

AUGUST 2015

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINE news™

COMPOUNDED Fractures

The metabolic bone disorder hypophosphatasia typically occurs once in every 100,000 births.

There's a lot clinicians need to know about the diagnosis and treatment of this rare and sometimes fatal condition.

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10



14



18

COVER STORY**10 Compounded Fractures***By Glenda Fautleroy*

The metabolic bone disorder hypophosphatasia typically occurs once in every 100,000 births. There's a lot clinicians need to know about the diagnosis and treatment of this rare and sometimes fatal condition.

14 True Detectives*By Derek Bagley*

From dealing with difficult patients to time constraints and those perplexing cases, all endocrinologists become adept at problem solving one way or another.

18 Breaking the Code*By Melissa Mapes*

As science has progressed, more research has uncovered the secrets locked within the human epigenome. Could new treatments and possible cures for a variety of endocrine disorders be the next discoveries?

22 Connected: Diabetes Data Management Made Easy*By Varun Iyengar*

New software solutions that communicate among differing brands of meters, monitors, and pumps make downloading a patient's glucose data less time-consuming for both physician and patient.

24 The Best Laboratory Products of 2015*By Melissa Mapes*

Scientists weigh in on what products they have discovered that make their lives in the lab a little easier.

DEPARTMENTS**4 President's Viewpoint**

Preparing the Society for the Future

5 Editor's Page

Featuring rare endocrine disorders

7 Trends & Insights

A look at the latest research

26 Advocacy

Congress' Continuing Education

28 InTouch

EPA revamps EDC tests

31 Classifieds

Career opportunities

32 Research RoundUp

Society journal studies

33 Hormone Health Network

The truth about testosterone treatments



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ENDOCRINE SOCIETY

Hormone Science to Health

Strategies Align to Prepare the Endocrine Society for the Future



Lisa H. Fish, MD

As president of the Endocrine Society, I am committed to ensuring that we are forward-thinking in how we can continue to enhance our reputation as a champion of endocrine science and practice, as well as serve as a valuable resource for our members. Our current Strategic Plan (SP3) gives direction to our member and staff leadership in their work for the Society. The core of the plan is:

Direction I: Leadership: Lead endocrine science and medicine toward the goal of improved human health worldwide.

Direction II: Impact and Influence: Position the Society and its Hormone Health Network as the authoritative and trusted source of knowledge that drives sound health and science policy and informs the public.

Direction III: Member Value: Deliver a dynamic portfolio of programs and services that enrich the professional lives of Society members across the continuum of their careers.

Direction IV: Capacity to Lead: Build greater leadership capabilities in every facet of the Endocrine Society and ensure an agile, technologically sophisticated organization and infrastructure to support the Society's goals.

At our recent Council meeting, we invited the editors-in-chief and committee chairs to join the elected Council and discuss three topics that are relevant to our members. It is our hope that by discussing these issues and identifying opportunities for the Society, we can develop initiatives that will support our strategic directions and our members. The topics we discussed were:

Influence of Technology on Endocrine Science and Practice

Technology plays a critical role in the advancement of endocrine science and practice, and its influence will only continue to grow. Applied technology impacts how scientists make discoveries and share their data, how physicians interact with patients, and how patients use personal health data and learn more about their conditions. As a Society, it is important to discuss how technology will impact our work, how we deliver information and resources to our members about future technologies, and how our members contribute to Society initiatives as new technologies are developed.

Diversity and Inclusion: Leveraging Next Gen Strategies to Strengthen Our Approach

As one of the world's leading organizations supporting

the field of endocrinology, the Society has a major responsibility to ensure strong recruitment and retention of diverse talent. It is also critically important that Society members and leaders reflect the diversity of the biomedical field, and that we develop a leadership pipeline to ensure that this happens. For the Society, diversity and inclusion are defined broadly to encompass all aspects of diversity — cultural, ethnic, racial, gender, sexual orientation, etc. As we move forward we need to continue to foster an inclusive environment and ensure that there are opportunities for all of our members to be involved and pursue leadership opportunities both in the field and within the Society.

Increasing the Visibility of Hormone Research, the Practice of Endocrinology, and Their Impact on Public Health

The public is often unaware of the field of endocrinology and endocrine-related diseases and disorders. Increasing this understanding, filling gaps in available public information, and correcting misinformation will raise the visibility of endocrinology to key audiences like patients, policy makers, and regulators. This will have a positive impact on increased research funding, patient referrals, as well as heighten the interest of young people to enter the field as researchers and clinicians. We should explore potential opportunities for the Society to take a proactive role in educating the public and advocating for our members.

The outcomes from the meeting included identification of further discussion topics and a need to engage our members in the creation of strategies in these areas. We will be sharing the meeting notes with the Endocrine Society committees and task forces so that they can begin discussions to address these issues in their work.

We also want to hear from you. If you have a particular interest in any of these topics, please let us know. We want you to share your ideas on how the Society can best support our members in these areas. Please email volunteers@endocrine.org, and let us know how you would like to be involved and/or your suggestions for potential Society initiatives. **EN**

Lisa H. Fish, MD
President, Endocrine Society

AUGUST 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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There's something about rare disorders that has always intrigued me as a journalist. Granted, they're not that common so many clinicians don't necessarily come in contact with them very often. However, it's that oddity that makes them so interesting and in my mind, makes it so vital that we include them in *Endocrine News*. In the past, we've devoted a great deal of ink to some fairly rare endocrine disorders — acromegaly, Cushing's syndrome, hypoparathyroidism, to name a few.

We're continuing the trend this month by featuring the rare and often deadly metabolic bone disorder, hypophosphatasia, in the cover story "Compounded Fractures" by Glenda Fauntleroy on page 10. As with many rare disorders, it is often misdiagnosed and then treated improperly when all it usually takes for an accurate diagnosis is one standard blood test that measures the enzyme alkaline phosphatase. According to Cheryl Rockman-Greenberg, MD, a professor in the Departments of Pediatrics & Child Health and Biochemistry and Medical Genetics at the University of Manitoba in Winnipeg, it behooves medical professionals who work with families and children with hypophosphatasia to make sure people are aware of this disorder. "It's important to help support health professionals in terms of being able to make the diagnosis and to help support families," she says, "to make sure that the right diagnosis is made in a timely way."

One of the aspects of the profession that has drawn so many of you to endocrinology is the chance to really delve into a specific case and unlock the secrets that surround getting to the bottom of a tricky diagnosis. Associate editor Derek Bagley spoke in-depth with Society past president, Richard J. Santen, MD, about the skills needed by today's endocrinologists to truly get to the bottom of a variety of challenging cases in "True Detectives" (p. 14). Whether it's the occasional difficult patient, time constraints, or the aforementioned puzzling case, a variety of problem-solving skills is another requirement in today's ever-changing medical environment.

As medical technology improves, the hope is that patient management will also improve and make treatment easier for both the patient and the physician. Unfortunately, that has not always been the case especially when the various continuous glucose monitors, insulin pumps, and blood glucose meters are not allowed to communicate with each other, the doctor, and the patient. Fortunately, strides have been made in this arena, and some of the latest breakthroughs are featured in "Connected: Diabetes Data Management Made Easy" (p. 22) by Varun Iyengar.

As usual, if you have any topics you think would be a great fit for *Endocrine News*, be sure to let me know at mnewman@endocrine.org.

Mark A. Newman, Editor, *Endocrine News*



Mark A. Newman

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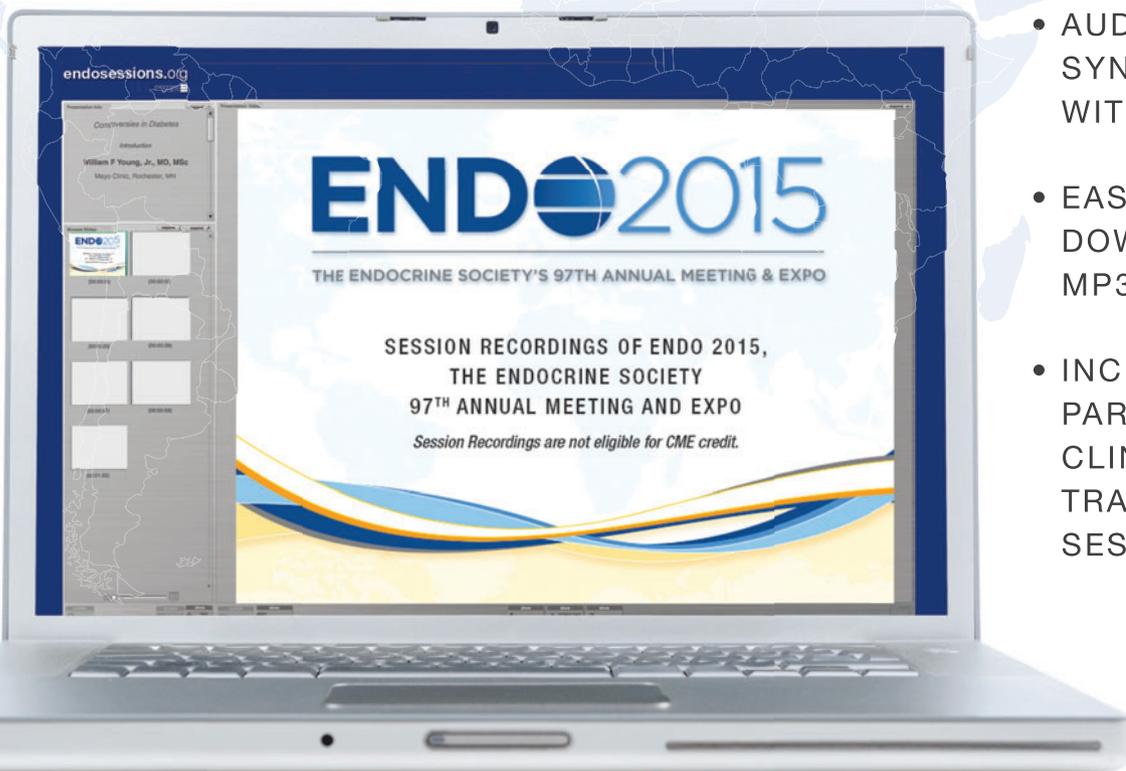


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By Derek Bagley

Beta Blockers May Lessen Risperidone-Induced Bone Loss

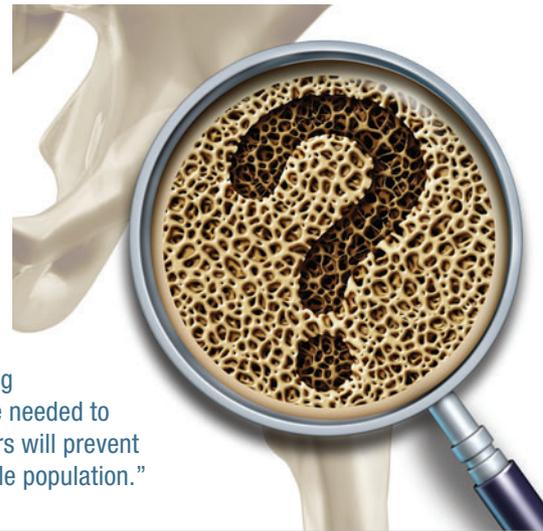
A recent mouse study has shown that beta blockers could reduce bone loss caused by the atypical antipsychotic (AA) drug risperidone (RIS). The study was published recently in *Endocrinology*.

Researchers led by Katherine J. Motyl, PhD, of the Maine Medical Center Research Institute in Scarborough, and Karen L. Houseknecht, PhD, of the University of New England in Biddeford, pointed out that clinical data has shown that AA drugs “are associated with significant side effects, including obesity, hyperglycemia, and dyslipidemia,” as well as causing an increased risk in fracture risk and bone loss. Therefore, schizophrenic patients have a higher risk of fractures than the general population.

Motyl and her team wrote that “the pharmacology underlying the adverse effects on bone is unknown,” but they theorized that the central nervous system could be the culprit, since the sympathetic nervous system (SNS) “is known to uncouple bone remodeling” and RIS treatment in mice eroded bone and reduced bone formation. “Even a single dose of RIS transiently elevated expression of brown adipose tissue markers of SNS activity and thermogenesis, *Pgc1a* and *Ucp1*,” they wrote.

