

# ENDOCRINE<sup>TM</sup>news

## DEEP IMPACT

Fracking uses hundreds of chemicals, many of which may have adverse effects on the endocrine system. However, more research is needed to prove if this process is causing health issues in nearby residents.

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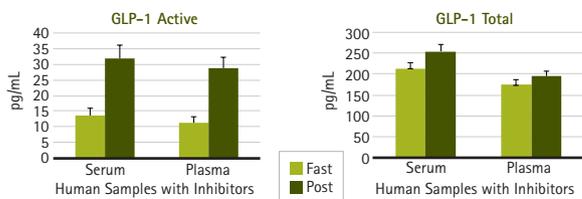
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*By Glenda Fauntleroy*

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## Introducing the New President: **Lisa H. Fish**



Lisa H. Fish, MD

**T**he Endocrine Society is pleased to welcome its president for 2015 — 2016, Lisa H. Fish, MD, FACP, who took office March 9. An endocrinologist at Hennepin County Medical Center in Minneapolis, she sees patients dealing with a wide variety of endocrine issues, from thyroid disease to osteoporosis. Her interests include diabetes, osteoporosis, thyroid and adrenal disease in pregnancy, and hormone abuse, with a particular interest in diabetes issues during pregnancy.

“I am honored to have been elected president of the Endocrine Society,” Fish says. “It is a great privilege to serve in this capacity, and I look forward to working with the talented staff and members as we approach the 100th anniversary of the Endocrine Society.”

Fish succeeds Richard J. Santen, as the Society continues its rotation of presidents who represent its core constituencies: basic researchers, clinical researchers, and clinical practitioners. Fish has been a clinician for more than 20 years. After receiving her medical degree from Brown University and training in internal medicine and endocrinology at the University of Minnesota, she went to San Diego and did a year of diabetes work at the University of California, San Diego before returning to Minnesota. “I worked for 20 years at a large private clinic,” she says, “and then about three years ago moved to the Minneapolis county teaching hospital, where I see patients and teach medical students, residents, and fellows.”

Fish first joined the Society nearly 25 years ago, and since then, she has been very active and involved, serving as a member, chair, or liaison to various committees, including the Clinical Affairs Core Committee, the Hormone Health Network Committee, the Hormone Abuse Task Force, the Advocacy and Public Outreach Core Committee, and many others. In those roles, she helped influence and shape clinical endocrinology. For instance, while serving on the Hormone Health Network Committee, she played a pivotal role in helping the foundation become a leading source of hormone-related health information for the public through its patient-oriented website, bilingual fact sheets, and Clinical Guideline summaries. Fish has also served on council and as vice president, in addition to winning many Society awards, including the Sidney H. Ingbar

Distinguished Service Award and the Distinguished Physician Award.

Fish’s dedication to her work is apparent, and she says it’s the challenges and the rewards that come from overcoming those challenges that first drew her to endocrinology. “I love figuring out what is wrong and why,” she says, “and endocrinology is full of disorders with mechanisms that have been worked out and are treatable. It is a very rewarding specialty and keeps me constantly challenged.”

As president, with all of her experience and love of a good puzzle, Fish is starting an initiative to serve young patients with diabetes in areas where education and treatments are scarce. “I am starting a social responsibility program called Endo Cares in which we provide services of education, medications, and ongoing involvement to improve the care of young people with diabetes in underserved areas,” she says. “We will be starting in 2016 with diabetes camps in several countries and plan to involve all segments of our society in the program.”

**“I am starting a social responsibility program called Endo Cares in which we provide services of education, medications, and ongoing involvement to improve the care of young people with diabetes in underserved areas,”** says Fish. “We will be starting in 2016 with diabetes camps in several countries and plan to involve all segments of our society in the program.”

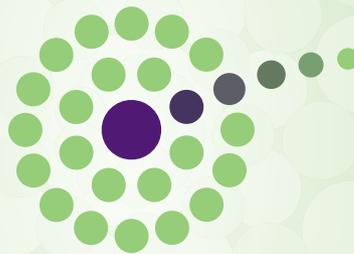
Fish envisions a bright future for the Society, one in which it at once expands and focuses, and helps shape the future generations of endocrinologists. “The Endocrine Society is strong and growing, with over 18,000 members in over 120 countries,” she says. “We want to continue to strengthen our international programs, to focus on obesity as an important clinical area, to work on

knowledge integration of our extensive written materials, to develop the curriculum for endocrine fellowship training, and to continue to improve our endocrine publications and scientific and clinical meetings.”

Fish also sees opportunity for more collaboration with other endocrine organizations, since everyone in that field is working toward the same goal. “We want to build strong partnerships with other endocrine organizations both in the U.S. and abroad and to work closely with them in the many areas where we can accomplish more as a united voice,” she says. **EN**

Lisa H. Fish, MD, FACP  
President, Endocrine Society

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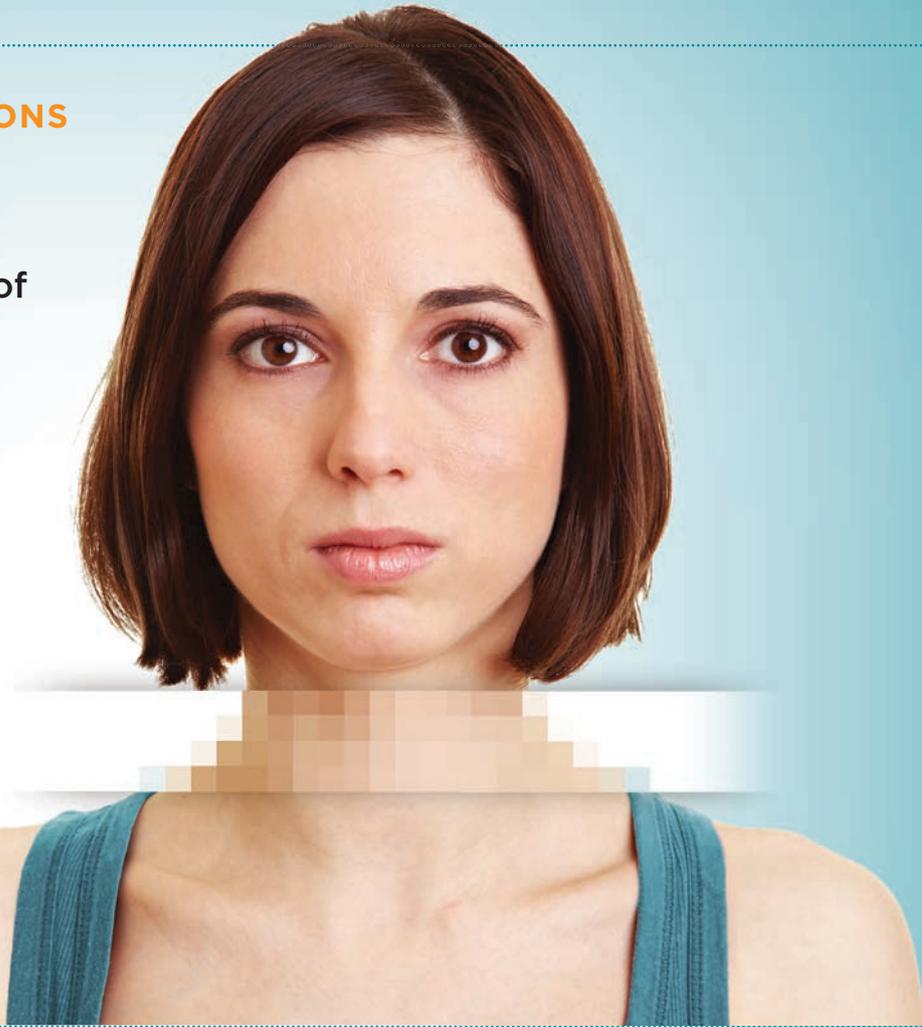
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1. Beaudenon-Huibregtse S, Alexander EK, Guttler RB, et al. Centralized molecular testing for oncogenic gene mutations complements the local cytopathological diagnosis of thyroid nodules [published online ahead of print June 18, 2014]. *Thyroid*.
2. Ferraz C, Eszlinger M, Paschke R. Current state and future perspective of molecular diagnosis of fine-needle aspiration biopsy of thyroid nodules. *J Clin Endocrinol Metab*. 2011;96(7):2016-2206.

APRIL 2015

# ENDOCRINE NEWS

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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

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

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This month's cover story is about a topic that has gotten a lot of attention in the mainstream media — fracking. Associate editor Derek Bagley hones in on this topic in his article, “Deep Impact” (p. 12), as fracking applies to endocrine-disrupting chemicals. The hundreds of chemicals used in this process are possible endocrine-disrupting chemicals, but linking fracking with the adverse health effects of nearby residents has still proven to be somewhat elusive. Endocrinology editor-in-chief Andrea Gore, PhD, says that while some may argue that the chemicals used in fracking are diluted, “endocrinologists are aware that even very low dose exposure to endocrine-disrupting chemicals can have effects in the bodies of exposed individuals.” However, all the researchers quoted in the article agree that future studies are needed to conclusively prove whether or not fracking is harmful to the people, animals, plant life, and water in close proximity to these drilling sites.

On page 16, Glenda Fauntleroy explores a topic that has many endocrinologists and primary care physicians who treat diabetic patients very concerned: the use of alternative medicines. In “A La Carte: Dietary Supplements and Diabetes,” she reports that research shows that most patients who take these supplements neglect to report them to their physicians, which could result in troubling outcomes, especially if the patients are getting their complementary and alternative medicines from less-than-reliable sources. Brent A. Bauer, MD, director of the Complementary and Integrative Medicine Program at the Mayo Clinic in Rochester, Minn., says that it is imperative for physicians to ask their patients about these substances. “Much better for us to be directly involved in helping make sure they have solid information so they can make an evidence-based and informed decision” about whether or not to use these alternative medicines.

If you have an MBA or other business degree in addition to your MD or PhD, you possibly have a competitive advantage over your colleagues, according to “Mixing Business and Medicine” by Melissa Mapes (p. 26). Aside from information from the book *Private Practice: What You Don't Learn as a Resident* by Society member Elliott G. Levy, MD, the article also has a number of business resources specifically for physicians. Moving from the office to the lab, we are debuting a new type of Laboratory Notes article this month, featuring a Q&A with a researcher (p. 30). This month, *Endocrine News* interviews Sarat Chandralapaty, MD, PhD, about his work with genetic mutations and breast cancer, and what impact it could have on the field of endocrinology.

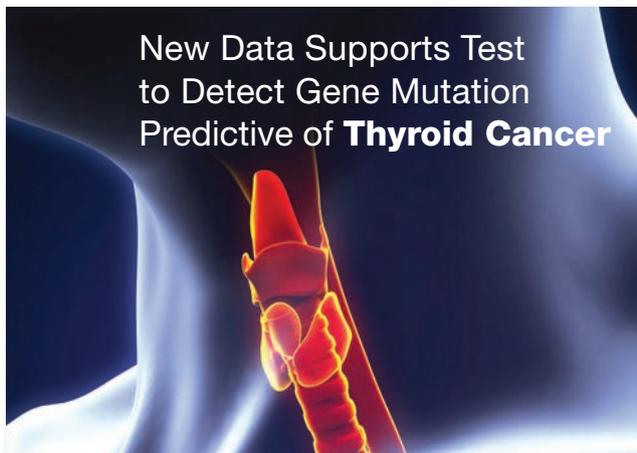
I hope the more than 8,500 of you who attended ENDO 2015 in sunny San Diego have recovered, and for those of you who weren't able to make it, we will be running a “highlights” article next month. Feel free to contact me with any comments or suggestions at [mnewman@endocrine.org](mailto:mnewman@endocrine.org). EN

Mark A. Newman,  
Editor, Endocrine News



Mark A. Newman

By Derek Bagley



**New Data Supports Test to Detect Gene Mutation Predictive of Thyroid Cancer**

A new preoperative molecular malignancy classifier for identifying BRAF V600E mutation status among thyroid nodule biopsies has been shown to be clinically valid, according to a study recently published in *Proceedings of the Pacific Symposium on Biocomputing*. The data from the study show that the classifier detects the BRAF V600E mutation — often predictive of papillary thyroid cancer (PTC) — with high diagnostic accuracy. This new test is marketed as Afirma BRAF by Veracyte, Inc., and is part of a broader offering that centers on a genomic test to identify benign thyroid nodules among those deemed indeterminate by cytopathology to enable these patients to avoid unnecessary surgery.

When surgery is warranted, preoperative identification of BRAF V600E in thyroid nodule fine needle

aspiration biopsies (FNABs) may enable physicians to better assess individual patients' risk of cancer and determine the most appropriate surgical strategy, such as whether to perform a total or partial thyroidectomy. PCR- or sequencing-based DNA analysis is often limited by the need for a DNA quantity that is difficult to procure from an FNA biopsy.

Researchers led by Giulia C. Kennedy, PhD, chief scientific officer and senior vice president of research, product, and clinical development at Veracyte, evaluated 535 FNA samples using both its Afirma RNA-based classifier and a sensitive, standard PCR DNA-based test. The Afirma BRAF RNA-based classifier accurately determined the presence or absence of the BRAF V600E DNA mutation with equal performance but with a lower non-diagnostic rate than the DNA-based test (7.6% vs. 24.5%). According to the authors, since Afirma BRAF uses a genomic expression signature associated with altered BRAF signaling, it has the potential to detect BRAF mutations other than V600E, giving it a broader clinical utility.

The authors concluded, "Afirma BRAF accurately determined the presence or absence of the BRAF V600E DNA mutation in FNABs, a collection method directly relevant to solid tumor assessment, with performance equal to that of an established, highly sensitive DNA-based assay and with a lower nondiagnostic rate. This is the first such test in thyroid cancer to undergo sufficient analytical and clinical validation for real-world use in a personalized medicine context to frame individual patient risk and inform surgical choice."

