if it gets diverted from legitimate routes to be sold through gray market vendors, as happened in 2009 when insulin stolen out of North Carolina showed up in a sick diabetes patient in Houston. (To this day, only 3 percent of the 129,000 vials stolen have been recovered.)

Obtaining the equipment and supplies to produce fakes and creating the online pharmacies from which to sell them are simple, experts say. "You can pretty much go from soup to nuts in creating your own online pharmacy," says Tim Mackey, a doctoral researcher at the University of California, San Diego School of Medicine. "You can get the API [active pharmaceutical ingredient] from China, you can get the pill printers from China."

Slap together a pretty Web page and you're good to go. "Literally, if we sat here for about 45 minutes, we could create our own online pharmacy," says Bryan Liang, executive director of the Institute of Health Law Studies and Mackey's advisor. "By the end of the day, we'd have orders."

Accountability for these pharmacies is nonexistent for the most part. Of 10,065 Internet drug outlets surveyed by the National Association of Boards of Pharmacy, only 73 sites (0.73 percent) had been accredited through the association's verification programs and 9,734 (96.7 percent) were out of compliance with legal or patient safety standards.

Although the majority of people who buy medicines on the Internet use pharmacies associated with their health insurance plan or a local pharmacy, FDA spokesperson Sarah Lynn-Clark writes in an email, "We are concerned about the portion of Internet purchases from online sources that may be from fraudulent, illegal online pharmacies."

Global Pharmaceuticals

Another element feeding the phenomenon is the globalization of the pharmaceutical industry. As with electronics, medicine making has become a team sport. According to

What's in Fake Medicine?

Photographs courtesy of U.S. FDA.

The FDA's CD3 detector identifies the fakes.

FDA commissioner Margaret Hamburg, 80 percent of the ingredient-manufacturing sites for FDA-approved drugs sit outside the United States, located in one of the 300,000 facilities across 150 different countries that export FDA-regulated products into the United States. Every link in the chain offers criminals a weak point from which to steal or introduce adulterated and counterfeit products.

"It is an enormous task keeping track of that and keeping it from being contaminated," Shepherd says. "They can do the spectrophotometry analysis and sometimes it works, and sometimes it doesn't"—as with the fatally contaminated heparin in 2007 that killed at least 149 people.

However, nations and regulators are fighting back. The past decade has seen breakthrough collaborations between national and international public health agencies. The FDA and WHO have joined forces with law enforcement organizations like Homeland Security Investigations, Customs and Border Protection, and Interpol. Agencies also team up with private pharmaceutical companies and technology players, among them Google and GoDaddy, whose accessible services are often exploited by counterfeit rings. The largest such venture to date, a 100-country, WHO-led sting operation this fall called PANGEA V, seized 3.75 million doses of counterfeit and illicit drugs and resulted in the arrest or ongoing investigation of 79 people, as well as the elimination of more than 18,000 illegal online pharmacies.

Meanwhile, pharmaceutical manufacturers and the FDA continue to develop new anti-counterfeiting techniques in what has become an arms race against drug forgers. The FDA recently unrolled a new, handheld counterfeit detection device—CD3—designed to analyze chemicals and potential tampering in everything from outsets to inserts, hidden codes, and print—in real time. Relatively cheap ($1,000), battery-operated, and easy to use with a minimum of training, the technology has already become a valuable tool for the FDA. "Due to its portability, it is currently being used by FDA agents in the field to rapidly screen for potentially problem products," Clark writes.

Similarly, many pharmaceuticals now put identifying markers on drug packaging. Some of these can be seen with the naked eye—like holograms—or can be scanned in bulk from a distance, like radio frequency identification (RFID) tags. Others are more covert: UV fibers woven into the packaging, inks and images that can be seen only under specific wavelengths or filters. Nanotechnological markers and DNA or chemical tags incorporated into the makeup of the drugs themselves add a further layer of complexity to the drug-counterfeiting process. Illinois-based NanoGuardian, for instance, has created a multi-layer nanotechnology that can embed everything from the drug's strength and expiration date to its origin and destination—more than 350 codes of information—carved directly onto the drug in a space smaller than the width of a single hair.

These technologies will mitigate the risk, but "none is perfect," warns Sebastian Mollo, Intelligence Director for the Americas at the Pharmaceutical Security Institute. "They don't solve the problem. They're just one piece of the puzzle." Although agencies focus on Web site marketing, counterfeiters are moving on to new territory: in a recent study, Liang found illicit contraceptive sellers targeting consumers through social media platforms like Facebook, Twitter, and Flickr.

A WHO-led sting operation seized 3.75 million doses of counterfeit and illicit drugs and resulted in the arrest or investigation of 79 people and the elimination of more than 18,000 illegal online pharmacies.

Still, Liang is optimistic. The increase in private and public agency collaboration marks a significant step forward, and transparency and public awareness are at unprecedented highs. It's still early days, he says, but "we are starting to see both technology and global governance that can integrate and get the job done of ensuring a safe drug supply." ■

Fischer is a freelance science writer in Boston.

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The Society Begins Dialogue with Health Disparities Institute

By Loretta L. Doan, Ph.D.

As part of its comprehensive advocacy program, The Endocrine Society regularly meets with the leadership of relevant institutes and centers in the National Institutes of Health (NIH). These high-level meetings serve to raise the profile of endocrinology among NIH research portfolios and to advance the Society's initiatives and goals that are in common with those of the NIH. Society leaders use these meetings to identify priority research areas and to discuss potential collaborative efforts. Over the years, the Society has met with the leadership of the National Institute of Diabetes and Digestive and Kidney Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Environmental Health Sciences, and the National Institute on Aging.

On September 12, 2012, Society leadership and staff met with senior leaders of the National Institute on Minority Health and Health Disparities (NIMHD) to discuss the Society's and the Institute's objectives and potential areas of collaboration. This was the first meeting between the Society's leadership and that of NIMHD. Given the Society's continued focus on health disparities, Society leaders anticipate ongoing discussion and cooperation with the Institute. During this inaugural meeting, participants discussed the Society's programs and initiatives in support of its commitment to reducing or eliminating health disparities in endocrine disorders and the Institute's programs and offerings in support of its mission to lead scientific research to improve minority health and eliminate health disparities.

Immediate Past President Janet Hall, M.D., led the Society delegation and described her presidential initiative to focus and enhance the Society's disparities initiatives to provide a high-profile framework in which these programs can grow and expand. Dr. Hall highlighted the Society's 2007 white paper, "Increasing Minority Participation in Clinical Research," and its 2012 Scientific Statement, "Health Disparities in Endocrine Disorders: Biological, Clinical, and Nonclinical Factors." She also described the Society's Minority Access Program (MAP) and Future Leaders Advancing Research in Endocrinology (FLARE) program. Finally, Dr. Hall invited NIMHD officials to participate in the Society's planned March 2013 summit on health disparities and in **ENDO 2013**.

