

APRIL 2013

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**COVER Story****10 Metabolic Breakthrough***By Eric Seaborg*

The hormone fibroblast growth factor 21 (FGF21) may hold the key to increasing insulin sensitivity, improving lipid profiles, and reducing weight—all while minimizing side effects.

17 The 38,460 Menace*By Kelly Horvath*

Pancreatic cancer will claim the lives of nearly 40,000 Americans in 2013. New treatments remain elusive as doctors resort to combinations of chemotherapy and surgery to find the right approach for patients.

22 New Hope for Adrenal Cancer*By John Bohannon, PhD*

Because adrenal cancer is so rare, patient groups and researchers are pulling together to advocate for treatment. Researchers are now studying insulin-like growth factor 2 (IGF2), β -Catenin, and p53 for potential drug treatments.

CORRECTION

The February 2013 issue of *Endocrine News* included an error in the article "Better Thyroid Management During Pregnancy" on page 17. It should have stated, "Most women will have to return to lower levels of T4 replacement after the baby is delivered."

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Reducing GLOBAL HEALTH DISPARITIES

Last year, under the leadership of then-President Dr. Janet E. Hall, The Endocrine Society launched an exciting new initiative to address health disparities in endocrine diseases and related conditions such as diabetes, obesity, hormone-responsive cancers, and reproductive disorders. The Reducing Health Disparities and Improving Care Through Endocrine Science initiative was established as the Society's platform for helping to reduce global endocrine health disparities. It is our hope that we can begin bridging the gap in the prevalence of these endocrine disorders by creating opportunities for the research and advocacy communities to raise awareness of the extent of endocrine health disparities, to share information on current relevant research, and to build collaborations.



William F. Young Jr., MD, MSc

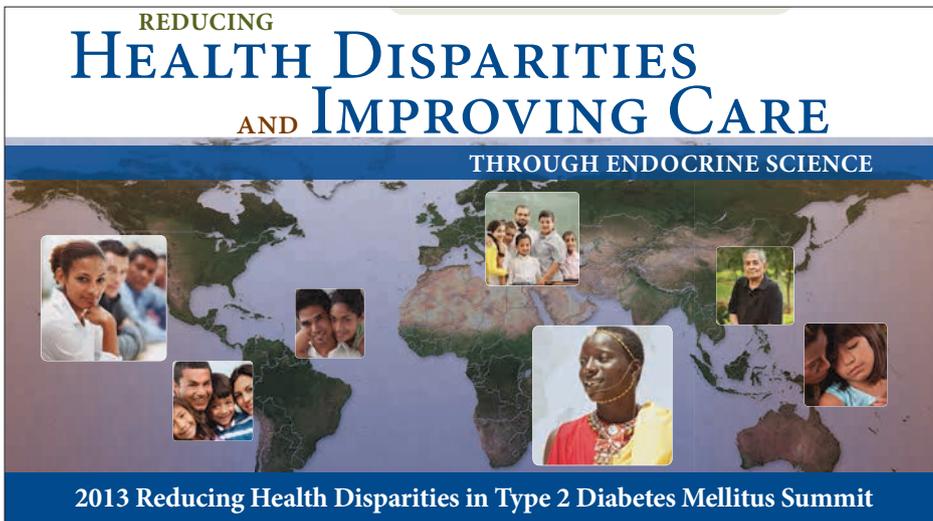
affecting health disparities in type 2 diabetes and would be able to participate in creative discussions about how individuals, communities (policy, scientific, and clinical), and professional organizations can collaborate to reduce health disparities in this area.

The program welcomed experts in the fields of health disparities and type 2 diabetes, including Dr. Joyce Hunter, deputy director of the National Institute of Minority Health and Health Disparities; Dr. Griffin Rodgers, director of the National Institute of Diabetes and Digestive and Kidney Diseases; Dr. Rahn K. Bailey, president of the National Medical Association and member of the American Medical Association Commission to End Health Disparities; and Dr. Louis Sullivan, former U.S. surgeon general and professor emeritus of the Morehouse School of Medicine. Representatives from the Agency for Healthcare Research and Quality's Center for Quality Improvement and Patient Safety, the Food and Drug Administration Office of Minority Health, the Pan American World Health Organization, the American Diabetes Association and other nonprofit organizations, and the private sector, as well as biomedical and clinical researchers and allied health professionals, were part of this remarkable lineup of speakers.

I would like to commend immediate-Past President Dr. Janet E. Hall on her visionary approach to address global endocrine health disparities, which led to this initiative. I would also like to congratulate the members of the Society's Minority Affairs Committee and Health Disparities Inter-Committee Work Group for their outstanding efforts in creating the Reducing Health Disparities Summit programming that has helped foster a growing awareness of this issue. The opportunities presented during the summit to learn, engage, and connect with others doing this type of work will be invaluable to continued endeavors to close the gap in health disparities and inequities.

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

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



One of the first stages in building the foundation of the Reducing Health Disparities initiative was to convene a summit for the research and advocacy communities to discuss disparities in diabetes from U.S. and global perspectives. The inaugural Reducing Health Disparities in Type 2 Diabetes Mellitus Summit was held on March 22-23, 2013, in Baltimore. Researchers, clinicians, health educators, and public and community health leaders dedicated to building partnerships to reduce health disparities convened to discuss everything from the biologic bases of endocrine health disparities to advocacy efforts aimed at increasing minority participation in clinical trials. Sessions were structured so that the audience would gain knowledge of the factors

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ENDOCRINE NEWS

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

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

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As I was reading this issue's content, I was reminded of the challenge to constantly innovate. From devising highly specific patient treatments to seeking scientific discoveries for new cures, the medical field labors under a constant deadline—a deadline that is, in fact, a matter of life and death.

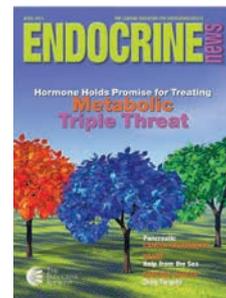
Consider this issue's feature on pancreatic cancer, now the fourth-leading cause of U.S. cancer deaths. Although new treatments are vigorously sought, advances in the main approaches—chemotherapy/radiation and/or surgery—have proven difficult to come by. The best approach for now, is for doctors to carefully identify patient and tumor features and devise the most specific treatment approach based on those characteristics. It's a tall order, and even then, the prognosis is often grim.

But then there are some successes. In this issue, you'll also learn about a glue that could be used in treatments for a number of cardiovascular diseases. A glue secreted by mussels has provided a recipe for a gel that stabilizes damaged blood vessels. Dr. Christian Kastrup, and the rest of his team at the University of British Columbia, made the discovery while searching for an underwater adhesive that would not easily wash away under blood flow. The benefits of the glue could be far-reaching if it receives approval for human application. Cardiovascular disease is still the number one cause of death in the U.S., with one out of every three people dying of a heart attack or stroke. Many years of research and trials are ahead before the gel can be translated into practice, but it's a step in the right direction.

At The Endocrine Society, we also feel the challenge to innovate, especially when it comes to helping you stay current on new advances in the field. I hope you have an opportunity to visit our journal Focus sites, the first of which is the JCEM Diabetes Focus. As part of our digital strategy to further enhance the value of our publications, the Focus sites were created to provide direct access to critical information on endocrine disorders. JCEM's Diabetes Focus is now available, with others launching soon.

In the meantime, enjoy the issue you hold in your hands. I hope you're inspired to innovate!

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.



Weight Loss Side Effect

Women who become pregnant after bariatric surgery are more likely to have babies born small.



GH Therapy and Heart Health

After 15 years of growth hormone replacement therapy, patients with GH deficiency may lower their cardiovascular risks.

Pathways to DELIVERY

Glucocorticoid receptor signaling could play a greater role in the development of the placenta than previously believed, according to a new study.



Glucocorticoids inhibit corticotropin-releasing hormone (CRH) production in the hypothalamus, but stimulate its production in the placenta, where it is involved

in determining the duration of pregnancy. Understanding how CRH is regulated could elucidate the working of the placental clock and the mechanisms that lead to parturition.

To this end, a team of researchers led by BingBing Wang, MD, PhD, of the University of Medicine and Dentistry of New Jersey in New Brunswick tested the hypothesis that glucocorticoid receptor signaling regulates a little-studied pathway in the placenta. This pathway involves NF- κ B, a nuclear factor protein complex that controls DNA transcription. NK-B target genes are

widely expressed in many types of cells. In a previous study, the researchers showed that this NF- κ B signaling plays a key role in regulation of placental CRH.

In the new study, to be published in *Molecular Endocrinology*, they conclude that glucocorticoid signaling activates this “non-canonical” NK-B pathway, which in turn upregulates placental CRH and other NF- κ B responsive genes involved in the onset of parturition. The pathway’s importance indicates that glucocorticoid receptor signaling may play a central role in regulating pregnancy length.

—Eric Seaborg

RESPIRATORY SYMPTOMS Change with Menstrual Cycle

Because respiratory symptoms vary rhythmically during the menstrual cycle, a new study recommends that asthmatic women should consider adjusting their medications in relation to their cycles.

The study found that wheezing and shortness of breath peaked during the mid-luteal and mid-follicular phases, with a dip in between them at the presumed time of ovulation. Coughing showed similar peaks before and after ovulation, as well as prior to menses onset. It was lower after menses.

The study included almost 4,000 women with regular cycles who were not taking exogenous sex hormones as part of Respiratory Health in Northern Europe, a population-based, multi-center postal-questionnaire-based effort.

Researchers, led by Ferenc Macsali, MD, of Haukeland University Hospital in Bergen, Norway, found that body mass index, smoking, and asthma status affected the patterns. They found variations according to body mass index that indicate a metabolic component in airways symptoms and patterns reflecting known hormonal influences of smoking.

Writing in the *American Journal of Respiratory and Critical Care Medicine*, the researchers say their findings illustrate a link between respiratory symptoms and changes in hormone status. They propose asthmatic women document their patterns by recording their symptoms during several cycles using the asthma control test or a peak flow meter, then use this information to adjust their medications.

—Eric Seaborg



CARROTS Counter Diabetes-Causing Genes?

Individuals harboring genes that predispose them to diabetes may have an

antidote: beta carotenes from carrots may reduce their symptoms.

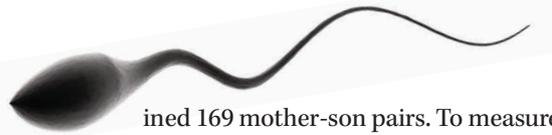
Genome-wide association studies (GWAS) have identified many common single nucleotide polymorphisms (SNPs) or gene mutations associated with the risk of developing type 2 diabetes (T2DM). However, genes are only part of the equation—the environment also plays a role. Combining efforts from GWAS studies and environmental-association studies, Atul Butte, MD, PhD, from Stanford University, and his group screened blood of volunteers from the National Health and Nutrition Examination Survey for 18 SNPs and 5 serum-based environmental factors, from dietary micronutrients to synthetic pollutants, for interaction in association to T2D.

They report in the journal *Human Genetics* that beta carotene, found in carrots and other vegetables, and gamma tocopherol, found in soybeans and margarine, had opposing effects on the SNP SLC30A4, which codes for a zinc-transporting protein found in abundance in pancreatic β -cells and is essential for insulin release. Individuals who harbored two copies of the variant in SLC30A4 and had higher beta-carotene levels and lower blood glucose levels. Those who had both mutations and higher levels of gamma tocopherol had higher blood glucose levels, and thus a higher risk for the disease.