**Novel Drug Candidate Regenerates Pancreatic Cells Lost to Diabetes**

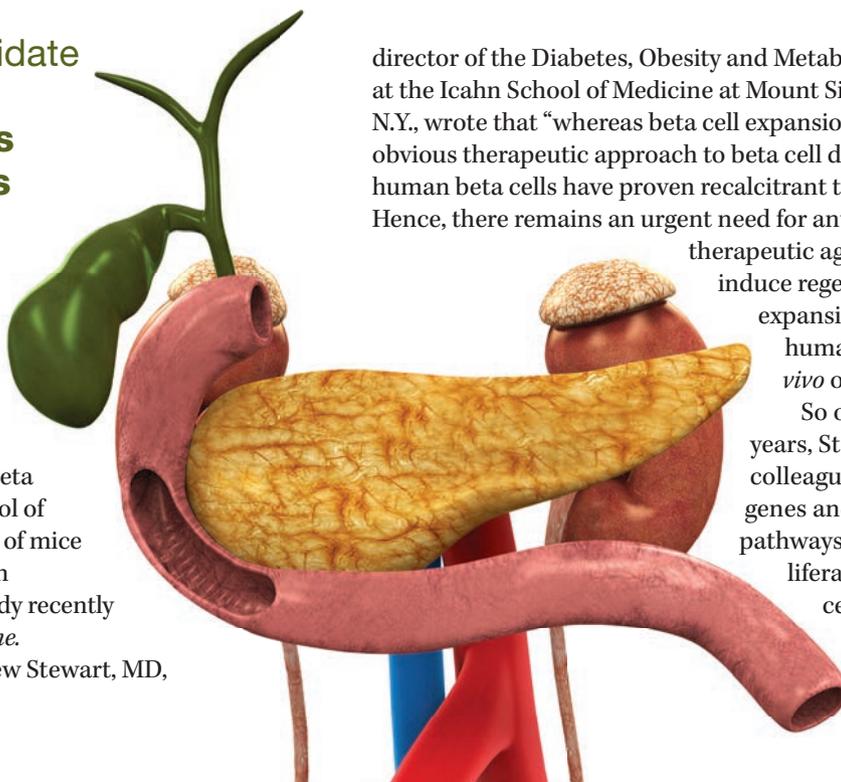
After a screen of more than 100,000 chemicals, harmine emerged as a drug class that drives the sustained division and multiplication of adult human beta cells in culture and tripled the number of beta cells and led to better control of blood sugar in three groups of mice engineered to mimic human diabetes, according to a study recently published in *Nature Medicine*.

Researchers led by Andrew Stewart, MD,

director of the Diabetes, Obesity and Metabolism Institute at the Icahn School of Medicine at Mount Sinai, New York, N.Y., wrote that "whereas beta cell expansion seems an obvious therapeutic approach to beta cell deficiency, adult human beta cells have proven recalcitrant to such efforts. Hence, there remains an urgent need for antidiabetic

therapeutic agents that can induce regeneration and expansion of adult human beta cells in vivo or ex vivo."

So over several years, Stewart and his colleagues unraveled genes and signaling pathways that drive proliferation of beta cells, and then confirmed proposed



## Interventions Lower Diabetes Risk in Women Who had Gestational Diabetes

Women with a history of gestational diabetes face a heightened risk of developing type 2 diabetes for years after giving birth, but intensive lifestyle intervention or a medication regimen can have a protective effect in this population, according to a study recently published in the *Journal of Clinical Endocrinology & Metabolism*.

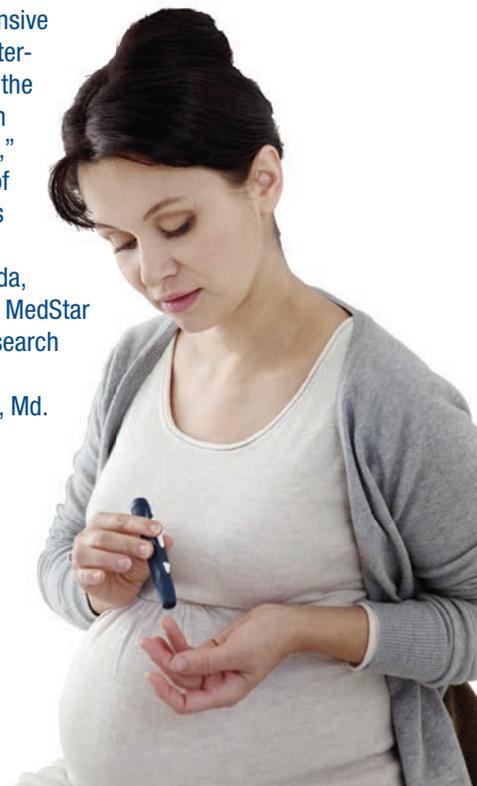
The Diabetes Prevention Program Outcomes Study (DPPOS) analyzed long-term metabolic health in 288 women who had a previous diagnosis of gestational diabetes and 1,226 mothers who did not have a history of the condition. The women all participated in the initial DPPOS, a randomized clinical trial where they were assigned to intensive lifestyle intervention, the diabetes medication metformin, or a placebo. The intensive lifestyle intervention was aimed at reducing body weight by 7 percent and participating in moderate cardio exercise for 150 minutes a week.

During the DPPOS, the women continued to have their blood

glucose levels measured twice a year for six years. The study looked at long-term health outcomes in participants for about a decade after the women first enrolled in the study. Women with a history of gestational diabetes who were assigned to take the medication metformin or undergo the intensive lifestyle intervention were less likely to develop type 2 diabetes than women who received the placebo. When they were assigned the placebo, women who had a history of gestational diabetes had a 48.0% higher risk of developing diabetes compared to women who were never diagnosed with the condition. Women who had been diagnosed with gestational diabetes and underwent intensive lifestyle intervention had a 35.2% reduction in their risk of developing type 2 diabetes. The risk was reduced by 40.4% among women with a history of the condition who were assigned to take metformin.

**“Our long-term follow-up study found**

**the elevated risk of developing type 2 diabetes persisted for years in women who had been diagnosed with gestational diabetes, and this long-term risk can be reduced with either intensive lifestyle intervention or the medication metformin,”** says one of the study’s authors, **Vanita Aroda, MD, of the MedStar Health Research Institute in Hyattsville, Md.**



mechanisms with gene therapy. Based on the study results, the team believes a particular enzyme, “dual specificity tyrosine-regulated kinase-1a (DYRK1A),” is the likely target of harmine. With this discovery, DYRK1A, known from past studies to drive cell division in other cell types, becomes a drug development target.

“We found that harmine, likely by interacting with DYRK1A, increases levels of other known drivers of cell division,” says Peng Wang, PhD, assistant professor of Medicine, Endocrinology, Diabetes, and Bone Disease at the Icahn School of Medicine and first author of the paper. “These drivers include the protein c-MYC, the gene for which was the basis of the screen we used to identify harmine as a potential treatment.”

Wang says the team designed a sensor to glow (thanks to a firefly gene) when any compound activated the promoter DNA snippet responsible for turning on the c-MYC gene. Of more than 100,000 compounds analyzed in a high-speed robotic screen, harmine was among 86 that caused the brightest glow and was the only one of

these that caused beta cell proliferation. The c-MYC pathway appeared to some researchers to be an unlikely therapeutic target for beta cell regeneration because past studies had found it to cause beta cell death when activated in high doses. However, the current study found that harmine causes only modest increases in c-MYC levels and no beta cell death. The research team will now focus on making changes to the harmine and its relatives (harmaloges) to find drug candidates that target only beta cells.

“Our results provide a large body of evidence demonstrating that the harmine drug class can make human beta cells proliferate at levels that may be relevant for diabetes treatment,” says Stewart, who is a former Annual Meeting steering committee chair, past council member, past secretary-treasurer, and “longtime fan” of the Endocrine Society. “While we still have a lot of work to do in improving the specificity and potency of the harmine and related compounds, we believe these results represent a key step toward more effective future treatment of diabetes.”

## Vitamin D Deficiency Linked More Closely to Diabetes than Obesity



People who have low levels of vitamin D are more likely to have diabetes, regardless of how much they weigh, according to a new study published in the *Journal of Clinical Endocrinology & Metabolism*.

“The major strength of this study is that it compares vitamin D levels in people at a wide range of weights (from lean to morbidly obese subjects) while taking whether they had diabetes into account,” says one of the study’s authors, Mercedes Clemente-Postigo, MSc, of Instituto de Investigación Biomédica de Málaga (IBIMA) at Complejo Hospitalario de Málaga (Virgen de la Victoria) and Universidad de Málaga in Malaga, Spain.

The cross-sectional study compared vitamin D biomarkers in 118 participants at the university hospital Virgen de la Victoria in Malaga as well as 30 participants from the Hospital Universitari Dr.

Josep Trueta in Girona, Spain. All participants were classified by their body mass index (BMI) as well as whether they had diabetes, prediabetes, or no glycemic disorders. Researchers measured levels of vitamin D in the participants’ blood streams and vitamin D receptor gene expression in adipose tissue.

The analysis found that obese subjects who did not have glucose metabolism disorders had higher levels of vitamin D than diabetic subjects. Likewise, lean subjects with diabetes or another glucose metabolism disorder were more likely to have low levels of vitamin D. Vitamin D levels were directly correlated with glucose levels but not with BMI.

“Our findings indicate that vitamin D is associated more closely with glucose metabolism than obesity,” says one of the study’s authors, Manuel Macías-González, PhD, of Complejo Hospitalario de Málaga (Virgen de la Victoria) and the University of Málaga. “The study suggests that vitamin D deficiency and obesity interact synergistically to heighten the risk of diabetes and other metabolic disorders. The average person may be able to reduce their risk by maintaining a healthy diet and getting enough outdoor activity.”

# Fast FACTS About Fracking

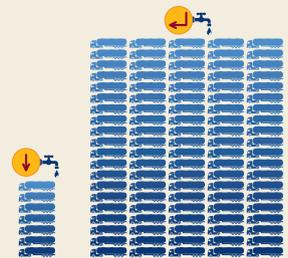


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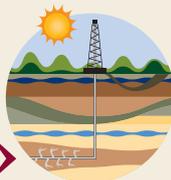
50,000 to 350,000 gallons of water may be required to fracture one well in a coalbed formation while 2 to 5 million gallons of water may be necessary to fracture one horizontal well in a shale formation.



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There are more than 1 million active oil and gas wells in the U.S.

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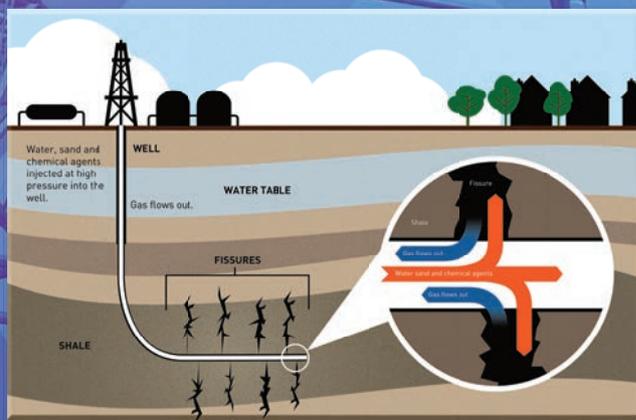


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# DEEP IMPACT

Fracking uses hundreds of chemicals, many of which may have adverse effects on the endocrine system. However, more research is needed to prove if this process is causing health issues in nearby residents.

By Derek Bagley



Garfield County sits in the northwestern quadrant of Colorado, a vast swath of picturesque land that attracts outdoor adventurers and serenity seekers alike. But Garfield County has also become very attractive to those who engage in hydraulic fracturing — fracking — a process that forces sand, millions of gallons of water, and a mixture of chemicals into the earth to extract natural gas and oil from shale. These operations have recently come under closer scrutiny after residents in drilling regions, environmental advocates, and medical investigators expressed concerns about the effects these chemicals have on the air they breathe and the water they drink. Some endocrinologists are especially concerned, since the process involves more than 750 chemicals, many of which are known to disrupt hormone function.

Investigators at the University of Missouri, led by Susan C. Nagel, PhD, and Christopher Kassotis, a doctoral candidate, chose Garfield County, Colo. — an area with more than 10,000 active natural gas wells and a history of accidents and spills — to test fracking's effects on endocrine disrupting activity in water. They hypothesized that the surface and ground water and a

selected subset of chemicals used in natural gas drilling operations there would exhibit endocrine-disrupting activities, namely on estrogen and androgen receptors. “We wanted to think about the worst case scenario to test this idea that drilling might be contaminating surface and/or ground water,” Nagel says.

Some residents may already be experiencing the worst case scenario. “For that first study,” Nagel says, “it was not hard to find people who wanted us to come and sample.”

One of the individuals they talked to, whose property was near a fracking accident site, had a “very severe” contamination of his drinking water, which flowed into a pond at his hunting operation on a plateau. “He came up there in the spring to open up the operation,” Nagel says. “He had a tradition of every time he drove up there from his house down below he’d throw a stick out into the pond, and his dog would go out and get it.”

The dog died a couple of months after the incident that polluted the pond, and the man himself experienced “a lot of short- and long-term health problems” because he drank from the spring that feeds the pond, before realizing it had been contaminated. “Actually, in addition to endocrine-disrupting activity, the pond was the most toxic of any of our samples in that study,” Nagel says. “They have since settled with one of the oil and gas companies.”

“Folks by and large felt like their health was being compromised,” she continues, “[as well as] their pets’ or livestock’s [health].”

### Worthwhile Investigation

Fracking is a very hotly contested issue in the United States. Proponents of the process have pointed to fracking as a boon for local communities, providing jobs and tax revenue, and being partially responsible for the recent dip in gas prices. Fracking is being closely watched as researchers also recognize more and more how the environment influences health and development.

But even the National Institute of Environmental Health Sciences cannot take an official position on fracking, saying that “the short answer is [they] don’t know” whether fracking poses health risks to the people living near drilling sites, since the science is still ongoing and nothing has been proven conclusively. For instance, according to a 2014 paper published in *Environmental Health Perspectives*, in 2009 the U.S. Environmental Protection Agency found evidence that groundwater in Pavillion, Wyo., was contaminated with benzene, xylenes, gasoline range organics, diesel range organics, and total volatile hydrocarbons in shallow wells above 169 gas-producing fracking sites.

The authors, led by Trevor M. Penning, PhD, of the University of Pennsylvania, wrote that the pollution was attributed to 33 nearby surface pits used to store drilling waste water, but since there had been no baseline water quality measurements before the drilling started, it could not be determined for certain whether fracking had caused the pollution.

So harmful chemicals are found in the fracking process, and the people who live near drilling sites may experience health problems, but correlation does not equal causation, and it’s impossible to test on human subjects, for obvious reasons. It’s a worthwhile investigation, though, because the impacts on the public health could be huge.

### “Very Troubling” Findings

The University of Missouri team initially chose five different accident or spill sites to test in Garfield County, rural areas with well water, sparsely populated scenic strips of land — an area called the Grand Valley where mountains rise on either side of the Colorado River. The first site they hiked down to was a property adjacent to a drilling site (fracking had gone on under this property), with a creek where bubbles had started appearing a few years prior. The researchers collected samples from the surface water of the creek there and from the two monitoring wells that had been installed after the bubble incident.