NIMHD officials provided an overview of the Institute and highlighted some of its grant mechanisms that Society members might be interested in. These include a Transdisciplinary Collaborative Centers for Health Disparities Research U54, a Community-Based Participatory Research R24, and two separate R01 opportunities for health disparities—one for Social, Behavioral, Health Services, and Policy Research and the other for Basic and Applied Biomedical Research. They also provided some details about the Institute's conference, "The Science of Eliminating Health Disparities," which is scheduled for December 17-19, 2012 at the Gaylord National Center. Outcomes from NIH's evaluation of disparities in success of grant applicants and opportunities for the Society to comment on the draft NIH disparities strategic plan were also discussed.

In addition to Dr. Hall, Society participants were Janet Kreizman, Deputy Executive Director & Chief Policy Officer; Wanda Johnson, Senior Director, Meetings and Education; and Loretta Doan, Ph.D., Director, Science Policy. NIMHD participants were Joyce Hunter, Ph.D., deputy director, Extramural Research; M. Roy Wilson, M.D., M.S., deputy director, Strategic Scientific Planning and Program Coordination; Nathaniel Stinson, Jr., M.D., Ph.D., M.P.H., acting director, Office of Scientific Programs; and Francisco Sy, M.D., Dr.P.H., director, Office of Extramural Research Administration. The Society is excited about this new step forward in its commitment to alleviating health disparities. NIMHD is a critical partner in this goal, and the Society looks forward to continuing to build its relationship with the Institute to further enhance the objectives of both organizations.

With this meeting, the Society and NIMHD have begun a formal dialogue to explore areas of common interest and to identify collaborative opportunities. Society members are encouraged to consider the complex issue of disparities as they design and implement their research programs and to explore grant opportunities from the Institute. ■

Doan is Director of Science Policy at The Endocrine Society

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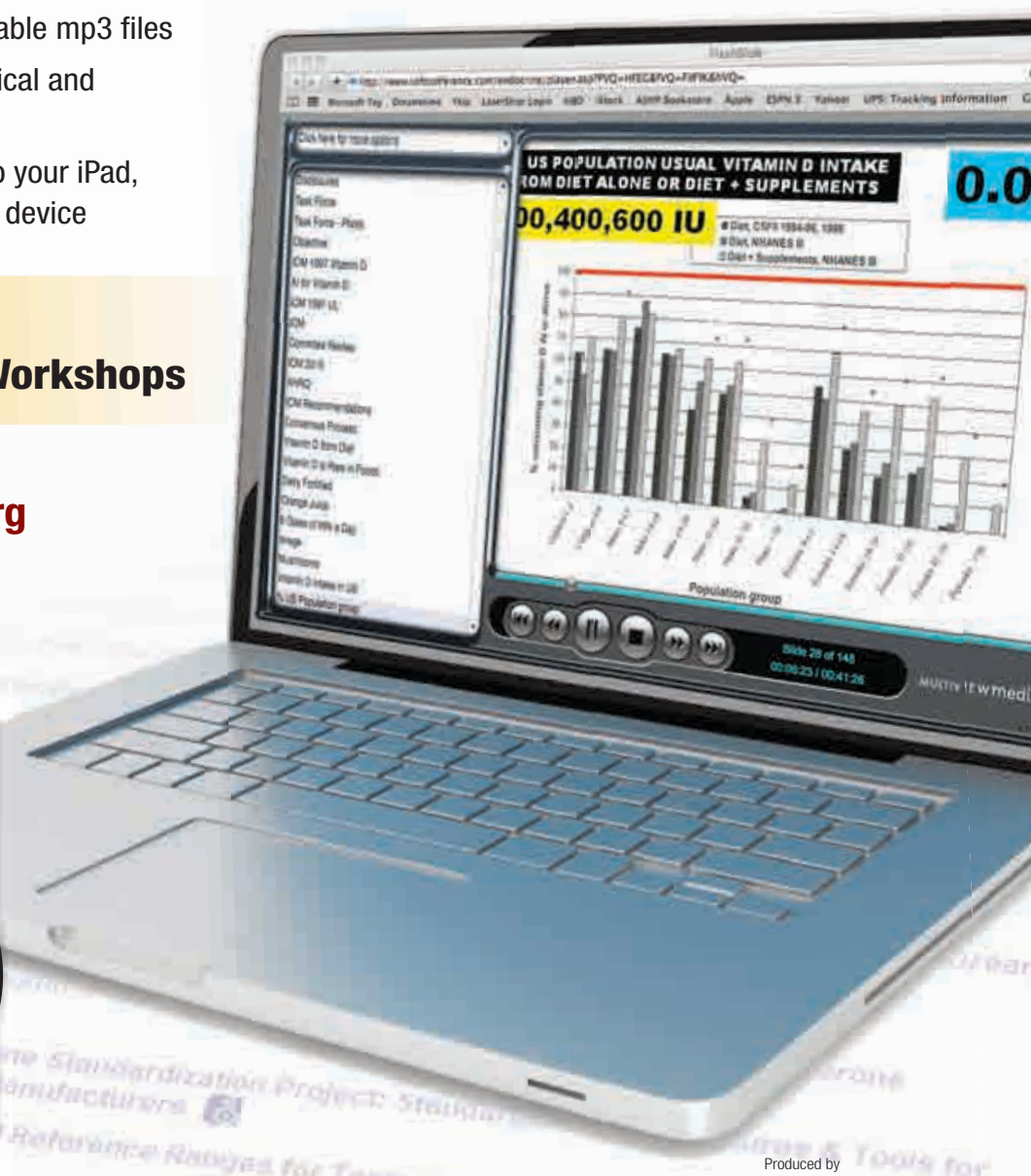

