

FEBRUARY 2013

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ENDOCRINE news



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**COVER Story****16 Thyroid Management During Pregnancy Gets Better***By Melissa Mapes*

New advances are improving outcomes for pregnant mothers with unruly thyroids, prompting new practice guidelines. Physicians now have the latest recommendations for everything from screening to antithyroid drugs.

20 Acromegaly Diagnosis Still a Tall Order*By Eric Seaborg*

Treatment of acromegaly is complex, involving a multidisciplinary team, but the most common progression remains the triad of surgery, drugs, and radiotherapy. Still, the biggest challenge remains identifying the patients who need it.

35 ENDO 2013: New Schedule, New Features*By Melissa Mapes*

With a daily start time of 7:30 a.m., The Endocrine Society's 95th Annual Meeting & Expo brings the addition of exciting new sessions and easier travel plans for attendees.

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Collaborations Support Goals to Improve **WORLDWIDE HEALTH**

The Society's latest and third Strategic Plan, SP3, calls for a global collaborative approach toward the goal of improved human health worldwide. We recognize that we cannot accomplish this ambitious goal alone and that collaborative efforts and partnerships have become increasingly important. In recent years, the Society has taken steps to increase its outreach and further meet the needs of international endocrinologists and patients.



William F. Young, Jr., MD, MSc

Committee Appointments

Approximately 300 member volunteers participate on 21 Society committees. In previous years, the number of international appointees to committees averaged 12 to 15 percent of the total number of appointments. For 2012 we increased the number of international appointees to 26 percent—including members from countries not previously represented on our committees such as China, India, Mexico, and the Philippines, to name a few.

International Activities in 2012

In 2012, the Society actively participated in the joint meeting of the International Congress of Endocrinology (ICE) and European Congress of Endocrinology meeting in Florence, Italy. In addition to having an exhibit booth and presenting a plenary lecture, The Endocrine Society hosted a reception for the leaders of other international organizations. At ENDO 2012 in Houston, we held our Global Leadership Exchange dinner where attendees were asked to identify the prime endocrine issues that could be addressed at the ICE/ENDO 2014 meeting.

A Global Leadership Exchange session is planned for ENDO 2013 to continue these discussions and to share plans for ICE/ENDO 2014, which will be held in conjunction with the International Society of Endocrinology in Chicago.

In August 2012, The Endocrine Society hosted its 3rd India Summit in Mumbai, where approximately 180 endocrinologists from all over India attended a one-day meeting that covered topics in the areas of thyroid, pituitary, female reproduction, and adrenal. A similar meeting is planned annually through 2015.

In late November, I was invited to the 52nd Congress of the Mexican Society of Nutrition and Endocrinology (SMNE) in Leon, Mexico, to present a plenary lecture. Additionally,

the Society had an exhibit booth that was very well attended, recruiting more than 100 new members from Mexico.

In early December, the Society hosted a Thyroid Ultrasound Workshop, similar to the one held at ENDO, at the Endocrine Society of India's Congress, ESICON. This was the first time this workshop was presented abroad, and we hope that we can use this model for other international meetings in the future.

Outreach Plans for 2013 and Beyond

Several activities and collaborations are planned for 2013. The Ambassador Exchange Program launched in January and will continue through early June, ending with the international participants' attendance at the ENDO meeting in San Francisco. More articles on the program will appear in upcoming issues of *Endocrine News*.

Among the meetings Society leadership will attend in 2013 are the European Congress of Endocrinology (ECE) in Copenhagen, in late April-early May; the Society of Endocrinology and Metabolism of Turkey (SEMT) meeting in Antalya, Turkey, in mid-May; and the SMNE Congress in Cancun, Mexico, in mid-November. A Society exhibit booth at each meeting will promote new membership and Society publications.

Another initiative in the works is a portfolio of options from the Society's annual meeting (ENDO) to be exported and presented in conjunction with national endocrine meetings across the world. The content of each program will be determined by the needs of the host national society. We are currently working with the leadership of societies in Brazil, China, Mexico, and Russia who have expressed interest in this program.

Other collaborations include a joint program with the Society of Endocrinology and Metabolism of Turkey in October 2013 in Turkey and a Clinical Update Training Program in India, in conjunction with the International Society of Endocrinology, the Society of Endocrinology (UK), and the Endocrine Society of India.

The Endocrine Society leadership is committed to these international outreach activities and productive and successful collaborations worldwide. Send your comments or suggestions to president@endo-society.org.

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



The Endocrine Society's exhibit booth at the 52nd CONGRESS OF SMNE in Leon, Mexico.

FEBRUARY 2013

ENDOCRINE NEWS

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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

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

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Stratton Publishing & Marketing Inc.
www.strattonpublishing.com

Prepress & Printing: **Genveo Publishing Services**
www.cadmus.com

Endocrine News is published 12 times a year by
The Endocrine Society, 8401 Connecticut Ave.,
Suite 900, Chevy Chase, MD 20815
Phone 301-941-0200 • Fax 301-941-0259
www.endo-society.org.

Print ISSN 2157-2089 Online ISSN 2157-2097
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Last year, The Endocrine Society conducted an in-depth study of *Endocrine News*. Many of you responded to our reader survey, and we are grateful for your feedback. We were especially pleased that you overwhelmingly chose *Endocrine News* as the top publication in the field. But most importantly, you asked us for more coverage of several topics, such as new technology, along with more quick reads of news items to complement the in-depth features in each issue.

We want you to know that we listened.

In this issue and every issue this year, you'll find more coverage of the topics that are important to you, with practical applications and insights you won't find anywhere else. You told us that you read *Endocrine News* to keep up with new developments in the field and new research studies. We'll continue to deliver just that.

This issue is a great example. This month, our cover story looks at the latest advancements for the diagnosis and treatment of thyroid issues in pregnant women. This complex field of medicine has made significant advances in the past 5 years. In addition to updates on The Endocrine Society's new guidelines, you'll find quick tips on identifying moms-to-be who may be at risk.

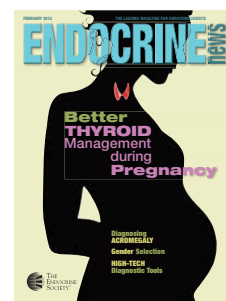
Another especially interesting feature story this month studies acromegaly, a particularly difficult-to-diagnose condition that's seeing new treatment options today.

And finally, we give you more details about ENDO 2013, which promises to be the best conference ever with a new schedule and new opportunities for professional development.

Be sure to check out *Endocrine News*' regular lineup of columns and departments, now more readable and focused on you.

We hope you enjoy this month's issue. Please give us your feedback at endocrineneeds@endo-society.org.

Eleanore Tapscott
Senior Director of Publications



ENDOCRINE NEWS ONLINE EXCLUSIVES

The articles below are online only at www.endo-society.org/endo_news.
See *Endocrine News Online* to read them and related links.



HT and the Obesity Battle

The debate over whether hormone therapy (HT) for postmenopausal women benefits outweigh cardiovascular and cancer risks for postmenopausal women wages on.



Worming Away Infection

Infection by the flatworms that cause schistosomiasis could have the side benefit of reducing the risk of diabetes, a new study indicates.



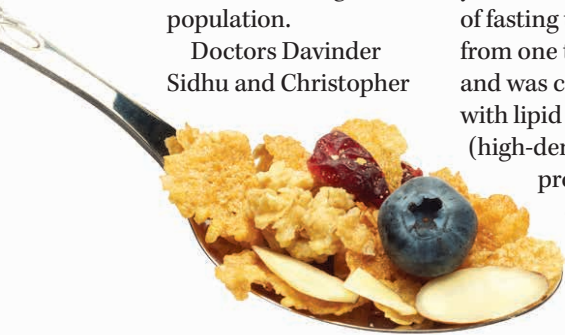
Low Vitamin D3 and Type 1 Diabetes

Individuals with low levels of Vitamin D3 are more likely to develop type 1 diabetes than those with the highest levels, study finds.

Go Ahead, **EAT BREAKFAST**

Current guidelines recommend an eight-hour fast before a cholesterol test, which is burdensome to both patients and laboratories. Previous studies comparing cholesterol levels in fasting versus non-fasting states used selected patient populations rather than the general population.

Doctors Davinder Sidhu and Christopher



Naugler at the University of Calgary in Canada conducted a study, published Nov. 12, 2012, online in the *Archives of Internal Medicine*, to determine the relationships between

fasting times and blood lipid parameters. Researchers analyzed laboratory data from 209,180 people (53 percent female, 47 percent male) in the Calgary, Alberta, Canada area. The average age in the study was 53 years, and ranged from 0 to 103 years old. The duration of fasting time ranged from one to 16 hours and was correlated with lipid test panels (high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides).

The length of fasting time prior to having blood drawn had little effect on blood lipid levels. The average HDL and total cholesterol

varied by less than 2 percent, the average LDL varied by less than 10 percent, and the average triglycerides varied by less than 20 percent.

The authors suggested that fasting before routine blood cholesterol screenings may be unnecessary and that dropping the fasting requirement may improve patient compliance. They also noted that more studies are needed to confirm their results before moving to routine non-fasting lipid screening. **Finding little effect on blood lipid levels, researchers suggest fasting before routine blood cholesterol screenings may be unnecessary, and dropping the fasting requirement may improve patient compliance.**

—Joanne McAndrews, PhD



COGNITIVE DECLINE Linked to Fat Consumption Mitigated with Exercise

Exercise might ward off cognitive decline brought on by high fat consumption. University of Minnesota researchers taught mice a memory task, then fed half the group a 40 percent fat diet and watched their cognitive function decline. Using an exercise wheel returned cognitive function to baseline within seven weeks. Non-exercising mice remained impaired. If the research holds up for humans, exercise may become an important tool in addressing Alzheimer's disease. **Using exercise to combat high fat consumption may play critical role in addressing Alzheimer's and memory disorders.**

—Carol Bengle Gilbert

POTENTIAL TARGET for Beta Cell Protection

A protein involved in modulating programmed cell death in pancreatic beta cells could offer a therapeutic target for preserving beta cell mass and slowing the pathogenesis of diabetes.

Epidermal growth factor (EGF) stimulates cell growth, proliferation, and differentiation by binding to its receptor on cells, EGFR. Mitogen-inducible gene 6 (Mig6) is a stress response protein that can interfere with this process by binding to EGFR, downregulating its signaling. Mig6 has been viewed as a molecular brake on proliferation, so a team led by Patrick T. Fueger, PhD, of Indiana University School of Medicine in Indianapolis decided to study its role

in apoptosis and endoplasmic reticulum (ER) stress.

Using adenoviral vectors to manipulate Mig6 expression in mice, they found that Mig6 overexpression exacerbated beta cell apoptosis through pathways mediated by caspase 3, a protease that plays a key role in programmed cell death. Silencing of Mig6 mitigated the apoptosis.

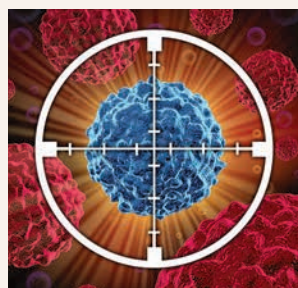
The high glucose and lipid levels typical of diabetes compromise the integrity of the endoplasmic reticulum in pancreatic beta cells, triggering pathways

leading to cell death. The researchers suggest that Mig6 regulates pancreatic beta cell apoptosis during ER stress via a new pathway, perhaps by compromising cell survival signals mediated by growth factor receptors.

In an article in *Molecular Endocrinology*, they propose that targeting Mig6—preventing its induction, translation, or function—could be a strategy for increasing beta cell survival.

Mig6 regulates pancreatic beta cell apoptosis during ER stress via a new pathway, perhaps by compromising cell survival signals mediated by growth factor receptors.

—Eric Seaborg





Graves' Orbitopathy COSTS GERMANY Up to \$3.7B Annually

In a first-of-its-kind study appearing in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournal.org], researchers from the Gutenberg University Medical Center in Mainz, Germany, set out to measure the direct and indirect costs of Graves' orbitopathy (GO). The researchers estimated GO costs the German nation more than \$200 million per year in direct costs and between \$1.7 and \$3.5 billion per year in indirect costs. The direct costs consist of treatment expenditures, while sick leave and disability payments constitute the indirect costs.

The researchers noted their estimates are low due to the study's cross-sectional design. That design prevented consideration of the disease's typical one-to-two-year active phase in measuring direct costs and the long-term, indirect costs occurring outside the study period.

The study relied upon clinical data and cost information from 310 GO patients and 370 controls from 2005 to 2009.

In estimates that may still be low, German researchers find that Graves' orbitopathy costs the country more than \$200 million per year in treatment expenditures and between \$1.7 and \$3.5 billion per year in sick leave and disability payments.

—Carol Bengle Gilbert

Androgen Receptor Ablation Improves Bone Marrow Grafting

Androgen deprivation therapy (ADT) has been the treatment of choice for prostate cancer and is also used adjunctively in bone marrow transplantation (BMT) to promote T-cell survival. However, ADT not only comes with significant side effects associated with loss of sex steroids, but also has proven ineffective to treat prostate cancer. What if the androgen receptor (AR) is somehow implicated here, rather than the androgen itself?

Chawnsiang Chang, PhD, at the University of Rochester Medical Center, New York, led a team of scientists to uncover how thymic cellularity affects T-cell exportation and, in

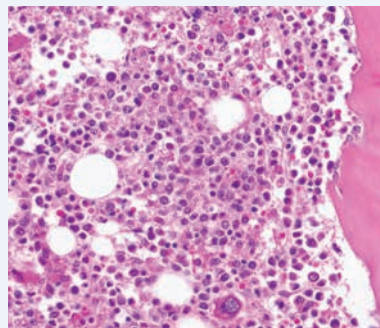
turn, the immune response in epithelial AR knock-out mice. In their paper, to be published soon in *Molecular Endocrinology*, the researchers report that the mice showed both increased thymopoiesis and T-cell availability, which collectively produced a better immune response during BMT. This finding held up when a synthetic AR degradation enhancer was used.