“These were sites that had very dense drilling around them (40–130 plus wells within one mile) and that had experienced some sort of spill of the fracking fluids over the last few years at the site,” Kassotis says. “We then collected samples from within the same shale region but outside the drilling area, and also some here in Missouri.”

### AT-A-GLANCE

- Hydraulic fracturing, or fracking, involves more than 750 chemicals, many of which are known EDCs.
- Researchers are working to determine whether these chemicals adversely affect health outcomes in people who live near fracking sites.
- Future studies are needed to prove conclusively whether fracking is safe or harmful.

“When the industry makes a statement saying that the underground injection [fracking] of these fluids has not been linked to cases of water contamination, **they are sidestepping the numerous surface spills of these fluids and the other routes of contamination present throughout the cradle to grave process. The same goes for health statements.**”

— Christopher Kassotis,  
PhD candidate,  
University of Missouri,  
Columbia, Mo.

For the first study, the team analyzed 12 suspected or known endocrine-disrupting chemicals (EDCs) used in fracking operations to determine just how much these chemicals affected the body's reproductive hormones. They found that the water samples collected from the drilling sites exhibited higher levels of EDC (estrogenic, anti-estrogenic, and anti-androgenic) activity than the samples from the control sites in the drilling-sparse areas of Garfield County and Boone County, Mo., and published their results in the March 2014 issue of *Endocrinology*.

"The strongest case here is that samples taken outside the drilling-dense region that had not experienced spills did not exhibit the activity seen at our oil/gas sites," Kassotis says. "As we expect that other hormonal contributors to water within a region are relatively similar, that is compelling evidence that we may be seeing activity due to the spills. This is further substantiated in that we absolutely biased our sampling in this initial work. These were sites that we knew had spills that had impacted water. So we do suspect that the activity was likely due to fracking operations."

"This finding was very troubling," says Andrea Gore, PhD, of the University of Texas, and editor-in-chief of *Endocrinology*, "because the fracking process uses large volumes of water, and mixing chemicals into the water can contaminate the watershed. While some may argue that the chemicals are diluted, endocrinologists are aware that even very low dose exposures to endocrine-disrupting chemicals can have effects in the bodies of exposed individuals. Furthermore, without knowing much about the nature of these chemicals, it is possible that some are long-lived and may remain in the environment for long periods of time."

Nagel, Kassotis, and their team were careful with their interpretation of the data and made no claims linking the drilling operations to EDC activity. "We cannot say [the observed EDC activity was due to fracking] conclusively until we have done effect-directed analysis work on those samples," Kassotis says. "That is, combining our bioassays in the lab with the work of an analytical chemist to determine exactly which chemicals are contributing to the activity that we observe."

### Adverse Effects

And yet, the evidence of adverse health effects experienced by the residents of these drilling-dense areas in the U.S. is hard to ignore. A study published in *Environmental Health Perspectives* led by Peter M. Rabinowitz, MD, MPH, of Yale University School of Medicine, found that the number of reported health problems was greater in residents living closer to natural gas wells in Pennsylvania than those further away, with skin conditions and upper respiratory symptoms reported most frequently. The interesting thing is that fracking was never mentioned to the participants, only later correlated to distance from the nearest site.

Another study published in *Environmental Health Perspectives* led by Lisa M. McKenzie, of the Colorado School of Public Health in Aurora, found an increased risk of congenital heart defects and neural tube defects in children born to mothers living near natural gas wells during pregnancy. However, the researchers could not determine causation, as they did not have blood levels of these chemicals, though it was controlled for confounders.

The question remains whether these people experience more adverse health outcomes than those in similar regions without fracking, Kassotis says. "There have been anecdotal reports about adverse health effects that span the spectrum — endocrine/fertility, nausea, dizziness, tremors, headaches, nosebleeds, negative birth outcomes, respiratory issues, etc. The controlled work to really see whether these are greater near these operations though, is largely lacking," he says.

### Digging Deeper

After that initial study, the University of Missouri researchers extended their analysis to determine whether the fracking chemicals affected other key hormone receptors besides estrogen and androgen receptors. They repeatedly tested 24 chemicals for EDC activity in human cells and found that 23 of those 24 chemicals block the activity of one or more important hormone receptors, not just androgen and estrogen receptors but glucocorticoid, progesterone, and thyroid hormone receptors as well.

But again, the presence of these chemicals in the samples doesn't prove causation, as Kassotis pointed out when presenting these results at **ICE/ENDO 2014** in Chicago. EDCs are contributed to water from a large number of sources — aquatic organisms that excrete or release hormones, livestock, pharmaceuticals that enter the water after not being removed in wastewater treatment plants, agricultural pesticides run-off, and waste from urban, industrial, and medical areas.

The University of Missouri team's current work has now extended their previous studies to *in vitro* and *in vivo* analyses of the mixtures of chemicals they had previously evaluated — testing several mixtures in estrogen, androgen, thyroid, progesterone, and glucocorticoid receptor reporter gene assays in human breast cancer cells, which they say "has provided evidence of additive antagonist



"While some may argue that the chemicals [used in fracking] are diluted, endocrinologists are aware that even very low dose exposures to endocrine-disrupting chemicals can have effects in the bodies of exposed individuals.

**Furthermore, without knowing much about the nature of these chemicals, it is possible that some are long-lived and may remain in the environment for long periods of time."**

— Andrea Gore, PhD, University of Texas; editor-in-chief, *Endocrinology*

activity for several of these mixtures.” The team is also wrapping up its first large mouse experiment, exposing mice during gestation to a laboratory-created mixture of 23 of the aforementioned chemicals, writing that the “completion of these studies should substantially increase our knowledge of consequences of prenatal exposure to a complex mixture of hydraulic fracturing chemicals and of potential health risks associated with this process.”

They will then move forward with more animal work, as well as more comprehensive water sampling in Garfield County and other drilling regions across the country. The researchers also intend to do effect-directed analysis work with their chemist, Chung-Ho Lin, PhD, moving forward to determine which chemicals are contributing to the observed activity. “Coming out of this I expect we will be in a much better position to judge whether drilling operations are the source of the activity we saw previously,” Kassotis says.

Nagel says that they have mapped out more experiments to take place over the next few years, including trying to pinpoint exactly which chemicals are used that may be causing the endocrine-disrupting activity, expanding the types of endocrine-disrupting activity they’re analyzing, and looking at animal endpoints, with both adult and developmental exposures.

“Once we work through all of this data, we may be able to target specific organs or endpoints going forward to look at in greater detail,” Kassotis says. “For instance, decreased sperm counts in males or decreased follicle counts in females (or altered testes/ovary weights) might suggest impaired fertility. We could absolutely then examine fertility in the animals in a more comprehensive way and work out exactly what is going on.”

## The Role of Research

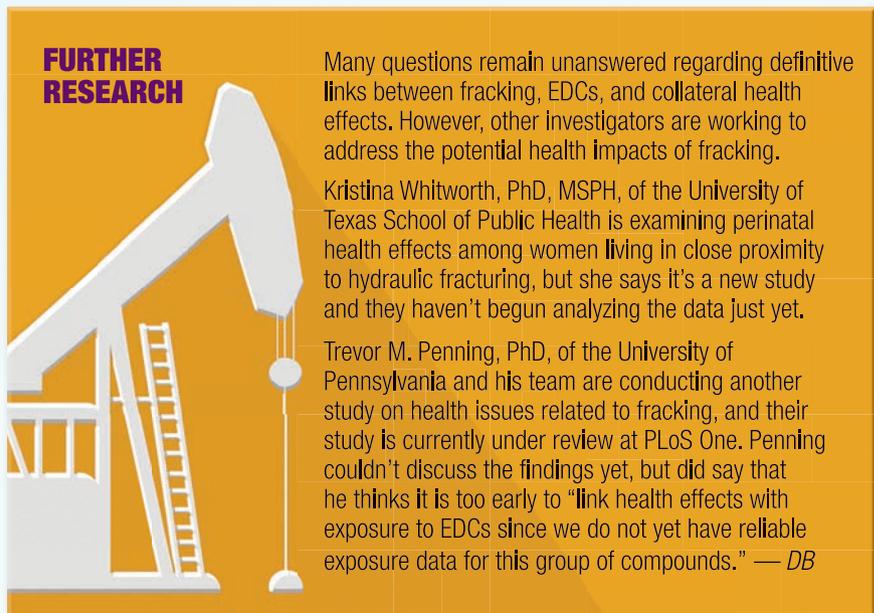
Late last year, New York’s acting commissioner of health, Howard A. Zucker, MD, JD, wrote a letter to Joseph Martens, the commissioner of the New York State Department of Environmental Conservation, describing the need to consider the science regarding High Volume Hydraulic Fracturing (HVHF) and public health risks. Zucker writes that New York’s Department of Health recommends that fracking not proceed in New York until the science provides more conclusive evidence to determine what level of risk to the public health fracking carries.

This is still all very new, and Nagel says these are questions that are “just now being asked.” For the time being, fracking remains a polarizing issue. New York banned fracking after a Public Health Review, and researchers are continuing work on exploring fracking’s effects on human health. But parties interested in these operations continue to produce and air advertisements touting fracking’s safety. And while that may turn out to be true, it’s not the whole story. “Fracking is only one part of the entire process, and chemicals are added throughout the entire drilling and production processes,” Kassotis says. “So when the industry makes a statement saying that the underground injection [fracking] of these fluids has not been linked to cases of water contamination, they are sidestepping the numerous surface spills of these fluids and the other routes of contamination present throughout the cradle to grave process. The same goes for health statements.”

Indeed, the researchers don’t necessarily want to end natural gas drilling; they just want to make certain that drillers are going about it as intelligently as possible. During the Missouri team’s most recent trip, while meeting with landowners to coordinate sampling efforts, Kassotis says, one of the residents made the comment that they felt it was important to say they were not so-called “fracktivists.”

“They were just interested in having clear information on potential health risks, chemicals used, and greater overall transparency from industry,” he continues. “In a way, that’s how I view the role of research — to help fill those gaps, inform the public, and to help industry adjust methods, when necessary, to achieve as safe a process [or product] as possible.” **EN**

— Bagley is the associate editor of Endocrine News. He wrote about radio personality Froggy and his mission to get the word out about acromegaly in the February issue.



**FURTHER RESEARCH**

Many questions remain unanswered regarding definitive links between fracking, EDCs, and collateral health effects. However, other investigators are working to address the potential health impacts of fracking.

Kristina Whitworth, PhD, MSPH, of the University of Texas School of Public Health is examining perinatal health effects among women living in close proximity to hydraulic fracturing, but she says it’s a new study and they haven’t begun analyzing the data just yet.

Trevor M. Penning, PhD, of the University of Pennsylvania and his team are conducting another study on health issues related to fracking, and their study is currently under review at PLoS One. Penning couldn’t discuss the findings yet, but did say that he thinks it is too early to “link health effects with exposure to EDCs since we do not yet have reliable exposure data for this group of compounds.” — DB

# A LA CARTE: Dietary Supplements and Diabetes

An estimated one-third of all diabetes patients are using some form of alternative medicines. Whether this is a passing fad or the wave of the future remains to be seen, but the impacts of these therapies are still largely unknown and more studies are needed.

By Glenda Fautleroy

The estimated number of adults with diabetes who use some type of complementary and alternative medicine (CAM) now hovers at more than 33%. An ever-growing population of diabetes patients is turning to dietary supplements, herbs, and mind-body medicine to improve the outcomes of their disease and for overall good health. The trend has made fielding patients' questions about dietary supplements a common part of the day for today's physicians.

Brent A. Bauer, MD, director of the Complementary and Integrative Medicine Program at the Mayo Clinic, says he faces these questions almost every day — mostly centered on what are the risks and benefits of products such as cinnamon and chromium for managing diabetes.

"I always 'back the train up' and spend time reviewing with the patient what they are doing from a lifestyle approach first," Bauer says. "We want to make sure they have optimized health and wellness promoting activities within each of the four key domains that have been associated with optimizing health, even at the genetic level."

"These [domains] include nutrition, mostly a whole-foods, largely plant-based approach; daily exercise; daily practice of a formal stress management program; and maintenance of a formal support network," Bauer continues. "Only if we have paid full attention to each of these areas, and optimized our wellness activities within each, should we consider the possible role of a supplement."

Bauer says once that solid foundation is in place, he helps patients explore targeted, evidence-based use of a particular supplement, individualized for that specific patient's overall condition.

While physicians, such as Bauer, in the CAM specialty may have regular dialogues with their patients on the topic, a 2010 study in *Clinical Diabetes* reported that at least 63% of the general population does not disclose use of CAM therapies to their physicians.

Bauer says, however, he thinks most physicians

"Most substances like cinnamon and bitter melon rather than being prescribed as medicines are consumed as everyday accompaniments at their daily meal. As such, the amount of active ingredients ingested are limited compared to the concentrated extracts that have been used in trials."

— Arjuna Medagama,  
MD, University of  
Peradeniya, Sri Lanka

recognize that CAM is now part of the U.S. healthcare approach.

"Increasingly, we recognize that not asking about CAM use only ensures that the patient will obtain their information somewhere else, such as a doctor on a TV show, a friend, or an Internet ad," Bauer says. "Much better for us to be directly involved in helping make sure they have solid information so that they can make an evidence-based and informed decision about the use, or not, of any supplement."

