

AUGUST 2013

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

ENDOCRINE news



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COVER Story**20 Diabetes Technology Continues Its Advance***By Eric Seaborg*

Technology surrounding the treatment and monitoring of diabetes has been evolving rapidly over the past several years. However, real progress will only be accomplished once patients and physicians fully embrace these breakthroughs.

24 Career Burnout*By Glenda Fauntleroy*

According to a recent survey, almost 40% of endocrinologists report feeling burned out. Long hours and too much red tape top the list of complaints, but how do you overcome this career ennui?

26 Bridging the Gap*By Melissa Mapes*

As The Endocrine Society's inaugural Ambassador Exchange Program successfully wraps up, endocrinologists are left with a better understanding of international practices as well as cultures.

29 Tri-Point: Calcium-Sensing Receptors: Their Roles in Disease and Their Promise in Future Treatments*By Wenhan Chang, PhD, Dolores Shoback, MD, and Seth M. Arum, MD, FACE*

Calcium-sensing receptors are the gatekeepers for the parathyroid hormone. A basic researcher, a clinical practitioner, and a clinical researcher give their insights on this Class C, G protein-coupled receptor and its roles in disease, mutation, and future uses in treatments.

34 A Meeting of the Minds*By Derek Bagley*

Now that ENDO 2013 is officially in the record books, here are a few highlights of the research presented in San Francisco. From diabetes and obesity to genetics and thyroid cancer, researchers and clinicians from all corners of the endocrinology world presented a wealth of information at this year's annual conference.

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Traumatic Brain Injury: Effects on the Endocrine System

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Setting Goals for the Next Year

As I begin my term as president of The Endocrine Society, I would like to thank my predecessor, Bill Young, for his extraordinary leadership and vision. I would like to share some of the activities that I will be focusing on during my presidential year. First and foremost, I will ensure that some of the initiatives that were launched by now past presidents Jan Hall and Bill Young continue moving forward, such as the focus on health disparities and international outreach, which will no doubt become part of The Endocrine Society's core activities.



Teresa K. Woodruff, PhD

ICE/ENDO 2014

Next year, our annual meeting will be a combination of the 96th meeting of The Endocrine Society and the 16th annual meeting of the International Congress of Endocrinology. This is the first **ICE/ENDO** in the U.S. since 1996, and it promises to be an exceptionally powerful way for endocrinologists from around the world to communicate their latest findings in research and clinical practice in a setting of powerful educational activities. The Annual Meeting Steering Committee co-chairs Derek LeRoith, Kevin Grove, Matthew Ringel, and Carol Wysham will lead the planning committee in developing a top-quality meeting, with outstanding content for each of our constituencies. Stay tuned for more details on the **ICE/ENDO 2014** meeting later this fall.



THE ENDOCRINE SOCIETY'S 96th ANNUAL MEETING & EXPO

Branding Initiative

The Society is in the process of evaluating and refreshing its brand (logo, key messages, tone, style) to ensure that its visual identity, products, services, and messaging relate cohesively to an overall brand.

We have engaged an expert branding consultant, who over the last few months has conducted interviews with a range of Society leaders and facilitated an in-depth discussion with Council and committee chairs to get broad perspective and input into this process. A Branding Task Force with diverse representation from all constituencies was appointed in January by then president Bill Young to work

closely with key staff and the branding consultant on this project. This has been a very thoughtful and inclusive process and we hope to unveil the final product in early 2014.

Awards

The Society has an amazing portfolio of awards ranging from the Laureate Awards to the Trainee and Early Career Professional Awards, totaling over \$700,000. An Awards Task Force was established earlier this year to review the existing portfolio of awards with a more strategic focus, ensuring that they meet the needs of various appropriate constituencies for recognition. The objective of this task force was to evaluate the Society's awards program, reconfiguring some of the awards to better promote the awardees, their science, and the Society, and to explore the feasibility of a new high-profile award.

Some of the initial task force recommendations will be implemented in the next award cycle later this year. However, the Awards Task Force will continue to meet to

"The objective of the new Awards Task Force

is to evaluate the Society's awards program, reconfiguring some of the awards to better promote the awardees, their science, and the Society, and to explore the feasibility of a new high profile award."

consider a new award category that identifies the most important achievements in endocrine research and treatment, and provides incentives to continue groundbreaking research. More details will be provided once the award is fleshed out and a feasible and sustainable financing mechanism is identified.

There are many other areas that will require our attention in the coming year, and I am looking forward to the challenges and opportunities that will make The Endocrine Society more visible, viable, and valuable to our members around the globe.

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

Teresa K. Woodruff, PhD
President, The Endocrine Society

AUGUST 2013

ENDOCRINE NEWS

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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

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

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As you can see, our cover story is on the advances made in technology surrounding the monitoring and treatment of diabetes. Unfortunately, the product we originally had on the cover—a Medtronic Paradigm insulin pump—had an adverse event report from the Food & Drug Administration after the manufacturer issued a safety notification to all users and distributors of the pump. Specifically, the problem lies in the pump's tubing connectors. If insulin or other fluids come in contact with the inside of the tubing connector, it can temporarily block the vents that allow the pump to properly prime. This can result in too much or too little insulin being delivered, resulting in hypoglycemia or hyperglycemia, which can be severe and lead to serious illness, according to the FDA.



Mark A. Newman,
Managing Editor

So far, no deaths have been linked to this malfunction, but there have been a few cases of users being hospitalized. Affected models were manufactured from October 2001 to June 2013 and distributed from December 2001 to June 2013.

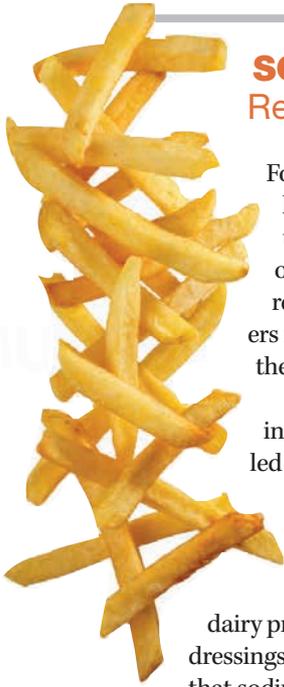
Despite this recall, technology in the world of diabetes monitoring and care will continue to move forward. These items are highlighted in the cover story by Eric Seaborg that discusses breakthroughs in this quickly changing realm (p. 20). However, even though these new developments are changing the way patients are treated (and treating themselves in many cases), the article poses an interesting question: What if physicians and patients opt out?

In a recently published survey by Medscape's *Physician Lifestyle Report*, 40% of endocrinologists suffer from job burnout. Maybe that's not surprising considering the ever-growing number of hoops physicians of all stripes are expected to jump through. And with the implementation of the Affordable Care Act looming, more endocrinologists may succumb to ennui than ever before. What is surprising was that the survey showed that up to 26% of endocrinologists experience this feeling early in their careers, between the ages of 36 and 45. On page 24 Glenda Fauntleroy discusses this phenomenon as well as the reasons and possible solutions to conquer this feeling.

Anyone who made the trip to San Francisco for ENDO 2013 saw firsthand the voluminous amount of research that was presented. Associate editor Derek Bagley gives a brief overview of some of the data presented at the conference on page 34. From studies on diabetes and obesity to new findings on genetics and thyroid cancer, clinicians and researchers from all corners of the field of endocrinology gave some compelling presentations.

If you have any story ideas or topics you'd like to see covered in *Endocrine News*, don't hesitate to drop me a line at mnewman@endocrine.org. I look forward to hearing from you. **EN**

Mark A. Newman
Managing Editor, *Endocrine News*



SODIUM LEVELS in Processed and Restaurant Food Largely Unchanged

Food manufacturers have not lived up to their pledge to voluntarily reduce the amount of sodium in packaged and restaurant foods, say researchers for the Center for Science in the Public Interest.

In a study published online in *JAMA* on May 13, the team, led by Robert McCarter, ScD, assessed sodium levels in 402 packaged foods in 2005, 2008, and 2011. These foods included baked goods,

dairy products, meats, sauces and dressings, and soups. The team found that sodium decreased in 41.8%, increased in 29.6%, and did not change in 28.6% of the products, leading to an average

decrease of just 3.5% between 2005 and 2011.

The researchers also obtained sodium values for 78 items offered by fast-food and large chain restaurants, including burgers, chicken, fries, and pizza. Sodium levels decreased in 42.3%, increased in 55.1%, and did not change in 2.6% of the products, leading to an average increase of 2.3%.

In their conclusion, the researchers note that physicians often tell patients to reduce salt intake as a way of treating and preventing high blood pressure, but that such counseling “places unrealistic demands on both patients and physicians given the high sodium levels currently present in processed and restaurant foods.” They call for regulatory action and recommend that sodium in these foods be gradually lowered 50% over the next 10 years.

—Terri D’Arrigo

LIVER HORMONE Shows Promise for Diabetes Treatment

Researchers at the Harvard Stem Cell Institute have identified a hormone in mice that promotes the growth and expansion of insulin-producing beta cells in pancreatic islets, a finding that opens up the possibility of new treatments for diabetes should the hormone, dubbed betatrophin, work the same way in humans. The team, led by Douglas A. Melton, PhD, made the discovery while conducting experiments to better understand how the pancreas increases beta-cell production in response to the greater demands for insulin caused by pregnancy or peripheral insulin resistance.

In their research, published online in *Cell* on May 9, the team injected mice with a peptide that blocks insulin receptors. This made the mice insulin-resistant and prompted their pancreases to ramp up beta-cell production. When seeking to understand the genes involved in this process, the team found one activated in the liver and fat that encodes for a protein that prompts beta cells to proliferate. **In a separate experiment, the team injected normal mice with the betatrophin gene and saw that beta-cell proliferation increased 17- to 33-fold compared to that of mice that had not been injected with betatrophin. The betatrophin-injected mice also performed better on glucose tolerance tests compared to the control mice.**

—Terri D’Arrigo

LOW VITAMIN D LEVELS Associated with Physical Limitations and Functional Decline in Older Individuals

Beginning a vitamin D regimen may be the key in maintaining mobility later in life, according to a recent study published in the *Journal of Clinical Endocrinology and Metabolism*.

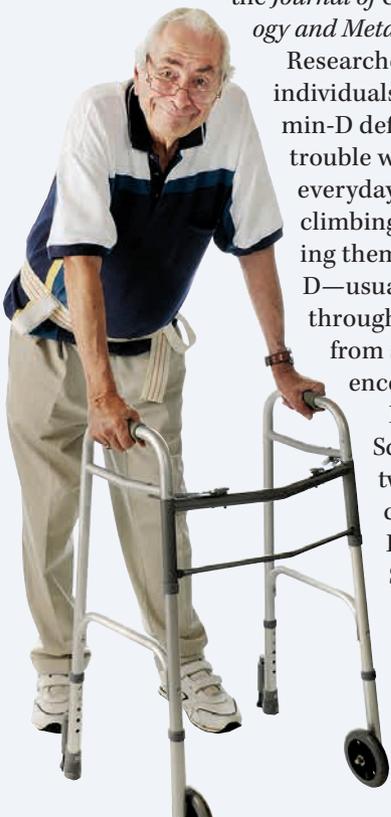
Researchers showed that individuals who are vitamin-D deficient had more trouble with performing everyday tasks, such as climbing stairs and dressing themselves. Vitamin D—usually ingested through diet or absorbed from sunlight—influences muscle health.

For six years, Scientists followed two independent cohorts from the Longitudinal Aging Study Amsterdam. The first group comprised people aged 65 – 88, while the second

group was made up of people aged 55 – 65. The subjects had their vitamin D levels measured and were split into three groups: highest vitamin D levels, moderate, and lowest. The subjects were then asked a series of questions to gauge their ability performing six daily tasks.

Subjects in both groups with the lowest levels of vitamin D were about twice as likely to have at least one limitation when compared to the subjects with the highest levels of vitamin D. Subjects with low vitamin D levels were also shown to regress even further over time. In the older cohort, low vitamin D was associated with developing additional physical limitations after only three years, while in the younger cohort, more limitations manifested after six years. **The authors concluded that vitamin D status is indeed associated with physical and functional limitations in the older population, individuals aged 55 – 88 years, and there could be some benefit in taking vitamin D supplements. However, this idea should be tested in additional studies.**

—Derek Bagley



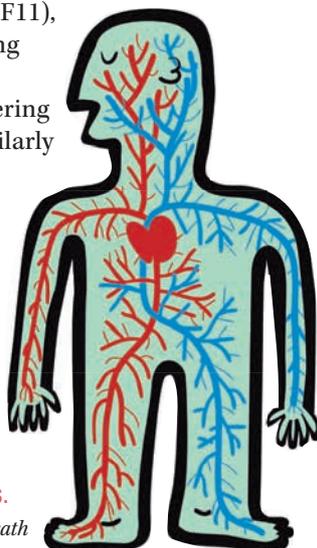
Circulatory FOUNTAIN OF YOUTH

Heterochronic parabiosis is a 19th-century surgery joining two living animals together to merge their circulatory systems into a single shared circulation. In a new study, scientists used this technique in mice to elucidate whether cardiac hypertrophy, which accompanies the most common form of heart failure in older adults, is caused by circulating factors.

Drs. Amy J. Wagers, PhD, and Richard T. Lee, MD, both of the Harvard Stem Cell Institute and Brigham and Women's Hospital, Boston, and their team of researchers paired up five very old mice (age two years) with two-month-old counterparts. In their paper, published in *Cell*, the researchers report that after four weeks, the cardiac tissue in the old mice had dramatically thinned and softened as expected, and the young mice hearts were also still strong. Long suspecting a bloodborne cause for age-related hypertrophy, they used aptamer-based proteomics to find that circulating growth differentiation factor 11 (GDF11), a member of the transforming growth factor β superfamily, declines with age. Administering GDF11 to the aged mice similarly reversed hypertrophy.

The researchers next want to find whether these effects can be replicated in humans, whether GDF11 can remodel cardiac tissue damaged via means other than aging (e.g., myocardial infarction), and also whether GDF11 can restore other tissues affected by aging back to youthful states.

—Kelly Horvath



PFCS and THYROID FUNCTION



Women who are exposed to perfluorinated chemicals (PFCs) have a higher risk of developing mild hypothyroidism, according to findings recently published in the *Journal of Clinical Endocrinology and Metabolism*.

PFCs have been linked to changes in thyroid function, and are found in myriad common products, from carpets to cosmetics. Hypothyroidism can cause fatigue, depression, weight gain, constipation, and menstrual irregularities, as well as feeling cold and dry skin and hair.

Researchers analyzed 1,181 subjects, women aged 20 and over, who participated in a National

Health and Nutrition Examination Survey (NHANES), 2007–2008 and 2009–2010, in order to determine whether there was a correlation between PFCs and thyroid function.

Women with higher levels of the PFC perfluorooctanoate (PFOA) showed an increase in the concentration of the thyroid hormone total triiodothyronine (T3), while levels of the thyroid hormone total thyroxine (T4) were elevated by an increase in concentrations of the PFC perfluorohexane sulfonate (PFHxS). However, men exposed to PFHxS showed a decrease in free T4. The authors concluded that while further research needs to be done to determine whether this correlation is in fact causation, higher concentrations of PFOA and PFHxS are associated with total T3, total T4, and free T4 in the U.S. general population, as well as mild hypothyroidism in women.

—Derek Bagley

VITAMIN D and Infants

Breast-feeding confers many benefits on infants, but it can come up short in providing them with the vitamin D they need for healthy bones. To compensate, the American Academy of Pediatrics recommends supplementation with 400 IU of vitamin D daily. New research published by a team at McGill University in Montreal in the May 1 issue of *JAMA* has found that this dose is sufficient and that higher doses do not provide greater benefit.