The researchers conclude that AR signaling modulates T-cell selection and that targeting AR promotes T-cell survival. AR ablation not only improves BMT outcomes without adverse side effects but is also a promising future therapy for other

AR-related diseases. "Using ASC-J9, the first AR degradation enhancer to target AR in selective cells, led to good efficacy to treat acne, wound healing, spinal and bulbar muscular atrophy, and prostate and liver cancers," said Dr. Chang.

Androgen receptor ablation improves bone marrow transplantation outcomes without adverse side effects and holds promise as a future therapy for other AR-related diseases.

—Kelly Horvath



Lean Men Also Face DIABETES RISK Due to OSA

Obstructive sleep apnea (OSA), a disorder in which the throat muscles relax and block or narrow the airways to the lungs during sleep, has long been associated with insulin resistance and an increased risk of type 2 diabetes in people who are overweight or obese. But now a study published in the November 2012 issue of *Diabetes Care* by researchers at the University of Chicago suggests that the condition may increase diabetes risk in young, lean men, as well.

In the study, 52 men between the ages of 18 and 30 with body mass indexes between 18 and 25 underwent sleep studies. The next morning they took an

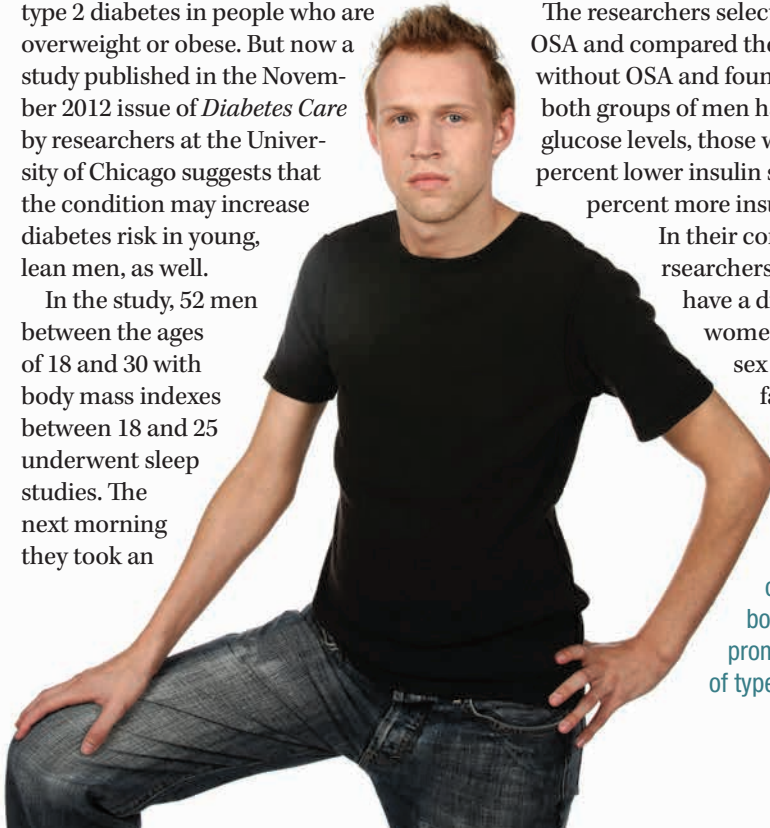
oral glucose tolerance test in which they consumed a sugary drink and researchers measured their blood glucose and insulin concentrations at 30, 60, 90, and 120 minutes.

The researchers selected 12 men with OSA and compared them to 20 men without OSA and found that even though both groups of men had similar blood glucose levels, those with OSA had 27 percent lower insulin sensitivity and 37 percent more insulin secretion.

In their conclusion, the researchers note that OSA may have a different effect on women because of known sex disparities in body fat distribution.

The presence of obstructive sleep apnea, in the absence of increased body fat or other cardiometabolic risk factors, may promote the development of type 2 diabetes in men.

—Terri D'Arrigo

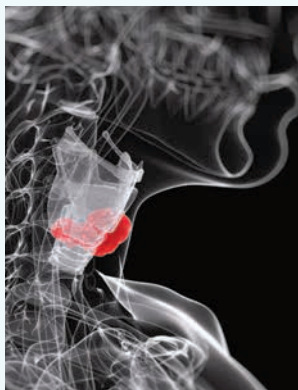


Promising **THYROID CANCER** Treatments

Two compounds, decitabine and zebularine, show promise for treating thyroid tumors and should be investigated for that purpose, say researchers at the National Cancer Institute (NCI) in Bethesda, Maryland.

Decitabine is currently used to treat myelodysplastic syndrome, or MDS, a group of conditions in which the bone marrow produces misshapen blood cells. Zebularine is currently being studied for use in treating breast cancer. Both compounds were shown to affect genes that direct the growth of thyroid tumors.

In a three-pronged study appearing in the January 2013 issue of *Endocrinology*, researchers led by Won



Gu Kim, MD, PhD, first examined human thyroid cancer tissue samples and determined that the expression of a gene called *THRB* is lower in people who have thyroid cancer, and that lower levels of *THRB* correlate to greater cancer progression. Next, the researchers bathed cancerous human thyroid

and neck lymph node cells in either decitabine or zebularine and found that these agents promoted the expression of the *THRB* gene.

The researchers further studied decitabine's effectiveness in slowing tumor growth in mice. They inoculated 12 mice with human thyroid cancer cells, and then separated the mice into two groups. Six mice received injections of decitabine while the remaining mice were injected with inactive solution. Tumors grew more slowly in the mice treated with decitabine than those injected with inactive solution.

Compounds decitabine and zebularine show promise for the potential treatment of thyroid tumors.

—Terri D'Arrigo



Pepsi has launched a product that promises to put a new spin on diet soda. The Pepsi Special on sale in Japan contains dextrin, a water-soluble fiber supplement that acts as stomach filler. Pepsi says its new drink will "minimize the absorption of fats" or block the fat.

—Glenda Fauntleroy

Lower Stress, **HIGHER FERTILITY**

There may be a nugget of truth in the old wives' tale that women trying to get pregnant should just relax. New findings on the effects of corticotropin-releasing hormone (CRH) at the ovarian follicle level suggest that lowering stress levels could increase a women's fertility.

A neuropeptide secreted by the hypothalamus in response to stress, CRH is a major regulator of the hypothalamic-pituitary-adrenal axis. Researchers, led by Dimitris Loutradis, MD, PhD, of the University of Athens School of Medicine, Greece, decided to look at CRH's effects on preantral mouse follicles, steroidogenesis, and embryo development, because their previous studies showed that CRH inhibits in vitro oocyte maturation in mice.

When the researchers cultured preantral follicles in the presence of CRH, they found a marked reduction in estradiol and progesterone concentrations compared with controls. The addition of antalarmin, a synthetic antagonist of CRH receptor type 1, reversed the

reduction of both hormone levels.

The researchers then cultured embryos, finding that exposure to CRH significantly slowed their development rates. The addition of antalarmin to these cultures yielded higher survival rates in all embryo stages.

In an article pending publication in *The Journal of Clinical Endocrinology & Metabolism*, researchers say they found a new mechanism by which CRH retards oocyte maturation. CRH not only interferes with nuclear maturation, but also seems to affect cytoplasmic maturation through its anti-estrogen actions. Antalarmin can reverse this mechanism, demonstrating the role of CRH in all these processes.

Because increased stress levels can induce regional CRH secretion in the ovary and fallopian tubes, where the hormone can have these interfering effects, it follows that oocyte quality and embryo development could be enhanced by lowering patient stress.

Exposure to corticotropin-releasing hormone significantly slows embryo development rates, indicating lowering patient stress could enhance oocyte quality and embryo development.

—Eric Seaborg





DIABETES and OBESITY on the Brain

Hoping to discover potential therapeutic pathways to reverse the obesity and diabetes trend, Karen Ryan, PhD, and colleagues at the University of Cincinnati studied the effects of fibroblast growth factor-19 (FGF19) and its rodent ortholog, FGF15, in the brain on food intake and glucose tolerance. Their findings will be published in an upcoming issue of *Endocrinology* [endo.endojournals.org].

Using a male rat model, the presence of FGF-receptors 1 and 4 in the hypothalamus was confirmed, and the expression of the FGF-1 receptor mRNA was 60 percent lower in high-fat fed rats as compared with lean control animals. FGF-4 receptor mRNA was also reduced in the high-fat fed animals compared with controls. When FGF19 was directly infused into the brain via the third cerebral ventricle, 24-hour food intake and body weight decreased, and glucose tolerance was improved. In contrast, administration of an FGF-receptor inhibitor into the third cerebral ventricle increased food intake and impaired glucose tolerance.

Findings pointed to the brain as a possible target for the positive effects of FGF19 for the treatment of obesity and diabetes. They also called for more research in this area to clarify the effects on lipid and carbohydrate metabolism and inter-related pathways.

—Joanne McAndrews, PhD

Metabolic Syndrome Contributes to **CARDIOVASCULAR RISK** with HT

Amid the controversy over the cardiovascular risks v. the overall benefits of hormone therapy (HT), Robert A. Wild, MD, MPH, PhD, at the University Health Sciences Center, in Oklahoma City, Oklahoma, led a team of scientists to investigate whether metabolic syndrome contributes to coronary event incidence with oral HT.

Using Women's Health Initiative demographic and metabolic data to assess "baseline cardiometabolic risk status," the team conducted a nested case-control study of 269 women without prior cardiovascular disease (CVD) and a second composed of 166 women without prior diabetes or hypertension all who developed CVD within the first 4 years of HT. Average age of participants was 66 years.

In their paper, published in *Menopause: The Journal of The North American*

Menopause Society, the researchers report that women who had risk factors for CVD or had metabolic syndrome (defined by specific parameters) were more likely to have a coronary event on HT, possibly because of a strong circulating fatty acid-induced inflammatory response, precipitating atherosclerotic plaque rupture.

The researchers conclude that CVD risk status should be evaluated before initiating oral HT. Alternative preparations might confer greater safety and should be investigated for effect on CVD, they add. **Women with risk factors for CVD or with metabolic syndrome may be more likely to have a coronary event on HT, possibly because of a strong circulating fatty acid-induced inflammatory response, precipitating atherosclerotic plaque rupture.**

—Kelly Horvath

Obesity Puts Boys at Higher Risk of **ASTHMA**

While past research has shown overweight and obese children develop asthma at greater rates than their normal-weight peers, a new literature review reveals that obese boys are at the greatest risk.

Childhood obesity has reached epidemic numbers, with more than 42 million children under the age of 5 now overweight, according to the World Health Organization.



Reviewers from National Taiwan University in Taipei evaluated six studies that included 18,760 children between the ages of 6 and 18. Overweight was considered a body mass index greater than the 85th percentile on a children's growth chart, and obesity was defined as greater than the 95th percentile.

The review found the incidence of asthma increases by 20 percent in overweight children and by a twofold risk in obese children compared with children of normal weight. Also, gender made a significant difference in the respiratory health risk for obese children. Obese boys were more likely than obese girls to develop asthma, with a relative risk of 2.47 compared to 1.25. The

authors suggested that pulmonary mechanics, sleep disordered breathing, and leptin levels may account for the gender difference.

"Obese children might get benefit in asthma prevention if they try to lose weight," says Yungling Leo Lee, who co-authored the article appearing in *Obesity Reviews* [iaso.org].

The authors concluded that health policy makers and parents should pay more attention to preventing obesity-associated risk and environments.

The incidence of asthma increases by 20 percent in overweight children and by a twofold risk in obese children compared with children of normal weight—with risk higher among boys.

—Glenda Fauntleroy

HIGH BONE MASS in Women May Signal Higher Weight

Scientists in the U.K. recently investigated the relationship between bone and fat, screening more than 219,000 dual-energy x-ray absorptiometry (DXA) scans from country's health centers. They found 0.2 percent of the DXA scans had high bone mass.



In the new study, 153 men and women with unexplained high bone mass were recruited along with 138 of the individuals' first-degree relatives and 39 spouses. Participants' bone formation and reabsorption markers were also measured.

In their article published in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], the researchers found that total body fat mass was about 9 kilograms higher in women with high bone mass than in the controls. Their fat mass also stayed constant with age compared with the inverse association found in the controls. The increased fat mass in males with high bone mass was less significant. Osteocalcin (a bone formation marker)

was also lower in females with high bone mass than in the controls.

"The key take-home message for clinicians is that research assessing an extreme bone phenotype suggests bone acts to regulate fat metabolism, which raises the possibility that current treatments of osteoporosis may affect fat metabolism and obesity risk," says lead investigator Celia Gregson, PhD, from the University of Bristol.

Gregson added that her team is currently working to answer these questions. **In a study of men and women with high bone mass, researchers found that total body fat mass was about 9 kilograms higher in women and that their fat mass stayed constant with age.**

—Glenda Fauntleroy



Prostaglandin Could Inhibit PROSTATE CANCER

Prostate cancer can often be held in check with androgen deprivation therapy, but eventually seems to break through to a "castration-resistant" form, leaving researchers to search for new treatment approaches.

Because chronic inflammation has been linked in general to carcinogenesis through increased production of reactive oxygen species, and in particular to cancerous growth in the prostate, inflammation's role offers a promising avenue to explore for these new approaches.