But don't stock up on carrots or throw out the margarine just yet. The Butte lab still needs to confirm in animal studies whether purified beta carotene and gamma tocopherol will prevent or accelerate the disease.

—Jacqueline Ruttimann Oberst, PhD

Certain Detergents Prove Deleterious to **HUMAN SPERM**



Used to repel dirt and oil off of fabrics and food, perfluorinated alkyl acids (PFAA) may have one accusation that sticks: One of its compounds, perfluorooctanoic acid (PFOA), could affect male fertility.

The idea of these chemicals being endocrine disruptors is not far-fetched. Both PFOA and sister compound perfluorooctane sulfonic acid (PFOS) are found in everyone's blood and can cross the placental barrier. Also, certain aspects of male infertility, such as the reduction in semen quality and altered reproductive hormones, have been found in rats previously exposed to PFOA and PFOS.

Anne Vested, MS, PhD candidate at Aarhus University Hospital in Denmark, led a research team in which they exam-

ined 169 mother-son pairs. To measure in utero exposure, PFOA and PFOS were measured in the mothers when they were 30 weeks pregnant. The sons, who were 19-21 years old, submitted blood to measure hormone levels and semen samples to examine for sperm concentration, total count, motility, and morphology.

In an article published in *Environmental Health Perspectives*, the group reported that sons exposed in utero to high levels of PFOA had lower sperm concentration and number and higher levels of the reproductive hormones luteinizing hormone and follicle stimulating hormone than those that had a lower level of exposure. PFOS did not have any effect. These findings may partially explain the increase in male infertility. Normal sperm count—from 20 million to 300 million per milliliter of semen—is falling worldwide.

—Jacqueline Ruttimann Oberst, PhD

MOUSE MODEL Gives Clues to Pituitary Deficiencies

A new study sheds light on the genetic abnormalities that can affect pituitary disorders.

The LHX3 LIM-homeodomain transcription factor plays an essential role during the early stages of pituitary and nervous system development. Mutations in the human LHX3 gene are associated deficits in a host of anterior pituitary hormones, which leads to combined pituitary hormone deficiency diseases. These patients have severe problems, including short stature, developmental delays, and reproductive difficulties.

Mice lacking LHX3 gene function exhibit similar symptoms, so a team of researchers led by Simon J. Rhodes, PhD, of Indiana University-Purdue University in Indianapolis developed a strain with a mutation similar to the human problem-creating mutation, in which a stop codon results in a truncated LHX3 protein that lacks the transcriptional activation domains required for pituitary gene activation. In the mouse model, the pituitary deficiencies started early in embryonic development, consistent with an important role for LHX3 in organogenesis of the pituitary gland. In an article accepted for publication in *Endocrinology*, the researchers propose that this mouse strain lacking LHX3 gene function will be a useful model to facilitate

future molecular and cellular studies of pituitary hormone disease onset.

—Eric Seaborg

Missing Protein Implicated in **OBESITY**

The lack of a protein in adipose tissue could contribute to obesity, a new study indicates. Scaffold proteins are important mediators in selective cell signal



transduction. The scaffold protein, p62, is involved in signaling pathways affecting a number of important processes, including inflammation, cell differentiation, cell growth, and tumorigenesis.

A research team led by Matthias Tschöp, MD, of the Technical University Munich, showed in a previous study that global ablation of p62 in mice results in obesity and insulin resistance. In an article just published in *The Journal of Clinical Investigation*, they homed in on the target tissue leading to these effects.

Using knockout mice that lacked p62 in specific tissues and organs, they showed that p62 deficiency in the central nervous system, liver, muscle, and cells of the myeloid lineage caused no metabolic symptoms. However, the lack of p62 in adipose tissue alone was sufficient to cause obesity and impaired glucose metabolism. Brown adipose tissue in particular was the main organ responsible for the disrupted energy metabolism, with p62 exerting direct regulatory control of the brown adipocytes' mitochondrial function. The absence of p62 led to impaired mitochondrial structure and dysfunction. The findings could point to new strategies for combating obesity, the researchers believe.

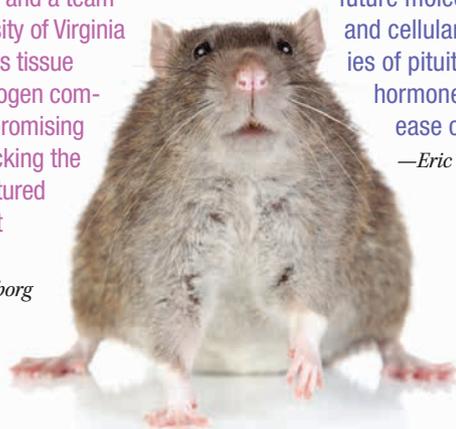
—Eric Seaborg

New Combination for **HORMONE THERAPY**

Women on combined estrogen-progestin menopausal hormone therapy have an increased risk of breast cancer compared with those who receive estrogen alone. However, the progestin is needed to prevent estrogen-induced uterine cancer.

A proposed alternative formulation combines the selective estrogen-receptor modulator, bazedoxifene, with conjugated estrogens to form what is called a tissue selective estrogen complex. In a study in *Endocrinology*, Wei Yue, PhD, and a team at the University of Virginia report that this tissue selective estrogen complex offered promising results in blocking the growth of cultured human breast cancer cells.

—Eric Seaborg



Insulin Therapy Associated with GREATER MORTALITY

Insulin therapy is one of the big guns in the treatment of people with type 2 diabetes, but new evidence indicates that recipients risk being victims of friendly fire.

Diabetes treatment generally focuses on control of blood glucose levels. If metformin and a sulfonylurea drug do not keep it in line, some guidelines are calling for a faster move to insulin injections, even though insulin use is coming under increased scrutiny. In an attempt to sort out the relative risks of these therapies, a team led by

Craig Currie, PhD, of Cardiff University School of Medicine in the U.K., compared the outcomes of various treatment regimens in almost 85,000 primary care patients with diabetes.



Patients who received insulin had a wide variety of worse outcomes compared with those treated with metformin alone, including more cardiovascular events, stroke, solid-tumor cancers, neuropathy, eye complications, renal disease, and all-cause mortality. This finding is consistent with previous evidence, including from other large, population-based observation studies.

In an article accepted for publication in *The Journal of Clinical Endocrinology & Metabolism*, the researchers write that “unquestionably, exogenous insulin can produce large reductions in blood glucose,” but “there is a clear need to review the way in which exogenous insulin is used in people with type 2 diabetes and to quantify in much greater detail its risk–benefit profile.”

—Eric Seaborg

Nursing Induces HPA CHANGES

New mothers may report feeling stressed out, but nursing mothers of the murine variety are remarkably immune to stress as their hypothalamus-pituitary-adrenal (HPA) axes adjust to meeting the metabolic demands of the post-partum period.

The HPA axis, with its regulation of corticosteroids, is particularly important during pregnancy and lactation when the need to be eating for two—or a litter—requires ramping up the

metabolism. To get a better idea of the adaptations involved, researchers led by Richard Windle, PhD, of the University of Nottingham in the U.K. used dynamic blood sampling to follow corticosterone levels in rats in the days following giving birth. They also tested the effects of a forced weaning by removing the young 10 days after birth.

The HPA axis normally acts through secretory pulses every 60 to 90 minutes, with the amplitude varying in a diurnal pattern. The lactating animals displayed a marked flattening of the diurnal pattern of basal corticosterone secretion as well as an absence of a stress reaction, which together resulted in steadier corticosteroid levels.

Stable corticosteroid levels may be important for maintaining the mother's metabolic activity and avoiding exposing the suckling young to corticosterone spikes, the researchers say in an upcoming *Endocrinology* article. These changes were largely reversed shortly after removal of the young, which led to marked suppression of basal corticosterone secretion. The stress response not only returned, but was prolonged.

—Eric Seaborg

ADULTS GUESS LOW When Estimating Weight, HIGH on Height



When asked to estimate their size, Irish adults routinely guess low on weight and high on height, University of Cork researchers say. Not only that, people's skill at guessing their own weight appears to be worsening. The findings result from analyzing 10 years of Surveys of Lifestyle Attitudes and Nutrition data.

The research, published in *PLoS ONE*, tracked Irish adults for nine years, comparing their own estimates of their heights and weights to measurements made by researchers. From 1998 to 2009, estimation accuracy for body mass index (BMI) calculated from self-reported weight and height dropped from 80 percent to 53 percent. The overreporting of height was consistent over time but the underreporting of weight worsened with time and with degree of overweight. Self-reported weight bias occurred independent of gender, age, and awareness of impending verification; height bias was independent of gender, age, and clinically determined BMI category.

When applying BMI classifications to the weight data, the increased weight bias for males showed up only in the obese category, while it affected females in both the overweight and obese categories. These findings challenge the prevailing view that both self-reported height bias and self-reported weight bias contribute equally to BMI underestimation in large population surveys. The researchers urge caution in using the study results, however, noting data collection methods changed during the study period.

—Carol Bengle Gilbert



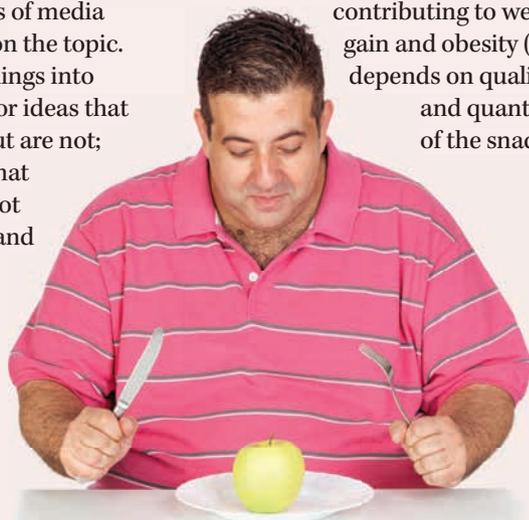
Separating Fact from Fiction in **OBESITY**

Not everything we “think” we know about obesity is correct, according to a recent study in *The New England Journal of Medicine*. Seeking to sort fact from fiction, David B. Allison, PhD, at the University of Alabama at Birmingham, and his team performed Internet searches of media and scientific literature on the topic. They identified their findings into three categories: myths, or ideas that are believed to be true but are not; presumptions, or ideas that might be true but have not been sufficiently tested; and facts, or ideas that have the support of sufficient scientific evidence.

Seven obesity-related myths stemmed from their study, ranging from the idea that breastfeeding is protec-

tive against obesity to another where a bout of sexual activity burns 100 to 300 kcal for each person involved (a scientific study found that the latter activity only burns 21 calories in men).

Six presumptions also emerged, such as the concept of snacking contributing to weight gain and obesity (it depends on quality and quantity of the snack)

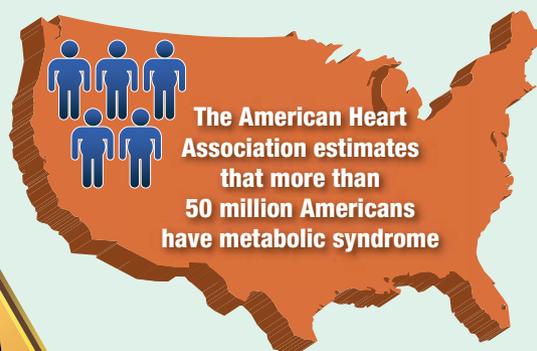


or that simply eating more fruits and vegetables without conducting any exercise or further diet modifications will result in weight loss or less weight gain. Lastly, nine truths or facts stood up to rigorous scientific review; for example, weight loss programs for overweight children that involve the parents and home environment yield greater weight reduction than those that do not, and diets generally do not do well in the long-term for effective weight reduction.