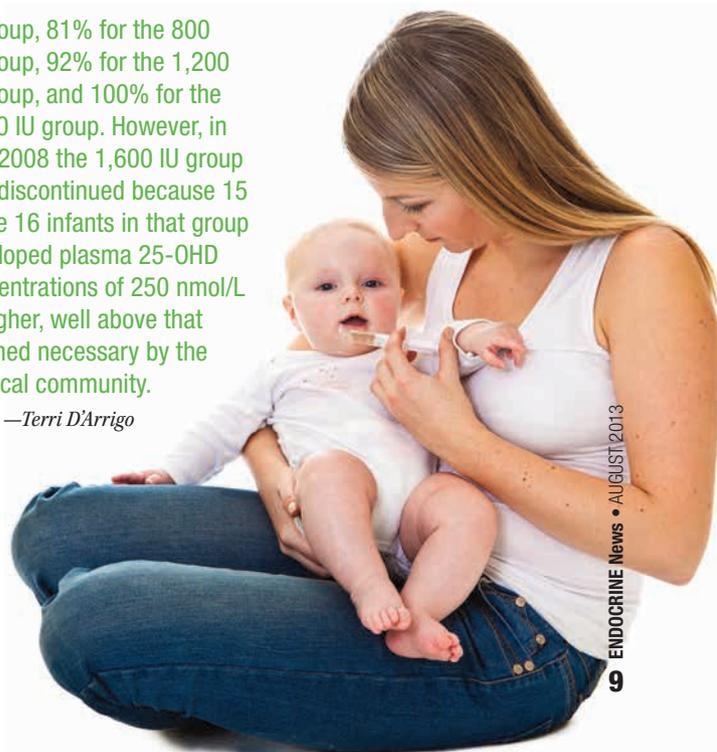
Between March 2007 and

August 2011, the team, led by Hope Weiler, RD, PhD, randomly assigned 132 infants to 400, 800, 1,200, or 1,600 IU of vitamin D daily. They sought to discover which doses would best help the infants attain plasma concentrations of the vitamin D metabolite 25-OHD of 75 nmol/L by three months of age. (This concentration represents a middle ground in the medical community, as some groups recommend a range of 40–50 nmol/L and others recommend a range of 75–150 nmol/L.)

The percentages of infants achieving the 75 nmol/L goal were 55% for the 400

IU group, 81% for the 800 IU group, 92% for the 1,200 IU group, and 100% for the 1,600 IU group. However, in July 2008 the 1,600 IU group was discontinued because 15 of the 16 infants in that group developed plasma 25-OHD concentrations of 250 nmol/L or higher, well above that deemed necessary by the medical community.

—Terri D'Arrigo



Glucocorticoids Increase VENOUS THROMBOEMBOLISM RISK

Because high levels of cortisol have been implicated in venous thromboembolism (VTE) risk, a new study investigated whether the association holds up with exogenous glucocorticoids, which are prescribed for many conditions.

Dr. Sigrun A. Johannesdottir, BSc, at Aarhus Universitets-hospital, Denmark, and her team of researchers undertook a Danish population-based study of 38,765 VTE cases diagnosed between January 1, 2005 and December 31, 2011, dividing them into three cohorts of glucocorticoid users: former, those who had discontinued use for at least one year; recent, those who had discontinued use for between three months and one year; and present (subdivided into new and continuing groups), those who had

filled a prescription within the prior three months and performing regression analysis. In their paper, published in *JAMA Internal Medicine*, the researchers report that VTE incidence was triple for new and double for continuing users, and 1.2 times higher for recent users. Risk also doubled with doses of 1,000–2,000 mg, whereas risk was no higher at doses of 10 mg.

The researchers conclude that carefully weighing risks against benefits is crucial when prescribing glucocorticoids because even after adjusting for confounders such as preexisting VTE risk factors, new glucocorticoid users and those taking high doses showed significantly higher risk of developing VTEs. Hunting down the causative biological mechanism is a potential research avenue, they add.

—Kelly Horvath



BEHAVIORAL WEIGHT LOSS Better for Mentally Ill

Among sufferers of serious mental illness, obesity is epidemic according to research recently published in the *New England Journal of Medicine*. Traditional lifestyle interventions exclude the needs of the seriously mentally ill as cognitive impairment causes difficulty in holding to weight loss regimens. In the published study, led by Gail L. Daumit, MD of Johns Hopkins Medical Institute, participants significantly increased their weight loss with interventions tailored to their behaviors.

Nearly 60% of the 291 participants were either schizophrenic or had a schizoaffective disorder, the remainder diagnosed with bipolar disorder or major depression. All were recruited from psychiatric outpatient programs local to the community and randomized between an intervention group and a control.

Average weight among all participants was 226 lbs. with a mean body mass index of 36. Provided with behavioral weight management and group exercise sessions, 38% of the intervention group lost at least 5% of their starting weight at the end of 18 months. Only 22% of the control had similar weight loss.

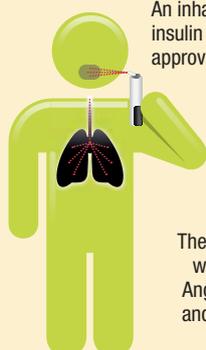
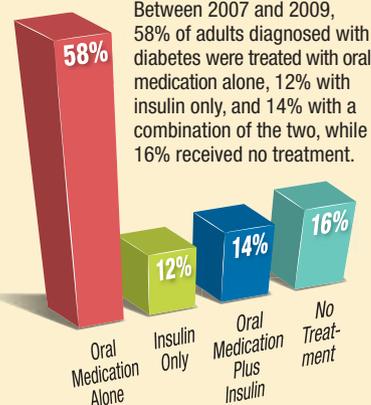
The progressive weight loss shown in this study, the authors hope, supports interventions targeting behaviors of a population at high-risk of obesity and weight-related disease.

—Dan Kelly

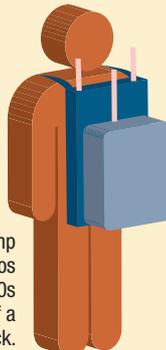
Fast FACTS About Diabetes Technology



Comprehensive foot care programs can reduce amputations by as much as 85%.

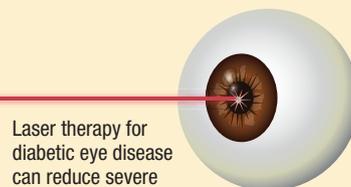


An inhaled form of insulin was first approved in 2006.



The first insulin pump was invented in Los Angeles in the 1960s and was the size of a large backpack.

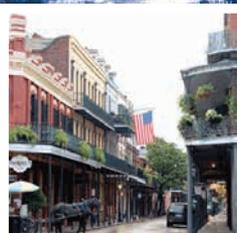
Ancient physicians treated diabetes with things like rose oil, sweet almonds, and even viper's flesh.



Laser therapy for diabetic eye disease can reduce severe vision loss by up to 60%.

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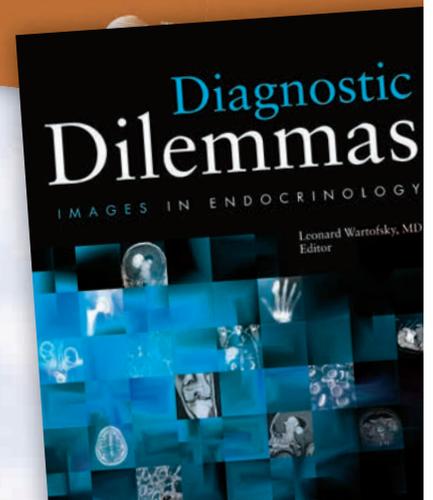
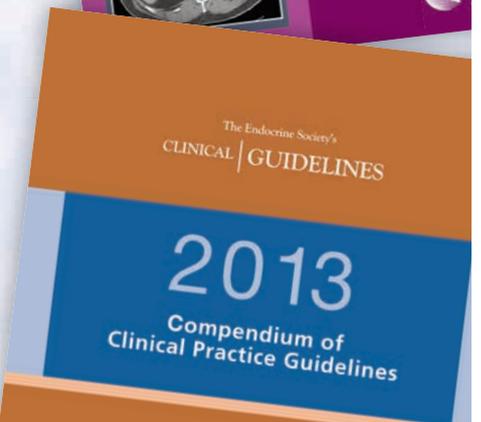
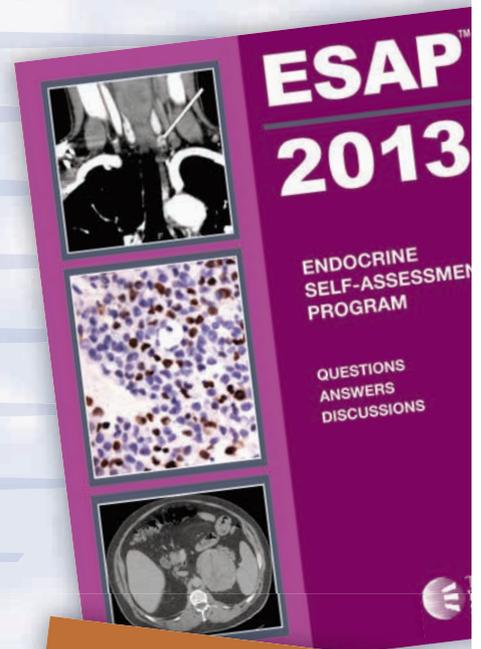
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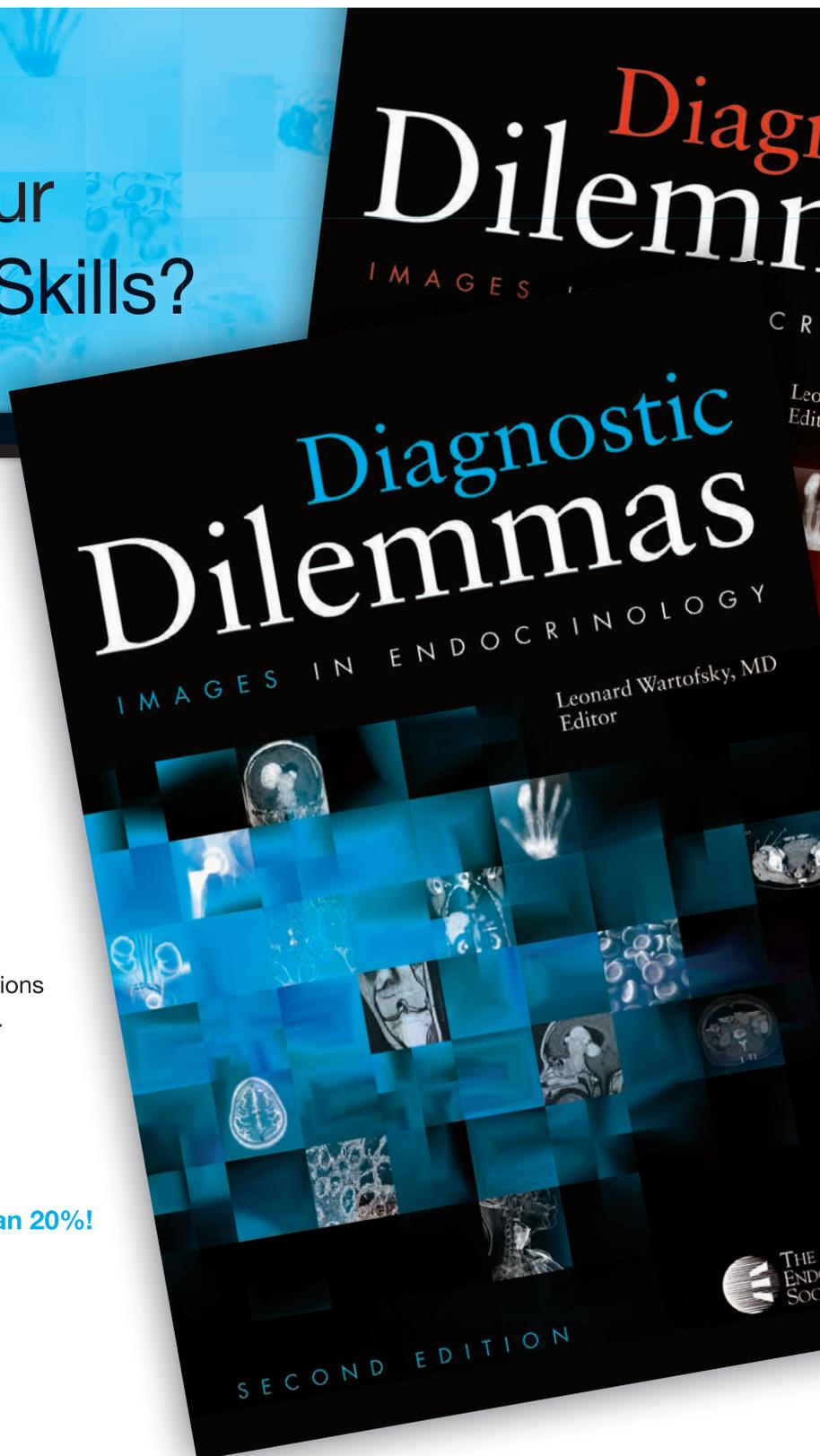
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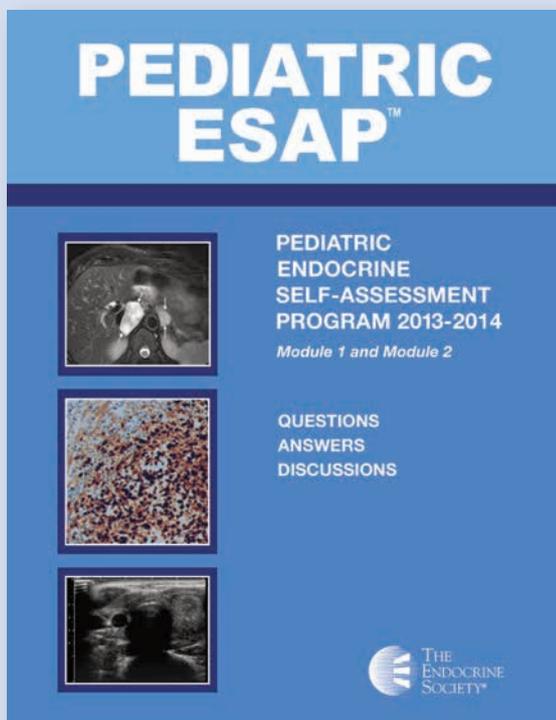


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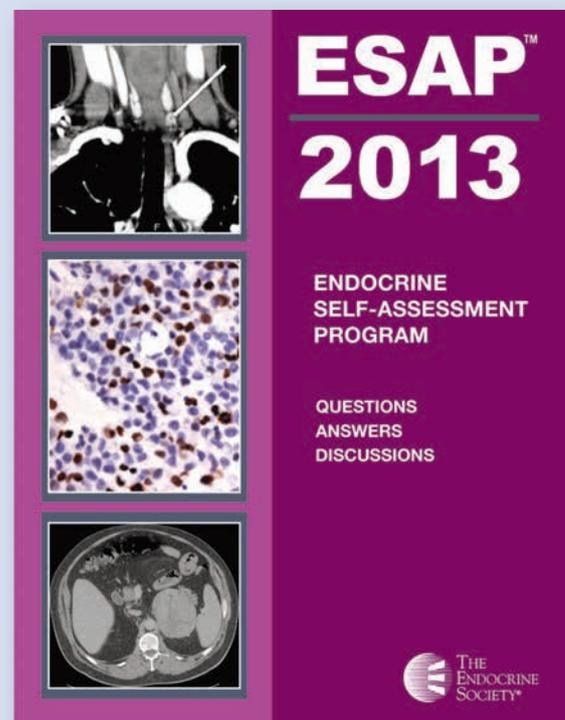


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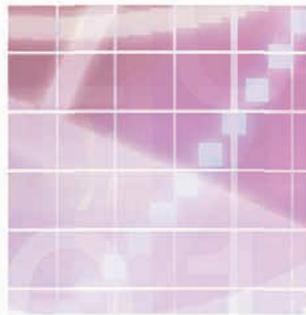


DIABETES Technology CONTINUES ITS ADVANCE



But will patients and physicians take advantage of its promise?

By Eric Seaborg



The Difficult Learning Curve for PROPER CGM USAGE



Irl Hirsch, MD, professor of medicine at the University of Washington Medical Center, Seattle



Stephen Ponder, MD, pediatric endocrinologist at Texas A&M University, College Station

Ponder and Hirsch both said they see patients who have a bad experience or do not improve quickly and give up on the sensors, often because there is no one in their physicians' offices who can give them adequate guidance. Compounding that problem is that under current reimbursement models, practices are not paid to provide the education and training needed for diabetic patients to take advantage of the technology that offers better control of their conditions.

AT-A-GLANCE:

- **Continuous glucose monitors have proven their clinical utility and merit wider use.**
- **A wealth of computer, online, and smartphone applications can address myriad situations.**
- **Patient education in the use of new devices is critical to achieving better care.**

Technological advances have changed the face of diabetes treatment in recent years, with the advent of continuous glucose monitors and new insulin types to complement improvements in insulin pumps and delivery systems.