A research team led by Joma J. Palvimo, PhD, of the University of Eastern Finland in Kuopio, investigated the effects of the 15-deoxy- $\Delta^{12,14}$ -prostaglandin J_A_2 (15d-PG J_A_2), which has anti-inflammatory properties, on the activity of androgen receptors in prostate cancer cells.

When the researchers exposed prostate cancer cells to 15d-PG J_A_2 , it repressed androgen receptor target genes and inhibited the activity of the androgen receptors, apparently by forming adducts with them. This inhibitory effect was more efficient than the effects of bicalutamide, one of the antiandrogens currently used in clinical treatment.

In an article accepted for publication in *Molecular Endocrinology*, the researchers conclude that 15d-PG J_A_2 is a potent and direct inhibitor of androgen receptor signaling. **Endogenous prostaglandin could provide a new approach to restricting androgen receptor activity in prostate cancer cells.**

—Eric Seaborg

Quick Weight Gain in Newborns Raises HEART HEALTH RISKS

Babies who gain too much weight soon after birth may already be at risk for later health problems, a new study finds.

Researchers led by Annemieke Evelein, MD, of the Julius Center for Health Sciences and Primary Care in Utrecht, The Netherlands, found that weight and the growth of a child in the first three months after birth is linked with cardiovascular disease, as evident by thicker arterial walls.

In their study published in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], the team used data from an ongoing Netherlands population study to look at the birth and weight of children from newborn to 3 months. Scientists checked in with 333 children at the age of 5—measuring the ratio of their weight gain rate for length gain rate (WLG) and also performing ultrasound measurements of the right carotid artery.

The results showed that the thinner the children were at birth, the stiffer the

arteries were with increasing WLG. Higher WLG was linked with higher weight, height, body mass index, and waist circumference at age 5.

"Pediatricians could look for possible improvements in the environment of the baby who has established risk factors, such as asking the parents for their feeding habits," says Evelein.

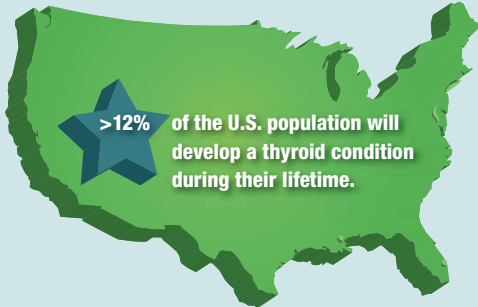
Newborns who gain weight quickly show higher weight, height, body mass index, and waist circumference by age 5, putting them at greater cardiovascular risk.

—Glenda Fauntleroy



Fast FACTS about Thyroid Disorders

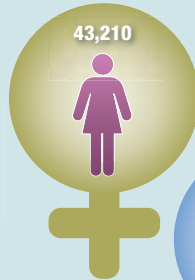
Thyroid conditions affect a large chunk of the U.S. population.



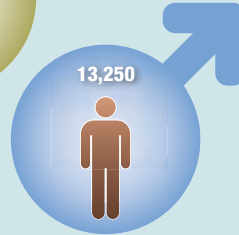
The chance of being diagnosed with thyroid cancer has risen in recent years and is now more than twice what it was in 1990.



Some studies show that up to 50% of depression is caused by an undiagnosed thyroid condition.



About 56,460 new cases of thyroid cancer were diagnosed in 2012



About 1,780 deaths from thyroid cancer occurred in 2012



An estimated 20 million Americans have some form of thyroid disease.

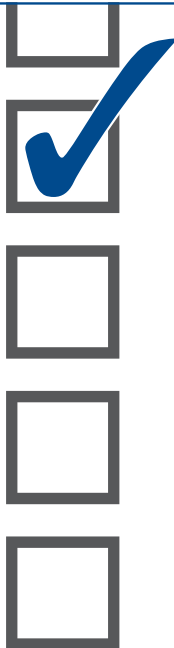


Up to 60 percent of those with thyroid disease are unaware of their condition.



In 2009, individuals with diabetes and thyroid disorders had significantly greater total healthcare expenditures than those without the disorders.

Sources: American Cancer Society, American Thyroid Institute, *Journal of Thyroid Research*, National Thyroid Institute



LAST CALL VOTE 2013 ELECTION

TIME IS RUNNING OUT TO VOTE.

Election ballots were sent to members with voting privileges in early January 2013. Information for online voting can be accessed by visiting www.endo-society.org/membership/election.cfm.

Questions should be directed to Elizabeth Kan at 301.941.0206 or ekan@endo-society.org.

ELECTRONIC VOTES MUST BE RECEIVED BY MIDNIGHT EST ON MARCH 3, 2013.



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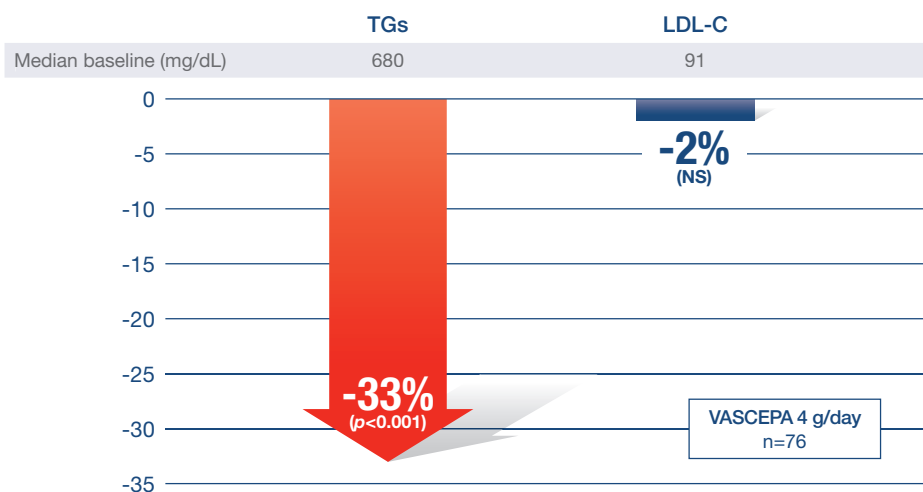
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VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.



VASCEPA significantly reduced TG levels *without* increasing LDL-C¹

Placebo-Adjusted Median Percent Change From Baseline^{1,2}



- The effects of VASCEPA 4 grams per day were assessed in a 12-week, randomized, placebo-controlled, double-blind, parallel-group study evaluating patients with fasting TG levels ≥ 500 mg/dL and ≤ 2000 mg/dL (with or without statin therapy).¹
 - The primary study end point was the placebo-adjusted median percent change in TG levels from baseline.²
 - TGs: VASCEPA, 27% median decrease from baseline; placebo (n=75), 10% increase.
 - LDL-C: VASCEPA, 5% median decrease from baseline; placebo (n=75), 3% decrease.
- NS=not significant.



VASCEPA demonstrated a tolerability and side-effect profile similar to placebo^{1,2}

- The only adverse event occurring at an incidence $>2\%$ and greater than placebo was arthralgia (2.3% for VASCEPA vs 1.0% for placebo)*

*Studies included patients with TG levels of 200 to 2000 mg/dL.

Limitations of Use for VASCEPA

- The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.
- The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

VASCEPA is covered on the majority of plans with minimal restrictions.

Please see Brief Summary at the conclusion of this ad or visit www.VASCEPA.com for full Prescribing Information for VASCEPA.

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(triglyceride levels ≥ 500 mg/dL)

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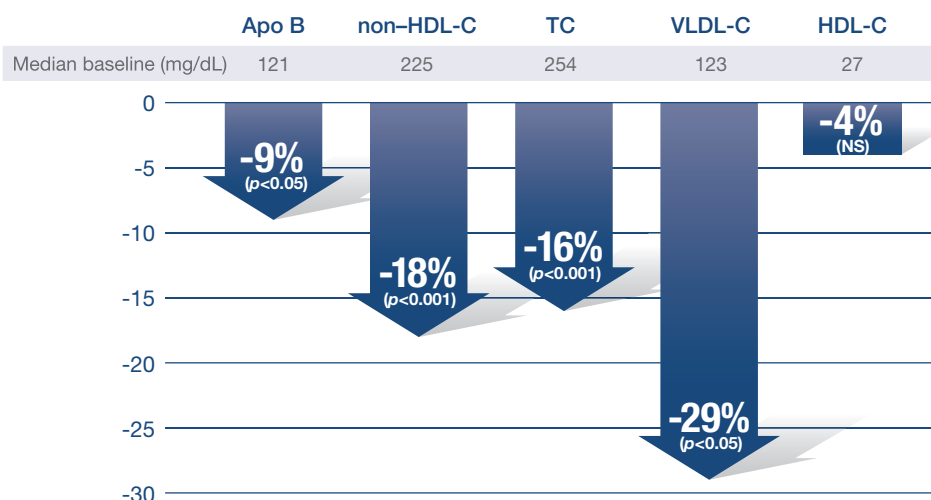
TG Therapy Redefined:

VASCEPA significantly reduced TG levels *without increasing LDL-C*¹



VASCEPA significantly improved multiple lipid parameters^{1,2}

Placebo-Adjusted Median Percent Change From Baseline^{1,2}



- VASCEPA 4 g/day, n=76; placebo, n=75.
 - Apo B: VASCEPA, 4% median decrease from baseline; placebo, 4% increase.
 - Non-HDL-C: VASCEPA, 8% median decrease from baseline; placebo, 8% increase.
 - TC: VASCEPA, 7% median decrease from baseline; placebo, 8% increase.
 - VLDL-C: VASCEPA, 20% median decrease from baseline; placebo, 14% increase.
 - HDL-C: VASCEPA, 4% median decrease from baseline; placebo, no change.
- NS=not significant.



VASCEPA dose is 4 g/day, 2 capsules twice daily with food¹

Important Safety Information for VASCEPA

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
- Use with caution in patients with known hypersensitivity to fish and/or shellfish.
- The most common reported adverse reaction (incidence $>2\%$ and greater than placebo) was arthralgia.
- Patients should be advised to swallow VASCEPA capsules whole; not to break open, crush, dissolve, or chew VASCEPA.

Apo B=Apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; VLDL-C=very low-density lipoprotein cholesterol.

References: 1. VASCEPA [package insert]. Bedminster, NJ: Amarin Pharma Inc.; 2012. 2. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol.* 2011;108(5):682-690.

130022 01/13

Vascepa[®]
(icosapent ethyl)

VASCEPA® (icosapent ethyl) Capsules, for oral use

Brief summary of Prescribing Information

Please see Full Prescribing Information for additional information about Vascepa.

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen with VASCEPA.

Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate. [see Indications and Usage (1)].

Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food.

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

5.2 Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

6 ADVERSE REACTIONS

6.1 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.

Adverse reactions reported in at least 2% and at a greater rate than placebo for patients treated with VASCEPA based on pooled data across two clinical studies are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

Adverse Reaction	Placebo (N=309)		VASCEPA (N=622)	
	n	%	n	%
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.

An additional adverse reaction from clinical studies was oropharyngeal pain.

7 DRUG INTERACTIONS

7.1 Anticoagulants

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2 g/kg/day group at 5 times

human systemic exposure following an oral dose of 4 g/day based on body surface area comparison.

In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic nerves and unilateral testes atrophy were observed at ≥ 0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/day based on body surface area comparisons across species. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. In lactating rats, given oral gavage ¹⁴C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 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.

9 DRUG ABUSE AND DEPENDENCE

VASCEPA does not have any known drug abuse or withdrawal effects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

See VASCEPA Full Package Insert for Patient Counseling Information.

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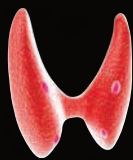
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Better THYROID

By Melissa Mapes

Latest advances prompt
new guidelines for
screening and treatment

An unruly thyroid during pregnancy puts both mother and child at great risk for complications. Fortunately, this complex field of medicine has made significant advances in the past 5 years. The recent benchmarks motivated The Endocrine Society to release updated guidelines (August 2012), which give physicians the latest recommendations for everything from screening to antithyroid drugs.

A team of experts, led by Dr. Leslie De Groot of the University of Chicago Medical Center, rewrote the 2007 version after extended discussion and debate, ultimately producing *Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline*.

The report is organized around eight different conditions, including management of hypothyroidism, management of hyperthyroidism, gestational hyperemesis and hyperthyroidism, autoimmune thyroid disease and miscarriage, thyroid nodules and cancer, iodine nutrition, postpartum thyroiditis, and screening for thyroid dysfunction during pregnancy. The strength of each recommendation made in the guideline received a rating of A, B, C, D, or I for “insufficient,” along with visual indicators for quality of evidence.

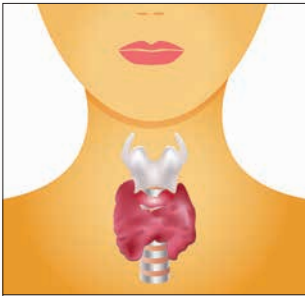
Rethinking Diagnoses

The diagnosis of hypothyroidism is one of the first changes in the new report. De Groot describes the well-known effects of maternal hypothyroidism on unborn children as, “a common cause of mental deficiency around the world due to iodide deficiency.” Hypothyroid women are

AT-A-GLANCE:

- Laboratories should establish trimester-specific ranges of free T4 level norms and conduct alternative measurements.
- All women of childbearing age should consume 150ug of iodine per day to maintain normal thyroid activity.
- Committee differed on whether the serum TSH of all women should be tested within the first nine weeks of pregnancy.