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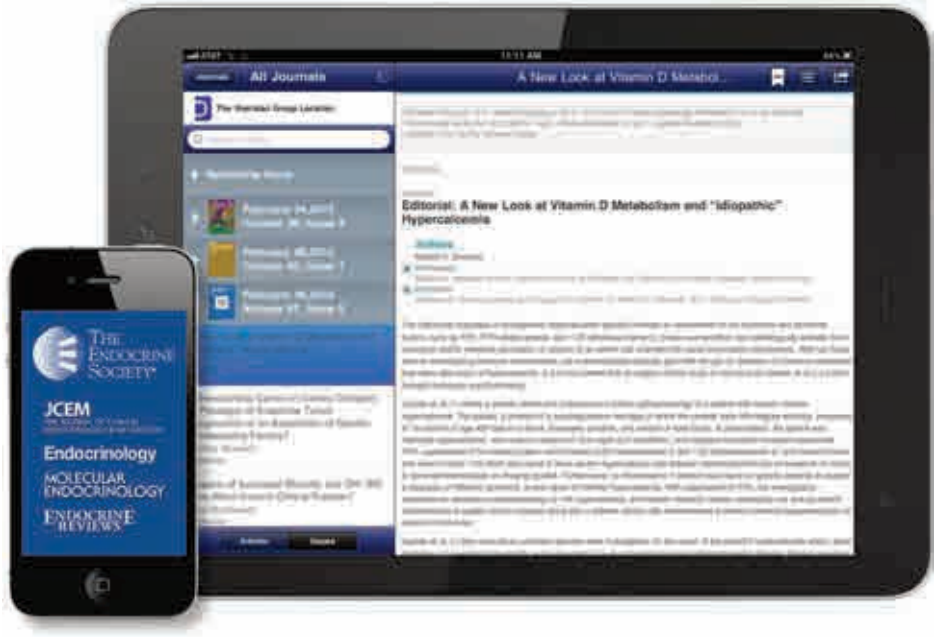

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THE ENDOCRINE SOCIETY®

www.endo-society.org

ENDOCRINE Society update

ENDO 2013 Abstract Submission is Now Open

Abstracts are now being accepted! **ENDO 2013** features basic, clinical, and translational research, and clinical trials scientific abstracts. The deadline for abstract submission is January 30, 2013, 12:00 PM (noon) ET.

NEW THIS YEAR! "Featured Poster Presenters." A small number of poster presenters with high-scoring abstracts will be invited to give a brief podium presentation as a preview of their poster.

ENDO 2013 provides multiple opportunities for you to showcase your research to colleagues and leaders in the field, including an invitation for presenters with high-scoring abstracts to preview their posters by giving brief podium presentations. Top abstracts in various categories will be featured throughout the meeting sessions. Students and fellows are particularly encouraged to submit their research because numerous awards and travel grants are available.

A complete list of more than 120 abstract categories is available at the official **ENDO 2013** Web site, *www.endo-society.org/endo2013*.

Renew Before December 31 to Win!

We have had four lucky winners so far in the "Renew Early to Win!" drawing. Have you renewed your membership for 2013 yet? Two prizes still remain to be given away—a **$250 Apple gift card** and a complimentary registration for **ENDO 2013, the 95th Annual Meeting & Expo** in San Francisco. Need another reason to renew? There is **no dues increase** for 2013! If you haven't renewed yet, be sure to do it today at *www.endo-society.org/renew* to maintain access to all of your benefits AND be entered into the drawing.

Female Sexual Dysfunction Patient Fact Sheet

An estimated 40 to 50 percent of women experience persistent, recurrent problems that cause a disturbance in, or discomfort during, the sexual act. Many women find the impact on their sex lives distressing. The Hormone Health Network's patient fact sheet, *Female Sexual Dysfunction* (FSD), describes the physical and emotional factors that contribute to this condition. The fact sheet reassures patients that FSD is both common and treatable, and it outlines interventions available for the different causes. Visit *www.hormone.org* to read and download the fact sheet.

Pediatric Endocrine Board Review

If you're preparing to sit for your certification or recertification exam, or you are in need of a comprehensive review of your pediatric endocrinology knowledge, the **Pediatric Endocrine Board Review** is the meeting for you. Experience the most in-depth and intense knowledge assessment at this two-day meeting, which is slated for September 24 and 25, 2013, in New Orleans, Louisiana. It provides an interactive mock exam, with case-based questions using an Audience Response System to poll responses. See *www.endo-society.org/PEBR2013* for more details on the meeting.

MAC Promotes Diverse Membership for the Society

The Minority Affairs Committee (MAC) continued its efforts to increase cultural diversity in the Society and in the field of endocrinology by exhibiting and networking with attendees at the 2012 SACNAS National Conference. SACNAS, the Society for Advancement of Chicanos and Native Americans in Science, was held on October 11–14 in Seattle.

The conference targets underrepresented students from around the country who are interested in pursuing scientific research and teaching careers. MAC representatives offered information on MAC and Society programs to undergraduate and graduate students considering careers in endocrinology,

generating new in-training memberships in the Society.

The Endocrine Society has participated in the SACNAS conference since 2001, recruiting promising young endocrinologists to join the Society and to participate in research and leadership programs, such as the Minority Access Program (MAP). This program encourages participating students to share their research at scientific meetings like SACNAS. This year, 1,235 students presented their research at SACNAS. Among 117 undergraduate students, Carlos Santos, from the University of Puerto Rico at Cayey and a 2012 MAP graduate, received the 2012 SACNAS Undergraduate Student Poster Presentation Award.

The Endocrine Legacy

The Endocrine Legacy captures nearly a century of developments and groundbreaking achievements in endocrinology and is free to all Society members. *The Endocrine Legacy* includes the complete archive—back to volume 1, issue 1—of four seminal Society journals: ***The Journal of Clinical Endocrinology & Metabolism, Molecular Endocrinology, Endocrinology,*** and ***Endocrine Reviews***.

For more information on this essential member benefit, visit *www.endo-society.org/legacy* or contact Society Services at *societyservices@endo-society.org*.

Visit The Endocrine Society's Online Store for Year-End Discounts

For a limited time, valuable self-assessment products, reference materials, and study guides are on sale. From now through the end of the year, members and trainees can benefit from discounts of 10 percent or more on many of our most popular products, such as *ESAP* and the *Endocrine Board Review*. This offer ends on December 31, 2012, so don't wait. To view products and/or order, visit The Endocrine Society's online store: *www.endo-society.org/store*. ■

Smart Moves

developments in the endocrinology world

Reid B. Blackwelder, M.D., F.A.A.F.P., was chosen president-elect of the American Academy of Family Physicians. Dr. Blackwelder is a professor of family medicine and director of the Medical Student Education Division for the Department of Family Medicine at East Tennessee State University's James H. Quillen College of Medicine in Johnson City.

Jeffrey J. Cain, M.D., F.A.A.F.P., assumed the role of president of the American Academy of Family Physicians. Dr. Cain serves as the chief of family medicine at Children's Hospital Colorado and practices family medicine at the AF Williams Family Medicine Center in Denver. He also is an associate professor in the Department of Family Medicine at the University of Colorado Health Sciences Center.