The new techniques have demonstrated the ability to improve care, but require an investment in education from both practitioners and patients. Innovations can make diabetes management simpler and more effective over time, but a patient's commitment and understanding are keys to making them work.

Monitors Improve Care

Experts singled out continuous glucose monitors (CGMs) as being on the cutting edge for improving care because as the monitors shrink and become easier to use, studies back their effectiveness.

Their evolution has been similar to that of insulin pumps, which were, at first, too big and uncomfortable, said Stephen Ponder, MD, a pediatric endocrinologist at Texas A&M University. The first pumps were challenging to wear and use. Some patients compared the first CGM sensors to harpoons, but the sensors have become small wires with shallower penetration that no longer cause bruising. CGMs offer long-lived sensors and batteries, safety alarms, and sophisticated software.

A recent literature review by an Endocrine Society expert panel confirmed that the monitors improve control of glycosylated hemoglobin levels while limiting the risk of hypoglycemia. The panel's clinical practice guideline calls for more widespread use of CGMs by children, adolescent, and adult outpatients.

The monitors measure glucose levels in the interstitial fluid and require regular calibration based on blood-prick measurements by a glucose meter. CGMs are still not FDA-approved for use in treatment decisions, but patients regularly use them successfully in off-label fashion for determining their insulin doses, said Irl Hirsch, MD, professor of medicine at the University of Washington Medical Center in Seattle. The additional data they provide can be extremely helpful by enabling the user to quickly spot and respond to upward and downward trends.

Although the monitors bring to mind children as the target population, adults stand to benefit a great deal. Long-term patients striving to maintain tight blood-sugar control risk episodes of severe hypoglycemia.



Insulin was first administered in 1922, and it was hailed worldwide as a miracle extract.

— Diabetes Health



OneTouch® Ping®

Meter-Remote and Insulin Pump Johnson & Johnson, Animas® Corporation



MyGlucoHealth Wireless

transmits glucose readings via mobile phone Entra Health Systems

Hirsch said that in people who have had diabetes for more than 40 years, the frequency of hypoglycemic seizures or comas is 12% per year. He described a 63-year-old patient who was having monthly hypoglycemic events requiring intervention by paramedics, but hasn't had a single incident since he began wearing a CGM two years ago.

There are only a few CGMs currently on the U.S. market. The Dexcom G4 Platinum (for adult use) and the Medtronic Guardian Real-Time (for pediatric and adult use) are both standalone CGMs. The Medtronic MiniMed Paradigm Real-time Revel (for pediatric and adult use) is a combination CGM and insulin pump [Editor's Note: See page 7 for information on a recent safety alert regarding the Medtronic Paradigm insulin pump.] The Abbott Navigator CGM was withdrawn from the U.S. market but is still available in Europe and some other countries.

The biggest drawback is, of course, the cost, some \$1,000 or more for the meter itself, along with continued cost of consumables. Some insurance plans now cover them, but Medicare does not.

“Our insulins are not fast enough, our sensors are not accurate enough, and the algorithms are not quite there yet to make it so that we can do a better job than a very adherent and knowledgeable patient can do on their own. Still, these first steps are exciting.”

— Irl Hirsch, MD, Washington Medical Center, Seattle

The other difficulty is the learning curve for using them properly. Ponder and Hirsch both said they often see patients who have a bad experience or do not improve quickly and give up on the sensors, often because there is no one in their physicians’ offices who can give them adequate guidance. Compounding that problem is that under current reimbursement models, practices are not paid to provide the education and training needed for diabetic patients to take advantage of the technology that offers better control of their conditions.

Computer and Phone Tracking

Online data tracking and phone apps sound great, but can they improve outcomes?

Studies say yes.

Ponder’s team developed a program designed to generate easy-to-understand graphs and feedback. They reported last year in *Diabetes Care* on a randomized, year-long clinical trial among 48 children under 12 years old who used standard blood glucose meters and test strips. The experimental group received a system that automatically collected their blood glucose values and sent an email with a 21-day blood glucose trending report each night. The children in the experimental group had significantly lower glycosylated hemoglobin levels. They also became

more meticulous in their diabetes self-care.

There are so many online and phone apps to choose from that narrowing down which to use can be a daunting task. The American Diabetes Association (ADA) offers an online tool called Diabetes 24/7 that is tied in to Microsoft’s HealthVault data storage center. The user can import and track factors such as blood glucose, A1C, blood pressure, cholesterol, physical activity, weight, and medications, and share the information with physicians and others, according to Matt Petersen, the ADA’s managing director of medical information and professional engagement.

The program Hirsch considers the “gold standard as far as insulin management” is Carelink, a Medtronic product. It works with a Medtronic insulin pump, but can download data from most glucose meters.

Phone Apps

In terms of phone apps, the user may need to concentrate on particular needs they want to address. Hirsch’s patients have had success with RapidCalc by Gilport Enterprises, an Australian company: “It is a bolus calculator that can work on your iPhone or your iPad, for people who are not on pumps.”

Petersen said that the company WellDoc has published clinical trial data to back up the effectiveness of its DiabetesManager System app, which integrates mobile phones and the Internet, but is available only through disease management organizations such as Alere or through some employers. Later this year, the company expects to release a version available by prescription that will feature automated clinical coaching, a medication adherence program, and capture and transmission of blood glucose data for type 2 diabetes patients.

The MyGlucoHealth (Entra Health Systems) glucose monitor has offered wireless Bluetooth technology to talk with a variety of smartphones for several years, and LifeScan gained FDA approval for the first monitor with Bluetooth capability for iPhone and other Apple products earlier this year.

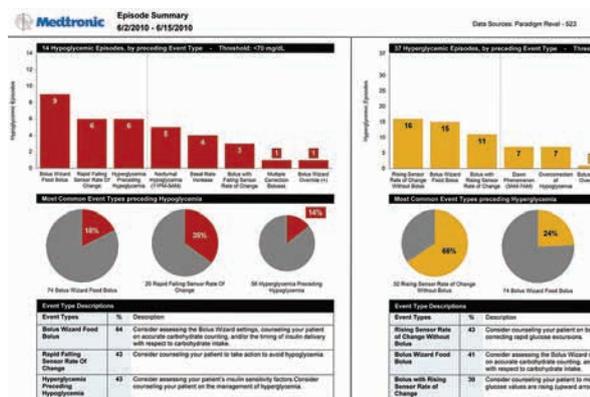
Today’s glucose meters are all built with capabilities that make it easy to download a wealth of potentially helpful information, but there is a limiting factor: physicians themselves. “Most physicians don’t download glucose meters,” Hirsch said, which is a shame because the data is easy to see and figure out and “has opened up our eyes as a tremendous tool for both patients to help themselves and for doctors and other educators to help patients.”

Insulin Delivery: Pens vs. Syringes

No one claims to have a certain answer: Why are syringes more popular than pens for insulin delivery in the U.S., when pens are the standard in Europe? One factor may be that insulin from pens is more expensive. Another is



Dexcom G4 PLATINUM Receiver with Transmitter Courtesy DexCom, Inc.



CareLink Pro 3.0 Episode Summary Courtesy Medtronic, Inc.

that European insurance coverage was faster and more certain to include pens. U.S. insurance coverage has at least been perceived to be spotty, although a study in the *Journal of Medical Economics* found that 90% of U.S. private plans cover pens (although sometimes with higher co-pays). And another factor could simply be a resistance by U.S. caregivers to change.

But pens have been growing in popularity among U.S. patients. “I’ve seen pens catch on in the past four or five years,” Ponder said. Perhaps as basal-bolus therapy became standard, the convenience of the pens became more compelling.

About 20% of Americans with type 1 diabetes use the most expensive option—insulin pumps. The pumps continue to shrink in size and grow in convenience and, of course, offer the advantage of data downloads for tracking insulin use and patient behavior.

Artificial Pancreas on the Horizon?

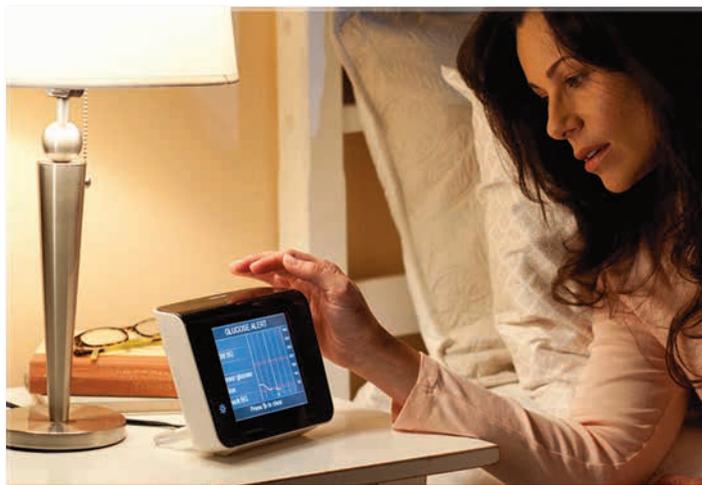
An artificial pancreas has been called the holy grail of diabetes technology, and it appears to be getting closer. Patients already use insulin pumps and continuous glucose monitors, so couldn’t forming a feedback loop mimic the job of the pancreas to pump out insulin when it senses the hormone level is low?

Medtronic, the leader in insulin pump and CGM sales, submitted for FDA review in June 2012 a device that if approved would be the only integrated insulin pump and continuous glucose monitor in the U.S. to feature “low glucose suspend.” It automatically suspends insulin delivery if the sensor glucose value drops below a threshold level. A pump with that feature has been in use in Europe since 2009.

Johnson & Johnson’s Animas division has a similar system in trials consisting of a subcutaneous insulin pump, CGM, and software in what it calls the hypoglycemia-hyperglycemia minimizer system designed to automatically predict rises and falls in glucose and respond with anticipatory insulin delivery.

And there are other researchers attacking the problem. For example, a group at the University of Virginia is adapting a CGM and insulin pump loop controlled by a smartphone.

Researchers report progress, but Hirsch says: “The problem is, our insulins are not fast enough, our sensors are not accurate enough, and the algorithms are not quite there yet to make it so that we can do a better job than a very adherent and knowledgeable patient can do on their own. Still, these first steps are exciting.” Of course, the many less-than-adherent patients having a hard time controlling their glucose levels may benefit the most.



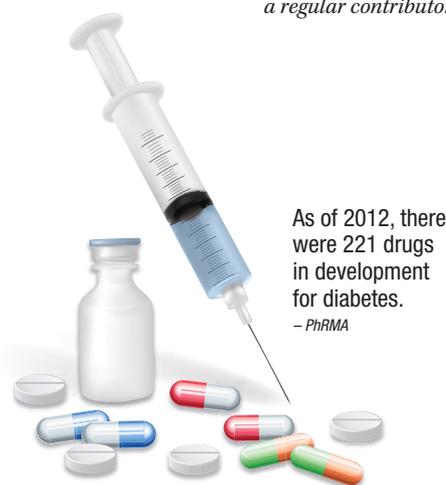
mySentry™ Remote Glucose Monitor Courtesy Medtronic, Inc.

The Promise and the Problem

With the promise of innovations like the artificial pancreas, recent advances may be only the beginning. “I think we are going to see tremendous gains in technology in the next five years,” Hirsch said. But, he is frustrated that too few physicians are enthusiastic about introducing their patients to the benefits of new technology, in large part because of reimbursement policies that will not pay for the investment of practice time required to educate patients about the proper use of gadgets like CGMs.

Ponder said the advances in technology offer great opportunities, but successful diabetes management continues to be driven by the motivation of patients to devote their time and energy to keeping their blood sugar levels in line, and their physicians can play a key role in leading the way. **EN**

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



As of 2012, there were 221 drugs in development for diabetes.

—PhRMA

OnPOINT from The Endocrine Society

The Endocrine Society has issued a Clinical Practice Guideline that outlines best practice guidelines for determining settings where patients are most likely to benefit from the use of continuous glucose monitoring (CGM). The Guideline contains evidence-

based recommendations about where CGM can be beneficial in maintaining target levels of glycemia and limiting the risk of hypoglycemia. Both strength of recommendations and quality of evidence were accounted for. See: www.endocrine.org/cgm.

Career **BURNOUT**

New survey finds stress is high for endocrinologists

By Glenda Fauntleroy

While patient health and insurance coverage have garnered recent headlines, the physicians who provide their care are experiencing high levels of stress in dealing with changes happening in the industry.

In a new *Physician Lifestyle Report* published by Medscape, nearly 40% of endocrinologists reported being burned out—defined as a loss of enthusiasm for work, feelings of cynicism, and a low sense of personal accomplishment. More than 24,000 physicians participated in the survey, and endocrinologists ranked 14th among the list of 24 specialties. Physicians in emergency medicine and critical care topped the list with the highest levels of burnout.

Burnout in endocrinology varies by gender and age, according to the survey. Many more female endocrinologists reported burnout than men (54% vs. 33%). And the symptoms peak fairly early in the career, with 28% of endocrinologists aged 36–45 years reporting burnout compared with 23% between 46 and 65 years of age.

Finding the Cause

When asked what factors contribute to their feelings of burnout, leading the list of endocrinologists' complaints were: too many bureaucratic tasks, long work hours, insufficient income, and the impact of the Affordable Care Act.

For Todd Brown, MD, PhD, associate professor of medicine in John Hopkins University's Division of Endocrinology and Metabolism, although hearing the number of endocrinologists reporting burnout was surprising, he understands the reasons.

"It has been more difficult to practice medicine lately," he says. "There are more administrative duties than previous and it's only getting worse, in terms of insurance approvals, documentation, and all things that people didn't use to have to deal with in practicing medicine when they could just focus on forming relationships with their patients and treating them the best way they can."

"It doesn't bode too well for the medical profession," Brown adds. "I think people are still interested in the field, but I think there's some idealism that quickly goes away."

A 2012 article in the *Archives of Internal Medicine* also showed similar results of physician burnout. Physicians suffered more than any other U.S. worker surveyed with almost 46% reporting at least one burnout symptom.

So what explains the divide between professions?

"The biggest problem is that as a society, the professional class has clearly bought into the notion that more work to create more wealth is the only thing that can insulate us from all this bad news," suggests John Buse, MD, division chief of the Diabetes Center at the University of North Carolina at Chapel Hill.

"People work too hard to make too much money to buy too many things



AT-A-GLANCE:

- Close to 40% of endocrinologists suffer from burnout, according to a new Medscape survey
- Too many bureaucratic tasks and long work hours top the list of complaints
- Caregiver Resiliency course at Duke University promises solutions

that they do not need based on marketing messages that bombard us with the news instead of doing what they love," he adds.

Finding Solutions

"Burnout is not an individual problem, it's an environmental problem," explains J. Bryan Sexton, PhD, psychologist and associate professor and director of The Patient Safety Center for the Duke University Health System.

"If you work at a hospital or clinic, you are highly susceptible to burnout," he continues. "And if a doctor is burned out, then the secretaries, nurses, and IT people are most likely miserable as well."

Sexton is an expert in patient safety and a few years ago realized his quality improvement projects were not achieving the desired results. He traced the cause to the stress and burnout symptoms of the hospital staff.

"Our work-life balance was awful," Sexton recalls. "Our staff wasn't taking care of themselves, they weren't eating well, not sleeping, and not seeing their families for days on end."

"The burnout level in a clinical area predicts everything, including clinical outcomes, mortality rates, patient satisfaction, staff turnover, and disruptive behavior rates," he adds. "We found that clinical outcomes improved when burnout was low."

It was then that Sexton shifted his focus to helping healthcare workers better cope.

He developed the "Enhancing Caregiver Resiliency: Burnout & Quality Improvement Full Course"—a three-day course with CME credits offered at Duke twice a year in May and November and attended by more than 3,500 healthcare workers annually. It's also available as a webinar series www.dukepatientsafetycenter.com.

The resiliency course teaches participants 17 different tools, all based on social science, to cope with burnout. The first step is explaining the prevalence and severity of the condition and also includes coaching on fatigue management and self-reflection.

No matter what, experts agree that taking time for leisure activities is critical to staving off burnout. Some good news from the Medscape survey: 60% of endocrinologists exercise at least twice a week, and 65% take more than two weeks of vacation leave each year.

"I think the path to happiness is to recognize that money is not adequate compensation for our time if we do not enjoy doing what we do," Buse says. "You should be resting or being with those who you love." **EN**

—Glenda Fauntleroy is a freelance writer based in Carmel, Ind.