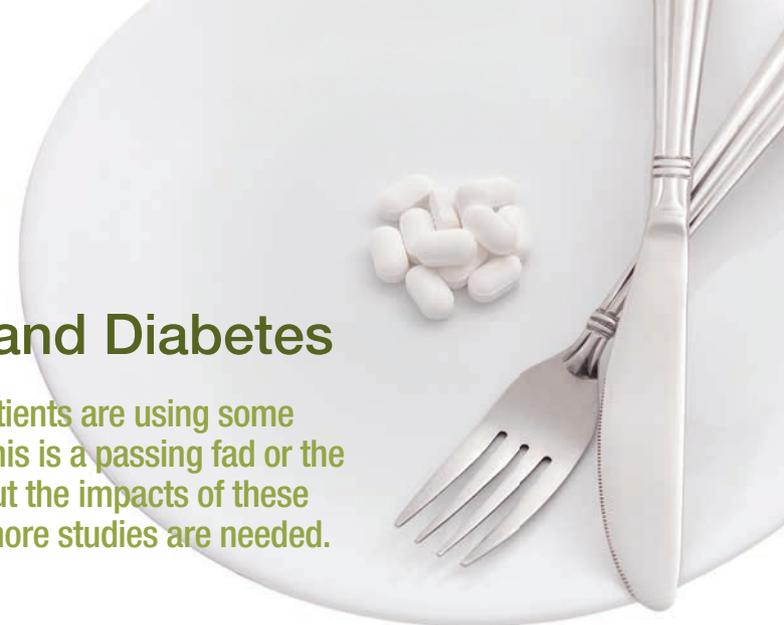
And while the National Center for Complementary and Alternative Medicine believes there is not enough scientific evidence to show any dietary supplements can help prevent or manage diabetes, some studies have yielded positive results. Here, we take a look at some of the latest research findings of the most common dietary supplements used to treat the disease:

## Chromium

A 2014 systematic review in the *Journal of Clinical Pharmacy and Therapeutics* of 25 randomized controlled trials concluded that evidence suggests daily doses of more than 200 µg chromium monosupplementation has favorable effects on glycemic control in patients with diabetes. Chromium monotherapy also significantly reduced triglycerides and increased HDL-C levels. The improvements on glucose and triglycerides levels were evident especially with chromium picolinate. At usual doses, the supplement did not increase the risk of adverse events compared with placebo. Still, long-term benefit and safety remain to be further investigated.

## Alpha-lipoic acid

As an antioxidant, alpha-lipoic acid (ALA) has been studied for its ability to decrease high levels of oxidative stress, which contributes to high blood glucose in diabetes patients as well as other secondary complications. In a 2011 clinical trial of 102 diabetes patients, published in *Diabetes Research and Clinical Practice*, daily supplements of 600 mg ALA and 800 mg vitamin E supplements (alpha-tocopherol) taken together



## AT-A-GLANCE

- An ever-growing population of diabetes patients is turning to dietary supplements, herbs, and mind-body medicine to improve the outcomes of their disease.
- At least 63% of the general population does not disclose use of CAM therapies to their physicians.
- Not asking about CAM use only ensures that the patient will obtain their information somewhere else.



FENUGREEK



CINNAMON



OMEGA-3 FATTY ACIDS



COPTIDIS  
RHIZOMA



BITTER GOURD



ALPHA-TOCOPHEROL  
FOOD

or separately for four months did not improve cholesterol levels or insulin responses.

### Herbs

A recent review in *Nutrition Journal* evaluated the available evidence of five herbs gaining popular use worldwide, including cinnamon, bitter gourd, and fenugreek. The review cautions, “herbal medicines constitute many hundreds to thousands of active and inactive ingredients, the effects of which are not known when used outside the plants’ natural use. Many trials have used large doses of naturally occurring substances, which would be many times the ordinary intake.”

Lead author Arjuna Medagama, MD, of the University of Peradeniya in Sri Lanka, tells *Endocrine News* most of the complementary medicines in use today have their roots in Asia.

“Most substances like cinnamon and bitter gourd rather than being prescribed as medicines are consumed as everyday accompaniments at their daily meal,” he says. “As such, the amount of active ingredients ingested are limited compared to the concentrated extracts that have been used in trials.”

“This point has not been widely acknowledged, and the trials we see today are too short and the participants are few,” Medagama adds. “Therefore, caution needs to be exerted when complementary medicines are advocated.”

Medagama says despite the fact that the evidence base for most substances are limited, cinnamon happens to be widely studied and seems to be effective when used alone in mild diabetes and in patients who have poor initial glycemic control.

“Bitter gourd, too, seems to show promise, but further research is required regarding the type of preparation that is effective. The available evidence seems to favor raw bitter gourd juice,” he advises.

### Cinnamon

In another analysis, a 2013 systemic review in the *Annals of Family Medicine* evaluated 10 randomized controlled studies of 543 type 2 diabetes patients who consumed daily cinnamon doses of 120 mg to 6 g for four to 18 weeks. The patients had reduced levels of fasting blood glucose, total cholesterol, and triglycerides. Cinnamon also increased levels of HDL-C. It did not, however, have any effect on hemoglobin A1C levels.

### Tianqi

The Chinese herb known as Tianqi was found to reduce the progression of prediabetes to type 2 diabetes by almost a third (32.1%) in a recent study in the *Journal of Clinical Endocrinology & Metabolism*. Tianqi is a combination of 10 Chinese medicinal herbs in a capsule, with the key herb reported as Huanglian (Coptidis Rhizoma). The researchers from the University of Chicago reported that in its randomized trial of 420 patients with impaired glucose tolerance, those who received Tianqi over 12 months compared to those in the placebo group had a significantly decreased incidence of type 2 diabetes — and the herbal drug was found safe to use.

### Magnesium

Clinical trials have not proven that magnesium supplements help manage type 2 diabetes symptoms. According to a large 2007 analysis, however, people who had a diet rich in magnesium from foods (whole grains, nuts, and green leafy vegetables) and supplements had a 15% reduced risk of developing the disease.

### Omega-3 Fatty Acids

As one of the most common dietary supplements taken in the U.S., omega-3s have been found useful in reducing the risk of heart disease and decreasing triglyceride levels. A 2008 systematic review, however, of 23 trials reported omega-3 fatty acids had no significant changes in fasting glucose, A1C, or fasting insulin in patients with type 2 diabetes.

### More to Come

As researchers around the globe continue to explore the possibilities of dietary supplement use for treating diabetes, patients are awaiting news of promising results. Currently, dozens of clinical trials are recruiting diabetes patients of different ages, disease states, and races — all aiming to provide solid scientific evidence of the effectiveness of alternative medicine. **EN**

— *Fauntleroy is a Carmel, Ind.-based freelance writer and regular contributor to Endocrine News. She wrote about treating drug-addicted diabetes patients in the January issue.*

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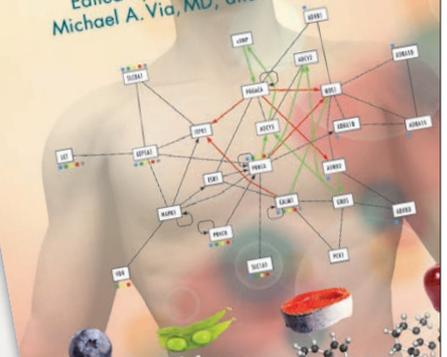
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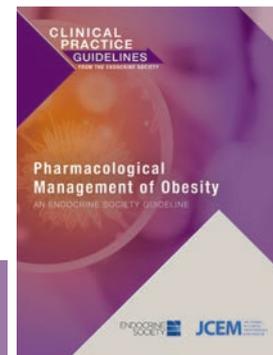


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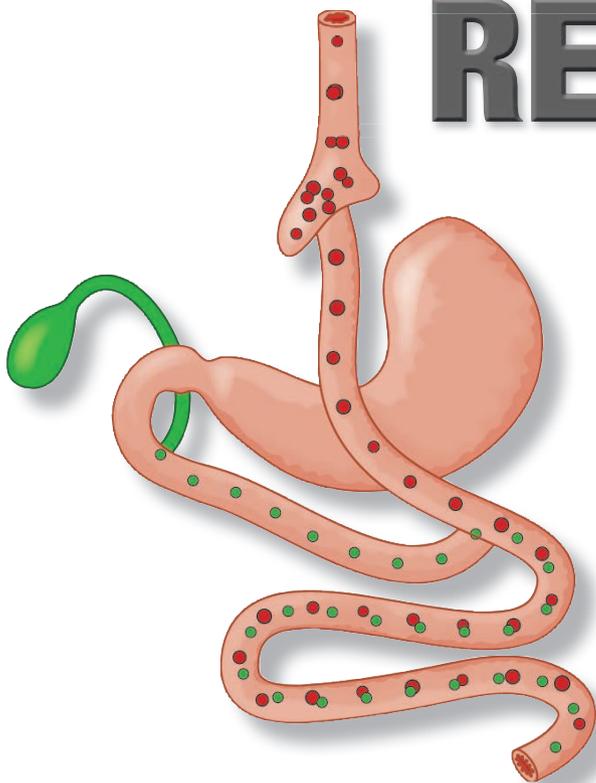
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# A ROAD TO REMISSION:



## Multiple Perspectives of Bariatric Surgery and Its Effects on Metabolic Disease



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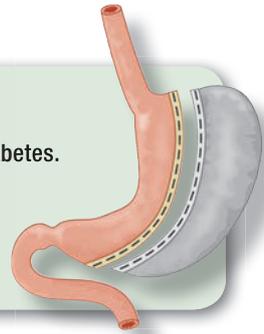


**BASIC RESEARCHER**  
*Bethany Cummings, DVM,*  
PhD, Assistant Professor,  
Veterinary Medicine, Cornell  
University, Ithaca, N.Y.

**T**he prevalence of obesity and its comorbidities, including cardiovascular disease and type 2 diabetes is expanding worldwide. Therefore, there is a pressing need for the development of new and effective strategies for the prevention and treatment of obesity and metabolic disease. Bariatric surgery remains the most effective long-term treatment for obesity. It is defined as a surgical manipulation of the gut performed for the purpose of weight loss and improvement of metabolic disease. Certain bariatric procedures, such as Roux-en-Y gastric bypass (RYGB), can cause type 2 diabetes remission within days after surgery, before any significant weight loss. This clinical observation has sparked intensive research in humans and animal models to identify the mechanisms underlying the metabolic benefits gained from bariatric surgery. Ideally, such research will lead to the development of new therapies or combination of therapies that can reproduce these metabolic benefits with minimal risk and in a durable fashion. In this TriPoint article, a bariatric surgeon-in-practice discusses type 2 diabetes remission and improvement following surgery, predictors of remission, and durability of remission; a clinical researcher provides perspective on contributions that human clinical studies have made to our understanding of the metabolic benefits of bariatric surgery and highlights areas in which more clinical data is needed; and a basic researcher reviews the contributions that work in rodent models of bariatric surgery have made toward our current understanding of the mechanisms driving the metabolic improvements observed after bariatric surgery.

## HIGHLIGHTS

- Bariatric surgery has been documented to **induce improvement or remission in some cases of type 2 diabetes.**
- **Macro- and micro-vascular complications of type 2 diabetes are reduced** in bariatric surgery patients.
- **Preoperative beta cell function** predicts remission and relapse of type 2 diabetes.



## CLINICAL PRACTITIONER'S PERSPECTIVE — *Joshua B. Alley, MD, FACS*

In 1967, a surgeon from Iowa named Edward Mason, MD reported a modification of a procedure for peptic ulcer disease that could be used to induce weight loss in patients suffering from severe obesity. He called the new procedure “gastric bypass.” Shortly after performing the first several dozen procedures, it was noted that patients with type 2 diabetes very often saw a resolution of their clinical condition to a normoglycemic state. Through the years, this procedure has been modified, refined, and standardized. It is performed by creating a small stomach pouch that bypasses the duodenum and is connected directly to the jejunum. It is now performed almost exclusively laparoscopically, through small abdominal incisions with the aid of a video laparoscope in the abdomen. In the past 15 years, laparoscopic adjustable gastric banding (band placed around the stomach and tightened by injecting saline) and laparoscopic vertical sleeve gastrectomy (VSG, a newer procedure involving removal of a portion of the stomach to leave behind a narrow, “sleeve”-shaped portion of the lesser curvature) are surgical procedures that have also been applied to treat morbid obesity, but laparoscopic RYGB remains the most common procedure used by bariatric surgeons in situations where the patient suffers from both severe obesity and type 2 diabetes.

### Type 2 Diabetes Remission

The term “remission,” rather than “cure,” is typically used today when describing the effect of bariatric surgery on type 2 diabetes, to emphasize that the disease is rendered inactive rather than extirpated, and as a reminder that recurrence (or relapse) is possible. The rate and degree of remission varies by patient population and by procedure. Dixon, et al. reported type 2 diabetes remission of 73% at two years post lap band surgery (versus 13% in medically managed patients), in a very highly selected group of patients with newly diagnosed, mild type 2 diabetes. The more recent STAMPEDE trial was a randomized, controlled trial that enrolled 50 subjects with type 2 diabetes in three treatment arms: intensive medical therapy, RYGB, or VSG. The study groups each had a mean BMI of 36 (Class II obesity), with mean duration of type 2 diabetes of more than eight years and mean glycated hemoglobin A1C (HbA1C), an index of plasma glucose

concentration over time of 8.9% or greater, suggesting that these research cohorts more accurately reflect real-world conditions of poor type 2 diabetes control. Forty-four percent of each group used insulin, and more than 90% of the subjects in each group met criteria for metabolic syndrome. At one year, achievement of the primary endpoint (HbA1C  $\leq$  6% with no type 2 diabetes medications) was as follows: 0% in medical therapy group, 42% in RYGB group, and 27% in VSG group. At three years, the numbers were 0%, 35%, and 20%, respectively. Significant improvement in glycemic control and medication use were observed in the surgery groups, even among those who did not see a complete type 2 diabetes remission.

A Swedish longitudinal observational study of patients undergoing a mix of various bariatric surgical procedures evaluated long-term remission rates and macrovascular and microvascular complications of type 2 diabetes after bariatric surgery and compared rates to those in a matched cohort. With remission defined as fasting glucose  $<100\text{mg/dL}$  and no diabetes medication, one-year remission rates for type 2 diabetes were 16% for the control group and 73% for the bariatric surgery group. Fifteen-year remission rates declined to 6.5% and 30.0%, respectively. Macrovascular and microvascular complications of type 2 diabetes were significantly lower in the bariatric surgery group at a median follow-up of  $\sim 18$  years.

### Predictors of Remission and Relapse

A common question that I am asked in the clinic is “How likely is it that my diabetes will go away?” Several studies have examined predictors of type 2 diabetes remission and relapse, with most of them focusing on RYGB (rather than adjustable gastric banding or sleeve gastrectomy). The common factors that emerge from the published literature suggest that preoperative type 2 diabetes severity and duration are inversely correlated with likelihood of remission (long-term, insulin-dependent diabetic patients are less likely to see a complete remission and are more likely to relapse). One study helped reveal some reasons for this pattern. Nannipieri, et al. showed that pancreatic beta cells exhibit baseline (preoperative) glucose insensitivity in patients with type 2 diabetes, greater than in other obese patients

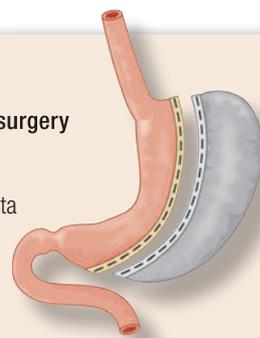
without type 2 diabetes. The beta cell glucose sensitivity improved early after surgery but plateaued thereafter, and never achieved glucose sensitivity equivalent to that of normal controls. Another study bolsters this “beta cell reserve” argument, showing that preoperative C-peptide levels (a marker for insulin biosynthesis and release) correlated with achievement of type 2 diabetes remission; a preoperative C-peptide level of <3 ng/mL resulted in remission after one year in only 55% of patients with type 2 diabetes, while C-peptide levels between 3-6 ng/mL and >6 ng/mL were associated with remission rates of 82% and 90%, respectively.