Maria L. Dufau, M.D., Ph.D.,** received the RAICES Prize from the Ministry of Science Technology and Scientific Innovation of Argentina. The award is given to scientists born in Argentina residing abroad who have promoted ties that strengthened the science and technology of Argentina. As chief of the Molecular Endocrinology Section at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in the National Institutes of Health in Bethesda, Maryland, Dr. Dufau has trained and hosted many fellows and scientists from Argentina. Dr. Dufau has served on the editorial boards of ***Endocrinology and ***Endocrine Reviews***.

***Andrew F. Stewart, M.D.,** was named director of the Diabetes, Obesity, and Metabolism Institute at Mount Sinai Medical Center in New York City. Dr. Stewart was previously the chief of the Division of Endocrinology and Metabolism at the University of Pittsburgh School of Medicine.

Glen R. Stream, M.D., M.B.I., F.A.A.F.P., became the board chair of the American Academy of Family Physicians. Dr. Stream is also chief medical information officer at the Rockwood Clinic in Spokane, Washington.

** Member of The Endocrine Society.*

In Memoriam

Robert L. Sutherland, Ph.D., D.Sc. (Hon), A.O., F.A.A.
Sydney, Australia
1947–2012

calendar

DEC 15–19: SAN FRANCISCO
American Society for Cell Biology Annual Meeting.
www.ascb.org/meetings

See more events at *www.endosociety.org*, on the **Worldwide Endocrine Events Calendar.**

2013 Laureate Award Winners

For more than 70 years, The Endocrine Society has recognized endocrinologists worldwide through the Laureate Awards. Valued at $89,000, the 13 Laureate Awards represent the pinnacle of achievement in the field of endocrinology. The accomplishments of these distinguished recipients are unmatched in a broad spectrum of activities, including science, leadership, education, service, and practice. The dedication, commitment, and achievements of these winners have earned them a place beside some of the greatest endocrinologists in history.

It gives me great pleasure to announce the 2013 Laureate Award winners and congratulate each on their outstanding accomplishments (see below). The Endocrine Society's Laureate awards are presented in recognition of extraordinary achievements in the field of endocrinology. Award recipients are the top clinical and basic scientists, innovators, leaders, educators, and practitioners whose dedication and accomplishments are unmatched.

Awards will be presented at **ENDO 2013** in San Francisco, June 15–18, 2013. I am delighted to announce that this year the Society established two new awards—International Excellence and Outstanding Clinical Practitioner Awards.

REMINDER: Don't forget that in **January 2013**, the Laureate Awards Committee will begin accepting nominations from Society members for the 2014 Laureate Awards. We encourage your participation to expand the pool of eligible and diverse candidates for each award category.

For more information about these prestigious awards, please see *www.endo-society.org/awards/LaureateAwards/index.cfm*.

Margaret E. Wierman, M.D.
Laureate Awards Committee Chair

THE ENDOCRINE SOCIETY
is pleased to announce the

2013 Laureate Awards Winners

The Endocrine Society®

The awardees will be honored during The 95th Annual Meeting & Expo.

Fred Conrad Koch Award
Michael O. Thorner, MBBS, DSc

Robert H Williams Distinguished Leadership Award
John W. Funder, MD, PhD

Sidney H Ingbar Distinguished Service Award
Irving M. Spitz, MD, DSc, FRCP

Distinguished Educator Award
Mark E. Molitch, MD

Distinguished Physician Award
Michael T. McDermott, MD

Outstanding Clinical Practitioner
Steven B. Nagelberg, MD

International Excellence Award
Berenice B. de Mendonça, MD

Edwin B Astwood Award Lecture
Gary D. Hammer, MD, PhD

Gerald D Aurbach Award Lecture
Mitchell A. Lazar, MD, PhD

Roy O Greep Award Lecture
Donald P. McDonnell, PhD

Clinical Investigator Award Lecture
Steven E. Kahn, MB, ChB

Ernst Oppenheimer Award
Doris Adelheid Stoffers, MD, PhD

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Tony K. T. Lam, PhD

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A Campaign for the Clark T. Sawin Memorial Library & Resource Center

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When measuring glycemic control
in adult patients with type 2 diabetes

Victoza®—proven superior efficacy versus Januvia®.

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Victoza® delivered superior A1C reductions of 1.2%-1.5% vs 0.9%,* with additional benefits:

	Victoza®	Januvia
MORE THAN TWICE AS MANY PATIENTS TO A1C <7%	44% and 56%	22%
GREATER FPG REDUCTIONS	-34 mg/dL to -39 mg/dL	-15 mg/dL
GREATER WEIGHT LOSS	-5.9 lb to -7.3 lb	-1.8 lb

Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials.

*A 26-week, open-label, active-comparator, 3-armed, parallel-group trial to compare the efficacy and safety of Victoza® with sitagliptin for the treatment of type 2 diabetes. Patients with type 2 diabetes inadequately controlled on metformin (n=665) were randomized to receive once-daily Victoza® (1.2 mg or 1.8 mg) or Januvia (100 mg). The primary outcome was change in A1C.[1]

Safety and tolerability versus Januvia.

Most common adverse reactions	Victoza® + metformin (n=439)		Januvia 100 mg + metformin (n=219)
NAUSEA	23.9%	VS	4.6%
HEADACHE	10.3%	VS	10.0%
DIARRHEA	9.3%	VS	4.6%
VOMITING	8.7%	VS	4.1%
MINOR HYPOGLYCEMIA	5.0%	VS	5.0%

Indications and Usage

Victoza® (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Victoza® has not been studied in combination with prandial insulin.

Important Safety Information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Renal impairment has been reported post-marketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® (liraglutide [rDNA origin] injection) in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during post marketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

There is limited data in patients with renal or hepatic impairment.

Reference: 1. Pratley RE, Nauck M, Bailey T, et al; for the 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet.* 2010;375(9724):1447-1456.

Please see brief summary of Prescribing Information on adjacent page.

