FEBRUARY 2018

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

Endocrine news

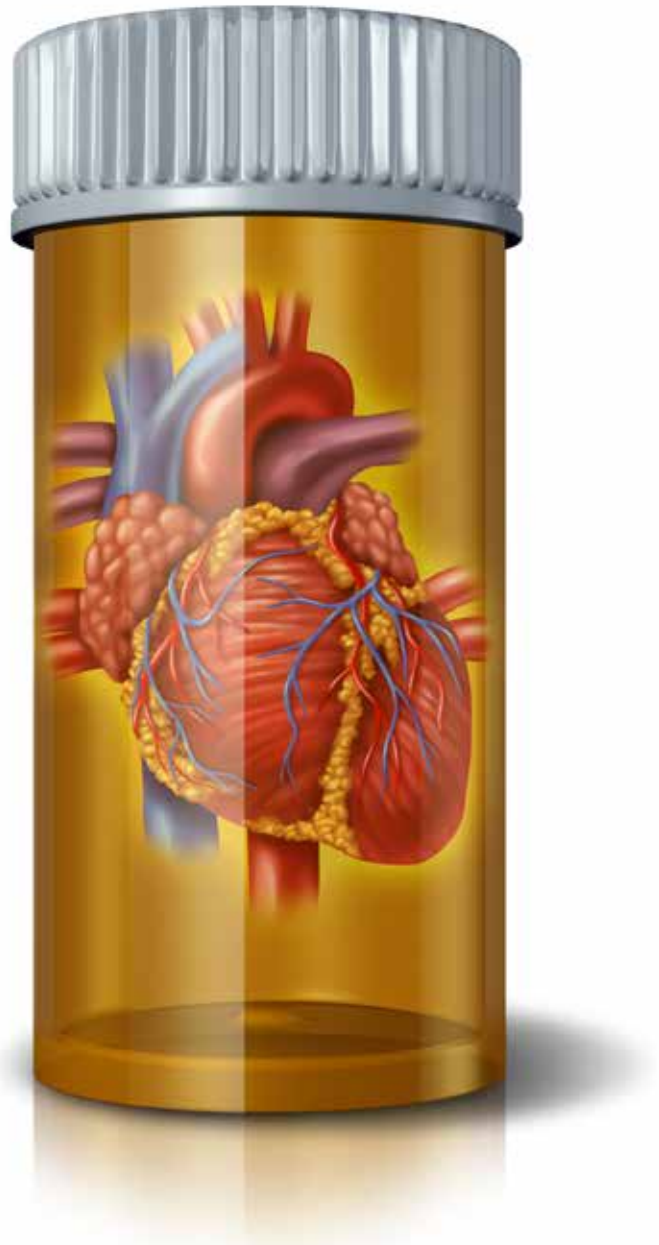
INTERNATIONAL

A Heart to Heart Talk:

The Statin Intolerance Controversy

As **ENDO 2018** quickly approaches, the University of Kentucky's Lisa Tannock, MD, details her Meet the Professor session on statin intolerance and explains why this topic inspires so much passion on both sides.

- **The impact of newly available PCSK9 inhibitors.**
- **Why have clinical trials proven so inconclusive?**
- **Determining when benefits outweigh risks.**
- **How patients can guide treatment protocols.**



YOUNG HEARTS:
Obese youth risk middle-age cardiac death.

MYRIAD COMPLICATIONS:
A closer look at diabetic microvascular disease.

ENDOCRINE SOCIETY
Hormone Science to Health

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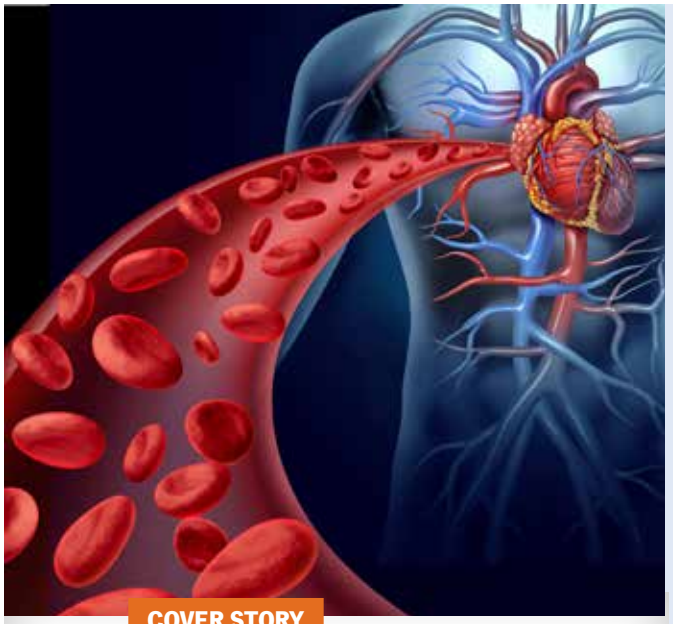

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BY KELLY HORVATH

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ENDOCRINE SOCIETY
Hormone Science to Health

As ENDO 2018 Looms, New Opportunities Bloom

BY THE TIME THIS REACHES YOU, ENDO 2018 will be right around the corner, and with it, the peaceful transfer of the presidency to Susan Mandel, MD, MPH, and the beginning of our implementation of Strategic Plan 4 (SP4). In this letter, I'd like to point out some of the new offerings at the meeting, and to update you on some of the early implementation of SP4.

John Newell-Price, MD, PhD, FRCP, and his able team of co-chairs and steering committee have come up with a dizzying array of offerings at the meeting (March 17-20, Chicago). I love to find out about new things or things that I don't work on myself, and just the symposia titles suggest that this will be a great year. A few examples:

- **Mission to Mars: Will Our Fertility Survive Interplanetary Space Travel and Colonization?**
- **Translating [GPCR] Bias: Moving Functional Selectivity into the Clinic**
- **Novel Sites and Actions of Mineralocorticoid Receptor Signaling: What's New?**
- **Fat on Fire: Role of Adipose Inflammation**
- **Endocrine Systems on a Chip**
- **Exosome Signaling**

This year's Presidential Plenary session, Translating Basic Discovery into Reproductive Health, is a departure from the usual single story about a single seminal development. Andre Ulmann, MD, PhD, this year's winner of the Baxter Prize, will speak on "The Journey of an Entrepreneur, from Hormones to Women's Health" and Diana Blithe, PhD, will review a similar journey: "Male Contraception: Prospects, Clinical Pipeline, and Future Directions." Both talks will illustrate ways in which an important public health goal is achieved through technology transfer.

> "I encourage everyone to visit the meeting website ahead of ENDO 2018 to set up your calendar."

There will be two other sessions related to getting your research results into the public domain. The first is a Career Development Workshop on the entrepreneurial side of science and medicine. Also, I will moderate a new type of session with three other inventors and the director of innovation from Northwestern, who will give a primer on issues related to intellectual property. The others have all "translated" our work in different ways. We hope that these sessions will stimulate your interest in bringing your discovery to market.

I encourage everyone to visit the meeting website ahead of **ENDO 2018** to set up your calendar. You will see that in addition to the explicit "science pathways" that allow you to find cross-cutting sessions in an area of interest, there are also many cross-cutting sessions that examine interactions between systems (particularly inflammation and metabolism). For those of you drawn to all things visual, there are sessions related to the use of imaging technologies in basic and clinical research. I have heard that there will be a new T-shirt for sale, and with the Chicago River dyed green for St. Patrick's Day, I anticipate that there will be something for everyone!

Regarding SP4, we will initially create three new working groups. One will address ways to expand and enhance the clinical practice guidelines to make them more globally relevant, easier to read, and potentially more frequently updated. A second working group, chaired by Dale Abel, MBBS, MD, PhD, will work to identify high-impact initiatives to support basic science. A third group, which I will chair, will make recommendations about the "governance" of the Society. As you know, governance is a term that encompasses the structures and processes that allow us to make policies, set priorities, and carry out those goals. At the Endocrine Society, the over-arching governance is provided by the Officers and Council, and implementation of the goals is carried out by our

member working groups (e.g. committees, task forces) and our talented staff.

The Governance Task Force (GTF) is charged with looking at who we are (our demographics) and what we want to do (SP4), and then considering whether changes in our structure or processes are needed. Since most of the GTF don't think about these things from day to day, we will have

> "I love to find out about new things or things that I don't work on myself, and just the symposia titles suggest that this will be a great year."

the benefit of two experts in governance, our own CEO, Barbara Byrd Keenan, CAE, and Paul Meyer. Similarly, since most of our members don't think much about governance on a daily basis, I am sure that you will be hearing more about the subject. In the meantime, for those of you interested in learning more, we recommend: **https://www.endocrine.org/GovernWell**

I hope to see you in Chicago. EN

— **Lynnette Nieman,** MD, President, Endocrine Society

FROM THE **EDITOR**

Taking Cardiovascular Health to Heart

OUR COVER STORY TAKES A UNIQUE APPROACH THIS ISSUE; not only is it a Q&A but it is also an **ENDO 2018** preview of a Meet the Professor session conducted by Lisa Tannock, MD, who gives us the details on the controversial topic of statin intolerance in "A Heart to Heart Talk" on page 28. Senior editor Derek Bagley spoke with Dr. Tannock about what attendees to her session can expect and why the topic inspires so much passion from people on both sides of this issue and she even says that when she speaks on this topic there are always people in the audience who have completely opposite views than she does. She explains that it's a challenge every time she speaks about statin intolerance: "There's a handful of people, often doctors, who themselves had muscle aches and pains on statins, and used their personal experience. They will challenge me, and I'm not sure I look forward to that challenge, but I expect it and I don't walk away from it. I'm happy to discuss it." Find out what all the controversy is about in Chicago when Dr. Tannock gives her talk on Monday morning March 19 at 9:45 and again at 10:45.

A bit less controversial topic, but no less important, deals with a study published in *The Journal of Clinical Endocrinology & Metabolism* focusing on pediatric patients, which found that heavier children have an increased risk of cardiovascular event death in middle age. In "Young Hearts Run Free," (p. 40) Kelly Horvath spoke with one of the study's authors, Gilad Twig, MD, PhD, who explains that their work was focused primarily on the association between adolescent body mass index (BMI) and cardiovascular mortality (other than CHD or stroke) among young adults. Among other findings, one of the most interesting conclusions the researchers come to is the need to reconsider what is considered a "normal" BMI in children.

In "Untangling the Web" (p. 34), writer Eric Seaborg examines a Scientific Statement from the Endocrine Society that focuses on diabetic microvascular disease. Published in the December issue of *The Journal of Clinical Endocrinology & Metabolism*, "Diabetic Microvascular Disease: An Endocrine Society Scientific Statement" summarizes the state of knowledge as well as best practices in managing diabetic microvascular disease and, not surprisingly, points to hyperglycemia as the major risk factor for developing these myriad complications. According to George L. King, MD, who served on the statement's task force, this new statement is "a go-to site if you don't have time to read a hundred papers on each of the complications. Reading even selected parts of it will give you to a very good, up-to-date understanding of each complication." EN

— **Mark A. Newman**, Editor, *Endocrine News*

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Endocrine Society and SAIC Collaborate at Joint Meeting in Argentina

In November 2017, Endocrine Society members joined researchers and clinicians from 10 Argentine scientific societies for the Joint Meeting of Argentine Bioscience Societies at the Palais Rouge in Buenos Aires, Argentina.

The conference program included poster sessions, symposia, and plenary lectures by internationally recognized experts, including basic and clinical research sessions on topics such as G protein-coupled receptor signaling, stress and reproduction, and metabolic syndrome.

The Argentine Society for Clinical Investigation (SAIC), which was the organizing society for the meeting, is one of the main scientific societies in Argentina, bringing together researchers and scholars from various branches of biomedicine, building insights to translational medicine. The Endocrine Society collaborated with SAIC to deliver several unique sessions highlighting new endocrine research and providing educational opportunities for early career investigators. SAIC president, Graciela Cremaschi, PhD, and treasurer, Roxana Schillaci, PhD, were thrilled to work with the Endocrine Society on innovative new sessions for conference attendees. All of the joint sessions and activities had an energetic and engaged audience with enthusiastic questions and dialogue among presenters and attendees. Many of the attendees were young researchers, postdoctoral fellows, and graduate students who gave very positive feedback on the SAIC and ENDO activities.

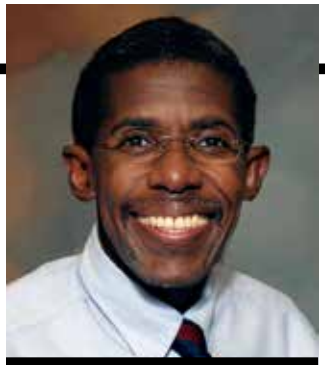
On November 15, Patricia Elizalde, PhD, and Claudia Pellizas, PhD, chaired a joint symposium "Integrating Genomic and Nongenomic Action of Nuclear Receptor Hormones in Physiology and Pathology." Symposium speakers included Endocrine Society members Sandra Incerpi, PhD, Richard Santen, MD, John Cidlowski, PhD, and Cecilia Proietti, PhD. Participants discussed new basic and clinical research on nuclear receptor hormones and took questions from the audience.

On November 16, Santen led a grant-writing workshop, "Grant Writing Pearls for Next-Gen Investigators." Workshop participants received advice on how to clearly communicate their research to reviewers, with a focus on the specific aims section of grant applications. The workshop was filled to capacity, and participants had the opportunity to discuss specific grant-writing issues with Santen and other conference organizers.

Finally, the Endocrine Society and SAIC held a poster competition with a panel of judges including Endocrine Society Members Graciela Diaz, Elizalde, and Santen. The winner was Paula Aliberti, a PhD student from the Servicio de Endocrinología, Hospital de Pediatría Garrahan, CONICET and member of SAIC. Aliberti presented her work on "Gonadotropin independent steroidogenesis in the human prepubertal testis." As winner, she will receive a complimentary registration to **ENDO 2018** in Chicago and an invitation to participate in the KnockOut Rounds Program.

The joint meeting offered the chance for the Endocrine Society to exchange information with attendees in an interdisciplinary setting and meet with international scientists at all career stages. For more information about the meeting and program, please see the conference website at **www.reunionbiociencias2017.com.ar**.

Five Endocrine Society Leaders Join Governing Council


E. Dale Abel, MD, PhD


Henry Anhalt, DO


Ann Danhoff, MD


Stephen M. Rosenthal, MD


Dolores M. Shoback, MD

The Endocrine Society is pleased to announce that five new officers and council members will join the ranks of leaders to help guide the Society's future.

The new officers and council members are: E. Dale Abel, MD, PhD, president-elect; Dolores M. Shoback, MD, secretary/treasurer elect; Stephen M. Rosenthal, MD, council member, clinical scientist seat; Henry Anhalt, DO, council member, physician-in-practice seat; and Ann Danoff, MD, council member, at-large seat.

Abel, the chair of the Department of Internal Medicine and Director of the Fraternal Order of Eagles Diabetes Research Center at the Carver College of Medicine of the University of Iowa, where he holds the John B. Stokes III Chair in Diabetes Research and the François M. Abboud Chair in Internal Medicine, will serve as president-elect in 2018-2019 and then as president in 2019-2020. His research focuses on cardiovascular complications of obesity and insulin resistance.

Abel has received numerous awards for scholarship and mentorship, including the Society's Gerald Aurbach Award for Research, election to the National Academy of Medicine, Distinguished Mentor Awards from the University of Iowa and the University of Utah, and the Established Investigator Award from the American Heart Association. He was appointed to the Advisory Council of the National Heart Lung and Blood Institute in 2016.

Shoback, professor of medicine and associate program director of the Fellowship Program in Diabetes, Endocrinology and Metabolism at the University of California, San Francisco School of Medicine, will serve as secretary treasurer-elect for one year and then begin a three-year term as secretary treasurer (2019-2022). She is active in basic and clinical research involving calcium-sensing receptors and parathyroid disorders. She served as associate editor for *The Journal of Clinical Endocrinology & Metabolism* and co-edited the last three editions of the *Textbook of Endocrinology and Metabolism*.

Shoback has been honored with the Society's Sidney Ingbar Award for Distinguished Service, the Parathyroid Medal from the Fondazione Raffaella Becaglia in Florence, Italy; and the UCSF Class of 2015 Teaching Award for Clinical Faculty. She chaired the Endocrine Society's 2009 Annual Meeting.

Rosenthal will serve a three-year term as vice president, clinical scientist (2018-2021). He is professor of pediatrics at the University of California, San Francisco School of Medicine, has served as program director for Pediatric Endocrinology and director of the Pediatric Endocrine

Clinics, and currently serves as founder and medical director of the UCSF Child and Adolescent Gender Center. Rosenthal is a co-author of the Society's Clinical Practice Guideline on Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons. His research focuses on medical treatment for transgender youth. Rosenthal is immediate past president of the Pediatric Endocrine Society and serves as chair of its Honors and Awards Committee.

Anhalt will serve a three-year term in the physician-in-practice designated seat on Council (2018-2021). He is a physician scientist who has had a career spanning academia, industry, non-profit and most recently biotech at a start-up called Science37 where he serves as vice president of medical affairs. Science37 aims to democratize science by bringing clinical trials to the homes of patients. Anhalt also maintains a practice in Hackensack, N.J. He serves on the editorial boards of *Endocrine Reviews* and *Endocrine News*, and has served on several Society committees, including as chair of both the Hormone Health Network Committee and the Advocacy and Public Outreach Core Committee.

Chief of medicine at the Corporal Michael J. Crescenz Veterans Administration Hospital in Philadelphia, Penn., and vice chair of medicine at the Perelman School of Medicine at the University of Pennsylvania, Danoff will serve a three-year term as an at-large member of Council (2018-2021). She has served as president of the Association of Program Directors in Endocrinology and Metabolism (APDEM) and in that role, she was a charter member of the APDEM/AACE Joint Liaison Education Committee. She has served as the physician-in-practice chair for the Society's annual meetings for the past two years and previously chaired the Society's Trainee Day and its Board Review Course.

The new officers and council members will assume their new positions at **ENDO 2018** in Chicago, Ill., from March 17-20.

JES Articles Now Searchable in PubMed Central, Listed in the *Emerging Sources Citation Index*

Barely one year since its launch, the Society's open access journal, *Journal of the Endocrine Society* (JES), has already achieved multiple major milestones in recognition of its rigorous peer review and value to authors worldwide.

All JES content back to issue 1 is now available in full-text form in PubMed Central, the National Library of Medicine's archive of biomedical and life sciences journal literature. The Society has an agreement to deposit all future JES articles with PubMed Central upon publication in their final form, and they will appear there within a few weeks of deposit. Articles are subsequently indexed in PubMed and receive PMIDs. The arrangement will make JES articles, which are continuously published and freely available to all, significantly more discoverable.

Furthermore, JES has been accepted for inclusion in Clarivate's *Emerging Sources Citation Index*, a part of the Web of Science for newer journals. It is scheduled to appear in the Index by the end of this month. JES is also now included in the highly selective, global *Directory of Open Access Journals* (DOAJ).

The first issue of JES was published in January 2017 and the journal has published more than 180 articles to date. The completed deposit of JES in PubMed Central after just a year, together with the other listings, is a testament to the journal's scientific quality under the leadership of editor-in-chief J. Larry Jameson, MD, PhD, the technical quality of its presentation, and the global reach of its Oxford University Press platform (https://academic.oup.com/jes).

> *Endocrine Reviews'* articles play a key role in ensuring cutting-edge research is leveraged to achieve meaningful advances in public health.

Daniel J. Drucker, MD, Named Editor-in-Chief of *Endocrine Reviews*

Daniel J. Drucker, MD, professor of medicine and the Banting and Best Diabetes Centre-Novo Nordisk Chair in Incretin Biology at the University of Toronto, and a senior scientist at the Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital in Toronto, Ontario, Canada, has been named editor-in-chief of *Endocrine Reviews*.

"It is truly an honor to lead a journal that is such a jewel in the world of scholarly publishing," Drucker says. "*Endocrine Reviews*' articles play a key role in ensuring cutting-edge research is leveraged to achieve meaningful advances in public health."

Drucker's laboratory studies the molecular biology and physiology of gut hormones, with a focus on the glucagon-like peptides. Drucker's scientific studies have identified multiple novel mechanisms of hormone action, enabling the development of new drug classes for diabetes, obesity, and intestinal failure.

A Fellow of the Royal Society, London, Drucker's discoveries have been recognized by numerous scientific and medical societies. He has been honored with the Endocrine Society's Clinical Investigator Award, the American Diabetes Association's Banting Award, the Claude Bernard Award from the European Foundation for the Study of Diabetes, the Manpei Suzuki International Prize, the Rolf Luft Award from the Karolinska Institute, and the Harrington Prize for Innovation in Medicine.

Endocrine Reviews publishes comprehensive, authoritative and timely review articles balancing both experimental and clinical endocrinology themes. The journal features Essential Points summaries for each article and professionally prepared illustrations that can be downloaded for presentations and teaching. The journal's Impact Factor ranks among the top of the more than 100 journals in the "Endocrinology & Metabolism" category of Clarivate Analytics' Journal Citation Reports.

Drucker's term as editor-in-chief will begin July 1, 2018.

ENDO2018

Chicago, Ill.
March 17 – 20, 2018
www.endocrine.org/endo-2018

With over 7,000 attendees, nearly 2,000 abstracts, and over 200 other sessions, **ENDO 2018** is the leading global meeting for endocrinology research and clinical care. Join us for the most well attended and valued translational endocrinology meeting in the world. Bringing together leading experts, researchers, and the most respected clinicians in the field, **ENDO 2018** represents a convergence of science and practice that highlights and facilitates breakthrough discoveries in the field of endocrinology. Spend time connecting with peers and colleagues, exchanging ideas and information, and getting out in front of the latest trends and advancements in hormone health. The meeting also hosts other satellite and pre-conference events.

Key Dates:

- **Housing Deadline:** February 22, 2018
- **Late/Onsite Registration:** March 20, 2018, 2018

2018 ISCD Annual Meeting

Boston, Ma., February 28 – March 3, 2018

The International Society for Clinical Densitometry's Annual Meeting will provide thought-provoking, case-based Plenary Lectures, Ask-the-Expert sessions and special education sessions covering the latest research, diagnosis, treatment and advances in bone densitometry and osteoporosis.
www.icsd.org/

9th International Congress of Neuroendocrinology

Toronto, Ontario, Canada, July 15 – 18, 2018

At the ICN 2018, 64 state-of-the-art speakers and eight plenary lecturers will cover the excitement of modern neuroendocrinology from molecules to behavior, across four main themes – metabolism, reproduction, stress, and timing. Highlights include four concurrent symposium sessions, poster sessions with networking opportunities, and top research in neuroendocrinology from around the world.
www.icn2018.org

2018 Clinical Endocrinology Update East/Endocrine Board Review

Miami, Fla., Sept. - 8, 2018

Each year CEU brings together hundreds of endocrine clinicians for a unique learning experience and opportunities to network with expert faculty and colleagues. Unlike other board preparation meetings, the EBR offers a comprehensive mock-exam format with case-based American Board of Internal Medicine (ABIM)–style questions forming the bulk of the presentations.
www.endocrine.org/ceu

EndoBridge 2018

Antalya, Turkey, October 2 – 28, 2018

Jointly organized by the Endocrine Society, European Society of Endocrinology, and The Society of Endocrinology and Metabolism of Turkey, EndoBridge will provide a comprehensive update in the field of endocrinology. Held on October 25–28, 2018 in Antalya, Turkey, this meeting is designed for the clinical endocrinologist. The official language of the meeting is English, but simultaneous translation will be available in Russian, Arabic, and Turkish.
www.endobridge.org

18th International Congress of Endocrinology and 53rd SEMDSA Congress

Cape Town, South Africa, December 1 – 4, 2018

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) is proud and excited to have been selected to host ICE 2018 together with the 53rd annual SEMDSA Congress. The Program Organizing Committee is currently putting together a stimulating program including cutting-edge academic endocrinology for basic scientists and clinicians, as well as practical clinical sessions empowering doctors with the knowledge to optimize care for their patients with endocrine disorders.
www.ice2018.org

WHY **ENDOCRINOLOGY?**

Everything but Everydayness

BY LIUSKA PESCE, MD, Clinical Associate Professor of Pediatrics, University of Iowa, Stead Family Department of Pediatrics, Division of Endocrinology and Diabetes, Iowa City

I enjoy thinking. I love physiology. I am a listener. I want to work miracles.

My first encounter with endocrinology was in my first year of medical school. I was listening to a lecture explaining the menstrual cycle. I went home and planned to take the hormone-containing pills only; I did not want menstrual bleeding on our family trip to the beach. It worked.

I had several encounters since, knowing physiology works.

As a pediatrics intern, Dr. Randy Poncher asked me about my plans after residency. I said that I was considering a path in endocrinology. He told me that only if I could read, understand, and enjoy the Sperling book on pediatric endocrinology [*Pediatric Endocrinology: Expert Consult,* 4th Edition by Mark A. Sperling MD], that I should consider becoming a pediatric endocrinologist. I bought the book the next day and decided to request my first elective in endocrinology during my internship. I have never made a better decision.

My endocrinology journey has been fulfilled with mentors from the present such as Dr. Sonya Pang, Dr. Ying T. Chan, Dr. Donald Zimmerman, Dr. Reema Habiby, Dr. Mary Kreiter, Dr. Wendy Brickman, and Dr. Peter Kopp. I have also met mentors from the past, such as Dr. Fuller Albright, Dr. Edward Kendall, and Dr. Lawson Wilkins. They all have made an impact in my life. They continue to make an impact in my goal to become a master clinician and be a mentor for the future.

> **“I witness growth, from fetal life into adulthood. I witness the miracle of life. I am also part of it, and continue to marvel by the new discoveries and our better understanding of previously uncharted territories every day.”**

I have been blessed with getting to know kindred spirits who share my passion for the thyroid in the American Thyroid Association and my passion for endocrinology, new knowledge, and education in the Endocrine Society and the Pediatric Endocrine Society.

Ten years have passed since I finished my fellowship. Some days, I walk into a room and I can make a diagnosis just by observing the patient. Some days, I need to ask very good questions and listen. Some days, the most important clue is found after touching the patient. Sometimes, I don't know the right diagnosis, but I keep looking for signs. Then, I order some confirmatory tests. I still feel like a clinician.

I witness growth, from fetal life into adulthood. I witness the miracle of life. I am also part of it, and continue to marvel by the new discoveries and our better understanding of previously uncharted territories every day.

If you would like to share your story with our readers around the world, contact Editor Mark A. Newman at **mnewman@endocrine.org**.

I recently read *The Moviegoer* by Walker Percy and fell in love with the following quote: "The search is what anyone would undertake if he were not sunk in the everydayness of his own life. To become aware of the possibility of the search is to be onto something. Not to be onto something is to be in despair."

> **Some days, the most important clue is found after touching the patient.**

When you can save lives, prevent mental retardation from happening, prevent storms, treat cancer without chemotherapy, save babies before they die at 15 days of life, stop growth plates from fusing, help children grow, change the salt concentration in inner seas, help parents decide about the sex of rearing of their children, change the body of adolescents to make them be who they really are, stop seizures in a moment, re-shape bones, stop bleeding, replace lost hopes after losing them from radiating suns, and stop giants… you know that what you do is everything but everydayness. EN

EDITOR'S NOTE: The opinions and views of the author do not necessarily represent those of *Endocrine News* or the Endocrine Society.

BY DEREK BAGLEY
Senior Editor

High-Fat, High-Sugar Diet May Negatively Impact Fertility

> HFHS rats exhibited irregular estrous cyclicity, with substantially less time in proestrus and more time in estrus compared with the controls. A greater proportion of time spent in estrus is associated with anovulation, reproductive senescence, and impaired fertility.

A high-fat, high-sugar (HFHS) diet may cause obesity-related reproductive dysfunction, according to an animal study that was recently published in the *Journal of the Endocrine Society.*

Researchers led by Natalia Toporikova, PhD, of Washington and Lee University in Lexington, Va., point out that obesity is associated with multiple metabolic and reproductive disorders, but the mechanisms aren't fully understood. "Studies have suggested that impairments in hormone signaling are associated with the development of symptoms such as acyclicity and ovarian cysts," the authors write. "However, these studies have often failed to address how these hormonal changes arise and how they might contribute to the progression of reproductive diseases."

So the researchers fed female rats a HFHS diet to induce obesity and determine changes in critical reproductive hormones. The HFHS rats ate this diet for 14 weeks, and by the end of the study, "HFHS rats exhibited irregular estrous cyclicity, with substantially less time in proestrus and more time in estrus compared with the controls," the authors write. "A greater proportion of time spent in estrus is associated with anovulation, reproductive senescence, and impaired fertility."

The HFHS rats also exhibited impaired estradiol, progesterone, and luteinizing hormone surges before ovulation. "Furthermore, alterations in the basal [progesterone/testosterone] ratio correlated strongly with ovarian cyst formation in HFHS rats," the authors write.

Findings: **Based on these results, the authors conclude that the "HFHS diet resulted in an impaired preovulatory hormonal surge and altered basal hormone levels. An imbalance in basal steroid hormones further correlated strongly with ovarian cyst formation."**

"Thus," they continue, "our model offers a method to examine the morphological and physiological changes that might contribute to the disruption of reproductive cycle. Our study ultimately contributes to the understanding of the direct role that diet plays in the generation of reproductive dysfunction."

Pulmonary Function Should Be Target in Diabetes Care, Researchers Report

Doctors treating patients with type 2 diabetes should consider pulmonary function when providing care to these patients, according to a paper recently published in *Endocrine Reviews*.

The review, by Albert Lecube, of the Universitat de Lleida, Spain, et al, points out that the lung is not usually included in the list of organs affected by type 2 diabetes. However, the authors write, "[the lung's] great vascularization and abundant collagen and elastin fibers make the lung parenchyma a potential target for chronic hyperglycemia." The authors go on to write that there are good reasons to believe the same physiologic problems disturbances that account for complications in other organs may also affect pulmonary function.

According to the review, type 2 diabetes hinders pulmonary function, and that reduced lung function is negatively associated with fasting plasma glucose, glycated hemoglobin, and diabetes duration and severity. Type 2 diabetes also affects breathing during sleep, so it becomes a risk factor for sleep apnea.

Based on this review of the literature, the authors write that the central issue is whether normalizing blood glucose levels can improve lung function and sleep breathing. "However," they write, "only experimental data and pilot interventional studies aimed at exploring the impact on respiratory parameters of some therapeutic options such as the effect of improving glycemic control on sleep breathing are currently available. Therefore, further research on this issue is warranted."

Findings: **There's also the issue of which patients with type 2 diabetes are at risk for pulmonary disease and how to screen for these patients in the most cost-effective manner. The authors also raise the question of whether lung dysfunction will modify therapy for type 2 diabetes and how lung dysfunction and sleep-breathing disorders affect patients with type 2 diabetes. "In summary," the authors conclude, "the current evidence strongly supports the link between [type 2 diabetes] and respiratory dysfunction and indicates that pulmonary function should be taken into consideration by health care providers. Specific pilot screening programs would be very useful for obtaining preliminary results, which could provide further general guidance on this issue. The current evidence points to the lung as an end target for [type 2 diabetes] complications and supports the recommendation that patients with [type 2 diabetes] be considered a vulnerable group for pulmonary dysfunction."**

"Only experimental data and pilot interventional studies aimed at exploring the impact on respiratory parameters of some therapeutic options such as the effect of improving glycemic control on sleep breathing are currently available. Therefore, further research on this issue is warranted."

Common Birth Control Shot Linked to Risk of HIV Infection

Transitioning away from a popular contraceptive shot known as DMPA could help protect women in Sub-Saharan Africa and other high-risk regions from becoming infected with HIV, according to a research review published in *Endocrine Reviews*.

The predominant contraceptive in Sub-Saharan Africa is depot-medroxyprogesterone acetate (DMPA)—a birth control shot administered every three months. Human studies suggest DMPA use may raise the risk of HIV infection by 40 percent. Other forms of contraceptive shots do not show the same correlation with HIV infection. In this article, the authors review the underlying biological mechanisms that could contribute to increased risk of HIV infection for certain hormonal contraceptives but not others.

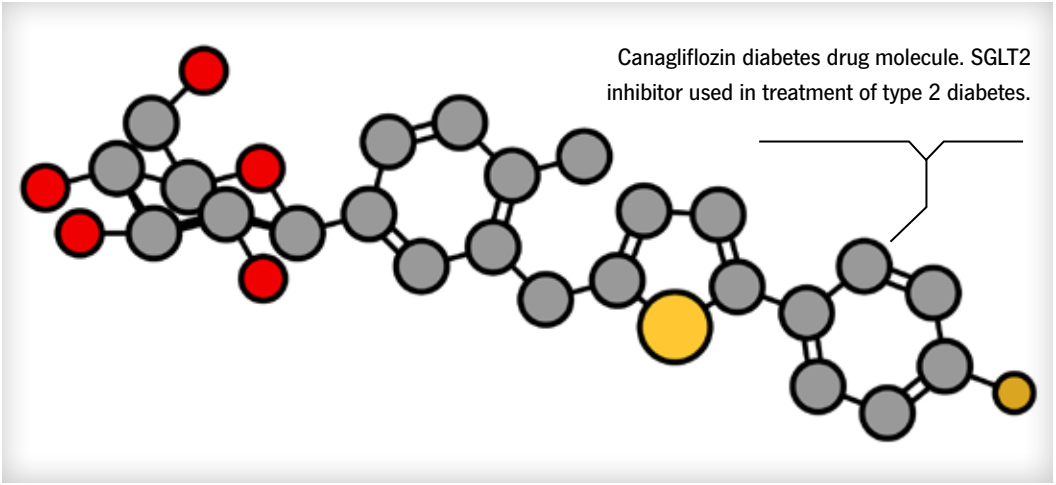
"To protect individual and public health, it is important to ensure women in areas with high rates of HIV infection have access to affordable contraceptive options," says the review's first author, Prof. Janet P. Hapgood, PhD, of the University of Cape Town, South Africa. "Increasing availability of contraceptives that use a different form of the female hormone progestin than the one found in DMPA could help reduce the risk of HIV transmission."

In addition to these clinical studies, the review's authors examined animal, cell and biochemical research on the form of progestin used in DMPA—medroxprogesterone acetate, or MPA. The analysis revealed MPA acts differently than other forms of progestin used in contraceptives. MPA behaves like the stress hormone cortisol in the cells of the genital tract that can come in contact with HIV.

Findings: **"The increased rate of HIV infection among women using DMPA contraceptive shots is likely due to multiple reasons, including decreases in immune function and the protective barrier function of the female genital tract," Hapgood says. "Studying the biology of MPA helps us understand what may be driving the increased rate of HIV infection seen in human research. These findings suggest other forms of birth control should rapidly replace DMPA shots."**

"To protect individual and public health, it is important to ensure women in areas with high rates of HIV infection have access to affordable contraceptive options. Increasing availability of contraceptives that use a different form of the female hormone progestin than the one found in DMPA could help reduce the risk of HIV transmission."

Study Design of CREDENCE, Renal Outcome Trial in Patients with Type 2 Diabetes, Published



Canagliflozin diabetes drug molecule. SGLT2 inhibitor used in treatment of type 2 diabetes.

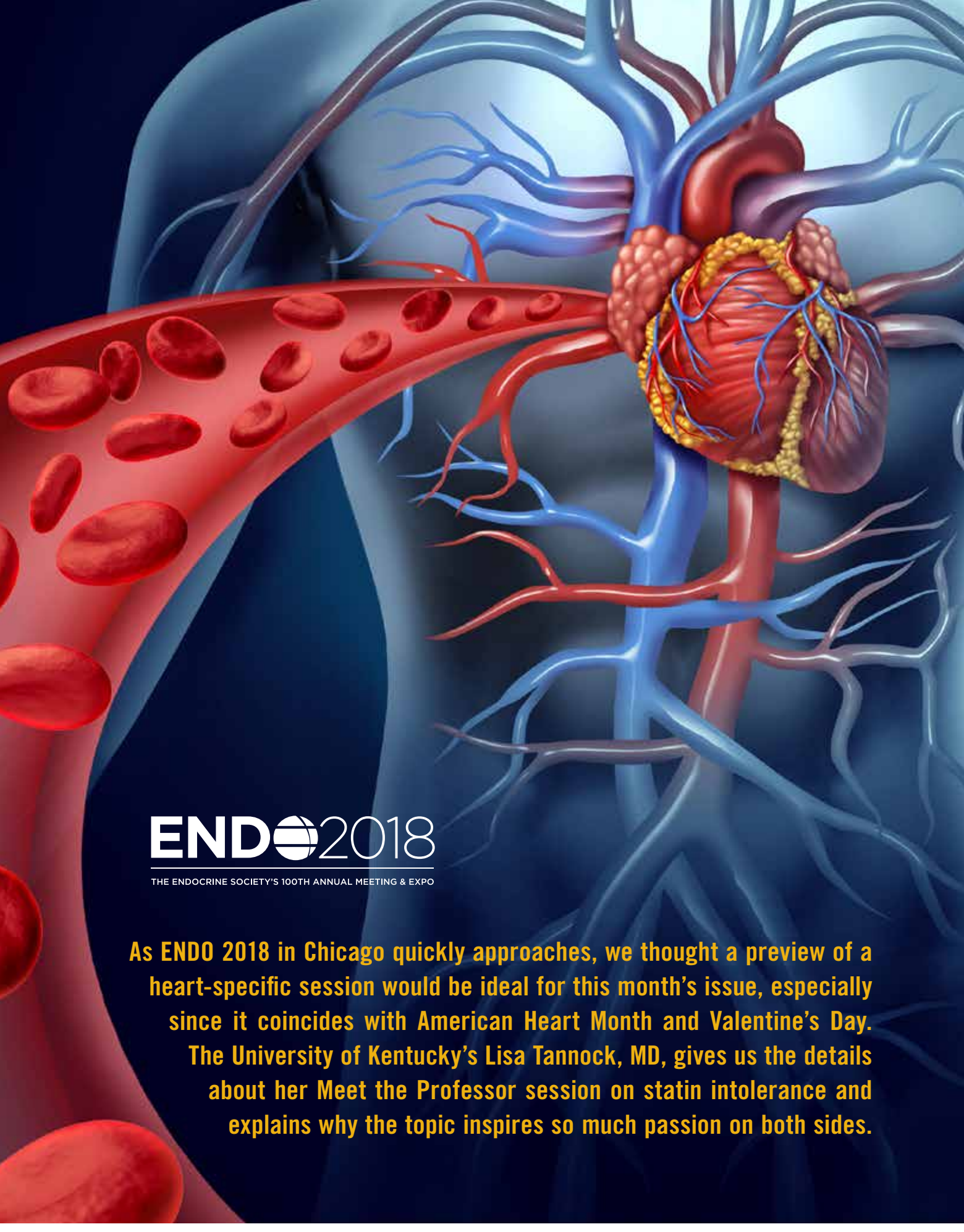
Last month, the *Journal of Nephrology* published an article on the study design of CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Neuropathy Clinical Evaluation), the first dedicated renal outcome trial in patients with type 2 diabetes and kidney disease to explore a hard-primary composite endpoint with an SGLT2 inhibitor.

CREDENCE is a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial conducted in 695 sites across 34 countries in North America, Latin America, Europe, South Africa, and Asia. This trial aims to compare the efficacy and safety of canagliflozin versus placebo at preventing kidney and cardiovascular problems in patients with type 2 diabetes. The study has a projected duration of about 5.5 years, enrolling 4,401 adults with type 2 diabetes.

The estimated glomerular filtration rate ≥30 to <90 mL/min/1.73 m2, and albuminuria (urinary albumin:creatinine ratio >300 to ≤5,000 mg/g). "The study has 90% power to detect a 20% reduction in the risk of the primary outcome (α = 0.05), the composite of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death," write the paper's authors, led by Meg J. Jardine, MD, PhD, FRACP, of the George Institute for Global Health in Newtown, New South Wales, Australia.

Findings: **"In conclusion," the authors continue, the existing evidence base for canagliflozin and other SGLT2 inhibitors in patients with normal or mildly impaired renal function supports a potential benefit for these therapies on renal and cardiovascular outcomes in patients with impaired kidney function. CREDENCE is specifically designed to assess the effects of canagliflozin on renal and cardiovascular outcomes in patients with [type 2 diabetes] at high risk of kidney disease and provide definitive evidence for the effect of SGLT2 inhibition in this population. If the promising preliminary data are confirmed, canagliflozin could lead to a substantial reduction in the global burden of kidney failure due to [type 2 diabetes]."** EN

"CREDENCE is a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial conducted in 695 sites across 34 countries in North America, Latin America, Europe, South Africa, and Asia. This trial aims to compare the efficacy and safety of canagliflozin versus placebo at preventing kidney and cardiovascular problems in patients with type 2 diabetes. The study has a projected duration of about 5.5 years, enrolling 4,401 adults with type 2 diabetes."



As ENDO 2018 in Chicago quickly approaches, we thought a preview of a heart-specific session would be ideal for this month's issue, especially since it coincides with American Heart Month and Valentine's Day. The University of Kentucky's Lisa Tannock, MD, gives us the details about her Meet the Professor session on statin intolerance and explains why the topic inspires so much passion on both sides.

A Heart to Heart TALK

THE STATIN INTOLERANCE CONTROVERSY AT ENDO 2018

BY DEREK BAGLEY

February's focus is on cardiovascular endocrinology, but it's also the month before ENDO 2018 in Chicago.

Lisa Tannock, MD, an endocrinologist and lipidologist at the University of Kentucky in Lexington, will be presenting a Meet the Professor session on statin intolerance, which is sure to lead to some lively discussion, given that the topic is so controversial.

Endocrine News caught up with Tannock to talk about what makes statin intolerance so divisive and get a preview what she plans to present.

Endocrine News: Your Meet the Professor session is on statin intolerance. What should readers know about that?

Lisa Tannock: I guess the biggest thing to know about statin intolerance is that it's very controversial, and it triggers a lot of emotion on both sides. When I speak on this, for example, there's always a few people in the audience who have complete opposite beliefs than I do. Part of the controversy right now is that a new class of drugs called the PCSK9 Inhibitors are now available. They're not indicated for statin intolerance, but prior to their existence, there weren't really good alternatives to patients or providers who thought their patients were statin intolerant. Now these are available, they don't have that indication so it sort of increased the controversy, if you will.

> I guess the biggest thing to know about statin intolerance is that **it's very controversial,** and it triggers a lot of emotion on both sides."

EN: Why is statin intolerance controversial in the first place? If these patients can't tolerate statins, then they need to be treated some other way, correct?

LT: That's the question. Part of the controversy is, what is statin intolerance? The vast majority of the time when we are talking about statin intolerance, we are talking about muscle aches and pains, and there's a number of really good clinical studies that have not found any statistically significant difference in muscle aches and pains between statin users and the people assigned to placebo. And so that's the side that I come down on. In my opinion the clinical trial evidence doesn't show a difference between statin and placebo, and when I get cynical I say, "It's 2018, who doesn't have muscle aches and pains?"

But that's very controversial, and so for people who do have muscle aches and pains, I'm not saying they're not real; I'm just saying that the preponderance of evidence suggests that they're not attributable to statins. I think that's what's very controversial. There's a lot of research, clinical studies, there's been some muscle biopsy type studies, trying to find the pathology of it, and there's an extreme condition called rhabdomyolysis that is real. That's not what we're talking about here. We're talking about muscle aches and pains, usually with no biochemical abnormalities. I'm never saying the pain is not real; it's whether it's truly due to statins or not.

For example, there are studies where they take people who report muscle aches and pains to two or more statins, typically. Then they randomize them, blinded to either statin or placebo and about two thirds of the patients have muscle aches and pains, regardless, and only about one third, if that, have aches and pains only on the statin and not on the placebo. And so maybe there's a very small subset that do have statin-specific muscle aches and pains, but the vast majority of patients who have muscle aches and pains on statins have it also on placebo in these studies.

EN: Do you have patients who refuse to take statins?

LT: That's one of the big issues. A lot of times, patients say, "Oh, I can't take statins, because I have muscle aches and pains," and yet if we could do a blinded placebo controlled study on an individual patient, they might have the same aches and pains to anything we gave them, regardless. That's a challenge and there's a group of providers out there that adamantly believe in this, and they will tell a patient that they're statin intolerant, that they should never, ever take a statin. And in my opinion, the only person who should be told that is someone who has had rhabdomyolysis. It's a challenge for how to manage the cardiovascular risk of these patients, given that statins are so clearly beneficial in so many ways, and up until recently it was a choice only between a statin or really and truly second best, the other lipid-lowering agents we had, which are

ENDO 2018 is happening in Chicago, Ill., March 17-20. For more information, visit **www.endocrine.org/endo-2018**

all a little inferior to statins in terms of the cardiovascular outcomes data that we have.

But with the PCSK9 Inhibitors, these guys are more potent than statins in terms of LDL lowering, and although the studies have only been done in really high-risk patients at this time, they also lower cardiovascular outcomes, so the PCSK9 Inhibitors are a great class of drugs. Incredibly expensive, but there's also a potential market for them for the companies that make them, to recoup some of the [research and development] dollars if they can get the indication for statin intolerance, then that hugely expands their current indications and would hugely expand their market.

EN: Sounds like patients are doing some research themselves.

LT: I don't understand the link, but there's the mind over medicine concept, right? If a patient believes they're in pain, they're in pain. If a patient believes they're not in pain, they're not in pain. There's no way for us to quantify or measure that or test it.

EN: Is there research on the other side? If the patients stopped taking statins, do their aches and pains magically go away but their cardiovascular outcomes get worse?

LT: Yes. If you have a patient with aches and pains on statins and you take their statins away, their aches and pains get better because they're *believing* it's better. We know that cardiovascular disease is higher in non-statin users than it is in statin users.

SEE THE SESSION

Tannock's Meet the Professor session on statin intolerance is on Monday March 19 at 9:45 AM. And again at 10:45.

ENDO2018
THE ENDOCRINE SOCIETY'S 100TH ANNUAL MEETING & EXPO

> **"The vast majority of the time when we are talking about statin intolerance, we are talking about muscle aches and pains,** and there's a number of really good clinical studies that have not found any statistically significant difference in muscle aches and pains between statin users and the people assigned to placebo. In my opinion the clinical trial evidence doesn't show a difference between statin and placebo, and when I get cynical I say, **'It's 2018, who doesn't have muscle aches and pains?'"**

EN: Tell me about your presentation that you're working on for ENDO 2018.

LT: Meet the Professor is usually a case-based discussion, and I've done Meet the Professors on a number of different topics, all lipid related, and usually I try to go through two or three cases, just to share the experience and the alternative plan and what you're able to do with a patient. If a patient refuses to take a statin, what are the alternatives? PCSK9 Inhibitors are one, but then we've got the good old standbys. We've got bile acid resins, niacin, fibrates, and ezetimibe. I talk about the different options that we can do. But part of what I typically try to talk about is some of the success that I personally have had with patients, leading a patient to recognize that they have muscle aches and pains that are independent of the statin use. I had this one patient, years and years ago, who kept a really detailed symptom diary, and what she eventually realized is she still had aches and pains even when she wasn't on the statin, and of course she knew if she was on the statin or not.

When she wasn't on the statin, her symptoms were pretty much the same. It's just that when she was on the statin, she had a target to aim her frustration at. I used that as an example. That was a particularly successful patient who eventually came around to understand that she had muscle aches and pains, no matter what. We never did find a diagnosis and she eventually came around to believe that her cardiovascular risk would be lowered by use of a statin, and chose to go on it, and really per her symptom diary, she continued to have muscle aches and pains but it wasn't worse. And so I try to do that with a lot of my patients and that's an example I usually talk about.

EN: You talked about leading a patient to realize statins are beneficial.

LT: If I have someone who was referred to me with statin intolerance, which is typically the way they get in to see me, my preferred approach is to review which statins they have tried and to try at least one or two more, and to work with the symptom diary when they are on statin, off statin, to try to see if there's a difference. Like I said, one patient in particular said, "I have the same symptoms regardless." Leading someone to self-recognition is a great step. But a lot of times, when I do that, patients say they have symptoms only on that statin, and not when they're not on the statin, and of course I can't do a blinded placebo trial, so they're reporting on their recollections and impressions.

Then I talk about the next approaches, and look at the cardiovascular risk and using the risk calculators — a lot of times these patients have already had a heart attack — that's usually who's sent to me and we talk about all of the other things we can do to try and reduce that risk: blood pressure, aspirin, and quitting smoking, and all those things. Then we talk about the different ways to treat their lipids. I work in Kentucky, and my patient practice is very heavy Medicaid and Medicare, and so I don't have a lot of access to PCSK9 Inhibitor drugs, because it's not what they're indicated for. I think in my practice I have maybe three or four

> **If a patient believes they're in pain, they're in pain. If a patient believes they're not in pain, they're not in pain. There's no way for us to quantify or measure that or test it."**

patients on those right now, so that's not an option for me. A provider who works in a major metropolitan area with a lot of their patients having private insurance may have a lot more access to those drugs. They're great drugs. As far as we know, they're great drugs, and I'm not bashing them, I just don't think they need to be used in many cases.

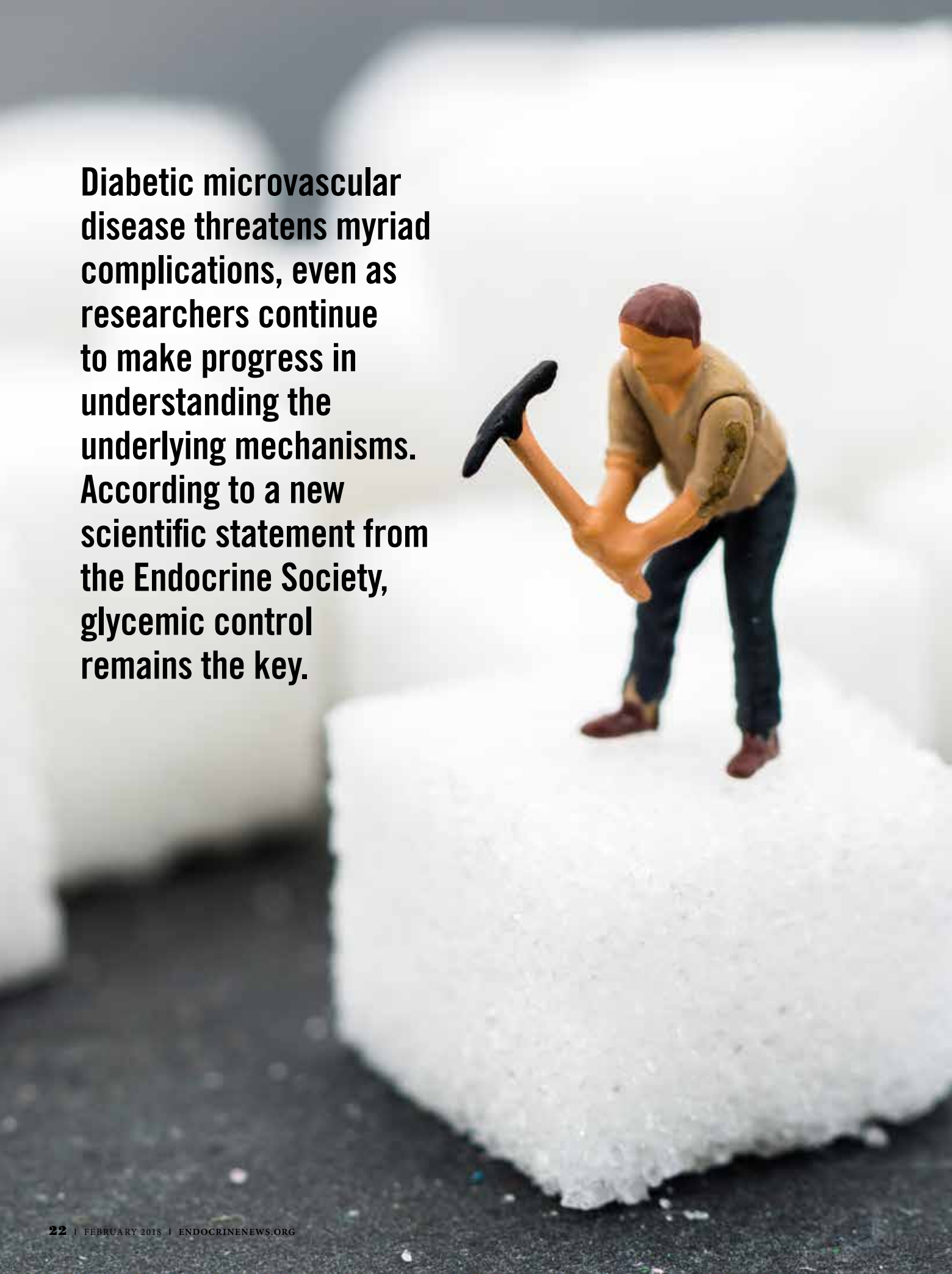
EN: Since this topic is so controversial, I'm sure you're expecting some people to stand up and refute you or ask questions, so what would you say you want to get out ahead of that?

LT: Basically, it's a challenge every time I give a talk on this topic. There's a handful of people, often doctors, who themselves had muscle aches and pains on statins, and used their personal experience. They will challenge me, and I'm not sure I look forward to that challenge, but I expect it and I don't walk away from it. I'm happy to discuss it. I just try to talk about my knowledge of the literature. And you know an anecdotal experience, especially if it's yourself, is a very different experience than what the literature reports on, tens of thousands of patients at this point in all the statin studies.

I gave a talk on this topic at my own institution a year or two ago and one of my colleagues — another internal medicine subspecialist — said that he himself had had debilitating muscle aches and pains on a statin, and what was interesting was that he disclosed that he truly believed it was statin-related, but he also believed the benefits of statins outweighed the risks, and so he had tried every single statin out there and finally found one that he found at least tolerable. And I said, "That's a good point, this is someone who knows — he's a physician, he knows the literature and he knows the benefit and he chose to live with his muscle aches and pains because he thought the benefits outweigh the harm that he was experiencing." So sometimes, we get there. EN

BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. HE WROTE ABOUT THE CONTROVERSIES SURROUNDING IMAGING OF PEDIATRIC PATIENTS TO DIAGNOSE CONGENITAL HYPOTHYROIDISM IN THE JANUARY ISSUE.

Diabetic microvascular disease threatens myriad complications, even as researchers continue to make progress in understanding the underlying mechanisms. According to a new scientific statement from the Endocrine Society, glycemic control remains the key.



DIGGING FOR ANSWERS:

Controlling Diabetic Microvascular Disease

BY ERIC SEABORG

"Vascular complications are the major cause of morbidity and mortality in diabetic patients," according to a new Endocrine Society scientific statement summarizing the state of knowledge and best practices in managing diabetic microvascular disease. Not surprisingly, it points to hyperglycemia as the major risk factor for developing these complications.

"The latest research shows that maintaining tight control over blood sugar levels and blood pressure can help to reduce the risk of complications such as diabetic retinopathy," says Eugene J. Barrett, MD, PhD, of the University of Virginia, who chaired the task force that developed the statement. "The issue is these goals also can put individuals at elevated risk for dangerous episodes of hypoglycemia or cardiovascular complications. Healthcare providers need to balance the competing goals and consider the individual patient's needs to develop an appropriate treatment plan."

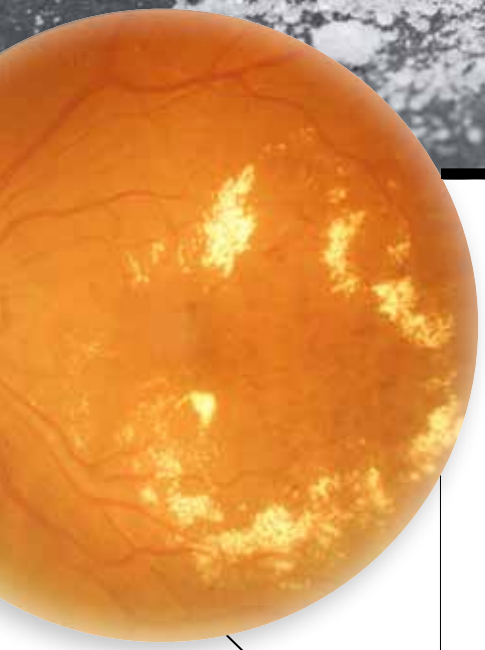
"Diabetic Microvascular Disease: An Endocrine Society Scientific Statement" was published in the December issue of *The Journal of Clinical Endocrinology & Metabolism*. The statement is timely because "multiple levels of breakthroughs have happened in the last 10 years on what could be causing the cells to be dysfunctional when exposed to high glucose," says George L. King, MD, chief scientific officer at Harvard's Joslin Diabetes Center, who served on the task force.

BIOCHEMICAL PATHWAYS OF MICROVASCULAR INJURY

Diabetes affects both injury and repair processes in a manner distinct from other vascular diseases, so the document summarizes both the general molecular processes involved in diabetic microvascular disease and many of their tissue-specific expressions.

It discusses many cellular mechanisms linked to vascular complications: nonenzymatic glycation and the formation of advanced glycation end products (AGEs); enhanced reactive oxygen production and actions; and endoplasmic reticulum stress. Biochemical pathways implicated include the activation of the polyol pathway, excessive oxidants, chronic inflammation, the diacylglycerol–protein kinase C (PKC) pathway, Src homology-2 domain-containing phosphatase-1 (SHP-1), the renin-angiotensin system, and the kallikrein-bradykinin system.

The statement notes that its descriptions generally apply to both type 1 and type 2 diabetes — along with secondary



The "quintessential microvascular complication," diabetic retinopathy is often treated with ACE inhibitors which have shown to reduce the rate of this complication in normotensive patients.

forms of diabetes resulting from genetic mutations, pharmaceuticals, or surgical interventions — because despite the disparate pathogenesis of these conditions, they all share microvascular dysfunction as a chronic outcome.

The statement mainly focuses on injury to the "three classical diabetes microvascular target tissues — the eye, the kidney, and the peripheral nervous system." Not surprisingly, the number one factor in staving off progression of symptoms in all of them is tight glycemic control.

Additional treatments include those "to inhibit the major mechanisms that hyperglycemia activates to induce vascular dysfunction; neutralize accelerants, such as inflammation and oxidative stress; and activate tissue-specific protective factors." The statement also describes recently discovered endogenous protective processes that neutralize some hyperglycemia-induced toxins.

RETINOPATHY

Diabetic retinopathy is considered a "quintessential microvascular complication" with the diagnosis of diabetes resting on the level of blood glucose associated with eye injury. Thus, the "primary method currently used to prevent or retard the progression of diabetic retinopathy is the judicious use of hypoglycemic agents," the statement notes but it also describes the successes and failures of treatments designed to interfere with the biochemical pathways that can lead to damage. For severe forms of retinopathy, inhibitors of vascular endothelial growth factor are playing a critical therapeutic role in preserving vision. Studies have reported that angiotensin-converting enzyme (ACE) inhibitors targeting the renin-angiotensin system and the lipid-lowering nonstatin fenofibrate reduce the progression of diabetic retinopathy in normotensive patients. However, inhibitors of aldose reductase, protein kinase C, and metalloproteinases have not shown efficacy in preventing its progression.

The statement emphasizes the efficacy of intensive glycemic and blood pressure control, but notes the importance that "each person be treated individually, balancing microvascular and macrovascular risk against the risk of hypoglycemia and cardiovascular disease mortality."

> **Treatment should target different aspects of the disease in the following order:** first, underlying pathogenic mechanisms; second, symptoms and improvement in quality of life; and third, the complications of neuropathy and their progression."
>
> — "DIABETIC MICROVASCULAR DISEASE: AN ENDOCRINE SOCIETY SCIENTIFIC STATEMENT"

RENAL MICROVASCULAR DISEASE

"Microvascular renal disease is … a major contributor to the development of end-stage kidney disease (ESKD) in the developed world," the statement says. "Therapies to prevent or slow [its] development are multifactorial and include lowering blood sugar levels with medications, diet, and exercise, as well as treating hypertension and hyperlipidemia."

Agents that block the renin-angiotensin aldosterone system have also been shown to be effective at slowing its development, particularly in patients with high levels of proteinuria, but they do not halt the progression to ESKD. ACE inhibitors and angiotensin receptor blockers also slow the progression of kidney disease but do not stop it, says Barry I. Freedman, MD, professor of internal medicine and chief of nephrology at Wake Forest School of Medicine, who worked on the renal section of the statement.

One of the brightest spots in kidney research has been the identification of genes related to nondiabetic forms of kidney disease — such as the *APOL-1* gene, which contributes to 30%–40% of ESKD in the African-American population. But "it is sobering" that researchers have not been able to reproducibly identify genes with a similar effect in diabetic kidney disease, despite clear evidence that "these diseases run in families," Freedman says.

DIABETIC NEUROPATHY

"Diabetic neuropathies are very common and troublesome complications of diabetes that lead to morbidity and mortality and a huge economic burden for diabetes care," the statement says, but they are underdiagnosed because they can be silent and go undetected while causing damage or they may present with nonspecific symptoms that mimic those of other disease: "Even when symptomatic, less than one third of

AT A GLANCE

- **The three classic targets of diabetic microvascular disease remain the eye, kidney, and peripheral nerves, but complications can involve many other parts of the body.**
- **Maintaining tight glycemic control to slow the development and progression of complications remains the most effective approach.**
- **Therapeutic agents that counter underlying molecular mechanisms are finding increasing success.**

> **The statement is an in-depth, detailed report on some of the major microvascular complications of diabetes.** It's a go-to site if you don't have time to read a hundred papers on each of the complications. Reading even selected parts of it will give you a very good, up-to-date understanding of each complication."
>
> — GEORGE L. KING, MD, CHIEF SCIENTIFIC OFFICER, HARVARD'S JOSLIN DIABETES CENTER, BOSTON

physicians recognize diabetic neuropathy or discuss it with their patients."

"Treatment should target different aspects of the disease in the following order: first, underlying pathogenic mechanisms; second, symptoms and improvement in quality of life; and third, the complications of neuropathy and their progression," the statement says.

Intensive glycemic and metabolic control can significantly influence its progression, but not reverse established neuropathy. Therapies that have shown encouraging results by reducing oxidative and nitrosative stress include benfotiamine (a vitamin B1 prodrug), aldose reductase inhibitors, Metanx (a prescription vitamin-B complex), and alpha-lipoic acid (ALA). In addition to the retinopathy, kidney, and neuropathy segments, the statement also includes sections dealing with microvascular effects on the brain, skeletal and cardiac muscle, adipose tissue, and skin.

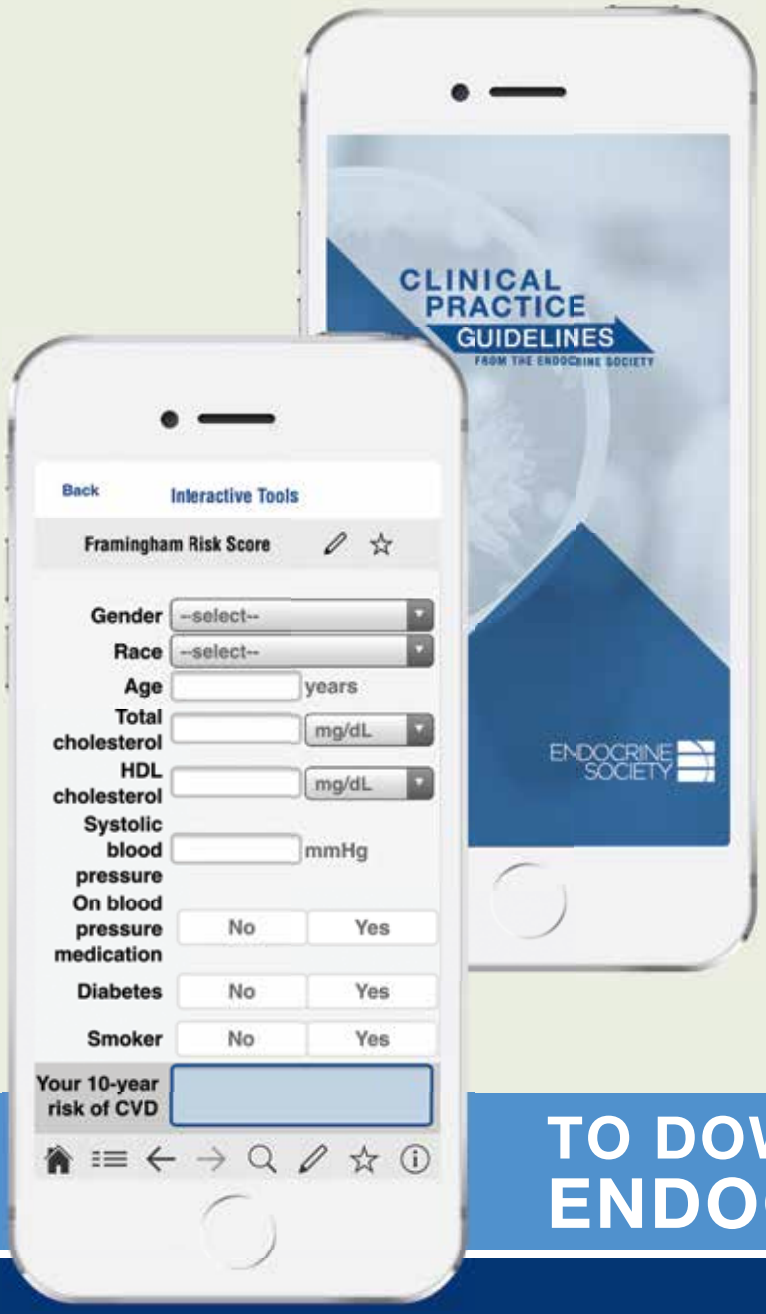
IN DEPTH AND UP TO DATE

"The statement is an in-depth, detailed report on some of the major microvascular complications of diabetes. It's a go-to site if you don't have time to read a hundred papers on each of the complications. Reading even selected parts of it will give you a very good, up-to-date understanding of each complication," King says.

"Diabetic Microvascular Disease: An Endocrine Society Scientific Statement" is available online at **www.endocrine.org/DiabeticMicrovascDisease.** EN

SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA. HE WROTE ABOUT NEW TURNER SYNDROME TREATMENT PROTOCOLS IN THE JANUARY ISSUE.

NEW GUIDELINES ADDED



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ENDOCRINE SOCIETY

A new study shows that heavier adolescents may have an increased risk of succumbing to a cardiovascular event death in middle age. What can be done earlier in life to forestall these events, and should researchers take another look at what constitutes an ideal body mass index for kids?

Young Hearts RUN FREE

(Or Risk Cardiac Death in Middle Age)

BY KELLY HORVATH

February is American Heart Month and generally a time to highlight measures we can take to promote cardiovascular health. In "Adolescent Body Mass Index and Cardiovascular Disease – Specific Mortality by Midlife," however, study authors demonstrate that for some adults, the damage may have been done long ago. Endocrine Facts and Figures reports that a staggering 31.8% of individuals younger than age 20 years are overweight and 16.9% are obese. Even at healthy adult weights, unless they can turn back the clock, it could be too late to mend their broken hearts.

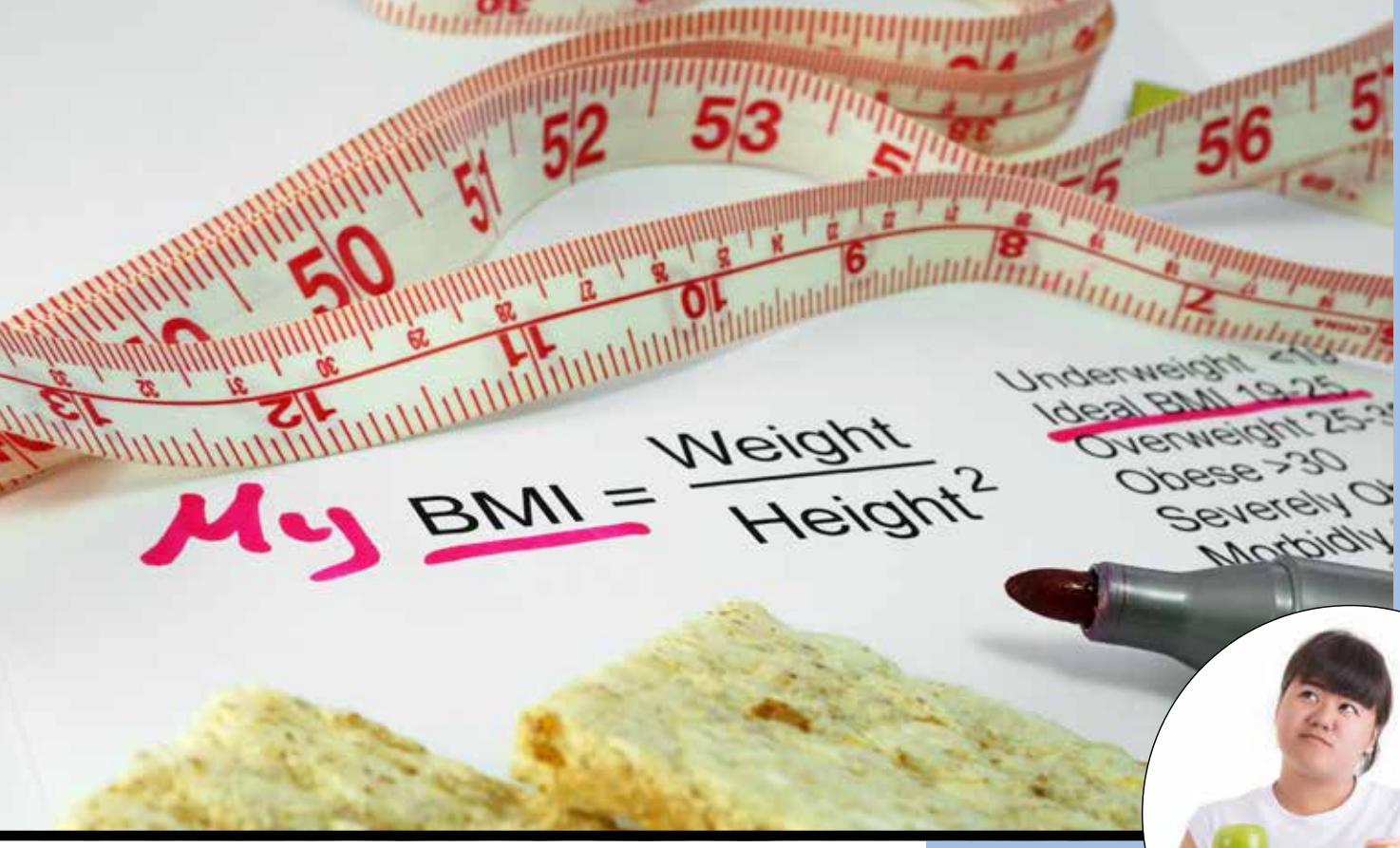
Following Their Hearts

The study, published in *The Journal of Clinical Endocrinology & Metabolism* in August 2017, represented 45 years of follow-up research on more than 2 million adolescents from 1967 through 2010. Recognizing that obesity and overweight in adolescence increases risk for coronary heart disease (CHD) and stroke, researchers sought to determine whether these adolescent conditions predisposed individuals to additional cardiovascular problems. Gilad Twig, MD, PhD, of the Medical Corps of the Israel Defense Forces, and one of the study's authors, explains, "our work focused on the association between adolescent body mass index (BMI) and cardiovascular mortality, other than CHD or stroke among young adults. This is important because while CHD and stroke mortality of adults younger than age 50 have declined in most Western countries in the last two decades, cardiovascular mortality (other than CHD or stroke), has increased. Examples of such causes include pulmonary embolism, heart failure, hypertensive heart disease, fatal arrhythmias, and cardiomyopathy."

Study participants included 2,294,139 Jewish males and nonorthodox Jewish females ages 16 to 19 years (by age 17 years, growth is about 98% complete), who were eligible for mandatory Israeli military service and consequently underwent medical exams. Researchers excluded those for whom BMI measurements were not available and who died before 1981, which is the first year they had access to underlying cause of death data. BMI was calculated by military physicians using World Health Organization (WHO) standardized height and weight measurements. Age- and sex-adjusted U.S. Centers for Disease Control and Prevention (CDC) BMI percentiles, categorized as <5th, underweight; 5th to 49th, low-normal; 50th to 84th, high-normal; 85th to 94th, overweight; and >95th, obese, were a secondary point of analysis.

BMI Reset

They found, perhaps not surprisingly, that BMI was consistently associated with risk for all of the primary non-coronary, non-stroke cardiovascular-specific study outcomes. During the study timeframe, 32,127 deaths occurred, approximately 10% (3,178) of which were attributed to cardiovascular disease: 279 from cardiac arrest and ventricular fibrillation, 122 from hypertensive heart disease, 121 from cardiomyopathy, 114 from arterial disease, 94 from heart failure, and 70 from pulmonary embolisms. Furthermore, the researchers published a study in 2016 using the same cohort that suggested that what is considered normal adolescent BMI, a range from 18.5 to 25.0, might be misleading in terms of masking risk for later cardiovascular disease development. That study found that overweight in adolescence doubled risk of cardiovascular disease–related death in later life.



"Our findings emphasized the devastating consequences of adolescent overweight and obesity, which were strongly associated with increased risk for all study outcomes," Twig says. "The range of normal BMI is relatively broad and we also found here that 'optimal' BMI for 17 years old is at the low-normal range (18.5–22.0 kg/m2)."

Researchers also looked at BMI as a "categorical variable" and demonstrated that increased risk directly correlated with increase in BMI, as evident in progression from high-normal, to overweight, to obese divisions. When the team subjected their results to sensitivity analyses, such as to pre-1981 participants to ensure at least 30 years of follow-up as well as to healthy, cancer-free participants, and differentiated by biological sex, their findings held.

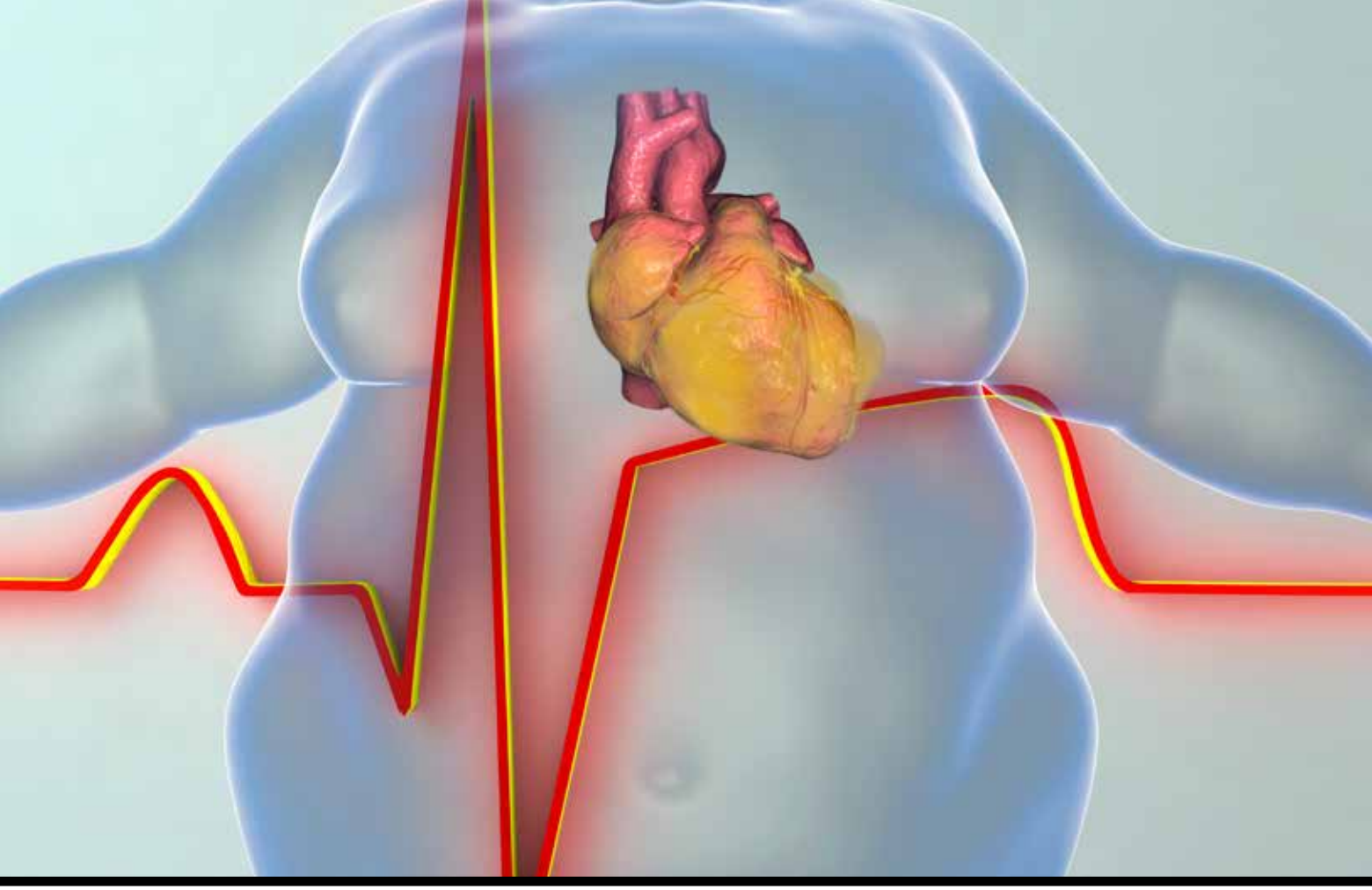
Although the study had limitations, such as lack of adult BMI data, lack of abdominal adiposity data (a measurement well known to confer increased cardiovascular risks independent of BMI), and inability to control for lifestyle habits like exercise and smoking status, its power derives from its use of standardization to measure height and weight rather than relying on subjective recall and its large scale in terms of both sample size and follow-up.

Broken Hearts

According to other studies, this unfortunate link between high adolescent BMI and adult cardiovascular disease may be caused by cardiac remodeling and functional alterations. Associations with undesirable structural changes in the

AT A GLANCE

- **Higher BMI (as well as high-normal BMI) in late adolescence may increase risk of death in mid-adulthood from cardiovascular-specific diseases (i.e., non-coronary, non-stroke related).**
- **Among the cardiovascular disease–specific outcomes (fatal arrhythmia, hypertensive heart disease, cardiomyopathy, arterial disease, heart failure, and pulmonary embolism), hypertensive mortality was most strongly associated with adolescent BMI.**
- **Optimal adolescent BMI is likely lower than previously understood, by both WHO and CDC standards.**



> **Our findings emphasized the devastating consequences of adolescent overweight and obesity,** which were strongly associated with increased risk for all study outcomes."
>
> — GILAD TWIG, MD, PHD, MEDICAL CORPS OF THE ISRAEL DEFENSE FORCES, RAMAT GAN, ISRAEL

arterial wall, increased left ventricular mass, and increased left atrial size, as well as lengthening of the QT interval have been shown and are independent of adult BMI.

"The findings were based on 800 deaths attributed to non-CHD non-stroke cardiovascular causes that were recorded during three decades of follow-up in a population of 2.3 million adolescents (60% men). The findings were strikingly persistent in extensive sensitivity analyses. When taken together with a previous study that was based on this cohort that looked on the association between adolescent BMI and mortality (*New England Journal of Medicine*, 2016 Jun 23;374(25):2430-40), our findings pinpoint the need to narrow what is considered to be the normal BMI range. Nevertheless, additional studies are needed to confirm these results in order to revisit the currently accepted BMI range in adolescents," Twig says.