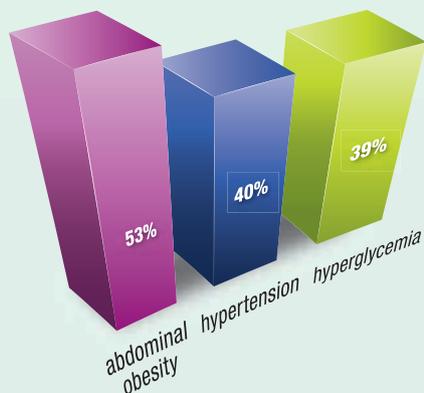
So what's the danger in these white lies or untruths? “When the public, mass media, government agencies, and even academic scientists espouse unsupported beliefs, the result may be ineffective policy, unhelpful or unsafe clinical and public health recommendations, and an unproductive allocation of resources,” the authors write.

—Jacqueline Ruttimann Oberst, PhD

Fast **FACTS** about Metabolic Syndrome



The most frequently occurring risk factors for metabolic syndrome:



Metabolic syndrome increases the risk for coronary heart disease and diabetes 2 to 6 fold and 3.5 fold, respectively



One-fourth of U.S. adults are estimated to have metabolic syndrome

Metabolic Breakthrough

Hormone fibroblast growth factor 21 holds promise for treating diabetes, obesity, and metabolic syndrome, but new drug treatments remain years away

What is FGF21?

FGF21 is an anomalous member of the FGF family. Most FGFs are heparin-binding proteins that act locally in an autocrine or paracrine manner in growth and differentiation. Produced by the pancreas, liver, and adipose tissue, FGF21, however, is part of a three-member subfamily that lacks the heparin-binding domain, which allows them to diffuse into the circulation. Rather than promoting growth, they act as endocrine hormones that regulate metabolism.



By Eric Seaborg, PhD

A safe drug for increasing insulin sensitivity, improving lipid profiles, and reducing weight would be in instant demand for treating a host of patients, and many researchers believe the hormone fibroblast growth factor 21 (FGF21) could do all these things and more. What's more, FGF21's unusual binding properties could enable it to work in a targeted fashion that could minimize side effects. Several drug companies are exploring the preclinical possibilities, with impressive results in rodents and primates.

"FGF21 burst onto the scene in 2005 with this paper by Eli Lilly describing its really remarkable effects in obese rodents," says Steven Kliewer, PhD, professor of molecular biology at the University of Texas Southwestern Medical Center.

In a landmark study in *The Journal of Clinical Investigation*, a team led by Alexei Kharitonov, PhD, group

leader of diabetes research at Eli Lilly and Co., showed that, among its benefits, FGF21 could lower plasma glucose and triglycerides to near normal levels in diabetic mice. The effects lasted for 24 hours or more following the cessation of FGF21 administration, with no mitogenicity, hypoglycemia, or weight gain at any dose in diabetic, healthy, or transgenic mice.

Since that paper, a plethora of studies have found similar beneficial effects in nonhuman primates, and the race has been on to explore its therapeutic potential to treat diabetes, obesity, and metabolic syndrome.

Longevity and Potency Issues

The research identified FGF21 as an anomalous member of the FGF family. Most FGFs are true to the name—heparin-



AT-A-GLANCE:

- **Landmark 2005 study found that FGF21 could lower plasma glucose and triglycerides to near normal levels in diabetic mice.**
- **A drug that could work better than thiazolidinediones would be extremely valuable for metabolic syndrome treatment.**
- **Developing a new treatment without major side effects faces uphill climb.**

binding proteins that act locally in an autocrine or paracrine manner in growth and differentiation. Produced by the pancreas, liver, and adipose tissue, FGF21 is part of a three-member subfamily that lacks the heparin-binding domain, which allows them to diffuse into the circulation. Rather than promoting growth, they act as endocrine hormones that regulate metabolism.

“FGF21 shows a strong preference for one of the four FGF receptors, FGFR1c,” Kliewer says. “It requires a second protein to function, called β Klotho, another membrane-spanning cell-surface protein.” FGF21 needs to bind to this receptor β Klotho complex to exert its actions. “This is probably why FGF21 doesn’t have the growth-promoting actions of other FGF family members,” Kliewer says. And it is probably why FGF21 is free of the proliferative and tumorigenic effects of most members of the FGF family.

FGF21 is not a natural when it comes to use as a pharmaceutical, however, because of issues with its potency and longevity. Although its effects can last for 24 hours in mice and nonhuman primates, it has a half-life of about 30 minutes in rodents and two hours in cynomolgus monkeys, and remains in human circulation for less than five hours. Just the same, the group at Lilly, many collaborators, and other researchers have published abundant data using FGF21 and longer-lived analogs. “There are several ways you can modify the biological and biopharmaceutical properties of the protein FGF21,” Kharitonov told *Endocrine News*.

Monoclonal Antibody Solution

Other researchers have looked to sidestep these problems through a relatively new technology by developing a monoclonal antibody that mimics FGF21 action.

More than 30 monoclonal antibodies are currently used to treat cancer, as well as autoimmune,

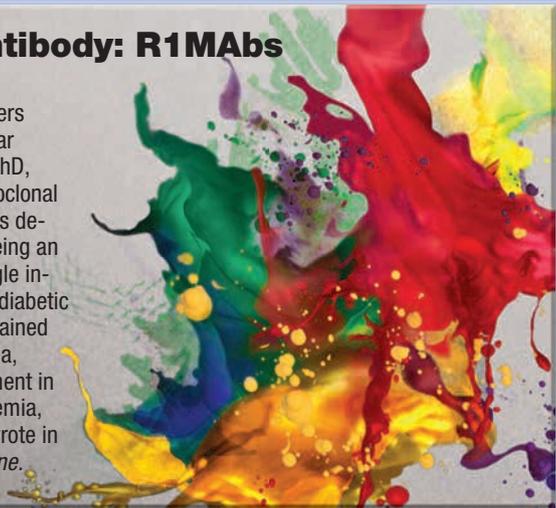
inflammatory, and infectious diseases, but most are antagonists or inhibitory in action. The FGF21 mimetics are among the first to use an antibody as an agonist to stimulate FGF21’s effects by activating its receptor complex.

“Antibodies may have several advantages,” says Yang Li, PhD, scientific director at the pharmaceutical company Amgen. “One potential advantage is their extended pharmacokinetic properties in plasma. Usually as a class, they can circulate for days in the plasma, so you can design a therapy that perhaps does not require frequent injections. Another advantage is that antibodies are quite specific for their targets, and this can usually lead to reduced potential side-effect concerns with your therapeutic molecule. And manufacturing processes for antibodies continue to improve as well.”

In December 2011, researchers at Genentech, led by molecular biologist Junichiro Sonoda, PhD, published findings on a monoclonal antibody they named R1MAbs designed to mimic FGF21 by being an agonist of the FGFR1. “A single injection of R1MAb into obese diabetic mice induced acute and sustained amelioration of hyperglycemia-

Monoclonal Antibody: R1MAbs

In December 2011, researchers at Genentech led by molecular biologist Junichiro Sonoda, PhD, published findings on a monoclonal antibody they named R1MAbs designed to mimic FGF21 by being an agonist of the FGFR1. “A single injection of R1MAb into obese diabetic mice induced acute and sustained amelioration of hyperglycemia, along with marked improvement in hyperinsulinemia, hyperlipidemia, and hepatosteatosis,” they wrote in *Science Translational Medicine*.



mia, along with marked improvement in hyperinsulinemia, hyperlipidemia, and hepatosteatosis,” they wrote in *Science Translational Medicine*. Blood glucose concentrations in the treated mice normalized within a week, and remained lower than levels in placebo-treated mice for a month. The antibody acted on FGFR1 without involvement of β Klotho, and some of the results indicated that R1MAB was not as targeted as FGF21 itself.

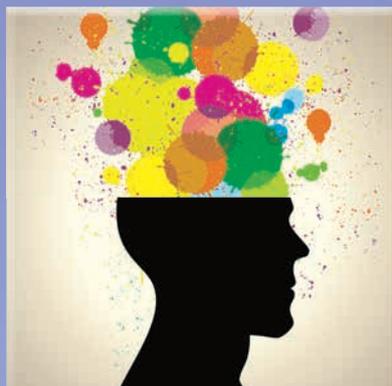
A year later, Li’s group at Amgen upped the ante by developing mimAb1, an antibody that works with the FGFR1c/ β Klotho complex, and testing it in monkeys. “In obese cynomolgus monkeys, injection of mimAb1 led to FGF21-like metabolic effects, including decreases in body weight, plasma insulin, triglycerides, and glucose during tolerance testing,” the researchers wrote in *Science Translational Medicine*. “Because mimAb1 depends on β Klotho to activate FGFR1c, it is not expected to induce side effects caused by activating FGFR1c alone.”

The effects of mimAb1 were closer than those of R1MAB to FGF21’s, but still not identical. And the effects were also very long lasting. Many of the benefits lasted at least five weeks, and after a second injection, the reduction in body weight lasted for nine weeks.

Amgen’s Li credited the long-lasting effects primarily to the extended time the antibody remains in circulation, and Genentech’s Sonoda suggested that an additional contribution may come from the ability of the antibody to modify the underlying disease itself and not simply treat symptoms. For example, by removing excess lipids, it leaves the body in a healthier state.

Paradoxical Roles?

Researchers will be busy for some time sorting out FGF21’s various roles and mechanisms of action. FGF21 acts on both liver and adipose tissue, but the antibody forms



Metabolic Syndrome DIAGNOSIS

- Blood pressure equal to or higher than 130/85 mmHg
- Fasting blood glucose equal to or higher than 100 mg/dL
- Large waist circumference:
Men: 40 inches or more
Women: 35 inches or more
- Low HDL cholesterol:
Men: under 40 mg/dL
Women: under 50 mg/dL
- Triglycerides equal to or higher than 150 mg/dL

Source: A.D.A.M. Medical Encyclopedia

appear to bypass the liver and act directly on adipose tissues in achieving some of their antidiabetic effects.

FGF21 levels are higher in patients who are obese or have type 2 diabetes, and yet it plays a role in the starvation response. The liver increases FGF21 production in response to fasting, and FGF21 affects starvation adaptations such as suppressing the activity of growth hormone and reducing the production of insulin-like growth factor.

Kliwer and colleagues recently published in *eLife* a study that found that FGF21 overexpression in transgenic mice can lead to the same kind of lifetime extension that can be induced by severe caloric restriction. The study turned up some side effects, however, including infertility in female mice and smaller size and bone density loss in both sexes.