Management during Pregnancy



EIGHT HIGHLIGHTED CONDITIONS OF THYROID DYSFUNCTION

- Hypothyroidism
- Hyperthyroidism
- Gestational hyperemesis and hyperthyroidism
- Autoimmune thyroid disease and miscarriage
- Thyroid nodules and cancer
- Iodine nutrition
- Postpartum thyroiditis
- Screening for thyroid dysfunction during pregnancy

already predisposed to infertility, abortion, postpartum hemorrhage, and a number of other negative symptoms. But, it is not yet proven that detecting hypothyroidism in non-iodide deficient parts of the world and treating it will prevent damage to fetal mental development. The committee thus cautioned physicians in their interpretation of free T4 levels during pregnancy, noting that laboratories should establish trimester-specific ranges of

typical goiter and TSH receptor antibodies. If physicians discover Graves' disease or thyroid nodules, antithyroid (ATD) drug therapy should begin as quickly as possible, ideally before pregnancy.

The committee recommends propylthiouracil (PTU) as the first defense against hyperthyroidism, but only during the first trimester. Methimazole (MMI) can be prescribed for the remainder of gestation, but the slim risk of congenital abnormalities during the first dozen weeks of pregnancy makes it a slightly lesser option for the beginning. Unfortunately, PTU has been tied to very rare incidences of severe liver toxicity, which is why the new guidelines suggest switching to MMI after 3 months.

"The problem is that the FDA has recommended that doctors avoid using propylthiouracil during pregnancy, or anytime, because of the low, but possible, risk of liver damage. And the other problem is that methimazole is

norms and conduct alternative measurements.

"We recommend maintaining pregnant women with a total thyroxine at 1.5 times that of normal levels," De Groot remarks. The free thyroxine index, also known as adjusted T4, is recommended as a reliable assay by the report. If the mother is found to be positive for thyroid peroxidase antibodies, T4 replacement is suggested and dosage should be reevaluated every four to six weeks of pregnancy, because an increase up to 30 percent may be necessary. Most women will have to return to higher levels of T4 replacement after the baby is delivered.

Hyperthyroidism requires entirely different action. For diagnosis, physicians can determine whether subnormal serum TSH concentration is a symptom of gestational thyrotoxicosis or Graves' disease by looking for a



LIKELY SUSPECTS

Recommended patient profiles for targeted thyroid disease case finding in women seeking pregnancy or newly pregnant:

- Over age 30
- Family history of autoimmune thyroid disease or hypothyroidism
- Goiter
- Thyroid antibodies, primarily thyroid peroxidase antibodies
- Symptoms or clinical signs suggestive of thyroid hypofunction
- Type 1 DM or other autoimmune disorders
- Infertility
- Prior history of miscarriage or preterm delivery
- Prior therapeutic head or neck irradiation or prior thyroid surgery
- Currently receiving levothyroxine replacement
- Living in a region with presumed iodine deficiency

“Maternal hypothyroidism in pregnancy is not rare and assessing the status of the fetus is a problem.

There is a serious risk for fetal problems, and the methods of detection are not good.”

— Dr. Leslie De Groot
of the University of Chicago Medical Center

known to have the rare but recognized possibility of causing abnormalities in the fetus during the first trimester, so we recommend that doctors put their patients on PTU and switch to MMI,” De Groot explains.

That said, practitioners should use their professional judgment when deciding a course of treatment. If a patient cannot tolerate one of the drugs, the other drug will likely yield satisfactory results throughout pregnancy without hurting fetus or mother. “The high probability is that either drug would work out without any trouble,” De Groot says. Patients that convert from PTU to MMI should have thyroid function checked after two weeks and in two-to-four-week intervals thereafter. Liver function may be monitored in those on PTU every three to four weeks and patients should be told to keep a careful eye out for any new symptoms.

Fetal Interventions

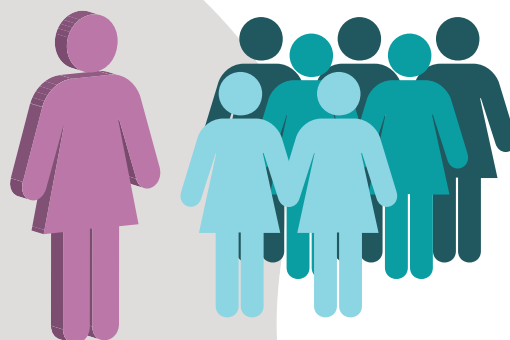
Controlling the effects of hyperthyroidism in the fetus is trickier than in the mother. De Groot hopes that testing mechanisms for the thyroid condition of an unborn child will soon improve.

“Maternal hypothyroidism in pregnancy is not rare and assessing the status of the fetus is a problem,” he explains. The medication and antibodies both cross the placenta and affect the fetal thyroid, but how much can be difficult to determine. “There is a serious risk for fetal problems, and the methods of detection are not good.”

should be screened for thyroid dysfunction, such as a fetal goiter or heart failure, both of which may happen if the unborn child becomes hypothyroid.

Treatment Risk Assessment

The guidelines committee also commented on whether it is appropriate to give thyroxine to mothers with antibodies, due to the relationship with miscarriage. A recent study in Finland found that the children of women who were positive for antibodies in the first trimester were more likely to give birth preterm and the children had a mean intelligence score of 10 points lower than control children at 25-30 months of age. One school of thought is to treat such mothers with antithyroid pills, but the guidelines reject this notion based on a lack of evidence. More research is needed to prove that the benefits outweigh the risks because, as always, overtreatment can be just as detrimental as undertreatment.



ONE WOMAN IN EIGHT will develop a thyroid disorder during her lifetime.

FETAL THYROID DYSFUNCTION

Right now, physicians rely on ultrasounds and the mother's free T4 to screen for fetal thyroid dysfunction. Diagnosis can be challenging, and testing umbilical cord blood instead poses danger to the child that is only worth the risk under certain conditions.

Right now, physicians rely on ultrasounds and the mother's free T4 to screen for fetal thyroid dysfunction. Diagnosis can be challenging, and testing umbilical cord blood instead poses danger to the child that is only worth the risk under certain conditions.

In some cases, Graves' disease may be a motivating factor for the riskier but more direct cord blood test. Unborn infants with a family history of Graves' should be checked by ultrasound to ensure that their thyroid is functioning properly by the 22nd week of gestation. “The change is that we made more explicit the timing and indications for measuring the antibodies,” De Groot explains. If antibodies exceed 2-3 times the normal level, the fetus

This philosophy also comes into play when thyroid nodules are found in a pregnant woman. Although the use of fine needle aspiration (FNA) has become more general in the new recommendations, surgery on even malignant tumors should be delayed until the second trimester. Any nodule over one centimeter in size may undergo FNA, but in women with a history of thyroid dysfunction, FNA may be applied to nodules as small as five millimeters. Radiation should be entirely avoided during pregnancy and until at least four weeks after breastfeeding has ended.

Among other notable updates in the new guidelines, the experts now encourage all women of childbearing age to consume 150ug of iodine per day to maintain normal thyroid activity. Even before conception, women intending to become pregnant should increase to 250ug and continue supplementation throughout gestation and breastfeeding. “Women taking vitamins should verify that they contain that much iodine,” says De Groot. Those living in countries with known iodine deficiency must take special care to ensure adequate intake.

Value of Early Testing

The largest point of controversy among the committee centered on testing for thyroid issues during the early weeks of pregnancy. “Our committee did not agree on that, and we had long and complicated debates,” De Groot explains.



The symptoms of dysfunction can be confused with normal discomforts of pregnancy, which can lead to problems if left untreated. De Groot believes that the serum TSH of all women should be tested within the first nine weeks of pregnancy to make sure the thyroid is working normally, but roughly half of the committee differed, so they decided to make a set of recommendations for practitioners of each philosophy. A recent editorial from the *Journal of Clinical Endocrinology & Metabolism*, titled “When Thyroidologists Agree to Disagree,” describes the deliberation that occurred during the creation of the guidelines.

The pro-testing group encourages testing of all pregnant women by the ninth week, while the other group believes testing is only necessary in at-risk women, such as those with a history of thyroid malfunction. For practitioners against universal screening, aggressive case finding can help ensure that patients with thyroid issues do not go untreated. De Groot hopes that the next committee will reach an agreement on whether or not testing should be mandatory.

De Groot has further ambitions for thyroid management in pregnancy and postpartum that he anticipates the upcoming generation of researchers will accomplish. “I hope that we’ll have a more uniformly available and well-validated assay of free thyroid hormones in pregnant women. That would be universally valuable.”

He also sees the questions about thyroid drugs being

NOTABLE GUIDELINE UPDATES

- Use free T4 index to diagnose hypothyroidism and multiply non-pregnant levels by 1.5 to determine 2nd & 3rd trimester range
- First-line treatment for hyperthyroidism changes from propylthiouracil (PTU) to methimazole (MMI) after 1st trimester
- Fine needle aspiration (FNA) should be performed for solid thyroid nodules over 1cm, or over 5mm for high-risk women
- All women of childbearing age should consume 150ug of iodine per day and all pregnant or breastfeeding women should take 250ug/d
- Use aggressive case finding to screen at-risk women if not universally screening patients for thyroid dysfunction by the 9th week of gestation

answered, such as the potential issues with PTU and MMI. Though treatments are yet to be perfected, the immense advances made between the 2007 and 2012 guidelines provide a brighter future for women with thyroid dysfunction and their children. **EN**

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

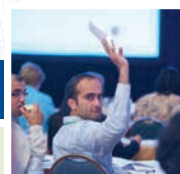
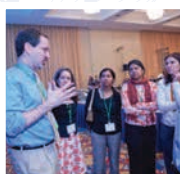


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ACROMEGALY

By Eric Seaborg

Is there an endocrinologist who wouldn't appreciate the challenge of trying to stop the tallest man in the world from growing?

When the Discovery Channel called to ask Mary Lee Vance, MD, to see Sultan Kosen, Guinness world record holder for his 8-feet, 3-inch stature, his diagnosis of gigantism and acromegaly was clear. But despite the best efforts of doctors in his native Turkey, including two operations to remove a pituitary tumor and ongoing medications, he was still growing in his 20s. The tumor was simply too big and invasive to eradicate, causing the gland to pump out too much growth hormone.

Vance, a professor of internal medicine and neurosurgery at the University of Virginia and a principal at one of the world's leading pituitary centers, first adjusted Kosen's medications, then arranged to have him return in a few months so a colleague could perform stereotactic radiation surgery using a Gamma Knife. That procedure knocked back the tumor enough that an aggressive combination of medications has Kosen's disease in check. Two years post-operation, he isn't growing and his growth hormone and insulin-like growth factor 1 (IGF-1) levels are under control.

A Stealthy Danger

When an 8-foot patient walks into your office, the obvious

In 99 percent of acromegaly cases, the culprit is **a benign pituitary tumor**, a somatotroph adenoma, causing hypersecretion of growth hormone and often other hormones.

Diagnosis Still a Tall Order

While treatments improve, the biggest challenge remains identifying patients

response is to look to the pituitary for acromegaly, but Kosen's gigantism, in which the tumor takes hold in childhood, is the rarest form of a rare disease. Most acromegaly sufferers go years before receiving the correct diagnosis. Vance cited a more typical case of a woman who had been experiencing an odd assortment of symptoms for years. Her wedding rings became tight, her shoe size went up two sizes and expanded from medium to extra-wide, her nose enlarged, and she developed sleep apnea and carpal tunnel syndrome. When symptoms like these occur gradually, they're often blamed on aging.

Then one day the woman fainted at work and the rescue squad took her to the hospital. An MRI showed an obvious pituitary tumor. In 99 percent of acromegaly cases, the culprit is a benign pituitary tumor, a somatotroph adenoma, causing hypersecretion of growth hormone and often other hormones.

The patient was referred to an experienced endocrinologist, who recognized the disorder with a glance at the patient's face, hands, and feet. "That's a very common story. She had had symptoms for 10 years, but no one had ever entertained the diagnosis of acromegaly," Vance told *Endocrine News*.

A survey by Vance revealed that most



WORLD'S TALLEST MAN

Sultan Kosen, Guinness world record holder for his 8-feet, 3-inch stature, is diagnosed with gigantism and acromegaly. The most common symptoms of acromegaly are acral (hands and feet) enlargement and face and jaw changes.

acromegaly patients experience symptoms for 8 to 10 years before being diagnosed. Diagnosis is important because growth hormone affects nearly every tissue in the body, and the disease is associated with at least a doubled mortality risk.

"The morbidity is pretty severe, which is one of the reasons we try to be very aggressive in treating these patients," Vance said. Normalization of GH and IGF-1 levels can negate the increased mortality and counter many symptoms.

Rare and Present Danger

One factor making diagnosis difficult is the disease's rarity—four cases per million per year and prevalence of 40 to 125 per million, although some recent studies have suggested that the prevalence could actually be three to five times higher. "It's very likely that this disease is highly underdiagnosed," said Laurence Katznelson, MD, medical director of the pituitary center at Stanford University Medical Center. Katznelson chaired a panel for the American Association of Clinical Endocrinologists (AACE) that published treatment guidelines for acromegaly last year.

Another reason that it goes undiagnosed is its creeping, insidious nature. The disease generally begins in adulthood, which means that the long bones have stopped growing, so the patient doesn't increase in height.

OnPOINT from The Endocrine Society

Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab* 2009 May;94(5):1509–17. (Acromegaly Consensus Group of the Pituitary Society and the European Neuroendocrine Society.)

AT-A-GLANCE:

- Patients can have symptoms for 8 to 10 years before being diagnosed.
- Most common treatment includes surgery, drugs, and radiotherapy.
- Stereotactic radiation is replacing fractionated radiation as preferred method.