The researchers administered RIS or a vehicle to eight-week-old female mice that were also receiving the nonselective betablocker propranolol to test their theory. They found that RIS did not erode bone or hinder bone formation or cause any changes in bone volume. “Furthermore,” the authors wrote, “ β 2-adrenergic receptor null (*Adrb2*^{-/-}) mice were also protected from RIS-induced bone loss.”

This is the first time RIS has been linked to SNS-mediated bone loss, and the authors concluded that bone loss could be attenuated by beta-blockers. “Because AA medications are widely prescribed,” they wrote, “especially to young adults, clinical studies are needed to assess whether β -blockers will prevent bone loss in this vulnerable population.”



Testosterone Therapy Fails to Treat Ejaculatory Dysfunction

Men who have ejaculatory disorders and low testosterone levels did not experience improved sexual function after undergoing testosterone replacement therapy, according to a new study published in the *Journal of Clinical Endocrinology & Metabolism*.

Researchers led by Darius A. Paduch, MD, PhD, of NewYork-Presbyterian Hospital and Weill Cornell Medical Center in New York, N.Y., conducted a multi-center, double-blind, randomized, placebo-controlled, 16-week trial, in which 76 men with ejaculatory dysfunction were assigned to receive either

a 2% testosterone solution applied on the skin or a placebo. Sixty-six men completed the study. The men were all age 26 years or older with total testosterone levels of less than 300 ng/dL found on two separate tests.

During the study, participants had their testosterone levels measured periodically to determine how well the hormone replacement therapy was working. To gauge ejaculatory function, researchers collected semen samples and had participants complete sexual health questionnaires and logs.

Although the men who received testosterone replacement therapy had higher scores on the Men's Sexual Health Questionnaire on ejaculatory dysfunction than the men who took the placebo, the difference was too small to be statistically significant. The researchers also found little to no improvement in ejaculate volume or orgasmic function.

“This is the first clinical trial examining the treatment of a very common but poorly understood condition that affects men's physical health as well as their interpersonal relationships,” Paduch says. “Although the participants in this study did not experience any significant improvement in ejaculatory function, we hope our work will spur the development of additional clinical trials to find treatments for this condition.”

“Our findings suggest physicians who are treating men with ejaculatory dysfunction should be cautious about prescribing testosterone therapy on an off-label basis,” said another of the study's authors, Shehzad Basaria, MD, of Brigham and Women's Hospital and Harvard Medical School in Boston, Mass. “More research is needed to determine whether a longer course of testosterone therapy or other treatment options can benefit men with ejaculatory dysfunction.”



Food Order Found to Have Significant Impact on Glucose and Insulin Levels

Eating protein and vegetables before carbohydrates leads to lower post-meal glucose and insulin levels in obese patients with type 2 diabetes (T2D), according to a study published recently in *Diabetes Care*. This research could impact the way clinicians advise diabetic patients and other high-risk individuals to eat, focusing not only on how much but also on when carbohydrates are consumed.

Researchers led by Louis Aronne, MD, of Weill Cornell Medical College in New York, N.Y., looked to validate and advance previous research that showed eating vegetables or protein before carbohydrates leads to lower post-meal glucose levels. This time, though, investigators looked at a whole, typically Western meal, with a good mix of vegetables, protein, carbohydrates, and fat.

“We’re always looking for ways to help people with diabetes lower their blood sugar,” Aronne says. “We rely on medicine, but diet is an important part of this process, too. Unfortunately, we’ve found that it’s difficult to get people to change their eating habits.”

“Carbohydrates raise blood sugar, but if you tell someone not to eat them — or to drastically cut back — it’s hard for them to comply,” Aronne continues. “This study points to an easier way that patients might lower their blood sugar and insulin levels.”

The researchers worked with 11 patients, all of whom are obese and have T2D, and take metformin. To see how food order impacted post-meal glucose levels, they had the patients eat a meal, consisting of carbohydrates (ciabatta bread and orange juice), protein, vegetables, and fat (chicken breast, lettuce, and tomato salad with low-fat dressing and steamed broccoli with butter) twice, on separate days a week apart.

On the day of their first meal, researchers collected a fasting glucose level in the morning, 12 hours after the patients last ate. The participants were then instructed to eat their carbohydrates first, followed 15 minutes later by the protein, vegetables, and fat. The scientists then checked the patients’ post-meal glucose levels via blood tests at 30-, 60-, and 120-minute intervals. A week later, researchers again checked the

patients’ fasting glucose levels and then had them eat the same meal, but with the food order reversed: protein, vegetables, and fat first, followed 15 minutes later by the carbohydrates. The same post-meal glucose levels were then collected.

The results showed that glucose levels were much lower at the 30-, 60-, and 120-minute checks — by about 29%, 37%, and 17%, respectively — when vegetables and protein were eaten before the carbohydrates. Insulin was also significantly lower when protein and vegetables were eaten first. This finding confirms that the order in which we eat food matters and points to a new way to effectively control post-meal glucose levels in diabetic patients.

“Based on this finding, instead of saying ‘don’t eat that’ to their patients, clinicians might instead say, ‘eat this before that,’” Aronne says. “While we need to do some follow-up work, based on this finding, patients with type 2 might be able to make a simple change to lower their blood sugar throughout the day, decrease how much insulin they need to take, and potentially have a long-lasting, positive impact on their health.”



Bariatric Surgery Linked to Bone Loss

Bariatric surgery may be associated with bone loss that could lead to fracture, according to a study recently published in *Obesity*.

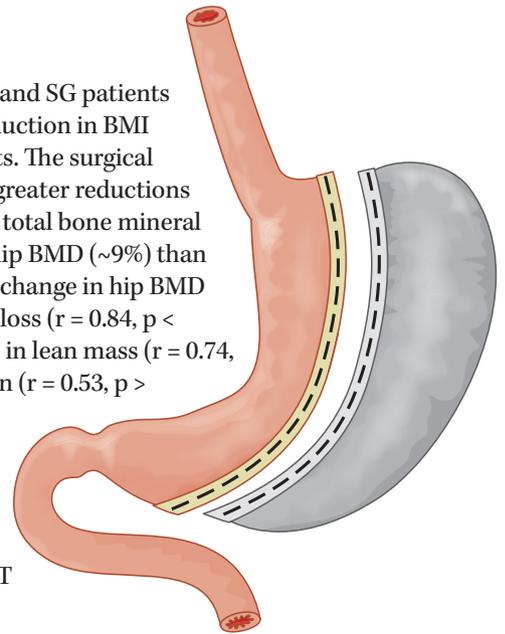
Researchers led by Sangeeta R. Kashyap, MD, of the Cleveland Clinic in Ohio, studied two-year outcomes of patients with type 2 diabetes in the STAMPEDE trial who underwent Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), or intensive medical therapy (IMT). They looked at the respective treatments' effects on lean body mass, total bone mass, and bone mineral density (BMD) measures. Kashyap and her team previously studied the impact of bariatric surgery on diabetes remission.

The authors noted that some studies have an increased fracture risk in patients with type 2 diabetes (T2D), but the fracture risk in obese patients with T2D who undergo bariatric surgery are not well depicted. "Reduction in BMD attributed to surgically induced weight loss has been reported in severely obese post-bariatric subjects," they wrote, "many additional factors contribute to the impact on bone health, including adipokines, menopause status, medication usage such as proton pump inhibitors/tzds, and smoking."

The researchers analyzed 54 participants with T2D who were randomized to IMT, RYGB, or SG and underwent dual-energy X-ray absorptiometry (DXA) at baseline. At

two years, the RYGB and SG patients showed a greater reduction in BMI than the IMT patients. The surgical cohort also showed greater reductions in lean mass (~10%), total bone mineral content (~8%), and hip BMD (~9%) than the IMT group. "The change in hip BMD correlated to weight loss ($r = 0.84$, $p < 0.0001$), and changes in lean mass ($r = 0.74$, $p < 0.0001$), and leptin ($r = 0.53$, $p > 0.0001$). Peripheral fractures were self-reported in RYGB (4/18 patients), SG (2/19 patients) and the IMT (4/16 patients)," the authors wrote.

Kashyap and her team concluded that surgically induced weight loss is linked to modest reductions in lean mass, bone mineral content, and BMD, despite calcium and vitamin D supplements taken by obese T2D patients at two years following surgery. "In addition," they wrote, "vigilance for on-going nutritional deficiencies and bone loss in patients before and after bariatric surgery, especially sleeve gastrectomy, is critical."



Fast FACTS About Hypophosphatasia



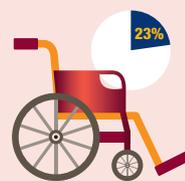
One in 300 people in the U.S. is thought to be a carrier of hypophosphatasia.



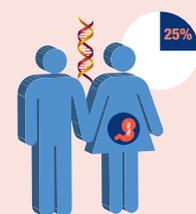
At least six clinical forms of hypophosphatasia have been reported.



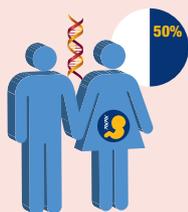
In some specific populations like Canadian Mennonites, hypophosphatasia occurs in one case per 2,500 live births.



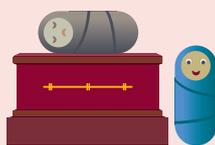
23% of adults with hypophosphatasia use a wheelchair.



The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy.



The risk of having a child who is a carrier like the parents is 50% with each pregnancy.



The mortality rate is 50% for infants who develop hypophosphatasia within six months of birth.



25% of adults with hypophosphatasia require a walking device.



Hypophosphatasia is estimated to occur in one case per 100,000 live births.

COMPOUNDED Fractures

The metabolic bone disorder hypophosphatasia typically occurs once in every 100,000 births. There's a lot clinicians need to know about the diagnosis and treatment of this rare and sometimes fatal condition.

By Glenda Fauntleroy

AT-A-GLANCE

- The very early loss of baby teeth often before ages two or three can be the signal of a very rare metabolic bone disorder known as hypophosphatasia.
- Making a diagnosis comes down to ordering one standard blood test — measuring the enzyme alkaline phosphatase.
- Physicians need to be alert that patients with fractures and bone density scans indicating “osteoporosis” but low ALP levels might be mutation carriers.

The loss of the first baby tooth is generally seen in healthy kids between ages six and seven. The very early loss of baby teeth often before ages two or three, however, can be the signal of a very rare metabolic bone disorder known as hypophosphatasia (HPP).

“Generally, the number of deciduous teeth lost prematurely reflects the severity of hypophosphatasia,” says Michael Whyte, MD, professor of Medicine, Pediatrics, and Genetics at Washington University School of Medicine in St. Louis, Mo. Whyte co-authored a recent study in the June issue of *Bone* that evaluated 173 childhood cases of HPP.

Patients with the mild childhood form of this genetic disease are typically quite functional and grow along within the normal growth curve, he explains. “They are not physically disabled or in chronic pain.”

“In contrast, with severe childhood HPP there is muscle weakness often with a waddling gait, sometimes obvious rachitic deformities of the skeleton such as bowed legs or knocked knees, bony aches and pains, sometimes fracturing, and an increased likelihood of below average stature,” Whyte adds.

HPP is caused by mutations in the tissue-nonspecific alkaline phosphatase gene. When especially severe, it can be associated with seizures, respiratory failure, and premature death. The inheritance patterns indicate an equal number of affected males and females, but the prevalence of the various forms is not well understood, according to Whyte.

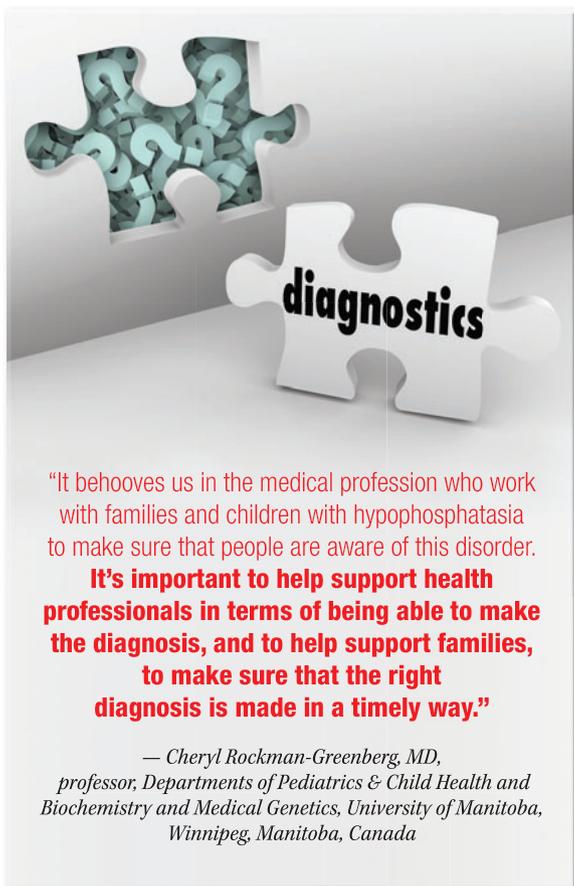
Milder cases can go undiagnosed or misdiagnosed, yet the National Organization for Rare Disorders estimates that severe forms of HPP affect one in 100,000 births in Canada.