0512-00009509-1 September 2012

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

Victoza® (liraglutide [rDNA origin] injection)
Rx Only
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza, there were more cases of pancreatitis with Victoza than with comparators. Victoza has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis. Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza and prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Do not use in patients with a prior serious hypersensitivity reaction to Victoza or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications]*. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Adverse Reactions]*. **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Reaction	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Reaction	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6

Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4

Add-on to Metformin + Rosiglitazone		
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175
Adverse Reaction	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Headache	8.2	4.6
Constipation	5.1	1.1

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

Immunogenicity: Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In the five double-blind clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five double-blind clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia* :In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self–treat	0.1 (0.001)	0	0
Patient able to self–treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self–treat	0.1 (0.003)	0	0
Patient able to self–treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self–treat	0	—	0
Patient able to self–treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self–treat	2.2 (0.06)	0	0
Patient able to self–treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established *[see Warnings and Precautions]*. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea *[see Warnings and Precautions];* Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions];* Angioedema and anaphylactic reactions *[see Contraindications, Warnings and Precautions]*

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

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VICTOZA®
liraglutide (rDNA origin) injection

Endocrinology Enhances Zoo Breeding Strategies

By Dan Kelly

Reproductive physiologist Janine L. Brown may say she's a "lab geek" who "hides behind hormones," but her groundbreaking work in endocrine monitoring at the Smithsonian Conservation Biology Institute in Front Royal, Virginia, reaches around the globe.

Her staff has trained researchers at China's Panda Breeding Center, Chiang Mai University in Thailand, and the Pinnawala Elephant Orphanage in Sri Lanka. Through the National Zoo's Elephant Endocrine Diagnostic Laboratory, she monitors the reproductive health of zoo elephants throughout the United States, analyzing more than 7,000 serum samples per year to monitor reproductive cycles, schedule breeding, and determine reasons for infertility.

Joining the Smithsonian in 1991, Brown, who has an M.S. and a Ph.D. in animal sciences, says her first 10 years were spent learning where different steroids are secreted—whether in urine or feces—in order to develop non-invasive hormone monitoring techniques. Steroid metabolism and routes of excretion can vary widely across species, so proper assay development is critical. Ultimately, 70 percent of her lab's research involves fecal monitoring to assess fertility in just about any animal in captivity.

Brown recently assisted in timing the artificial insemination of the National Zoo's female panda, Mei Xiang, whose chances of conceiving were rated at less than ten percent because she had already had five false pregnancies. Tragically, the cub born in August died a week later from liver and lung complications.

"Our endocrine lab lived and breathed panda hormones for five months," says Brown. "We experienced immense elation at the birth, followed by intense heartbreak over the cub's death."

Studying daily urine samples, Brown and her staff had followed 14-year-old Mei Xiang's estrogen conjugates as they rose. Once estrogen levels peak and ovulation occurs, female pandas have a two- to three-day window to conceive. "As with most mammals, the egg is only viable for a short time," Brown said, "so by monitoring the hormones the staff knows precisely when to conduct the inseminations."

Artificial insemination (AI) is often done with captive pandas because natural mating attempts fail. "For some reason, males don't position the female properly for breeding, so we need to step in and do AI," Brown adds.

A very frustrating aspect of the process is not being able to tell whether or not a panda is pregnant, Brown says. "The estrogen and progesterone profiles are exactly the same for pregnant and pseudopregnant luteal phases, so we can't know for sure [she is pregnant]." A panda fetus is very difficult to detect on ultrasound because it remains very small up until the last two weeks. "Even at birth a panda cub weighs less than a stick of butter," Brown says, noting that "many births have occurred when ultrasound saw nothing."

Because the cub's death was not due to Mei Xiang's health, Brown is confident she can yet conceive and deliver successfully. "Are we up to trying again?" she wrote in an email. "You bet we are!"

Brown also monitored Mei Xiang's hormones leading up to the conception and birth of her first cub, Tai Shan, in 2005. A very popular zoo attraction for several years, he was sent to China in 2010 as part of an earlier agreement.

Brown's career in animal fertility, however, started with elephants. Regardless of the species, she begins with hormonal analyses to learn about their basic biology, like what

is the length of their estrous cycle, whether reproduction is seasonal, and how to tell when females are pregnant.

"You figure all that out and then you're better able to figure out reproductive problems in individual animals and develop treatments," she says. "We rely heavily on endocrinology to determine how well our hormonal therapies are working, including those used with AI."

One of Brown's most famous successful pregnancies was that of Shanthi, the National Zoo's Asian elephant. Brown and her staff began tracking the length of follicular and luteal phases in Shanthi in the 1990s to determine the most opportune time for artificial insemination.

"Identifying a unique hormone pattern in elephants, which involves two luteinizing hormone surges during the follicular phase, was key," she says. The first surge begins within one to three weeks after the luteal phase ends, when progesterone levels drop to a base line. After another three weeks, the second surge occurs.

"We breed elephants based on finding the first surge, using daily blood samples and then schedule natural mating or artificial insemination three weeks later," Brown explained. There are few experts in elephant ultrasound and artificial insemination and they need as much lead time as possible. Using the endocrine procedures developed by Brown's staff is essential to getting the timing right.

"This is routinely done now," she says, "with ours being the primary lab for these services."

Artificially inseminated using a revolutionary catheter technique developed in Germany, Shanthi gave birth to Kandula in 2001. He is one of three Asian elephants at the National Zoo in Washington, D.C.

Although endocrine monitoring is useful for timing fertility in zoos, farther afield it is essential in assessing the welfare of other captive populations. Logging camps in Burma and ecotourism centers in Thailand rely on the use of captive elephants. These populations of elephants are extremely important, Brown says, because habitat for the Asian elephant, an endangered species, shrinks yearly from human expansion.

"These may well end up being the only ones left until we can figure out how to preserve habitat."

To help protect them, Brown is currently validating a technique to measure stress through cortisol levels in elephant hair so adjustments can be made to the work environment of these labor populations.

Closer to home, she is one of nine researchers assessing the welfare of captive elephants in 70 zoos across the United States, Canada, and Mexico, measuring hormone levels associated with reproductive health, thyroid function, nutritional status, health, and stress. The resulting data will be critically important in understanding how current zoo management affects elephant welfare.

Brown admits there is plenty left to learn. For 20 years, she has been studying ovarian acyclicity in captive African elephants, a major fertility problem that prevents the establishment of self-sustaining populations in zoos.