However, the hands, feet, facial bones, nose, and tongue all enlarge. Because the changes occur over a period of years, the patient may not find them remarkable.

Clinicians can miss the significance of other symptoms, such as sleep apnea. The rise in obesity is driving an increase in sleep apnea, so physicians may be complacent about looking for an underlying cause, even though these patients are unlikely to be obese. Acromegaly patients can develop sleep apnea because enlargement of the tongue and neck tissues can make it hard to breathe at night. Many common symptoms do not necessarily point to the pituitary (see sidebar).

Both Vance and Katznelson described patients who were treated for heart problems for years, but their cardiomyopathy turned out to be the result of excess growth hormone leading to muscle thickening. "I've had two patients on the heart transplant list because their heart was failing. When we treated their acromegaly, it reversed, and they are fine now," Vance says.

SIGNS AND SYMPTOMS

The AACE guidelines recommend considering a diagnosis of acromegaly in patients with two or more of the following:

- New-onset diabetes
- Diffuse arthralgias (joint pain)
- New-onset or difficult-to-control hypertension
- Cardiac disease, including biventricular hypertrophy and diastolic or systolic dysfunction
- Fatigue
- Headaches
- Carpal tunnel syndrome
- Sleep apnea syndrome
- Excessive sweating
- Loss of vision
- Colon polyps
- Progressive jaw malocclusion

Diagnosis and Outcomes

The hardest part of the diagnosis may be thinking of it at all. Once a physician looks for acromegaly, the biochemical diagnosis is straightforward. Screening tests include serum IGF-1 and growth hormone. The IGF-1 level needs to be checked against age- and sex-matched controls. The oral glucose tolerance test remains the gold standard for growth hormone, with a patient's inability to suppress serum growth hormone to less than 1ng/mL considered diagnostic for acromegaly. Another key hormone to be aware of is prolactin, because it is hypersecreted in about 20 percent of cases.

The next step is dedicated pituitary MRIs, with and without contrast medium, to look for a tumor.

Treatment is complex, involving a multidisciplinary team, but the most common progression remains the triad of surgery, drugs, and radiotherapy.

The best outcome, of course, is physical removal of the tumor, so transsphenoidal surgery is indicated for microadenomas confined to the sella turcica, non-invasive macroadenomas (tumors greater than one centimeter), and tumors that are causing compression symptoms (such as pressing on the optic nerves). The guideline notes that experienced surgeons achieve appreciably better cure rates as well as lower morbidity and mortality.

The smaller the tumor, the greater the likelihood of a surgical cure. But about two thirds of the patients have macroadenomas, perhaps due to the long lag time before diagnosis. And only about 45 percent of these patients experience a surgical cure.

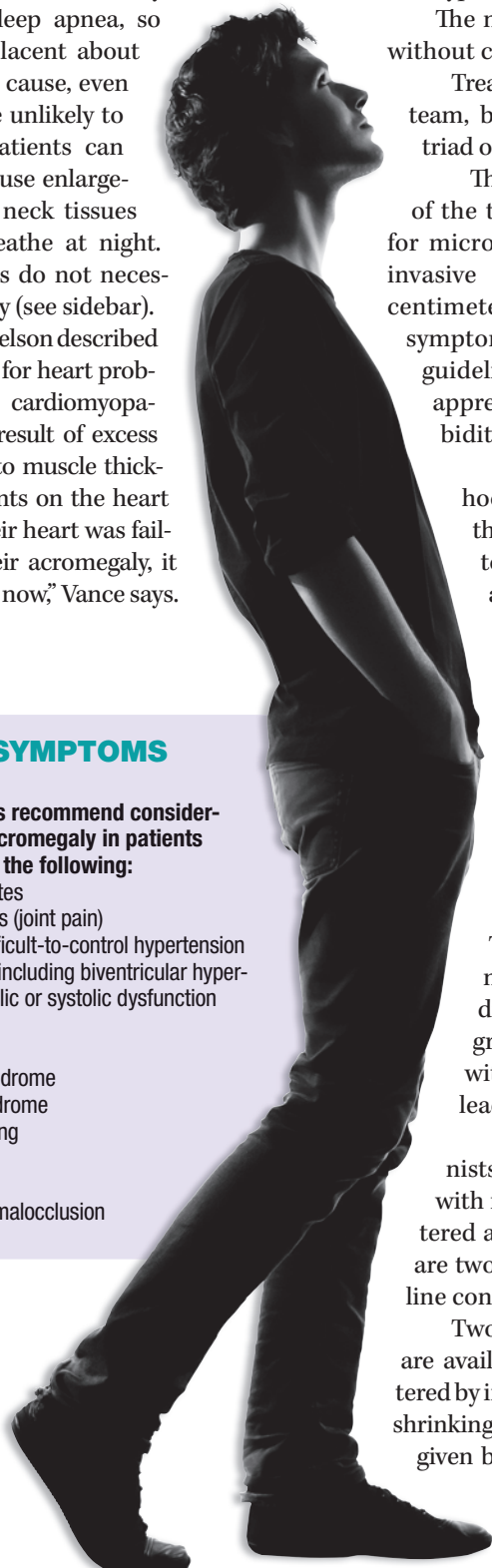
This relatively low success rate, combined with the number of patients who must forgo surgery because they are poor risks or have invasive, inoperable tumors, means that a large proportion of patients require drug therapy to control or counter their hormone overproduction.

Drug and Radiation Therapies

There are three main drug approaches. Dopamine agonists and somatostatin analogs both directly inhibit growth hormone secretion. A growth hormone receptor antagonist interferes with its action by blocking its receptors, thereby leading to reduced IGF-1 secretion.

The AACE guideline considers dopamine agonists to be the first-line medical therapy in patients with modest disease because they are orally administered and less expensive than the other options. There are two, cabergoline and bromocriptine, with cabergoline considered more effective and better tolerated.

Two somatostatin analogs, octreotide and lanreotide, are available in long-acting formulations, both administered by injection, and have the added benefit of sometimes shrinking the tumor. For this reason, they are sometimes given before surgery, either to increase the cure rate or



to ease the surgical experience. The AACE guideline concludes there is insufficient evidence to support their use to increase cure rate. The data supporting the theory that they make surgery easier are also limited, but the guideline suggests considering this use on a case-by-case basis, for example, when a patient with a swollen pharynx and surrounding tissues may have difficulty with intubation.

The growth hormone receptor antagonist, pegvisomant, is effective in normalizing IGF-1 values and at improving glucose homeostasis in patients with diabetes mellitus. It is administered by injection.

The drugs are often used in combination when a single agent doesn't achieve growth hormone and IGF-1 targets.

As Sultan Kosen's experience shows, radiation therapy is an alternative when patients don't adequately respond to surgical and medical treatment. In recent years, stereotactic radiation, the most common of which is the Gamma Knife, has been making inroads to replace conventional fractionated radiation. Stereotactic radiation offers the advantage of a focused dose delivered to a limited area in a single operation. Fractionated radiation is delivered through each temple and the frontal area, exposing more areas of the brain to radiation, and is given repeatedly over a six-week period.

"We have treated a lot of patients [with the Gamma Knife] and we see about 52 percent remission rate at about two years after treatment," Vance says. "Fractionated radiation usually took 10 to 20 years to be effective. We've treated over 500 patients with pituitary tumors with the

Gamma Knife and we find it to be very safe and effective."

Katznelson said the guideline committee found no real data to indicate that one form of radiotherapy is better than the other. Although there are some suggestions that stereotactic radiation is faster-acting, the side effect profiles are not significantly different. There's no evidence of a difference in cure results, particularly over the long-

term. Nonetheless, the guideline says: "Because of technical advances and convenience, stereotactic radio-surgery may be considered the preferred mode."

Either form can lead to a loss of pituitary function, but Vance notes "that's not so bad because you are preventing tumor growth and curing acromegaly. We can always replace the missing hormones."

While strides continue to be made in treatment, the biggest challenge remains identifying the patients who need it. Katznelson said that many patients are identified when they change to a new dentist who notices their jaw is growing, change physicians, or see a long-lost relative who wonders why their face looks so different. That's why the guideline emphasizes the "need to educate primary care physicians and other medical groups about the constellation of signs and symptoms to facilitate earlier detection." **EN**

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

One factor making diagnosis difficult is the disease's rarity—four cases per million per year and prevalence of 40 to 125 per million, although some recent studies have suggested acromegaly prevalence could actually be three to five times higher.



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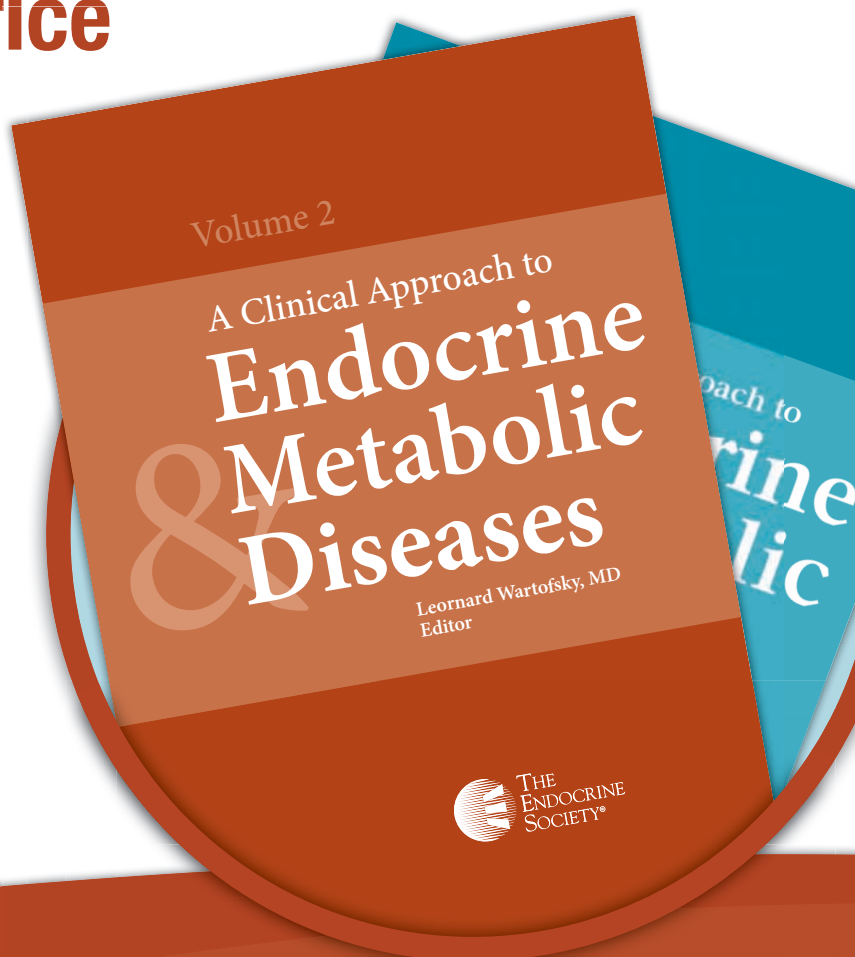
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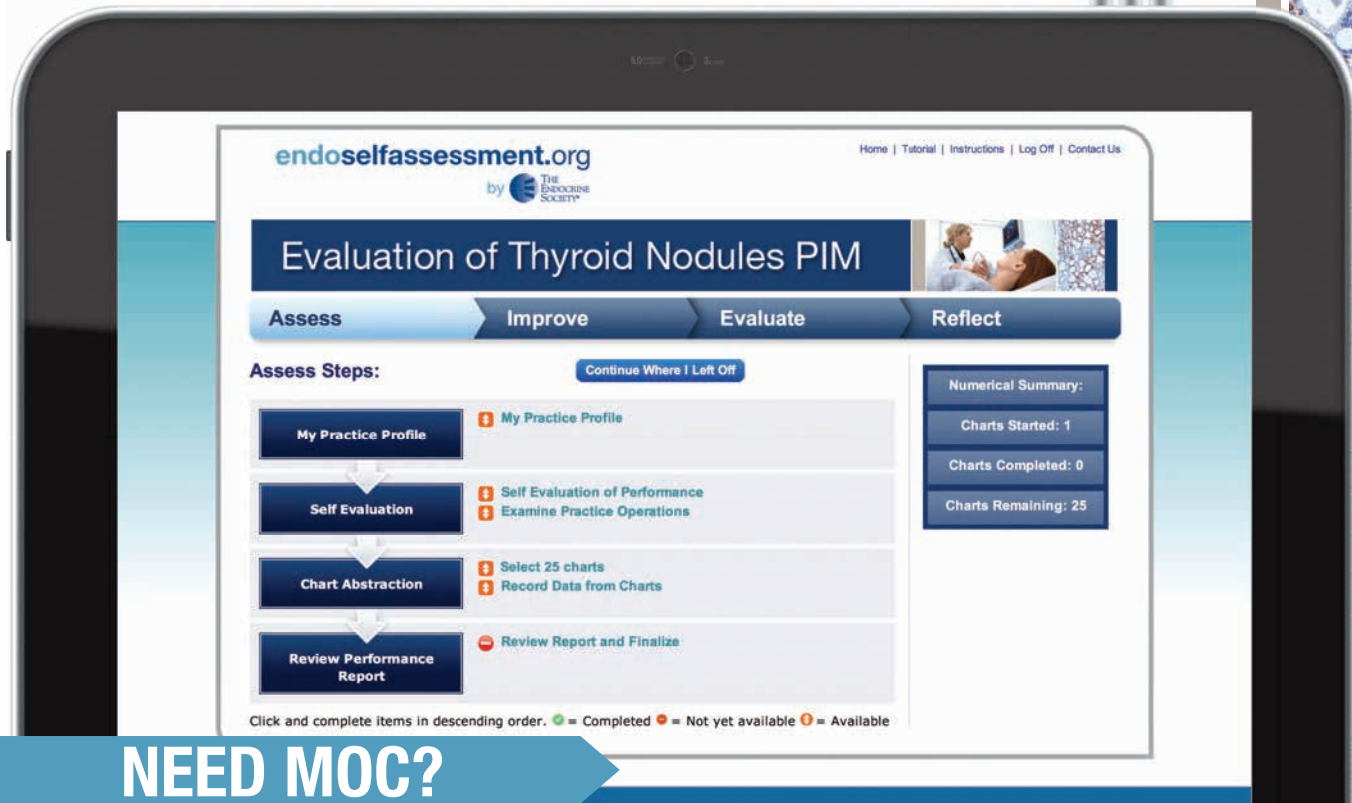
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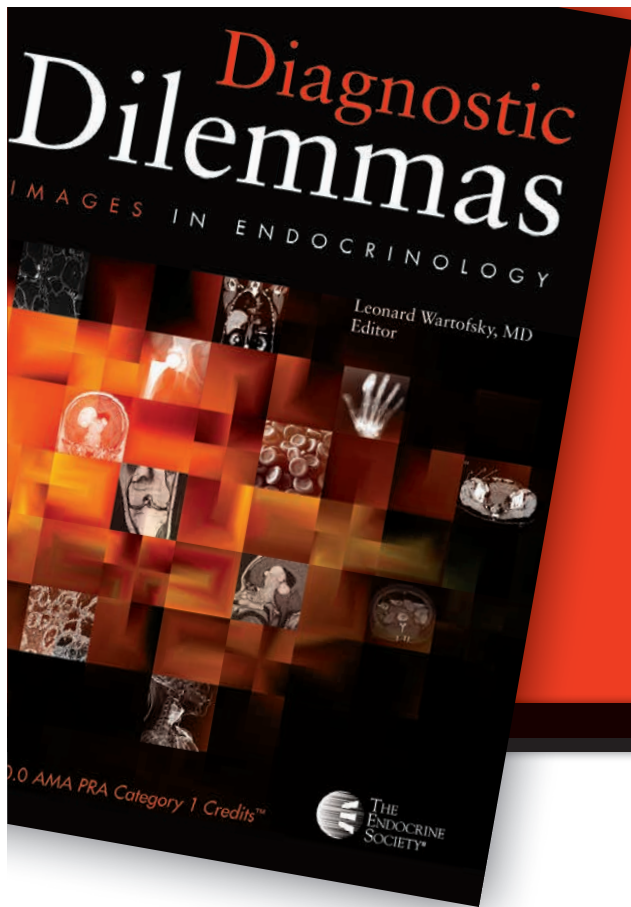
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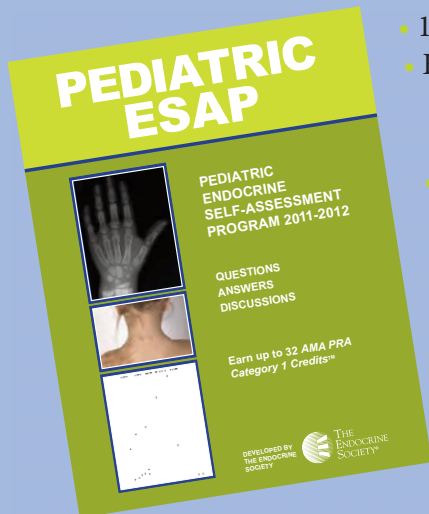
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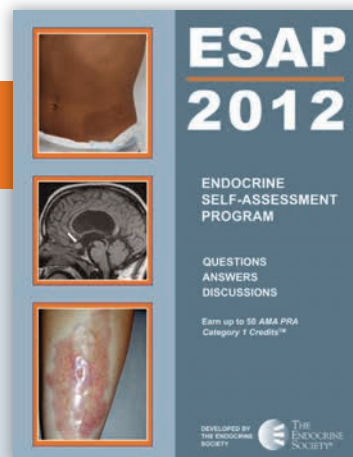
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TREATING TYPE 2 DIABETES Presents Jigsaw Puzzle of Options