An Often Missed, Yet Simple, Diagnosis

“A missed or incorrect diagnosis at first, or delayed diagnosis, is not uncommon for hypophosphatasia,” says Whyte.

“We do not really know without delving deeper into our files how many of our children were first considered as having something else,” he continues. “But we certainly know about children whose first worries included muscular dystrophy because of the weakness; concern about an underlying leukemia because of the nature of some of the radiographic changes; vitamin D deficiency as a cause of the rickets; and even osteomyelitis to explain the x-ray changes and bone and joint pains.”

Cheryl Rockman-Greenberg, MD, a professor in the Departments of Pediatrics & Child Health and Biochemistry and Medical Genetics at the University of Manitoba, Winnipeg, Manitoba, Canada, says it’s not uncommon for people who have very rare disorders such as HPP to wait months, if not years, for a diagnosis. “It’s not because the healthcare professionals aren’t working carefully through the symptoms and signs described by the patient and his/her family,” she says. “But if you have not had much experience with the disease, then it’s not unusual for there to be a really long delay in making a diagnosis.”



“It behooves us in the medical profession who work with families and children with hypophosphatasia to make sure that people are aware of this disorder.

It’s important to help support health professionals in terms of being able to make the diagnosis, and to help support families, to make sure that the right diagnosis is made in a timely way.”

— Cheryl Rockman-Greenberg, MD,
professor, Departments of Pediatrics & Child Health and
Biochemistry and Medical Genetics, University of Manitoba,
Winnipeg, Manitoba, Canada

Yet with HPP, both Whyte and Rockman-Greenberg stress that making a diagnosis comes down to ordering one standard blood test — measuring the enzyme alkaline phosphatase. “When you order blood tests, many healthcare professionals are looking for elevated enzymes,” Rockman-Greenberg says. “But we don’t pay enough attention to a low level of an enzyme, and in hypophosphatasia, there’s a deficiency of the activity of alkaline phosphatase.”

She adds that, “people also don’t have a good understanding that they have to look at the age of the patient and make sure they have the right age range for alkaline phosphatase that is reported.”

The levels of alkaline phosphatase change with age groups, she continues. The range of alkaline phosphatase in infants is different from children, and different from teenagers and adults. And different things can cause low alkaline phosphatase that should first be ruled out.

An Important Contraindication

An important aspect of treating patients with HPP is to know what treatment to avoid. “Adults with hypophosphatasia often get drugs called bisphosphonates, like Fosamax, and these actually exacerbate symptoms and are contraindicated in HPP,” says Rockman-Greenberg. “So it’s important to make an accurate diagnosis and not just offer the supportive therapy, but to know what to avoid.”

An article in the *Journal of Bone and Mineral Research* recently featured a case study illustrating the contraindication.

Author Tim Cundy, MD, from the Department of Medicine at the University of Auckland, New Zealand, led a team of researchers who treated a 55-year-old man suffering from severe bone pain and multiple fractures that happened over a two-year period. The man had developed hypertension at age 40 and at age 50 had renal failure. He

had been in excellent health before then.

“This patient had been asymptomatic so his condition had never been suspected until things dramatically changed when he went into renal failure,” Cundy explains. “And after having a metatarsal fracture and being incorrectly diagnosed with osteoporosis, he was started on a bisphosphonate.”

“The milder adult forms [of HPP] may have very little or nothing in the way of symptoms,” Cundy says. “Physicians need to be alert that patients with fractures and bone density scans indicating ‘osteoporosis’ but low alkaline phosphatase (ALP) levels might be mutation carriers.”

Cundy and his team stopped the bisphosphonate therapy and treated the patient with teriparatide for six months, followed by a kidney transplant. “We were able to reverse the bone disease.”

“The concern is that bisphosphonates can worsen the mineralization defect, cause osteomalacia, or inhibit bone turnover to the extent that ‘atypical’ femoral fractures can occur,” Cundy says. “We need more information and research in this area.”

Waiting for New Therapies

There are no medications or treatments yet approved to treat HPP, but Whyte hopes the Food and Drug Administration (FDA) will soon approve the drug asfotase alfa for severely affected HPP patients. The biologic, being evaluated by Alexion Pharmaceuticals, is an enzyme replacement therapy for treating patients with pediatric-onset HPP. The FDA granted priority review for asfotase alfa in March 2015.

Rockman-Greenberg says in the meantime patients may benefit from supportive measures, including diet and careful orthopedic and pain management. Families coping with HPP also can benefit from psychosocial support, physiotherapy, and respite care, she explains.

“It behooves us in the medical profession who work with families and children with hypophosphatasia to make sure that people are aware of this disorder,” she says. “It’s important to help support health professionals in terms of being able to make the diagnosis, and to help support families, to make sure that the right diagnosis is made in a timely way.” **EN**

— Fauntleroy is a freelance writer based in Carmel, Ind., and a regular contributor to Endocrine News. She wrote about bariatric surgery emergencies in the June issue.

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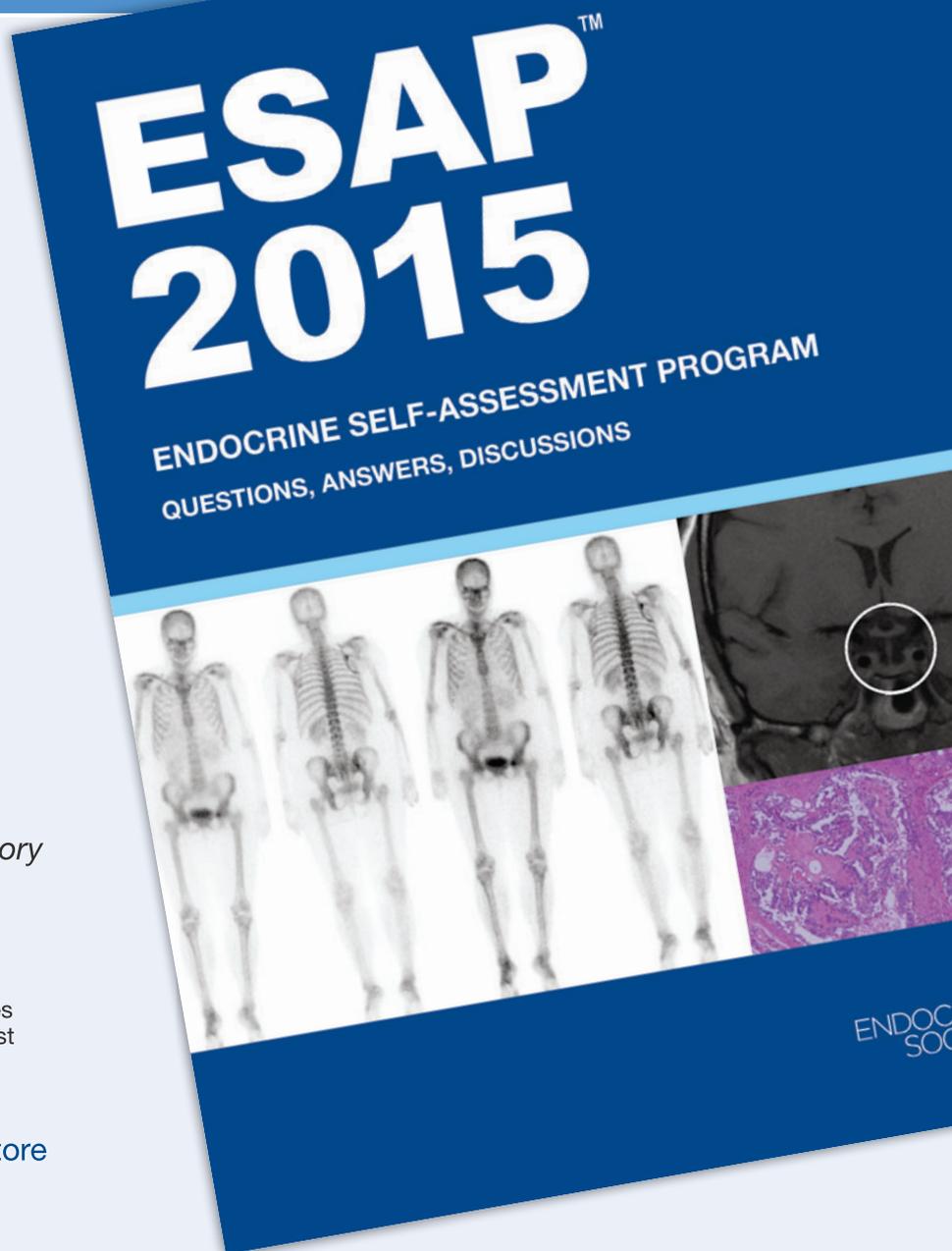
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TRUE DETECTIVES

From dealing with difficult patients to time constraints and those perplexing cases, all endocrinologists become adept at problem solving one way or another.

By Derek Bagley

Every clinician will have at least one: the patient whose name on the chart instills a feeling of anxiety or even dread, the patient whose presence in the waiting room sets off loud sighs and rolling eyes among the staff...the “difficult” patient.

About 15% of doctor-patient relationships rate as “difficult” by the physicians themselves, and that can be for any number of reasons. The patient can be defensive or distrustful, or there could simply be a breakdown in communication between physician and patient.

Another issue is that the patient can present with a highly unusual case, and the doctor is only allotted a short time to figure out the best course of action, which can call for different approaches, creative maneuvering, and a bit of luck.

Indeed, maintaining a healthy doctor-patient relationship is of the utmost importance, even in the face of whatever challenges may arise. Here, we’ll look at some problems that may present in your practice and ways to tackle them and maintain a relationship that is beneficial to both physician and patient.

The Difficult Patient

Some patients come to the clinic ready to spar with their doctors. They’re sick or in pain, nervous about what diagnosis they may receive, or misinformed about treatment options. They can be non-compliant and distrustful, and that can certainly damage the doctor-patient relationship.

For Richard J. Santen, MD, a professor of medicine at the University of Virginia, a practicing endocrinologist in Charlottesville, and former president of the Endocrine Society, it’s a matter of being patient with the patient. He admits that obtaining a patient’s trust is not usually a problem, since he’s a specialist that the patient has been referred to. “When this does occur,” he says, “time usually

AT-A-GLANCE

- Patients deemed “difficult” can be stressful and time consuming not only for the physician but for the physician’s office staff as well.
- The time many physicians are able to spend face-to-face with a patient has often been limited due to dictums issued by departments, facilities, or even insurance companies.
- Patients who present with rare and unusual symptoms often challenge physicians in terms of treatment plans. The trick is to know where to look and with whom to consult.



solves the problem. On repeat follow up, the patient realizes that the physician is knowledgeable. However, I have had instances when that trust did not develop for six months to one year of taking care of the patient. In these situations, developing an effective interpersonal relationship with the patient over time is key.”

But sometimes the patients are not so distrustful or defensive; it’s just that they don’t know how to communicate what’s wrong with them. They have unfocused methods of expressing and characterizing their symptoms, which is understandable, since they have no medical training.

In medical school, it’s often taught that non-directed questions work best, but Santen says that strategy often does not work, and clinicians need to ask specifically about how, when, why, how severe, how often, and so on in a directed fashion. “If I have a patient with hyperthyroidism and ask the non-directed question ‘How are you feeling?’ I might get one of several answers,” he says.

Santen says it’s better to ask questions related to what he knows can be experienced by hyperthyroid patients: Do you have palpitations? Have you lost weight and specifically how many pounds over the last six months? Do you have muscle weakness and cannot get up from a chair without difficulty? These are direct questions that can draw more meaningful and substantive answers.

Time Constraints

And, of course, substantive, knowledgeable answers are what you’re looking for from your patients. So what happens when you only have 20 minutes allocated by your healthcare system to discuss complex issues with your patients?