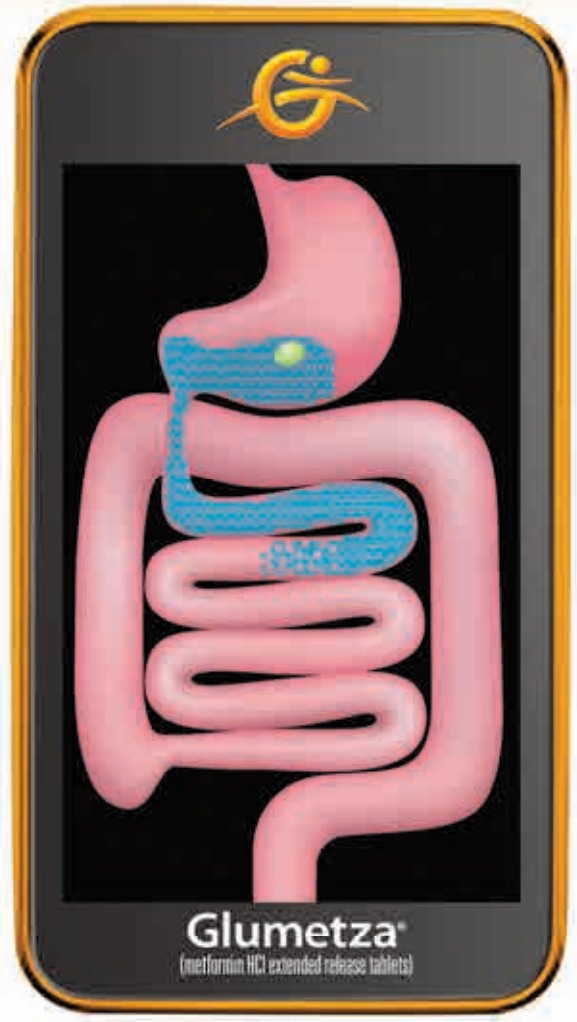
"I keep saying, as soon as I figure out how to fix acyclicity in African elephants, I can retire," Brown says. "We have a whole list of things it's not related to, but I still don't know how to fix it. And at this rate I think I'll never be able to retire."

The zoos of the world might thank her. ■

'Our endocrine lab lived and breathed panda hormones for five months,' says Brown. 'We experienced immense elation at the birth, followed by intense heartbreak over the cub's death.'

Kelly is a freelance writer in Silver Spring, Maryland.

GLUMETZA®: Unique, controlled delivery may improve



IMPORTANT SAFETY INFORMATION ABOUT GLUMETZA

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning

- Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)
- If acidosis is suspected, discontinue GLUMETZA and hospitalize the patient immediately. (5.1)

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS and PRECAUTIONS** (5) of the Full Prescribing Information).
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those

tolerability and help more patients get to A1C goal

TECHNOLOGY

GLUMETZA provides a unique, advanced polymer technology* that may help reduce GI adverse events in your patients

- GLUMETZA targets the upper GI tract for slow delivery over 8-9 hours,[1] providing consistent 24-hour control

TOLERABILITY

Well tolerated, with no significant increase in adverse events at higher doses

- <1% of GLUMETZA patients discontinued due to GI adverse events in Week 1[2†]; starting dose was 1000 mg

A1C CONTROL

Improved tolerability‡ may help more patients reach A1C goal

- More patients reached goal with GLUMETZA 2000 mg QD versus Glucophage® 1500 mg/day[1,3§]

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with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

In clinical trials, the most common side effects with GLUMETZA monotherapy were diarrhea, nausea, dyspepsia, and upper abdominal pain. In clinical trials of GLUMETZA combined with a sulfonylurea, the most common side effects included hypoglycemia, diarrhea, and nausea.

*GLUMETZA 500 mg utilizes patented AcuForm® gastric retention technology. GLUMETZA 1000 mg utilizes patented Smartcoat® gastric retention technology.[4]

†Findings from a 24-week, noninferiority clinical trial comparing different GLUMETZA dosing regimens vs Glucophage® (metformin hydrochloride tablets). GLUMETZA patients were initiated with 1000 mg (2 X 500 mg QD) for 1 week, then titrated to their randomly assigned dose over 2 to 3 weeks, and remained on this dose for the remainder of the study unless discontinuation was warranted.

‡The overall incidence of drug-related adverse events was similar with GLUMETZA dosed up to 2000 mg/day vs Glucophage 1500 mg/day: 33% vs 35%, respectively.[2§]

§From a supplementary analysis of the findings from a 24-week, 4-arm, noninferiority trial comparing different GLUMETZA dosing regimens vs Glucophage. Note: 40.6% of patients (n=182) reached A1C goal with GLUMETZA 1500 mg BID (dosed 500 mg AM; 1000 mg PM).

‖Some restrictions apply. Please see the eVoucherRx™ and Savings Card Program Brochure for Terms and Conditions. Santarus reserves the right to modify or cancel these offerings at any time.

References: 1. Foster RH, Keam SJ. Metformin extended release. *Am J Drug Deliv.* 2006;4(3):1-11. **2.** Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care.* 2006;29(4):759-764. **3.** Glumetza [package insert]. San Diego, CA. Santarus, Inc. 2011. **4.** Data on file. Santarus, Inc.

Glumetza®
(metformin HCl extended release tablets)

SANTARUS, INC.®

 1-GLM12199 08/2012

GLUMETZA®
(metformin hydrochloride extended release tablets)
BRIEF SUMMARY OF PRESCRIBING INFORMATION

BEFORE PRESCRIBING, CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USE—GLUMETZA (metformin hydrochloride extended release tablets) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS—

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. (See **WARNINGS AND PRECAUTIONS**)
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUMETZA and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUMETZA. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUMETZA treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, GLUMETZA should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking GLUMETZA, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, GLUMETZA should be temporarily discontinued prior to any intra vascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (In controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. (See Drug Interactions and Clinical Pharmacology) The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms should they occur. If present, GLUMETZA should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUMETZA, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUMETZA do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUMETZA, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See CONTRAINDICATIONS)

Monitoring of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore GLUMETZA is contraindicated in patients with renal impairment.

Before initiation of GLUMETZA and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and GLUMETZA discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

Use of concomitant medications that may affect renal function or metformin disposition — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**), should be used with caution.

Radiological studies and surgical procedures:

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, GLUMETZA should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

GLUMETZA therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUMETZA therapy, the drug should be promptly discontinued

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving GLUMETZA

Impaired Hepatic Function

Because impaired hepatic function has been associated with some cases of lactic acidosis GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels

In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUMETZA or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUMETZA or any other oral anti-diabetic drug.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with GLUMETZA 1500-2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

In the 24-week monotherapy trial comparing GLUMETZA to immediate-release metformin, serious adverse reactions were reported in 3.6% (19/528) of the GLUMETZA-treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received GLUMETZA and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9/431) of the GLUMETZA and glyburide-treated patients compared to 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and add-on to sulfonylurea clinical trials were combined, the most frequently (incidence ≥ 0.5%) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of GLUMETZA-treated patients compared to 0% of patients not treated with GLUMETZA) and cardiac disorders (0.4% of GLUMETZA-treated patients compared to 0.5% of patients not treated with GLUMETZA). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2]) were reported in more than one GLUMETZA-treated patient.

Adverse reactions reported in greater than 5% of patients treated with GLUMETZA that were more common in the combined GLUMETZA and glyburide group than in the placebo and glyburide group are shown in Table 1.