## Conclusion

In conclusion, while bariatric surgery offers the potential for long-term improvement or remission of type 2 diabetes and other obesity-related comorbidities, bariatric surgeons have learned to temper their enthusiasm for this important therapy with the understanding that type 2 diabetes remission is not complete or lifelong in every bariatric surgery patient. We will need to tailor combinations of medical, surgical, and lifestyle interventions, in collaborative ways, to best achieve the patient’s desired outcome as we treat the chronic diseases of type 2 diabetes and obesity. **EN**

## HIGHLIGHTS

- Observational studies and small-scale randomized controlled trials show the **superiority of bariatric surgery compared to medical therapy in sustained weight loss and diabetes remission.**
- **Predictors of outcome of the sustainability of weight loss are still unknown**, and there are no data on the long-term resolution of comorbidities, quality of life, complications, and cost.
- When matching for weight loss, **RYGB shows similar effect on insulin sensitivity and beta cell function** compared to other surgeries or with caloric restriction alone.
- **Incretin hormones play a significant role** in the post-prandial metabolic and endocrine response after gastric bypass surgery.



## CLINICAL RESEARCHER’S PERSPECTIVE — *Blandine Laferrère, MD*

### Clinical Impact of Bariatric Surgery in Individuals with Severe Obesity

About 35% of American adults and 17% of American children are obese. By 2020, the prevalence of severe obesity, class 2 (BMI>35), class 3 (BMI> 40), and class 4 (BMI> 45), respectively, is expected to increase to 16.4%, 6.3%, and 3.1% for men and 25.3%, 12.8%, and 5.8% for women. Bariatric surgery, the treatment of choice for class 2-4 obesity, is the only treatment that results in large ~30% weight loss, often sustained over time. Data from retrospective and observational clinical studies, and from small-scale, short-term randomized control trials, support a high rate of short-term (one to two years) improvement and/or resolution of comorbidities after surgery, including remission of type 2 diabetes in 40% to 80% of cases. Individuals with diabetes of short duration, well controlled and not on insulin, are more likely to experience remission. Weight loss amount and type of surgery are also important determinants of the rate of remission, with a clear advantage for more invasive surgeries such as biliopancreatic diversion (BPD), RYGB, and VSG, over adjustable gastric banding and compared to diet and medical therapy.

### Is There More Than Weight Loss After Bypass Surgeries?

The rapid and greater resolution of type 2 diabetes after

BPD and RYGB has led to the hypothesis that mechanisms other than weight loss, possibly gut-derived factors, may be responsible for the improved glucose control after these surgeries. However, the greater weight loss after BPD and RYGB compared to restrictive surgeries is a confounding factor. Smaller-scale mechanistic studies have attempted to circumvent the weight loss variable by studying the effect of different types of bariatric surgery, or diet-induced weight loss, at matched weight loss. Interestingly, these studies show little to no difference between procedures and/or between surgery and calorie-restrictive diet on insulin secretion, insulin sensitivity, and body composition. Therefore, weight loss, rather than mode of weight loss, is the important variable for diabetes remission. One exception to that rule is the incretin effect during meals, defined as the largest insulin response to oral versus intravenous isoglycemic glucose challenge. The endocrine response to a meal shows a clear boost of the incretin effect, after RYGB. This is not surprising as post-prandial GLP-1 release is enhanced after RYGB, as a consequence of accelerated nutrient transit time. The enhanced GLP-1 release results in greater meal-related insulin secretion, and in some patients, triggers reactive hypoglycemia. In addition to the change in gut peptide release, novel areas of interest include the role of bile acid and FGF19 signaling and

microbiota, all possible factors in improved metabolism and sustained weight loss after surgery. Understanding the mechanisms of the altered taste, food choices, and brain circuitry may also provide clues to understand why weight loss is sustained after surgery.

### Importance of Long-Term Studies to Measure Clinical Outcomes

The major limitation of past clinical, observational, and randomized studies is their short duration. Both obesity and type 2 diabetes are lifetime diseases. Studies looking at the effect of an intervention over one or two years are largely inadequate. The unique Swedish Obesity Study provides valuable long-term data. As described above, the 20-year follow-up made it possible to demonstrate a lower rate of microvascular and macrovascular complications after bariatric surgery compared to usual medical care in a subgroup of patients with diabetes. Moreover, long follow-up allowed calculation of diabetes relapse. At two years, 72.3% of patients were in diabetes remission, but only 30.4% were free of disease at 15 years. Interestingly, only minimal weight regain occurred between two years (21.2% weight loss) and 10 years (18% weight loss),

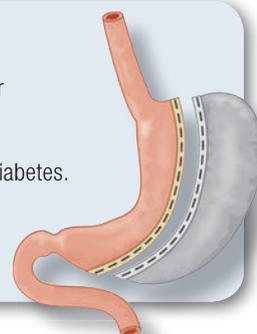
and cannot alone explain diabetes relapse in two-thirds of subjects. More recently, the use of electronic medical records offers a cheaper alternative to large multicenter clinical trials. Arterburn, et al. also showed diabetes relapse five to eight years after RYGB in more than 35% of patients who initially experienced remission.

### What Else Needs to be Done?

Bariatric providers, researchers, and patients have remaining questions. What are the predictors of weight loss outcomes, long-term (lifetime) complications, long-term survival, microvascular and macrovascular events, mental health outcomes, and costs? The importance of studies to assess durability of the effect of surgery and predictors of success, as well as the need for comparative studies of different treatment modalities, was highlighted during an NIH symposium (Courcoulas et al. JAMA Surg 2014 Dec; 149(12):1323-9). Results from these studies will be particularly important for younger patients having bariatric surgery in their twenties, at the beginning of their reproductive life, and who may expect to spend at least 50 years of their life in the post-bariatric state. **EN**

## HIGHLIGHTS

- **Genetic and pharmaceutical ablation techniques** in rodent models of bariatric surgery are improving our understanding of the mechanisms responsible for the metabolic benefits of bariatric surgery.
- **Increases in circulating bile acid concentrations** may contribute to post-operative resolution of type 2 diabetes.
- **Alterations in the gut microbiota** may contribute to post-operative metabolic improvements and may be related to alterations in bile acid metabolism.



## BASIC RESEARCHER'S PERSPECTIVE — *Bethany Cummings, DVM, PhD*

### How Does Bariatric Surgery Result in Type 2 Diabetes Remission?

Many postoperative changes noted after bariatric surgery have been hypothesized to contribute to the metabolic benefits of these procedures. These changes include: increases in post-prandial glucagon-like peptide-1 (GLP-1) secretion; increases in circulating bile acid concentrations; and alterations in gut microbial populations. Much of the previous work supporting these candidate mechanisms was purely correlative; however, recent work in rodent models of bariatric surgery has begun to test and quantify the actual contributions made by these proposed mechanisms.

#### Role of GLP-1

Post-prandial increases in GLP-1 secretion have been noted in many human clinical studies, and after several types of bariatric surgery, such as RYGB and VSG. GLP-1

is a hormone produced by gut enteroendocrine L-cells that has numerous antidiabetic actions. Therefore, the initial findings that GLP-1 secretion is elevated after various bariatric procedures was met with enthusiasm and the assumption that GLP-1 is a major driver for type 2 diabetes remission after bariatric surgery. However, studies using genetic and pharmaceutical ablation of GLP-1 receptor signaling in rodent models of VSG and RYGB have revealed no significant detriment in bariatric-associated improvements in body weight and glucose homeostasis. These studies suggest that increases in GLP-1 receptor signaling may not be playing a prominent role in the glucoregulatory benefits of bariatric surgery.

#### Role of Bile Acids

Bile acids are amphipathic steroid molecules that have a well-known role in lipid digestion and absorption.

However, bile acids also play an important role in the regulation of glucose homeostasis. Two bile acid receptors, Farnesoid X Receptor (FXR) and G-protein coupled bile acid receptor (TGR5), have been identified as mediators of the glucoregulatory effects of bile acids. The antidiabetic effects of bile acid signaling through FXR include: decreased liver triglyceride content, decreased hepatic gluconeogenesis, and increased insulin secretion. The antidiabetic effects of TGR5 signaling include increased GLP-1 secretion, increased energy expenditure, and decreased inflammatory cytokine release from immune cells.

Circulating bile acid concentrations are elevated after RYGB and VSG in human bariatric patients and in rodent models. Increased bile acid signaling has been suggested to contribute to metabolic improvements after bariatric surgery. This was assessed by studying the effects of VSG in high-fat fed wild type and whole-body FXR knockout mice. In the absence of FXR signaling, VSG-induced improvements in body weight and glucose tolerance were blunted compared with wild type mice. Furthermore, my laboratory has unpublished data demonstrating a relative impairment in the improvement of glucose tolerance after VSG surgery in whole-body TGR5 knockout mice compared to wild type controls. Overall, the emerging mouse data suggest that increases in bile acid signaling may be contributing to improvements in glucose homeostasis after bariatric surgery.

### Role of the Gut Microbiome

In recent years, specific gut microbial populations have been implicated as regulators of metabolic homeostasis. Pioneering studies demonstrated that obesity is associated with an increased Firmicutes to Bacteroides ratio. Furthermore, obese and lean phenotypes are transmissible via inoculation of germ-free mice with obese or lean microbiomes, strongly suggesting that gut microbial populations can influence body weight and may represent a new therapeutic target in the treatment of obesity.

Rodent and human studies report increases in Gamma-proteobacteria and decreases in Firmicutes after RYGB. Furthermore, inoculation of gnotobiotic mice with gut microbiome derived from mice after RYGB produces greater weight loss and metabolic improvement than inoculation of gnotobiotic mice with gut microbiome derived from sham-operated mice.

Notably, bile acids have an interdependent relationship with the gut microbiota. Gut microbes can deconjugate and convert primary to secondary bile acids during enterohepatic recirculation. Conversely, bile acids regulate gut microbial growth and composition. In addition to the reported reliance of VSG-induced improvements in body weight and glucose tolerance on FXR signaling, Ryan, et al. also reported that some of the postoperative changes in gut microbial composition rely on FXR signaling. In particular, the prevalence of Roseburia is elevated after VSG surgery in wild type mice, but this is not the case in VSG-operated FXR knockout mice. These data suggest that there is important cross-talk between postoperative changes in bile acid signaling and alterations in the gut microbiome. While alterations in gut microbial populations appear to play an important role in producing the metabolic benefits of bariatric surgery, the specific role of these bacteria remain to be elucidated.

### Conclusion

In summary, genetic and pharmaceutical studies in rodent models of bariatric surgery are improving our understanding of the relevance of certain postoperative changes in mediating the metabolic benefits of bariatric surgery. Such studies suggest that changes in bile acid signaling and the gut microbiome are key contributors to postoperative improvements in glucose homeostasis. It is likely that further studies in rodents will identify other key contributors. However, whether these systems can be safely and effectively targeted in human patients to recapitulate the metabolic benefits of bariatric surgery remains to be determined. EN

**GAIN NEW INSIGHT INTO TREATING COMPLEX ENDOCRINE EMERGENCIES**

Editor, Glenn Matfin, MSc (Oxon)

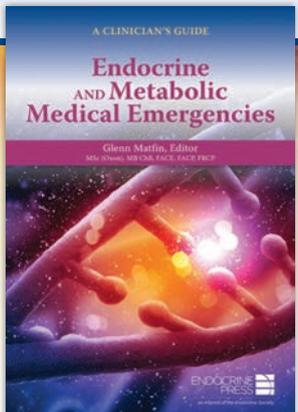
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# MIXING BUSINESS AND MEDICINE

In today's roiling healthcare market, simply being a skilled practitioner is not enough. A skilled physician with even a modicum of business training will fare much better in the current environment.

By Melissa Mapes

A successful practice takes more than quality medical care. With reimbursements decreasing, physicians are facing pay cuts of up to 24%, according to *Forbes* magazine. Most residents continue to launch their careers without business training — often feeling unconfident in their ability to financially support themselves and their families.

After speaking about the business side of endocrinology at an event for fellows, Elliot G. Levy, MD, FACP, FACE, was approached by numerous young physicians who felt unprepared. He decided to compile the business knowledge gained from more than 30 years of experience and publish it as a book, *Private Practice: What You Don't Learn as a Resident*, published by the Endocrine Society.

“They may have discovered that their practices have not been able to provide them with either the professional satisfaction or the income that they expected,” he wrote. In his book, Levy aims to offer timeless tenants of advice that allow providers to thrive, rather than struggle, in their practice.

## The Office

In private practice, physicians should think of their office as their “home away from home.” As part of a group, a provider may not have full say over the ambiance and operations of the clinic but should seize the opportunity to make certain improvements whenever possible.

The most important factor for an office is its location, according to Levy. It needs to be easily accessible to the population it is intended to serve. For example, if a physician knows that his or her patients frequent a certain hospital for testing or other medical needs, it would be judicious to establish the practice close to that hospital.

Other advantages to pursue include nearby pharmacies, parking options, and public transit. The right spot may seem expensive in some cases but is likely worth the investment.

One must also decide whether to rent or buy. With

rental space, no equity is provided, but the practice will have more flexibility in terms of moving if necessary. By purchasing an office, a physician or group may one day profit if the value appreciates but runs the risk of depreciation as well.

“Be a little brave in planning for the future, especially if you can see how rapidly your practice is growing and how you might need to hire other doctors in the future,” Levy advises.

Staffing comes as the next big challenge. How many employees does a practice need?

While numbers will vary under differing circumstances, Levy says to use a general rule of thumb: two – three employees per doctor.

He categorizes staff into two groups. The first group handles administrative tasks that do not generate income but are essential to the practice, such as scheduling appointments, communicating with insurance companies, and processing payments. The second group generates income by performing medical tasks such as testing blood samples.

Employees are one of the three major expenses of private practice — in line with rent and insurance — but it makes good sense to have an administrative assistant, who is likely paid about \$25 an hour, taking care of office tasks so that the physicians, who perhaps bill \$350 an hour, have more time to see patients and generate income.