A drug that could work better than the out-of-favor thiazolidinediones—without dangerous side effects and with weight loss

instead of weight gain—would certainly be remarkably valuable for treating diabetes and metabolic syndrome. But the history of the thiazolidinediones illustrates that any such drug will face a very high bar in proving more effective than current treatments without major side effects. And although FGF21 researchers are excited about its promise, with the published data currently in the pre-clinical stage, any new therapy remains years away. **EN**

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



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**NOW
AVAILABLE**

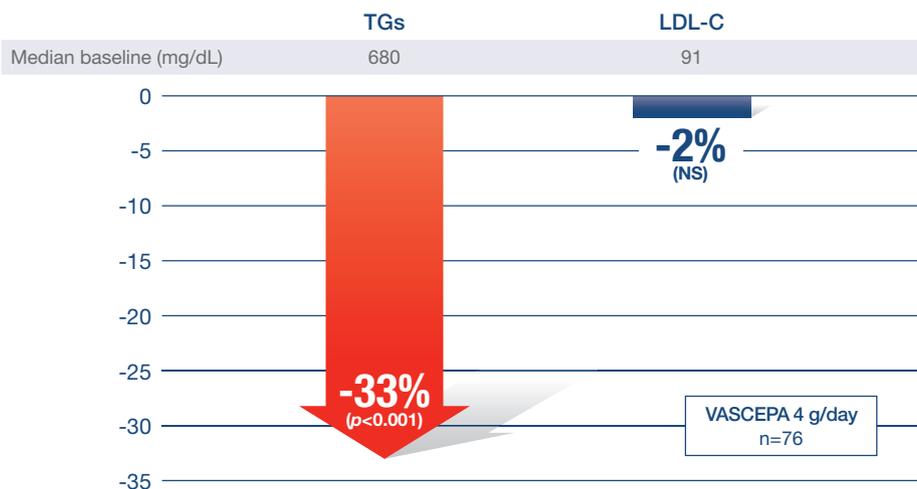
The first FDA-approved EPA-only omega-3

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-C*¹

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.

For the treatment of severe hypertriglyceridemia
(triglyceride levels ≥ 500 mg/dL)

Introducing VASCEPA[®]

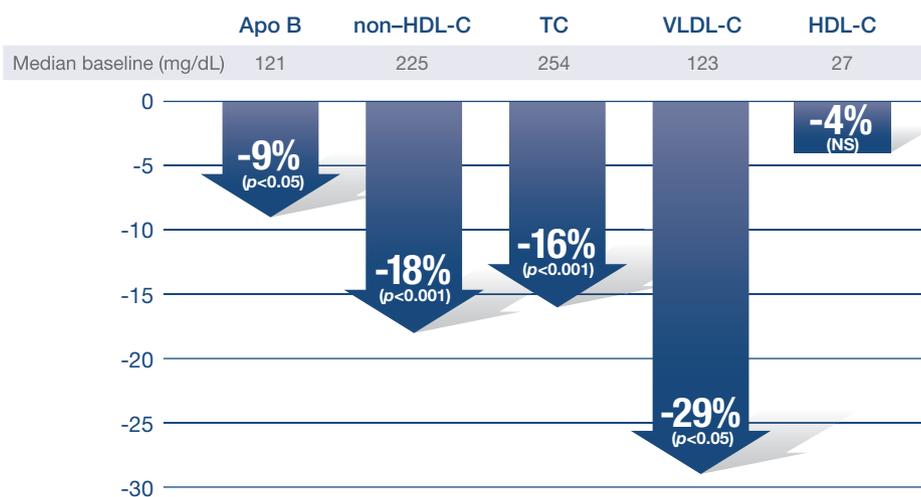
TG Therapy Redefined:

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.

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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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The **38,460** **MENACE**

Deadly pancreatic cancer demands resourceful treatment approach

By Kelly Horvath

In 2013, an estimated 45,220 new cases of pancreatic cancer will be diagnosed, affecting men and women nearly equally, and an estimated 38,460 deaths will occur, making pancreatic carcinoma the fourth-leading cause of U.S. cancer deaths, with incidence slowly but steadily increasing in the last decade. This especially deadly cancer has an overall survival rate of less than 4 percent and a five-year survival of 6 percent in both the United States and Europe. In about 90 percent of cases, pancreatic cancer has already metastasized by the time of diagnosis, which partly accounts for its high mortality rate. Of the 10 percent in which the tumor is still local, only half are surgery candidates.



AT-A-GLANCE:

- **Pancreatic carcinoma is the fourth-leading cause of U.S. cancer deaths, and that rate is increasing.**
- **Advances in the main treatment approaches—chemotherapy/radiation and/or surgery—have been difficult to come by.**
- **For less than 20 percent of patients, Whipple procedure improves five-year survival to 18 to 24 percent.**

Pancreatic cancer is frequently in the news for reasons in addition to its intractability. Recently, celebrities including Luciano Pavarotti, Patrick Swayze, Steve Jobs, and Bonnie Franklin have succumbed to it, and the resulting media coverage has raised public awareness. Although new treatments are vigorously sought, advances in the main approaches—chemotherapy/radiation and/or surgery—have proven difficult to come by. Improvements in survival are still measured only in months; for most patients, treatment is palliative at best. Disease profile (i.e., whether the mass is located in the pancreas head, body, tail, or uncinate process, as well as whether or not it has spread) guides treatment choice, but many consider

staging unhelpful beyond the broad categories of resectable or not when resection is currently the only hope of cure. Most pancreatic cancers are adenocarcinomas (95%), by far the most difficult to treat.

With the large majority facing grim prognoses, patients are commonly encouraged to participate in clinical trials.

Surgery

Surgery is considered the primary treatment modality when possible because it offers the highest degree of palliation and, in some cases, increases short-term survival.

For less than 20 percent of patients, with small tumors localized to the pancreas head and/or neck, complete resection with pancreatoduodenectomy (Whipple procedure) improves five-year survival to 18 to 24 percent. However, the resulting reduction in islet cells impairs insulin production and often causes secondary diabetes, especially in those who were already experiencing blood sugar control difficulty (the jury is still out in these cases, whether the cancer caused the islet dysfunction or vice versa).

Still, for some patients, “the original problem is much worse than having diabetes so the treatment is worth the risk,” says Jay H. Shubrook Jr., DO, of the UMA Diabetes and Endocrine Clinical Care and Research Center in Athens, Ohio.

A study conducted at Johns Hopkins University in Baltimore found that having Whipple done by an experienced surgeon at a center where the procedure is commonly done improves outcome more than any other prognostic indicator.

In a trial at the University of Texas Cancer Center, researchers led by Mark J. Truty, MD, reevaluated a cohort



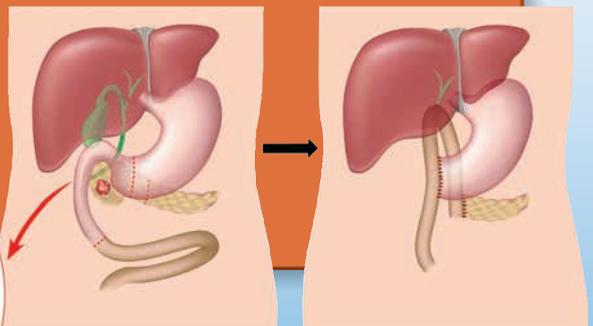
Photo credit: Marko Rapana, Featured/Flash/Shutterstock.com

Celebrities that recently succumbed to pancreatic cancer include: Steve Jobs in 2011, Patrick Swayze in 2009, Bonnie Franklin in 2013, and Luciano Pavarotti in 2007.



Allen Whipple

A study conducted at Johns Hopkins University found that having Whipple done by an experienced surgeon at a center where the procedure is commonly done **improves outcome more than any other prognostic indicator.**



of 88 high-risk patients with a previous failed surgery and deemed 81 eligible for another attempt at resection. After restaging the tumor, surgeons used chemoradiation before again attempting resection. Of the 81 patients, 66 underwent successful pancreatectomy and had an average survival of about 2.5 years. Multimodal treatment has demonstrated conflicting results, but this trial reversed the typical sequence of treatments by doing chemoradiation before surgery rather than postoperatively. Adjuvant therapy can be done at any treatment stage.

Patients with unresectable cancers may benefit from palliative surgery, and particular symptoms may depend on tumor location and extent. For patients with biliary obstruction, a stent placed during endoscopic retrograde cholangiopancreatography (ERCP) can relieve associated symptoms, such as jaundice, nausea, and vomiting. Celiac axis and intrapleural nerve block helps reduce tumor-associated pain. Psychologic treatment can also be implemented to address the disabling effects that receiving this grim diagnosis can produce.

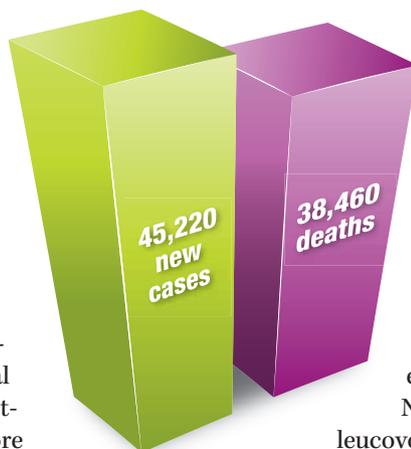
For now, the best approach seems to be differentiated treatment, which takes into account individualized factors, including genetic markers, tumor staging, and overall patient health.

Short of complete resection, although quality of life improves, overall survival does not. Researchers are now turning to genetics to try to better understand pancreatic cancer, with the recent discovery that pancreatic adenocarcinoma develops over many years through progressive pancreatic intraepithelial neoplasia, commonly diagnosed with ERCP. Thus, targeted therapies are another area showing promise. Erlotinib ablates epidermal growth factor receptor, for example, to stunt tumor growth.

Chemotherapy

Hands down the best news in pancreatic cancer research comes from the chemotherapy sector, with two new drug combinations making inroads as potential new first-line therapies. For many years, first-line chemotherapy has consisted of the single agent gemcitabine, increasing survival by five to seven months. Trials adding various cytotoxic agents to the gemcitabine regimen generally did not increase survival beyond what gemcitabine alone accomplished.

Until recently, that is. Phase 3 of the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) study of 861 patients, which was presented at the January 2013 Gastrointestinal Cancers Symposium, “demonstrated a survival benefit of gemcitabine/nab-paclitaxel over gemcitabine,” says Andrew H. Ko, MD of the University of California in San Francisco. Although the survival benefit is modest at overall two months, researchers are encouraged with any



survival increase with this notoriously tough cancer. Nab (nanoparticle albumin-bound)-paclitaxel is currently indicated for breast cancer.

Gemcitabine, alone or in combination, was considered the “reference regimen” for pancreatic cancer chemotherapy until FOLFIRINOX improved survival time better than any other agent(s) in a 2005–2009 French study led by Thierry Conroy, MD, at Université de Lorraine, Nancy, France. This regimen of fluorouracil,

leucovorin, irinotecan, and oxaliplatin not only nearly doubled survival time to 11.1 v. 6.8 months compared to gemcitabine in phase 3 of the study, but it also increased time until quality-of-life deterioration, with 31 percent reporting significant decrease.

However, FOLFIRINOX users had higher incidences of adverse events including neutropenia, thrombocytopenia, diarrhea, sensory neuropathy, and alopecia. Researchers concluded that FOLFIRINOX is a first-line choice for advanced-stage disease patients age younger than 76 years with healthy hearts and livers who are still either as active as or slightly less active than they were prior to diagnosis. A subsequent companion French study published in 2012 with quality of life as the primary endpoint demonstrated that FOLFIRINOX outperformed gemcitabine.

While hopeful, the FOLFIRINOX findings do not apply to most pancreatic adenocarcinoma patients, who would not meet the treatment criteria and for whom the drug combination would prove too toxic. For these less robust patients, nab-paclitaxel is perhaps soon to be an option, though a more expensive one.

For now, the best approach seems to be differentiated treatment, which takes into account individualized factors, including genetic markers, tumor staging, and overall patient health.

“With the greater array of options that physicians and patients will have to choose from in the future, the key will be to identify patient and tumor features that help guide this decision-making process,” says Ko. **EN**

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

FOLFIRINOX Regimen

- First-line choice for advanced-stage disease patients age younger than 76 years with healthy hearts and livers.
- Doubled survival time to 11.1 v. 6.8 months.
- Increased time until quality of life deterioration.
- Higher incidence of adverse events.