Making Time for LEISURE

When asked how they enjoy spending time away from the office, here's how endocrinologists ranked their top 10 favorite pastimes:

1. Spending time with family (87%)
2. Exercise (68%)
3. Travel (65%)
4. Reading (62%)
5. Attending cultural events (48%)
6. Enjoying good food and wine (39%)
7. Surfing the Web (20%)
8. Gardening (15%)
9. Musical activities (15%)
10. Visual arts (e.g., photography, painting, sculpture) (12%)

Source: Medscape's 2013 Physician Lifestyle Report

BRIDGING THE GAP

Inaugural Ambassador Exchange Program successfully wraps up with a better understanding of international practices and culture



By Melissa Mapes

In 1977, Dr. Susan Mandel, MD, MPH, of the University of Pennsylvania, lived in South Africa for several months through a high school exchange program. She could have never guessed that she would be returning to Johannesburg three and a half decades later to share her skills as one of the world's premier thyroid experts.



From left to right: Ilona Lorincz, MD, endocrinology trainee from the Hospital of the University of Pennsylvania (HUP); Susan Mandel, MD, MPH, professor of medicine and radiology at HUP; Roy Shires, MBBCh, PhD, FRCP, professor at the Chris Hani Baragwanath Hospital, and Kershlin Naidu, B.Med.Sci, MBBCh, FCP, MMed, endocrinology trainee at Baragwanath.

Much had changed since her first trip, thanks to the end of apartheid. But despite promising social progress in South Africa, the Chris Hani Baragwanath Hospital in the Soweto area of Johannesburg still serves an enormous underprivileged population, including many advanced cases of endocrine diseases. Mandel and her trainee, Ilona Lorincz, MD, found themselves immersed in this vibrant and welcoming community of physicians and patients last April, allowing them to gain hands-on experience in an entirely different context. She described her return to Africa as “a really powerful and rewarding experience, both academically and personally.”

Crossing Borders

Mandel and Lorincz spent two weeks working and traveling in South Africa as part of The Endocrine Society's inaugural Ambassador Exchange Program, which sends two American endocrinologists to an international hospital in a developing area. In January 2013, Gary Hammer, MD, PhD, and his trainee Tobias Else, MD, of the University of Michigan, went to the King Edward Memorial Hospital in Mumbai as the first ambassadors, where Nalini Shah, DM, and Shruti Khare, MBBS, MD, hosted them. Similarly, Roy Shires, MBBCh, PhD, FRCP, of Baragwanath and his trainee Kershlin Naidu, BMedSci, MBBCh, FCP, MMed, acted as guides to the endo-

crine community and culture of South Africa during Mandel's April trip. She returned the favor by receiving Shires and Naidu at the University of Pennsylvania in June.

At Baragwanath Hospital, Mandel conducted special seminars with the radiology and surgery groups. Her surgery seminar was attended by almost 100 practitioners, and the hospital organized a three-hour session for radiologists where she gave an introductory lecture on thyroid ultrasound and then demonstrated on 15 patient volunteers with different thyroid or parathyroid issues. “Everybody was so open to our visit and so engaged with us,” she said. “We never felt like we were observers.” Mandel's visit also included participation in the annual Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMSDA) meeting where she presented a plenary lecture and a “meet the professor” session.

The experience extended beyond the endocrinology ward as well. The doctors met practitioners from the entire department of medicine, including the chief of medicine, and visited a rural diabetes clinic. Mandel was struck by the scale of physical exams performed by the South African physicians they encountered during the trip. “What's happened in the U.S. is that we rely more and more on technology for diagnosis and less on our physical examination skills,” she explained. Although technological resources are invaluable, so is a physician's ability to diagnose and treat by listening to and examining a patient. This is an integral part of medical training in South Africa and other parts of the world, and Mandel believes it would be a worthwhile effort to incorporate more of such education into American programs.

She went on to describe the extraordinary quality and compassion of the physicians she met, but lamented the difference in resources. Due to the poverty in the areas surrounding Baragwanath, many patients come in with advanced stage diseases that are rarer in U.S. hospitals. Mandel saw numerous unusual cases, such as children with precocious puberty that began at age 2 but was not caught until age 8. The most interesting case, as described by Lorincz, was of a young, pregnant woman with a large pheochromocytoma encasing her celiac trunk. She had previously terminated a pregnancy, but elected to try for a child the second time. They saw her on several occasions over the course of their time in Johannesburg, and later heard from Naidu that she successfully delivered a 5.5 lb .baby girl. The patient was able to have 90% of the pheochromocytoma resected after her C-section.

When Shires and Naidu arrived at the University of Pennsylvania, they also had a full itinerary. In addition to participating in ENDO 2013, they attended clinics with endocrine

AN EXPLANATION FOR A DECREASED LIBIDO: A Case Study from ESAP™

A 36-year-old man presents for evaluation of fatigue and decreased libido. Over the past six months, he has noted a progressive decline in his energy level, as well as in sexual function. He has few, if any, morning erections and is unable to sustain an erection to have intercourse. He has also noted a decreased frequency of shaving and a generalized darkening of his skin, despite a lack of sun exposure. He reports no heat or cold intolerance, headache, or change in vision.

He saw his primary care physician four months ago and had a random blood glucose concentration greater than 300 mg/dL on two occasions. He was counseled on a proper diet, taught how to monitor his glycemic control at home, and prescribed glipizide, 2.5 mg daily. With those interventions, he has noted a slight improvement in his diabetes with glucose concentrations of 100 to 250 mg/dL in the morning without any evidence of hypoglycemia.

Physical examination reveals normal vital signs. His skin is tanned without any tan lines. He has no goiter. His lungs are clear. He has no gynecomastia. His liver is palpable 2 cm below the costal margin, and his liver span is increased. Genitourinary examination reveals a normal phallus and testes.

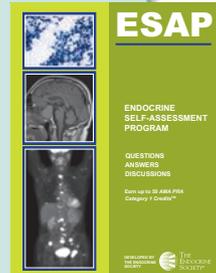
His testosterone concentration is 180 ng/dL. Thus, you also order DXA to assess his risk of a fragility fracture.

answer on page 28

QUESTION

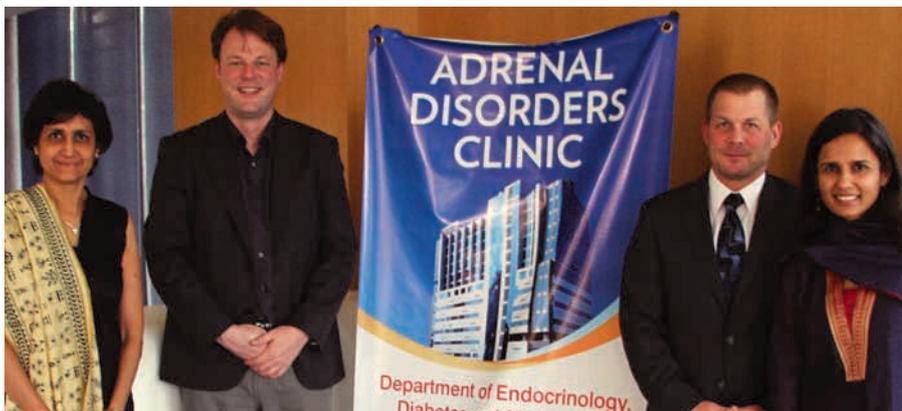
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is a self-study program aimed at physicians seeking certification or recertification in endocrinology, program directors interested in a testing and training instrument, and individuals simply wanting a self-assessment and a broad review of endocrinology. ESAP is available in both print and online formats. It consists of 160 multiple-choice questions in all areas of endocrinology, diabetes, and metabolism. There is extensive discussion of each correct answer, a comprehensive syllabus, and references. ESAP is updated annually with new questions and new syllabus materials. Learn more at www.endoselfassessment.org.



Which one of the following patterns of laboratory results (obtained at 8 AM) and radiographic findings best fit his diagnosis?

ANSWER	LH, IU/L	CORTISOL, µg/DL	ESTRADIOL, PG/ML	PROLACTIN, NG/ML	LUMBAR SPINE Z SCORE
A	4	13	39	8	0.4
B	3	12	15	99	-1.4
C	40	12	15	7	-1.0
D	2	11	10	9	-1.2
E	3	2	15	6	1.1



From left to right: Drs. Nalini Shah, Tobias Else, Gary Hammer, and Shruti Khare.

attendings and joined the inpatient endocrine and diabetes teams on rounds during general medicine service. Other days were dedicated to teaching sessions like the diabetes conference and thyroid case conference. Both Naidu and Shires gave lectures to the division and worked as the guest attendings for a resident report on calcium cases. On the social side, they

had dinners with colleagues, went to a baseball game, and explored the Barnes Museum.

The delegates from both countries felt that the exchange brought incredible value. Each institution has already taken steps to incorporate lessons learned from their respective trips. Mandel was so impressed with the overall experience that she is considering a sabbatical to South Africa in the near future. She claims that the The Endocrine Society's Ambassador

Exchange Program "exceeded all expectations" and sincerely hopes that it becomes a permanent fixture. Shires says that Baragwanath would love the opportunity to host more endocrine ambassadors as well. www.endocrine.org/advocacy/legislative/letters. **EN**

—Mapes is a freelance writer based in Washington, D.C.

AN EXPLANATION FOR A DECREASED LIBIDO: A Case Study from ESAP™

ANSWER

The Endocrine Self-Assessment Program (ESAP)

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question on page 27

The answer is: D

This patient has hypogonadism secondary to hemochromatosis. Iron deposition in the liver, skin, and pancreatic islet cells accounts for his hepatomegaly, change in skin color, and recently developed diabetes mellitus. Interestingly, in men with hemochromatosis, sex hormone-binding globulin and estradiol levels are normal and gynecomastia is rare. In most affected men, secondary hypogonadism is the most common cause of gonadal failure. To a lesser extent, primary gonadal dysfunction (even concurrent with pituitary involvement) can occur. In cases of hypogonadism, subsequent to the loss of androgens, marked reductions in bone mineral density can be seen in both men and women. Interestingly, the gonadotropes are more predisposed to iron deposition than other cells. Thus, panhypopituitarism is rare, and secondary hypothyroidism or secondary adrenal insufficiency is not often encountered.

The pattern in Answer A is seen in patients with chronic liver disease. These findings are more likely to be seen in patients with alcohol-induced liver disease, although liver

disease of any etiology can present with this biochemical profile. Alcohol can directly reduce androgen levels. In addition, any damage to hepatocyte function results in a reduction in estrogen degradation, thereby increasing circulating estradiol levels (some patients presenting with gynecomastia). Furthermore, high estrogen levels lead to a reduction in testosterone levels via negative feedback at the level of hypothalamus/pituitary. Despite low androgen levels, these individuals may not lose bone mass because of elevated serum estrogen levels.

The pattern in Answer B suggests hypogonadotropic hypogonadism that is secondary to hyperprolactinemia. Although both hemochromatosis (with pituitary involvement) and hyperprolactinemia present with low gonadotropins and testosterone levels, hemochromatosis is characterized by normal or even low prolactin levels (presumably due to damage to the lactotrophs from iron deposition).

The pattern in Answer C is typical for a man with hypergonadotropic hypogonadism due to primary testicular failure. Although primary hypogonadism can be seen in persons with hemochromatosis, it is less likely than a central etiology.

The pattern in Answer D is consistent with pituitary insufficiency. Concentrations of both androgens and estrogen are low because of low gonadotropin concentrations. In addition, affected persons have a blunted response to GnRH in terms of LH secretion and have reduced responses to compounds such as clomiphene citrate, which, via its estrogen-antagonist action, should increase gonadotropin secretion. The low bone density is a result of the hypogonadism that has probably been present for some time, and the normal 8 AM cortisol concentration reflects sparing of other anterior pituitary trophic hormones in the setting of hemochromatosis.

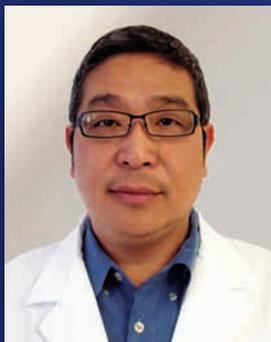
The pattern in Answer E also represents hypogonadotropic hypogonadism, although with concurrent adrenal insufficiency. In the face of cortisol deficiency, the finding of hyperglycemia (or lack of hypoglycemia after initiation of a sulfonylurea) would be less likely. Although panhypopituitarism is unlikely, so too is the increased bone mineral density. As noted, in men with hypogonadism, one would predict a reduced bone mass.

Treatment of the hemochromatosis has variable results. In some individuals, pituitary function can be restored with serial phlebotomy. The response is slow, and normalization of the hypothalamic-pituitary-gonadal axis may take months of treatment. In many patients, despite adequate control of iron balance, hypopituitarism persists and androgen replacement is needed. **EN**

Calcium-Sensing Receptors: Their Roles in Disease and Their Promise in Future Treatments

Calcium mediates many physiologic processes and hence its tight regulation is critical. The calcium-sensing receptor (CaSR), a G protein-coupled receptor (GPCR) on the surface of parathyroid cells, is sensitive to changes in extracellular ionized calcium and thereby controls parathyroid hormone (PTH) secretion, regulating circulating calcium concentrations. Since its cloning in 1993, the CaSR has been implicated in several disorders of calcium metabolism, including familial hypocalciuric hypercalcemia (FHH) and autosomal dominant hypocalcemia (ADH). The more recent discovery of CaSR expression in other tissues, including kidney,

bone, intestine, pancreas, thyroid, placenta, central nervous system, heart, epidermis, and breast, suggests widespread and diverse functions for the receptor. This TriPoint: (1) chronicles the basic science investigations that led to identification and characterization of the receptor in parathyroid and non-parathyroid tissues; (2) examines the role of the CaSR in human disease, including how human mutations enlighten our understanding of receptor function; and (3) describes the patient populations that may benefit, now and in the future, from drugs that activate (calcimimetics) or antagonize (calcilytics) the CaSR.



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BASIC RESEARCHER PERSPECTIVE

HIGHLIGHTS

- Studies of patients with parathyroid disorders and CaSR knockout mouse models confirm that the **CaSR is the molecular basis for extracellular Ca²⁺-sensing by parathyroid cells.**
- Burgeoning studies of tissue-specific CaSR knockout mice reveal **vital actions of the CaSR** in skeleton, central nervous system, and other peripheral tissues regulating mineral homeostasis, general growth, skeletal development, and energy metabolism.
- **Specificity in the actions of the CaSR** is determined by inter-tissue differences in post-translational modifications, complex formation with other family C GPCR members, and interactions with signaling molecules.

The Development of the Concept of Extracellular Ca²⁺-Sensing in Parathyroid (PT) Cells

Sydney Ringer was the first to demonstrate the biological function of ionized calcium (Ca²⁺) by showing the ability of a trace amount of Ca²⁺ from tap water to induce contractions of frog hearts *in vitro*. This unique cation was later shown to be a critical intracellular signaling molecule that mediates diverse functions in literally every cell system. Accompanying these findings was the question of how cells in the most basic unicellular or complex multicellular organisms control intracellular Ca²⁺ homeostasis in response to fluctuations in the availability of Ca²⁺ in their immediate environment. This question began to be answered when Brown, Shoback, and colleagues demonstrated the ability of a minute change in the concentration of extracellular Ca²⁺ ([Ca²⁺]_o) to excite several acute (in seconds to minutes) signaling responses in PT cells, including: (1) increases in intracellular [Ca²⁺]; (2) inhibition of cAMP production via coupling to G-protein subunit G α I; (3) stimulation of mitogen-activated protein kinases; and (4) activation of diacylglycerol/protein kinase C pathways.

In contrast to other endocrine systems where these intracellular signaling events generally stimulate hormone secretion, activation of these signaling responses by Ca²⁺ actually inhibits the release of PTH in PT cells. These observations led to the hypothesis that a plasma membrane-delimited GPCR was responsible for

sensing changes in [Ca²⁺]_o, allowing cells to adjust their cellular functions according to extracellular Ca²⁺ availability. This concept was firmly established by: (1) the cloning of the CaSR from bovine PT glands in 1993; (2) the linkage of large numbers of activating and inactivating mutations in this receptor to the disorders of FHH and ADH; (3) the manifestation of neonatal severe hyperparathyroidism in a mouse model with global deletion of exon 5 of the CaSR gene; and (4) the inability of PT glands lacking CaSR expression to respond to changes in [Ca²⁺]_o in culture.