By John Bohannon

With the number of cases increasing more than 10-fold over the past 50 years, diabetes is now the world's most expensive endocrine disease, and it's only getting worse. Today, almost one in 10 Americans are diabetic, rising to one in four among adults age 65-plus. Diabetes doubles the risk of death from heart disease and stroke and costs the U.S. \$175 billion per year—most of it for drugs and medical devices.

These grim facts have been on my mind ever since my father was diagnosed with diabetes. Like the vast majority, he has type 2 diabetes.

Luckily, diabetes is imminently treatable. My dad takes seven different medications per day. He uses a finger-pricking computer to keep track of his glucose levels. All of this costs about \$200 each month. That made me wonder, how much choice do doctors have when designing a treatment for diabetes patients? With the help of Michelle Bolek and Christopher Kelly, public affairs officers at the U.S. Food and Drug Administration, I took a virtual walk down the aisle of diabetes drugs and devices.

Abundant Meds and Devices

Various concoctions of insulin comprise a third of the 33 FDA-approved drugs for diabetes. Unlike most of the small molecular compounds in a pharmacy, insulin is a protein encoded by a human gene. Animal proteins tend to be unstable and expensive to harvest. Luckily, insulin is far more affordable, thanks to a 1982 breakthrough that allowed the insulin gene to be transplanted into bacteria and yeast for mass-production.

The next-most-important drug for type 2 diabetes is Metformin. Its target is farther upstream. It acts on the liver to reduce the rate at which glucose is released into the blood. Since its FDA approval for diabetes treatment in 1994, Metformin has become the most widely prescribed drug for diabetes.

The dozens of other drugs mostly treat the symptoms of diabetes. Lucentis helps treat damage that diabetes can cause in the back of the eye known as macular edema. The drug was already approved for treating a different type of macular degeneration. Drugs for treating the core problem—glucose levels—are continually approved. Last year was Tradjenta, a new drug for controlling blood glucose levels. This year it was a long-acting version of the injectable glucose-regulating drug Byetta.

On the other side of the diabetes aisle is a mind-boggling choice of devices. The FDA approved more than 200 of them in 2012. Most are variations on a few themes: hundreds of glucose monitors, 178 gadgets for pumping insulin, and dozens of “infusion sets” for delivering the insulin to the blood.

Glucose monitors are standard issue to almost every

patient. Now many of these meters can even send data to your iPhone.

The newest glucose meters don't require daily finger pricks. Instead, a tiny sensor stays just under the skin of the abdomen. The newest, made by a company called Dexcom, automatically alerts you if your blood sugar is trending toward dangerously high or low levels.

Weighty Issue

Of course, all of these drugs and devices are treatment rather than cure. Ask any overweight diabetes patient about gastric bypass surgery. The procedure is risky, like all major surgery, but it does return blood sugar levels to normal in most diabetes patients.

The tantalizing possibility of a less dangerous cure arrived last year. A British study found that seven out of 11 type 2 diabetes patients who underwent two months of radical dieting—about 600 calories per day—became free of diabetes symptoms. Longer follow-up is needed to see whether this is a permanent cure, but my dad is already planning on trying it. He is about 100 pounds overweight, so he sees it as two birds with one stone.

It shocks me that the causes of type II diabetes remain unknown. Glucose regulation is one of the most thoroughly studied systems in the body. But that is the nature of the disease, says Sue Lynn Lau, a diabetes researcher at the Garvan Institute in Sydney, Australia. “It is much harder to piece together a jigsaw puzzle than identify a single missing part. In type 2 diabetes, there are multiple contributing factors that combine to produce the final outcome of impaired glucose metabolism. Each one alone might not be enough, but it's the interaction of all these factors with each other over time that matters. Not everybody has exactly the same factors in the same amounts—the picture might look the same, but each person is a different jigsaw... Where do you start studying, and how do you know what came first?”

One thing is certain, at least. Diabetes can be prevented with nearly 100 percent success through diet and exercise. It's too late for my dad, but the rest of us are taking a hard look at our daily routines. **EN**

— Bohannon is a freelance writer and contributing correspondent to Science magazine.

KEEPING INSULIN IN CHECK

- **Metformin** acts on the liver to reduce the rate at which glucose is released into the blood
- **Lucentis** helps treat damage that diabetes can cause in the back of the eye known as macular edema
- **Tradjenta** controls blood glucose levels
- **Byetta** is a long-acting injectable glucose-regulating drug
- A device from **Dexcom** automatically alerts you if your blood sugar is trending toward dangerous levels



JUST AS PLANNED

Pre-implantation genetic diagnosis gains traction for gender selection

By Shari Roan

Rarely a day goes by, even a Sunday, when patients aren't biding their time in the waiting room of The Fertility Institutes in Encino, California. Some have come from half a world away.

While director Jeffrey Steinberg, MD, can't guarantee his patients a baby, he makes sure women who do give birth get specifically what they came for—a boy or a girl—through pre-implantation genetic diagnosis. In the 11 years

'Listen doc, we don't have any genetic disorders, we just want a boy or we just want a girl. Can you do it?'

since the American Society for Reproductive Medicine softened its guidelines discouraging gender selection for non-medical uses, Steinberg's practice has soared.

"As we've dedicated more time to it, we've become quite good at it," says Steinberg, sitting in his office, the site of the former DreamWorks Studio offices located at the divide of urban Los Angeles and the San Fernando Valley. "It's a worldwide marketplace."

How It Works

Pre-implantation genetic diagnosis (PGD) was originally developed to screen for single-gene disorders, such as Tay Sachs, in families with a known history. Certain genetic disorders are sex linked, such as hemophilia A and B.

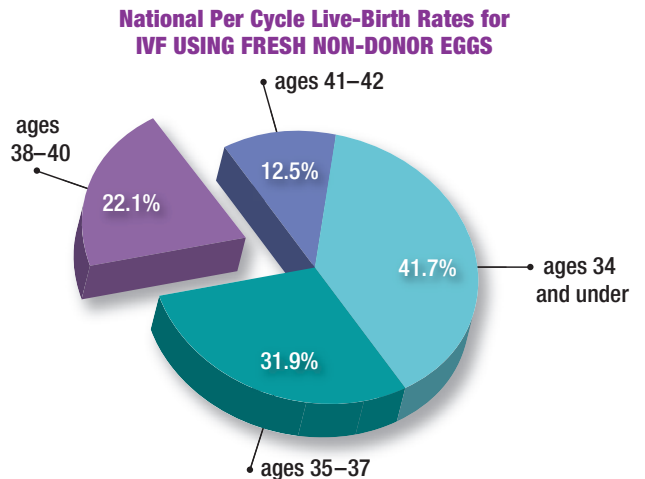
"That is where determining gender became important," says Steinberg, who trained at Cambridge University in England with Patrick Steptoe, MD, and Robert Edwards, PhD,

the creators of in vitro fertilization. "Then I started getting requests from a lot of people saying, 'Listen doc, we don't have any genetic disorders, we just want a boy or we just want a girl. Can you do it?'"

The process is straightforward but highly dependent on the expertise of the embryologist. Eggs are retrieved and fertilized. When the resulting embryos divide to eight cells, the embryologist pierces the embryo and removes a single cell for chromosomal analysis. Only the embryos of the desired sex—typically one or two embryos—are implanted.

"It's standard in vitro fertilization. The only difference is we've added PGD gender selection," Steinberg says.

The clinic includes a room that generates purified air to feed the adjacent clean room, where biopsies are performed. The embryologist's work station floats on a nitrogen bed to absorb vibrations. Biopsies are completed in 20 to 30 seconds.





RECIPE FOR SUCCESS

- Eggs are retrieved and fertilized
- The resulting embryos divide to eight cells
- The embryologist pierces the embryo
- Embryologist removes a single cell for chromosomal analysis
- Finally, only the embryos of the desired sex—typically one or two—are implanted



THE ETHICS OF IT ALL

The ASRM ethics committee will likely issue an updated guideline next year. Gender selection for non-medical purposes is forbidden in 31 countries.

“Embryos don’t like being out very long,” Steinberg says. “It needs to be done fast and efficiently. I think what a lot of centers don’t realize is you can’t really dip your toes into this once or twice a year. It’s like anything else, you want a doctor who does it all the time.”

And Steinberg is successful. The national per cycle live-birth rates for IVF using fresh, non-donor eggs are 41.7 percent (ages 34 and under), 31.9 percent (ages 35 to 37), 22.1 percent (ages 38 to 40), and 12.5 (ages 41 to 42), according to the Society for Assisted Reproductive Technologies.

Steinberg’s corresponding statistics are 58.8 percent, 47.5 percent, 47.1 percent, and 28.1 percent. Many of his patients, however, are healthy and would not have required assisted reproductive technologies to become pregnant.

High Accuracy and High Cost

The accuracy of gender selection is near perfect. Steinberg says he has never had a patient give birth to a child of the undesired gender. Only mosaicism, which is rare, could result in failed gender selection.

The major risk to patients is ovarian hypersensitivity, which can occur in standard IVF. Cost may be the biggest deterrent to gender selection. IVF with PGD averages about \$18,000 compared to about \$11,000 for standard IVF.

Melissa Smerker and her husband Kevin underwent gender selection and welcomed twin girls to their family in March. The couple has four boys, but Melissa longed for a girl. “It’s not that I didn’t appreciate my children. They are beautiful, healthy boys. But there was that desire for a little girl,” Melissa Smerker says. “I assumed that someday I would get past it. But the longing never went away.”