Note: FOLFIRINOX findings do not apply to most pancreatic adenocarcinoma patients, who would not meet the treatment criteria and for whom the drug combination would prove too toxic.



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

Flexing MUSSELS

Glue secreted by these bivalves could prove effective in treatments for numerous cardiovascular diseases

By **Melissa Mapes**

Mussels have been the scourge of boat hulls since mankind first set sail. Built to withstand the corrosive powers of the sea, these mollusks are nearly impossible to dislodge once they take root. Aside from when sautéed with white wine, mussels are frequently considered no more than a pest, but their reputation may soon improve. A team of researchers at the Massachusetts Institute of Technology recently found a way to make use of the sticky bivalves. The glue secreted by mussels when latching onto the surfaces of rocks and boats has provided a recipe for a gel that stabilizes damaged blood vessels and has the potential to treat numerous cardiovascular diseases.

Dr. Christian Kastrup, assistant professor at the University of British Columbia's Michael Smith Laboratories in the Department of Biochemistry and Molecular Biology and lead researcher on the project, was searching for an underwater adhesive that would not easily wash away under blood flow. He wanted to develop an alternative to the usual mechanical treatments for atherosclerosis, such as stents, which can cause significant damage. "We were really interested in finding a way to gently implant materials onto blood vessel walls," he explains. A special glue was one option under consideration.

Surprising Results

He asked around different departments at MIT in search of inspiration. The interdisciplinary team he assembled kept a running list of possible adhesives, but one in particular stood out. "Other researchers had found that the proteins mussels use to stick to rocks worked extremely well and could be mimicked in synthetic systems." Kastrup was both skeptical and intrigued, but decided to give it a shot.

The process involved experts in the fields of polymer chemistry, controlled release, transcatheter procedures, radiologists, and pathologists. After much tinkering in the lab, the researchers formulated a synthetic version of the glue using an alginate base. The adhesive gel was then applied in a thin layer via catheter over plaque build-up in the vessel walls in mice. Surprisingly, it was able to withstand blood flow for months before degrading, and left a stabilized vessel in its wake. The results were even better than Kastrup had imagined.

"It's what we had set out to do, but I had many doubts in mind. I was really surprised, especially by how long it adhered." In preliminary studies, the glue stayed put for about one to four months, but researchers believe it has the potential to last even longer. "That is one thing we still have to evaluate," he says.

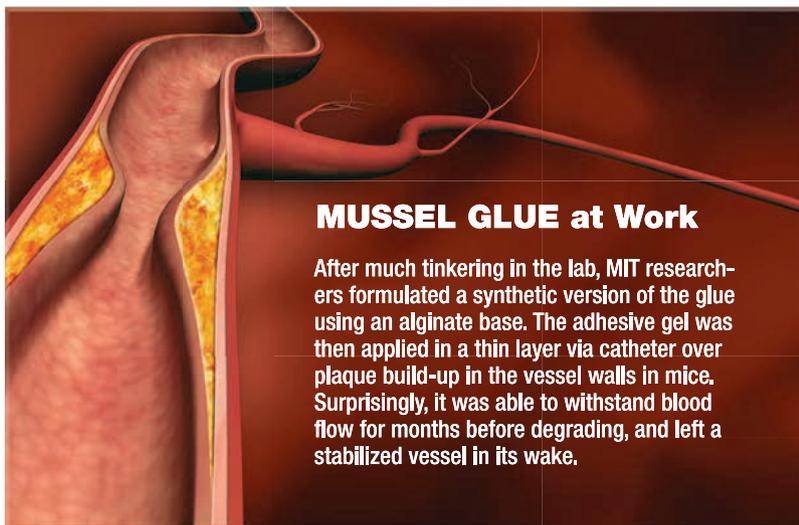
Far-Reaching Benefits

Kastrup experimented with drug-elution by adding steroids to the gel. The drug-infused adhesive formed a protective cap over the plaque and released the medication, leading to reduced macrophage content and plasma cytokine levels.

Inflammation diminished and rupture no longer appeared to be a threat. Mechanical drug-eluting devices have been used to achieve the same results, but can cause damage of their own.

The benefits of the glue could be far-reaching if it receives approval for human application. Cardiovascular disease is still the number one cause of death in the United States, with one out of every three people dying of a heart attack or stroke. Kastrup's mussel gel may be able to help prevent the clots that often lead to these events by stabilizing damaged vasculature and preventing plaque from breaking off and blocking blood flow. Unfortunately, many years

continued on page 25



MUSSEL GLUE at Work

After much tinkering in the lab, MIT researchers formulated a synthetic version of the glue using an alginate base. The adhesive gel was then applied in a thin layer via catheter over plaque build-up in the vessel walls in mice. Surprisingly, it was able to withstand blood flow for months before degrading, and left a stabilized vessel in its wake.

HYPERTENSION MYSTERY: A Case Study From ESAP™

A 45-year-old woman presents with a nine-year history of hypertension. Her current antihypertensive medications include amlodipine, 10 mg daily; lisinopril, 20 mg daily; and KCl, 20 mEq twice daily. Her serum sodium concentration is 143 mEq/L, and her serum potassium concentration is 3.5 mEq/L. She has no family history of hypertension. She is keen to consider a surgical procedure if it would correct her hypokalemia and improve or cure her hypertension.

On physical examination, blood pressure is 150/90 mm Hg, heart rate is 88 beats/min, and BMI is 29.6 kg/m². Her excess body weight is diffusely and not centrally distributed. Findings from examinations of the heart and abdomen are normal, and peripheral pulses are intact.

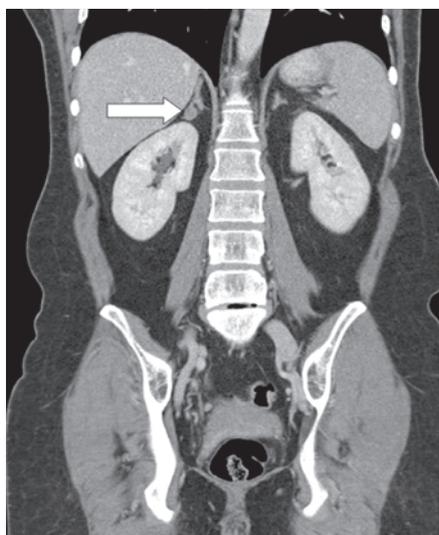
Recent laboratory studies from her primary care physician's office include the following:

Blood

- Aldosterone = 19 ng/dL
- Plasma renin activity = <0.6 ng/mL per h
- 1-mg overnight dexamethasone suppression test = <1.0 µg/dL

Urine

- Urinary aldosterone excretion with oral sodium loading = 18 µg/24 h (urinary sodium = 222 mEq/24 h)
- CT of the abdomen is performed, and a 7-mm right adrenal nodule is identified (arrow):



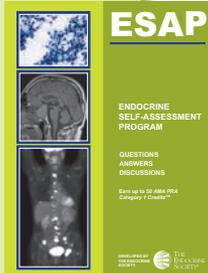
Adrenal venous sampling is performed during cosyntropin infusion, 50 mcg/h.

Measurement	Right Adrenal Vein	Inferior Vena Cava	Left Adrenal Vein
Aldosterone, ng/dL	3200	40	1600
Cortisol, µg/dL	1000	20	500

QUESTION

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Which one of the following is the best next step in management?

- Perform laparoscopic right adrenalectomy
- Perform another adrenal venous sampling for aldosterone and cortisol
- Perform 6β-¹³¹I-iodomethyl-19-norcholesterol (NP-59) scintigraphy
- Initiate medical therapy with a mineralocorticoid receptor antagonist
- Perform laparoscopic left adrenalectomy

answer on page 32

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New HOPE for Adrenal Cancer

Despite some disappointing studies, researchers pursue IGF2 and other suspects for drug targets

By John Bohannon, PhD

Most cancers are neighborhood bullies, stealing blood and pushing into the surrounding tissues. Unless a tumor compromises a vital organ, people can live for years, sometimes a lifetime, with cancer as a passenger. But cancers that take root in the endocrine system are terrorists. Even a tiny group of cells overproducing hormones can throw the rest of the body into chaos. And adrenal cancer is one of the worst.

It is a rare disease, striking about one in a million people each year, but adrenal cancer is one of the most deadly. Like most rare diseases, adrenal cancer treatment was hampered by a lack of government funding, industry interest, and the basic challenge of having so few patients to study. But the adrenal cancer community of researchers and patients pulled together, sharing their data and resources.

"The patient groups have galvanized and that has made all the difference," says Gary Hammer, an adrenal cancer researcher at the University of Michigan and an Endocrine Society ambassador.

One crucial insight has come from Brazil where adrenal cancer rates are more than 10 times higher than the rest of the world. A mutation responsible for this boost has been spotted, and that is shining new light on the inner workings of the disease. (See sidebar.)

Chasing an Orphan

The adrenal glands look like a pair of hats worn by the kidneys. Among their many jobs, they are best known for marshalling the body's "fight or flight" response by releasing adrenalin into the bloodstream. But they also produce cortisol in response to stress, aldosterone to regulate kidney function, and androgens for developing and maintaining male and female sex traits. Different cells

ADRENAL Roles

- Marshall the body's "fight or flight" response by releasing adrenalin.
- Produce cortisol in response to stress.
- Produce aldosterone to regulate kidney function.
- Produce androgens for developing and maintaining sex traits.

AT-A-GLANCE:

- Adrenal cancer patient groups and researchers pull together to advocate for treatment.
- When cancer takes root in the adrenal gland, it becomes a lottery of terrible symptoms.
- Researchers are studying insulin-like growth factor 2 (IGF2), β -Catenin, and p53 for potential drug treatments.

within the adrenal gland are responsible for producing each hormone. So when cancer takes root in the adrenal gland, it becomes a lottery of terrible symptoms.

One of the most bizarre outcomes is a sudden outward sex change if androgen levels go off kilter. Both young girls and adult women can suffer virilization, sprouting hair all over their bodies. Boys and men can feminize, growing breasts. If an adrenal cancer overproduces cortisol, the body blows up with fat in strange places. Pads of fat form on the back of the neck like a water buffalo, and the face can swell into a moon. If aldosterone is overproduced, blood pressure goes through the roof.

Having any of these symptoms can be a life-saver for adrenal cancer victims, because they can lead to a quick diagnosis. "But for the rest, it's pretty horrible," says Pierre Val, an endocrinologist who studies adrenal cancer at Clermont University in Aubiere, France. "The unlucky ones just suffer from a diffuse, nonspecific body pain. By the time it is found, the tumor can sometimes be as large as 2 or 3 kilograms. That is so enormous that they often have digestive trouble. By then there is usually nothing to be done for them."

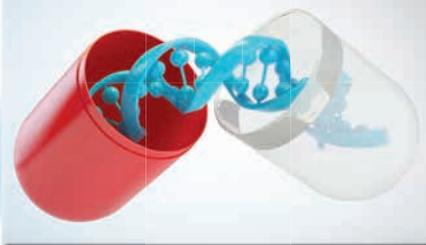
Catching adrenal cancer is among the most aggressive. The adrenal glands have direct access to the heart via the vena cava, so metastatic adrenal cancer cells have a superhighway for reaching the rest of the body. The best way to survive is early diagnosis and surgery.