“On repeat follow up, the patient realizes that the physician is knowledgeable. However, I have had instances when that trust did not develop for six months to one year of taking care of the patient. In these situations, developing an effective interpersonal relationship with the patient over time is key.”

— Richard J. Santen, MD,
professor of medicine at the
University of Virginia,
practicing endocrinologist,
Charlottesville, Va.

The first thing to do is explain briefly to the patient that you have a limited time frame, especially if your patients are used to seeing you for longer. “For years I was allowed 30 minutes to see a follow-up patient and 60 minutes for a new patient,” Santen says. “The hospital and department dictated that all faculty members must see follow-up patients in 20 minutes and new patients in 40. My patients in general are quite complex. Before the more rigorous time constraint, I felt that if a patient had an internal medicine problem that was not related to endocrinology, for example, a urinary tract infection, I would take care of that on the visit. My patients were used to this approach. When the 20-minute rule came in, I explained to them how I would have to change my practice and focus only on the endocrine problem. When carefully explained, the patients

understood and in general were willing to see another physician for the non-endocrine problems.”

Written materials — handouts, pamphlets, etc. — are excellent resources to give to these patients. It’s also a good idea to refer them to patient education resources like the Hormone Health Network. The patients can then read and study the materials so they can be armed with more knowledge and you can have a more meaningful discussion at the next visit.

Make use of newer technologies as well. Put up a general discussion on YouTube that the patient can access. This can be an effective way for patients to get the information on issues that physicians have to explain repeatedly — menopausal hormone therapy, how to take thyroid hormone levels and measure their effects, and so on.

You can also use phone time to discuss issues with your patients, although the drawback to that is that it's not reimbursable. Santen says he calls patients to report abnormal lab results or follow up if clinic time is insufficient. "The electronic medical record makes it easy to document time spent on the phone," he says. "If physicians would be able to bill for phone time, I believe that this use of the phone will become common. This approach is more personal, and patients feel that the physician is particularly concerned if he or she calls the patient. Some of our older physicians use the phone commonly also but as mentioned, this is a generational thing."

The Unusual Case

It's bound to happen in your practice, especially as an endocrinologist. A patient will present with a highly unusual case — a rare disease or an odd array of symptoms or a patient who does not respond to first-line therapies. The first course of action is to know where to look in the literature to find an answer. It also never hurts to walk down the hall and consult a colleague or send an email to an expert for a little assistance.

Santen describes the case of a woman with Riedel's thyroiditis, a rare disease that causes thyroid enlargement that is like scar tissue. If left untreated, the thyroid can grow and cut off the wind pipe. Santen treated this patient for three years, and in that time her windpipe became progressively smaller and her shortness of breath increased. The medical literature suggested using high doses of corticosteroids to treat her. But she didn't respond, and worse, she developed all of the side effects of this type of therapy — weight gain, frequent bruising of the skin without trauma, high blood sugar, weakness of her legs, and high blood pressure. Santen tried several other drugs, but none were successful.

So Santen looked for outside help. "I consulted several of the world's experts to see if there were any new therapies that might work and tried them all — five in total," he says. He found that the only way to benefit her was to perform a tracheotomy, even though it would interfere with speaking and require a tube in her throat for the rest of her life. The patient agreed to the procedure when her shortness of breath became unbearable.

"In the medical literature," Santen says, "it is stated that the scar tissue characteristics of Riedel's thyroiditis

are so great that surgical removal of the thyroid is not possible. The patient understood this but was willing to go ahead with the surgery. Because she had been on so many medications to try to shrink the thyroid in the months prior to surgery, we thought that there might be a chance that the surgeon could remove some thyroid tissue." Santen and his team asked the surgeon to try and remove the thyroid tissue if he could. The surgeon spent five hours meticulously dissecting out one side of the thyroid, which freed up the patient's windpipe and eliminated the need for tracheotomy.

"When she woke up after the surgery," Santen says, "she thought that a miracle had been performed. She could breathe normally and did not have a tracheotomy. What a wonderful feeling as a physician that this took place." He says that they speculated that all the anti-inflammatory and anti-immune drugs used allowed the surgeon to cut around the thyroid to allow removal.

"Over the last six months, the patient has continued to breathe relatively normally, and for the first time in many years to be able to sleep lying flat at night," Santen says. "One experience like this for a physician trumps all of the difficulties encountered otherwise in a practice." **EN**

— Bagley is the associate editor of Endocrine News. He wrote about stem cell tourism in the June issue.

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BREAKING THE CODE

As science has progressed, more research has uncovered the secrets locked within the human epigenome. Could new treatments and possible cures for a variety of endocrine disorders be the next discoveries?

By **Melissa Mapes**



There was a time when mapping the human genome seemed like an impossible task. Yet, through a vast collaborative effort that took 13 years, the Human Genome Project managed to sequence an impressive 99% of the human genome's gene-containing regions — marking one of mankind's greatest scientific achievements.

As genetic research and therapies continue to advance at a tremendous pace, scientists have once again started looking to the future for the next great breakthrough. A growing number of experts believe they have found an even larger and more ambitious undertaking, one with enormous implications for the health and well-being of the world's population: the epigenome.

Rather than operating on a consistent code, epigenetics focuses on alterations and variability in DNA transcription and gene expression that could be influenced by everything from the climate in which one lives to the diet of their ancestors. The dynamic nature of the epigenome makes it an incredibly complex puzzle to decode — a challenge that was unfathomable until several years ago.

The Roadmap Epigenomics Project

The advent of better tools and technology, combined with growing collaboration between the dominions of computer science and medical research, has brought a map of the epigenome into the realm of possibility.

A consortium of North American scientists recently completed the Roadmap Epigenomics Project — a NIH-funded inquiry — into the epigenetic mechanisms that shape the human body and also result in many of our ailments. The researchers analyzed 150 billion sequencing reads, which is a feat equivalent to about 3,000 times the coverage of the human genome. These reads were taken from different antibodies and cell types and translated into a meaningful annotation of 111 primary cell and tissue types.

This data culminated in 24 coordinated publications in *Nature* and other *Nature* journals, including an integrative analysis paper spanning the completed data set.

“The field has made tremendous progress over the last few years,” says Manolis Kellis, PhD, a professor of computer science at MIT, in Cambridge, Mass., and the leader of this integrative analysis.

Kellis' team of bioinformatics experts developed algorithms that learn the patterns of behavior in the chemical modifications on DNA, as well as the histone proteins that the DNA wraps around. These chemical signatures were then systematically mapped across a spectrum of cell types.

“We've been able to elucidate the chemical signatures

associated with different types of elements — promoter regions, enhancer regions, repressor regions, and so on,” Kellis explains.

By decoding these regulatory elements, researchers are able to use genomic association studies to uncover the locations where epigenetic variation is associated with disease.

The data was collected by a cooperative of mapping centers across the U.S. and Canada, and is being used for a variety of different purposes. It operates as a public database of epigenetic findings that can be searched, visualized, and extracted.

What Is Epigenetics?

Like control dials on our DNA, epigenetic marks direct the activity level of genes. This can mean differentiating cell types, like instructing a cell to become a liver cell instead of a heart cell or controlling the genes that regulate the development of certain diseases.

“Genes need a specific epigenetic program to function properly,” explains Moshe Szyf, PhD, professor of pharmacology at McGill Medical School in Montreal, Quebec, and a pioneer of epigenetic research, who was not involved in the Roadmap Epigenomics Project. “The same gene can work differently in response to different signals or might be completely silent in some cells but highly active in others.”

The implications of this are far reaching. Szyf believes that the epigenome plays some role in almost every single disease in existence. He has studied the ties between epigenetics and cancer, and more recently the relationship between behaviors and epigenetics.

There is growing evidence that the behaviors and environmental exposures of parents, and even grandparents, affect the development and health of individuals on an epigenetic level. This implies that inheritance happens through more than just genetic code; we may also inherit past generations’ experiences in the form of epigenetic marks.

Szyf is currently investigating how behaviors like cocaine addiction are related to epigenetics, in addition to experiments involving post-traumatic stress syndrome and prenatally stressed mothers and their children. He is also researching how DNA methylation — a primary building block of epigenetics — may be used as a marker of cancer progression.

The Secrets of Cell Differentiation and Regulation

One of the main goals of the Roadmap Epigenomics Project is to elucidate the inner workings of our cells.



The Roadmap Epigenomics Project

The Roadmap Epigenomics Project became available online as a public resource for research and learning in February 2015 (roadmapepigenomics.org). Additional databases of epigenetic marks can be accessed through the International Human Epigenome Consortium (IHEC), which aims to decipher a minimum of 1,000 epigenomes in less than a decade (ihec-epigenomes.org).

The actual differences between cell types have remained somewhat mysterious despite the many scientific advances made over the ages. By mapping the epigenome, researchers have been able to isolate the regulatory regions on our DNA that determine this across the 111 cell types included in the project.

“It is generally not known which regulators control what tissues and what genes are controlled together,” says Kellis. “We exploited the dynamics of the epigenome to actually link together modules of regulatory regions that act in coordination and discover regulatory patterns that appear extreme, implying that they could be controlling these regions.”

Researchers are now using this information to further our understanding of the circuitry of human cells and the molecular basis of human disease.

The Role of Methylation

Methylation describes the addition of a methyl group to a protein or strand of DNA, thereby altering gene expression and transcriptional activity. When cancer develops, the genes that promote cancer become unmethylated and genes that suppress cancer become methylated. This process can similarly cause stimulation or suppression of countless other diseases.

“The big question is: Why do changes in methylation from the ‘normal’ program of DNA methylation happen?” Szyf posits. “Is it just an accident? Or is it the response to an experience or an exposure?”

The chemical interactions that cause changes in DNA methylation are not well understood. However, if scientists can isolate environmental factors that cause variation in epigenetic marks, they might be able to find prevention strategies for some illnesses. “I think that’s



Epigenetic Inheritance

The famous Överkalix study launched epigenetics into the public eye with alarming revelations about the population of a remote area in northern Sweden. The people of Överkalix parish kept incredibly detailed historical records of their lives, allowing Lars Olov Bygren, a professor at Umeå University in Sweden, to measure the transgenerational effect of food supply on their children and grandchildren.

His first paper showed that boys who experienced a rare and bountiful winter, during which they indulged in a lot of overeating, eventually passed along a shorter lifespan to their sons and grandsons. The offspring of those who suffered through food scarcity lived an average of six years longer than the descendants of the boys who ate their fill. After controlling for relevant variables, the difference in longevity skyrocketed to 32 years.

Since publishing those first findings, Bygren and his colleagues have produced mounting evidence that supports the theory of epigenetic inheritance — an idea that was rejected by the scientific community only a couple decades ago.

where epigenetics will make its biggest contribution: by tying together the environment and disease,” Szyf says.

Some factors, like smoking and exposure to certain chemicals, have become well-recognized modifiers of DNA methylation, but the data is still sparse on a long list of other possible factors.

Epigenetic Influence

So far, the Roadmap has helped researchers discover patterns that explain the origins of phenotypes ranging from height and cholesterol levels to ADHD and multiple sclerosis. The results have often been surprising.

It is widely known that Alzheimer’s disease is associated with neurodegeneration, which is accompanied by inflammation. This inflammation has always been considered a consequence of the neurodegenerative process. But the genetic variants that predispose individuals to Alzheimer’s disease are not localized in the control regions of the neurons that die — instead, they are localized in the control regions of immune cells. This suggests that the inflammation may actually be driving neurodegeneration rather than the reverse.

Kellis hopes that the Roadmap will also catalyze the development of many medical applications for epigenetics. Progress in cancer diagnosis is picking up speed, and he anticipates that oncologists will soon be able to use epigenetic marks to find the source of metastatic cancers with unknown origins in the body.

Szyf agrees. “I think the diagnostic DNA methylation marker market is going to explode,” he says. “It will provide exquisite tools to differentiate both in mental health and physical health like cancer, diabetes, stages of different kinds of diseases as well as predict diseases.”

Epigenetic Therapies

In addition to diagnostic and predictive potential, epigenetic therapies are also in development. The U.S. Food and Drug Administration has approved several already, most recently a drug called panobinostat for the treatment of multiple myeloma. Panobinostat blocks a harmful enzyme that can change the epigenetic properties of DNA, thereby inhibiting the growth of the cancer.