Extracellular Ca²⁺-Sensing in Non-Parathyroid (Non-PT) Tissues

The cloning of bovine parathyroid CaSR also allowed characterization of its orthologs in other species ranging from elasmobranch fish to humans, demonstrating >85% similarity at the protein level, and permitted identification of the receptor in non-PT cells. The latter cells include those mediating classic calciotropic activities in the kidney, intestine, bone, cartilage, thyroid, placenta, and mammary gland and those not typically involved in maintaining Ca²⁺ homeostasis, like keratinocytes, neurons, pancreatic β -cells, and smooth and cardiac muscle cells.

To define the biological actions of CaSR in different tissues, a mouse model was generated that enabled the tissue- or cell-specific deletion of the receptor. For example, PT-specific CaSR KO mice, which retain CaSR functions in their kidneys, develop hypercalciuria. In contrast, when the receptor is deleted in all tissues, mice

are hypocalciuric, confirming that renal CaSRs are essential for promoting Ca²⁺ excretion.

CaSRs play non-redundant roles in mediating the growth, survival, and differentiation of chondrocytes and osteoblasts and in supporting embryonic and postnatal skeletal development. CaSRs expressed in intestinal epithelial cells prevent hyperproliferation, representing a novel target for prevention and/or treatment of colon cancer.

Preliminary studies of mice with CaSR ablated in neurons suggest that this receptor could also modulate general growth, energy metabolism, and skeletal homeostasis by mediating neuroendocrine functions in hypothalamic neurons and thereby the endocrine functions of the pituitary gland. In a transient global ischemia mouse model, CaSR overexpression appeared to be pivotal in the induction of neuronal injury. Studies of other tissue-specific CaSR KO mice are underway and are expected to reveal additional CaSR actions in both physiology and pathology.

Distinct Molecular Actions of CaSR in Pt Vs. Non-PT Tissues

Interestingly, CaSR mutations were often identified in patients with parathyroid disorders who showed none of the skeletal, neuroendocrine, or metabolic disorders seen in the conditional KO mice described above. These observations suggest that the actions of the CaSR in PT tissue are more sensitive to mutations than the CaSRs in non-PT tissues.

Based on cDNA sequences, CaSRs expressed in non-PT tissues are identical to that expressed in PT tissue, so the different CaSR actions in various tissues likely originate from differences in post-translational modifications and/or in its interactions with other accessory proteins and/or signaling molecules. In support of this idea, immunoblotting showed distinct glycosylation patterns of CaSR in non-PT compared to PT tissues.

Moreover, the CaSRs function in the form of multimeric complexes, interacting homomerically with themselves or heteromerically with other GPCR family C members, including type B γ -aminobutyric acid receptor (GABA-B-R) 1 and 2 and metabotropic glutamate receptors (mGluR1 and R5). Different stoichiometric interactions among these receptors, and perhaps with other undefined members of family C GPCRs, could produce receptor complexes with distinct molecular, signaling, and pharmacological characteristics. For example, the CaSR is expressed about 100-fold higher than the GABA-B-R1 in PT glands, favoring

CaSR homomeric complexes, whose functions are anticipated to be more susceptible to the mutations in the receptor and manifest dominant negative effects as seen in FHH.

In contrast, GABA-B-R1 expression is 10-fold higher than CaSR expression in chondrocytes and neurons, favoring CaSR/GABA-B-R1 heteromeric complexes, which are expected to be less sensitive to CaSR mutations. In addition to changes in their functionalities, these differences in receptor processing and complex formation also provide opportunities for the design of specific compounds to target the CaSR in different tissues.

Conclusions

Though genetic studies in humans and mice demonstrate that the CaSR provides the basis for extracellular Ca^{2+} -sensing by parathyroid cells, it is now clear that the protein plays additional roles in extra-PT tissues. The development and analysis of tissue-specific CaSR knockout models, coupled with biochemical characterization of the CaSR's processing, partnering, and signaling, will uncover the nature and basis of these novel functions. Such mechanistic insight will enable more rational approaches to the development of therapeutics targeting the CaSR in the parathyroid and other tissues. **EN**

CLINICAL RESEARCHER PERSPECTIVE

HIGHLIGHTS

- Clinical investigation supported the **importance of mutations of the CaSR in inherited disorders:** familial benign hypercalcemia, neonatal severe primary hyperparathyroidism, and autosomal dominant hypocalcemia.
- Work from several laboratories confirmed that CaSR mRNA and protein levels were reduced in **primary and uremic secondary hyperparathyroidism.**
- Clinical trials with calcimimetics, agonists acting as allosteric modulators of the CaSR, showed that **targeting parathyroid CaSRs improved biochemical parameters** in primary and uremic secondary hyperparathyroidism.

Extracellular Calcium-Sensing Receptors and Parathyroid Function in Vivo

Over 30 years ago, pharmacologic and signaling studies clearly documented the capacity of parathyroid and kidney cells to sense and respond to small but physiologically relevant changes in the extracellular concentration of calcium ($[\text{Ca}^{2+}]_e$). Clinical investigators meanwhile had described kindreds with hypocalciuric hypercalcemia (FHH), rarely in association with severe hyperparathyroidism (HPT) in infants, and families with autosomal dominant hypocalcemia (ADH). This work supported the hypothesis that a plasma membrane extracellular Ca^{2+} -sensing molecule, akin to members of

the G-protein coupled receptor superfamily, existed and might explain the remarkable sensitivity of parathyroid and kidney cells to changes in the extracellular concentration of Ca^{2+} and Mg^{2+} .

Once the extracellular Ca^{2+} -sensing receptor (CaSR) cDNA was cloned, progress was rapid in identifying human mutations in the CaSR gene. Inactivating mutations were found in families with FHH and neonatal severe primary HPT, while activating mutations explained the hypocalcemia and inappropriately low parathyroid hormone (PTH) levels in many families with ADH.

Inactivating CaSR mutations reduced the capacity of parathyroid and kidney cells to sense and respond

to changes in the $[\text{Ca}^{2+}]_e$ by several mechanisms: (1) Mutations, such as the insertion of a stop codon, disturbed intracellular CaSR biosynthesis and/or folding, and thereby reduced levels of membrane CaSR expression; (2) Point mutations in critical residues blunted the ability of CaSRs to couple to G-proteins and activate downstream signaling pathways mediating inhibition of PTH secretion; (3) Point mutations in the extracellular domain of the CaSR, critical to its ion-sensing function, and in key residues in transmembrane domains, shifted sensitivity of the receptor to changes in the $[\text{Ca}^{2+}]_e$; and (4) CaSRs form dimers in the membrane, and certain CaSR mutants act as “dominant-negatives,” suppressing the activation of wild-type CaSRs by high $[\text{Ca}^{2+}]_e$.

Conversely, activating mutations of the CaSR enhance coupling to downstream signaling pathways and/or possess increased sensitivity (i.e., shift to the left) to the $[\text{Ca}^{2+}]_e$ compared to wild-type CaSRs. Both mechanisms would be predicted to promote the inhibition of PTH secretion at physi-

ologically low $[Ca^{2+}]_i$. Other studies showed that glands from both sporadic primary HPTH (pHPT) and uremic secondary HPT (sHPT) had reduced (by ~50% on average) CaSR mRNA and protein levels. Taken together, this work set the stage for therapeutically targeting CaSRs in disorders of Ca^{2+} -sensing.

Targeting the CaSR to Achieve Therapeutic Efficacy

Shortly after CaSR cloning and expression studies, compounds with the ability to activate the receptor and downstream signaling pathways and modulate PTH secretion were reported. These drugs were designated calcimimetics because they could mimic the actions of Ca^{2+} on PTH secretion and signaling responses. One such compound cinacalcet has been tested in uremic sHPT and pHPT and is approved to treat both disorders with specific indications.

Uremic sHPT

Uremic sHPT is characterized by multiple derangements in serum biochemical parameters (elevated PTH, low 1,25-dihydroxyvitamin D, and high fibroblast growth factor 23 levels, along with hyperphosphatemia and high Ca^{2+} -phosphate product). High PTH levels have long been considered central to morbidity in chronic kidney disease (CKD). Thus, targeting the reduction of PTH levels in patients with stage 5 CKD with cinacalcet was an immediate goal of trials with calcimimetics.

Key studies demonstrated the effectiveness of this approach to treat HPT in short-term studies (26 weeks). Higher percentages of patients treated with cinacalcet reached National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) targets for PTH (56%), Ca^{2+} (49%), phosphate (46%), and Ca^{2+} -phosphate product (65%) compared to placebo-treated patients who met these goals for PTH (10%), Ca^{2+} (24%), phosphate (33%), and Ca^{2+} -phosphate product (36%). The main side effects of cinacalcet were nausea and hypocalcemia.

The EVOLVE trial examined the efficacy of cinacalcet vs. placebo to reduce composite cardiovascular/peripheral vascular endpoints in patients with stage 5 CKD and moderate to severe sHPT. By intention to treat analysis, the trial was nondefinitive in showing efficacy against cardiovascular/vascular and fracture endpoints. Whether targeting CaSRs has advantages over other approaches in CKD (phosphate binders, diet, vitamin D analogues) remains unproven.

pHPT

Patients with pHPT due to non-malignant and malignant parathyroid tumors have been treated with cinacalcet to lower PTH and serum Ca^{2+} levels. In one study, 78 patients with mild pHPT were randomized to cinacalcet or placebo for 52 weeks. In 80–90% of cinacalcet-treated patients, the serum $[Ca^{2+}]$ was normalized, accompanied by mild reductions in PTH and increases in serum phosphate levels.

Treatment with cinacalcet (up to five years) showed no significant effects on bone mineral density.

Patients with intractable pHPT with serum $[Ca^{2+}] > 12.5$ mg/dL were studied on cinacalcet (dosed up to four times daily) in an open-label trial. Serum $[Ca^{2+}]$ was decreased and quality of life assessments improved vs. baseline. In another trial, patients with severe hypercalcemia and inoperable parathyroid cancer were treated with cinacalcet. This approach produced moderate decrements in serum Ca^{2+} in the majority of patients. Thus, while skeletal and survival endpoints were not addressed in these small open-label trials, the potential for improving symptomatic hypercalcemia in such patients with moderate and severe HPT is an important clinical option.

Summary

Prescient clinical investigators first suspected that the parathyroid cell harbored a molecule, akin to the G-protein coupled receptors, in the 1970's when they identified families with apparently benign hypercalcemia and detectable (and even elevated) PTH levels. This clinically generated hypothesis combined with in vitro studies in parathyroid cells demonstrating their remarkable sensitivity to small changes in the ambient $[Ca^{2+}]$ led to the cloning of the CaSR. Knowledge that parathyroid tissues in states of HPT were also insensitive to high $[Ca^{2+}]$ set the stage for targeting CaSR with allosteric modulators to suppress the hypersecretion of PTH in these disorders—a practice that is now common in the clinic. EN

CLINICAL PRACTITIONER PERSPECTIVE

HIGHLIGHTS

- **The discovery of the calcium-sensing receptor** has revolutionized our understanding of calcium homeostasis and allowed us to define the etiology of certain disorders of calcium metabolism.
- **Calcimimetics** are compounds that activate or sensitize the receptor to extracellular calcium and can be used in various disorders of parathyroid excess.
- **Calcilytics** are compounds that antagonize the receptor, stimulating endogenous PTH secretion. These are being studied as a possible anabolic therapy for osteoporosis.

Evolution of Familial Hypocalciuric Hypercalcemia (FHH)

Prior to the widespread use of automated chemistry analyzers in the 1970's, hyperparathyroidism was generally considered an uncommon, symptomatic con-

dition with familial cases being quite rare. Once the frequency of hypercalcemia was more apparent, asymptomatic hyperparathyroidism and familial hyperparathyroidism became increasingly recognized.

Starting in the 1960's, families with "hereditary hyperparathyroidism" began to be described with relatively few clinical consequences from the disease, and they were also found to have persistent hypercalcemia despite sub-total parathyroidectomy. It was later realized that these families had low urinary calcium excretion, and that this could be used to distinguish families who might not benefit from parathyroid exploration. This new entity was called familial benign hypercalcemia or familial hypocalciuric hypercalcemia (FHH).

Discovery of the Calcium-Sensing Receptor and Its Connection to Human Disease

In the earliest descriptions of FHH, there was speculation about an "abnormality of the receptor mechanism for calcium," though no such receptor had been discovered for an ion to that point. After various lines of suggestive evidence throughout the 1980's, the calcium-sensing receptor (CaSR) was cloned and characterized in 1993. Simultaneously, the same group described inactivating mutations of the receptor as the most common cause of FHH. The following year, they described activating mutations as a cause of autosomal dominant hypocalcemia (ADH). These findings revolutionized our understanding of calcium homeostasis and led to various therapeutic advances for human disease.

Calcimimetics

Once the concept of the CaSR was solidified, it was not long before compounds were developed that modified the action of the receptor. Calcimimetics are compounds that activate, or sensitize the receptor to extracellular calcium. By doing so in the parathyroid chief cells, parathyroid hormone (PTH) secretion is suppressed with subsequent lowering of serum calcium levels. One agent

in this class, cinacalcet, has been approved since 2004 for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis as well as in patients with hypercalcemia from parathyroid carcinoma. There are reports of effective use in rare cases of FHH with more severe hypercalcemia, though given the generally benign nature of this uncommon disease, treatment would not typically be indicated for the majority of cases.

Based on cinacalcet's mechanism of action, there is a natural impulse to use the medication in the management of primary hyperparathyroidism. However, the drug was only approved by the FDA in 2011 for patients with primary hyperparathyroidism and severe hypercalcemia who are unable to undergo parathyroidectomy. The rationale for this has been practical, as surgery is usually an excellent option for a definitive cure. Additionally, while cinacalcet lowers serum calcium and PTH levels in patients with primary hyperparathyroidism, there is no improvement in bone mineral density (BMD) after five years of therapy. An improvement in BMD is typically seen after surgical cure of primary hyperparathyroidism, so it is unclear that cinacalcet will offer the same long-term benefits.

For these reasons, cinacalcet should not be considered an equivalent alternative to parathyroidectomy for patients in whom surgery would be indicated. Conversely, if surgery is not indicated, typically due to lack of symptoms and a low risk of complications from the hyperparathyroidism, cinacalcet would not likely offer benefit. Hence, cinacalcet would only be recommended for use in less common situations. As an example, I have helped manage a 65-year-old woman with primary hyperparathyroidism, corrected serum calcium levels as high as 11.7 mg/dL (normal <10.1 mg/dL), and progressive renal failure. No autonomous parathyroid tissue was localized despite various imaging modalities. Attempts at surgical exploration were postponed due to repeated bouts with decompensated congestive heart failure. Due to

progressive hypercalcemia, she was treated with cinacalcet. The starting dose of 30 mg twice daily actually caused modest, asymptomatic hypocalcemia (with similarly elevated PTH levels). She has since responded well to 600 mg of calcium carbonate twice daily and 50,000 international units of ergocalciferol weekly while continuing the same dose of cinacalcet.

Calcilytics

Calcilytics are compounds that antagonize the CaSR, thereby stimulating endogenous PTH secretion. Since brief, daily exposure to exogenous PTH or its analogs is known to stimulate anabolic bone growth with a reduction in fracture risk, agents in this class are being studied as a potential anabolic therapy for osteoporosis. The first generation of these agents was shown to cause a dramatic increase in bone turnover in ovariectomized rats, though there was no change in BMD. This was felt to be due to a longer duration of action leading to a more prolonged elevation of PTH (>4 hours). More recently, a shorter-acting calcilytic, ronacaleret, has been shown to increase trabecular BMD in postmenopausal women, though there were small decreases in cortical BMD, still implying excess PTH exposure. Therefore, while it is not clear where these agents will take us, they do offer the promise of an orally administered, anabolic therapy for osteoporosis.

Conclusion

The discovery of the CaSR has revolutionized our understanding of calcium homeostasis. Not only has it allowed us to define the etiology of certain disorders of calcium metabolism, but it has also provided a target at which to aim therapeutics for a wide array of pathologies. **EN**

A Meeting of THE MINDS

ENDO 2013

This year's annual conference of The Endocrine Society is officially one for the record books. Here are a few highlights detailing research that was presented at **ENDO 2013** in San Francisco.