It took years for the Vaughn, Montana, couple to save the money for the treatment, which was successful

on the second try.

Steinberg estimates that there are about five other U.S. clinics performing a “reasonable volume” of PGD for gender selection and that about 40 percent of infertility clinics provide it upon request. But professional attitudes regarding family balancing may be softening, says Paula Amato, MD, an associate professor at Oregon Health Sciences University and chairwoman of the ASRM ethics committee.

“I think it’s an issue where reasonable people can disagree,” Amato says. “Certainly ASRM has concerns related to gender equality and acceptance of offspring and the health risks that patients would have to undergo to have IVF if they are doing it just for this reason. Also, is this the most appropriate use of medical resources? For all those reasons, ASRM has concerns.”

The ethics committee will likely issue an updated guideline next year, she says. Gender selection for non-medical purposes is forbidden in 31 countries.

Future research papers may also persuade the medical world of the scientific value of his work, says Steinberg, who has one of the few ART databases on healthy women. He has found, for example, that a high number of his patients fail to produce the optimal number of eggs—a problem that was thought to be exclusive to infertile women. He has also found higher-than-

expected rates of aneuploidy in healthy, fertile women.

“This data is very exciting to us because there has never been a control group with in vitro fertilization,” he says. “It has given us a chance to study an entirely new patient population that would never have been studied.” **EN**

—Roan is a freelance writer in Los Angeles.

The accuracy of gender selection is near perfect. Steinberg says he has never had a patient give birth to a child of the undesired gender.



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

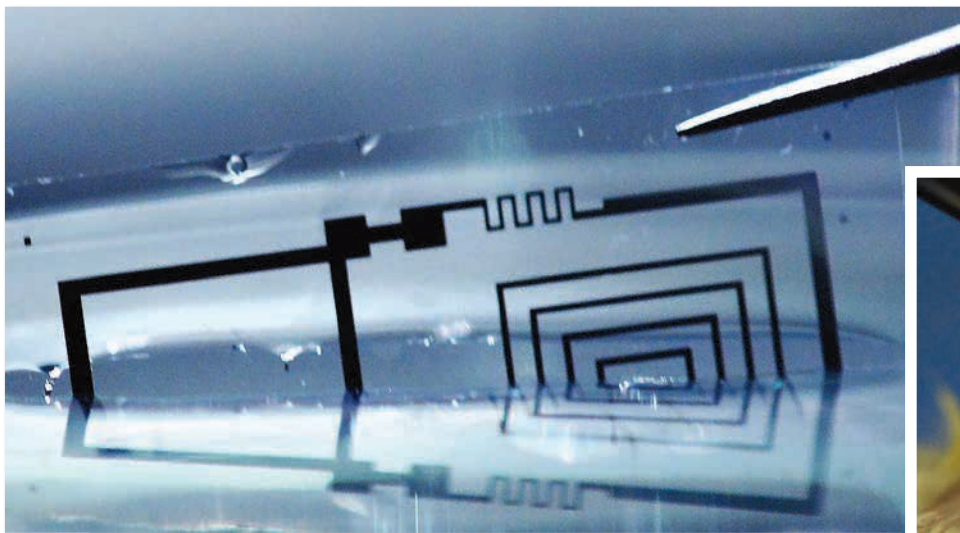
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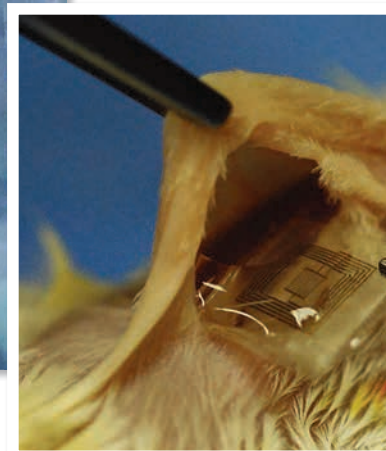


Photo Credit: Beckman Institute, University of Illinois, and Tufts University

By Terry D'Arrigo

When you think about electronics implanted in the body, a pacemaker—a solid, stable device meant to last a long time—is likely the first thing that comes to mind. But scientists at the University of Illinois at Urbana-Champaign, Northwestern University, and Tufts University are turning the notion of durability on its head by designing tiny electronic implants that dissolve in the body after a short period of time.

Called “transient” because of their temporary nature, these devices may one day help prevent infections at surgical incision sites, enhance wound-healing, deliver medication that is needed for only a few days, or monitor transplant patients’ reaction to their new organs.

“Surgical site infections are one of the leading causes for readmission to hospitals, and more and more of those infections are becoming resistant to antibiotics,” says John A. Rogers, PhD, Lee J. Flory-Founder professor of engineering at the University of Illinois. “So the thought here was that we might be able to use transient electronics in a form like a thin film appliqué that could be inserted before the patient is closed up. It could potentially be used to eliminate bacteria at the surgical site for the most critical risk period, which is about two to three weeks after surgery.”

In a recent issue of *Science*, the researchers described their first transient prototype, a tiny thermal electronic device designed to kill bacteria when implanted near a sur-

gical incision. Rogers and his colleagues tested the prototype in mice and found that it dissolved within three weeks with no ill effects on the animals. The high-tech gadgets can be designed to disintegrate at controlled rates, perhaps lasting a day, a few weeks, or months before completely vanishing in body fluids.

Transients in Practice

Like conventional integrated circuits, the transients are constructed of magnesium components and ultra-thin discs of silicon. The fragile electronics are then encapsulated in layers of silk protein from silk-worm cocoons that have been dissolved and recrystallized.

The prototype used in the mice is about the width of a nickel but only a fraction of the thickness of a human hair. Thickness is a critical aspect of transient electronics, said Yonggang Huang, PhD, Joseph Cummings professor of civil and mechanical engineering at Northwestern University.

“The thinner the device, the shorter [time] it lasts; so thickness is very important when controlling dissolution time. You want the device to dissolve, but not too fast, because you need it to do its job.”

The thickness and structure of the silk also helps fine-tune reabsorption, he adds. “Each layer adds to the time. We can control the dissolution time quite precisely, from a few hours to a few months. If doctors tell us how long they want

High-tech gadgets can be
**DESIGNED TO DISINTEGRATE
AT CONTROLLED RATES.**

a device to last, we'll be able to design it that way."

The thought of silicon and silk dissolving in the body may give the squeamish pause, but Rogers says the materials have a long history of use in medical implants, particularly in the permanent stents that are sometimes inserted into arteries during angioplasty and in internal sutures that eventually melt away. Silk is known to be a good matrix for drugs and hormones, Rogers says, and it is already approved by the Food and Drug Administration (FDA) for absorbable sutures.

Although people tend to be wary of silicon products, Rogers says they are exposed to more silicon when they take a dip in the ocean, where it occurs naturally, than they would be with a temporary implant. "The amount used for stents far exceeds anything [transient electronics] need for conducting," he adds. As for magnesium, a multivitamin or a few handfuls of mixed nuts has more: "The recommended daily intake is much larger than the amount we need for integrated circuits."

Numerous Applications

How the vanishing electronics' structural materials react with human tissue is a critical hurdle, making widespread use of transient electronics in humans still a long way off. "Human body fluid is a variable," says Huang. "You can't really control the pH value. Also, dissolution times at room temperature and body temperature are very different." Huang notes that both pH and temperature can vary from person to person, and even from time to time for the same person, as with a fever.

Regulatory agencies like the FDA would, of course, require extensive testing and proof of safety. "There would be a full range of trials in animals and humans long before anything like this is available on a large scale," Rogers adds.

Mass manufacturing poses another challenge, says Rogers. "We're designing these devices to be soluble in water, but a lot of the conventional steps for fabricating them use water."

Both Rogers and Huang defer to health professionals for determining the best use of transient electronics. "We're just the engineers," says Huang. But the pair envision many potential medical applications for the technology. For example, a device like the antibacterial prototype may be useful in healing diabetic foot ulcers. Transient electronics might also be used to target specific areas of the thyroid for iodine therapy in hyperthyroidism to zap "hot nodules" that produce too much thyroid hormone. Fertility treatments could be another area of consideration, with transient electronics delivering drugs that stimulate the production of eggs for in vitro fertilization, sparing women an uncomfortable series of injections.

Potential Medical Applications

- Healing diabetic foot ulcers
- Targeting specific areas of the thyroid for iodine therapy in hyperthyroidism
- In fertility treatments, delivering drugs that stimulate the production of eggs for in vitro fertilization

For now, Rogers, Huang, and their colleagues plan to continue studying different materials—in their study they noted collagen, iron, and zinc as possibilities—and experimenting with different prototypes. Their work is not limited to medical devices, however.


Transient electronics might one day be used for environmental purposes, perhaps in wireless sensors that could detect or monitor oil or chemical spills without having an effect on the ocean itself. The technology could also be used to create biodegradable components for cell phones, MP3 players, or other portable devices, thus cutting the amount of waste generated when consumers upgrade their gear.

"The concept of designing electronics that don't last forever is very new," says Huang. "There are probably many uses and applications we haven't even thought of yet." **EN**

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



For additional links related to this feature, please visit Endocrine News Online at www.endo-society.org/endo_news.



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ENDO 2013: New Schedule, New Features



By Melissa Mapes

A new schedule for **The Endocrine Society's 95th Annual Meeting & Expo** brings the addition of exciting new sessions and easier travel plans for attendees. The new plan also incorporates ample time in the afternoon and evenings for exploring San Francisco and networking with colleagues from around the world.

With the days' events starting at 7:30 a.m., you'll need to set your alarm clocks a little earlier at **ENDO 2013**. Plenary sessions featuring a number of notable experts will headline the first three days of the meeting:



Steven Kahn will present the Clinical Investigator Award Lecture, highlighting the roles of beta-cells in type 2 diabetes pathogenesis.



In the Gerald D. Aurbach Award Lecture, **Mitchell Lazar** will explore the influence of circadian epigenomic regulation on metabolism.



Donald McDonnell will examine the estrogen receptor's mediation of bone and breast pathologies in the Roy O. Greep Award Lecture.



Gary Hammer will present the Edwin B. Astwood Award Lecture on the implications of adrenal stem cells for human disease.

Posters and Symposia

ENDO 2013's innovative design has allowed the addition of the new Featured Poster Presentations, which will take place before the oral sessions from Saturday to Monday. During these events, authors of the top-rated studies from the poster sessions will present their studies, giving just enough background to entice attendees to the posters to

find out the results.

Tuesday, June 18, the final day of **ENDO 2013**, brings a tremendous number of excellent sessions, beginning at 7:30 a.m. with symposia featuring cutting-edge science in areas such as diabetes, tumor biology, and signaling. Clinicians will be interested in the Clinical Practice Guideline session, which will examine current best practices for treatment of diabetes during pregnancy. The highly popular Master Clinician series will include a Tuesday afternoon session focused on osteoporosis. Attendees interested in genomics will not want to miss Lynn Jorde's Year in Genomics nor Peggy Farnham's Special Scientific Session featuring a hands-on discussion on accessing and using genomic data.

Complementing the Year in GPCRs by Graeme Milligan, Jesse Roth will delve into more than a century of advances in endocrine signaling during the Clark T. Sawin Memorial History of Endocrinology Lecture.

Wait, There's More

While the main ENDO programing will end at 3 p.m. on Tuesday, the special forum "New Light on GPCRs in the Pathophysiology of Diabetes and Metabolic Disorders" will provide a unique opportunity to hear insights from global experts on the latest research into GPCR structure/function and roles in metabolic regulation.

In addition to a schedule packed with the very best in endocrine research and practice, the San Francisco location of **ENDO 2013** ensures that attendees will enjoy fantastic weather and diverse activities. To learn more or to register, visit www.endo-society.org/endo2013. **EN**

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

BUNDLE UP FOR SAVINGS

Now through June 13, enjoy the lowest price on the ENDO 2013 Session Library when you select the Premium Registration Package, which includes ENDO Registration, Session Library, and Meet-the-Professor Clinical Case Management 2013. VISIT www.endo-society.org/endo2013 to register today!





ENDO 2013: ARE YOU READY?

Take advantage of the early-bird registration rates and start making your travel plans to the leading event for endocrinologists, **ENDO 2013**, in beautiful San Francisco, June 15-18. **ENDO 2013** offers the ideal mix of

education, networking, and a wide range of exhibits at ENDOExpo.

ENDO 2013 brings a number of new professional development opportunities this year and will feature four “Year In” sessions, which will provide reviews of the significant advances over the past year in the fields of genomics, thyroid cancer, neuroendocrinology, and G Protein-Coupled Receptors. Lynn Jorde, PhD, will highlight the ever-increasing role of genomics in understanding human health, while Steven Sherman, MD, will present new treatments and diagnostic approaches for thyroid cancer and Susan Smith, M.S., PhD, will review the newly discovered pieces of the puzzle that is the endocrine brain. Especially timely in view of the 2012 Nobel Prize in Chemistry, Graeme Milligan, PhD, FRSE, will offer a review of advances in GPCR research.

REGISTER TODAY:

www.endo-society.org/endo2013

VIEW THE ONLINE SCIENTIFIC PROGRAM:

<https://endo.confex.com/endo/2013endo/webprogram/programs.html>

FLARE WORKSHOP BUILDS FUTURE LEADERS

Fourteen promising research fellows and graduate students recently received travel awards for the FLARE Workshop, held last month in San Diego. The Future Leaders Advancing Research in Endocrinology (FLARE) program helps trainees from underrepresented communities develop the essential leadership skills needed in order to have successful careers in biomedical research.