Pursuing Badly Needed Drugs

But not all adrenal cancer patients are good candidates for surgery. For some, the only option is chemotherapy and a drug called mitotane, the only proven adrenal cancer drug on the shelf. "Mitotane is very toxic," laments Val. "It's a pesticide, a derivative of DDT, and it must be taken orally." The side effects are miserable. And what's

Few DRUG Therapies

Mitotane is currently the only proven adrenal cancer drug on the shelf. However, several small biotech companies have new drugs in development for adrenal cancer, including Atterocor, which should be in phase 1 trials later this year.



worse, it is only barely effective. "A big international trial of chemotherapy and mitotane was published a few years ago. From a scientific point of view, it was pretty scary to see that the efficacy is pretty minor," he says. "You only get about five months of protection and then usually a relapse with a more aggressive tumor."

This is why new drug targets are so badly needed for adrenal cancer. But the hunt for them has really only picked up pace over the

past decade, says Hammer. The main challenge has been the small number of patients. "Until recently, for doctors who saw adrenal cancer it would be the only one they would see in their career." For so-called orphan diseases like these, the motivation just isn't there to spur government research funding or pharmaceutical industry investment.

But over the past decade, the community of adrenal cancer researchers, doctors, and patients has turned their situation upside down. Doctors and patients slashed through red tape to make adrenal tumor samples available for research. Centers of excellence for adrenal cancer treatment have popped up at the University of Michigan, Paris, and elsewhere. And perhaps the biggest coup came last year when the Cancer Genome Atlas chose adrenal cancer as its first rare cancer to sequence. Today adrenal cancer is considered a success story among orphan diseases.

Nonetheless, Val expects a long uphill battle. What is known so far is that several genetic changes occur in adrenal cells before they

"It's clear that controlling IGF2 alone will not be the cure." However, it is clearly involved, and it may be more important in a subset of adrenal cancers. "I am not yet convinced that the IGF story is dead."

— Martin Fassnacht, an adrenal cancer researcher at the University of Munich in Germany



The American Cancer Society estimates approximately 300 adrenal cancer cases each year. "The average age of those found with adrenal cancer is around 45 to 50, but it can happen at any age, even in children. It seems to occur more often in women," according to the American Cancer Society.

Mutation Responsible for MUCH HIGHER ADRENAL CANCER RATES IN BRAZIL

When Ana Claudia Latronica was a PhD student studying adrenal cancer in Brazil in the 1990s, the disease was shrouded in mystery. Adrenal cancer tends to hit people either in childhood or later as adults. The rate of childhood adrenal cancer in southern

Brazil is more than 10 times higher than the rest of the world.

"We thought that a potential environmental factor could be implicated," says Latronica. But the picture changed dramatically when a single mutation was found to be responsible.

Based on population genetics, the mutation seems to have appeared in native populations of southern Brazil about 10,000 years ago. It has stuck around ever since. And the gene that is changed by the mutation is p53, a classic cancer gene.

Latronica was hooked. After finishing her PhD in 1995, she dove into clinical research on adrenal cancer and never looked back. The hope is that some combination of

therapies that target p53 and the other genes known to be involved will save patients from what is usually unavoidable death.

For now, early detection offers the best chance of survival. "The population is aware about the high prevalence of adrenal cancer," says Latronica. "There is an obligatory neonatal genetic test available in the state of Parana. This test is a very controversial issue," she notes. Diagnosing adrenal cancer in children is relatively easy, since it often causes such dramatic problems due to hormonal imbalances. Meanwhile, not everyone who carries the mutation develops the cancer. Revealing the mutation can "sometimes cause panic or serious problems in these families," she says.



become cancerous. "We see the same mutations popping up," says Hammer. That indicates that there is a common set of pathways that new drugs might target.

The three main suspects are insulin-like growth factor 2 (IGF2), β -Catenin, and p53. Both Val and Hammer have been focusing on untangling the roles that these genes play in the disease, and focusing particularly on IGF2 as a drug target. "IGF inhibitors already exist," says Hammer. "They've just been waiting for a disease to treat." Last summer, Val and Hammer published their results within weeks of each other.

"It was a terrible disappointment," says Val. Neither study found that inhibiting IGF2 could stop adrenal cancer's progression. "We were all hopeful, but it's clear that controlling IGF2 alone will not be the cure." However, it is clearly involved, and it may be more important in a subset of adrenal cancers. "I am not yet convinced that the IGF story is dead," says Martin Fassnacht, an adrenal cancer researcher at the University of Munich in Germany. "We have here two patients who have a dramatic partial response [to an IGF inhibitor]." It could be just a stroke of rare good luck for these patients. "However, I am personally quite convinced that it is related to the IGF inhibitor," he says.

The pharmaceutical industry isn't sitting on its hands. Several small biotech companies have new drugs in development for adrenal cancer. One was started by Hammer called Atterocor hopes to be in phase 1 trials later this year.

Even without a cure yet in sight, researchers are giving hope for adrenal cancer patients. "The only way to make progress is to work together to understand the biology of the disease," says Hammer. "We have to work together." **EN**

—Bohannon is a freelance writer in Boston, and a regular contributor to Endocrine News.

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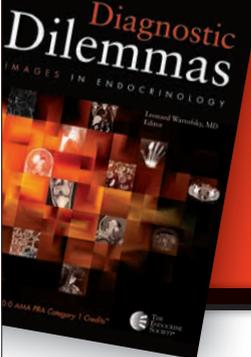


of research and trials are ahead before the gel can be translated into practice.

Though it is yet to be tested for uses beyond cardiovascular issues, the glue may be able to treat other maladies. "This material can be adhered to any region of vasculature where a catheter can reach, so potentially it could treat a number of different conditions, such as stabilizing aneurysms and embolizing tumors," Kastrup says. The current research has focused on painting thin layers over the endothelium, but such afflictions would necessitate larger implants of the glue. Kastrup is optimistic it will be an effective therapy for these conditions and looks forward to testing the theory.

The invention of the synthetic mussel glue functions as a reminder that great breakthroughs can come from unexpected places, such as Alexander Fleming's discovery of penicillin. It is still too soon to know if the mussel glue will revolutionize therapies for atherosclerosis and other vascular damage, but Kastrup and his colleagues are continuing their research. Now working in the Vancouver, British Columbia, area with the ocean and its many bivalves just a stone's throw away, it seems possible that his next big idea might also come from the sea. **EN**

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



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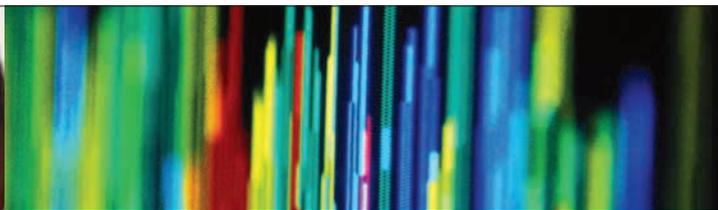
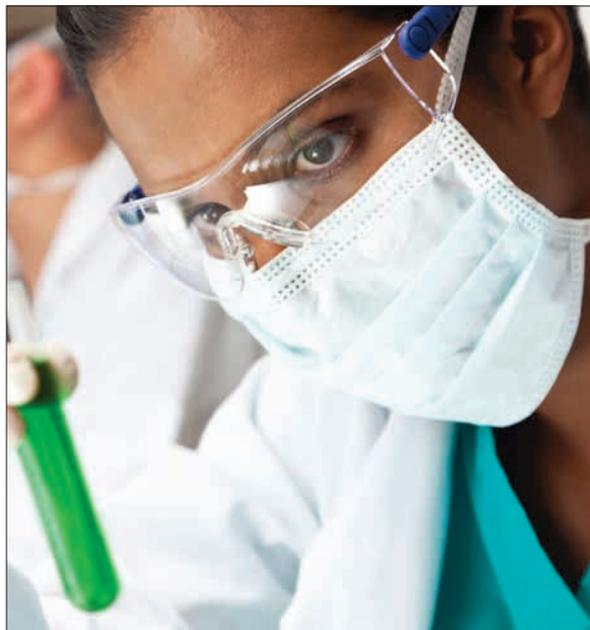
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Society's Agenda Drives Efforts to IMPROVE RESEARCH AND CLINICAL PRACTICE

This year, The Endocrine Society's advocacy agenda intentionally focuses on broad, complex issues that require ongoing effort to influence policy, so it's fairly constant from year to year. As was the case in 2012, biomedical research funding, diabetes, endocrinologist access and reimbursement, endocrinologist workforce issues, minority health disparities, and obesity are the 2013 priorities. The Endocrine Society's Council recently approved the agenda, which was developed by the Society's Advocacy and Public Outreach Core Committee.

In 2013, the Society will develop new strategies and tactics in each of the core areas identified to further advance its goals on behalf of its members.

The Society also will remain active on a number of other, more narrowly focused issues that impact endocrinologists, such as endocrine-disrupting chemicals, bioidentical hormone regulation, DXA payment cuts, rare cancers, women's health issues, and regulatory burdens.

Biomedical Research Funding

Because increasing funding for biomedical research remains a top advocacy priority, the Society will continue to work closely with congressional appropriators and President Obama's administration to advocate for steady, sustainable increases for federal agencies that fund biomedical research and to protect those agencies from the potentially devastating effects of sequestration. The Society will also maintain its leadership role in a number of coalitions that are working toward the same goal.

Diabetes

As the incidence of diabetes continues to rise, endocrinologists must spend an increasing amount of their time treating patients who suffer from diabetes and diabetes-related complications. The Society has consistently worked to address this epidemic by advocating for greater patient and physician education, improved screening programs, increased research funding to identify new treatments, and increased payments to physicians who treat these patients.

Access and Reimbursement

Despite much support among members of Congress to identify a replacement for the Sustainable Growth Rate

(SGR) formula, the \$300 billion cost is a deterrent to many during times of fiscal constraint. Flaws in the SGR are responsible for recurring large physician Medicare payment cuts that must be averted by an annual act of Congress. The Society will continue to be active in the medical community's efforts to replace the SGR and will also devote its energy to other issues that affect patient access to care by endocrinologists.

Workforce Issues

The endocrinologist workforce faces challenges in both its research and clinical arms. Researchers must compete for a dwindling pool of research funds, while working through the numerous regulatory burdens that dictate how they conduct their research. The Society will continue to work closely with the administration, the National Institutes of Health, and other federal agencies to emphasize the importance of endocrine research and its central role in finding treatments and cures for today's most vexing health issues. The Society will also advance its efforts to ease the regulatory burdens associated with research and identify additional funding opportunities.

Physicians are being required to expand their patient loads as the endocrinologist workforce struggles

under increasing demand. The Society will use the findings of its ongoing workforce study to inform policymakers and to identify solutions to the projected shortage of endocrinologists. The Society will also maintain its commitment to advocating for payments that recognize the value of care provided by endocrinologists.

Minority Health Disparities

Endocrine diseases and disorders are among those with the highest degree of disparities in prevalence and outcomes between minority groups and non-minorities, and the Society has long played an active role in public policy designed to address health-care disparities. In follow-up to its 2007 white paper on minority participation in clinical research, the Society has solidified its position as a thought leader on health disparities through the publication in 2012 of a Scientific Statement on health disparities in endocrine disorders.

Moving forward, the Society will focus on advancing the recommendations of the white paper and Scientific Statement as well as the goals that were identified through the March 2013 Reducing Health Disparities in Type 2 Diabetes Mellitus Summit.