A new study published in *Nature Medicine* shows that panobinostat slows the growth of DIPG — a fatal form of brain cancer that takes the lives of hundreds of children in the U.S. each year. The study implanted tumors into mice and found that the drug increased survivability. Although still in preclinical stages, the drug shows potential as a therapy for patients with this devastating diagnosis.

Szyf predicts that epigenetic therapies will be created for a wide range of diseases — from Alzheimer’s to schizophrenia to diabetes and beyond. “Drug development is still moving very slowly,” he says, “but, at some moment, there is going to be an inflection and epigenetic treatments will exponentially explode.”

Kellis encourages cautious optimism when it comes to finding epigenetic cures for diseases, though. “We get very excited when a correlation with a disease is found, but it’s often unclear whether that epigenetic variation is the cause of the disease or simply the consequence of the disease.”

For diseases that have epigenetic variation as a symptom instead of a cause, epigenetic therapy is probably not in the cards. Yet, the epigenome still contains many discoveries that are waiting to be made. **EN**

— Mapes is a Washington D.C.-based freelance writer and a regular contributor to Endocrine News. She wrote about the artificial pancreas in pediatric patients in the May issue.

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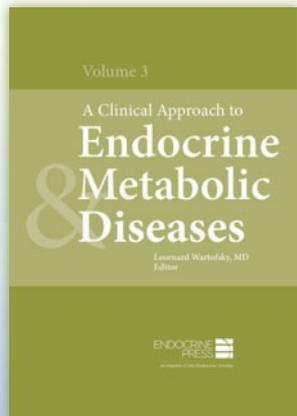
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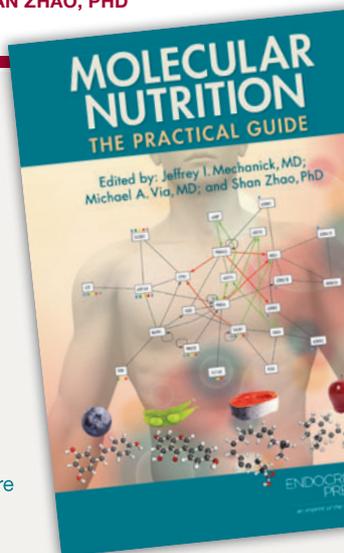
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CONNECTED: Diabetes Data Management Made Easy

New software solutions that communicate between differing brands of meters, monitors, and pumps make downloading a patient's glucose data less time-consuming for both physician and patient.

By Varun Iyengar

Imagine the following: You are caring for someone with a chronic, 24/7 disease where patients are asked to self-administer a potentially deadly drug every day, and you are only given 20 minutes with your patient a few times a year.

Oh, that's right — you don't have to imagine it. It's type 1 diabetes.

The Problem

A physician can only do so much for someone with type 1 diabetes in a short office visit. David Ahn, MD, a clinical instructor of endocrinology at UCLA, knows this burden well. "In my endocrinology practice, type 1 diabetes easily represents my biggest time management challenge," he says. "Unfortunately, it's almost a given that these visits will either run over time or end with some topics left unaddressed."

Ahn's words capture the whirlwind of challenges confronting endocrinologists seeing patients with diabetes. For one, the patient population is growing quickly; the International Diabetes Federation (IDF) has predicted that by 2035, the number of people with diabetes will near 600 million, a roughly 50% increase relative to its 2014 estimate of 400 million. Meanwhile, there is a shortage of endocrinologists. According to studies from the 2014 Center for Disease Control's *National Diabetes Statistics Report* and

Journal of Clinical Endocrinology and Metabolism, there is one endocrinologist for every 4,117 diabetes patients in the U.S. The cost of care has also become a huge problem for patients and the healthcare system; according to the IDF, diabetes expenditures in the U.S. reached \$612 billion in 2014. In short, endocrinologists have less time and fewer resources for patients than ever before.

Data Downloading

One aspect of care that often proves troublesome is data downloading. At the American Association of Diabetes Educators 2014 meeting, a poll revealed that only 5% of the 400 attendees worked with physician providers who routinely download continuous glucose monitors (CGM) and pump data. "We are constantly pressured to do more in shorter visits," Ahn says. "Something has to give, and it's often the downloading of glucose data."

Historically, the challenge of data downloading has been that information on blood glucose meters (BGM), CGMs, and insulin pumps has been handled in a very siloed way. Companies have designed devices to work only with proprietary hardware and software, making it inconvenient to download in the first place and even more difficult to integrate data from different devices (e.g., a pump and a meter).

As a result, the process of downloading glucose data

can be time-consuming and frustrating. Endocrinologists do not have time to fumble with what is often unwieldy software to download these data. This sentiment is well captured by Irl Hirsch, MD, professor of medicine at the University of Washington School of Medicine in Seattle, and an endocrinologist at the University of Washington. "It is difficult to convince physicians that downloading actually improves care and saves time in the long run," he says. "This is especially true for those providers who were not introduced to the benefits of downloading in their training. And for those who do understand the benefits of downloading, they work in clinics or offices without an infrastructure to do it efficiently and the frustration can be just as great."

A Solution

Hirsch's dilemma is a reminder that providers need convenient data download and interpretation solutions. This is where data management platforms come in; these "device-agnostic" systems reflect a growing trend in diabetes. They refer to software and hardware solutions that help download and consolidate data from multiple BGMs, CGMs, and insulin pumps into a single, standardized report. While currently available software and cables are often not interoperable, device agnostic data systems solve this problem by providing a single hardware/software solution that can download and integrate data from multiple devices.

In recent years, three companies have emerged with the goal of making data access easier and more convenient. After all, having this data is key to clinical decision making. They provide a way of looking at what actually happened, not just what patients can remember.

DIASEND[®]: diasend is a universal platform that enables providers to connect BGMs, CGMs, and insulin pumps to a single piece of mobile-enabled hardware that instantly uploads data online, thus eliminating any need for software to be installed at the clinic. The diasend system boasts more than 100 compatible devices and consolidates the information into a structured Web-based report, no matter the device or how the data are stored. The system also has an accompanying personal version that allows patients to upload the data at home using the software diasend Uploader (Mac and PC compatible) to upload and share data online with providers.

GLOOKO[®]: Glooko's MeterSync Blue is another piece of hardware that enables patients to upload data via Bluetooth from more than 30 glucose meters (~90% of the market) to Android and Apple apps. When a patient or provider wants to download data, they simply plug the MeterSync

DIABETES DATA MANAGEMENT

Glucose Data
Data Interpretation
Patient concerns

"It is difficult to convince physicians that downloading actually improves care and saves time in the long run. This is especially true for those providers who were not introduced to the benefits of downloading in their training."

— Irl Hirsch, MD,
professor of medicine, University of
Washington School of Medicine,
Seattle

Blue adapter into their meter and results are sent wirelessly to the app. Integration with insulin pumps and CGMs is not currently available but is in the works. Notably, the MeterSync Blue adapter can be left plugged in all the time, a patient convenience that essentially transforms those meters into 24/7 Bluetooth-enabled devices.

TIDEPPOOL[®]: Tidepool is developing a Web-based hub for diabetes data called Blip. It takes data from most BGMs, CGMs, and insulin pumps and consolidates that data into a single consolidated report. Tidepool is also working to develop the Tidepool Uploader, Web-based software that will connect with multiple devices and upload the data, eliminating the need for unique software for every single device. The Tidepool Uploader will support devices from Abbott, Bayer, Dexcom, Insulet, LifeScan, Medtronic, and Tandem. Blip and the Tidepool Uploader are not yet available commercially, but they are slated for release soon. Tidepool is a 501c3 nonprofit entity that intends to offer its software for free to patients and providers. In addition to offering Blip for data viewing, Tidepool will enable users to see their data in an eco-system of apps, fostering choice and interoperability.

Focusing on the Patient

While we have largely focused on providers, patients need more convenient data downloads as well. After all, they can enhance self-management and allow patients to begin to own their diabetes. The need for better solutions is well evidenced by data from the T1D Exchange Clinic Registry. This registry is made up of more than 26,000 individuals with type 1 diabetes who range in age, at time of enrollment, from less than one year to 93 years. Even in this group that represents some of the most engaged type 1 patients, more than 50% of pump/BGM/CGM users never upload their data, and less than 10% upload their data more than once per week. Many patients may be weighing the decision of whether to upload their data and concluding that the hassle is too great.

Data uploading platforms have the potential to facilitate better decision making, tighten patient-provider feedback loops, and inform more holistic self-management. They represent a new tool in the diabetes toolkit.

Of course, these platforms don't solve all the challenges confronting diabetes treatment and management, but they can make those challenges a little bit more manageable. **EN**

— Iyengar is an associate at Close Concerns, a healthcare information company located in San Francisco. He writes about diabetes technology and digital health.



The Best Laboratory Products of 2015

Scientists weigh in on what products they have discovered that have made their lab lives a little easier.

By Melissa Mapes

Each year, thousands of new and improved tools for scientific research hit the market, and it can be difficult to determine which products are worth the investment. To help researchers decide how to outfit their labs, ScienceSelect, an independent online resource for scientists, takes an annual vote on the best laboratory products in the world.

Called the “Scientists’ Choice Awards,” the rankings are based on nominations and votes by about 7,400 members of the global scientific community. The most recent winners were announced in Philadelphia at the annual meeting of the American Association for Cancer Research (AACR) this past April. There are three categories: Best New General Lab Product, Best New Separations Product, and Best New Spectroscopy Product. This year, ScienceSelect introduced an additional subset of awards called Reviewers’ Choice, which rewards the merits of top manufacturers.

Best New General Lab Product

Top prize in the general product realm went to the **1 Multipipette® M4/Repeater® M4**, made by Eppendorf. This handy little instrument allows lab workers to quickly and accurately pipet with one hand and can dispense up to 100 times without refill — higher than competing products.

The Repeater reduces the risk of contamination during dispensing actions with a special ejection tip that helps avoid contact and offers 20 volume settings.

It also contains a sensor that shows the tip volume on a display screen, which gets rid of manual calculations. To save power, a motion sensor allows the machine to automatically switch off when it is not being used. It is ideal for use with toxic and dangerous solutions and projects that require repetitive, precise dispensing.

Best New Separations Product

With a name reminiscent of a space-age death ray, the **2 Vanquish™ UHPLC System** immediately sets big expectations for its abilities. This high performance liquid chromatography (HPLC) instrument from Thermo Scientific apparently does not disappoint, as it took home first place in the separations category.

Among its attributes, the Vanquish system claims unparalleled sample dosage precision, air stream cooling to maintain sample integrity, automated workflows with barcode reading, and up to nine different solvent combinations. The system also runs on Chromatography Data Systems (CDS) software, specifically Chromeleon, which helps streamline processes and reduce training time with a user-friendly design. These features improve efficiency and separations, and allow for the expeditious analysis of samples.

Best New Spectroscopy Product

Like the other first prize winners, the **3 NexION 350 ICP-MS Spectrometer** received major points for its time-saving qualities. This machine boasts a data acquisition

1 Best New General Lab Product



2 Best New Separations Product



3 Best New Spectroscopy Product

5 Company of the Year Award

ThermoFisher
SCIENTIFIC

6 Best Customer Service



Agilent Technologies



4 Product of the Year

speed 10 times faster than any other ICP-MS on the market. Users claim that it “enhances signal stability” while simultaneously providing “superior uptime.”

Even with heavy use, the NexION 350 ICP-MS seems to uphold its performance. It requires less maintenance than other machines because it does not have extraction lenses to clean. Additionally, a triple cone interface offers the most tightly focused ion beam on the market and inhibits the build-up of sample deposits within the spectrometer.

In reviews, this spectrometer is described as easy to set up and operate, but users caution against processing high-salt solutions and say the software could be simpler. Overall, it is most recommended for routine work.

Reviewers' Choice Awards

Similar to the Scientists' Choice Awards, the new Reviewers' Choice Awards include three categories: Product of the Year, Company of the Year, and Customer Service of the year. These recommendations help researchers decide which manufacturers to purchase from, in addition to highlighting the most popular piece of equipment based on online reviews. Made by Waters Corporation, the 4 **ACQUITY Ultra-Performance Liquid Chromatography (UPLC) System** won the most positive reviews — a total of 84 — and was awarded Product of the Year. This UPLC system claims great speed, sensitivity, and resolution, and is described as ideal for drug discovery by the manufacturer.

Veronique Carrier, a reviewer from GlaxoSmith-Kline, writes, “[I] went from 60 minute runs to 3 minute runs. [It] saves a lot of time.”

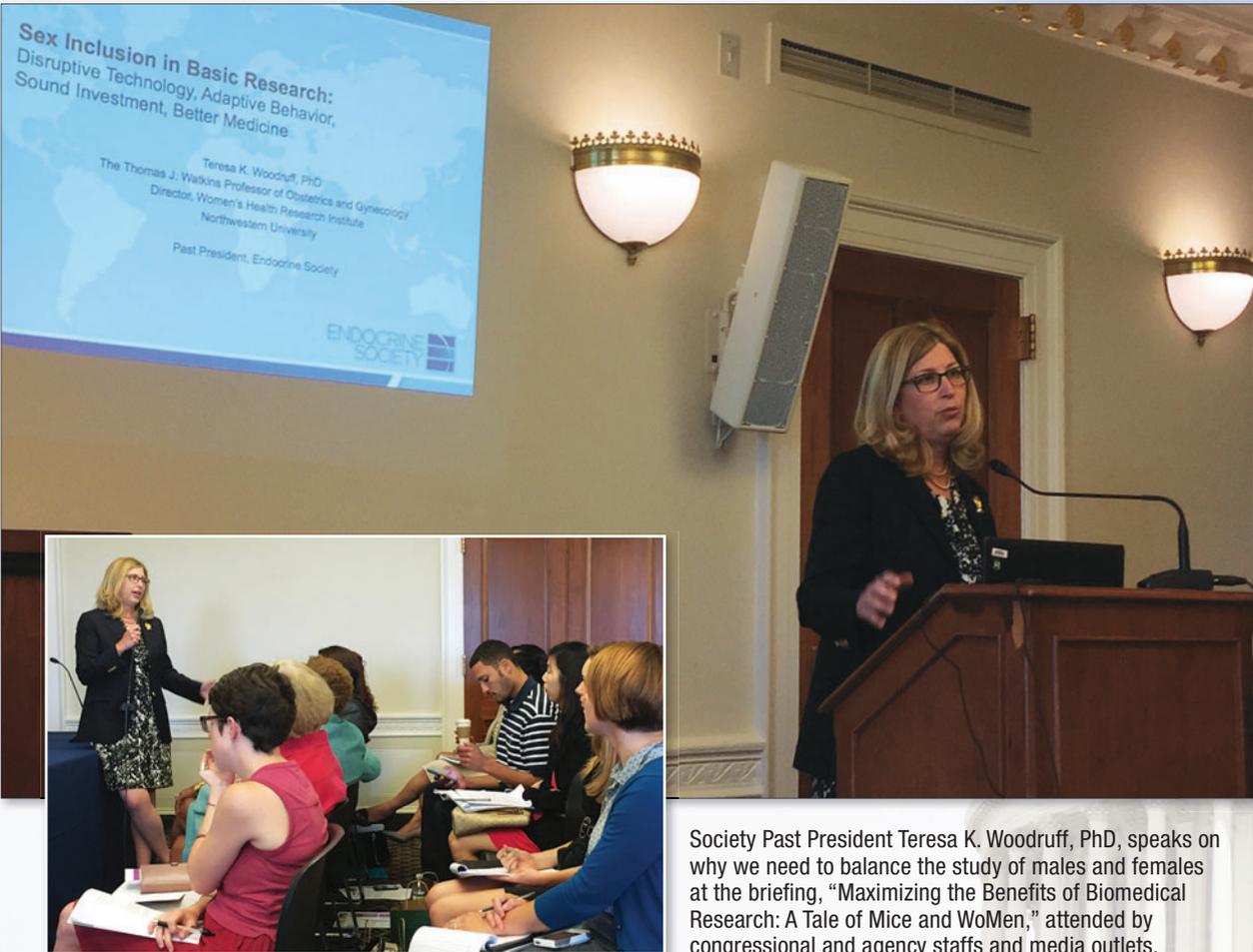
Among many positive reviews, there was also some criticism. A number of reviews cite issues with the software, while others say it often needs maintenance or repair. However, most reviewers agree that the system is easy to fix thanks to great after sales service.

The Company of the Year Award went to 5 **ThermoFisher Scientific** based on 540 reviews of its 1,087 products. The company provides products with a wide range of applications ranging from diagnostic equipment to reagents. Reviews consistently rank them highly for ease of use, after sales service, and value for money.

Similarly, 6 **Agilent Technologies** took home the prize for Best Customer Service based on positive user feedback. Agilent claims to be “the world’s premier measurement company and a technology leader in chemical analysis, life sciences, diagnostics, electronics, and communications.” The company employs over 20,000 people to help its customers across the globe.

Additional information and reviews on a wide variety of lab products can be found on the ScienceSelect website (www.selectscience.net). **EN**

— Mapes is a Washington D.C.-based freelance writer and a regular contributor to Endocrine News. She wrote about the artificial pancreas in pediatric patients in the May issue.



Society Past President Teresa K. Woodruff, PhD, speaks on why we need to balance the study of males and females at the briefing, "Maximizing the Benefits of Biomedical Research: A Tale of Mice and WoMen," attended by congressional and agency staffs and media outlets.

Society Stresses Sex Inclusion in Biomedical Research to Congress

On July 10 the Endocrine Society and the Society for Women's Health Research (SWHR) co-sponsored a briefing entitled, "Maximizing the Benefits of Biomedical Research: A Tale of Mice and WoMen, Why We Need to Balance the Study of Males and Females." Speakers included former Endocrine Society president Teresa K. Woodruff, PhD; Phyllis Greenberger, president and CEO of SWHR; Janine Clayton, MD, director of the NIH Office of Research on Women's Health; and Marsha B. Henderson, MCRP, director of the Office of Women's Health at the FDA. The briefing was designed to educate members of Congress and their staff about the need to include both sexes in all phases of biomedical research and support legislative language to help NIH implement new policies to promote sex inclusion in preclinical research.

During the briefing, Greenberger introduced the topic and described how drugs can affect men and women differently. Woodruff then discussed the need to address sex inclusion in preclinical research, highlighting recent Endocrine Facts and Figures data showing

several endocrine-related conditions that disproportionately affect women. Clayton and Henderson then described new policies and actions by federal agencies to promote the study of sex as a biological variable in research and clinical trials. Following the presentations, audience members took the opportunity to engage speakers in a question and answer session.

The briefing generated tremendous interest on Capitol Hill and among organizations throughout Washington DC. Available seats were rapidly filled and speakers delivered their presentations to a full room. In addition to Hill staff, attendees included representatives from federal agencies, research advocacy organizations, other scientific societies, and media outlets. The briefing was covered by various media outlets.

The event was particularly timely, as the Senate Health, Education, Labor, and Pensions (HELP) Committee is exploring ways to modernize the drug development process from basic research through FDA approval. The Endocrine Society believes that appropriate consideration of sex as a biological variable in

research is necessary to maximize the efficiency of the drug pipeline. Recently, the NIH issued a notice indicating the expectation “that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies” in grant applications, unless strong justification is provided to support the study of only one sex. The Society believes this a good first step, but legislation is still needed to give more teeth to the NIH policy intent.

To further advance the issue with Congress, Woodruff and Society staff met with the offices of several Senate HELP Committee members to discuss the importance of balancing males and females in preclinical research and to provide proposed text that could be incorporated into legislation.

Brat Amendment Defeated, House Passes 21st Century Cures Legislation

The Society’s grassroots advocacy helped defeat an amendment that would have made a new funding stream for the National Institutes of Health (NIH) discretionary rather than mandatory and clear the way for passage of the 21st Century Cures Act.

After a year and a half of consideration, the U.S. House of Representatives was ready to vote on the 21st Century Cures Act the second week in July. The Cures legislation has been a bipartisan effort to increase funding for medical research, overhaul drug development, and innovation to get lifesaving cures to people who need them faster.

Prior to the vote, however, an amendment was offered by Representative Dave Brat (R-VA) to make the Innovation Fund, which was created to provide \$1.75 billion per year for the next five years to the NIH as well as some additional funding for the FDA, discretionary rather than mandatory. The amendment would not only remove the assurance of increased funding for the NIH, but would almost certainly result in funding cuts to the other agencies in the public health service and jeopardize the passage of the 21st Century Cures Act. For these reasons, the Society opposed the amendment and encouraged its members to participate in an online advocacy campaign. In the end, the Brat Amendment failed in a 141-281 vote and 21st Century Cures passed by an overwhelming majority.

The Society is grateful to the House leadership and the members and staff of the House Energy and Commerce Committee for their vision and dedication to bringing 21st Century Cures legislation to a vote. We look forward to working with them as this legislation moves forward. The Society also thanks all of its members who participated in its advocacy efforts. Your voice made a difference!

Obama Nominates Slavitt as Medicare Administrator

President Barack Obama’s nomination of acting administrator Andy Slavitt to be administrator of the Centers for Medicare and Medicaid Services leaves Senate Republicans weighing how to orchestrate the confirmation process in their favor.

The Senate could use a confirmation hearing to rehash the stumbles of the 2010 healthcare overhaul, particularly the launch of the federal exchange website. They could cite Slavitt’s past involvement with a company working on the federal exchange. Both would deflect attention from Obama’s victory in June, when the Supreme Court said the law’s subsidies should be available in every state regardless of who runs the health insurance exchange.

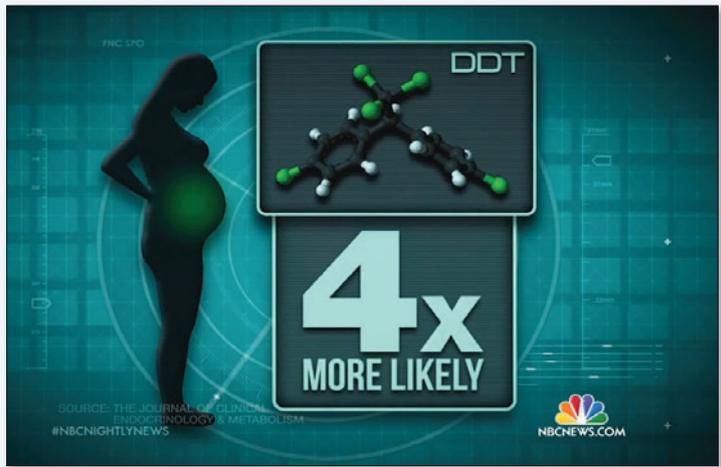
But Republicans may dislike giving Democrats a stage to pose easy questions and allow Slavitt to promote the law, including his role in improving the federal exchange. That is especially the case since the Republicans can do little to change the law for the remaining 17 months of Obama’s term. They may prefer to do nothing and leave Slavitt as acting administrator.

Slavitt worked for federal contractor Optum when it came in to fix healthcare.gov. But he was also with Optum when its subsidiary, Quality Software Services Inc., built the data hub for the federal exchange website. The hub was viewed as one of the few pieces of the IT apparatus that worked, but the company created the registration tool that caused bottlenecks after the troubled October 2013 launch. QSSI received a larger role during the cleanup effort later that month. Consequently, Slavitt could be painted as being both part of the problem and part of the solution.

It is also possible that the Senate will hold a hearing only to see the confirmation fizzle out later. Slavitt would replace Marilyn Tavenner, who stepped down in January to join America’s Health Insurance Plans as president and CEO, was the first Senate-approved administrator of CMS since Mark McClellan occupied the post from 2004 to 2006. Obama administration nominees haven’t been moving through the Senate particularly quickly since Republicans took control in the 114th Congress. Senate Majority Leader Mitch McConnell (R-KY), said Slavitt’s nomination “will receive thorough consideration” in a statement released after the July 9 announcement. **EN**



Andy Slavitt, President Obama’s nominee to head the Centers for Medicare and Medicaid Services.



JCEM Study on EDCs Garners Headlines Around the World

The Society advanced its thought leadership on endocrine-disrupting chemicals (EDCs) with a media campaign around a new *Journal of Clinical Endocrinology & Metabolism (JCEM)* study.

The *Washington Post*, *Forbes*, and *National Geographic* were among the top-tier outlets that covered the research. The study, “DDT Exposure in Utero and Breast Cancer,” found an association between prenatal exposure to the pesticide DDT and breast cancer risk in a group of women born between 1959 and 1967 in California. “NBC Nightly News” aired a story about it on June 21.

Other notable outlets that covered the study included *Time* magazine, Fox News, NBC News, CBS News, and *Science* magazine’s blog Science Shot.