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the FLARE program provides participation in a structured leadership development network to highly motivated basic science and clinical research trainees who have demonstrated achievement in



endocrine research. Learn more about the winners and the program at www.endo-society.org/FLARE.

NEW PUBERTY FACT SHEET AVAILABLE

Puberty is a time of great emotional as well as physical change for any adolescent. When puberty comes late, it can be equally emotional for a child who is not growing and developing as quickly as his or her peers. The Hormone Health Network's latest patient fact sheet, *Delayed Puberty*, defines this often hereditary condition and assures

teens and parents that it's most often a variant of normal development. While constitutional delay is the most common cause of delayed puberty, the fact sheet outlines underlying medical conditions that may also result in late onset puberty. Brief definitions and a list of suggested questions help patients have more informed conversations with their doctors. Visit www.hormone.org to download the fact sheet.

HEALTH DISPARITIES SUMMIT COMING TO BALTIMORE

This March, The Endocrine Society will bring together researchers, clinicians, health educators, and public and community health leaders who are dedicated to reducing health disparities. The inaugural Reducing Health Disparities Summit will be held at the Sheraton Baltimore Inner Harbor, March 22-23. Learn more or register at www.endo-society.org/disparities.

REDUCING HEALTH DISPARITIES AND IMPROVING CARE

THROUGH ENDOCRINE SCIENCE



2013 Reducing Health Disparities in Type 2 Diabetes Mellitus Summit

LEARN FROM PIONEERING ENDOCRINOLOGISTS



Now you can take a master lesson in the history of endocrinology from those who defined and refined the field. At the Clark T. Sawin Memorial Library and Resources Center website, you'll find 40 oral and video history interviews from pioneering endocrinologists. New interviews were just added this year. Visit www.endo-society.org/about/sawin/histories.cfm.

REGISTER NOW FOR ESAP™-ITE

Make certain your fellows and your program are on track by signing up!

Registration is now open for the ESAP In-Training Exam 2013 (*ESAP-ITE*), the premier online exam for fellows. In addition to the unique opportunity to assess your clinical training program, *ESAP-ITE* now delivers enhanced features that make it easier to manage your program's engage-

ment. The improved interface lets you:

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To learn more or register for *ESAP-ITE*, visit www.endoselfassessment.org/ite.aspx.

IN MEMORIAM



Dr. Elwood Jensen
1920–2012

Dr. Elwood Jensen, who served as president of The Endocrine Society June 1980-June 1981, died Dec. 16, 2012, in Cincinnati. Jensen earned the Society's Fred Conrad Koch Award in 1984, the highest honor bestowed by the Society, for his pioneering research in hormone receptors, which opened the door to new life-saving treatments for breast cancer.

Jensen's work led to the establishment of biochemical "receptors" as a new field of scientific research, leading to many more medical breakthroughs.

"Jensen's revolutionary research has saved lives and his discovery of estrogen receptors is clearly one of the highest achievements in the field of endocrinology," says Scott Hunt, executive director and CEO of The Endocrine Society. "He will be greatly missed."

Jensen served as the George J. and Elizabeth Wile Chair in Cancer Research at the University of Cincinnati and the Charles B. Huggins Distinguished Service Professor Emeritus in the Ben May Department for Cancer Research and the Department of Biochemistry and Molecular Biology at the University of Chicago. Additional honors bestowed upon Jensen during his distinguished career include the 2004 Albert Lasker Medical Research Award and multiple nominations for the Nobel Prize. **EN**

BoardReviewCALENDAR

Make your plans to attend the most trusted clinical update and board review at the Hyatt Regency New Orleans this fall.

PEDIATRIC ENDOCRINE BOARD REVIEW

September 24-25

ENDOCRINE BOARD REVIEW

September 24-25

CLINICAL ENDOCRINOLOGY UPDATE

September 26-28

REGISTER TODAY: www.endo-society.org/NOLA.

The Endocrine Society also mourns the recent deaths of members **Dr. Venkatesh Ganjam**, **Dr. Donald S. Layne**, **Dr. Thomas P. Segerson**, **Dr. Jan R. Stockigt**, and **Dr. James O. Wynn**.

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.



20(OH)D3, and other CYP11A1-derived products, are promising therapeutic candidates for scleroderma.

Slominski A, Janjetovic Z,

Tuckey RC, et al. *20S-hydroxyvitamin D3, noncalcemic product of CYP11A1 action on vitamin D3, exhibits potent antifibrogenic activity in vivo.*

PEDF, acting in reciprocity to vascular endothelial growth factor function, may become a novel replacement therapy for OHSS.

Chuderland D, Ben-Ami I, Kaplan-Kraicer R, Grossman H, Ron-El R, Shalgi R. *The role of pigment epithelium-derived factor in the pathophysiology and treatment of ovarian hyperstimulation syndrome in mice.*

Among dialysis patients with SHPT that are treated with cinacalcet and low vitamin D sterols, changes in functional parathyroid gland mass or detection of disease progression cannot be measured by the standardized calcium-mediated PTH suppression test.

Rodriguez M, Ureña-Torres P, Pétavy F, Cooper K, Farouk M, Goodman WG. *Calcium-mediated parathyroid hormone suppression to assess progression of secondary hyperparathyroidism during treatment among incident dialysis patients.*

TPHAbS could identify APS-1 patients who present with gastrointestinal dysfunction symptoms in the absence of other components of the syndrome.

Scarpa R, Alaggio R, Norberto L, et al. *Tryptophan hydroxylase autoantibodies as markers of a distinct autoimmune gastrointestinal component of autoimmune polyendocrine syndrome type 1.*

In recently menopausal women, MHT leads to preservation of cortical bone at the distal radius but does not prevent trabecular bone loss at the distal radius.

Farr JN, Khosla S, Miyabara Y, Miller VM, Kearns AE. *Effects of estrogen with micronized progesterone on cortical and trabecular bone mass and microstructure in recently menopausal women.*



A direct link exists between glucagon and stomach ghrelin production and secretion.

Gagnon J, Anini Y. *Glucagon stimulates ghrelin*

secretion through the activation of MAPK and EPAC and potentiates the effect of norepinephrine.

Notch and Nfatc1 regulate chondrocyte differentiation.

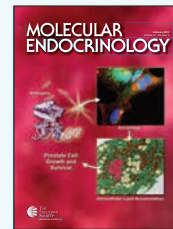
Zanotti S, Canalis E. *Notch suppresses nuclear factor of activated T-cells (NFAT) transactivation and Nfatc1 expression in chondrocytes.*

Prohibin and chemerin may contribute to the pathogenesis of polycystic ovarian syndrome.

Wang Q, Leader A, Tsang BK. *Inhibitory roles of prohibin and chemerin on FSH-induced rat granulosa cell steroidogenesis.*

Murine and ovine BMP15 differ from the human homologue in granulosa cell function activity at the type 1 receptor binding interface.

Al-Musawi SL, Walton KL, Heath D, Simpson CM, Harrison CA. *Species differences in the expression and activity of bone morphogenetic protein 15.*



Very limited metabolic redundancy exists within the homologous SRC coactivator family.

York B, Sagen JV, Tsimelzon A, et al.

Tissue- and pathway-specific metabolomics profiles of the steroid receptor coactivator (SRC) family.

Decidualization of the endometrium promotes the formation of a corticosteroid gradient at the fetomaternal interface.

Kuroda K, Vankatakrishnan R, Salker MS, et al. *Induction of 11β-hydroxysteroid dehydrogenase type 1 and activation of distinct mineralocorticoid receptor- and glucocorticoid receptor-dependent gene networks in decidualizing human endometrial stromal cells.*

The structural organization of AS enables rational design of more specific antihypertensive and oncologic agents.

Strushkevich N, Gilep AA, Shen L, et al. *Structural insights into aldosterone synthase substrate specificity and targeted inhibition.*



Manavathi B, Dey O, Gajulapalli VNR, Bhatia RS, Bugide S, Kumar R.

Derailed estrogen signaling and breast cancer: An authentic couple.

Girgis CM, Clifton-

Bligh RJ, Hamrick MW, Holick MF, Gunton JE.

The roles of vitamin D in skeletal muscle: Form, function, and metabolism.

Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM.

Diabetes and nonalcoholic fatty liver disease: A pathogenic duo.

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

Endocrinologist Tacoma, Washington

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 without 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. The area boasts 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.

Contact: For additional information regarding this position or to submit your CV, visit www.grouphealthphysicians.org or contact Cayley Crotty at crotty.c@ghc.org.

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EOE

ENDOCRINOLOGIST



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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.

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New Patient Fact Sheet Now Available! Female Sexual Dysfunction

Developed with the clinical and scientific expertise of The Endocrine Society, the Hormone Health Network's latest patient fact sheet, *Female Sexual Dysfunction (FSD)*, defines this condition and describes the physical and emotional factors that contribute to FSD. The fact sheet reassures patients that the condition is both common and treatable, and outlines interventions available to address the different causes of FSD.



Visit www.hormone.org to download this fact sheet and sign up for *Hormone Hotline*, our monthly e-update, to get the latest news on the Network's publications and events.

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- Medications and Bone Loss
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REDUCING
HEALTH DISPARITIES
AND **IMPROVING CARE**
THROUGH ENDOCRINE SCIENCE



2013 Reducing Health Disparities in Type 2 Diabetes Mellitus Summit

MARCH 22 – 23, 2013 | SHERATON INNER HARBOR HOTEL

As a recognized leader in this important field, The Endocrine Society is hosting its inaugural *Reducing Health Disparities Summit* in March 2013. This conference is designed to bring together researchers, clinicians, health educators, and public and community health leaders working to build partnerships to reduce health disparities.

CONFIRMED SPEAKERS:

Griffin Rodgers, MD, *Director of NIDDK*

Louis Sullivan, MD, *former U.S. Health and Human Services Secretary*

Sherita Golden, MD, *Chair of the Society's Health Disparities Scientific Statement*

Samuel Dagogo-Jack, MD, *Vice-President of Science and Medicine for the American Diabetes Association*

Rahn K. Bailey, MD, *President, National Medical Association*

Pam Allweiss, *Centers for Disease Control and Prevention*

Patrice Harris, MD, *Board Member, American Medical Association*

Abstracts that focus on health disparities in type 2 diabetes (T2D) from various perspectives will be considered for oral or poster presentation.

Key Dates: Registration Closes March 18 | Onsite Registration March 22 | Registration Fee: \$125

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

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

Prescribing information

Victoza® (liraglutide) 6 mg/ml solution for injection in pre-filled pen
Victoza® 3 ml pen
1 ml of solution contains 6 mg of liraglutide.

Indication: Treatment of adults with type 2 diabetes mellitus in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of metformin or sulphonylurea monotherapy; or in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy. **Dosage:** Victoza® is administered once daily by subcutaneous injection and at any time independent of meals however it is preferable to inject around the same time of day. Victoza® should not be administered intravenously or intramuscularly. Recommended starting dose is 0.6 mg daily, after at least one week, the dose should be increased to a maintenance dose of 1.2 mg. Based on clinical response, after at least one week the dose can be increased to 1.8 mg. Daily doses higher than 1.8 mg are not recommended. When added to existing sulphonylureas or in combination with metformin and sulphonylureas, a reduction in the dose of sulphonylurea may be necessary to reduce the risk of hypoglycaemia. Victoza® can be used in the elderly (>65 years) without dose adjustment but therapeutic experience in patients ≥75 years is limited. No dose adjustment for patients with mild renal impairment (creatinine clearance (CrCl) 60-90 ml/min). Due to lack of therapeutic experience Victoza® is not to be recommended for use in patients with moderate (CrCl of 30-59 ml/min), severe (CrCl < 30 ml/min) and end-stage renal disease or patients with hepatic impairment or children <18 years. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions for use:** Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. The addition of Victoza® in patients already treated with insulin has not been evaluated and is therefore not recommended. Limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Due to limited experience Victoza® is not recommended for patients with inflammatory bowel disease and diabetic gastroparesis. Victoza® is associated with transient gastrointestinal (GI) adverse reactions. GLP-1 analogues have been associated with pancreatitis; patients should be informed of symptoms

of acute pancreatitis if pancreatitis suspected, Victoza® and other suspect medicinal products should be discontinued. Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm reported in clinical trials particularly in patients with pre-existing thyroid disease. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. No studies on effects on ability to drive and use machinery. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulphonylureas. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products. **Fertility, pregnancy and lactation:** If a patient wishes to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued; use of insulin is recommended instead. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed. **Undesirable effects:** The most frequently observed adverse reactions which varied according to the combination used (sulphonylurea, metformin or a thiazolidinedione) were: Very common (≥ 1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulphonylureas, headache when used in combination with metformin and vomiting when used in combination with metformin and rosiglitazone; Common (≥1/10 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, gastroenteritis viral, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue and pyrexia. GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of; angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Rates of thyroid adverse events - 33.5, 30.0 and 21.7 events/1000 subject years of exposure for liraglutide, placebo and total comparators; Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently reported thyroid adverse events/1000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers:** Victoza® 2 x 3ml pre-filled pensEU/1/09/529/002. Victoza® 3 x 3ml pre-filled pensEU/1/09/529/003. **Legal Category:** POM. **Basic NHS Price:** Victoza® 2 x 3ml pre-filled pens: £ 78.48. Victoza® 3 x 3ml pre-filled pens: £117.72. **Further prescribing information can be obtained from:** Novo Nordisk Limited, Broadfield Park, Brighton Road, Crawley, West Sussex, RH11 9RT. **Date created:** March 2012.

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

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changing
diabetes™

Novo Nordisk is changing diabetes. We provide innovative treatment solutions that empower people to achieve and maintain good control of their diabetes.


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