## Billing

Most doctors have a murky idea of how billing works at best, according to Levy. “The days of traditional fee-for-service medicine are gone,” he wrote. “All of us, at least now, work for insurance companies, HMOs, Medicare, or Medicaid.”

Because of this, negotiating the best payment schedule possible is crucial at the initial contract stage. Practices that accept the beginning offer by an insurance company with no argument may miss out on potential revenue.

The implementation of electronic health records (EHR), or electronic medical records (EMR), have made it easier to track and submit claims. However, the issues of determining which current procedural technology (CPT) code to use and how much to charge still remain.

Levy recommends attending periodic coding seminars to ensure that the correct CPT codes are selected. But despite such training, assigning costs can be even more confusing than finding the proper CPT.

Recent government data on hospital procedure charges demonstrate this point. In Washington, DC, for example, two hospitals within a couple miles of each other charge wildly different prices for common CPT codes. At George Washington University Hospital, a lower joint replacement costs about \$69,000, while the same procedure at Sibley Memorial Hospital costs about \$30,000.

Physicians can reference resources such as FairHealthConsumer.org and Medicare statistics to find a baseline

## BUSINESS RESOURCES for Physicians

1. Private Practice: What You Don't Learn as a Resident (The Endocrine Society)  
[www.endocrine.org/store/books-and-publications/private-practice-what-you-dont-learn-as-a-resident](http://www.endocrine.org/store/books-and-publications/private-practice-what-you-dont-learn-as-a-resident)
2. Small Practice in America: A Series of Videos by the Center for Practice Innovation (American College of Physicians)  
[www.acponline.org/running\\_practice/practice\\_management/education/perspectives.htm](http://www.acponline.org/running_practice/practice_management/education/perspectives.htm)
3. Physician's Money Digest  
<http://www.hcplive.com/physicians-money-digest>
4. Physician Compensation Models: the Basics, the Pros, and the Cons (New England Journal of Medicine)  
[www.nejmcareercenter.org/article/physician-compensation-models-the-basics-the-pros-and-the-cons/](http://www.nejmcareercenter.org/article/physician-compensation-models-the-basics-the-pros-and-the-cons/)

of pricing and reimbursements for a wide variety of procedures. This can help determine if they are being compensated fairly for their work.

## Marketing

In medicine, building a strong patient base does not necessarily require paid advertising, but other facets of marketing can have a major influence on success. Firstly, Levy encourages providers to enforce a clear dress code for both their office staff and themselves.

Some practitioners may prefer surgical scrubs while others wear business attire under their lab coat, but, either way, “patients want their doctor to ‘look like a doctor.’” Flashy jewelry or watches can be off-putting, as can rumpled jeans and a t-shirt. The same goes for staff, as patients will also judge a practice by its employees.

Levy recommends updating office and exam room décor as well. Some framed posters on the walls and nice brochures about the practice can make a significant difference. Those that wish to go the extra mile can offer surveys for patients to fill out, which allows the collection of feedback for future application.

Every practice should have a working website and well-designed business cards. The cards become crucial at conferences and for patient referrals. A user-friendly website will allow patients to learn more about the practice when searching for a physician online.

There are still a relatively small number of educational resources for providers that wish to improve the business side of their practice. However, the recent surge in MD/MBA programs indicates that demand for this type of training has become a priority. In the near future, the healthcare industry may very well come to favor these business-savvy physicians. **EN**

— Mapes is a Washington D.C.-based freelance writer and a regular contributor to Endocrine News. She wrote about improving customer service in the March issue.

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



**Glycogenin-2 Is Dispensable for Liver Glycogen Synthesis and Glucagon-Stimulated Glucose Release** • Henrik U. Irgens, Karianne Fjeld, Bente B. Johansson, Monika Ringdal, Heike Immervoll, Sabine Leh, Oddmund Søvik, Stefan Johansson, Anders Molven, and Pål R. Njølstad • *These data indicate that GN2 is not required for liver glycogen synthesis and glucagon-stimulated glucose release.*

**Hip Axis Length is a FRAX and Bone Density Independent Risk Factor for Hip Fracture in Women** • William D. Leslie, Lisa M. Lix, Suzanne N. Morin, Helena Johansson, Anders Odén, Eugene V. McCloskey, and John A. Kanis • *DXA-derived hip geometry measurements are associated with incident hip fracture risk, but many do not confer significant independent predictive information. HAL was found to predict hip fractures when adjusted for BMD or FRAX score and may be of clinical value in refining hip fracture risk.*

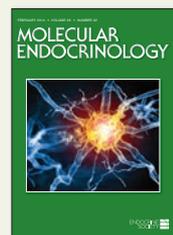
**Induction of Painless Thyroiditis in Patients Receiving Programmed Death 1 Receptor Immunotherapy for Metastatic Malignancies** • Steven Orlov, Farnaz Salari, Lawrence Kashat, and Paul G. Walfish • *Patients receiving anti-PD-1 mAb therapy should be monitored for signs and symptoms of PTS that may require supportive treatment with beta-blockers or thyroid hormone replacement. The anti-PD-1 mAb is a novel exogenous cause of PTS and provides new insight into the possible perturbations of the immune network that may modulate the development of endogenous PTS, including cases of sporadic and postpartum thyroiditis.*



**Genome-Wide Analysis of ChREBP Binding Sites on Male Mouse Liver and White Adipose Chromatin** • Naravat Pongvarin, Benny Chang, Minako Imamura, Junsheng Chen, Kanya Moolsuwan, Chanachai Sae-Lee, Wei Li, and Lawrence Chan • *The authors found that putative ChREBP binding sequences were enriched on promoters of genes involved in insulin signaling pathway, insulin resistance, and tumorigenesis.*

**Muscle-Specific Deletion of Comparative Gene Identification-58 (CGI-58) Causes Muscle Steatosis but Improves Insulin Sensitivity in Male Mice** • Ping Xie, Anil K. G. Kadegowda, Yinyan Ma, Feng Guo, Xianlin Han, Miao Wang, Leanne Groban, Bingzhong Xue, Hang Shi, Huihua Li, and Liqing Yu • *Muscle CGI-58 deficiency causes cardiac dysfunction and fat deposition in oxidative muscles but induces a series of favorable metabolic changes in mice fed a high-fat diet.*

**Molecular Cloning and Characterization of Anti-Müllerian Hormone (AMH) from the Japanese Wrinkled Frog, Rana rugosa** • Maho Kodama, Mari Suda, Daiki Sakamoto, Takehiro Iwasaki, Yasuki Matsuo, Yoshinobu Uno, Yoichi Matsuda, Yoriko Nakamura, Shun Maekawa, Yoshinao Katsu, and Masahisa Nakamura • *These results, taken together, suggest that AMH is probably involved in testicular differentiation in R. rugosa, although an additional, perhaps tissue-specific, transcription factor may be required for the regulation of AMH transcription.*



**Contribution of Intronic miR-338-3p and Its Hosting Gene AATK to Compensatory  $\beta$ -cell Mass Expansion** • Cécile Jacovetti, Veronica Jimenez, Eduard Ayuso, Ross Laybutt, Marie-Line Peyot, Marc Prentki, Fatima Bosch, and Romano Regazzi • *These results point to a coordinated reduction of miR-338-3p and AATK under insulin resistance conditions and provide evidence for a cooperative action of the microRNA and its hosting gene in compensatory  $\beta$ -cell mass expansion.*

**Activation of Melatonin Signaling Promotes Beta Cell Survival and Function** • Safia Costes, Marti Boss, Anthony P. Thomas, and Aleksey V. Matveyenko • *The authors' data suggest that beta cell MT signaling is important for regulation of beta cell survival and function and implies a preventative and therapeutic potential for preservation of beta cell mass and function in T2DM.*



**The Impact of Diabetes Treatments on Bone Health in Patients with Type 2 Diabetes Mellitus** • Matthew P. Gilbert and Richard E. Pratley • *In this review, the physiologic mechanisms and clinical impact of diabetes treatments on bone health and fracture risk in patients with T2DM are described.*

**Molecular Basis of Klotho: From Gene to Function in Aging** • Yuechi Xu and Zhongjie Sun • *This review focuses on the structure of the KL gene and the factors that regulate KL gene transcription; the key sites in the regulation of  $\alpha$ -Klotho enzyme activity; the  $\alpha$ -Klotho signaling pathways; and the molecular mechanisms that underlie  $\alpha$ -Klotho function. This current understanding of the molecular biology of the  $\alpha$ -Klotho protein may offer new insights into its function and role in aging.*



# QA

## Genetic Mutations and Breast Cancer

*Endocrine News* talks to Sarat Chandarlapaty, MD, PhD, about his research on genetic mutations and breast cancer, his methods, and what impact it might have on the field of endocrinology.

By **Melissa Mapes**

**E**strogen-disrupting therapies such as fulvestrant and tamoxifen have achieved great success in treating breast cancer. Such drugs, which block the estrogen receptor and inhibit the production of the hormone, stunt the growth of tumors and prevent the occurrence of breast cancer in at-risk individuals.

Unfortunately, patients frequently develop resistance to these drugs. The reasons remain ambiguous, but metastasis seems to coincide with reduced effectiveness. Researchers set out to find the root of this problem, and two teams simultaneously made a breakthrough.

### Medical Cryptanalysts

Their findings indicated that the genetics of the estrogen receptor affect both drug resistance and the building blocks of breast cancer. They discovered that mutations in the encoding endocrine receptor gene *ESR1* are likely leading to resistance. With this new information, scientists may soon uncover more effective therapies for treating patients with these genetic mutations.

A lead researcher on one of the ground-breaking studies was Sarat Chandarlapaty, MD, PhD, at Memorial Sloan-Kettering Cancer Center in New York, N.Y. He and his coauthors tested samples of metastatic tumors in patients with recurring breast cancer after months of hormonal treatment.

The team recognized a pattern of *ESR1* mutations that involved the ligand-binding region of the estrogen

receptor. The results have invigorated the field of breast cancer research to pursue related studies.

Chandarlapaty and his colleagues continue to go after the goal of eradicating breast cancer by working to better understand the molecular mechanisms at its root. He took some time to describe to *Endocrine News* the path that led him to this groundbreaking research, and what he aims to achieve in the future.

**Endocrine News:** What led you to breast cancer and genetics as your research topics?

**Chandarlapaty:** When I began my oncology fellowship, the therapeutic benefits of targeting HER2 in breast cancers showing amplification of the HER2 gene were just emerging. This was tremendously exciting as one of the early examples of how a deeper understanding of the genetics of a solid tumor like breast cancer was leading to breakthroughs in therapy. And as HER2 was only seen in about 20% of breast cancers, it seemed there might be more such exciting discoveries.

**Please describe the activities of your laboratory. How do you conduct your experiments?**

**Chandarlapaty:** We are investigating what causes breast cancers to become resistant to various treatments and then testing newer therapies against the resistant

cancers. We rely on cellular models of breast cancer to study the disease. Our experiments principally involve manipulating the genome of breast cancer models so they mirror certain states we see in the clinic; studying how those changes alter the cellular response to drugs; and evaluating how newer drugs perturb the cell.

#### What resources and equipment do you rely on the most?

**Chandarlapaty:** [We rely upon] cells derived from human breast cancer and drugs developed by both pharmaceutical companies and academic labs.

#### How has your research influenced, or is influencing, medicine? How is it influencing endocrinology specifically?

**Chandarlapaty:** I hope that we are influencing the design of clinical trials of newer therapies, specifically for the subtypes of breast cancer that are driven by the estrogen receptor as well as those driven by HER2. For endocrinology, I think our work on how breast cancers develop resistance to antiestrogen therapy will help the field to develop even better drugs for preventing or treating ER+ breast cancer.

#### If you had unlimited funding, how would you use it to upgrade your laboratory and advance your research?

**Chandarlapaty:** One [way] — develop more models of breast cancer from patients. By obtaining specimens from patients whose tumors have become resistant, we might be able to make better models of breast cancer for the lab to study the disease. This is a costly process.

#### Where do you see your scientific work heading in the future? How do you hope to affect change with your projects?

**Chandarlapaty:** I think we are just beginning in terms of understanding resistance to antiestrogens and the optimal strategies to deal with more treatment refractory cancers.

### The Next Steps

In the months since Chandarlapaty's study was published, pharmaceutical companies have been in a race to find an effective anti-resistance drug. While clinical trials are still a ways off, novel approaches with old therapies have begun to emerge.

According to *Bioscience Technology*, one example includes the use of an oral selective estrogen receptor down-regulator (SERD), ARN810, which is being administered in a trial at Memorial Sloan-Kettering Cancer Center, Massachusetts General Hospital, and Vanderbilt Ingram Cancer Center. Oncologists seem to view this study as an example with great potential.

Researchers expect that current drugs such as fulvestrant and tamoxifen will be found to perform better in higher concentrations. If studies that are underway support this hypothesis, the prescription of these hormonal therapies will include larger doses of the estrogen blockers until new medications based around ESR1 mutations are available.

The question remains of how to identify patients who may develop these mutations. Chandarlapaty's research focused on the metastatic tumors, within which the genetic deviance has appeared prevalent. Primary tumors seem to make for trickier subject matter. If physicians can find a way to screen patients with primary tumors for the mutation, they may be able to improve treatment plans and avoid metastasis.

With more patient samples, as Chandarlapaty suggested, researchers will be able to further refine their understanding of the mutation and its influence. One thing is for sure: Antiestrogens will continue to play a crucial role in breast cancer research and treatments.

—Mapes is a Washington D.C.-based freelance writer and a regular contributor to *Endocrine News*. She wrote about improving customer service in the March issue.

## Genetic mutations tied to BREAST CANCER

- **BRCA1 and BRCA2 mutations**  
Impair the stability of genetic material, and make it significantly more likely for cells to develop aberrations that lead to cancer. Certain ethnic groups are far more likely to carry the mutation. Also, patients with these mutations have a risk of developing a second primary contralateral breast cancer of about 40% to 65%.
- **p53**  
This protein keeps cell division in check, which helps control unruly growth, such as that of cancer. Accounts for only about 1% of breast cancer cases.
- **CHEK2**  
When DNA is damaged or strands are broken, this gene is usually activated to help the DNA repair itself or destruct in a controlled manner. Without it, DNA cell damage piles up.
- **ATM**  
Helps regulate the rate at which cells grow and divide from the nuclei. The body needs it to correctly repair DNA.
- **PALB2**  
Tied closely to BRCA2, these two proteins work together to suppress tumors. PALB2 stabilizes BRCA2 so that it can repair DNA issues.
- **ESR1**  
Seventy percent of breast cancer cases express estrogen receptor- $\alpha$ , which is encoded by ESR1. Mutations appear to inhibit the effectiveness of hormone therapies.