In 0.7% of patients treated with GLUMETZA and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group. Table 1: Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy from U.S. Studies

Table 1: Treatment-Emergent Adverse Reactions Reported By >5%* of Patients for the Combined GLUMETZA Group Versus Placebo Group

Adverse Reaction	GLUMETZA + Glyburide (n = 431)	Placebo + Glyburide (n = 144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

*AE's that were more common in the GLUMETZA-treated than in the placebo-treated patients.

Laboratory Tests

Vitamin B_{12} concentrations

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. (See **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors—

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

Cationic Drugs—

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUMETZA and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Drugs Affecting Glycemic Control—

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving GLUMETZA, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUMETZA, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

Labor and Delivery

The safety and effectiveness of GLUMETZA used during labor and delivery has not been evaluated in human studies.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. GLUMETZA is not recommended in pediatric patients below the age of 18 years.

Geriatric Use

Clinical studies of GLUMETZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. (See **WARNINGS AND PRECAUTIONS**)

OVERDOSAGE

No cases of overdose were reported during GLUMETZA clinical trials. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. (See **WARNINGS AND PRECAUTIONS**) Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Rx Only

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Revised August 2012 1-GLM12200

Glumetza®
(metformin HCl extended release tablets)

Classifieds

If you are interested in submitting classified advertising to **Endocrine News**, *please contact Christine Whorton at* endocareers@endo-society.org *or 800-361-3906.*

Minnesota Endocrinologist

Join a collegial group of three BC Endocrinologists, fellowship trained at Mayo Clinic & University of Iowa. Immediately busy, full time practice! Focus of diabetes, thyroid disease, osteoporosis, obesity and other endocrine disorders. Built-in referral base with 150 plus primary care physicians, excellent administrative support, EMR and a systematic approach to quality. Call 1:4 Salary plus Quality and wRVU bonuses with comprehensive benefits. Employment with HealthEast Care System, the largest non-profit system in the East Metro Minneapolis/St. Paul area with 4 acute care hospitals, 15 clinics, 7,000 employees and 1,400 physicians. Contact: Michael Griffin, Manager of Physician Recruitment: *mjgriffin@healtheast.org* or 651-232-2227.

Washington Endocrinologist

Group Health Permanente, the Pacific Northwest's top-rated multi-specialty group, is currently seeking a BC/BE Endocrinologist to join our Group Practice. Group Health is dedicated to providing comprehensive, innovative, and patient-centered care to our patients. We lead the nation in EMR integration. We are looking for an additional provider to join our Endocrinologists in a stimulating setting. This provider will help to expand our Endocrinology services in the Tacoma area. The practice is exclusively outpatient consulting Endocrinology with no disabilities or hospital responsibilities. We offer generous benefits, competitive salaries and the ability to become a shareholder in our Group Practice. Tacoma is located 20 miles south of Seattle. It is ideally situated along the saltwater banks of Puget Sound. Boasting stunning natural surroundings, you don't need to pack hiking boots to enjoy the mesmerizing outdoors. Explore the parks, gardens and wildlife that make Tacoma a nature wonderland. The nature in Tacoma extends beyond just land. Comb the beaches of the water's edge and test the open waters in a kayak or boat. For additional information regarding this position or to submit your CV, please visit our website at *www.grouphealthphysicians.org* or contact Cayley Crotty at *crotty.c@ghc.org.*

New York

Applications are invited for faculty positions in the Division of Endocrinology, Diabetes and Metabolism at SUNY Upstate Medical University in Syracuse, New York. One position will be focused primarily on patient care and teaching at our faculty group practice site (Joslin Diabetes Center, University Endocrinologists and Osteoporosis Center). We also seek physicians whose primary focus is clinical and translational research in diabetes and/or osteoporosis. Academic rank and competitive salary dependent on qualifications. Excellent benefits. The beautiful Central New York Finger Lakes region offers excellent schools, affordable housing, numerous recreational and social activities and gorgeous seasonal weather. MD/MBBS/DO, BC/BE in Endocrinology and New York State license or eligible. Please reply to: Dr. Ruth Weinstock, SUNY Upstate Medical University, Department of Medicine, Room 353 CWB, 750 East Adams Street, Syracuse, NY 13210. SUNY Upstate Medical University is an AA/EEO/ADA employer committed to excellence through diversity. Applications from women and minorities strongly encouraged.

Endocrinology Opportunity, Hellman & Rosen Endocrine Associates, PC, Kansas City, Missouri

Premier single-specialty group seeks an additional board eligible/board certified Endocrinologist to join their growing practice. In this position, you will join two well-established endocrinologists with a full range of clinical support staff, including four mid-level practitioners. The education program is ADA certified and there are a number of certified diabetes educators. There is a CLIA/COLA certified moderate complexity laboratory on-site; a DEXA Scan, and high-sensitivity thyroid ultrasound on-site. Additionally, the practice has a fully operative electronic medical record and an electronic registry for quality measurement. Position offers a competitive compensation package along with a full and comprehensive benefits package. Located in the Greater Kansas City metropolitan area, it offers outstanding schools; cultural and recreational opportunities; professional football, baseball, and soccer teams along with a wealth of other activities for all to enjoy. To learn more, contact: Danise Cooper at 800-678-7858 or via email *dcooper@cejkasearch.com*. ID#148052A15. ■

INTEGRIS Health Endocrinology is Growing

We're excited about our expansion and all of the accomplishments we have achieved along the way. Join our team and become a part of the **#1 Hospital in OKC** according to U.S. News & World Report. Additionally, INTEGRIS Baptist Medical Center was the first facility in Oklahoma to achieve certification in inpatient diabetes, and the first in the nation to accomplish certification in hyperglycemic care.

Making the move to Oklahoma City means you'll enjoy a city that is truly experiencing a **renaissance** – and one that offers a low cost of living, prosperous local economy and outstanding public schools. Check out the full details on our practice and investigate what's in it for you. If it sounds like a good fit – and we're confident it will be – give us a call. We're looking forward to showing you around.