Obesity

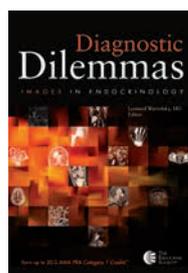
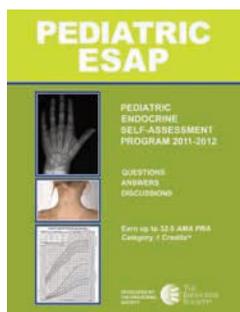
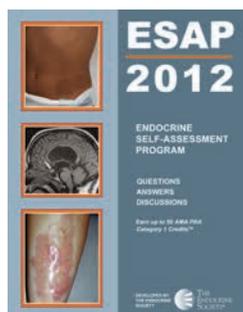
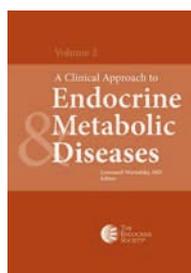
The Society has been a leading resource for legislators since the issue of obesity was first addressed in Congress. Through the Society's position statement on pediatric obesity, the Society will continue to work with policymakers to implement meaningful changes.

Through its advocacy work, the Society has established itself as one of the preeminent sources of information on these issues, and it will continue to build awareness about issues that impact endocrinologists and the patients that they treat. Watch for future updates on these issues in *Endocrine Insider*, and for opportunities to get involved in grassroots advocacy. **EN**



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question on page 21

The answer is:

D. Initiate medical therapy with a mineralocorticoid receptor antagonist

Measurement	Right Adrenal Vein	Inferior Vena Cava	Left Adrenal Vein
Aldosterone, ng/dL	3200	40	1600
Cortisol, µg/dL	1000	20	500



Aldosterone-producing adenoma (APA) and bilateral idiopathic hyperaldosteronism (IHA) are the two most common subtypes of primary aldosteronism—APA accounts for approximately 35 percent of cases and bilateral IHA accounts for approximately 60 percent of cases.

In patients with APA, unilateral adrenalectomy normalizes potassium levels in those who have hypokalemia on presentation, improves blood pressure in all, and normalizes blood pressure in approximately 30 percent to 60 percent. In patients with IHA, unilateral or bilateral adrenalectomy seldom corrects hypertension; thus, these patients should be treated medically with a mineralocorticoid receptor antagonist. In addition, lifelong treatment with a mineralocorticoid receptor antagonist is a reasonable alternative treatment strategy in patients with APA who are unwilling to undergo surgery, are elderly, or are afflicted by comorbid conditions that preclude the surgical option.

The treatment goals are to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage from aldosterone excess. Thus, a key diagnostic step in patients who want to pursue a surgical cure for primary aldosteronism is to distinguish

between APA and IHA.

Because of the efficient mineralocorticoid synthetic processes, APAs can be small (less than 1 cm in diameter) and still cause clinical hyperaldosteronism. Thus, because of their small size, APAs may not be morphologically detectable on adrenal-directed CT or MRI. In addition, IHA adrenal glands may appear normal on CT or show nodular changes. To confuse the picture even more, the development of adrenocortical nodularity is common in healthy persons and is, in part, a function of aging. Thus, it is impossible for a clinician to know whether a solitary adrenal nodule observed on CT in a patient older than 40 years with primary aldosteronism has any role in the pathogenesis of the aldosterone excess—it may be an APA or it may be a nonfunctioning cortical nodule (thus, in this patient with a 7-mm right adrenal cortical nodule, laparoscopic adrenalectomy [Answers A and E] is incorrect).

If such a patient wants to pursue a surgical cure of primary aldosteronism, additional testing is required to determine the source of excess aldosterone secretion. Adrenal venous sampling (AVS) is essential to direct appropriate therapy in many patients with primary aldosteronism who have a high probability of having APA and who seek a potential surgical cure.

This patient has confirmed primary aldosteronism. CT shows a 7-mm cortical adenoma in the right adrenal gland. AVS was indicated on the basis of the patient’s desire for surgery and CT’s inaccuracy. The AVS findings in this patient are consistent with IHA, and medical therapy with a mineralocorticoid receptor antagonist (Answer D) is the correct answer. There are two steps in interpreting AVS data. First, the clinician must confirm that both adrenal veins were successfully catheterized. With the continuous cosyntropin infusion protocol, the gradient in cortisol from the adrenal vein to the inferior vena cava is more than 5:1 (indeed, it is usually >10:1). If the cortisol gradient between an adrenal vein and the inferior vena cava is absent, then that adrenal vein was not successfully catheterized and the AVS data are useless in most cases. In this patient, the adrenal vein to inferior vena cava cortisol gradients were 50 on the right and 25 on the left. Thus, AVS in this patient was successful, and another AVS (Answer B) is not needed. When both cortisol and aldosterone autonomous secretion from an adrenal adenoma is suspected (e.g., if the 1-mg dexamethasone suppression test results in this patient were abnormal), then adrenal venous epinephrine concentrations may be used to document successful adrenal vein sampling.

The cortisol concentration from the left adrenal vein is usually lower than the cortisol concentration from the right adrenal vein because of the diluting effluent from the inferior phrenic vein on the left. The second step in analyz-

ing AVS data corrects for the dilution of the blood sample from the left adrenal vein—the adrenal vein aldosterone concentrations are divided by their corresponding cortisol concentrations. (The aldosterone to cortisol ratios in this patient were 3.2 on the right and 3.2 on the left.) The aldosterone to cortisol ratio from the high-side adrenal vein is divided by the aldosterone to cortisol ratio from the low-side adrenal vein ($3.2 \div 3.2 = 1.0$). Unilateral aldosterone excess is confirmed when the high-side adrenal vein aldosterone to cortisol ratio is more than four times higher than that of the low-side adrenal vein. AVS data are consistent with bilateral IHA when the high-side adrenal vein aldosterone to cortisol ratio is less than three times higher than that of the low-side adrenal vein. Ratios between 3:1 and 4:1 are an overlap zone between APA and IHA. In this patient, the cortisol-corrected adrenal vein aldosterone ratio was 1:1 (right-to-left), thus consistent with bilateral IHA. The right adrenal nodule was a nonfunctioning adrenal incidentaloma. Blood pressure markedly improved with the addition of a mineralocorticoid receptor antagonist (Answer D).

The 6β - 131 I-iodomethyl-19-norcholesterol (NP-59) scintigraphy (Answer C), performed with dexamethasone sup-

pression, has the advantage of correlating function with anatomic abnormalities. However, the sensitivity of this test depends heavily on the size of the adenoma. Because tracer uptake is poor in adenomas smaller than 1.5 cm in diameter, it is usually only helpful in determining whether unilateral aldosterone production is present in patients with bilateral adrenal macroadenomas. NP-59 scintigraphy is often not helpful in interpreting the clinical significance of micronodular findings observed on high-resolution CT.

In addition to its poor sensitivity, other reasons that NP-59 scintigraphy is rarely used in the U.S. include the following: (a) this methodology is not approved by the U.S. Food and Drug Administration, and its use requires institutional review board approval; (b) dexamethasone is administered at 1 mg every 6 hours starting 7 days before the NP-59 injection and is continued throughout the scanning period; (c) imaging starts on day 4 after the NP-59 injection and may continue daily through day 10; (d) a lateralizing scan can be seen in adrenal cortical adenomas that do not secrete aldosterone; and (e) no centers in the United States currently offer NP-59 scintigraphy. NP-59 is available and used in other countries to assist with the subtype evaluation of primary aldosteronism. **EN**

SWAN REPOSITORY

STUDY OF WOMEN'S HEALTH ACROSS THE NATION



The SWAN Repository has serum, plasma, urine, DNA and immortalized cells available to the scientific community as a resource for implementing studies of the health of women at the mid-life. SWAN is a longitudinal study of more than 3000 African American, Caucasian, Chinese, Hispanic and Japanese women focusing on the menopausal transition. The SWAN study is now finishing the 13th annual follow-up visit and provides rich multi-disciplinary data on these women, including bone, cardiovascular, cognitive function, physical function, sleep, depression, health behaviors and more.

- Serum, plasma, and urine specimens have been collected at annual visits.
- A subset of 800 women have provided daily urine samples during one menstrual cycle each year until reaching postmenopause. Known as the DHS (Daily Hormone Study), these samples provide unique and valuable research opportunities.
- The SWAN Repository also includes DNA and immortalized B-lymphocyte cells on a subset of 1538 women, suitable for studies of both proteomics and genomics.

Over 1.7 million total SWAN Repository samples are available for release. These samples are linked to and described by more than 20,000 variables – catalogued in an open, searchable online database at: datawarehouse.swanrepository.com. Find more information there or by email at: swanrepaadmin@umich.edu.





UNDERGRADUATE ENDOCRINOLOGY Course Directors Gather for Inaugural Meeting at ENDO 2013

For those who teach undergraduate medical students, The Endocrine Society will convene the first-ever **Endocrine Educators Forum** during ENDO 2013. The event, planned for June 16, 2:15-3:15pm, will feature group discussions of shared resources for disseminating curricula and teaching tools to support the undergraduate learner.

Graham McMahon, MD, program director at Harvard Medical School, describes the meeting as “an excellent opportunity to lay the groundwork for a new support network for clinical and basic science undergraduate course directors to share teaching resources and best practices.”



NEW FACT SHEET ON TRAUMATIC BRAIN INJURY

The **Hormone Health Network's** latest patient education fact sheet, **Traumatic Brain Injury: Effects on the Endocrine System**, is now available for download at www.hormone.org.

Traumatic brain injury (TBI) is a leading cause of death and disability in young adults living in industrialized countries, affecting 1.7 million Americans annually. Endocrine complications, such as hypopituitarism, can significantly impact the progress and outcomes of rehabilitation for survivors.

The new fact sheet defines TBI and explains how hormone function may be disrupted in a person with TBI, depending on the injury.

Maintenance of Certification at The Endocrine Society

World Leaders In Diabetes, Endocrinology & Metabolism



Stumped by MOC?

For board-certified endocrinologists, the **Maintenance of Certification (MOC)** process can feel overwhelming. ENDO 2013 would like to make it a little easier. Check out the MOC Made Easy session, June 17, 2-3pm, where you can learn more about the process for initial certification or recertification.

The session will share the latest news from the American Board of Internal Medicine and the American Board of Pediatrics MOC programs, as well as highlight lessons learned by members recently engaged in the recertification and initial certification processes.

Event CALENDAR

APRIL 11-13: SAN FRANCISCO
American College of Physicians (ACP)
<http://im2013.acponline.org/>

APRIL 20-24: BOSTON
Experimental Biology 2013
<http://experimentalbiology.org>

APRIL 27-MAY 1: COPENHAGEN, DENMARK
European Congress of Endocrinology
<http://www.ece2013.org/>

MAY 1-5: PHOENIX
American Association of Clinical Endocrinologists (AACE)
<http://am.aace.com/>

MAY 4-7: WASHINGTON, DC
Pediatric Academic Societies (PAS)
http://www.pas-meeting.org/2013DC/future_meetings.asp

MAY 4-8: NEW ORLEANS
American Congress of Obstetricians and Gynecologists (ACOG)
http://www.acog.org/About_ACOG/ACOG_Departments/Annual_Clinical_Meeting



SAWIN LIBRARY MAKES BOOKS AVAILABLE FOR LOAN

The Clark T. Sawin Memorial Library houses over 4,500 books. Visit www.endo-society.org/about/sawin and request books by contacting the Endocrine Society's librarian at librarian@endo-society.org.

IN MEMORIAM

The Endocrine Society is saddened by the passing of the following long-time members: **John E. Jones, MD**, of Midlothian, Virginia; **Erlio Gorpide, PhD**, of Chester, Connecticut; and **Dr. Charles Eugene (Gene) Jackson** of Carmel, Indiana.