## Society Advocates for Diabetes Prevention, Research, Treatment, & Coverage Legislation

As Congress moves forward with its health agenda, the Endocrine Society has a number of priorities for diabetes prevention, treatment, and research legislation under consideration. These priorities include funding for the National Diabetes Prevention Program (NDPP), renewal of the Special Diabetes Program (SDP), and Medicare coverage for continuous glucose monitoring (CGM).

### *National Diabetes Prevention Program Funding*

The Society is a leading advocate for funding for the NDPP, a program that uses lifestyle intervention to prevent or delay the onset of diabetes among individuals with prediabetes. The Society has advocated for increased funding for the program on Capitol Hill and with U.S. Surgeon General Vivek Murthy.

With support from the Society, the Chairs of the Congressional Diabetes Caucus (CDC) recently circulated a “Dear Colleague” letter requesting support for prioritizing funding for the National Institute for Diabetes and Digestive and Kidney Diseases, the CDC’s Division of Diabetes Translation, and the NDPP.

The NDPP has demonstrated great success through its expansion to over 794 sites in 39 states, and it could save the country as much as \$190 billion if fully expanded. A testament to this success is the launch of an initiative from the CDC and the American Medical Association called, Prevent Diabetes STAT: Screen, Test, Act—Today. The initiative intends to raise awareness about prediabetes and increase screening and referral to evidence-based diabetes prevention programs that are a part of the NDPP.

### *Special Diabetes Program Reauthorization*

In addition to funding for the NDPP, the SDP funding is scheduled to expire on September 30, 2015, if Congress fails to act. The SDP was created in 1997 to advance research for type 1 diabetes and to address the disproportionate burden of type 2

diabetes on American Indians and Alaska Natives (AIAN). Through this funding, the Special Type 1 Program has advanced research in islet cell transplantation, beta cell therapy, treatment for diabetic retinopathy, and innovative therapies like the artificial pancreas. The SDP for Indians has also shown great success by helping AIAN prevent and manage type 2 diabetes resulting in significant reductions in A1c and amputation as well as improvements in blood pressure and kidney function. The Society has advocated for funding of these programs for a number of years and continues to urge Congress to reauthorize the SDP by the September deadline in visits with Congress and in Society appropriations testimony.

### *Medicare Coverage for CGM*

Medicare coverage for CGM has been a key priority for the Society. Over the past two years, the Society has met with key officials at the Centers for Medicare and Medicaid Services, Health and Human Services, and the White House to secure Medicare coverage for CGM. Because Medicare coverage has not been resolved, the Society and its coalition partners worked to introduce the Medicare CGM Access Act last year. The legislation, which was sponsored by Senators Collins and Shaheen and Representatives DeGette and Whitfield, was reintroduced in Congress last month. The Society will continue to work to build support for this important legislation.

## Exposure to Endocrine-Disrupting Chemicals Costs EU Billions — EDC News Conference Simulcast at ENDO and in Europe

On Thursday, March 5, as part of the Endocrine Society’s media outreach, the Endocrine Society conducted a news conference at **ENDO 2015** focusing on the latest science surrounding endocrine-disrupting chemicals (EDCs). During the news conference, Leonardo Trasande, MD, presented the results from a series of four publications released on the same day in *The*

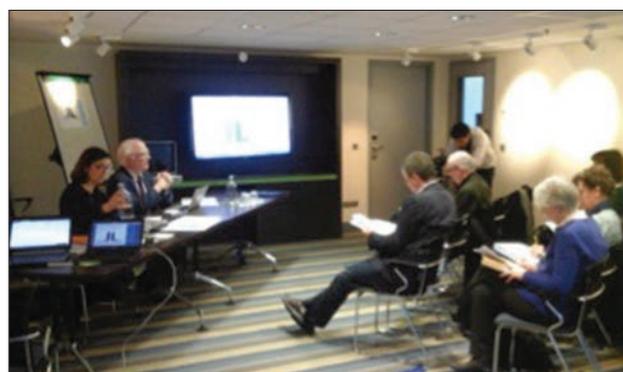
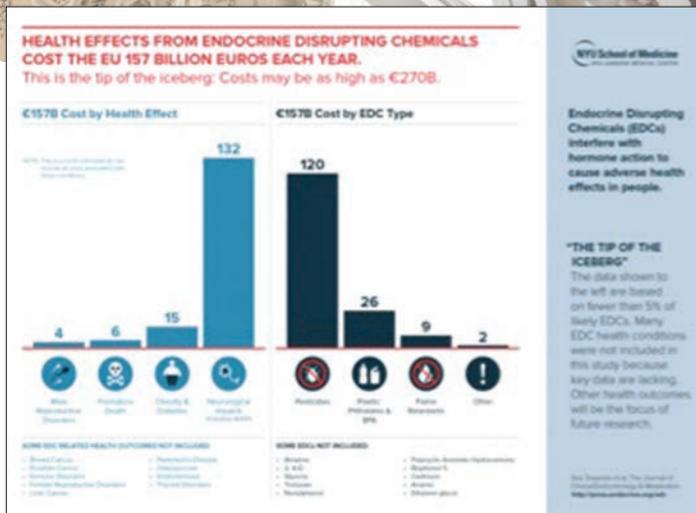


*Journal of Clinical Endocrinology & Metabolism (JCEM).*

The publications described the results of an economic analysis that found exposure to EDCs likely costs the European Union €157 billion (\$209 billion) a year in actual healthcare expenses and lost earnings potential. The analysis, conducted by a group of leading experts in several fields, concluded that infertility and male reproductive dysfunctions, birth defects, obesity, diabetes, cardiovascular disease, and neurobehavioral and learning disorders were among the conditions that can be attributed in part to exposure to EDCs. The €157 billion estimate is conservative and represents 1.23% of Europe's gross domestic product (GDP). These costs may actually be as high as €270 billion (\$359 billion), or 2% of GDP.

The results are particularly timely given that, at the time this article was written, the European Commission is conducting an impact assessment for EDCs. The impact assessment will weigh the health risks of exposure to EDCs, taking into account the latest science and input from public stakeholders, including the Endocrine Society. Importantly, the impact assessment will also include the anticipated economic costs of various regulatory approaches to EDCs. The new results presented by Trasande are, therefore, critically important to help the European Commission accurately assess the economic consequences of health impacts due to EDC exposures and balance this analysis against the anticipated costs of regulation.

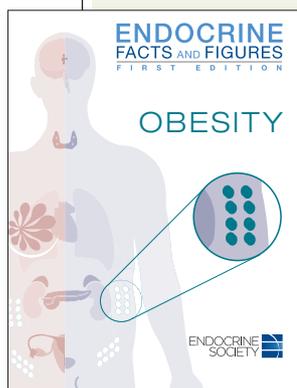
To ensure that the results achieve maximum impact in the European Union, the Endocrine Society simulcast the news conference at a special event in Brussels, Belgium. As part of the event, Endocrine Society member Philippe Grandjean, MD, moderated an educational briefing for participants following the news conference. Participants included representatives from international non-governmental organizations, members of the media, and a representative from the European Commission. These highly attended events, coupled with a strategic media outreach plan, resulted in press coverage from a number of high-profile media outlets including BBC News, *Le Monde*, *TIME* magazine, the Weather Channel's website, and *National Geographic*.



Endocrine Society press conference simulcast in Brussels, Belgium, March 5, 2015. Philippe Grandjean, MD, PhD, takes questions from the European press.



Endocrine Society press conference March 5, 2015, in San Diego focusing on the latest science surrounding EDCs. Leonardo Trasande, MD, presents results of an economic analysis.



## Society Publishes Comprehensive Report on HORMONE HEALTH STATISTICS

The Society has published the first chapter of a new report compiling the latest peer-reviewed statistics on hormone health conditions into a single resource.

“Endocrine Facts and Figures” provides patients, physicians, researchers, journalists, policy makers, and consumers with a comprehensive source of epidemiological data and trends on a breadth of endocrine diseases and related conditions.

“The Endocrine Society has created a compendium of data for anyone seeking to better understand the impact of hormone health conditions,” says Society past-president Robert A. Vigersky, MD, who chaired the Endocrine Facts and Figures Advisory Panel. “Endocrine diseases like obesity and diabetes affect millions of people. This report combines the best peer-reviewed data on these conditions in a single location.”

The initial chapter focuses on obesity, a condition that affects 35.1% of adults and 16.9% of children in the U.S. The report discusses important research breakthroughs and treatment options for obesity. In addition, the chapter provides statistics on metabolic syndrome, a related condition that occurs when a person has a cluster of risk factors, including excess body fat, which increase the chances of developing heart disease, stroke, and diabetes.

Future chapters scheduled to be published later this year will examine thyroid conditions, bone and calcium diseases, cardiovascular and lipid disorders, hypothalamic-pituitary disorders, adrenal health, cancers and neoplasias, reproductive and development disorders, and diabetes. The chapters are scheduled to be published on a monthly basis throughout the remainder of the year.

The Endocrine Society’s world-renowned physician and scientific experts compiled the data from peer-reviewed publications. The 2015 edition will focus on data from the U.S. Future updates will incorporate additional data from other countries.

In addition to Vigersky, other members of the Endocrine Facts and Figures Advisory Panel are Ursula B. Kaiser, MD, of Brigham and Women’s Hospital, in Boston; Sherita H. Golden, MD, MHS, of Johns Hopkins University, in Baltimore, Md.; Joanna L. Spencer-Segal, MD, PhD, of the University of Michigan, in Ann Arbor, Mich.; R. Michael Tuttle, MD, of Memorial Sloan Kettering Cancer Center, in New York; and Endocrine Society past-president William F. Young, Jr., MD, MSc, of the Mayo Clinic, in Rochester, Minn. George A. Bray, MD, of Pennington Biomedical Research Center, in Baton Rouge, La., and Marc-Andre Cornier, MD, of the University of Colorado, in Denver, served as expert reviewers for the obesity chapter.

To sign up for updates and to access digital versions of the report and related resources, visit [endocrinefacts.org](http://endocrinefacts.org). **EN**

## BBC News Receives Society Award for Excellence in Science and Medical Journalism

A team of BBC News journalists received the Endocrine Society’s annual Award for Excellence in Science and Medical Journalism.

BBC News Online health editor James Gallagher, medical producer Rachael Buchanan, and the BBC Visual Journalism team were honored at the Society’s 97th Annual Meeting & Expo in San Diego for the winning package, “*The Day of the Body Clock*.” The package included television, radio, and online coverage from May 13, 2014.

The BBC News team leveraged the news organization’s 24-hour nature to explore the way hormones influence the body’s daily rhythms. The journalists created an interactive body clock website, which shared information about hormones at different times of day. The website provided customized information based on the viewer’s time zone.

In addition, BBC News developed stories for its television stations, radio stations, and websites that delved into hormonal fluctuations at different times of day.

Established in 2008, the award was created to recognize outstanding reporting that enhances the public understanding of health issues pertaining to the field of endocrinology. The Award for Excellence in Science and Medical Journalism consisted of a presentation at the Society’s awards banquet, as well as travel and accommodations to attend the Society’s Annual Meeting.

More information on the Endocrine Society Award for Excellence in Science and Medical Journalism is available at: <https://www.endocrine.org/news-room/journalism-award>. **EN**

## Society Champions EDC Research in *Wall Street Journal* Letter

The Endocrine Society defended the importance of researching bisphenol A (BPA) and other endocrine-disrupting chemicals (EDCs) in a letter to the editor published in the *Wall Street Journal* on February 18.

The Society took quick action to respond to the newspaper’s February 12 editorial, which argued BPA was a safe chemical and called for a halt to spending federal funds supporting research in this area. The newspaper printed a letter to the editor from Society member and *Endocrinology* editor-in-chief Andrea C. Gore, PhD, which described the preponderance of scientific evidence demonstrating that BPA has harmful health effects.

“Despite this, the Food and Drug Administration continues to judge BPA using standards that have little relevance to endocrine disruptors,” Gore wrote. “Unlike poisons, endocrine disruptors can have different — and often more insidious — effects at low levels of exposure.”

The *Wall Street Journal* has a circulation of more than 3.6 million.

Gore’s letter was the lone response to the BPA editorial published in the newspaper. The letter helps solidify the Society’s position as a key thought leader on the emerging issue of EDCs. **EN**

## Society Honors 22 with 2015 HELMSLEY AWARDS

The Endocrine Society selected 22 winners of the Helmsley Charitable Trust Abstract Awards in Type 1 Diabetes, which recognize the outstanding work of trainees and early-career professionals in the diabetes field. The award honors researchers who are studying innovations in clinical care for people with type 1 diabetes as well as the underlying mechanisms and causes of the condition.

The award winners presented their work at **ENDO 2015** last month in San Diego. As part of the award, all honorees received travel grants to attend the annual meeting.