By Derek Bagley

On a bright, cool June Saturday morning, thousands of people converged on 747 Howard Street in San Francisco, their presence signaled by the ubiquitous black-and-purple tote bags, descending by foot from the hills or hopping off the city's famous cable cars or scurrying from myriad corner coffee shops and breakfast bistros. Practitioners, basic scientists, researchers, fellows, students, and media all gathered for an innovative educational program covering endocrinology from bench to bedside.

For four days, San Francisco's Moscone Center hosted The Endocrine Society's 95th Annual Meeting & Expo where a record-setting 9,300 attendees met to discuss the latest developments and advances, blockbusters, and bombshells in the world of endocrinology.

Outgoing Endocrine Society president William F. Young, Jr., MD, took the stage the morning of Saturday, June 15, before the first plenary lectures, and expressed his farewells, saying that it had been an "honor and career highlight" to serve as president. He proudly mentioned all of the wonderful things The Endocrine Society and its members had accomplished in the past year, and said a special thank you to Scott Hunt, who is retiring as CEO of The Endocrine Society after leading the association for 25 years and growing it by leaps and bounds.

The **ENDO 2013** participants



For four days, San Francisco's Moscone Center hosted a record-setting 9,300 participants who attended more than 350 presentations detailing everything from obesity, diabetes, endocrine disruptors, thyroid cancer, sex hormones, and more.

attended more than 350 presentations detailing everything from obesity, diabetes, endocrine disruptors, thyroid cancer, sex hormones, and more. Hundreds of people filled each room of the Moscone Center, the massive event halls and the intimate theaters, even the stairwells and hallways and tucked-away corners, to discuss the groundbreaking hot topics in their field.

New programs on the schedule for 2013 included feature poster presentations, which provided trainees with a kind of "lightning round" to showcase the information on their posters before inviting **ENDO** attendees to come by the Expo Hall to see them, as well as the "sandwich symposia," which allowed for junior presenters to be "sandwiched" among the more senior speakers.

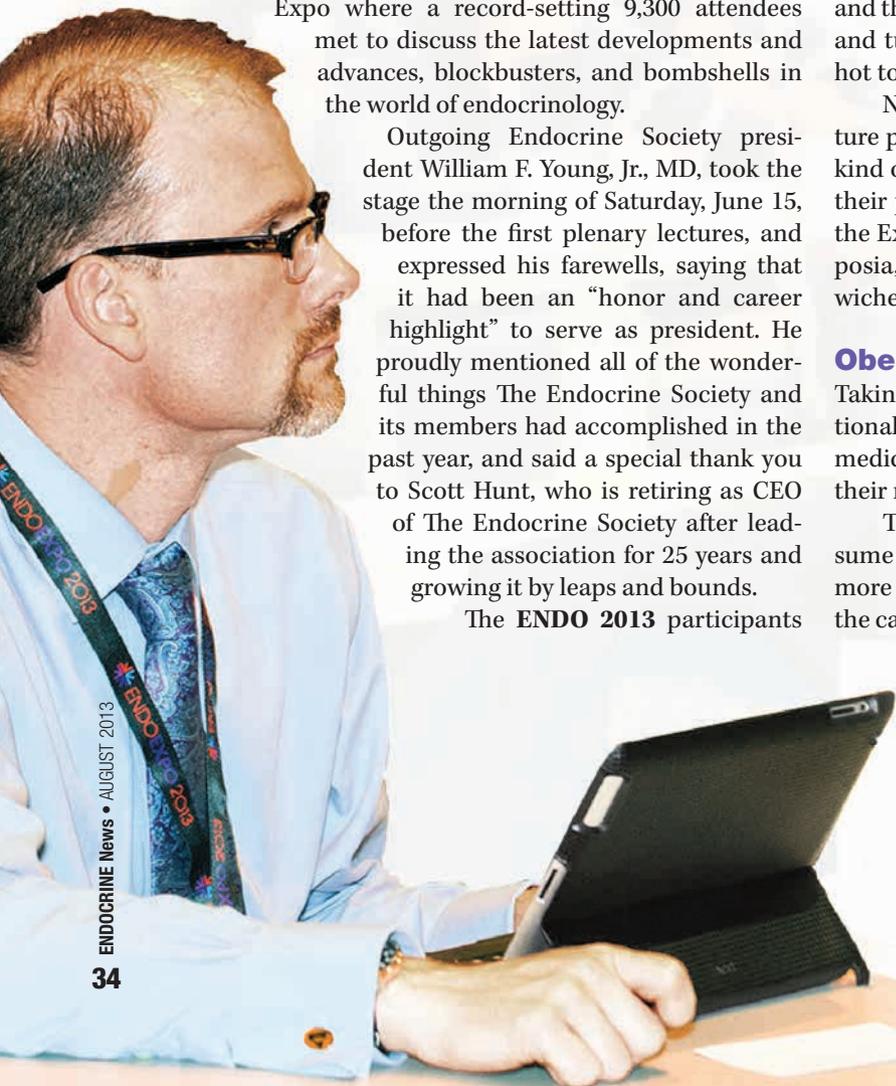
Obesity Takes Center Stage

Taking center stage this year was the growing international epidemic of obesity, which now accounts for 20% of medical expenditures worldwide, but the presenters and their research offered some avenues to solutions.

The overeating of high-fat diets that many people consume are obviously one of the main causes of more and more people growing overweight and becoming obese, but the causes for overeating itself are not exactly always clear.

It turns out there could be a number of reasons, whether people are depressed or stressed and are taking necessary medications to combat those emotions, or even something much more troublesome—food addiction.

"Addiction is amplified motivation," said Gina Leininger, PhD, assistant professor of physiology at Michigan State University, adding that palatable food especially can amplify the motivation to eat. Ralph DiLeone, associate professor of psychiatry and neurobiology at the Yale School of



Medicine, agreed, showing that stimulation of dopamine receptors in mice led to increased food intake, in both food-deprived and food-replete states.

Felicia Nowak, MD, PhD, an associate professor of molecular endocrinology at Ohio University, and her team showed that male mice whose fathers consumed high-fat diets before conception exhibited increased body weight, providing evidence that “paternal obesity is a predictor of childhood excess weight.” However, she said, these changes tend to be epigenetic—heritable alterations in gene expression—because the offspring weren’t able to observe their father’s eating habits and didn’t even have access to the same high-fat diets. Nowak went on to say that obesity in both parents “more than doubles” the chances that children will be born overweight.

One glimmer of hope, Nowak noted, was that the offspring of fathers who had high-fat diets ran more on their wheels, suggesting they were “programmed to avoid having fat in them.”

Obesity means a major risk factor for a large swath of endocrine disorders, especially diabetes. The disease costs diagnosed patients \$245 billion in the U.S. alone, but developing healthy eating habits—especially at a young age—has repeatedly shown to slow or even stop the progression of this lifelong and costly illness.

Breakfast skipping, for example, tends to be associated with a higher body mass index (BMI). And for women who skip breakfast, according to Elizabeth Thomas, an endocrinology fellow at the University of Colorado School of Medicine in Aurora, that could, in turn, lead to insulin resistance.

“Insulin resistance over time leads to other metabolic disorders,” Thomas said, “including type 2 diabetes.” The study she presented showed that acute insulin resistance developed after just one day of skipping breakfast.

But it’s not just poor diet that can lead to problems; so can a lack of sleep. The so-called “24/7 lifestyle” that many patients experience can make patients more susceptible to insulin resistance, the disorder that can cause type 2 diabetes, according to Peter Liu, MD, PhD, of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance, Calif. “We don’t think we need sleep,” Liu said, but longer sleep actually improves sensitivity, even if it’s “catch-up sleep” on the weekends.

Perhaps one of the more complicated ways (compared to diet and sleep) to help patients with diabetes



For women, skipping breakfast can lead to insulin resistance, according to Elizabeth Thomas, an endocrinology fellow at University of Colorado School of Medicine in Aurora.



“It has been an honor and career highlight to serve as president,” said William F. Young, Jr., MD, outgoing Endocrine Society president as he expressed his farewells.

was presented by Steven E. Kahn, MB, ChB, of the Veterans Administration Puget Sound Health Care System and the University of Washington, during the Clinical Investigator Award Lecture. His data suggested that beta-cell dysfunction was the key to the development of type 2 diabetes, as well as a new direction for clinical intervention, so long as swift and decisive action was taken. “If we can act aggressively early on,” Kahn said, “we can preserve beta-cell function and slow the progression of diabetes.”

Genetics & Early Intervention

Of course, intervening at an early age is a good idea for any sort of possible disease, and again, new studies presented at **ENDO 2013** showed promise for

helping adolescents and teens in myriad ways. Obese children and teens were shown to be more likely to develop chronic and persistent asthma and allergies when they have a vitamin D deficiency. And the problem is that vitamin D deficiency is common in obese individuals.

Even the fear of obesity is a significant factor in manifesting problems in young people. Anorexia nervosa, a severe eating disorder that especially affects teenage girls, is characterized by an extreme and distorted concern for body shape and image. However, it appears that there could be an endocrinological solution. The results of a new clinical trial showed that estrogen replacement therapy decreased anxiety in girls who suffer from anorexia nervosa.

Other concerns for pediatric populations presented at **ENDO 2013** included gene mutations, as well as growth hormone irregularities and deficiencies, which can cause any number of problems, from bone problems to short stature to mental defects.

And these disorders are often interconnected and become more apparent as children grow to adulthood. In fact, hypogonadism turns out to be a major risk factor for osteoporosis in men, an often underappreciated condition. Testosterone administration actually showed increased bone mineral density in men, but the treatment is still controversial, because there are still some doubts about that particular treatment’s efficacy.

Genetics plays a major role in the development of these issues; mutations interfere with hormone production, which regulates organ size, bone age, mental cognition, and even facial appearance.



“If we can act aggressively early on,” said Steve E. Kahn, MB, ChB, of the Veterans Administration Puget Sound Health Care System and the University of Washington, “we can preserve beta-cell function and slow the progression of diabetes.”

A Diabetes Pre-Show

Diabetes diagnosis and management has become such a major issue in endocrinology, that a special workshop co-sponsored by The Endocrine Society and the Hormone Health Network was held on Friday June 14, the day before ENDO 2013 officially began. This interactive program was led by 13 doctors and researchers who presented their findings and discussed their approaches to managing patients with diabetes and improving their respective lives. From new ways to hold informed conversations with patients to the new and improved drugs and advances in surgical techniques, participants had the opportunity to engage in discussions, learn from renowned clinicians and researchers, and even participate in Meet-the-Professor sessions.

Even though diabetes has been afflicting people for hundreds of years, treatment advances only just began expanding in the mid-1990s.

"There's considerable unmet need in the diabetes market," said Richard Pratley, MD, medical director of the Florida Hospital Diabetes Institute. But that could soon change; as of 2012 there were 221 drugs in development for diabetes. New pumps and sensors are being devised; there's even a re-emergence in interest for inhaled insulin.

But these novel therapeutics mean nothing without the proper guidance from healthcare professionals. Diabetes treatment involves constant and careful doctor/patient conversation, even for patients who experi-



Robert Gabbay, MD, chief medical officer of the Joslin Diabetes Center at Harvard Medical School, says doctors must involve patients in their treatment options as much as possible and engage in Shared Decision Making.

ence continuous glucose monitoring (CGM). Irl Hirsch, MD, a professor of medicine at the University of Washington, said there needs to be a "reality check" for CGM in the United States. The main thing for patients who wear sensors is realistic expectations, he said. Most patients eventually stop wearing their sensors because they have higher expectations that don't become a reality. Even for the ones who do stick with it, the majority require several months of use before they figure out how to use their sensors best, like learning when to override their bolus calculators, which Hirsch called the most important development in diabetes treatment.

The ancient Greeks had a very distinct system when it came to medicine, a kind of flowchart of best practices for healing the sick: First the word, then the herb, and lastly, the knife. Treating diabetes can be a costly and

lifelong commitment, and the disease often involves all three of these aspects. For Robert Gabbay, MD, chief medical officer of the Joslin Diabetes Center at Harvard Medical School, in order to first focus on "the word," doctors must involve their patients as much as possible in their treatment options.

"[Doctors are] expert advice-givers," he said, but the challenge is that ambivalence tends to be a part of human nature, and some patients don't respond well to certain forms of communication, especially if they feel like they're being talked down to or being persuaded. "The problem with persuasion is that you get pushback," Gabbay said, and if someone pushes too hard, you're likely to be resistant.

"We need to be mindful of the words we use," he said. "We can't force them, but we can guide them."

Floating Harbor Syndrome, a rare genetic disease that causes short stature, delayed bone age, and learning disability, is specifically characterized by facial features and is caused by a mutation of the gene SRCAP. Kym Boycott, an associate professor of medicine at the University of Ottawa, showed that the disease is especially given away by the patient's non-familial nose, "narrow at the root and wider at the nostrils."

IMaGE Syndrome, another rare disorder that causes short stature and distinctive facial features, is caused by the gene CDKN1C and inherited in a "genomically imprinted manner," said Eric Vilain, MD, PhD, an assistant professor of human genetics at UCLA. The disease also has more severe symptoms like hypoplasia, scoliosis, and osteoporosis.

New insights into diagnosis and treatment of thyroid cancer were offered as well. Brian Netzel, a researcher at the Mayo Clinic in Rochester, Minn., said that there is a need to reduce the difficulty in detecting and diagnosing the dis-

ease, which can be done one way by harmonizing assays.

Several presenters agreed that diagnosing and treating thyroid cancer is not only difficult, but expensive, and some tests unnecessarily expose the patients to radiation. Robert Smallridge, MD, an endocrinologist at the Mayo Clinic in Jacksonville, Fla., and Stephanie Fish, MD, an endocrinologist at Sloan-Kettering Cancer Center in New York City both warned that practitioners should use radioactive iodine cautiously as an empiric dose for diagnosis of thyroid cancer.

When it comes to diagnosing and treating patients with thyroid cancer, especially those with distant metastases, "new and better therapies are needed," Fish said.

Start clearing your calendar now to be in Chicago from June 21 to 24 for **ICE/ENDO 2014**, a joint International Congress of Endocrinology and Endocrine Society meeting. For more information, go to www.endocrine.org/meetings/ice-endo-2014/endo-2014#/nav/. **EN**

—Bagley is associate editor at Endocrine News.

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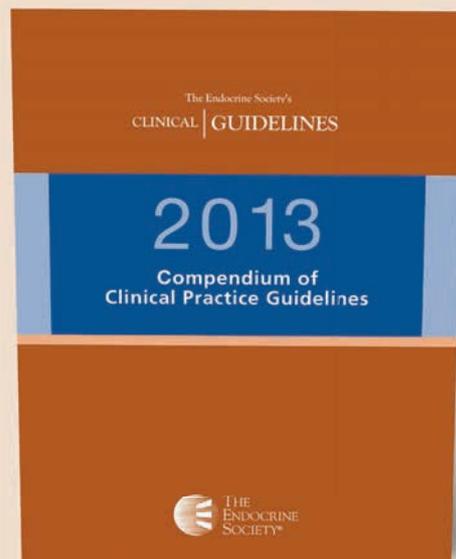
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- Evaluation and Management of Adult Hypoglycemic Disorders
- Endocrine Treatment of Transsexual Persons
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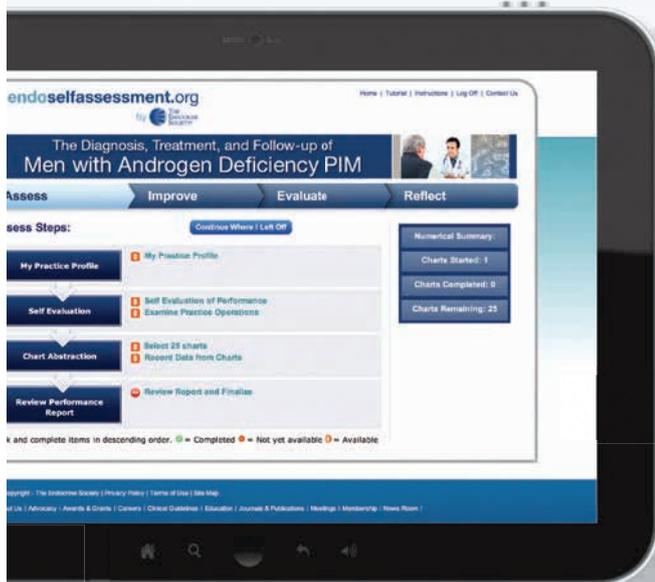
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Men with Androgen Deficiency PIM

This activity is supported by an educational grant from AbbVie, Inc. and Lilly USA, LLC. For more information concerning Lilly grant funding visit, www.lillygrantoffice.com.