No J1 Visas Accepted • Currently Accepting Applications from H1B Visa Candidates

Practice Details:

Inpatient & outpatient consultative service

- Electronic medical record & computer order entry – clinic & hospital
- Mid-level provider support – clinic & hospital
- Diverse patient population with a plethora of endocrine pathology
- NEW state-of-the-art office/clinic with procedure & education room
- MYLab40 ultrasound machine with specialized thyroid-enhanced imaging & Power Doppler
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- Joint Commissions certified in both inpatient diabetes & glycemic management
- Basal-bolus insulin in the hospital – no sliding scales
- Centralized education forum—referring physicians and patients throughout the community – preventative practices

Compensation Package Includes:

- Competitive salary
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- Employment bonus
- 5 days/$5,000 CME
- Comprehensive health plan
- Excellent retirement programs
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INTEGRIS Health

For more information, contact:
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405-945-4881 • integrisok.com/recruitment

ENDOCRINOLOGIST

Ochsner Health System

OCHSNER HEALTH SYSTEM in New Orleans is searching for a **BC/BE ENDOCRINOLOGIST to join our staff at Ochsner Baptist Medical Center**. Candidates with experience or directly from training are welcomed to apply. Areas of interest should include general endocrine disorders, diabetes, and endocrine disorders as related to pregnancy. This position is mainly outpatient based, but will serve a large Ob/Gyn group with significant inpatient consultation. Salary is competitive and commensurate with experience and training.

Ochsner Baptist Medical Center, with a deep-rooted history in Uptown New Orleans, is a fully accredited, full-service hospital staffed by more than 390 physicians. We have all private rooms, an ICU, 13 operating rooms, and a state-of-the art imaging center. We are proud to be distinguished by our excellence in specialty care and high patient satisfaction scores. Our newly renovated 24-hour full-service emergency department is staffed by a team of board-certified ER physicians.

The Ochsner Health System comprises 8 hospitals and more than 38 clinics across southeast Louisiana with over 1.5 million clinic patient visits annually. Ochsner is a major provider of graduate medical education with 23 ACGME-accredited residency and fellowship programs, including our Endocrinology Fellowship Program. Please visit our Web site at *www.ochsner.org*.

New Orleans is a cosmopolitan, historic city with a pleasant climate, unique architecture, multiple medical schools and academic centers, professional sports teams, world-class dining and cultural interests, and world-renowned live entertainment and music.

Please email CV to: *profrecruiting@ochsner.org*, Ref. # ABENDO1 or call 800-488-2240 for more information. EOE.

Sorry, no J-1 visa opportunities available.

PRESBYTERIAN

Albuquerque, NM

Presbyterian Healthcare Services is a non-profit organization consisting of a health plan, a system of hospitals, and an employed multispecialty medical group. With over $2 billion in revenues, we enjoy a national reputation of being one of America's top 10 integrated healthcare delivery systems. The medical group consists of over 600 physicians and mid-levels. We have the largest health plan in the state, Presbyterian Health Plan, which has over 400,000 covered lives. This year, our medical group and the delivery system (our hospitals) are joined together as a Pioneer Accountable Care Organization having been selected by CMS (Medicare). We are one of 32 such organizations selected nationwide. We are one of 65 hospitals, out of 1200, who were honored nationally by the Leapfrog Group for excellence in-patient safety.

Our Endocrinology Service currently employs 6 well established and respected physicians. The group is seeking a Medical Director who will share their time as a clinician and managing the group. Call is 1:7

PHS offers a guaranteed base salary for this position, plus production, sign on bonus, relocation, 403 (b) w/ PHS contribution and match, 457(b), health, dental, vision, life ins, short & long term disability, malpractice insurance. Visit our web site at *http://www.phs.org/*

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 more than 300 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 United States, American Indian Cultural activities and much more.

For more information regarding the opportunity, please contact Kelly Herrera at 505-823-8771 or *kherrera@phs.org*.
EOE

Victoza® (liraglutide [rDNA origin] injection)
Rx Only
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza, there were more cases of pancreatitis with Victoza than with comparators. Victoza has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis. Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza and prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Do not use in patients with a prior serious hypersensitivity reaction to Victoza or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications]*. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Adverse Reactions]*. **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® has been evaluated in 8 clinical trials*:* A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Reaction	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Reaction	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6

Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza® + Metformin + Rosiglitazone N = 355		Placebo + Metformin + Rosiglitazone N = 175
Adverse Reaction	(%)		(%)
Nausea	34.6		8.6
Diarrhea	14.1		6.3
Vomiting	12.4		2.9
Headache	8.2		4.6
Constipation	5.1		1.1

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

Immunogenicity: Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In the five double-blind clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five double-blind clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia* :In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self–treat	0.1 (0.001)	0	0
Patient able to self–treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self–treat	0.1 (0.003)	0	0
Patient able to self–treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self–treat	0	—	0
Patient able to self–treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self–treat	2.2 (0.06)	0	0
Patient able to self–treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established *[see Warnings and Precautions]*. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea *[see Warnings and Precautions]*; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions]*; Angioedema and anaphylactic reactions *[see Contraindications, Warnings and Precautions]*

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

For information about Victoza® contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, 1–877-484-2869

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novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

When measuring glycemic control in adult patients with type 2 diabetes

Victoza®—proven superior efficacy versus Januvia®.

Discover more updates and data at **VictozaPro.com.**

Victoza® delivered superior A1C reductions of 1.2%-1.5% vs 0.9%,* with additional benefits:

	Victoza®	Januvia
MORE THAN TWICE AS MANY PATIENTS TO A1C <7%	44% and 56%	22%
GREATER FPG REDUCTIONS	-34 mg/dL to -39 mg/dL	-15 mg/dL
GREATER WEIGHT LOSS	-5.9 lb to -7.3 lb	-1.8 lb

Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials.

*A 26-week, open-label, active-comparator, 3-armed, parallel-group trial to compare the efficacy and safety of Victoza® with sitagliptin for the treatment of type 2 diabetes. Patients with type 2 diabetes inadequately controlled on metformin (n=665) were randomized to receive once-daily Victoza® (1.2 mg or 1.8 mg) or Januvia (100 mg). The primary outcome was change in A1C.[1]

Safety and tolerability versus Januvia.

Most common adverse reactions	Victoza® + metformin (n=439)		Januvia 100 mg + metformin (n=219)
NAUSEA	23.9%	VS	4.6%
HEADACHE	10.3%	VS	10.0%
DIARRHEA	9.3%	VS	4.6%
VOMITING	8.7%	VS	4.1%
MINOR HYPOGLYCEMIA	5.0%	VS	5.0%

Indications and Usage

Victoza® (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Victoza® has not been studied in combination with prandial insulin.

Important Safety Information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Renal impairment has been reported post-marketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® (liraglutide [rDNA origin] injection) in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during post marketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

There is limited data in patients with renal or hepatic impairment.

Reference: 1. Pratley RE, Nauck M, Bailey T, et al; for the 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet.* 2010;375(9724):1447-1456.

Please see brief summary of Prescribing Information on adjacent page.

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novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection