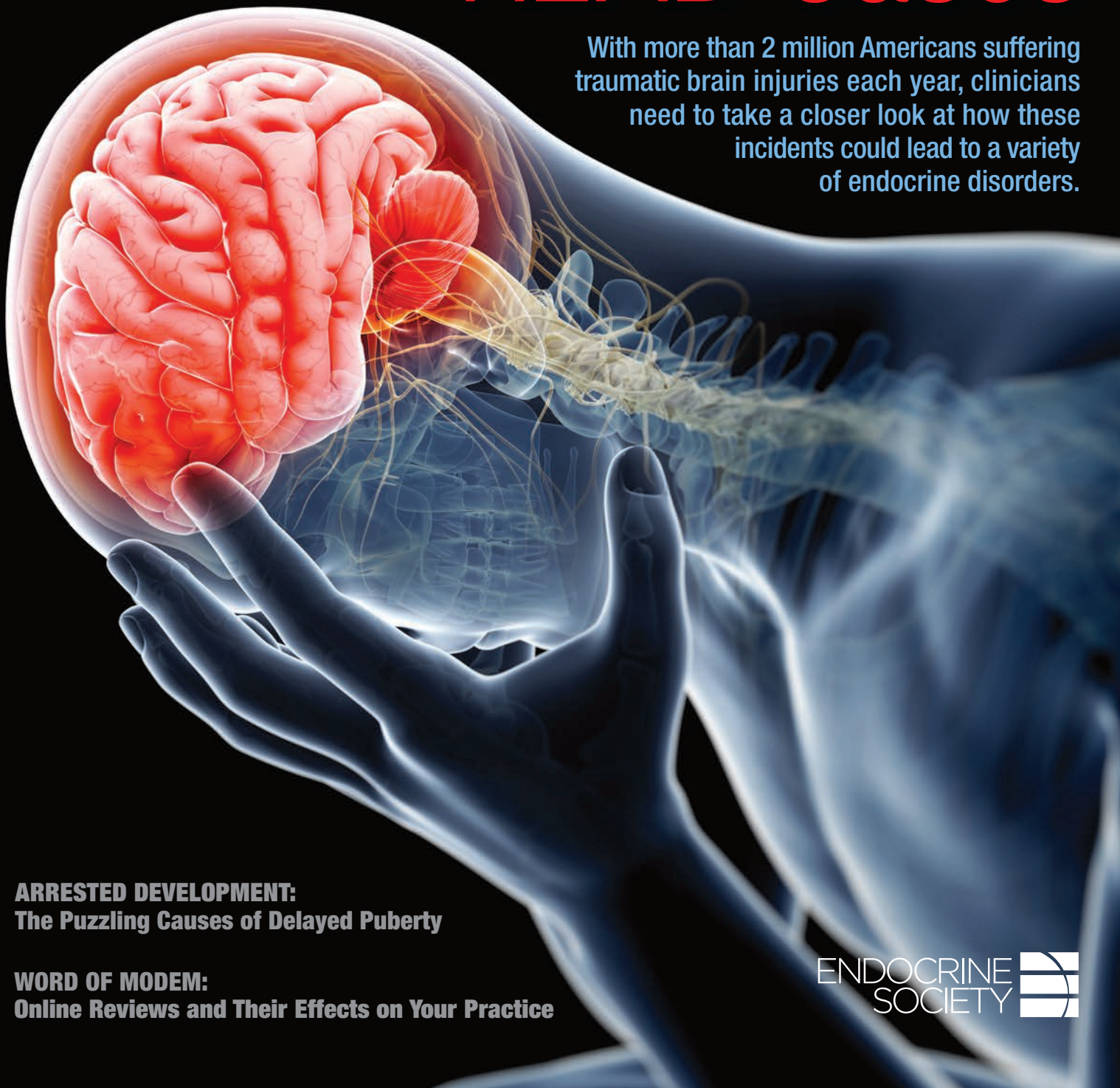
OCTOBER 2014

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINE news™

HEAD Cases

With more than 2 million Americans suffering traumatic brain injuries each year, clinicians need to take a closer look at how these incidents could lead to a variety of endocrine disorders.



ARRESTED DEVELOPMENT:
The Puzzling Causes of Delayed Puberty

WORD OF MODEM:
Online Reviews and Their Effects on Your Practice

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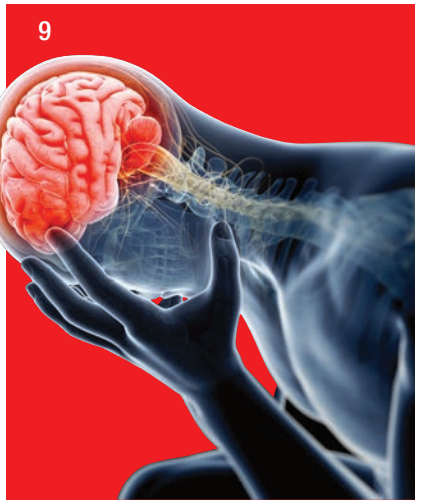

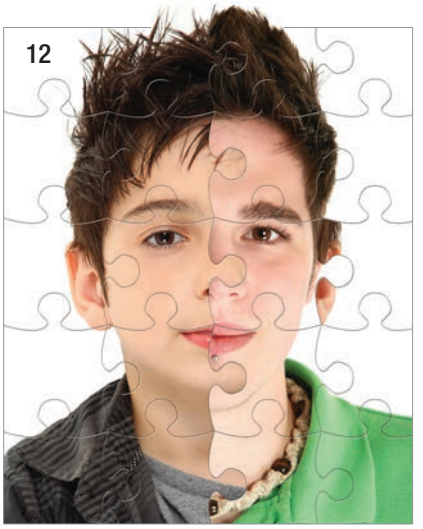

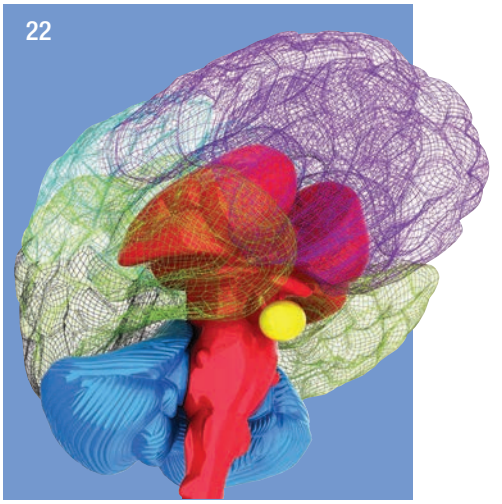

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ENDOCRINE SOCIETY
Hormone Science to Health

The Society Takes the Lead on **Diabetes and ACA Implementation**

Richard J. Santen, MD

When the Centers for Disease Control and Prevention (CDC) recently released its *2014 National Diabetes Statistics Report*, those of us in the endocrine community were not surprised: 29 million Americans are projected to have diabetes, another 86 million are expected to have prediabetes, and the economic burden of the disease is expected to worsen in the near future.

In an era of healthcare reform where millions of Americans are expected to gain insurance coverage, we expect to see improvements in the care of these patients in the future. But, for now, the diabetes epidemic is a key contributor to excessive healthcare costs and the seventh leading cause of death for Americans.

To more closely examine these data and determine where opportunities exist to improve care, the Society recently held a policy summit, *ACA Implementation: Impact on the Patient with Diabetes*. Robert Vigersky, MD, past president of Endocrine Society and director of the Diabetes Institute at Walter Reed National Military Medical Center, chaired the Summit where he also presented data on endocrine workforce shortages which are expected to be exacerbated in the coming years. The Summit featured talks from key officials at CDC, the Department of Health and Human Services, the U.S. Food and Drug Administration, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on the current clinical, economic, and political landscape and ways in which the healthcare community can innovate change to reduce the burden of diabetes in America.

Additional presentations on community health initiatives, healthcare delivery models, emerging therapies and devices for diabetes management, the bionic pancreas, and the intent of the ACA were also held and will be available to members of the Society at ***endosessions.org***.

In the coming months, the Society will release a white paper detailing policies that can help improve diabetes care as the implementation of the ACA continues to be underway. An outline of these recommendations was presented at the Summit, which included tactics aimed to implement patient interventions, to prevent complications and costs, to advance research and therapy options, and to address provider shortages. Encouraging team-based care, promoting adherence to screening recommendations, pilot testing new healthcare delivery models, and increasing research funding are several examples that were included and will continue to be explored. We will keep you informed as the Society continues to lead and influence important policy issues like diabetes.

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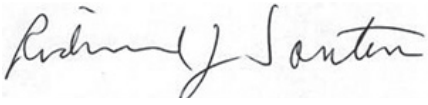
Elections and *Endocrine Reviews*

Finally, I want to remind all Society members that the 2015 Election for Society Officers and Council launched in early September. The election period will end on October 20 and I encourage all voting members to participate in this very important activity. Please remember to cast your vote and remind your colleagues as well. This is YOUR Society, and your participation in our election is vitally important!

Additionally, *Endocrine Reviews*, the Endocrine Society's bimonthly review journal, is currently seeking candidates to take on the role of editor-in-chief for a five-year term beginning in early 2015. *Endocrine Reviews* publishes comprehensive and timely review articles on a variety of topics in endocrinology and related areas. The application period is open until October 31st and I encourage those of you interested to visit "" for more information. EN



Richard J. Santen, MD
President, Endocrine Society

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ENDOCRINE news

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Mark A. Newman

This month's cover story deals with the topic of traumatic brain injuries and how they are often the cause of a variety of endocrine-related disorders that are often overlooked by primary care physicians. In "Head Cases" on page 9, Glenda Fauntleroy reports how these injuries can cause everything from growth problems, fatigue, weight gain, low blood pressure, and loss of muscle mass to reduced libido and amenorrhea. Unfortunately, the problem is that healthcare providers who treat these injuries don't consider the long-lasting effects of the trauma, especially on children. Johns Hopkins University neuroendocrinologist Gary Wand, MD, says that emergency room staff are usually thinking more about concussions and all the "old school" attributes that go along with them such as headaches, dizziness, and vomiting. "They're thinking the kids are going to get better, and they're just not aware that you can have these hormonal changes," he explains.

Delayed puberty has been puzzling doctors for years, especially when it comes to determining the exact cause. "Arrested Development," by Kelly Horvath (p. 12), shows that in some cases, slowed sexual maturation can be a sign of a systemic illness, endocrinopathy, or even psychosocial deprivation. Unfortunately, there is no biochemical test that can definitively distinguish constitutional delay of growth and puberty from other causes, and physicians must rely on long-term observation of the patient.

On page 17, associate editor Derek Bagley writes about a topic that many physicians may find obtrusive and bothersome: online review sites. "Word of Modem" explores this rating system that has gotten a lot of attention lately when some consumers' negative online reviews have led to legal action. Hopefully, you haven't had to go that far, but the article is loaded with tips and ideas on how to deal with this new grading system that you can use to your — and your practice's — advantage.

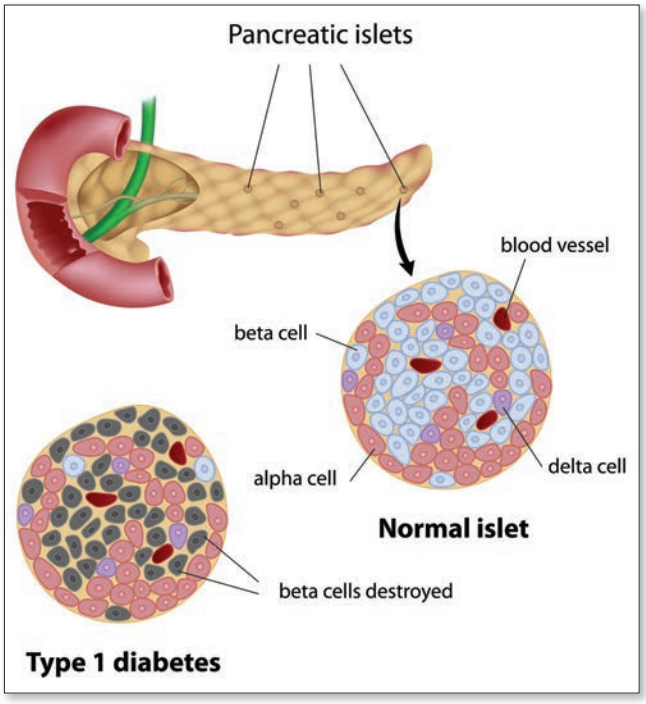
If any researchers out there are interested in coming in under budget while still finding the right lab equipment, you might want to skip over to "Best Buys" on page 20. Melissa Mapes details the means and methods of finding items for your lab that are a bit off the beaten path like craigslist, eBay, and even donations. Cheap equipment is great; free equipment is even better and will keep your lab budget in check.

Don't forget that **ENDO 2015** is three months earlier than normal, taking place in sunny San Diego, Calif., March 5 – 8. It's never too soon to register, so go to ***www.endocrine.org/endo-2015*** and sign up today. EN

Mark A. Newman,
Managing Editor, Endocrine News

By Derek Bagley

Researchers Find Link Between **PANCREATIC PROTEIN AND T2D**



Patients with type 2 diabetes (T2D) have elevated levels of human islet amyloid polypeptide (hIAPP), and researchers have linked its accumulation with the loss of insulin-producing beta cells.

In a study published online in the *Journal of Clinical Investigation*, Safia Costes, PhD, of the Larry L. Hillborn Islet Research Center at UCLA, and colleagues suggest that autophagy prevents the accumulation of toxic forms of hIAPP that contribute to the destruction of beta cells.

Because autophagy is known to play a critical role in clearing damaged and toxic proteins, this process does not appear to be at work in people with T2D.

"Only a few previous studies have reported that autophagy is important for beta cell function and survival," Costes said in a university release. "These studies, however, were not conducted to address the role of this pathway in the regulation of the amyloidogenic protein, which is an important contributor to type 2 diabetes."

The study also reveals some similarities between type 2 diabetes and neurodegenerative diseases such as Alzheimer's, diseases that share in common an accumulation of toxic forms of amyloid proteins, she added. "For instance, it demonstrates the importance of autophagy in clearing out these harmful proteins to prevent both type 2 diabetes and Alzheimer's," Costes said.

In order to investigate whether autophagy plays a role in hIAPP clearance, the researchers used pancreatic beta cells in a culture and isolated pancreatic islets from mice that express the human form of islet amyloid polypeptide as well as human islets. They also developed a novel mouse model deficient for autophagy specifically in beta cells with expression of the human form of islet amyloid polypeptide.

The scientists found that these mice developed diabetes. A loss of autophagy in combination with the expression of hIAPP resulted in an accumulation of hIAPP and increased beta cell death, which are characteristic of T2D in humans. "The goal of our work is to understand the cellular mechanisms responsible for beta cell destruction to enable identification and validation of novel targets for beta cell protection and allow the development of next generation treatments as well as combination therapies for type 2 diabetes," Costes said.

HYPERTHYROIDISM PATIENTS
More Likely to Take Extended Sick Leave than Healthy Peers

People who have hyperthyroidism are more likely to take sick leave for extended periods than their healthy colleagues, particularly in the first year after diagnosis, according to a new study published in the *Journal of Clinical Endocrinology & Metabolism*.

"When we examined sick leave records, our research found patients with hyperthyroidism faced a significantly higher risk of missing work for three weeks or longer due to illness compared to healthy controls," says one of the study's authors, Mette Andersen, MA, Nexø of the National Research Centre for the Working Environment and the University of Copenhagen in Denmark. "People who experienced eye complications from Graves' disease were the most likely to require extended sick leave. This same population also was the most likely to leave the workforce altogether and retire on a disability pension."

The longitudinal register study is the largest systematic assessment of the effect of thyroid conditions on the workplace conducted to date, Nexø says. Researchers analyzed sick leave and disability pension claims among 862 Danes who were treated in one of two university outpatient clinics in 2007 for a thyroid condition. The study authors then compared claim rates in this population to a group

of 7,043 controls using national and municipal records from 1994 to 2011. In Denmark, people who miss work for more than three weeks due to illness are compensated by local municipalities, so the researchers were able to track when subjects missed work for an extended period due to illness.

The analysis revealed that Graves' disease patients with eye complications were seven times more likely than healthy peers to have an extended sick leave from work within a year of diagnosis. In subsequent years, the risk diminished but remained twice as high compared to healthy peers. This population was more than four times as likely to retire on a disability pension compared to healthy controls.

People with hyperthyroidism without eye complications also faced a heightened risk of taking an extended sick leave. They were twice as likely as peers to miss weeks of work due to illness within a year of diagnosis. The study also examined records for people with hypothyroidism, or an underactive thyroid. While the risk of taking sick leave was not significantly affected, people with hypothyroidism faced longer recovery than healthy peers if they had to take sick leave in the first year after diagnosis. In subsequent years, the researchers did not find significant indication that the hypothyroidism affected workplace absenteeism.

"The findings demonstrate the potential socioeconomic effects thyroid conditions can have but also indicate that socioeconomic effects diminish once the disorders are treated," Nexø says. "It's important not only for patients but for employers and society as a whole, to ensure that people who have thyroid conditions receive the medical care they need."

Has a Link Been Found Between EDCs and **REDUCED TESTOSTERONE?**

While many studies have linked endocrine-disrupting chemicals (EDCs) to a variety of health concerns in both males and females of all ages, a recent study in the *Journal of Clinical Endocrinology & Metabolism* also seems to show a link between EDCs and reduced testosterone levels in not just men, but women and children as well. In a cross-sectional study of the general U.S. population from 2011 to 2012, data from the U.S. National Health and Nutrition Examination Survey showed that multiple phthalates were associated with significantly reduced testosterone in both males and females regardless of age.

"Because exposure to phthalates is so common and testosterone plays an important role in all life stages for both sexes, these findings could have large public health significance," says study co-author John D. Meeker, ScD, CIH, associate professor of environmental health sciences and associate dean for research at the School of Public Health at the University of Michigan in Ann Arbor. "Future efforts should focus on better defining and possibly intervening to reduce the impacts of these relationships."

Since various animal and cellular studies have shown that some phthalates block the effects of testosterone, Meeker and study co-author Kelly K. Ferguson, PhD, set out to prove if the same was true in humans. "Phthalates have been found to be anti-androgenic in animal and in vitro studies through a number of possible specific mechanisms," he explains. "We still don't know how this may be happening in males or females at different life stages in humans, and it is possible that the different specific phthalate chemicals may be acting through differing or multiple mechanisms simultaneously."

Phthalates are commonly found in plastics and personal care products, items that most people use on a regular basis. "Due to the increasing evidence in human studies that phthalates and other EDCs may impact male reproductive health or other systems, there is a point at which some level of precaution should kick in and efforts made to reduce the population's exposure to these chemicals," Meeker says, adding that since the study was conducted on the population level, how these findings might impact individuals is difficult to interpret. "Things are also complicated by the fact that most products that contain phthalates aren't labeled as such," he says, "making it very difficult for clinicians to be able to make sound recommendations for patients to avoid or reduce exposure."

— Mark A. Newman

BRAIN BENEFITS from Weight Loss Following Bariatric Surgery

Weight loss surgery can curb alterations in brain activity associated with obesity and improve cognitive function involved in planning, strategizing, and organizing, according to a new study published in *Journal of Clinical Endocrinology & Metabolism*.

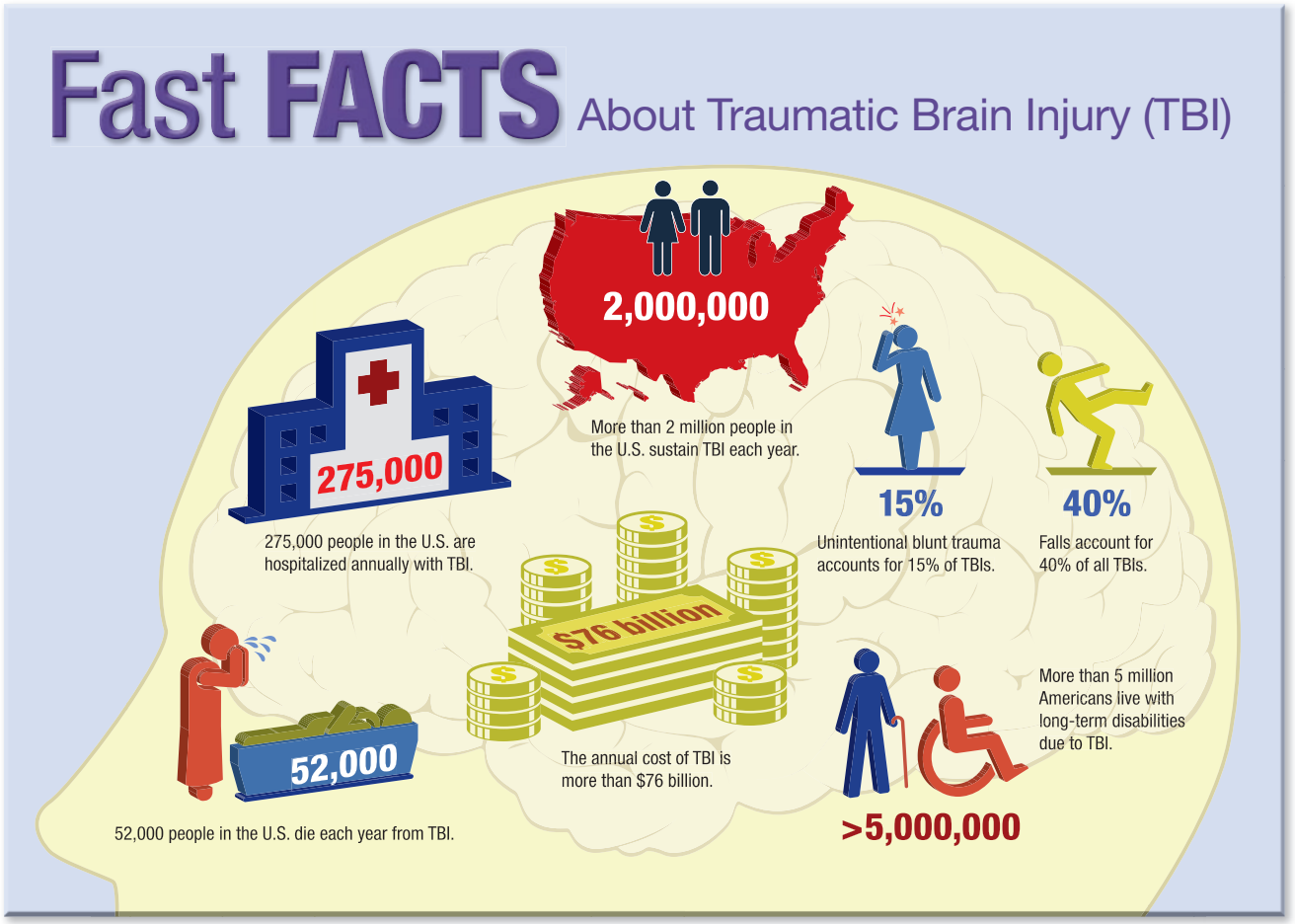
The longitudinal study led by Cintia Cercato, MD, PhD, of the University of São Paolo in São Paolo, Brazil, examined the effect of RYBG surgery on the brain function of 17 obese women. Researchers used positron emission tomography (PET) scans and neuropsychological tests to assess brain function and activity in the participants prior to surgery and six months after the procedure. The same tests also were run once on a control group of 16 lean women.

"When we studied obese women prior to bariatric surgery, we found some areas of their brains metabolized sugars at a higher rate than normal weight women," Cercato says. "In particular, obesity led to altered activity in a part of the brain linked to the development of Alzheimer's disease — the posterior cingulate gyrus. Since bariatric surgery reversed this activity, we suspect the procedure may contribute to a reduced risk of Alzheimer's disease and other forms of dementia."

Prior to surgery, the obese women had higher rates of metabolism in certain areas of the brain, including the posterior cingulate gyrus. Following surgery, there was no evidence of this exacerbated brain activity. Their brain metabolism rates were comparable to the activity seen in normal weight women.

After surgery, the obese women also performed better on a test measuring executive function — the brain's ability to connect past experience and present action — than they did before the procedure. Five other neuropsychological tests measuring various aspects of memory and cognitive function showed no change following the surgery.

"Our findings suggest the brain is another organ that benefits from weight loss induced by surgery," Cercato says. "The increased brain activity the obese women exhibited before undergoing surgery did not result in improved cognitive performance, which suggests obesity may force the brain to work harder to achieve the same level of cognition."

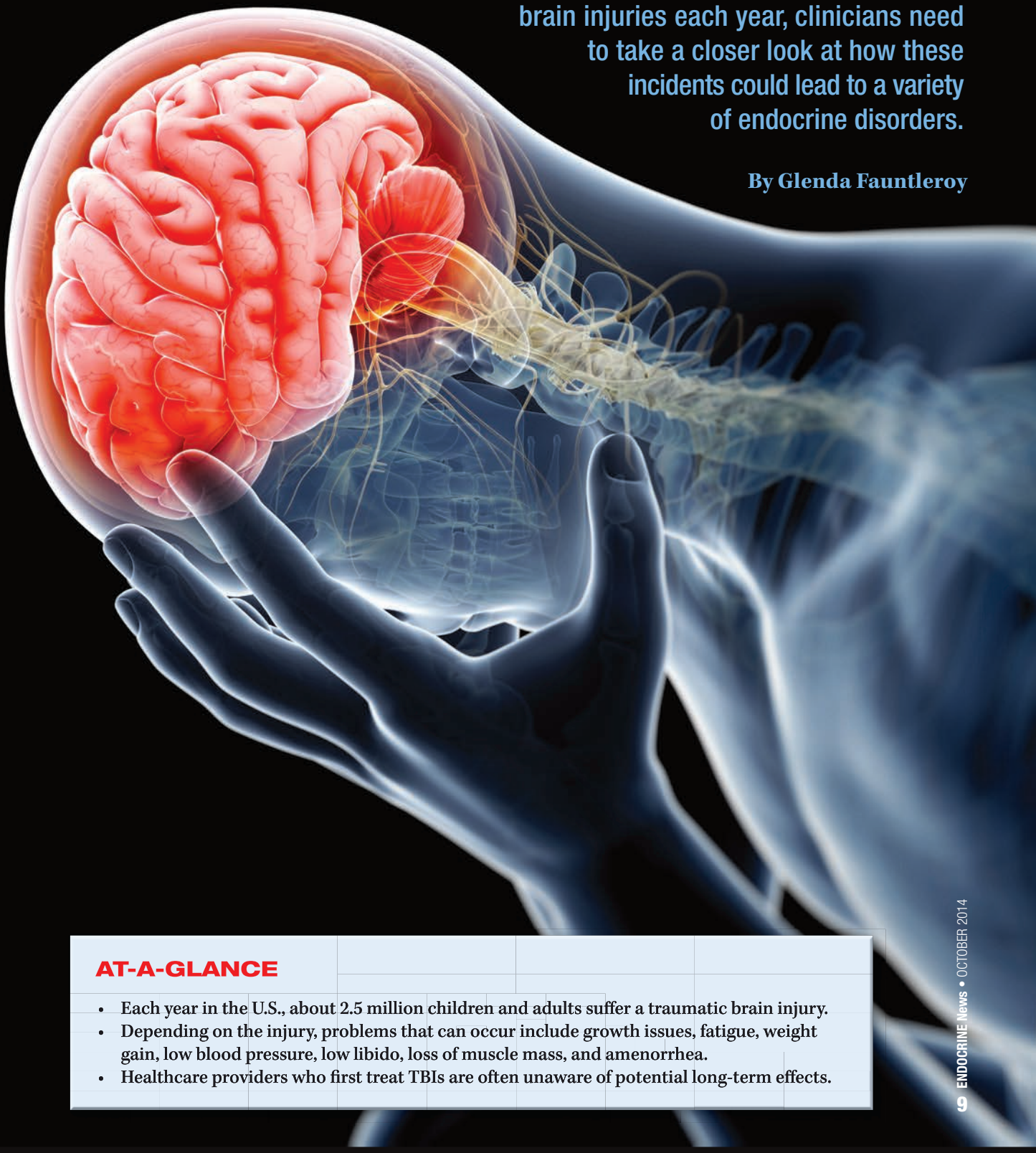


Sources: Centers for Disease Control, Brain Injury Association of America

HEAD Cases

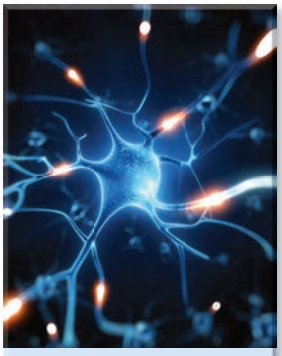
With more than 2 million Americans suffering traumatic brain injuries each year, clinicians need to take a closer look at how these incidents could lead to a variety of endocrine disorders.

By Glenda Fauntleroy



AT-A-GLANCE

- Each year in the U.S., about 2.5 million children and adults suffer a traumatic brain injury.
- Depending on the injury, problems that can occur include growth issues, fatigue, weight gain, low blood pressure, low libido, loss of muscle mass, and amenorrhea.
- Healthcare providers who first treat TBIs are often unaware of potential long-term effects.



"Emergency room staff [and primary care doctors] are the ones seeing the kids come in with the head injuries, and they're thinking concussion and all the old school stuff about concussion-causing headaches, maybe some dizziness, and vomiting," says Wand. **"They're thinking the kids are going to get better, and they're just not aware that you can have these hormonal changes."**

— Gary Wand, MD, neuroendocrinologist, Johns Hopkins University, Baltimore, Md.

Recent headlines of disabling head injuries to returning Iraq and Afghanistan war veterans as well as recurring concussions to professional athletes have placed the incidence of traumatic brain injuries (TBI) front and center in mainstream medical news. TBIs, however, have long been a leading cause of death and disability in the U.S., and what happens to the body's hormone system following these injuries has become an increasingly significant public health concern.

Each year in the U.S., about 2.5 million children and adults suffer a TBI caused by either a blow to the head, penetrating head injury, or repeated jolts to the head, according to the Centers for Disease Control and Prevention (CDC). And more than 5.3 million Americans are currently living with a lifelong disability due to TBI.

Injuries that disrupt the normal function of the brain can range from mild to severe. And, although, not usually referred to as such, concussions are TBIs. "A concussion is a mild, traumatic brain injury. It's just a euphemism," points out neurologist Brent E. Masel, MD, national medical director for the Brain Injury Association of America, Vienna, Va.

The most common causes of TBI depend on the age group. For children between the ages of birth and four years and seniors 65 years and older, falls cause the most hospitalizations, reports the CDC. Young adults ages 15–24 have the highest TBI hospitalizations due to motor vehicle traffic–related events. Violence (e.g., child abuse, gunshot wounds, or beatings) and injuries from sports or combat round out other common causes.

The Brain and Hormones Changes

Trauma to the brain may interfere with the normal production and regulation of the hormonal processes of the hypothalamus and pituitary glands. The hypothalamus and pituitary are the most vulnerable and often most affected by brain injury. Depending on the injury, problems that can occur right away include adrenal insufficiency, diabetes insipidus, and hyponatremia. Other problems may not surface until months or years later, and the most common are growth and gonadotropin hormone deficiencies leading to symptoms such as growth problems, fatigue, weight gain, low blood pressure, low libido, loss of muscle mass, and amenorrhea.

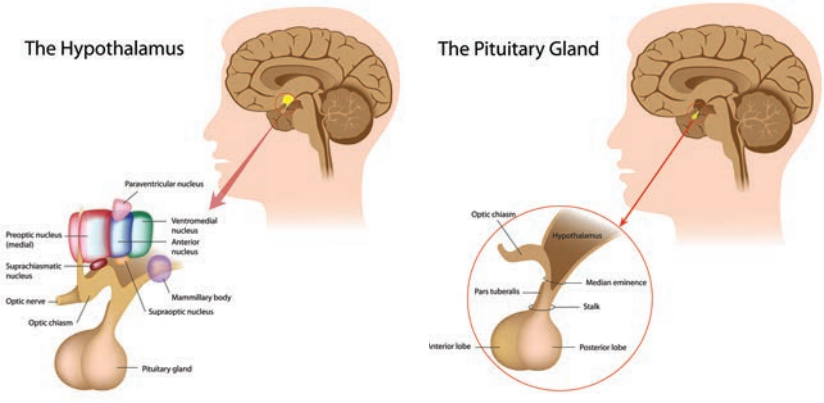
Many studies have shown that a high percentage of patients who suffer mild, moderate, or severe TBIs may have some form of pituitary dysfunction in the first three months following the injury. While most of these patients' symptoms go away over the following nine months or so, many still have pituitary hormone dysfunction by the end of a year.

In a literature review in the February issue of *Endocrine*, author Alan Rogol, MD, PhD, from the division of pediatric endocrinology at the University of Virginia in Charlottesville, reported the prevalence of pituitary dysfunction following TBIs among both children and adults ranges widely from 5% to 90%. A major reason for the studies' variation in ranges was the time interval between the injury and the screening for pituitary function, the review suggested.

"Head injuries are very common in children, and it is the vast minority that lead to endocrine dysfunction," Rogol says. In one of the larger studies cited of 1,000 TBI patients, there was a prevalence of some form of hypopituitarism in 27.5%.

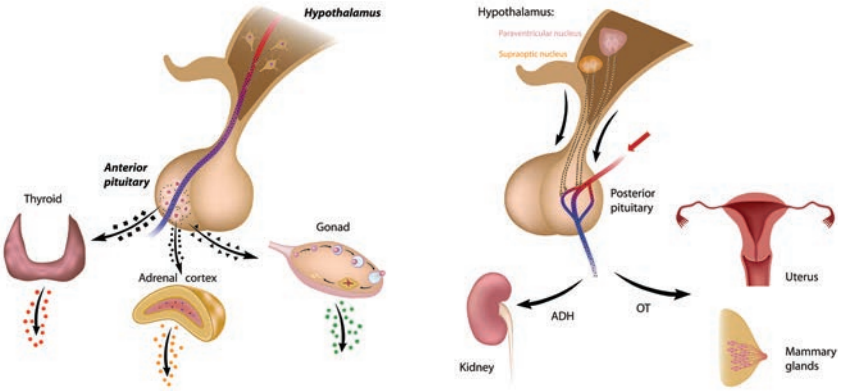
At Johns Hopkins University, neuroendocrinologist Gary Wand, MD, treats about four patients a year who experience pituitary dysfunction due to TBI, including professional athletes and war veterans. He stresses that when there are endocrine deficits, the most important of the impaired endocrine system is the pituitary's control over the adrenal axis, the stress hormone system, and the production of cortisol. "The adrenal axis is the one that can be life threatening early on in a traumatic brain injury because you can get hypotensive, so that system has to be assessed and the patient has to be supported in terms of replacement with stress hormones," he says.

"It turns out that the two systems that are most vulnerable to injury are the production of growth hormone and the production of sex hormones," Wand says, adding that growth hormone is not only a hormone for children to reach adult height; adults require growth hormone to maintain lean body mass, bone mass, bone strength, and bone density.



When to Screen, When to Treat?

There is no debate that TBI-related endocrine dysfunction is a widely missed diagnosis. The healthcare providers who are first to treat these injuries are often unaware of potential long-term effects.



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Diagnosing post-TBI dysfunction involves serum screening tests including: 0800 cortisol levels, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, IGF, free thyroxine, testosterone for male patients, and estradiol for females. However, there have been several published guidelines on the recommended screening intervals and even treatment.

Rogol says there are a lot of transient deficiencies in the first year that make it difficult to base lifelong treatment on early results. "The best screening is a careful history of symptoms of adrenal, thyroid, or gonadotropin deficiency or much more importantly, the quantitation of linear growth," he says.

In the February issue of the *Journal of Endocrinological Investigations*, researchers in Spain concluded that "invasive and expensive" endocrine assessments may not be warranted for children with mild to moderate TBIs.

The team evaluated 36 children with TBI (mean age seven), who all had skull fracture or intracranial hemorrhage. Nearly 37% had moderate to severe TBI, and the average time between the study assessment and injury was three years. No evidence of pituitary dysfunction was observed in these patients after clinical follow-up, repeated baseline hormone levels, or dynamic function tests.

"Based on our results, we consider it might not be justified to perform dynamic tests in children with mild to moderate TBI unless baseline hormonal levels are low or clinical findings suggest endocrine dysfunction," says author Itxaso Rica of the Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders. "Blood tests may represent a stressful event for children and their families. Also, they have to be taken at 8:00 a.m., which can make it more difficult for families," she adds. "Furthermore, stimulation tests are not free from risks and further costs."

When it comes to more serious brain injuries, differing opinions also raise questions on what is, indeed, the appropriate treatment course, says Masel. "The problem is that the endocrinologist will say you don't treat growth hormone deficiency until a year after a moderate to severe brain injury," he says. "There were some guidelines that were published and the feeling was that endocrinologists should wait until you're sure the deficit is stable because although you test a patient say three weeks after their brain injury, everything may be normal. But a fair percentage become abnormal by month 12."

"My personal feeling, is as soon as I'm medically stable [out of the ICU], screen me, and we'll go from there, but endocrinologists, I have learned, are very conservative," Masel adds.

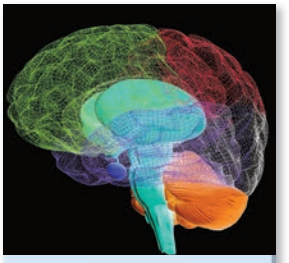
Wand cautions that there are two sides to the coin. "Remember, because the hormonal changes in many people were reversed, you certainly don't want to commit people to lifelong hormone replacement therapy until you know for sure they're not going to recover," he says. "At the same time, you don't want to make the mistake of leaving somebody without hormone replacement if they're not going to recover. So you know there's good judgment that needs to be taken into account for these cases."

In Rogol's *Endocrine* review, the authors concluded that growth hormone therapy showed some improvement across published literature, but recommended it only if the patient is "objectively deficient in GH."

Masel acknowledges the difficulty endocrinologists face and says more research is needed to foster more definitive treatment protocols. "As a physician, it's a pain in the butt," he says. "You have to screen them, and then you have to do a definitive test, and then you have to recommend a medication, and then you have to fight with an insurance company."

"Growth hormone is somewhere between $15,000 and $18,000 a year for an adult, and it's that way in an overwhelming number of people the rest of their lives, so insurance companies aren't keen about the diagnosis, so they put up roadblocks. I understand all that." EN

— A regular contributor to Endocrine News, *Fauntleroy is a freelance journalist based in Carmel, Ind. She wrote about food as medicine in the June issue.*



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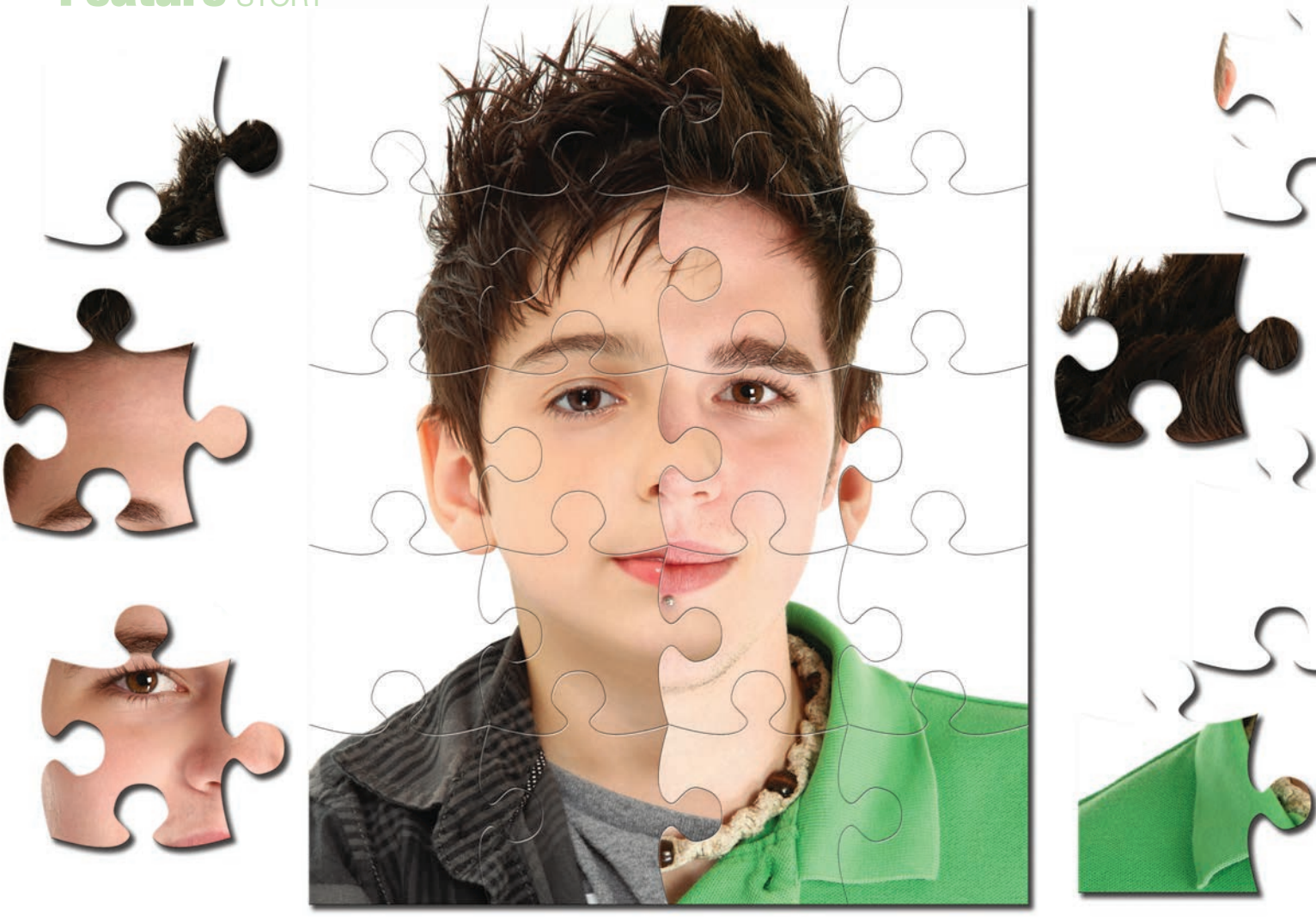


Arrested Development

Delayed puberty is not the mystery it once was. However, determining its causes can often present clinicians with a difficult puzzle to piece together.

By Kelly Horvath

Although delayed puberty is a common pediatric endocrine condition, determining its etiology can present a hefty clinical challenge. Defined as gonadarche in boys or thelarche in girls occurring later than 95% of the rest of the population (ages 14 and 13, respectively), overall delayed puberty affects about 3% of the population, but the precise incidence of this complex problem is unknown.

Boys are more often referred for clinical evaluation than girls, but some studies demonstrate that the condition affects both sexes about equally. Slowed growth commonly accompanies delayed puberty, as growth

AT-A-GLANCE

- Slowed growth and sexual maturation may signal an underlying disorder, such as systemic illness (e.g., cystic fibrosis, inflammatory bowel disease), endocrinopathy (e.g., hypothyroidism), or psychosocial deprivation (e.g., malnutrition or energy imbalance), whereas CDGP is a transient pubertal delay that occurs (likely due to genetic background) in the absence of an underlying condition.
- A biochemical test does not exist that can *definitively* distinguish CDPG from other causes of delayed puberty; serial observation is the most reliable approach.
- Short-term sex steroid hormone therapy may be considered when the delay is severe or the patient expressed considerable distress about it and is combined with GH administration only with demonstrated true GH deficiency.

hormone (GH) secretion is linked to stage of puberty rather than calendar age.

"Before you can treat it, you have to define it," says Alan D. Rogol, MD, PhD, professor emeritus at the University of Virginia School of Medicine, in Charlottesville. "Ninety-five percent of adolescents with delayed puberty have a variant of normal [physiologic]. Only 5% are pathologic." Although boys account for most overall referrals for delayed puberty, girls account for more cases of pathologic delayed puberty. Regardless of specific etiology, most delayed puberty stems from a delay in activation of the hypothalamic-pituitary-gonadal axis and, compared to peers, a relative gonadotropin-releasing hormone (GnRH) deficiency, which makes thorough evaluation that might reveal underlying illnesses or a familial predisposition even more critical. This overlap in clinical findings and lab evaluation can pose quite a conundrum. Although some clinical features and hormonal evaluations are more typical for each condition, they are not limited to one or the other. Clinicians must tease out the underlying mechanisms to differentiate among types.

"In patients with delayed puberty, administration of exogenous sex steroids not only leads to development of secondary sexual characteristics but usually also leads to acceleration in linear growth. Treatment with growth hormone does not appear to result in substantial gains in height compared to the administration of sex steroids, and its use is quite expensive."

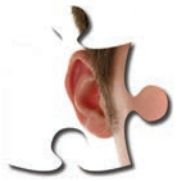
— Mark Palmert, MD, PhD, associate professor, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada

Defining It

Constitutional delay of growth and puberty (CDGP), which is by far the most common cause, represents a diagnosis of exclusion and is, by definition, transient. The three other main causes accounting for delayed puberty can be subdivided into primary and secondary hypogonadism, which distinction may be made by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Primary hypogonadism, also called *hypergonadotropic hypogonadism*, is characterized by high LH and FSH concentrations, usually as a result of gonadal disease, whereas secondary hypogonadism is characterized by low or normal serum LH and FSH concentrations, often as a result of a hypothalamic dysfunction. Secondary hypogonadism, *hypogonadotropic hypogonadism (HH)*, can be permanent — the result of an impaired hypothalamic-pituitary axis — or transient, *functional hypogonadotropic hypogonadism (FHH)* — in which dysfunction is the result of another underlying (often systemic) disorder.

To date, a definitive test does not exist to distinguish CDGP from other causes of delayed puberty. Therefore, a complete history and physical can offer important clues about the cause and should be undertaken first, before any diagnostic testing or imaging. Additionally, delayed puberty might point to a range of latent problems, from hypothyroidism to psychosocial deprivation.

CDGP has a strong genetic component, which is no surprise given that so much (as much as 50%–80%) of the variation in the timing of puberty relates to genetic factors, and more than half of CDGP cases reveal a family history of so-called "late bloomers." The key driver in CDGP is inadequate sex hormone secretion, which is caused by diminished production of hypothalamic GnRH, in turn causing delayed LH and FSH secretion, compared to peers. Importantly, these adolescents also have slowed but not stalled growth and skeletal maturation, as the growth pattern assessment will demonstrate. The detailed history should also include diet, exercise, prior illness, prior radiation therapy, and medication usage. Restricted or inadequate nutrition can delay puberty onset. This is an issue of energy balance; therefore, both intake and output should be considered.



Tanner staging is a key component of the physical exam. Micropenis or gynecomastia in males likely indicates permanent hypogonadism. A history of anosmia or hyposmia points to Kallmann syndrome, which is the result of a rare genetic mutation and can affect boys and girls. Resulting from a chromosomal abnormality, Klinefelter syndrome (47,XXY) patients often start pubertal maturation but then do not progress due to testicular failure. Other clinical signs include those of other manifestations of permanent hypogonadism in addition to behavioral and cognitive abnormalities. Adolescent girls with Turner syndrome (45,X) likewise present with behavioral and cognitive problems as well as underdeveloped, nonworking ovaries.

"Adolescents with secondary hypogonadism are often variations on normal.
The pathways for spermatogenesis and ovulation are asleep and just need to be given that awakening signal."

— Alan D. Rogol, MD, PhD, professor emeritus, University of Virginia School of Medicine, Charlottesville

Functional hypogonadism can result from chronic, systemic conditions, such as cystic fibrosis and inflammatory bowel syndrome, poor nutrition (energy balance), and various endocrinopathies, such as hypothyroidism and hyperprolactinemia, all of which result in symptoms in either the patient or the patient's parents that can sometimes be elicited during history-taking.

What the history and examination reveal guides next steps algorithmically. First tests should include biochemical studies and bone imaging. For example, an elevated FSH level suggests hypergonatropic hypogonadism, which prompts karyotyping. Low/normal LH and FSH suggest multiple differential diagnoses and may prompt genetic testing or additional testing for underlying chronic conditions. "We must be aware of clinical parameters (found in the patient's and his or her family's history and physical) that may signal the underlying condition," says Luiz Claudio G. Castro, of the Universidade de Brasília Medical School, in Brasilia, Brazil. "Sometimes we also use hormonal stimulation tests and brain images as tools to support the diagnosis or the presumptive diagnosis. Other times we may even start hormonal replacement for a short period, the patient develops puberty, then it's withdrawn and we evaluate if the patient is able to keep puberty development spontaneously or not."

"One important aspect is that there is not a rigid protocol with well-established test responses for diagnosing HH or CDGP,
because patients are different, and even the ones with similar clinical features and biochemical findings at one moment may have different maturation and outcomes throughout time.

— Luiz Claudio G. Castro, Universidade de Brasília Medical School, Brasilia, Brazil

Variations on Normal

"Adolescents with secondary hypogonadism are often variations on normal," says Rogol. "The pathways for spermatogenesis and ovulation are asleep and just need to be given that awakening signal." Furthermore, because much of the overall incidence of delayed puberty is transient, the decision to treat should be weighed very carefully. With CDGP, expectant management and reassurance may be all that is needed, with the decision to start sex steroid administration belonging to the patient, according to Mark Palmert, MD, PhD, associate professor, Department of Pediatrics at the Hospital for Sick Children, in Toronto, Canada. Psychosocially, the delayed puberty adolescent may be experiencing significant distress when comparing him or herself to peers and want to start sex steroid supplementation.

If the evaluation has uncovered any latent condition, therapy begins with targeting it, resolution of which can sometimes itself prompt sexual maturation, which identifies the delayed puberty as being due to FHH. "In any state of poor health, HH may occur and will reverse if the disease or condition is successfully treated and good health is restored," says Bradley D. Anawalt, MD, of the University of Washington, in Seattle.

However, as mentioned, teasing out other causes to determine a treatment basis is complicated by their shared relative GnRH deficiency component. In general, clinicians have two options in the latter case, either expectant management or prescribing sex steroid hormone therapy. For many patients, reassurance that they will catch up to their peers is sufficient.

Although many with CDGP undergo spontaneous progression through puberty, treatment with testosterone for boys and estrogen for girls can have benefits besides hastening the process.

Improvements in bone mass and muscle composition are seen, accelerating growth, and psychosocial anxiety may be significantly ameliorated. Moreover, short-term administration of sex steroids has not demonstrated significant adverse effects. Unless the patient has delayed puberty along with true GH deficiency (e.g., as might be seen with combined pituitary hormone deficiency), says Palmert, combined treatment of sex steroids and GH is not usually warranted, even with short stature/slowed growth. "In patients with delayed puberty, administration of exogenous sex steroids not only leads to development of secondary sexual characteristics but usually also leads to acceleration in linear growth. Treatment with GH does not appear to result in substantial gains in height compared to the administration of sex steroids alone, and its use is quite expensive," says Palmert. With permanent hypogonadism, sex steroid hormone therapy is initiated to induce secondary sex characteristics.

The Big Picture

The take-away for clinicians here is that distinguishing among causes of delayed puberty, although ultimately important, is neither easy nor necessarily critical at the initiation of therapy. "The real conundrum is how to discriminate permanent congenital hypogonadotropic hypogonadism (CHH) from CDGP," says Anawalt. "A family history of delayed puberty, delay in bone age, and stature below expected based on parental height are clues that the patient has the more common diagnosis, CDGP. Small testes and penis, bilateral cryptorchidism, and decreased sense of smell suggest CHH. Many times the only reliable way to discriminate between CDGP and permanent CHH is the passage of time. If there is no sign of puberty by 18, then permanent CHH is the diagnosis."

Castro agrees: "One important aspect is that there is not a rigid protocol with well-established test responses for diagnosing HH or CDGP, because patients are different, and even the ones with similar clinical features and biochemical findings at one moment may have different maturation and outcomes throughout time. Although HH is an organic disease in which sex hormone replacement is the standard therapy, CDGP is expected to be a normal variant of growth and pubertal maturation. There is no specific single test that can clearly make this differentiation, but we have to analyze clinical, hormonal, and imaging data in a dynamic way throughout the patient's follow-up. It's like building a puzzle, looking, at the same time, at each and every obtained piece and the way they fit with each other. The 'big picture' is our main tool used to discriminate between HH and CDGP." EN

— Horvath is a freelance writer based in Baltimore, Md. She wrote about thyroid storm in the August issue.

Cancer Cachexia Hub

Cancer Cachexia as a metabolic syndrome

Cancer cachexia, better referred to as cancer anorexia-cachexia syndrome (CACS), is a multifactorial syndrome that negatively impacts the functional performance, quality of life and prognosis of cancer patients.[1-5] Cancer cachexia is defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[1]

60%-80%
of patients with advanced cancer are at risk of developing cancer cachexia[6]

The pathophysiology of cancer cachexia is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.[2] In particular, cancer cachexia is often associated with an elevated basal metabolic rate, despite a decrease in physical activity and total energy expenditure. Muscle atrophy results from a decrease in protein synthesis, and increase in protein degradation, or a combination of both.[7]

A recent consensus definition of cachexia rightly emphasizes that it is a metabolic syndrome, as it affects glucose, lipid, protein, and energy metabolism [8,9]

Want to learn more about Cancer Cachexia?

www.cancercachexia.com

A new place where state-of-the-art knowledge on Cancer Cachexia is gathered and shared.

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WORD OF MODEM

If you don't know what your patients are saying about you online, it's time to log on and find out. You might be pleasantly surprised…or you might not.

By Derek Bagley

Google any physician's name, and a slew of information will turn up about him or her: Bios, CVs, bibliographies, listings. Information from all of these is collated, quantified, run through algorithms, and then displayed cleanly anywhere it is accessed. But it's not just the objective facts and figures that people want when they Google a doctor; they want opinions too, a glimpse of other patients' experiences before they decide to make that appointment.

It's a clear trend — a sort of self-sustaining service journalism for the modern, plugged-in, world. People will log on to Yelp or Amazon to voice complaints or compliments, for filet mignons that were overcooked, hotel rooms that smelled funny, televisions that malfunctioned after the first use, books they couldn't put down. Patients are doing the exact same thing with doctors they've seen.

While online reviews aren't an exact science, the factors that go into them "mean a tremendous amount to a patient, but often are never addressed or even considered by a doctor."

— Elliot Levy, MD, clinical professor of medicine, Division of Endocrinology, University of Miami School of Medicine

Earlier this year, the *Journal of the American Medical Association* published a research letter that acknowledged this trend of rating doctors online. Lead author David A. Hanauer, MD, of the University of Michigan, in Ann Arbor, wrote, "Patients are increasingly turning to online physician ratings, just as they have sought ratings for other products and services." Elliot Levy, MD, a clinical professor of medicine in the Division of Endocrinology at the University of Miami School of Medicine, Miami, Fla., pointed out that while online reviews aren't an exact science, the factors that go into them "mean a tremendous amount to a patient but often are never addressed or even considered by a doctor."

Patients as Consumers

While doctors may or may not be considering online reviews, patients certainly are, with more and more publishing their voices in cyberspace forever, no longer by word of mouth, but word of modem.

"In our study, we found that a majority of the public was aware of such sites, and about a quarter had visited them," says Hanauer, whose primary interest is clinical medical informatics, especially working with clinical data in electronic medical records. Among those visiting the sites, about one-third reported choosing a

Google YOURSELF

Whether you like it or not, online review sites aren't going anywhere. The more you learn about what's out there about you and your practice, the better prepared you'll be to deal with it. Here are a few steps to take as you merge onto the information superhighway.

- Even a cursory glance at patient review sites can give an indication of what patients value when they visit. Learn from them.
- Take a negative review to heart and communicate with your patient sincerely, openly, and compassionately. Apologize if necessary.
- Address internal problems with staff and office etiquette, especially if there are numerous complaints about the same thing.
- Think long and hard before responding publicly to a negative review. The Internet is rife with business owners' rebuttals that have turned into PR nightmares. Doubling down is almost never a good move.
- Encourage patients to submit online reviews, since most reviews are positive, and the positive reviews will eventually outweigh the negative ones.

doctor based on good ratings and a third avoided one due to bad ratings.

"Our survey was conducted almost two years ago," Hanauer says, "and my assumption is that overall awareness and usage is continuing to increase. Doctors should care about them because the public is using them to make decisions on selecting a doctor."

Hanauer's assumption is correct. Trends show that 80% to 90% of consumers say they check online reviews before they buy or hire anything. "Healthcare services are among those things consumers are reviewing," says Cheryl Reed, of Angie's List, a paid subscription review site. "This isn't something embraced only by younger, tech-savvy people. It's pervasive and can be greatly insightful."

Patients are responding to the fact that healthcare is becoming more competitive, says Clark Perry, DO, an endocrinologist with the Community Physician Network in Indianapolis, and ultimately, it all comes down to "What differentiates us?"

"I see patients, and in the first few minutes I know they've researched me, because they tell me," says Perry, who also points out that physicians should be aware when giving referrals. "Patients want the names of doctors you're referring them to, and they'll research them."

In 2010, Shaili Jain, MD, a psychiatrist at the Veterans Affairs Palo Alto Health Care System in California and an assistant professor at the Stanford University School of Medicine, published commentary in the *New England Journal of Medicine* titled "Googling Ourselves — What Physicians Can Learn from Online Rating Sites." The article is an irreverent and insightful look into the process of Googling yourself, from the initial anxiety of clicking on a site to see what your patients have said to the relief at seeing good reviews or disappointment in reading a bad one. Jain writes that sites such as "RateMDs, Vimo, and RevolutionHealth, offer patients an opportunity to rate physicians on their helpfulness, knowledge base, interpersonal skills, and punctuality. This has become a popular online activity, with hundreds of physician reviews appearing daily."

Jain notes this practice of patients advocating for themselves through these reviews, writing that proponents of these sites see "patients as consumers who have a right to express their opinions about services they pay for."

"Patients more and more don't view themselves as just patients blindly following their doctors' referrals blindly," Reed says. "They're consumers looking for doctors who will treat them with respect and offer them efficient, friendly service."

Rants and Raves

The natural assumption is that people tend to leave more negative reviews on these sites, that patients will only go to rant about how they were treated poorly or unfairly, often as a form of catharsis, and they never visit the site again. "I suspect people tend to write bad reviews much more frequently," says Allison B. Goldfine, MD, of Harvard Medical School, in Cambridge, Mass. This assumption was underscored even in the satirical newspaper, *The Onion*, in an article titled "Physician

SITE VISIT ★★★★★

A list of some of the more popular websites where physicians are rated.

healthgrades	Healthgrades.com
ZocDoc	Zocdoc.com
RateMDs DOCTORS YOU CAN TRUST	Ratemds.com
vitals	Vitals.com
Angie's list	Angieslist.com

Shoots Off A Few Adderall Prescriptions to Improve Yelp Rating."

Of course, this suspicion could be the reason that many doctors historically ignored or even discouraged online reviews, thinking that the review sites would comprise nothing but ill-informed, meaningless complaints that could do nothing but unfairly harm their reputations.

Indeed, a quick glance at some sites will turn up phrases like "worst doctor ever" and "I wouldn't let him/her treat my hamster," but these aren't the norm, according to Reed. "Actually, the majority of healthcare reviews on our site are positive," she says of the physician reviews on Angie's List. "More often than not, the negative is with the office staff, not the actual medical treatment given."

Hanauer and his team found similar results: 54% reported leaving a positive rating, while 19% left a negative rating. And while reviews like "worst doctor ever" might not be the most helpful or meaningful, some patients do take the time to go into detail about their experiences, raving about exactly how the staff made them comfortable, or ranting about exactly how the staff made them feel "like a criminal." Reviews like these can potentially provide teaching moments to physicians who decide to take their patients' stories to heart.

Jain writes that it's the stories like these that are the most helpful; the rave reviews inspiring her to "work harder and better" for her patients, and the rants about physicians being arrogant or failing to listen she reads "with regret because [she knows] they are not implausible."

"I feel like the proverbial fly on the wall," Jain writes. "I'm discovering what patients think makes a good doctor, what they value and deem essential to high-quality care, and what gets them really riled. These patients don't hold back, and their tales make for refreshing reading, a sea of patients' voices telling me how it really is."

"Listen In, Learn, and React"

Jain points out in her commentary that critics of review sites see the entire system as "fundamentally flawed," because there can be a lot of obstacles to navigate when dealing with negative reviews. The anonymity of these sites makes it hard to guarantee that the reviewer is even a patient and not someone with a grudge against the doctor or worse, just some "troll," who posts deliberately provocative messages to cause mayhem. Physicians have no opportunity for rebuttal because they are bound by privacy laws, and a handful of ratings may not be quite representative of a doctor who sees hundreds of patients a year.

"I see patients, and in the first few minutes I know they've researched me, because they tell me," says Perry, who also points out that physicians should be aware when giving referrals. "Patients want the names of doctors you're referring them to, and they'll research them."

— Clark Perry, DO, endocrinologist, Community Physician Network, Indianapolis

In actuality, a lot of the negative reviews have nothing to do with medical advice at all, so the physicians then have no expertise over the patients, who may be complaining about the nurses who were rude to them on the phone or never even bothered to call them back, the doctors who were distracted by personal phone calls, the unacceptably long wait times. (All of these complaints were actually voiced on Angie's List, and each reviewer ended up having positive things to say about the medical consults themselves.) And yet, none of these things requires an advanced degree to address, just an acknowledgement of the problem and a willingness to fix it.

"Physicians — or a designee — can learn a lot about what's working and what's not," says Reed, "and possibly where they can make back-office improvements to help with the overall experience.

"For years people have chatted about their healthcare experiences," she continues. "Online reviews give those being reviewed a way to listen in, learn, and react."

Still, negative reviews seem inevitable, especially now with the ubiquity and accessibility of these sites. A physician may make a mistake, may say something wrong during an exam, or the patient may simply be having a bad day. But patients are not unreasonable; they just want to feel respected and have a doctor who cares at a time when they're most vulnerable. "See through the patients' eyes," says Perry. "Patients expect to be treated at a certain standard."

The solutions then, seem obvious and simple, but only when the physician is aware of the problem(s), and that is more increasingly accomplished by reading and digesting patient reviews.

"I suppose the best way currently to counter negative ratings would be to try to get more positive ratings," Hanauer says," but this of course can lead to additional bias. But this is partly why doctors should care about the ratings. If nothing else, they should be thinking about how patients can get an unbiased, representative view of their practice, given that online doctor rating sites seem to be here to stay." EN

— Bagley is the associate editor of Endocrine News. *He wrote about the highlights of ICE/ENDO 2014 in the August issue.*

Best BUYS

From cruising the Internet to getting items donated, there are plenty of novel ways to find lab equipment that won't bust your budget.

By Melissa Mapes

Whether buying a new car or a mass spectrometer, nobody wants to pay the full sticker price. Finding a good deal on lab devices takes a bit of resourcefulness and negotiating but can generate major savings on annual operating costs.

The typical laboratory spends $347,302 per year on equipment, instruments, chemicals, and other products according to *Lab Manager* magazine — all of which can be obtained through unorthodox, yet cheaper, methods. A bit of extra effort can score great equipment and product finds for researchers on a budget.

Donations

As the saying goes, the best things in life are free. University laboratories, nonprofits, and self-funded studies might find a superlative deal by asking local companies for donations of their excess equipment and other lab materials. The company can potentially receive a tax write-off for the gift in lieu of payment, while scientists can save thousands of dollars.

The nonprofit Seeding Labs has proven the possibilities of unpaid acquisitions by collecting and distributing equipment to university and research institutions in developing countries. The organization opened its doors

in 2008 and has since placed more than $1.3 million in materials to laboratories in need. It has also outlined clear guidelines for donations to maximize the efficiency of it's operation.

Quality control can be challenge when receiving free items. One may go to great lengths to find, pick up, and test gifted gear only to discover that it is beyond repair. No financial loss may occur, but the time wasted could be costly to the progress of one's work. Seeding Labs requires that donated equipment is in good working condition, that it is not very old or obsolete, and that it is not custom-made or altered for specific needs. By developing long-term relationships with companies that can make quality gifts on a regular basis, it has been able to build a network of reliable donors.

Web Classifieds

Other potential sources of gratis lab materials can be found online. Craigslist.org offers a "free" section under items for sale, where individuals and businesses may post giveaways. The same concerns apply for condition and wasted time, but the ease of the searchable Internet database requires less effort than outreach to various companies and organizations. Popular free items often include computers and IT network equipment.

Of course, new and used equipment can also be purchased on Craigslist.org. Because of the lack of accountability for sellers on the site, there is no consumer protection and buyers must be wary of scams. A better option is the online auction site eBay.

eBay recently published a guide for purchasing lab equipment on the site, which offers basic descriptions of the items available and an overview of its buyer protection program. The guide recommends using the advanced search feature to narrow down the listings — starting with the "Business & Industrial" category, then selecting "Healthcare, Lab, & Life Science," and finally clicking "Lab Equipment" or "Lab Supplies" to see items for auction. Additional subcategories are also available.

Similarly, Amazon.com has extensive listings of everything from pH testers to centrifuges. The options available on Amazon and eBay are far larger and better organized than those on Craigslist. Both offer some sort of guarantee to ensure that purchasers get what they pay for.

A number of Web classifieds specifically for laboratories exist as well. LabX.com and LabMerchant.com are two of many such sites. Prices can quickly be compared for equipment across the Web to find the company with the best deal for a particular item.

Resellers

LabX and LabMerchant also operate as resale merchants for excess and used equipment. Prices will likely be higher than buying directly from a private seller, but if the laboratory materials in question are not available through cheaper avenues, resellers offer a reliable alternative.

These companies approach industry labs and other businesses with extra equipment and offer to buy supplies off their hands. Each item is added individually to their inventory and sold online for a profit. Often, they gather the best used or unneeded gear, and donation seekers must dig through what is left. On the bright side, most resellers offer buyer protection and sometimes even warranties on the items they sell — similar to Amazon and eBay — which one cannot get with free equipment.

Resale merchants still claim to be significantly cheaper than ordering new from a manufacturer. Dante LaTerra, CEO of American Laboratory Trading Inc., told *LabManager* magazine that his company aims to support underfunded science. "We are providing opportunities for startups, smaller companies, colleges and universities, and others with budget concerns to get high-quality technical equipment at a discounted price so that they can conduct their research and other projects and compete in their fields on a limited budget."

American Laboratory Trading offers buyers a 90-day warranty on any item purchased. Researchers can also trade their old equipment for a newer model or a different tool. Because LaTerra has trained technicians on staff for refurbishing, he often takes broken equipment from scientists in exchange for a credit toward a working replacement. According to the website, prices are 50% – 80% less than retail.

Internal Equipment Networks

Those working at academic institutions or other organizations with multiple labs may instead fill orders by tapping into an internal network. To avoid waste, many universities have put in place a system for trading tools and materials among their laboratories.

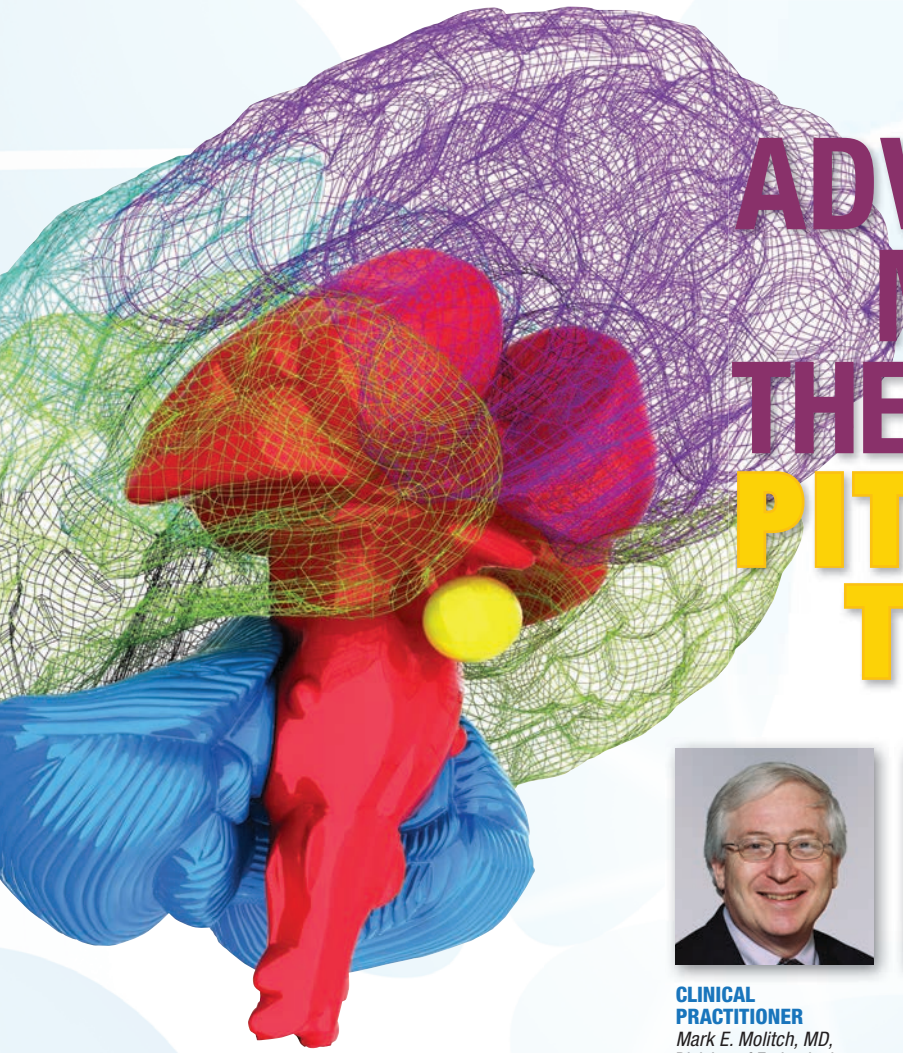
Harvard University's Office of Sustainability operates a "reuse room" and "green room" at two different campus locations where researchers can trade, share, and donate laboratory and office supplies. Basic everyday items like Styrofoam coolers can easily be obtained. It also runs an online database called the "lab reuse list" where people can trade, reuse, and share working laboratory equipment and other materials, in addition to saving precious research dollars.

Each novel method offers eco-friendly sensibilities in addition to cost-cutting benefits, as they encourage the reuse of old tools and reduce trash. Selling or donating unneeded lab gear rather than throwing it in the garbage is equally smart. By purchasing or offloading lab materials through these channels, scientists can feel confident about both their budget and their contribution to sustainable practices.

— Mapes is a Washington, D.C.–based freelance writer and a frequent contributor to Endocrine News. *She wrote about new technology in the September issue.*

Where to Look for DEALS ONLINE

ebay.com	usedlabequipment.com	labrecyclers.com
craigslist.org	labx.com	labequip.com
amazon.com	labmerchant.com	seedinglabs.org



Uncommon Knowledge: ADVANCING MEDICAL THERAPY OF PITUITARY TUMORS

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In the last four decades, endocrinologists have witnessed a small revolution in the medical therapy of pituitary tumors. Starting with the first reports on the efficacy of bromocriptine in the treatment of prolactinomas, considerable scientific advances have dramatically enhanced our therapeutic options. Currently, expression profiling of dopamine receptors in pituitary adenomas provides a clear rationale for the use of dopamine agonists as the first-line therapy for prolactinomas as well as in a subset of patients with GH, ACTH, and non-secreting adenomas. Somatostatin receptor profiling similarly provided the impetus to develop long-acting somatostatin analogues, which today are considered mainstays of acromegaly management. Despite this progress, many pituitary tumors remain poorly responsive to currently available drugs, highlighting the need for further studies to advance our understanding of the biological pathways underlying pituitary tumorigenesis. In this Tri-Point article, three experts discuss the most recent advances and the ongoing challenges in the medical therapy of pituitary tumors: a clinical practitioner focuses on the importance of "bench to bedside and back" for the clinical management of pituitary tumors; a basic researcher describes novel intracellular signaling pathways in pituitary tumorigenesis and the potential for targeting these pathways in future therapeutic applications; and a clinical researcher provides additional examples of the translation of novel discoveries in basic science to clinical trials and patient care.

HIGHLIGHTS

- The discovery and characterization of the hypothalamic releasing and inhibiting hormones and their receptors resulted in the generation of **remarkably successful and specific therapies for pituitary tumors**.
- **Not all tumors respond in the anticipated manner to such therapies**, necessitating additional research into why these unanticipated responses occur.
- Novel treatments continue to be developed based on **our understanding of the pathophysiology and pathogenesis of the various types of pituitary tumors.**

Bench to Bedside, and Bedside to Bench

The medical therapy of pituitary tumors is the poster child for the concept of bench to bedside and back. The foundations for current treatments were laid in the 1950s by Sir Geoffrey Harris and others who demonstrated the control of pituitary function by the hypothalamus and subsequently in the 1960s, 1970s, and 1980s by the laboratories of Roger Guillemin, Andrew Schally, and Wylie Vale who identified and characterized the hypothalamic releasing and inhibiting factors we now take for granted. With this newly acquired information regarding the regulation of pituitary hormone release, it was only a matter of time before this basic knowledge was applied to the treatment of pituitary diseases.

One of the first examples of the bench to bedside approach was the treatment of hyperprolactinemia. Following the discovery that dopamine was the prolactin (PRL) inhibitory factor, Peter Lutterbeck correctly reasoned that the dopaminergic properties of the ergot derivative bromocriptine might be effective in treating hyperprolactinemia. The success achieved in treating patients with prolactinomas initially with bromocriptine and later with cabergoline has been nothing short of astounding. But our now extensive experience with dopamine agonists has revealed several problems that need to be taken back to the bench, including: 1) uncommon patients who do not respond to dopamine agonists at all and 2) others who are resistant and require very high doses of dopamine agonists to normalize PRL levels. We do not fully understand the status of dopamine receptors in these patients, the relationship between their short and long isoforms, and receptor coupling to inhibitory transduction mechanisms. Do we need drugs working by different mechanisms of action for such patients?

There are other problems that require further research at the bench and in clinical studies. Cabergoline can cause cardiac valvular abnormalities when used in high doses for patients with Parkinson's disease, but standard doses used for most patients with prolactinomas apparently do not. We need to identify the threshold dose responsible for cardiac valvular abnormalities so as to guide us in our management of those uncommon patients with dopamine agonist resistance who need high doses of cabergoline.

Acromegaly

Treatment of acromegaly is another example of the bench-to-bedside approach. Hypothalamic extracts that could inhibit GH secretion were discovered in 1968. However, it was not until 1973 that somatostatin was characterized, 1978 that somatostatin receptors were discovered, 1984 that somatostatin analogues were shown to be beneficial for the treatment of acromegaly, and many years later that the long-acting versions of the somatostatin analogues octreotide and lanreotide became standard parts of clinical practice. Although initial studies showed quite high rates of success, more recent studies suggest that fewer than 50% of patients normalize GH and IGF-1 levels when prescribed these drugs following noncurative surgery. Continued clinic-to-bench interaction is needed here. Why is this success rate so low? Is this simply a somatostatin receptor issue? We have learned that many somatotroph tumors have dopamine receptors, and the use of dopamine agonists along with somatostatin analogues can be beneficial in many patients. Do dopamine agonists work through a second inhibitory pathway, or is there some synergism between activation of these pathways? Further help may arise from the bench as new somatostatin analogues, such as pasireotide and possibly oral somatostatin analogues, reach the clinic.

Looking Ahead — New Clinical Trials and Areas to Explore

Although the bench-to-bedside medical therapies affecting tumors are most visible with PRL- and GH-secreting pituitary adenomas, we have learned that dopamine receptors and somatostatin receptors are often present on ACTH-producing tumors causing Cushing syndrome and on clinically non-functioning pituitary tumors, which are usually gonadotroph adenomas. Small studies have shown some success with the use of dopamine agonists in these two conditions; but, large, prospective, randomized, multicenter studies have yet to be performed using dopamine agonists for non-functioning adenomas and Cushing syndrome. On the other hand, a large, prospective, randomized study has recently shown that pasireotide, the newest somatostatin receptor analog, which has activity at somatostatin receptor 5, can lower ACTH and cortisol

levels in many patients with Cushing disease, leading to its approval in many countries. One interesting area that also has clinical importance but has not been evaluated is the use of these drugs in patients with "silent" lactotroph, somatotroph, and corticotroph adenomas (i.e., tumors producing PRL, GH, or ACTH without clinical syndromes). Would the drugs that are effective in patients with the clinical syndrome be effective in preventing regrowth of their "silent" counterparts after surgery?

Clinicians and patients have benefited greatly from information generated in the laboratory and translated into pharmacologic agents with very high efficacy/adverse event ratios for pituitary tumors. Yet, some problem areas remain, and we trust that such continued collaboration will help solve them. EN

BASIC RESEARCHER PERSPECTIVE — *Shlomo Melmed, MD*

HIGHLIGHTS

- **Pituitary adenomas** arise from differentiated anterior pituitary cell types.
- These **benign monoclonal neoplasms may secrete PRL, GH, ACTH,** and very rarely gonadotrophin hormones or TSH. Some are nonfunctional and do not actively secrete hormones.
- These **tumors are almost invariably benign**, and understanding their cell cycle disruptions has enabled identification of novel subcellular therapeutic targets.

Pituitary Adenoma Pathogenesis

Pituitary tumorigenesis is characterized by a dual disorder of excessive cell proliferation coupled with dysregulated hormone hypersecretion. Differentiated anterior pituitary cells produce ACTH, GH, TSH, PRL, FSH, or LH, which selectively regulate target gland hormone secretion to elicit peripheral tissue effects (Table 1). Each cell type also expresses tissue/cell-specific transcription factor(s) determining hormone gene expression. Each cell type may give rise to a differentiated adenoma characterized by a unique clinical syndrome. Early pituitary progenitor or fully differentiated hormone-expressing cells give rise to pituitary tumors that are monoclonal benign adenomas, which possess a proliferative advantage. For example, in a mouse model, a pituitary cell lineage expressing the Pax7 transcription factor gave rise to cell lineages downstream of nestin-expressing stem cells.

Adenomatous pituitary cell proliferation is sustained by genetic or epigenetic abnormalities, paracrine growth factor disruptions, and/or an altered intrapituitary microenvironment, leading to oncoprotein activation or tumor suppressor gene inactivation, and ultimately pituitary cell cycle dysregulation. Multiple factors impinge on the pituitary cell to elicit hyperplastic or neoplastic growth as well as respective hormone hypersecretion (Table 2). Although inactivated or overexpressed cell cycle regulators may initiate pituitary hyperplasia and tumorigenesis in murine models, classic oncogene mutations are rarely encountered in human pituitary tumors. Activating proliferative changes only very rarely facilitate malignant transformation, and pituitary adenomas are characterized by protective mechanisms buffering against carcinoma development, including proliferative restraint at the microadenoma stage, and cell senescence occurring after macroadenoma development. These mechanisms prevent transformation to carcinoma, thereby, enabling the overwhelmingly benign phenotype. As pituitary tumor cells exhibit premature cell proliferative arrest while maintaining hormone hypersecretion, targeting cell cycle disruptions is an attractive approach for novel therapeutic applications.

As an example of this approach, evidence is presented for targeting cell cycle disruptions employing ErbB receptors, including epidermal growth factor receptor (EGFR) and HER2, which regulate both pituitary hormone secretion and cell proliferation.

Corticotroph Adenomas

Developing novel targeted medical therapy for ACTH-producing pituitary adenomas is an important current challenge. Most ACTH-secreting adenomas express the EGFR. Proopiomelanocortin (POMC) gene expression and ACTH secretion are induced by EGF in an EGFR-dependent manner. In addition, p27Kip1, a cyclin-dependent kinase (CDK) inhibitor, is down-regulated in tumors expressing EGFR. Therefore, the EGFR could be a novel target for Cushing disease therapy, targeting both hormone secretion and cell proliferation.

Gefitinib, a tyrosine kinase inhibitor (TKI), targets the EGFR, blocking the intracellular ATP-binding site of the tyrosine kinase domain and suppressing Pomc promoter activity and ACTH secretion in an EGFR-dependent manner. The suppression of POMC expression and ACTH secretion were also demonstrated

Table 1. Classification of pituitary adenomas

Cell type Adenoma type	Population prevalence (total/105)	Tumor transcription factor expression	Upregulated differentiated gene expression	Clinical features
Lactotroph	45–50	Pit-1	Prolactin	Hypogonadism and/or galactorhea
Sparsely or densely granulated				
Gonadotroph	15–20	SF-1, GATA-2	FSH and/or LH and/or glycoprotein subunit (depending on type, null, or oncocytic)	Silent or pituitary failure Ovarian hyperstimulation (reproductive age women) Testicular enlargement (prepubertal)
Somatotroph	10	Pit-1		
Sparsely granulated			GH	Acromegaly or gigantism
Densely granulated			GH	Acromegaly
Combined GH and PRL cells			GH and prolactin	Acromegaly or gigantism
Mixed GH and PRL			GH and prolactin	Hypogonadism and acromegaly
Mammosomatotroph			GH and prolactin	Acromegaly or gigantism
Acidophil Stem Cell			Prolactin and GH	Hypogonadism and acromegaly
Silent			GH	Hypopituitarism
Corticotroph	5	T-Pit	ACTH	
Cushing				Cushing Disease
Silent				Hypopituitarism
Nelson				Pituitary hyperplasia
Thyrotroph	<1	Pit-1	TSH	Hyperthyroidism
Plurihormonal	Unknown	All	GH, prolactin, ACTH, glycoprotein	Mixed

Reproduced from Melmed S, Nat Rev Endocrinol, 2011.

Table 2. Factors regulating pituitary cell proliferation and/or tumor formation

Pituitary hyperplasia
- Lactotroph
  - Pregnancy
  - Lactation
  - Excessive estrogen exposure
  - Stalk-section
- Somatotroph
  - Eutopic or Ectopic GHRH
  - McCune–Albright syndrome
  - Mammosomatotroph hyperplasia
- Corticotroph
  - Eutopic or Ectopic CRH production
  - Untreated adrenal failure
  - Cushing disease
  - Nelson syndrome
- Thyrotroph
  - Untreated thyroid failure
- Gonadotroph
  - Untreated gonadal failure
  - Klinefelter syndrome

Pituitary adenoma
- Hereditary syndrome
- Signal transduction mutation
- Loss of tumor suppressor gene function
- Disrupted paracrine growth factor or cytokine action
- Chromosomal instability
- Epigenetic events
- Cell adhesion molecule disruptions

From The American Society for Clinical Investigation Melmed S, J Clin Invest 112, 1603–1618 (2003).

in human pituitary corticotroph tumors and canine corticotroph adenoma cells. Gefitinib also attenuates the corticotroph cell cycle, as evidenced by decreased BrdU incorporation, reflecting drug effects on tumor cell proliferation. Finally, gefitinib induces p27kip1, the CDK inhibitor, which is down-regulated in most ACTH-secreting tumors.

In mice inoculated with explanted ACTH-secreting tumors, only animals with EGFR expressing tumors exhibited the attenuating effects of gefitinib on phenotypic features of hypercortisolism and the associated decreased serum corticosterone levels. Therefore, gefitinib action appears to be mediated by regulating EGFR signaling on corticotroph tumor cells. These results support the clinical rationale for blocking EGFR signaling to attenuate corticotroph adenoma growth and ACTH secretion.

Roscovitine, a CDK inhibitor, suppresses experimental corticotroph tumor growth and POMC gene expression in zebrafish and in murine xenografts. Transgenic zebrafish with zPttg overexpression targeted to pituitary POMC lineages (corticotrophs and melanotrophs) develop phenotypes reflective of Cushing disease, including neoplastic corticotrophs with partial glucocorticoid resistance, hypercortisolemia-mediated hyperglycemia, and fatty liver. PTTG is a pituitary transforming gene, and R-roscovitine suppressed PTTG-overexpressing corticotrophs. These inhibitory actions were

Table 3. Selected cell cycle–associated genes associated with pathogenesis of pituitary adenomas

Gene	Function	Mode of activation/inactivation
CCNB2	Cyclin	Induced by HMGA
CCND1	Oncogene	Overexpression
CDKNIB	CDK inhibitor	Inactivating
HMGA2	Oncogene	Overexpression
FGFR4	Oncogene	Alternative transcription
PTTG	Securin	Overexpression
Rb	Tumor suppressor	Epigenetic silencing
CDKN2A	Cyclin-dependent kinase inhibitor	Epigenetic silencing

Modified from Melmed S, J Clin Invest119, 3189–3202 (2009).

validated in murine corticotroph adenomas, supporting the use of selective CDK inhibitors as effective therapy for Cushing disease.

Prolactinomas

EGF, a pituitary cell growth factor, also directly induces prolactin synthesis. The EGFR family (ErbB receptors) and ligands are expressed in normal and tumorous lactotrophs, inducing PRL synthesis and secretion, and increases in prolactinoma size. Most prolactinomas exhibit variable ErbB expression, and selective ErbB receptor expression has been associated with tumor invasion and response to dopamine agonists. Therefore, ErbB inhibitors have been used in cell and animal models of prolactinomas. In primary cells derived from human prolactinomas, lapatinib, a dual ErbB tyrosine kinase inhibitor, suppresses PRL mRNA expression and protein secretion. Gefitinib decreases rat somato-lactotroph cell proliferation, PRL mRNA expression, and xenografted tumor PRL secretion in vivo. In stable cell transfectants of a constitutively active form of ErbB2 cDNA, lapatinib also suppresses EGF-induced ErB2 and MAPK phosphorylation, intracellular PRL levels and cell proliferation. Furthermore, in another animal model, estradiol-induced rat prolactinoma growth rate and prolactin production were inhibited by lapatinib.

As ErbB signaling is a determinant of prolactin synthesis, the association between ErbB receptors and clinical outcomes was examined. Immunofluorescent staining of EGFR, ErbB2, ErbB3, and ErbB4 in human prolactinoma tissue arrays correlated with clinical features of tumors. When two patients with aggressive resistant prolactinomas received daily lapatinib for six months, tumor growth was restrained and prolactin levels attenuated, both associated with ErbB receptor expression.

In summary, the pituitary gland is sensitive to cell-cycle disruptions mediated by dysregulated CDKs and by EGFRs (Table 3). Although CDK gene mutations have not been identified in human pituitary tumors, overexpressed cyclins and dysregulated CDK inhibitors observed in pituitary adenomas underscore the relevance of CDK activation for potential therapeutic targeting. The EGFR regulators r-roscovitine and TKIs discussed may represent small therapeutic molecules for those targets. EN

CLINICAL RESEARCHER PERSPECTIVE — *Aart Jan van der Lely, MD, PhD*

HIGHLIGHTS

- For the first time in history, **effective medical treatments of Cushing disease are taking shape** with the introduction of novel therapeutic agents.
- **Medical treatment of acromegaly is so effective today** that a more tailored approach to the individual patient is now possible.
- **To assess and control tissue-specific disease activity of acromegaly will become possible very soon,** which will not only control IGF-I but also improve quality of life in many patients.

Some Success Stories

One of the greatest achievements in the last decades has been the impressive increase in efficacy of medical treatments for hormone-producing pituitary tumors. The success of medical treatment for functioning pituitary tumors has enabled clinical researchers to shift focus from suppressing elevated pathological hormone secretion into the normal range to addressing other important issues in patients, such as quality of life and tissue-specific control of disease activity. Two specific examples highlight the visible shift of focus, while also directing researchers to unmet needs requiring future developments.

A Real Breakthrough in Cushing Disease?

The first example is Cushing disease in which ACTH production by the pituitary tumor is the driving force

behind the disease. Transsphenoidal removal of the tumor remains the cornerstone of proper disease management because the tumors are often relatively small and effective medical therapy is still in its infancy. However, current medical options are promising. Pasireotide, a somatostatin analog that lowers ACTH secretion, drops cortisol levels to the normal range. Although pasireotide monotherapy appears to be effective in only a minority of Cushing patients, this compound shows better efficacy when combined with cabergoline and/or ketoconazole.

Other lights at the end of the tunnel come from studies that investigated the therapeutic effects of glucocorticoid and ACTH receptor antagonists. Mifepristone, a glucocorticoid receptor antagonist, remains an option for treatment of Cushing syndrome. The problem with this type of therapy in everyday clinical use is that overtreatment with glucocorticoid receptor antagonists is difficult to assess. Cortisol levels themselves no longer give information about cortisol actions when the glucocorticoid receptors are blocked. ACTH receptor antagonists would alleviate the problem by blocking ACTH action and cortisol levels. Introducing ACTH receptor antagonists into clinical trials would make an incredible breakthrough in treatment trials.

Acromegaly is Now "Easy" to Treat

The second example of effective medical therapy for pituitary disease is, of course, the treatment of acromegaly. Nowadays, one can say that virtually all acromegaly patients can be controlled with medical therapy when serum IGF-I levels are used as a parameter of disease activity. After "only" 30 years in the evolution of medical treatment modalities, acromegaly patients are no longer untreatable. With the caveat that the high cost of intensive medical treatment [e.g., high dose somatostatin analogs (LA-SAs) or the growth hormone receptor antagonist pegvisomant] limits availability, virtually all patients can now be controlled. The next task for the medical community will be to understand and address tissue-specific aspects of the disease to optimize the necessary tailored approach to the individual patient.

But Do We Really Understand Disease Activity in Acromegaly?

These recent medical developments allowed clinical investigators to focus on quality of life (QoL) as a function of therapeutic modality. Differences in QoL are observed between patients with IGF-I levels normalized by surgery versus those with IGF-I levels normalized by the use of LA-SAs. Interestingly, QoL in the LA-SAs treated group was lower and correlated with growth hormone (GH) levels. In fact, GH levels in medically treated patients were almost twice as high as in the surgically treated subjects. This and other observations following GH receptor antagonists (pegvisomant) have shown that tissue-specific actions of LA-SAs differ from blocking GH or eliminating GH at the same tissues. These tissue-specific effects of low GH levels or GH blockade versus somatostatin suppression may explain the difference in QoL. LA-SAs decrease pathological GH levels, which will decrease IGF-I generation by the liver. Equally important, LA-SAs inhibit portal insulin secretion, both of which result in a relative GH-resistant state of the liver.

While only liver IGF-I production is controlled via direct and GH-dependent effects of LA-SAs, GH levels are still elevated. What remains is that the rest of the body still might have the disease in the sense that the slightly elevated GH levels do act on all tissues, except the liver, as this organ is made selectively GH resistant by the presence of LA-SAs. This discrepancy between GH and IGF-I levels in which GH levels are relatively high while IGF-I concentrations are normalized during LA-SA treatment might give the treating physician the wrong impression that the disease activity is controlled by LA-SAs. This concept of "extra-hepatic" acromegaly is the perfect example of the need to develop treatment goals that focus on tissue-specific activities of the disease that are modality and patient specific.

As an example, Neggers and co-workers studied 20 acromegaly subjects in which the disease was so-called controlled by LA-SAs (i.e., their IGF-I levels were normalized). Improvement in QoL was observed without significant change in IGF-I after the addition of 40 mg pegvisomant weekly to their monthly LA-SA therapy. These data question the current recommendations regarding assessment of disease activity in acromegaly during LA-SA therapy. Moreover, the findings question the validity of the current approach of medical treatment in which pegvisomant is used only when LA-SA therapy has failed to normalize IGF-I. EN

New Kids on the Block

One can expect some new kids on the block, as pasireotide and an orally administered form of octreotide are both in Phase III trials. These fascinating new developments may soon be complemented by potential new treatment modalities, such as GH-receptor antibodies and antisense GH-receptor approaches, which are in clinical development.

Therefore, future physicians may be able to not only control serum IGF-I levels but also offer patients a specific "cocktail of medications" that will treat disease activity in those organs and tissues in which they, as individual acromegaly patients, suffer from most. Taken together, clinical research in pituitary diseases is a very active field with many opportunities to improve patient care.

— This article was reviewed by Cesar Boguszewski, MD, PhD, and the Endocrine Society's Research Affairs Core Committee Co-Chairs Daniel J. Bernard, PhD, and Corrine Welt, MD.

Endocrine Society Tells FDA Testosterone Therapy Should Only Be for Men with Hypogonadism

The Endocrine Society testified at a September 17 meeting of the Food and Drug Administration (FDA) discussing the appropriate population for testosterone replacement therapy and the potential for adverse cardiovascular outcomes associated with its use. Though testosterone use has sharply increased among older men in the past decade, the Society told the FDA that testosterone therapy should be limited to men who meet the diagnostic guidelines for hypogonadism.

Testifying before the FDA joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on behalf of the Endocrine Society, Ronald Swerdloff, MD, professor at the David Geffen School of Medicine at UCLA, said testosterone treatment should be limited to men who have clinical manifestations of hypogonadism and consistently low testosterone levels.

"The Endocrine Society also recommends that more data be collected on men of different ages to better establish the serum testosterone thresholds for specific organ-related symptoms and signs, and to determine which clinical manifestations will benefit from replacement testosterone therapy," Swerdloff testified. Swerdloff was an author of the Endocrine Society's clinical practice guideline, "Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes."

The Society further recommended that a large-scale, well-controlled study be conducted to assess long-term cardiovascular and prostate risks associated with testosterone replacement treatment.

Society Advocacy Prompts Coverage of Artificial Pancreas Technology

The Endocrine Society recently learned that several private insurers were proposing to eliminate coverage for low-threshold suspend systems, which are the first devices to be classified as artificial pancreas technology. In response, the Society contacted these insurers and strongly opposed the elimination of coverage for artificial pancreas device systems, which are FDA-approved and have been used in numerous countries for several years. The Society provided these companies with clinical evidence.

On August 28, the Endocrine Society received a letter from Blue Cross Blue Shield Massachusetts (BCBSMA) stating that, due to our advocacy and that of other groups, BCBSMA has decided to cover low-threshold suspend systems effective December 1, 2014.

The Society has received responses from several other payers stating that they were reviewing their policies and would have a determination in the coming weeks. The Society will continue to advocate on behalf of coverage for the next generation of technologies that could pave the way for the artificial pancreas and will update its members when additional information becomes available.

Congress Passes Stopgap Funding Measure Before Elections; Advocacy Push for NIH Funding Needed During November "Lame Duck" Session

Although Congress is supposed to finalize funding bills by the start of the fiscal year, October 1, the House of Representatives and U.S. Senate left Washington for a seven-week recess on September 18 and will return following the mid-term elections in November for a "lame duck" session. Congress passed a temporary stopgap funding measure to keep the government running through December 11 at roughly last year's funding levels. This means there is no increase for funding for the National Institutes of Health (NIH). The concern by many policy analysts is that Congress may continue to delay final funding bills and simply pass another temporary measure in November, which would continue the negative impact on research funding.

Consequently, the Endocrine Society will increase its efforts to urge Congress to pass a funding bill that includes the NIH before the end of the calendar year. We urge Society members in the U. S. to share this message with their congressional delegations:

Congress needs to make appropriations legislation a priority in the "lame duck" session, and work in earnest to enact final spending legislation for fiscal year 2015 before the end of the calendar year. We are extremely disappointed in the breakdown of regular order in this year's appropriations process and the resulting short-term Continuing Resolution to provide temporary funding for public health, health research, and other core government functions. We are also concerned that funding for emergent needs has been offset by an across-the-board cut. While relatively small, this cut compounds the impact of deep cuts already taken since 2010 due to federal austerity measures, including sequestration.

To learn more about the status of NIH funding and how you can participate in Endocrine Society advocacy, please visit ***www.endocrine.org***

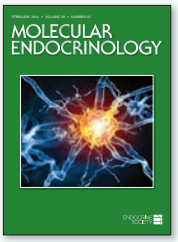
The following studies, among others, will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals at ***www.endocrine.org***.

Fat Quality and Incident Cardiovascular Disease, All-Cause Mortality and Cancer Mortality • Klara J. Rosenquist, Joseph M. Massaro, Alison Pedley, Michelle T. Long, Bernard E. Kreger, Ramachandran S. Vasan, Joanne M. Murabito, Udo Hoffmann, and Caroline S. Fox • *Fat quality, as estimated by CT attenuation, is associated with all-cause mortality, non-CVD death, and cancer death. These associations highlight how indirect indices of fat quality can potentially add to a better understanding of obesity-related complications.*

Serum Thyroglobulin (Tg) Monitoring of Patients with Differentiated Thyroid Cancer (DTC) using Sensitive (Second-Generation) Immunometric Assays ($Tg^{2G}IMA$) Can Be Disrupted by False-Negative and False-Positive Serum Thyroglobulin Autoantibody (TgAb) Misclassifications • Carole Spencer, Ivana Petrovic, Shireen Fatemi, and Jonathan LoPresti • *Reliable detection of interfering TgAb is method and cutoff dependent. No cutoff eliminated both false-negative and false-positive TgAb misclassifications. Functional sensitivity cutoffs were optimal for minimizing false-negatives, but have inherent imprecision (20%CV) that, exacerbated by TgAb biologic variability during DTC monitoring, could cause TgAb status to fluctuate for low TgAb patients, prompting unnecessary Tg method changes and disrupting Tg monitoring. Laboratories using reflexing should limit Tg method changes by considering patient Tg+TgAb history in addition to current TgAb status before Tg method selection.*

Prenatal Influence of an Androgen Agonist and Antagonist on the Differentiation of the Ovine Sexually Dimorphic Nucleus in Male and Female Lamb Fetuses • Charles E. Roselli, Radhika Reddy, Charles Estill, Melissa Scheldrup, Mary Meaker, Fred Stormshak, and Hernán J. Montilla • *This article concludes that, during the critical period, the male reproductive axis in long gestation species, such as sheep, is sufficiently developed to react to perturbations in serum androgens and mitigate disruptions in brain masculinization.*

Direct Regulation of Gonadotropin Release by Neurokinin B in Tilapia (Oreochromis niloticus) • J. Biran, M. Golan, N. Mizrahi, S. Ogawa, I. S. Parhar, and B. Levavi-Sivan • *The results of this study suggest that the members of the NKB/tac3r system may serve as paracrine/autocrine regulators of gonadotropin release in fish pituitary.*



Eukaryotic Initiation Factor 5A Plays an Essential Role in Luteinizing Hormone Receptor Regulation • Bindu Menon, Thippeswamy Gulappa, and K. M. J. Menon • *This study for the first time reveals the crucial role of eIF5A and its hypusination in the regulation of LH receptor expression in the ovary.*

Minireview: Steroid/Nuclear Receptor-Regulated Dynamics of Occluding and Anchoring Junctions • Gary L. Firestone and Bhumika J. Kapadia • *The focus of this minireview is to discuss molecular, cellular, and physiological studies that directly link nuclear receptor- and ligand-triggered signaling pathways to the regulation of occluding and anchoring junction dynamics.*

A Natural Androgen Receptor Antagonist Induces Cellular Senescence in Prostate Cancer Cells • Wiebke Hessenkemper, Julia Roediger, Sophie Bartsch, Adriaan B. Houtsmuller, Martin E. van Royen, Iver Petersen, Marc-Oliver Grimm, and Aria Baniahmad • *Taken together, these data indicate that AA exhibits novel features to inhibit AR amino/carboxy-terminal interaction, the AR-mediated nuclear activities and growth of PCa cells.*

Pharmacology, Physiology, and Mechanisms of Action of Dipeptidyl Peptidase-4 Inhibitors • Erin E. Mulvihill and Daniel J. Drucker • *This article reviews data identifying the roles of key DPP4 substrates in transducing the glucoregulatory, anti-inflammatory, and cardiometabolic actions of DPP4 inhibitors in both preclinical and clinical studies. Finally, it highlights experimental pitfalls and technical challenges encountered in studies designed to understand the mechanisms of action and downstream targets activated by inhibition of DPP4.*

Implications of Prenatal Steroid Perturbations for Neurodevelopment, Behavior, and Autism • Andrea C. Gore, Katherine M. Martien, Khatuna Gagnidze, and Donald Pfaff • *The purposes of this review are: (i.) to summarize some consequences of steroid exposures during pregnancy for the development of brain and behavior in the offspring; (ii.) to summarize what is known about the relationships between exposures and behavior, including autism spectrum disorders; (iii.) to discuss the molecular underpinnings of such effects, especially molecular epigenetic mechanisms of prenatal steroid manipulations, a field that may explain effects of direct exposures, and even transgenerational effects; and (iv.) for all of these, to add cautionary notes about their interpretation in the name of scientific rigor.*

*Data are from a 2006–2007 multinational survey, of which 2,334 patients were considered very high risk (defined as CHD plus two or more major risk factors). National Cholesterol Education Program (NCEP) Adult Treatment Panel III U.S. optional goal is <70 mg/dL (1.8 mmol/L). Countries in this analysis included the United States, Canada, Spain, the Netherlands, France, Taiwan, Korea, Brazil, and Mexico.

Reference: 1. Waters DD, Brotons C, Chiang CW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. *Circulation*. 2009;120:28-34.

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SOCIETY UPDATES: **Obesity Panel, Facts & Figures**

Daniel H. Bessesen, MD, professor of medicine at the University of Colorado, in Denver, has been appointed chair of the Society's new Obesity Expert Panel. This group will be comprised of leading experts in obesity science and medicine, and will guide the development of the Society's broader obesity strategy and implementation plan.

The Society is grateful to all the members who recommended names for consideration — there is now a robust list of 80 names to work from. In his first task as chair, Bessesen is leading efforts to narrow down the list to a final group of 12 individuals who are world-renowned experts in obesity and offer a broad spectrum of expertise.

The Society's obesity strategy is one of the four major dialogue sessions for the November Council planning meeting in Sonoma, Calif., November 7 and 8. The other three dialogue sessions are global strategy, innovating education, and Society leadership development. Bessesen will be leading the strategic discussion on obesity, while Al Powers, MD, Vanderbilt University Medical Center, will be leading the global strategy discussion; Graham McMahon, MD, MMSc, Brigham and Women's Hospital, will lead the innovating education discussion, which will include leveraging technology across the Society; and Paul Stewart, MD, University of Leeds (UK) and Peter Trainer, MD, the Christie NHS Foundation Trust (UK) will lead the discussion on Society leadership development. Elaine Kuttner, with Cambridge Concord Associates, will be moderating the discussions throughout the weekend.

Facts & Figures

The Endocrine Facts & Figures (EF&F) Advisory Panel has issued invitations to nearly 20 Endocrine Society members for the seven therapeutic areas to be covered in phase two of the project. At this time, six Working Groups are complete and include the following outstanding individuals:

- Hypothalamic-Pituitary: Larry Katznelson, MD, Stanford University; Andrea Utz, MD, PhD, Vanderbilt University; and Mark Molitch, MD, Northwestern University, Feinberg School of Medicine
- Adrenal: Lynnette Nieman, MD, NIH and Julia Kharlip, MD, University of Pennsylvania
- Cancers & Neoplasias: Constantine Stratakis, MD, NICHD/NIH; Anthony Heaney, MD, UCLA – David Geffen School of Medicine; and Tobias Else, MD, University of Michigan
- Obesity: George Bray, MD, Pennington Biomedical Research Center and Marc-Andre Cornier, MD, University of Colorado School of Medicine
- Reproductive-Developmental Disorders: Nanette Santoro, MD, University of Colorado School of Medicine, Aurora; Adrian Dobs, MD, MHS, Johns Hopkins University School of Medicine; Alice Chang, MD, MSc, Mayo Clinic; and Michael Irwig, MD, George Washington University
- Cardiovascular & Lipids: Robert Eckel, MD, University of Colorado School of Medicine and Vinaya Simha, MD, Mayo Clinic

The Bone & Calcium Working Group is in the final stages of completion. In addition, Mike Tuttle, MD, Memorial Sloan Kettering Cancer Center, has been appointed as the new Council liaison to the EF&F Advisory Panel to ensure that a current member of the leadership remains actively engaged with the project. Bill Young, MD, MSc, Mayo Clinic, and Ursula Kaiser, MD, Brigham and Women's Hospital/Harvard Medical School have recently completed their terms on Council but will continue with their service on the Advisory Panel.

The Society is excited to have such a strong group of members involved with the second half of this project. EN

Event **CALENDAR**

OCTOBER 9, 2014, CORDOBA, ARGENTINA
Highlights of ENDO • ***www.endocrine.org***

OCTOBER 17, 2014, PHILADELPHIA
3rd Annual Diabetes Symposium: New Advances and Trends • ***jeffersoncme@jefferson.edu***

OCTOBER 22 – 25, 2014, BOSTON
2014 Cardiometabolic Health Congress
www.cardiometabolichealth.org/

OCTOBER 23 – 26, 2014, ANTALYA, TURKEY
EndoBridge • ***www.endobridge.org/2014/***

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PPTOX IV: Environmental Stressors in Disease and Implications for Human Health • ***www.endocrine.org/meetings/pptox-iv***

OCTOBER 29 – NOVEMBER 2, 2014, CORONDO, CALIF.
84th Annual Meeting of the American Thyroid Association • ***www.thyroid.org***

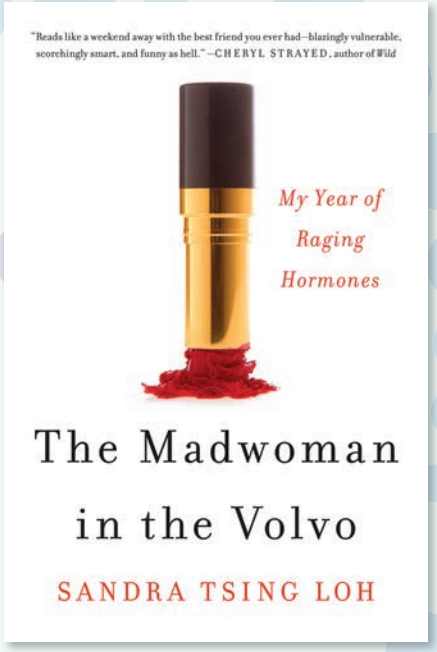
Hormone Health Network Partners with **Author Sandra Tsing Loh**

Sandra Tsing Loh knows exactly what it's like to go through menopause — and how to laugh through it. The writer, radio host, and actor has been through the fire, and now she's bringing her brand of witty — and sometimes acerbic — humor to other women, to let them know that there is hope with her book *The Madwoman in the Volvo.*

The memoir accurately and humorously portrays the harrowing journey through menopause, especially for women in today's fast-paced world, women who are part of what Loh calls "The Sandwich Generation," multitasking women who are at the age in which they're caring for their children and their parents.

The Madwoman in the Volvo is the year in the life of that menopausal woman, in which "every mood is admitted to. Maybe that can establish a conversation," Loh says. "People tend to tell me that they laugh through it and go 'Oh, that's me; I've already experienced way more horrible things,' and I think that sets the context for a pretty safe conversation."

Now, Loh is bringing that conversation to the Endocrine Society's Hormone Health Network, partnering with the organization to tout the Menopause Map, an interactive, peer-to-peer support tool for women in the throes of menopause. *The Madwoman in the Volvo* and the Menopause Map together are fostering that conversation for women whose self-help menopause books and five-minute doctor's office visits offer little help or comfort.



Sandra Tsing Loh, author of *The MadWoman in the Volvo.*

"When I first started going through perimenopause," Loh says, "I experienced really severe mood swings, and I think women find that embarrassing, when you just wake up and cry, and I think that's a hard thing to admit to anyone."

The symptoms of this embarrassment are everywhere, says Loh. Most menopause books have nice, soft, white covers with flowers, instead of what should be there, the "the howling Medusa mask." When a woman walks into a bank, and the teller asks how her Wednesday is going, most woman just smile and say fine, when they really want to curse the teller out. "We're a polite society," Loh says.

And those same menopause books all give identical medical advice — cut out alcohol, sugar, and caffeine; drink plenty of water; do yoga stretches before bed to help fight insomnia. "They're just more tasks for you to do," Loh says, "especially for women in the Sandwich Generation, if you're the multitasking mom." And for Loh, the alcohol, sugar, and caffeine go hand-in-hand with those precious few moments of the day a menopausal woman can get to herself, when she can have a glass of wine or a cup of coffee or a piece of chocolate. Ironically, Loh says, all the menopausal books give basically the same advice to women that pregnancy books give.

Faced with no help from the bookstore aisles, Loh decided it was best to look at menopause from a woman's point of view, women who are afraid to talk about what they're going through and whose doctors only talk with them for five minutes before sending them on their way.

The Menopause Map is a handy tool for women to educate themselves before going to see their endocrinologists and get the most out of those visits, "rather than have their doctor lecture them on the basics of menopause," Loh says. "If you can orient yourself first with the Menopause Map and get a lay of the land, that will save time at the doctor's office so that you can talk more freely about your various symptoms." The Menopause Map takes about five minutes to complete ("It's not like a DMV test," says Loh), and women can go to their doctors armed with the knowledge they gain using this tool.

It's also important for women to know that they're not going through menopause alone, which can be a common, shared feeling, even though menopause is a natural process. Still, menopause can make women feel like they're entering a "creepy club," a "team" they want no part of, because they already have too many other things to do.

But menopausal women are far from alone, and that team is growing. In fact, by 2015, almost half of all U.S. women will be menopausal, while more than half — the majority of women — will be age 45 and older, according to Loh. It makes sense; women are living longer now than ever before.

In the early 1900s, the average life expectancy for a woman was 48. Women now live into their 80s and 90s, "and our oldest citizen is a 116-year-old woman," Loh says. "[Women] are fertility machines and longevity machines. We can make children and outlive [men]. We're evolutionary rock stars."

For Loh, menopause is like a "welcome home party" for women, a return to their hormone levels before they hit puberty and became fertile. "It's reframing the whole discussion," she says. "Instead of menopause being 'the change,' because we live so much longer, we're only fertile that middle third of our lives. So menopause isn't the change. Fertility is the change. Menopause is a return to where you were before the fertility cloud came down."

And although menopause does have its drawbacks and negative connotations, it can ultimately be a "joyous time," Loh says, full of things to look forward to (an empty nest, grandchildren, the next season of *Downton Abbey*), so long as women can laugh about it and keep a positive attitude. "Everyone's going to get through this," she says. "There are many wonderful things about being a woman at this particular time in life. We have almost half our lives ahead of us. It's a wonderful time to be in this day and age, to see what the next decade or two or three will bring." — *Derek Bagkey*

2016 Laureate Awards
Nominate Now!

Beginning October 1 through December 19, 2014, the Laureate Awards Committee is accepting nominations for the Society's distinguished Laureate Awards.

These awards honor the outstanding achievements of endocrinologists, members and non-members alike. Current and past Laureates have left an indelible mark on the advancement of medicine, science, and public health worldwide. Future award recipients will continue to advance the science of endocrinology through new discoveries and the practice of clinical endocrinology.

Over the years, the Laureate Awards Committee has simplified the nomination process and developed useful resources. A fillable nomination form is easy to complete, and you can upload the nomination package with one click. Learn more by visiting ***endocrine.org/awards***.

I hope you will nominate one or more colleagues who have advanced the science or practice of endocrinology through their meritorious scientific research, clinical investigation, leadership, practice, or dedication to underserved populations.

—Nancy L. Weigel, PhD, Laureate Awards Committee Chair

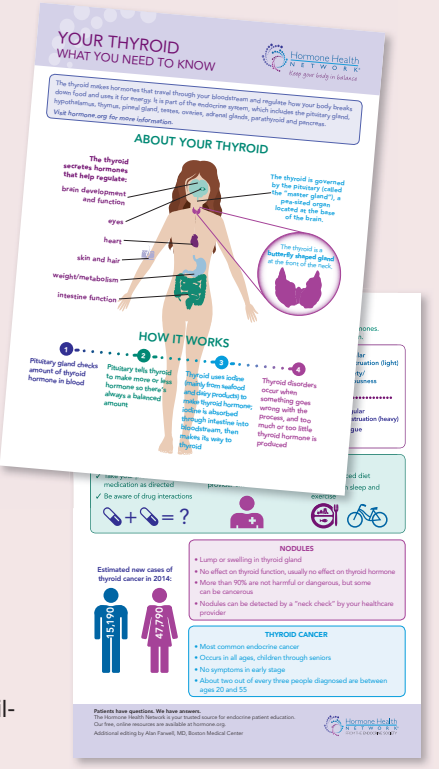
Hormone Health Network
INFOGRAPHIC BREAKS SOCIAL MEDIA RECORD

"Your Thyroid: What You Need to Know" has shattered the Hormone Health Network's social media average reach by more than 3,000% in its first two weeks.

"Chances are rather good that most people know they have a thyroid, but chances are also pretty decent they're not completely up to speed on exactly why they have one or even what it does," explains Cheretta Clerkley, director of the Hormone Health Network. "***On hormone.org***, the thyroid section of the site is the second most popular area, and we recognized that this would be a great infographic topic."

Since its publication on August 7, "Your Thyroid" has received more than 430 "shares," resulting in a total audience reach of over 37,000. "We were completely taken by surprise at how fast it started to grow on social media," Clerkley says. "Generally, our average reach for fact sheets is a little more than 2,500. However, since we released the thyroid infographic, we've had a total reach of over 37,000 and it's still continuing to grow. What the Network has learned from this is that translating complex health information into visuals is extremely powerful with patients and the general public, and we'll keep giving them what they want."

With depictions of the general workings of the thyroid and its effect on the body along with thyroid disorder treatment recommendations, this infographic was released just in time to promote Thyroid Cancer Awareness Month in September. The graphic is available at ***www.hormone.org***.



Explore Your Career Options at ENDO 2015

Sharpen critical skills, get expert advice, and make valuable connections that take your career to the next level in basic or clinical endocrinology. You can do it all at **ENDO 2015**, which offers resources for endocrinologists at every career level — from students and fellows to junior faculty and beyond.

EndoCareers Career Development Workshops: Wisdom for Every Stage

Four days of workshops — led by global experts in basic and clinical endocrinology — examine an array of topics tailored to help you build a long-lasting career. Distinguished speakers will present sessions that include a close look at the multitude of career options available for clinicians and scientists and how to navigate clinical training, board certification, and fellowships.

Learn the best practices for negotiating during the hiring, promotion, and tenure processes; see how successful endocrinologists set up and manage labs and practices; and find the keys to writing research grant and award applications that hit the mark.

EndoCareers Early Career Forum: Get Off to a Strong Start

Join us before **ENDO 2015** officially begins for a day full of Early Career Forum symposia, breakout sessions, and plenaries. Graduate and medical students, postdoctoral fellows, and clinical fellows alike will benefit from practical lessons and sessions.

The Forum starts with a plenary that traces a career of cutting-edge obesity research across a spectrum of scientific settings. Then select symposia and breakout sessions that focus on one of two areas of interest: basic science or clinical research and clinician education.

Breakout sessions — which run concurrently and are repeated — will highlight the transition from PhD to post-doc, teaching and publishing skills, careers in industry, academia, government and in a private practice, and more.

Lunch provides the ideal setting to get to know the faculty and seasoned professionals leading the sessions. The day concludes with a conversation on how to maximize your **ENDO 2015** experience in the days ahead.

Register Now

Secure your place at the earliest and most exciting **ENDO** yet. Just visit ***endo2015.org***.

MALE MENOPAUSE
MYTH VS. FACT

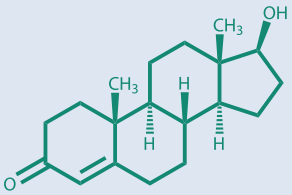
Hormone Health NETWORK®
Keep your body in balance

MYTH: Male menopause is real.

FACT: No, it's not real. The term "menopause" only pertains to the female condition when the ability to reproduce is halted.

Testosterone is the male sex hormone that is needed for growth of body hair, building strong bones and muscles, and producing sperm. As men age, testosterone levels (T-levels) can decline because of medication, illness, injury or lifestyle factors. This drop in testosterone is inaccurately classified as "male menopause," when in fact, should simply be considered a symptom of male aging, more clinically referred to as testosterone deficiency syndrome, androgen deficiency of the aging male, and late-onset hypogonadism.

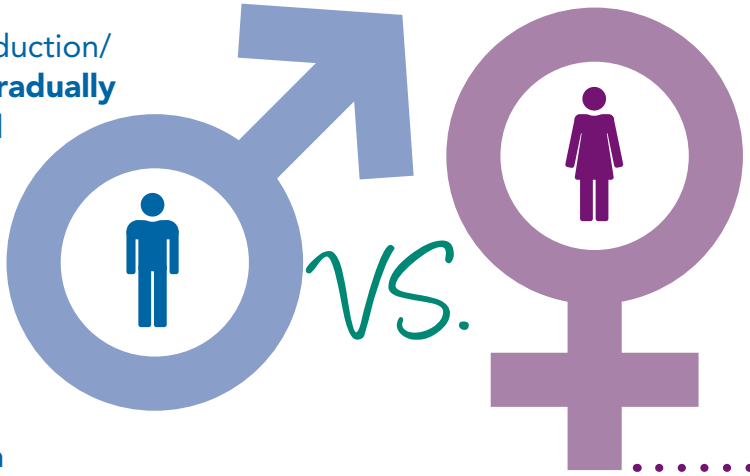
Visit hormone.org for more information.



Testosterone sequence

MALE AGING FACTS

- Testosterone production/ levels decrease **gradually** beginning around age 30
- Sperm production **does not stop**
- **Not all men** experience low testosterone and sperm production



FEMALE MENOPAUSE FACTS

- Estrogen (female sex hormone) production drops **rapidly** beginning around age 40
- Egg production **stops completely**
- **All women** experience low estrogen and egg production

***To learn more about female menopause, visit* menopausemap.org**

CAUSES OF LOW TESTOSTERONE

- Certain medications
- Hormone disorders
- Radiation/chemotherapy treatment
- Testicular injury
- Genetic condition
- Chronic illness (depression, diabetes, liver/ kidney disease, obesity, HIV/AIDS)

HOW IS LOW TESTOSTERONE DIAGNOSED?

- Physical exam by health care provider
- Tests to rule out other health problems
- Blood tests to check T-level. If T-level is low, you may be referred to an endocrinologist.

POSSIBLE SYMPTOMS OF LOW TESTOSTERONE

Not all men experience these symptoms. However, ones who do, encounter them for no apparent reason other than age, usually advanced age.

PRESCRIPTION TREATMENT OPTIONS

Long-term benefits and risks are unknown

- Patches/topical gels
- Shots/injections
- Tablets between cheeks and gums

You've seen the ads for over-the-counter supplements to help men with "low-T" (low testosterone), but do you really need them? **No.** There are ways for aging men to help **naturally maintain** health:

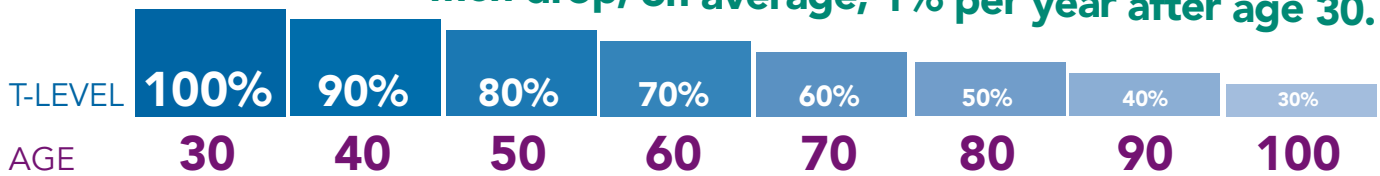
- Eat a healthy diet and maintain a healthy weight
- Get plenty of exercise
- Get enough sleep
- Find healthy ways to cope with stress

These lifestyle factors have not been shown to maintain T-levels.

Long-term use of testosterone treatment can cause:

- high red blood cell count
- acne
- breast enlargement
- sleep apnea (rare)
- fluid buildup in ankles, feet, and legs (rare)

Testosterone levels in men drop, on average, 1% per year after age 30.



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 Matsumoto, MD, University of Washington School of Medicine, and Bradley Anawalt, MD, University of Washington Medical Center

Hormone Health NETWORK® FROM THE ENDOCRINE SOCIETY

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

METABOLISM & ENDOCRINOLOGY PHYSICIANS

The Division of Metabolism and Endocrinology Products in the Office of Drug Evaluation II, Office of New Drugs, located on the FDA White Oak campus in Silver Spring, Maryland, is recruiting **Physicians who have a current state license to practice medicine and are board certified in Endocrinology, Diabetes and Metabolism** to serve in the dynamic, highly challenging and innovative atmosphere of drug development and clinical research. Medical Officers provide scientific and regulatory guidance to stakeholders developing novel therapies to treat endocrine and metabolic conditions. The primary responsibilities of Medical officers are to evaluate and provide written reviews for applications for new drugs and drug-device combinations, and investigational new drug protocols in the field of Endocrinology, Diabetes and Metabolism.

If you are looking for the opportunity to:

- *Advance the public health and contribute to new drug development*
- *Interact with stakeholders to advance clinical research in your field*
- *Experience teaching and training opportunities*
- *Work with a wide range of scientific disciplines in a team oriented atmosphere*

We offer:

- *Flexible work schedules*
- *Opportunities to continue Professional Development*

SALARY & BENEFITS: An excellent benefits package (health insurance, life insurance, thrift savings plan, retirement, etc.) and a civil service base salary at the GS-14 level plus an additional very generous supplemental allowance (determined by relevant experience and medical specialty).

GENERAL INFORMATION: Positions being filled as civil service or U.S. Commissioned Corps require U.S. citizenship. Permanent U.S. residents may apply for Staff Fellowship appointments in physician and scientist positions. Graduates of foreign colleges/universities must provide proof of U.S. education equivalency certification.

PHYSICIANS (Various medical specialties): Basic Requirements: Degree: Doctor of Medicine or Doctor of Osteopathy from a school in the United States or Canada approved by a recognized accrediting body in the year of the applicant's graduation. [A Doctor of Medicine or equivalent degree from a foreign medical school that provided education and medical knowledge substantially equivalent to accredited schools in the United States may be demonstrated by permanent certification by the Educational Commission for Foreign Medical Graduates (ECFMG) (or a fifth pathway certificate for Americans who completed premedical education in the United States and graduate education in a foreign country).]

FOR CONSIDERATION: Submit electronic curriculum vitae with a cover letter to Lena Staunton via e-mail at: Lena.Staunton@fda.hhs.gov no later than **December 31, 2014.**

FDA IS AN EQUAL OPPORTUNITY EMPLOYER AND HAS A SMOKE FREE ENVIRONMENT. MINORITIES, WOMEN, INDIVIDUALS WITH DISABILITIES AND VETERANS ARE ENCOURAGED TO APPLY.

Endocrinologist Opportunities

Geisinger Health System (GHS) is seeking Endocrinologists for three locations:

- **Geisinger Medical Center (GMC), Danville, Pa.**
- **Geisinger Wyoming Valley Medical Center (GWV), Wilkes-Barre, Pa.**
- **Geisinger-Patton Forrest, State College, Pa.**

About the Position at GMC

- Join a team of 4 Endocrinologists, 1 Nurse Practitioners and 2 Certified Diabetes Educators in 100% Subspecialty Endocrinology Clinical Practice.
- Work collaboratively with Geisinger's community practice network to enhance diabetes care, as well as to work with multiple subspecialties to enhance inpatient care.
- Opportunities for clinical practice include serving as investigator on diabetes clinical trials, US-guided Thyroid Fine Needle Aspiration Biopsies and Continuous Glucose Sensors interpretation
- Engage in clinical mentoring and educational programs for medical students on the GMC campus, as well as internal medicine residents on rotation at GMC

About the Position at GWV

- Join a team of 3 Endocrinologists, 2 Nurse Practitioners and 3 Certified Diabetes Educators, and is positioned for additional growth
- Work collaboratively with Geisinger's community practice network to enhance diabetes care, as well as to work with multiple subspecialties to enhance inpatient care
- Opportunities for clinical practice include serving as investigator on diabetes clinical trials, US-guided Thyroid Fine Needle Aspiration Biopsies, Continuous Glucose Sensors and Bone Density interpretation
- Engage in clinical mentoring and educational programs for medical students and family medicine residents on the GWV campus, as well as internal medicine residents on rotation at GWV

About the Position at Geisinger-Patton Forrest

- Join a growing endocrinology department in a thriving, multi-specialty group practice, located in a progressive university town
- Provide 100% endocrinology subspecialty outpatient care and inpatient consultations
- Provide consultative care at Mt. Nittany Medical Center, State College, Pa., and Lewistown Hospital, Lewistown, Pa.

Geisinger Health System serves nearly 3 million people in Northeastern and Central Pennsylvania and has been nationally recognized for innovative practices and quality care. A mature electronic health record connects a comprehensive network of 5 hospitals, 43 community practice sites and more than 1000 Geisinger primary and specialty care physicians.

For more information, please visit Geisinger.org/careers or contact: John W. Kennedy, MD, Endocrinology Department Director c/o Kathy Kardisco, Department of Professional Staffing, at 800.845.7112 or kkardisco@geisinger.edu.

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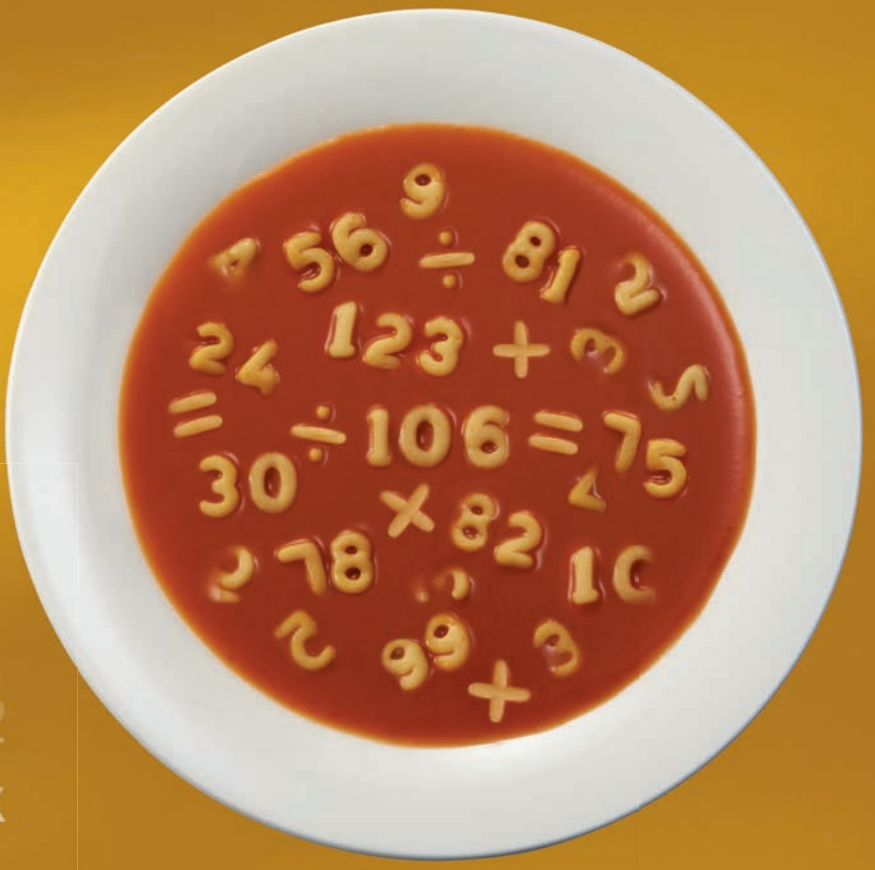

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For program details and registration deadlines, visit endocrine.org/PPTOX.

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