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Time-Telling Medicines for Diabetes and Obesity?

By Jacqueline Oberst, PhD

Nature has its own rhythm. Mimosa plants unfurl their leaves at day and shut them tight come nighttime. Bioluminescent bacteria flare up at nightfall and dim their lights when morning arrives. Our bodies also dance to a unique beat that is kept in time by internal circadian clocks.

For the past 50 years, the study of these clocks, known as chronobiology, looked at people with disrupted sleep-wake cycles or sleep disorders. Now, researchers are developing new tools to look at the role circadian clocks play in diseases such as cancer, diabetes, and metabolic syndrome, with the possibility that certain medications could help control these diseases.

“There’s a master synchronizing clock in the hypothalamus and a clock in every cell in your body that keeps track of the time of day,” explains psychiatrist David Welsh, MD, PhD, of the Center for Chronobiology at the University of California, San Diego. “Circadian clocks are really enmeshed in all of physiology.”

Timing Is Everything

By dismantling the pieces of the circadian clock, researchers have identified numerous genes, such as *CLOCK* and *BMAL1*. These genes encode transcription factors that regulate physiological activities such as cell proliferation and glucose control.

Taking these genes into account is important in cancer cells that run amok from a sped-up clock. Chronobiology is considered when oncologists determine how to deliver cancer chemotherapy, because time of dosing matters. As such, clinicians try to gauge when the chemotherapeutic drug dose would be most effective and least toxic to patients, according to the June 2003 issue of *Integrated Cancer Therapies*.

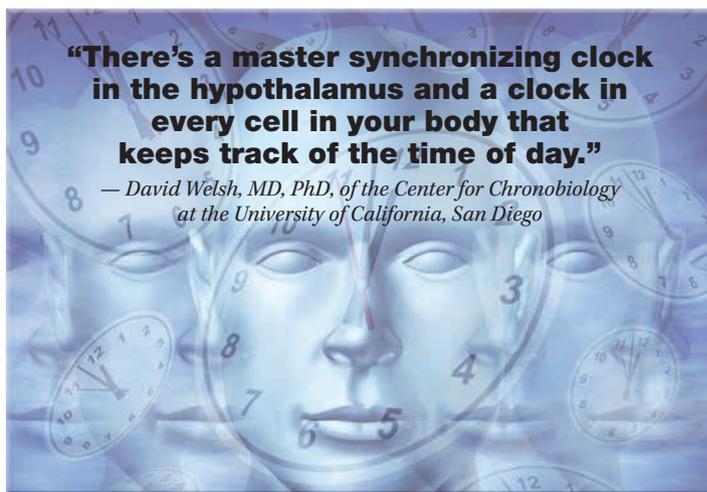
Chronobiology has also entered the realm of diabetes. For instance, pancreatic islet cells contain functioning *CLOCK* and *BMAL1* circadian clock genes. The July 2010 issue of *Nature* stated that mice with impairments in either of these genes displayed impaired glucose tolerance, reduced insulin secretion, and defects in size and proliferation in pancreatic beta cells that worsen with age. In short, disruption of the pancreatic clock can trigger the onset of diabetes.

Later in an article in the December 2011 issue of *Nature*, the authors proposed that in mice the circadian clock genes Cryptochrome 1 and 2 (Cry1 and Cry2) interact with glucocorticoid receptors to regulate glucose and steroid production but not inflammation. These results point to a possible therapeutic strategy for metabolic syndrome, which is plagued by chronic inflammation and poorly controlled glucose homeostasis. This strategy would try to

counter the side effects of glucocorticoids used in treating inflammation in these patients (e.g., weight gain, hyperglycemia, compromised immune system) by altering the timing of treatment or combining them with agents that stabilize Cry1 and/or Cry2 proteins.

Time Will Tell

Because the clock system influences physiology across many tissues and not just one in particular, developing chronobiology-based therapeutics might be tough.



But there are believers amongst the field.

Joseph Bass, MD, PhD, chief of the Division of Endocrinology, Metabolism and Molecular Medicine at Northwestern University, Chicago, who studies sleep, feeding, and metabolism — all components of the circadian clock — is a scientific advisor for Reset Therapeutics, Inc., a biotechnology firm involved in developing small molecules that manipulate the circadian clocks so as to help eradicate metabolic and related disorders such as diabetes, obesity, and cardiovascular disease.

“The circadian clock system is not so general as to be non-targetable,” says Bass. “We’re still in the early stages in therapeutics, but circadian clock drugs are a definite possibility.”

Drug companies have now developed various high-throughput screens for small molecules that affect clocks. These systems involve recording 24-hour clock gene expression in cells seeded in 384 well plates and subjected to a library of thousands of small molecules, some chemically synthesized, others borrowed from nature, such as plants and bacteria. **EN**

—Oberst is a freelance writer based in Bethesda, Md.

The Endocrine Society's 2013 LAUREATE AWARD WINNERS

The Endocrine Society Laureate Awards are presented to endocrinologists—members or nonmembers—from anywhere in the world for their exceptional contributions to endocrinology, whether they're in practice, research, or education. Each recipient, selected annually by the Awards Committee, is presented with an award certificate and is honored at the Society's annual Awards Dinner in June.



Michael O. Thorner, MBBS, DSc, a professor of medicine at the University of Virginia, received the 2013 Fred Conrad Koch Award. He is a basic and clinical research scientist with landmark contributions to the treatment of pituitary tumors, the discovery of GHRH and its receptor, and the actions and potential uses of GHRH and ghrelin mimetics in the treatment of sarcopenia of aging. This is the highest honor of the Society and is presented with the Koch Medal of The Endocrine Society.



Doris A. Stoffers, MD, PhD, professor of medicine at the Perelman School of Medicine at the University of Pennsylvania, is the recipient of The Endocrine Society's 2013 Ernst Oppenheimer Award. Stoffers has made a series of seminal observations that have informed our understanding of pancreas development and are improving our understanding of diabetes and its treatment. The Ernst Oppenheimer Memorial Award was first presented by The Endocrine Society in 1944 and is the premier award to a young investigator in recognition of meritorious accomplishments in the field of basic or clinical endocrinology.



The 2013 Robert H. Williams Distinguished Leadership Award was presented to **John Watson Funder, MD, PhD**, of Prince Henry's Institute in Melbourne, Australia. For over 40 years Funder has made outstanding contributions to endocrinology, from the laboratory to the clinic, from evolution to public policy. This award is presented annually in recognition of outstanding leadership in endocrinology as exemplified by the recipient's contributions and those of his/her trainees and associates to teaching, research, and administration. Distinguished leadership in endocrinology and metabolism

may be manifest in a variety of ways and activities (international, national, and local).



Gary D. Hammer, MD, PhD, a professor of medicine at the University of Michigan, received the 2013 Edwin B. Astwood Award Lecture of The Endocrine Society. Hammer has become a leader in adrenal developmental biology and a major force in endocrinology. The Edwin B. Astwood Award Lecture is awarded for outstanding research in endocrinology, and the recipient presents a plenary lecture at the annual meeting to honor the late Dr. Edwin B. Astwood of Boston.



The Endocrine Society presented this year's Clinical Investigator Award Lecture to **Steven E. Kahn, MB, ChB**, professor of medicine at the VA Puget Sound Health Care System and University of Washington. His broad and impactful contributions to our understanding of the pathophysiology and treatment of type 2 diabetes make Kahn a worthy recipient of the Society's highest honor, presented to an internationally recognized clinical investigator who has made major contributions to clinical research related to the pathogenesis, pathophysiology, and therapy of endocrine disease.



Mitchell A. Lazar, MD, PhD, received the 2013 Gerald D. Aurbach Award. Lazar, a professor of medicine at the University of Pennsylvania, has made seminal discoveries in the area of the nuclear hormone receptors and their coregulators, particularly corepressors. His pioneering studies at the intersection of transcriptional regulatory mechanisms with physiology and metabolism have had a major impact on our understanding of metabolic disease. This award is presented for outstanding contributions to research in endocrinology.



MEDICINES AND BONE LOSS

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The 2013 Sidney H. Ingbar Distinguished Service Award was given to **Irving Spitz, MD, DSc, FRCP**. Spitz is a professor of medicine at both Ben Gurion University in Israel and Weill Medical College of Cornell University. He advocated for the use of the progesterone receptor antagonist

RU486, now widely used in the safe termination of pregnancy in many countries throughout the world. The Sidney H. Ingbar Distinguished Service Award is named in honor of the 65th president of The Endocrine Society and presented in recognition of distinguished service in the field of endocrinology.



Donald P. McDonnell, PhD, received The Endocrine Society's 2013 Roy O. Greep Lecture Award for his exceptional contributions to endocrinology. As a professor of medicine at Duke University, his mechanistic insights and the translation of these

into the development of important therapeutics have had a major impact. The recipient of this award presents a plenary lecture at the annual meeting.



The Endocrine Society recognized **Mark Molitch, MD**, with the Distinguished Educator Award. Molitch is a professor of medicine at the Northwestern University Feinberg School of Medicine, where he has dedicated and committed his life to the education of his peers, clinical providers,

and patients. This award was established by the Society in 1998 to recognize exceptional achievement of educators in the field of endocrinology and metabolism.



Michael Thomas McDermott, MD, received the Distinguished Physician Award. McDermott is a professor of medicine at the University of Colorado and is widely known for the breadth of his mastery in the broad field of endocrinology and diabetes. His 18-year effort exemplifies both a deep and broad academic career; one that surely deserves the accolade, established by the Society

in 1998 to honor physicians who have made outstanding contributions to the practice of endocrinology.



Tony K. T. Lam, PhD, was awarded the Richard E. Weitzman Award, given to an exceptionally promising young investigator. Lam, an associate professor of physiology and medicine at the Toronto General Research Institute and University of Toronto, has greatly advanced our understanding

of how the gut communicates with the brain to regulate metabolism. Lam has identified novel therapeutic targets in the gut and the brain to lower blood glucose, lipid levels, and body weight in experimental models of diabetes and obesity.



Berenice Mendonca, MD, is the recipient of The Endocrine Society's International Excellence Award, a new laureate award that recognizes exceptional contributions to endocrinology either internationally or in the recipient's home country. Mendonca is a professor of medicine at the University of Sao Paulo and quintessential leader-role model, whose lifetime work bridges basic science, clinical investigation and practice, endocrine education, and administration. This distinction acknowledges the important impact of the legacy of her contributions and of the bridges built among many countries and continents.



Steven Nagelberg, MD, in practice with Endocrine Metabolic Associates in Philadelphia, received the inaugural Outstanding Clinical Practitioner Award, which recognizes clinical practitioner members of The Endocrine Society who have made extraordinary contributions in medicine and to the public. For almost three decades, Nagelberg has been an outstanding contributor to the field of endocrinology as a clinician, educator, and leader both in Philadelphia and nationally. He exemplifies the best qualities of the physician-in-practice membership of The Endocrine Society. **EN**

EndoCareers

The International Tools for obtaining a U.S. position

“I think you should leave the country.” I’ve always looked back, fondly, on this piece of advice from two of my influential mentors at Barts & the London. I like to think that Professors Monson and Burrin were encouraging me to broaden my horizons, and expand my resume by experiencing academic research in another country. At least, I’m sure that’s what they meant ...

Spending some of your formative years as an academic researcher in another country has long since been an established part of the scientist’s career path. I use the term “career path” very loosely, as there isn’t really much of a path for scientist’s careers in the U.K.; more like a mud track. So, taking the step to go and work abroad is one that many young trainee scientists at least consider early on. And coming to work in the U.S., for so many reasons, is a common choice for many non-U.S. scientists.

Event CALENDAR

SEPTEMBER 19-22: MILAN, ITALY

9th Joint Meeting of
Pediatric Endocrinology
www.jointmeeting2013.org/

SEPTEMBER 23-27: BARCELONA

European Association for the
Study of Diabetes
www.easd2013.com/

SEPTEMBER 24-28: NEW ORLEANS

Clinical Endocrinology Update
Endocrine Board Review
Pediatric Endocrine Board Review
www.endocrine.org/NOLA

SEPTEMBER 24-28: SAN DIEGO

AAFP - American Academy of
Family Physicians
<http://www.aafp.org/events/assembly.html>

Why and When Should You Go

Training and working overseas presents many interesting challenges as well as benefits, so your decision to move abroad shouldn’t be taken lightly. In the U.K., spending time in a U.S. lab (often referred to as getting your “Been-to America (BTA) degree”), has traditionally been seen as a way to enhance your career prospects, by exposing you to a more dynamic research environment (certainly one that has always promised a better funded environment) and the chance to work with prestigious principal investigators whose names you’ll be associated with for several years after you finish working with them. Having said that, some trainees are already well-placed within their current institutes, and perhaps have a career track laid open to them, without the need to move overseas. Whatever your motivation, making the commitment to relocate in order to train abroad can often be seen as an indication of your commitment to science, something that future employers also take notice of when making appointments at the faculty level.

The issue of timing can be critical; when is the best stage of your training to go? There is no right or wrong answer to this, as it depends entirely on what sort of individual you are and what the position is that you’re going to. If you choose to undertake your first post-doctoral position abroad, recently graduated with your PhD, then you need to make sure the lab that you are moving to is going to provide you with the required environment for you to thrive. Personally, I moved to University of California, San Francisco (UCSF) for 16 months, having already completed four years post-doctoral training in the U.K. Consequently, I was relatively experienced and self-sufficient, and found the challenges of deciding what

I wanted to work on (rather than being told what to do) invigorating and refreshing, rather than intimidating. On the other hand, a newly qualified post-doc might prefer to apply for a position that is supportive to their stage of career.

How to Get There

If you’ve made the decision to move to the U.S., great; but the work starts here. Finding a position can take some time, although the opportunities are often much greater in the U.S. than in other countries. There are several ways in which you can find your dream post-doc job. Many labs still advertise up-and-coming vacancies on either their lab Web pages, or through sites such as the EndoCareers® Placement Services. However, many other labs don’t advertise positions—instead, they are frequently approached by trainees, independently enquiring about potential opportunities. This second approach can work well. For example, I spent a little time considering which labs I wanted to work in, then I prepared an “application pack” that consisted of a cover letter, which was specific to the group that I was applying to, my up-to-date resume (CV), and three letters of support from my mentors; from six applications I received eight job offers, which is by no means any indication of how wonderful (or not) my application was, but more that good post-docs are always in demand. Of these eight offers, I chose to meet and interview with three labs, before finally making my decision to join the Ingraham Lab at UCSF. The whole process, for me, took just under six months, from application to receiving a contract.

Being able to visit the group that you want to work with is extremely useful, and something you might consider arranging as part of a trip to the annual ENDO conference (to save the expense of additional airfares). But if you can’t visit the lab of your

Members ON THE MOVE

Zhenqi Liu, MD, professor of medicine and chief of the Division of Endocrinology and Metabolism at the University of Virginia, was named president of the Chinese-American Diabetes Association, which fosters scientific exchange and collaboration among association members as well as developing strong ties with the burgeoning research enterprise in diabetes and obesity within China. Liu currently serves on the *JCEM* editorial board, the Trainee and Career Development Core Committee, and co-chairs the International Endocrine Scholars Program of The Endocrine Society.

William Chin, MD, became executive vice president of Science and Regulatory Affairs for the Pharmaceutical Research and Manufacturers of America (PhRMA). Chin—an internist and endocrinologist—manages the organization's regulatory affairs portfolio, including implementation of the Prescription Drug User Fee Act (PDUFA), clinical trials, and drug discovery and research collaboration, among other key issues. He had served as executive dean for research at Harvard Medical School since 2010, where he fostered interdisciplinary and interdepartmental research, and initiated a new program in therapeutics, including regulatory sciences.

Lovell A. Jones, PhD, will retire at the end of August from his position as the director of the Dorothy I. Height Center for Health Equity and Evaluation Research (DH-CHEER) at the University of Texas M.D. Anderson Cancer Center in Houston. Jones is a leading researcher, working especially to address the inequities in medicine that minorities face, and was the University of Texas M.D. Anderson's first tenured African American faculty member and the first and only African American full professor in the basic/behavior sciences. He says he will be looking at other opportunities to use his knowledge and skills.