### The Endocrine Society's 2015 Helmsley Charitable Trust Abstract Award winners are:

- **Shivani Agarwal**, University of Pennsylvania Health System, "A Multivariate Model of Demographic and Psychosocial Predictors of HbA1C in Adolescents with Type 1 Diabetes"
- **Sophia Ali, MD**, State University of New York at Buffalo, "Reversal of Effects of Liraglutide as Additional Treatment to Insulin in Patients with Type 1 Diabetes after Cessation of Therapy"
- **Shipra Bansal**, SUNY Downstate Medical Center, "Knowledge, Attitudes, and Practices of U.S. Residents Regarding Insulin Pump in Diabetics"
- **Sena Cantas Orsdemir, MD**, Baystate Medical Center, in Springfield, MA, "Are Families of Children with Type 1 DM Ready for Televisits?"
- **Julia Cartaya, MD**, Joslin Diabetes Center, in Boston, MA, "Predictors of Visits with a Registered Dietitian (RD) for Youth and Young Adults with Type 1 Diabetes (T1D)"
- **Tamara Casteels**, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, in Austria, "Epigenome-Wide Screen for Alpha to Beta Cell Transdifferentiation"
- **E. Danielle Dean, PhD**, Vanderbilt University Medical Center, "Hepatic-Derived Factor Stimulates Alpha Cell Proliferation"
- **Aoife Egan, MB, BCh, BAO**, National University of Ireland Galway, "A Regional Prepregnancy Care Program for Women with Pregestational Diabetes: Is It Worthwhile?"
- **Mohamed Elsayed**, Beckman Research Institute of City of Hope, in Duarte, CA, "Methylation-Specific PCR Assay for Detection of Beta Cell Death in Newly Onset Type 1 Diabetes"
- **Manivel Eswaran, MD, MS**, University of Texas Medical Branch at Galveston, TX, "Type 1 Diabetes and Bone Marrow Transplantation"
- **Sana Hasan, DO**, University of Nebraska Medical Center, "The Effect of All Trans Retinoic Acid on Insulinitis and Beta Cell Apoptosis in NOD Mice"
- **Mark Husing, PhD**, University of California, Davis, "Urocortin3 Triggers Somatostatin-Mediated Negative Feedback to Control Insulin Secretion"
- **Chad Hunter, PhD**, University of Alabama at Birmingham, "Single-Stranded DNA Binding Protein 3 (SSBP3) Participates in Ldb1 and Islet-1 Mediated Transcriptional Complexes in Pancreatic Beta Cells"
- **Philippe Klee**, University Hospitals of Geneva, Switzerland, "Choline Protects Human and Murine Beta-Cells in Vitro Against Cytokines By Decreasing Mitochondrial Permeability Transition"
- **Michelle Mangual, MD**, San Juan City Hospital in Puerto Rico, "Type 1 Diabetes Mellitus Related to Acute Liver Failure: a Challenging Diagnosis"
- **Sara McMillin, PhD**, Johns Hopkins School of Medicine, in Baltimore, MD, "Assessing the Relative Contributions of Three Transcriptional Co-Activators to Hepatic Gluconeogenesis in Vivo"
- **Geetha Mukerji, MD, MSc**, Women's College Hospital Institute for Health System Solutions and Virtual Care, in Toronto, Ontario, Canada, "Improving Transitions of Care in Young Adults with Type 1 Diabetes"
- **Kadapalakere Reddy, MBBS**, State University of New York at Buffalo, "Metastatic Germ Cell Testicular Tumor with High Testosterone Levels. Is That True?"
- **Kanika Shanker, MD**, Emory University, in Atlanta, Georgia, "Autoimmune Hypoglycemia in a Young Girl with Autoimmune Overlap Syndrome"
- **David Weber, MD, MSCE**, University of Rochester, in Rochester, NY, "Sex Differences in Bone Density and Body Composition in Children Newly Diagnosed with Type 1 Diabetes"
- **Feng Wu, MD**, Center for Stem Cell Biology, Roger Williams Medical Center, Boston University School of Medicine, in Massachusetts, "Bone Marrow Stem Cells Support Human Islet Beta Cell Function in an Encapsulated Microenvironment"
- **Mingfeng Zhang, PhD**, Beckman Research Institute of City of Hope, in Duarte, CA, "Induction of Mixed Chimerism for Cure of Overt Type 1 Diabetes in NOD Mice, Using Clinically Available Reagents without Radiation"

The **Leona M. and Harry B. Helmsley Charitable Trust** aspires to improve lives by supporting exceptional nonprofits and other mission-aligned organizations in health, selected place-based initiatives, and education and human services. Since 2008, when the Trust began its active grantmaking, it has committed more than \$1 billion. The Helmsley Type 1 Diabetes Program is the largest private foundation funder of T1D in the nation focused on understanding the disease, developing better treatments, and improving care and access. For more information, visit [www.helmsleytrust.org](http://www.helmsleytrust.org).



**Assistant/Associate Professor, Division of Endocrinology, Diabetes & Metabolism, University of Florida/Shands.**

The University of Florida, Department of Medicine, Division of Endocrinology, Diabetes & Metabolism is seeking applications for full-time, 1.0 FTE clinical track positions at the Assistant/Associate/Professor level. The position seeks talented endocrinologists with a strong interest in developing a career in academic medicine with an emphasis on clinical responsibilities, but with options to perform teaching and clinical translational research. We enjoy a collaborative relationship with UF Health Shands Hospital which is nationally ranked among the top-50 in ten specialties in the 2013 edition of America's Best Hospitals, published by U.S. News & World Reports.

Resources for professional development at the University of Florida HSC include leadership, education, and research tracks, formal mentorship programs, and supported opportunities for teaching and research. The position has the option to include a part-time appointment at the immediately adjacent VA Hospital. Requisite attributes include a strong sense of teamwork and a desire to train tomorrow's doctors through our fellowship program. The Gainesville community has superb weather, nationally ranked schools, multiple year-round recreational opportunities, and is surrounded by several major metropolitan areas. Foreign national candidates whose employment conditions meet federal and University requirements under an immigrant classification are eligible to apply. The University of Florida is an equal opportunity institution dedicated to building a broadly diverse faculty and staff. Qualifications: Applicants must be board-certified or board eligible in Endocrinology, Diabetes and Metabolism.

Send Curriculum Vitae and three (3) letters of recommendation to:

**Kenneth Cusi, MD, Chair**

**UF Department of Medicine, Endocrinology  
P.O. Box 100226, Gainesville, FL 32610  
kcusi@ufl.edu**

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# BRAINY HORMONES

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## HORMONES PRODUCED IN THE HYPOTHALAMUS

Found deep inside the brain, the hypothalamus produces releasing and inhibiting hormones and controls the “master gland”— the pituitary. Together, the hypothalamus and pituitary tell the other endocrine glands in your body to make the hormones that affect and protect every aspect of your health.



### ANTI-DIURETIC HORMONE

Regulates water levels in the body; affects blood pressure and volume

### CORTICOTROPIN-RELEASING HORMONE

Drives the body's response to physical and emotional stress; stimulates anxiety; suppresses appetite

### GONADOTROPIN-RELEASING HORMONE

Stimulates release of hormones that act on testes and ovaries to initiate and maintain reproductive function; levels increase in puberty to trigger sexual maturation (puberty depends upon the appropriate timing and release of hormones)

### GROWTH HORMONE-RELEASING HORMONE

Controls normal physical development in children, metabolism in adults; increased by sleep, stress, exercise, and low blood glucose

### OXYTOCIN

Controls aspects of some human behavior (sexual arousal, recognition, trust, anxiety, and mother-infant bonding) and key aspects of reproductive system (childbirth and lactation in women, ejaculation and conversion of testosterone into dihydrotestosterone in men)

### SOMATOSTATIN

In the central nervous system, works to inhibit other hormones, most notably growth and thyroid-stimulating hormones

### THYROTROPIN-RELEASING HORMONE

Stimulates production of thyroid hormone, which plays important role in the body's metabolism, heart and digestive functions, muscle control, brain development, and preservation of bones

**TRAUMATIC BRAIN INJURY** can affect the production levels of hormones that originate in the brain and can lead to serious physical diseases and disorders.

Genetics can also play a role in causing these conditions, and others beyond the central nervous system. **See an endocrinologist to get tested!**



HORMONE	TOO HIGH	TOO LOW
<b>ANTI-DIURETIC HORMONE</b> 	Water retention, diluted blood, seizure	Dehydration, blood pressure drop
<b>CORTICOTROPIN-RELEASING HORMONE</b> 	Diabetes, high blood pressure, osteoporosis, abdominal obesity, acne, dysfunctional menstrual cycle, infertility, muscle loss and weakness (i.e. Cushing's syndrome)	Weight loss, low blood pressure, gastrointestinal distress, anorexia nervosa, increased skin pigmentation in areas not exposed to sun (e.g. hand creases, genitals)
<b>GONADOTROPIN-RELEASING HORMONE</b> 	Disrupted connection between the hypothalamus, pituitary gland, and gonads (i.e. menopause, removal of the testes or ovaries)	Poor bone health, no puberty, infertility (i.e. Kallmann syndrome)
<b>GROWTH HORMONE-RELEASING HORMONE</b> 	Abnormal enlargement of hands, feet, and skull which alter facial features (i.e. acromegaly), diabetes, menstrual disorders	In children—delayed physical growth, delayed puberty In adults—decreased muscle mass and increased body fat
<b>OXYTOCIN</b> 	Beyond the brain, linked to enlarged prostate resulting in urination difficulty	Linked to breastfeeding difficulty in women, and autism/poor social functioning in developing children
<b>SOMATOSTATIN (aka GROWTH HORMONE-INHIBITING HORMONE)</b> 	Beyond the brain, diabetes, gallstones, intolerance to fat in the diet, and diarrhea	Variety of physiological problems, including uncontrolled growth hormone secretion
<b>THYROTROPIN-RELEASING HORMONE</b> 	Fatigue, depression, weight gain, feeling cold, constipation, dry skin and hair, hair loss, heart problems, dyslipidemia, irregular menstrual cycles (i.e. hypothyroidism)	Weight loss, weak muscles, excessive sweating, excessive menstrual flow (i.e. hyperthyroidism)

**You have questions. We have answers.**

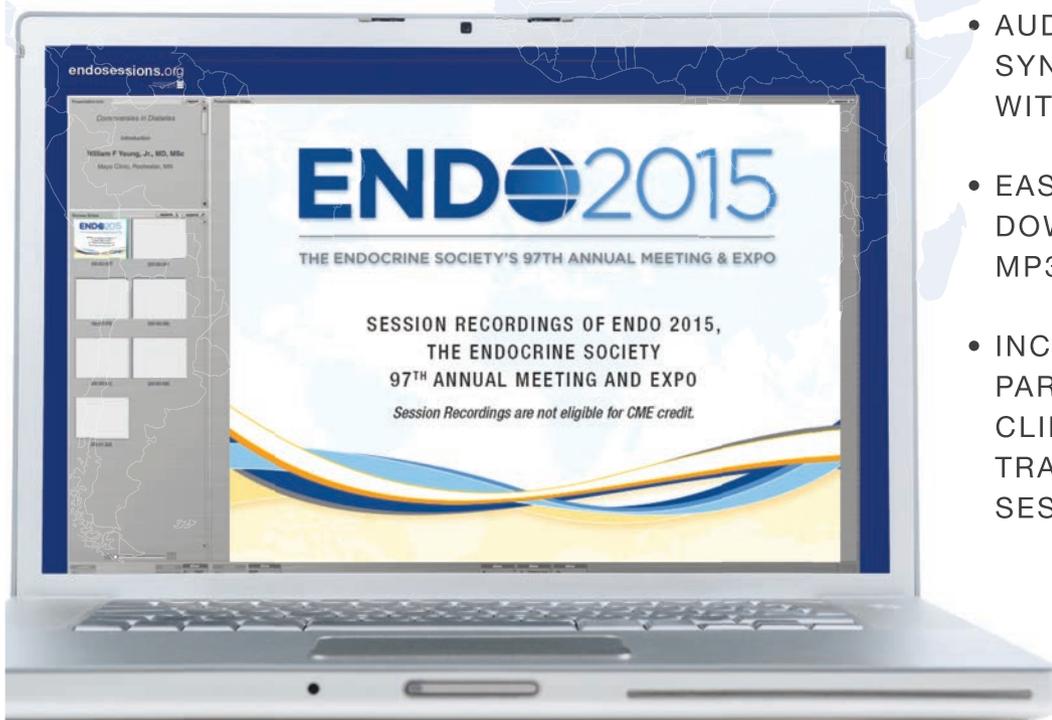
The Hormone Health Network is your trusted source for endocrine patient education. Our free, online resources are available at [hormone.org](http://hormone.org).

Additional editing by Genevieve Neal-Perry, MD, PhD, University of Washington

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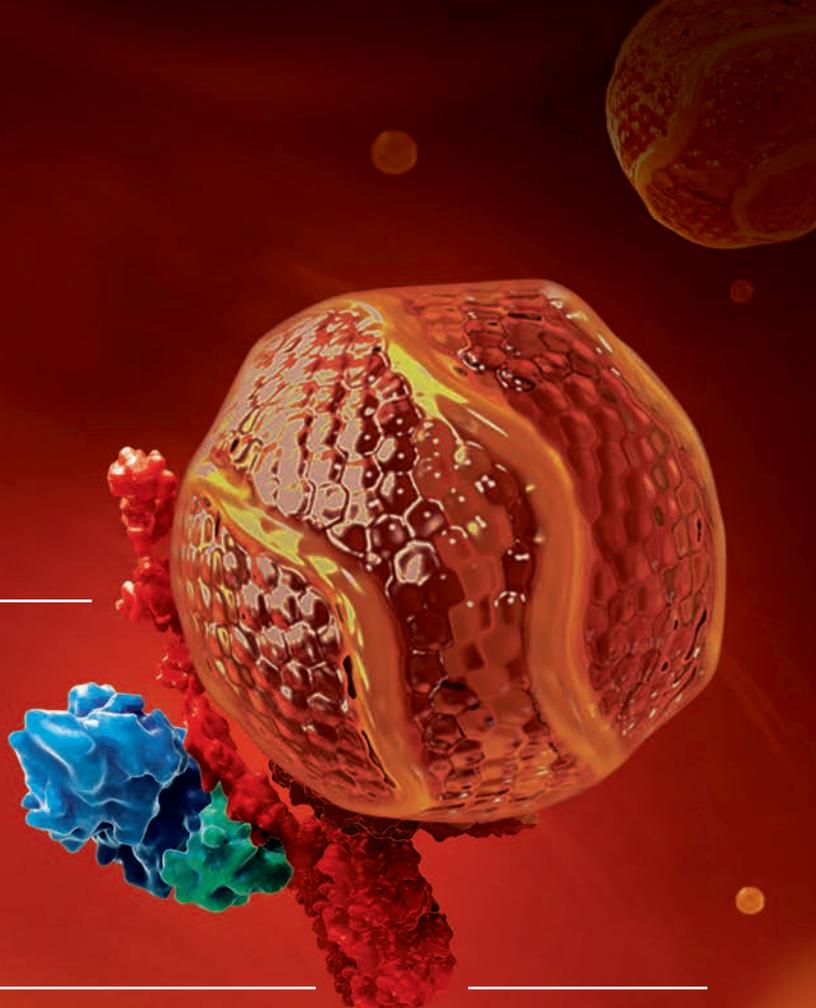


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Cardiovascular

**LDL** = low-density lipoprotein; **LDL-C** = low-density lipoprotein cholesterol;  
**PCSK9** = proprotein convertase subtilisin/kexin type 9.

**References:** **1.** Lambert G, Sjouke B, Choque B, Kastelein JJP, Hovingh GK. *J Lipid Res.* 2012;53:2515-2524.  
**2.** Zhang D-W, Lagace TA, Garuti R, et al. *J Biol Chem.* 2007;282:18602-18612. **3.** Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res.* 2007;48(7):1488-1498.

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