To support ongoing EDC advocacy efforts in the European Union, the Society also distributed the press release to media contacts at key outlets there, including *The Times of London*, Spanish newspaper *El Mundo*, and *Journal de l’Environnement*. The Parisian newspaper *Le Monde* published a front page story on the JCEM study on June 18. **EN**

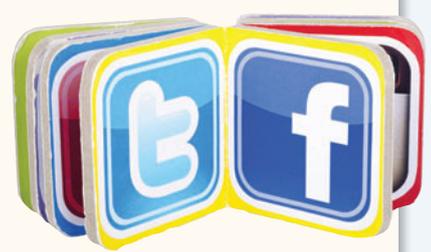


Social Media Is Increasing Society Journal Citations

The Society is leveraging the staff’s social media expertise to help members promote their research in the digital realm. Do you know the saying, “If you teach a man to fish...”? Well if you teach an endocrinologist to tweet, he or she will be well positioned to drive readers to his or her published work and potentially increase citations of his or her papers. If enough members take up this social media approach, the attention papers generate might even raise the Impact Factor of our journals!

Endocrinology editor-in-chief Andrea Gore, PhD, University of Texas at Austin, agreed to give Twitter and Facebook a whirl to promote her recent article that focused on developing an animal model of menopause. With a coordinated campaign utilizing Gore’s new personal accounts (follow her on Twitter at **@andreaagore**), the Society’s platforms, and the University’s accounts, we saw impressive results. During the first week of the campaign, Gore’s paper received 10 times more clicks than two other *Endocrinology* papers that debuted the same day.

The staff is looking for other newly accepted papers to promote in a follow-up case study. Once we have sufficient data, we plan to develop online resources to teach members and journal authors how to use social media to spread the word about their work. Stay tuned!



Endocrine Reviews Maintains Top Impact Factor

The Society's journal *Endocrine Reviews* ranked first in Impact Factor in the "Endocrinology and Metabolism" category, according to Thomson Reuters' recently released annual Journal Citation Report (JCR) for 2014.

Endocrine Reviews led the 128 journals in the "Endocrinology and Metabolism" category and has ranked at the top of the category for more than five years. A highly regarded metric used to measure the success of scholarly journals, the 2014 Impact Factor is calculated by tracking how many times articles that were published in 2012 and 2013 were cited during 2014. The number of citations is then divided by the total number of articles published in 2012 and 2013 to arrive at the Impact Factor.

Endocrine Reviews retained its ranking as the top journal in the field of Endocrinology & Metabolism, with an Impact Factor of 21.059 for 2014. The journal's Impact Factor rose from 19.358 in 2013.

"It is an honor to see *Endocrine Reviews* has once again earned the highest Impact Factor in the Endocrinology & Metabolism category," says Leonard Wartofsky, MD, who was named editor-in-chief of the journal in April. "This is a fitting tribute to the quality work our authors, reviewers, and editors produce. I am pleased to be part of the journal's tradition of excellence."

Endocrine Reviews publishes bimonthly comprehensive, authoritative, and timely review articles balancing both experimental and clinical endocrinology themes.



Society Participates in NIAMS Advisory Council Meeting

As part of the Society's comprehensive approach to enhance the visibility of endocrinology among research funding agencies, the Endocrine Society participated in the June 16 meeting of the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Advisory Council. The Council advises the director of NIAMS on research, support activities, and functions of the Institute.

During the meeting, the Council heard a presentation by John Gallin, MD, director of the NIH Clinical Center. Gallin gave an overview of resources at the NIH Clinical Center and described opportunities for the extramural community to collaborate with the intramural researchers at the Center on research projects. Several specific resources were highlighted during the presentation as areas where the NIH can bring unique value to projects. Some examples of the NIH Clinical Center specialties and resources include deep phenotyping, metabolic chambers, a biomechanics lab, a cell-processing facility, and a focus on rare diseases. The Clinical Center also offers opportunities for training, for example, for PhD students interested in learning more

about clinical research.

Council also reviewed the NIAMS K award program for mentored clinical research. The NIAMS presented data on the fraction of K08 and K23 awardees who continue on a research track and transition to independent funding e.g., through the R01 mechanism. The Institute noted that nearly 40% to 50% of K08 awardees become independent investigators, while turnover for K23 awardees was more variable, with 36% to 80% becoming R01-funded investigators. The NIAMS further noted that the overall number of R01 applications from K awardees was on a downward trend, implying that K awardees are facing new challenges that could incentivize nonresearch career paths. Council discussed three areas where The NIAMS could help K awardees overcome challenges, including increasing salary caps, enabling awardees to collect supplemental salary on the final two years of the K award, or create a limited FOA specifically for K awardees. Council encouraged NIAMS to look for opportunities to ensure that K awardees have protected time for research. **EN**

— Joe Laakso

Event CALENDAR

SEPTEMBER 8 – 12, MIAMI
Clinical Endocrinology Update
www.endocrine.org/ceu

OCTOBER 9 – 12, SEATTLE
American Society for Bone and Mineral Research Annual Meeting
www.asbmr.org

OCTOBER 17 – 21, CHICAGO
Neuroscience 2015
www.sfn.org

OCTOBER 18 – 23, ORLANDO
Thyroid ITC 2015
www.thyroid.org

NOVEMBER 1 – 7, LOS ANGELES
Obesity Week 2015
www.obesity.org

APRIL 1 – 4, BOSTON
ENDO 2016
www.endocrine.org/endo-2016

The Society Receives Accreditation with Commendation from ACCME

The Endocrine Society has been resurveyed by the Accreditation Council for Continuing Medical Education (ACCME) and awarded Accreditation with Commendation for six years as a provider of continuing medical education for physicians.

The accomplishment is recognition of superior work of our member leaders and staff, including those involved in educational planning and delivery. The decision also reflects the work of the Society as a whole, with efforts from across the organization that contributed directly to the Society's Commendation status. This includes the Society's QI program, clinical practice guidelines, performance measures, and PIMs; patient education, publications, newsletters, and social media; efforts regarding health disparities, insurance, Meaningful Use, and workforce issues; collaborations with APDEM, ABIM's Choosing Wisely campaign, and ACGME; and the leadership provided by our volunteer committees.

ACCME accreditation seeks to assure the medical community and the public that the Endocrine Society



provides physicians with relevant, effective, practice-based continuing medical education that supports U.S. health-care quality improvement. The ACCME employs a rigorous, multilevel process for evaluating institutions' continuing medical education programs according to the high accreditation standards adopted by all seven ACCME member organizations: the American Board of Medical Specialties, the American Board

of Medical Specialties, the American Hospital Association, the American Medical Association, the Association for Hospital Medical Education, the Association of American Medical Colleges, the Council of Medical Specialty Societies, and the Federation of State Medical Boards of the U.S., Inc.

Under the guidance of the Scientific and Education Core Committee (SCIED) and the Clinical Endocrine Education Committee (CEEC), the Society first earned Accreditation with Commendation in 2009, being one of the first to do so under the ACCME's 2008 Criteria. **EN**

EPA Announces Changes to Screening Tests

On Friday, June 19, the Environmental Protection Agency (EPA) released a notice announcing their intention to change the agency's approach to screening chemicals for endocrine activity. The Endocrine Disruptor Screening Program (EDSP) was established in 1996 by the EPA in response to amendments to the Food Quality Protection Act and Safe Drinking Water Act. To evaluate chemicals for endocrine activity, the EDSP sets criteria to require screening and develops and validates two tiers of assays to test chemicals for endocrine activity. Tier 1 screens are designed to identify chemicals with the potential for endocrine activity, while the Tier 2 screening battery is designed to identify specific endocrine effects at various doses.

The EPA plans to incorporate

"validated high throughput assays and a computational model" as alternatives for three of the current assays in the Tier 1 screening battery. Specifically, the EPA proposes to use the 18 Estrogen Receptor (ER) screening assays from the ToxCast™ER Model for bioactivity. ToxCast is the EPA's Toxicity Forecaster, a program that "uses automated, robotics-assisted high throughput assays to expose living cells or proteins to chemicals and measure the results." ToxCast data are made available to the public through the integrated Chemical Safety for Sustainability (iCSS) dashboard.

Take Action: The Endocrine Society wants to ensure that the Tier 1 screening battery maintains the ability to identify all chemicals that have the potential for endocrine activity. We encourage interested members of the

Society to examine the *Federal Register* notice proposing the integration of ToxCast into the EDSP and submit comments to the EPA.



To provide input on the Endocrine Society's formal response, please send your comments to Joseph Laakso, Associate Director of Science Policy at jlaakso@endocrine.org. **EN**



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, Chief, UF Department of Medicine, Endocrinology, P.O. Box 100226, Gainesville, FL 32610; kenneth.cusi@medicine.ufl.edu.



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FAES Endocrinology Update & Review Course at NIH

October 12 - 16, 2015

Double Tree Hotel | 8120 Wisconsin Ave. | Bethesda, MD | 20814

Course Purpose

Intended for physicians preparing for the Endocrinology Board Examination, and physicians certified in Endocrinology who wish to remain abreast of recent field advances.

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faestraining.org/index.php/conferences-bootcamps
Email: registration@faes.org | Telephone (301) 451-1434

Tuition

Physicians:
\$1,395.00

Fellows/Other Medical Professionals:
\$895.00

Manual Only:
\$595.00

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.



Subclinical Vascular Dysfunction Associated with Metabolic Syndrome in African Americans and Whites

• Jia Shen, Joseph C. Poole, Matthew L. Topel, Aurelian Bidulescu, Alanna A. Morris, Riyaz S. Patel, Jose G. Binongo, Sandra B Dunbar, Lawrence Phillips, Viola Vaccarino, Gary H. Gibbons, and Arshed A. Quyyumi • *Although MetS is*

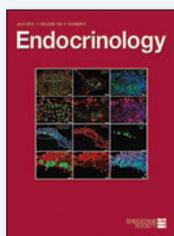
associated with microvascular dysfunction and increased arterial stiffness in both racial groups, AA without MetS have greater vascular dysfunction compared to whites. Additional weighting for hypertension in AA attenuated the racial differences in subclinical disease associated with MetS.

Radioactive Iodine Therapy Did Not Significantly Increase the Incidence and Recurrence of Subsequent Breast Cancer

• Hwa Young Ahn, Hye Sook Min, Yohwan Yeo, Seung Hyun Ma, Yunji Hwang, Jee Hyun An, Hoon Sung Choi, Bhumsuk Keam, Seock-Ah Im, Do Joon Park, In Ae Park, Dong-Young Noh, Yeo-Kyu Youn, June-Key Chung, Bo Youn Cho, Sue K. Park, and Young Joo Park • *The long-term follow-up results of this study suggest that RAI treatment for thyroid cancer patients may not increase the risk or recurrence of breast cancer.*

Lower Preprandial Insulin and Altered Fuel Utilization in HIV/Antiretroviral-Exposed Infants in Cameroon

• Jennifer Jao, Brian Kirmse, Chunli Yu, Yunping Qiu, Kathleen Powis, Emmanuel Nshom, Fanny Epie, Pius Muffih Tih, Rhoda S. Sperling, Elaine J. Abrams, Mitchell E. Geffner, Derek LeRoith, and Irwin J. Kurland • *HEU-A and HEU-N infants have lower preprandial insulin levels at six weeks of age and appear to utilize metabolic fuel substrates differently than HUU infants. Future studies are warranted to determine whether observed differences have lasting metabolic implications, such as later insulin resistance.*



Osteocalcin Effect on Human Beta Cells Mass and Function

• Omaira M. Sabek, Satoru Ken Nishimoto, Daniel Fraga, Neelam Tejpal, Camillo Ricordi, and A.O. Gaber • *These data for the first time show decarboxylated osteocalcin-enhanced β -cell function in human islets and support future exploitation of decarboxylated*

osteocalcin-mediated β -cell regulation for developing useful clinical treatments for patients with diabetes.