IN MEMORIAM

The Endocrine Society this month is sad to announce the passing of three of its members.

William H. Daughaday, MD, died after a protracted illness on May 3, 2013 in Milwaukee. He was 95. As the former director of the metabolism division at Washington University School of Medicine in St. Louis, Daughaday was a prominent and preeminent diabetes researcher. He also contributed trailblazing work in the study of growth hormones. Daughaday served as president of The Endocrine Society from 1971–1972, and for all his extraordinary work, he received the 1975 Fred Conrad Koch Award, the Society's highest honor.

Ernest Louis Mazzaferri, Sr., MD, MACP, a highly decorated endocrinologist and leader in his field, passed away on May 14, 2013. Mazzaferri provided excellent care for his patients, and his contributions to medicine have inspired generations of physicians and faculty to rise to his level of excellence.

Usman Ahmad, MD, FACP, an endocrinologist and diabetes specialist in McKeesport, Pa., died suddenly on Monday, May 27, 2013. He was 67. Ahmad co-founded the University of Pittsburgh Medical Center McKeesport's Lions Diabetes Center and was chairman of the Department of Internal Medicine. Ahmad himself suffered from diabetes and did not hesitate to tell his patients about his own experiences with the disease.

choice, then you should at least e-mail some of the people that work there currently, or recent lab alumni; these people will give you an idea of what life is like in that lab, and often they can be refreshingly honest!

Funding Your Experience

Many people receive their initial funding in the U.S. from the principal investigator of the group that they go to work for. However, there are opportunities to obtain travel fellowships from certain organizations (e.g. The Royal Society, HFSP, EMBO), and there are few things more impressive than turning up at your new lab with your own

salary! If you are not able to bring your own funding, then discuss the option of applying for additional funding once you get to the U.S., as several funding schemes are open to non-U.S. citizens (e.g. AHA, NARSAD, Lalor Foundation). You might not be successful, but it's a good training experience to write a grant (and it impresses your boss, if you can be bothered to try and obtain your own funding!).

The Outcome

So, what do you hope to get out of your time in the U.S.? For many of us who have been on this journey, the experience has served as a stepping-

stone to a faculty position back in our home countries. For others, the lure of staying in the U.S. has proved too strong, and they have made a more permanent transition to working in the U.S. for the long term. Whatever happens, time spent in a good U.S. research group is rarely time wasted, with the contacts and networks that you make proving invaluable in future years as you strive to make a career for yourself as an independent researcher. Was it worth it? For me, I'd do it all again tomorrow, if I could! **EN**

— *Dr. Rob Fowkes, Senior Lecturer, Royal Veterinary College Member, Trainee & Career Development Core Committee*

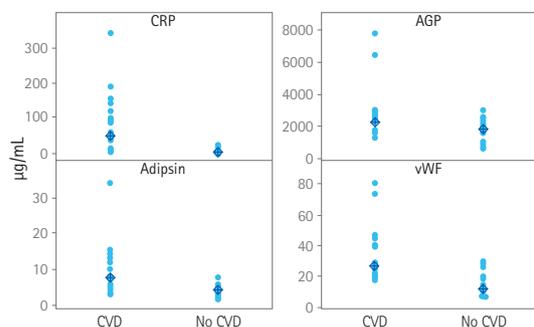
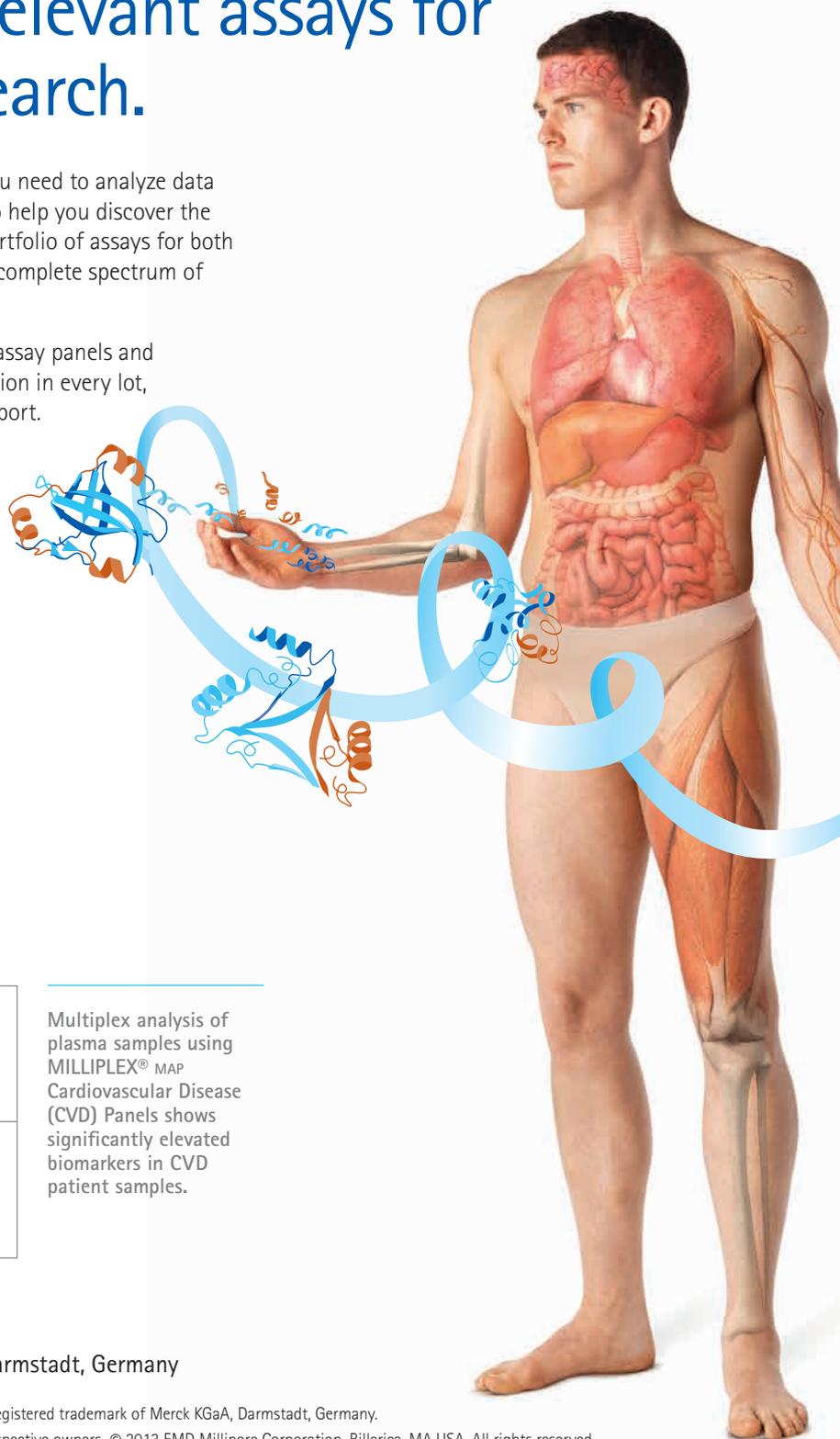
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Traumatic Brain Injury:

Effects on the Endocrine System

WHAT IS TRAUMATIC BRAIN INJURY?

Traumatic brain injury, also called TBI, is sudden damage to the brain. It happens when the head hits something violently or is hit again and again, or when an object goes through the skull and into the brain. Causes include

- Falls
- Motor vehicle accidents
- Violence, such as gunshot wounds, child abuse, or beatings
- Injuries from sports or during combat (such as explosions)

DID YOU KNOW?

The hypothalamus and the pituitary gland are like orchestra conductors. Their job is to tell other endocrine glands throughout the body to make the hormones that affect and protect every aspect of your health.

WHAT IS THE ENDOCRINE SYSTEM?

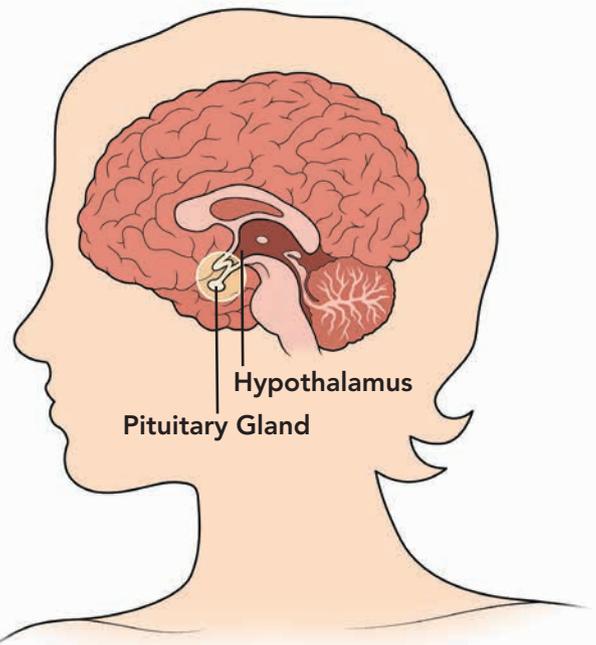
Your endocrine system includes glands and organs that make and release hormones, which are chemicals that help your body work properly. They control growth, sexual development, how your body uses and stores energy (metabolism), how it deals with illness, and more. You need proper types and amounts of hormones to feel well.

HOW CAN TBI AFFECT THE ENDOCRINE SYSTEM?

Two important parts of the endocrine system—the pituitary gland and the hypothalamus—are located in or near the brain. TBI can injure them, causing hormone problems. A person with TBI may have hormone problems right away or months or even years after the injury.

DEFINITIONS

- **Hypothalamus:** a part of the brain that controls the release of hormones made by the pituitary gland
- **Pituitary gland:** located at the base of the brain, it's called the "master gland" because it makes hormones that tell other glands (such as the thyroid or adrenal glands) to make other kinds of hormones
- **Thyroid gland:** found in the neck, it makes thyroid hormones, which control metabolism; helps the heart, muscles, and other organs work properly
- **Adrenal glands:** one located on top of each kidney, they make cortisol, which helps the body cope with stress, illness, and injury



SOME HORMONES MADE BY THE PITUITARY GLAND AND WHAT THEY DO

ACTH (adrenocorticotropin)	Tells the adrenal glands to make cortisol (the "stress" hormone).
ADH (antidiuretic hormone)	Helps control the amount of water in the body.
FSH (follicle-stimulating hormone) and LH (luteinizing hormone)	Help ovaries and testes (testicles) work properly.
GH (growth hormone)	In kids, helps them grow taller, increases muscle, and decreases body fat. In adults, helps metabolism. Helps keep muscle and bone healthy.
Prolactin	Starts breast milk production after childbirth; can affect sex hormones.
TSH (thyroid-stimulating hormone)	Tells the thyroid gland to make thyroid hormones.

WHAT HORMONE PROBLEMS CAN HAPPEN WITH TBI?

Someone with TBI can have one or more problems, depending on the injury. Problems that often occur soon after TBI include

- Adrenal insufficiency: when the adrenal glands don't make enough hormones; results in fatigue, weight loss, low blood pressure, vomiting, and dehydration. Adrenal insufficiency can be life-threatening if not treated.
- Diabetes insipidus: when the pituitary doesn't make enough ADH; results in frequent urination and extreme thirst.
- Hyponatremia: when certain hormone problems upset the balance of salt and water in the body; can result in headache, fatigue, vomiting, confusion, and convulsions.

Problems that may occur later and their symptoms include

- Hypothyroidism (not enough thyroid hormone): fatigue, constipation, weight gain, irregular menstrual periods, cold intolerance
- Hypogonadism (not enough sex hormones): in women, a stop in menstruation and loss of body hair; in men, sexual dysfunction, breast enlargement, loss of body hair, and muscle loss
- Growth hormone deficiency (not enough growth hormone): in adults, increased fat, loss of muscle and bone, and decreased energy; in kids, growth problems
- Hyperprolactinemia (too much prolactin): irregular menstrual periods, nipple discharge, and erectile dysfunction

HOW ARE TBI-RELATED HORMONE PROBLEMS DIAGNOSED?

Your doctor will ask about your medical history and do a physical exam. Blood tests are done to check your hormone levels. You may have an MRI to look at the pituitary gland and check for tumors, cysts, or other problems.

WHAT IS THE TREATMENT FOR TBI-RELATED HORMONE PROBLEMS?

Often, you will take hormones to replace what's missing (called hormone therapy). Other problems require various treatments, such as treating hyponatremia by cutting back on fluid intake, getting an IV (through a vein) salt solution, and taking medicines.

WHAT'S THE LONG-TERM OUTLOOK FOR TBI-RELATED HORMONE PROBLEMS?

The outlook depends on the type of problem and how severe it is. Some endocrine problems may be temporary and disappear within a year after TBI. Hormone therapy is a very important part of treatment. It can restore your health, relieve symptoms, and improve your quality of life. In some cases, it can save your life.

Questions to ask your doctor

- What specific hormones are affected by my injury and how can they be replaced?
- Will treatment relieve my symptoms?
- How long will I need treatment?
- What are the risks and benefits of the treatment?
- How will I know whether my hormone function is returning on its own?
- How often will I need to be checked?
- Will the dose of hormones change as I get older?

RESOURCES

- Find-an-Endocrinologist: www.hormone.org or call 1-800-HORMONE (1-800-467-6663)
- Hormone Health Network information about pituitary gland disorders: www.hormone.org/Pituitary/overview.cfm
- Mayo Clinic information about TBI: www.mayoclinic.com/health/traumatic-brain-injury/DS00552
- National Institutes of Health information about TBI: www.ninds.nih.gov/disorders/tbi/tbi.htm

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The Hormone Health Network offers free, online resources based on the most advanced clinical and scientific knowledge from The Endocrine Society (www.endo-society.org). The Network's goal is to move patients from educated to engaged, from informed to active partners in their health care. This fact sheet is also available in Spanish at www.hormone.org/Spanish.

Traumatic Brain Injury: Effects on the Endocrine System Fact Sheet



www.hormone.org

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

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TEXAS:

BC/BE Endocrinologist position in Department of Internal Medicine at Texas Tech University Health Sciences Center at El Paso, Texas. Responsibilities include inpatient and outpatient clinical work as well as teaching

residents and medical students in the clinic and hospital setting. Clinical research opportunities for qualified candidates. Competitive salary with excellent benefits. The department is part of a growing and dynamic campus in a bicultural community along the US-Mexico border. Applicants should apply online at <http://jobs.texastech.edu> Requisition no. 88393: Debabrata Mukherjee, MD, Acting Chair, Department of Internal Medicine, Texas Tech University HSC, 4800 Alberta Avenue, El Paso, TX 79905. Tel: 915-545-6627, Fax: 915-545-6634. E-mail: carlos.franco@ttuhsc.edu No J-1.



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Please send curriculum vitae and names of three references to:

Kenneth Cusi, M.D., F.A.C.P., F.A.C.E.
Chief, Division of Endocrinology, Diabetes and Metabolism
Email: Kenneth.Cusi@medicine.ufl.edu

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

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

Prescribing information

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

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

of acute pancreatitis if pancreatitis suspected, Victoza® and other suspect medicinal products should be discontinued. Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm reported in clinical trials particularly in patients with pre-existing thyroid disease. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. No studies on effects on ability to drive and use machinery. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulphonylureas. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products. **Fertility, pregnancy and lactation:** If a patient wishes to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued; use of insulin is recommended instead. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed. **Undesirable effects:** The most frequently observed adverse reactions which varied according to the combination used (sulphonylurea, metformin or a thiazolidinedione) were: Very common (≥ 1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulphonylureas, headache when used in combination with metformin and vomiting when used in combination with metformin and rosiglitazone; Common (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, gastroenteritis viral, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue and pyrexia. GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of; angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Rates of thyroid adverse events - 33.5, 30.0 and 21.7 events/1000 subject years of exposure for liraglutide, placebo and total comparators; Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently reported thyroid adverse events/1000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers:** Victoza® 2 x 3ml pre-filled pensEU/1/09/529/002. Victoza® 3 x 3ml pre-filled pensEU/1/09/529/003. **Legal Category:** POM. **Basic NHS Price:** Victoza® 2 x 3ml pre-filled pens: £ 78.48. Victoza® 3 x 3ml pre-filled pens: £117.72. **Further prescribing information can be obtained from:** Novo Nordisk Limited, Broadfield Park, Brighton Road, Crawley, West Sussex, RH11 9RT. **Date created:** March 2012.

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

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