INAUGURAL FLARE PROGRAM A SUCCESS



The inaugural FLARE Program is off to a brilliant start, according to FLARE awardees. At the FLARE

Workshop in San Diego January 25-26, students and fellows networked with faculty and received hands-on instruction and thoughtful advice in areas ranging from job hunting to conflict resolution. Now, winners of the FLARE Mentoring Network Travel Award are gearing up to visit their mentors in-person. The award covers the costs of travel so that students and fellows can stretch their professional horizons beyond their home institutions. Finally, the program is preparing to place FLARE interns into Society governance committees for the 2013-2014 service year. To learn more about this exciting program and how you can take part next year, visit www.endo-society.org/FLARE.



Michelle Rivera-Vega, MD, is a clinical fellow at Children's Hospital of Pittsburgh. Lindsey Trevino, PhD, is a postdoctoral fellow at Baylor College of Medicine. "It was a truly amazing experience," says Trevino.

Journal FOCUS: Direct access to endocrine disorder content

Launching this month is the **Journal of Clinical Endocrinology and Metabolism (JCEM) Diabetes Focus**, the first of several microsites collating journal content on various endocrine disorders. The **JCEM Diabetes Focus** maximizes discoverability of patient care articles and clinical reviews.

"Readers look to *JCEM* for the latest advances in diabetes management," says Dr. Leonard Wartofsky, *JCEM* editor-in-chief, "and visitors to the diabetes microsite will enjoy up-to-date and important information relevant to their interest in diabetes."

Not only does the **JCEM Diabetes Focus** provide links to articles published in *JCEM*, it also includes links to relevant content published in the Society's other journals. All articles listed on the Focus are freely accessible. Additionally, the Focus automatically updates as new articles in the subject area are published in the journal.

Although April is the launch for the **JCEM Diabetes Focus**, microsites are in development for *Endocrinology*, *Endocrine Reviews*, and *Molecular Endocrinology*. Reproduction, neuroendocrinology, and physiology are some of the Focus topics.

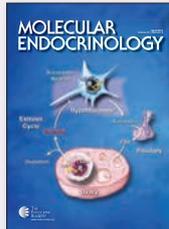
Accessing the **JCEM Diabetes Focus** is easy. Simply visit jcem.endojournals.org and click on the button next to the journal cover to connect to the **Diabetes Focus**.

The following studies, among others, will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals at www.endo-society.org.



Oral vitamin D3 raises prostate calcitriol levels (level 1 evidence) and modestly lowers both PSA and PTH, justifying continued clinical research. Dennis

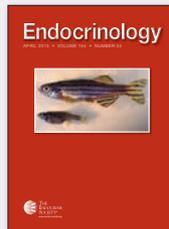
Wagner, Dominique Trudel, Theodoros Van der Kwast, Larisa Nonn, Angeline Antonio Giangreco, Doris Li, Andre Dias, Monique Cardoza, Sanda Laszlo, Karen Hersey, Laurence Klotz, Antonio Finelli, Neil Fleshner, and Reinhold Vieth. *Randomized Clinical Trial of Vitamin D3 Doses on Prostatic Vitamin D Metabolite Levels and Ki67 Labeling in Prostate Cancer Patients.*



ARF has novel function in modulation of AR transactivation in PCa. Wenfu Lu, Yingqiu Xie, Yufang Ma, Robert J. Matusik, and Zhenbang Chen.

ARF Represses Androgen Receptor Transactivation in Prostate Cancer.

Feng Cai, Yong Yao, Yakun Yang, Ming Feng, Kan Deng, Guiling Li, Wenbing Ma, Bing Xin, Wei Lian, Guangya Xiang, Bo Zhang, and Renzhi Wang. *Antiproliferative, Antiinvasive, and Proapoptotic Activity of Folate Receptor α -Targeted Liposomal Doxorubicin in Nonfunctional Pituitary Adenoma Cells.*



Cancer-Oncogenes: FR α plays a critical role in mediating the antitumor effect of F-L-DOX.

Xiaohai Liu, Sihai Ma, Congxin Dai,



Franck Mauvais-Jarvis, Deborah J. Clegg, and Andrea L. Hevener. *The Role of Estrogens in Control of Energy Balance and Glucose Homeostasis.*

DRUM ROLL ANNOUNCING THE 2013 ELECTION RESULTS

The Endocrine Society's Nominating Committee is pleased to announce the results of the 2013 Election that concluded on March 3, 2013. Congratulations to the following Society leaders who will assume their new positions at the Society's Annual Business Meeting on June 18, 2013 during ENDO 2013 in San Francisco.

President-Elect (Clinical Scientist)
Richard Santen, MD

Vice President (Physician-in-Practice)
Susan Mandel, MD, MPH

Council (Basic Scientist Seat)
Diane Robins, PhD

Council (At Large Seats)
Ana Latronico, MD, PhD
Mitchell Lazar, MD, PhD



www.endo-society.org/membership/election.cfm



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

Washington Endocrinologist:

Group Health Permanente, the Pacific Northwest's top-rated multi-specialty group, is currently seeking a BC/BE Endocrinologist to join our Group Practice. Group Health is dedicated to providing comprehensive, innovative, and patient-centered care to our patients. We lead the nation in EMR integration. We are looking for an additional provider to join our Endocrinologists in a stimulating setting. This provider will help to expand our Endocrinology services in the Seattle area with circuit-riding to Tacoma. 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. For additional information regarding this position or to submit your CV, please visit our website at www.grouphealthphysicians.org.

Virginia Mason Medical Center, Seattle, WA:

Endocrinologist for superb endocrinology team. Thyroid disease program and outstanding surgical support. Consultative practice with interesting Endocrine disorders. Regional referral center. Robust internal medicine residency and opportunity to teach. ADA-recognized diabetes education and insulin pump programs, and Diabetes Clinical Research Unit. CV to gail.donovan@vmmc.org.

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JOBS SUPPLEMENT AND BONUS DISTRIBUTION AT ENDO 2013

- Place a print ad in the *ENDO 2013 Jobs Supplement* (\$450 for unlimited text) and also benefit from a free 90 day job posting on our website. Two great ways to get your ad in front of the most qualified job seekers.
- Advertise in the June issue of *Endocrine News* or *The Journal of Clinical Endocrinology & Metabolism (JCEM)* and receive bonus distribution at ENDO 2013 — June 15–18, in San Francisco. **DEADLINE: April 23, 2013.**
- Stop by EndoCareers® in The Endocrine Society booth and pick up your BLUE DOT. Let everyone know you are looking for excellent job candidates!



WWW.ENDOCAREERS.ORG

CONTACT: Christine Whorton, EndoCareers®
endocareers@endo-society.org | 1.800.361.3906

ENDOCRINOLOGIST



OCHSNER HEALTH SYSTEM in New Orleans is searching for a **BC/BE ENDOCRINOLOGIST to join our staff at Ochsner Baptist Medical Center.**

Candidates with experience or directly from training are welcomed to apply. Areas of interest should include general endocrine disorders, diabetes, and endocrine disorders as related to pregnancy. This position is mainly outpatient based, but will serve a large Ob/Gyn group with significant inpatient consultation. Salary is competitive and commensurate with experience and training.

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

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

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

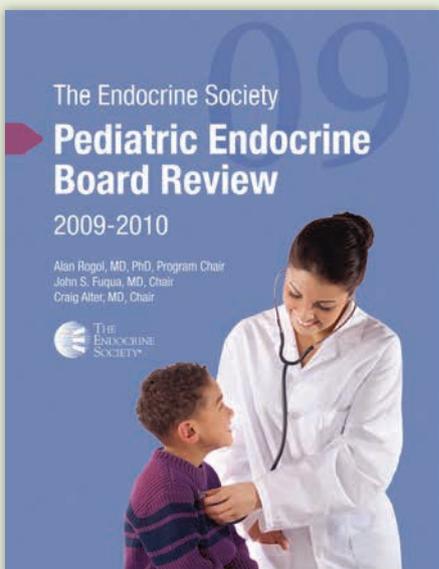
Please email CV to: profrecruiting@ochsner.org, Ref. # ABENDO1 or call 800-488-2240 for more information. EOE.



Sorry, no J-1 visa opportunities available.

Precious Patients, Require Specialty Care

Make sure your patients get the best treatment with these great resources from The Endocrine Society



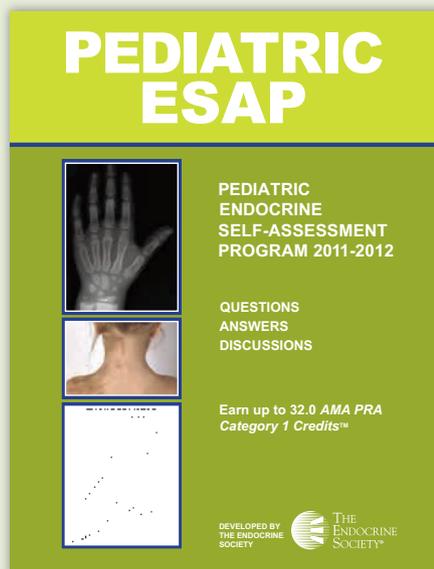
Pediatric Endocrine Board Review (2009-2010) is a distinct resource with 290 questions and detailed answers designed for fellows and clinicians preparing for certification or recertification. Earn up to 12.0 *AMA PRA Category 1 Credits*[™].

Nonmembers: \$190

Members: \$150

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To order visit, www.endo-society.org/store



Pediatric ESAP keeps your pediatric endocrinology expertise up-to-date with 100 clinical case vignettes and multiple-choice questions to sharpen your knowledge and evaluate your ability to diagnose and treat pediatric patients. *Pediatric ESAP* includes an online interactive module and printed book. Earn up to 32.0 *AMA PRA Category 1 Credits*[™].

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PEDIATRIC
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September 24-25, 2013

Pediatric Endocrine Board Review

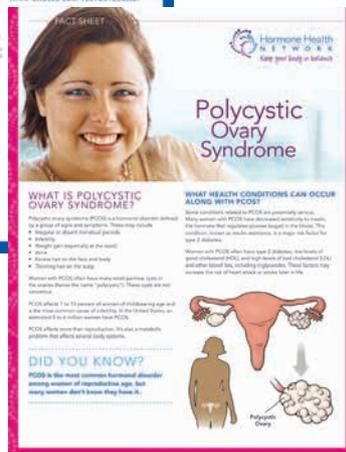
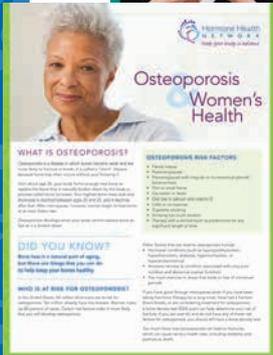
Hyatt Regency New Orleans

New Orleans, LA

For more information visit, www.endo-society.org/PEBR



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Keep your body in balance



Your Partner in Patient Education

The Hormone Health Network joins Society members, health care professionals, patients, and the public in meaningful, informed discussions about hormones and health. Available in both English and Spanish, the Network's bilingual fact sheet series provides patients with accurate, expert-reviewed information on more than 80 endocrine-related topics in an easy-to-understand format.



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

Together, we can move patients from educated to engaged, from informed to active partners in their healthcare.

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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 (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, gastroenteritis viral, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue and pyrexia. GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of; angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Rates of thyroid adverse events - 33.5, 30.0 and 21.7 events/1000 subject years of exposure for liraglutide, placebo and total comparators; Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently reported thyroid adverse events/1000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers:** Victoza® 2 x 3ml pre-filled pens EU/1/09/529/002. Victoza® 3 x 3ml pre-filled pens EU/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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