Sympathetic Nerve Activity Maintains an Anti-inflammatory State in Adipose Tissue in Male Mice by Inhibiting TNF- α Gene Expression in Macrophages

• Lijun Tang, Shiki Okamoto, Tetsuya Shiuchi, Chitoku Toda, Kazuyo

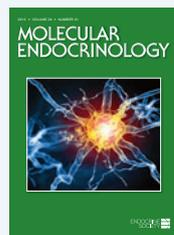
Takagi, Tatsuya Sato, Kumiko Saito, Shigefumi Yokota, and Yasuhiko Minokoshi • *These results show that the SNS and β 2-AR-PKA pathway maintain an anti-inflammatory state in ATMs of lean mice in vivo, and that the brain melanocortin pathway plays a role in maintaining this state in WAT of lean mice via the SNS.*

The Effects of a Single Developmentally Entrained Pulse of Testosterone in Female Neonatal Mice on Reproductive and Metabolic Functions in Adult Life

• Hyeran Jang, Shalender Bhasin, Tyler Guarneri, Carlo Serra, Mary Schneider, Mi-Jeong Lee, Wen Guo, Susan K. Fried, Karol Pencina, and Ravi Jasuja • *Collectively, these data suggest that sustained reproductive and metabolic alterations may result in female mice from a transient exposure to testosterone during a narrow postnatal developmental window.*

TNF- α Suppressed FSH-Induced LH Receptor Expression through Transcriptional Regulation in Rat Granulosa Cells

• Kohshiro Nakao, Hiroshi Kishi, Fumiharu Imai, Hiroto Suwa, Takashi Hirakawa, and Takashi Minegishi • *Taken together, these results suggest that the interaction of NF- β B p65 with HDAC in the promoter region of rat Lhcgr might be responsible for TNF- α action on the regulation of LHR.*



Bone Morphogenic Protein 4 Mediates NOX1-Dependent eNOS Uncoupling, Endothelial Dysfunction and COX2 Induction in Type 2 Diabetes Mellitus

• Ji-Youn Youn, Jun Zhou, and Hua Cai • *Taken together, these data for the first time reveal a novel role of BMP4 in inducing NOX1-dependent eNOS uncoupling in T2DM, which may*

promote development of new therapeutics restoring endothelial function in T2DM.

The Complexities of IGF/Insulin Signaling in Aging: Why Flies and Worms Are not Humans

• Christian Sell • *This review examines the differences in the insulin/IGF-1 axis between invertebrate and mammalian systems and discusses implications of these differences in terms of lifespan modulation.*

COPII Dependent ER Export: a Critical Component of Insulin Biogenesis and Beta Cell ER Homeostasis

• Jingye Fang, Ming Liu, Xuebao Zhang, Takeshi Sakamoto, Douglas J. Taatjes, Bhanu P. Jena, Fei Sun, James Woods, Tim Bryson, Anjaneyulu Kowluru, Kezhong Zhang, and Xuequn Chen • *Collectively, results from this study demonstrate that COPII-dependent ER export plays a vital role in insulin biogenesis, ER homeostasis, and beta cell survival.*

THE TRUTH ABOUT TESTOSTERONE TREATMENTS

You've seen the ads. You've heard the hype. But testosterone supplements aren't the anti-aging cure-alls that they're marketed as. The use of doctor-prescribed testosterone replacement therapy, however, is safe and can be effective for men who are diagnosed with consistently abnormal low testosterone production and symptoms that are associated with this type of androgen deficiency.

Visit hormone.org for more information.

TESTOSTERONE FACTS FOR MEN

-  **Age** Low testosterone comes with age — T levels naturally decrease by 1% each year after age 30, though don't severely deplete, even in advanced age
-  T production may be disrupted by disorders of the testicles, pituitary gland, or brain
-  T levels change from hour to hour — highest in the am; lowest at night
-  T levels can temporarily lower due to too much exercise, poor nutrition, severe illness, and with certain medications
-  Normal T levels should be between 300-1,000 ng/dL (nanograms per deciliter), depending on age and lab used
-  Testosterone must be measured more than once for accurate assessment

TESTOSTERONE THERAPY IS ONLY RECOMMENDED FOR HYPOGONADISM PATIENTS

 Boosting testosterone is NOT approved by the US Food and Drug Administration (FDA) to help improve your strength, athletic performance, physical appearance, or to treat or prevent problems associated with aging. Using testosterone for these purposes may be harmful to your health.

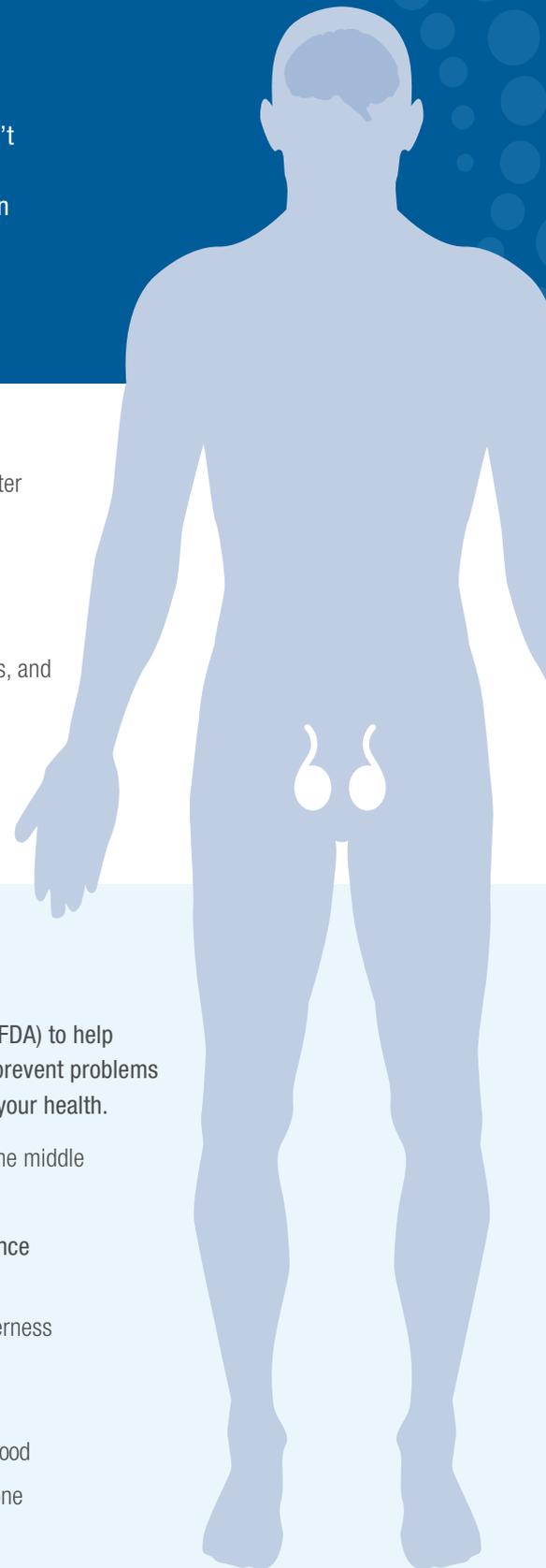
Men with **HYPOGONADISM** are prescribed testosterone treatment to raise levels to the middle of the normal range, in turn addressing related symptoms of androgen deficiency.

MALE HYPOGONADISM = a combination of low testosterone levels and the presence of any of these symptoms:

- Drop in sex drive (libido)
- Erectile dysfunction (ED — inability to get or keep an erection) and loss of spontaneous erections
- Lowered sperm count and infertility (inability to have children)
- Breast enlargement or tenderness
- Reduced energy
- Increased irritability, inability to concentrate, and depressed mood
- Hot flashes (when testosterone levels are very low)

 You should not receive testosterone therapy if you have:

- Prostate or breast cancer (or suspected)
- Uncontrolled heart failure
- Enlarged prostate causing difficulty with urination
- Untreated sleep apnea (obstructed breathing during sleep)
- High number of red blood cells



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THERE ARE VARIOUS METHODS OF TESTOSTERONE THERAPY

Method of treatment depends on the cause of low testosterone, the patient's preferences, cost, tolerance, and concern about fertility.



Injections: self or doctor administered in a muscle every 1-2 weeks; administered at a clinic every 10 weeks for longer-acting. Side effects: uncomfortable, fluctuating symptoms.



Gels/Solutions: apply to upper arm, shoulder, inner thigh, armpit. Side effects: may transfer to others via skin contact — must wait to absorb completely into skin.



Patches: adhere on skin every day to back, abdomen, upper arm, thigh; rotate locations to lessen skin reaction. Side effects: skin redness and rashes.



Buccal Tablets: sticky pill applied to gums 2x a day, absorbs quickly into bloodstream through gums. Side effects: gum irritation.



Pellets: implanted under skin surgically every 3-6 months for consistent and long-term dosages. Side effects: pellet coming out through skin, site infection/bleeding (rare), dose decreasing over time and hypogonadism symptoms possibly returning towards the end of dose period.



Nasal Gel: applied by pump into each nostril 3x a day. Side effects: nasal irritation or congestion.

THERE ARE RISKS TO TESTOSTERONE THERAPY

- Elevated red blood cell count
- Acne
- Sleep apnea
- Possible prostate and/or breast enlargement

There is no firm scientific evidence that long-term testosterone replacement is associated with either prostate cancer or cardiovascular events.

The FDA requires that patients are made aware that the possibility of cardiovascular events may exist during treatment.

Prostate cells are stimulated by testosterone, so be extra vigilant about cancer screenings.

African American men over age 45 — especially those with family history of cancer — are already at risk for prostate cancer.



YOUR DOCTOR SHOULD BE YOUR PARTNER IN CARE

If you are concerned about your testosterone levels and interested in learning more about ways to manage hypogonadism, an endocrinologist can help.

Visit “Find an Endocrinologist” at hormone.org.

You have questions. We have answers.

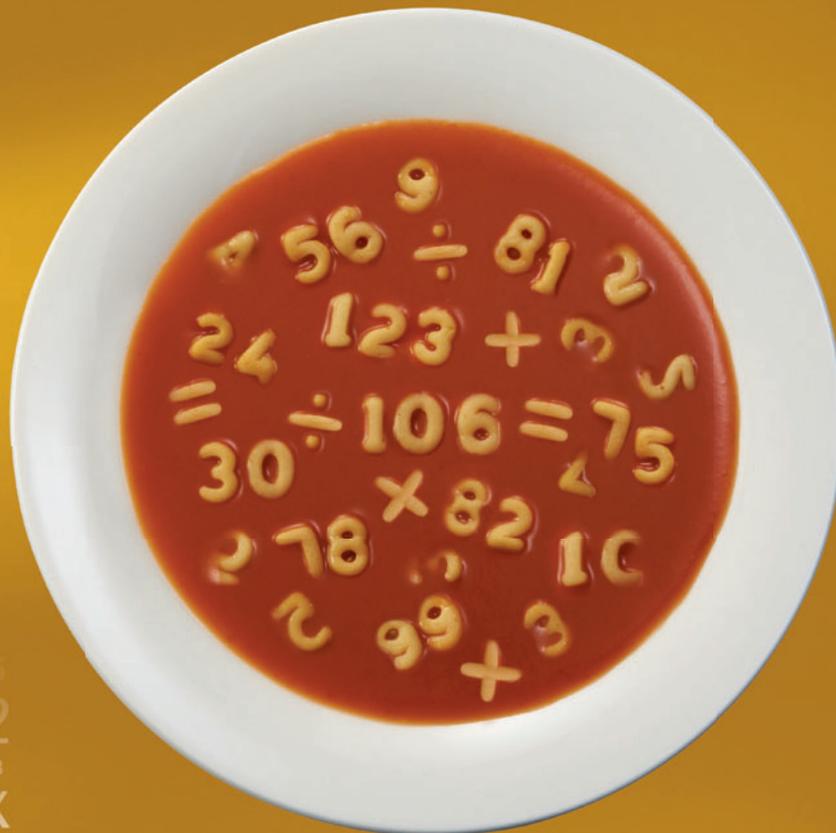
The Hormone Health Network is your trusted source for endocrine patient education. Our free, online resources are available at hormone.org.

*Additional editing by Alvin M. Matsumoto, MD,
University of Washington School of Medicine*



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106 + 70 = 106
 48 = 90 82
 70 100 42 28
 31 ÷ 28 58 X
 33 + 35 63



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PCSK9: It has LDL receptors in a serious bind¹

Recent discoveries show there's an important new factor to consider. PCSK9 is a protein that promotes degradation of the LDL receptor within hepatocytes, thereby increasing plasma LDL-C levels.^{2,3} Amgen Cardiovascular is proud to be a leader in PCSK9 research and remains dedicated to deepening our understanding of the critical role it plays in cholesterol metabolism. **PCSK9 means it's time to discuss cholesterol differently.**



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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.
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