Future Directions

The team is currently working on several projects that might contribute to the discussion on re-calibrating the normal BMI. "Given that women are generally underrepresented in cardiovascular studies and a significant portion of the literature in this field is limited to men, we will conduct studies that are aimed to peak sex-specific differences," Twig says. They will also be looking at major outcomes such as onset of diabetes, major cardiovascular events, and other chronic diseases. EN

HORVATH IS A FREELANCE WRITER BASED IN BALTMORE, MD. SHE WROTE ABOUT NEW BREAKTHROUGHS IN ENDOCRINE SCIENCE RESEARCH IN THE DECEMBER 2017 ISSUE.

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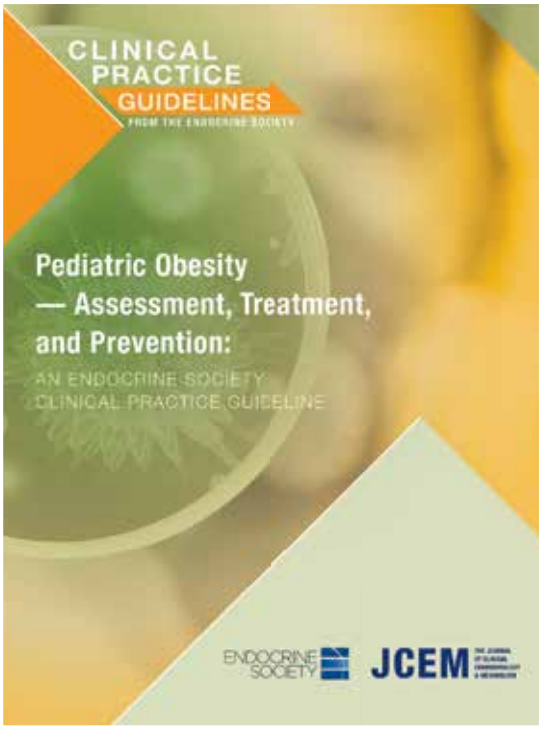

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- Children or teens with BMI ≥ the 85th percentile should be evaluated for related conditions such as metabolic syndrome and diabetes
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- About 7 percent of children with extreme obesity may have rare chromosomal abnormalities or genetic mutations
- Specific genetic testing when there is early onset obesity (before 5 years old)

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BY GLENDA FAUNTLEROY

Millennials IN THE Lab

While much of the media laments millennials and their lackadaisical work ethic, labs are flourishing as they bring new skills that help all generations advance endocrine science.

Millennials have been getting a bad reputation in the press lately. Headlines blame them for "killing department stores" and claim they have an exploitive sense of entitlement. Many Gen Xers (born 1965–1979) also say millennials (born in 1980s and 90s) have shaken up the workplace. The latter, however, may indeed be true as the younger generation of workers are making an impact on what it means to spend the day at work. Millennials will soon represent 44% of the U.S. workforce and here's just some of what's been written about them:

- **More comfortable with technology and automation** — They grew up surrounded by ever-present technology in an era of instant answers.
- **Desire flexibility and work-life balance** — Many are frustrated by traditional office hierarchies, "cube life," and the vague notion of a 9-to-5 job.
- **Multi-tasking is a way of life** — Working with multiple screens and windows while responding to numerous text messages? No problem! The American Press Institute reported that 51% say they are mostly or almost always online and connected.

Endocrine News spoke with two scientists to see what impact millennials were having in endocrinology laboratories as well.

Andrew Demidowich, MD, an adult endocrinology staff clinician at the National Institutes of Health in Bethesda, Md., works with young students and fellows who, he says, possess a wide range of work styles.

"I don't think there is a 'one style fits all' trait that applies to the work habits of millennials working in our laboratory," he says. "Those who progressed from young graduate students to successful senior mentors likely had the greatest determination, work ethic, and drive among their peers. Those who are the most productive and successful actually have very similar work styles to more senior mentors."

While he agrees, however, that millennials are usually more comfortable with technology, he doesn't think they edge older scientists in the ability to do more than two things at once.

"Senior mentors seem more facile at multi-tasking, probably because they have had more time to develop and hone this skill," Demidowich adds.

J. Paige Souder, a fourth-year MD/PhD student working in the lab of Daniel Gorelick, PhD, at The University of Alabama at Birmingham, affirms the idea that work strategies are different between younger and older lab members.

"Perhaps a product of a childhood spent watching TV and a busy-body personality, I will spend a lot of my time working in coffee shops or at home and always with music playing rather than in a quiet office," Souder says. "More senior members of the lab tend to spend more time in the office setting and keep work at work, though work at home is not frowned upon."

She also agrees that her generation is more comfortable with technology and automation. "I think primarily because we were born into a society dominated by technology and have grown up with it, particularly during a time while it is rapidly advancing, so we are used to adapting to changing software/interfaces/machinery and using it immediately," Soulder says. "This is advantageous in a lab setting where new technologies are arising and we are not only eager to use them, but equipped to adapt to them quickly and use them for new discovery."

Souder can set her own hours in the lab and says as long as she works hard while there, she can make time to have a well-balanced life as well.

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— ANDREW DEMIDOWICH, MD

"One example is working on the weekends," she says. "I can leave the lab at 4 or 5 pm to go walk my dog or catch a weekday concert, but I compensate for this by going into the lab late at night or on the weekend, and there is rarely a weekend I don't go into the lab for a least a couple of hours. Our lab manager, however, who is nearing retirement consistently works 9 to 5 plus or minus an hour and has his weekends completely free."

With these differing work styles between these two age groups, managers often question how best to manage the younger generation. A recent *Forbes* article offered a few tips:

- **Provide opportunities for learning and development. Frequently assign new and different projects.**
- **Be mentors, not bosses. Millennials' upbringing has been much more lax and permissive, so they do not respond well to rigid protocols or displays of power. Rather, they need their leaders to be approachable, to encourage and guide them.**
- **Recognize their need for recognition. Offer words of approval and regular feedback.**
- **Don't hinder the use of technology and social media. Take advantage of it with inverse mentoring programs that could help older employees learn from millennials' technological skills.** EN

FAUNTLEROY IS A MEDICAL EDITOR AND WRITER WITH MORE THAN 20 YEARS' EXPERIENCE. SHE HAS BEEN A REGULAR CONTRIBUTOR TO *ENDOCRINE NEWS* SINCE 2010.

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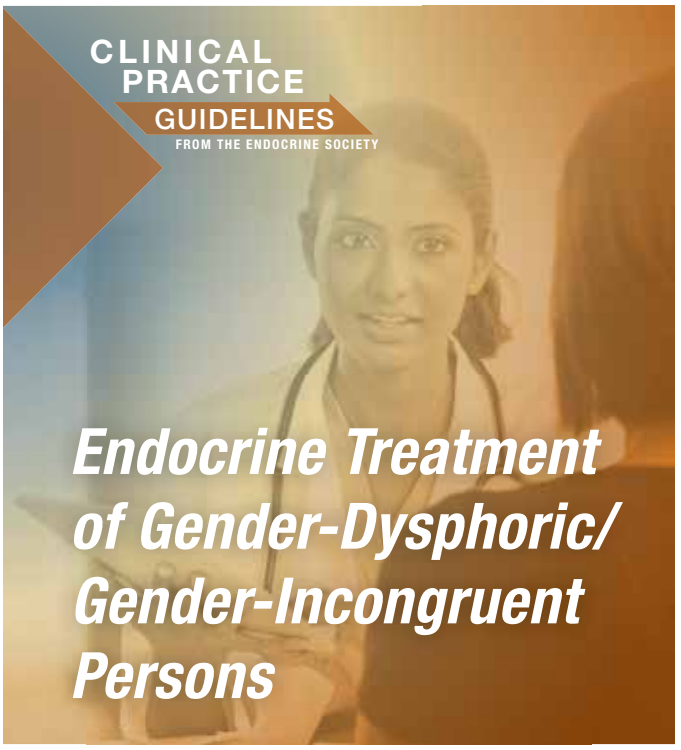

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The Latest Clinical Practice Guideline Recommends:

- Adolescents with Gender Dysphoria/Gender Incongruence may block and replace their sex steroids with those of the appropriate gender.
- Adults for whom gender change is recommended may suppress sex steroids and replace with those of the appropriate gender.
- Gender Dysphoric/Gender Incongruent persons may have surgery to enhance the appropriate gender.

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Continuing Resolution Passes; SDP Renewed

Earlier this month, Congress passed a Continuing Resolution (CR) that will keep the federal government open through March 23. Included in this legislation was a provision to renew the Special Diabetes Program (SDP) for two years at $300 million per year and a sweeping bipartisan budget deal that raises existing federal spending caps to free up billions of dollars for priority issues, including: increasing funding for the National Institutes of Health (NIH), extending the Children's Health Insurance Program, and closing Medicare Part D's "donut hole" in faster. Both renewal of the SDP and raising the budget caps were legislative priorities of the Society. We are very proud of these victories, which will benefit our members, endocrine research, and patients.

Over the past year, the Society has been a leader in calling for funding for the SDP. We met with Representatives and Senators, conducted educational briefings for Congress with the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), sent letters to Congress, engaged in social media campaigns, and rallied our members to contact their members of Congress about the need to fund the SDP. We also worked closely with the leaders of the Congressional Diabetes Caucus to renew SDP alongside the February 8 CR and we were instrumental in adding language to ensure NIDDK research would not be disrupted this year.

We also worked as a tireless advocate for raising the budget caps – a measure that was necessary if we were to achieve any increase for NIH funding. The budget agreement includes a commitment to provide $2 billion for important research at NIH (above CURES Act increases) over two years. We will continue to work to further increase NIH funding when the Appropriations Committees finalize spending decisions for FY 2018 before March 23 and also to increase NIH funding during the FY 2019 appropriations process that will begin immediately after.

Thank you to all of our members who participated in our various advocacy efforts. Your emails, calls, and visits helped achieve our goals! Please join us in thanking your representative and senators for their support for SDP and NIH by participating in our thank you campaign: **www.endocrine.org/advocacy/thankyouletter**

Learn How YOU Can Make a Difference at New ENDO 2018 Advocacy Session

Do you want to learn how to impact policy that affects your patients, practice, or research? Would you like to become more involved in the Society's advocacy efforts? If so, you should join us at **ENDO 2018** for a special session hosted by the Advocacy and Public Outreach Core Committee (APOCC).

The purpose of the session is to discuss the Society's advocacy priorities, how we achieve our "wins," and how you – our members – can be involved in the process. We will offer four different ways for you to participate, including: advocacy opportunities in Washington, D.C., sharing your expertise to advise us on policy and position statements, and using social media as an advocacy tool. This is also a great opportunity to hear from seasoned "endocrine advocates" about their experience in impacting policy both on Capitol Hill and from the comfort of their own home.

The session takes place on Saturday, March 17 from 12:00-12:50 p.m. in the Science Hub. If you have questions or would like to participate in this session, please write to the Government & Public Affairs department at **govt-prof@endocrine.org.** We hope you will join us!

Endocrine Society Weighs In on EDC Criteria Implementation in the European Union

Following the announcement of revised criteria for the identification of endocrine-disrupting chemicals (EDCs) in pesticides and biocides, the European Commission requested that the European Food Safety Agency (EFSA) and European Chemicals Agency (ECHA) develop a guidance document for implementation of the EDC criteria. On December 7, 2017, EFSA and ECHA announced a public consultation to collect broad stakeholder input on the draft document.

Endocrine Society members have been highly engaged throughout the development of the EDC criteria through approval by the European Parliament. Recognizing the importance of having accurate guidance to inform an efficient and effective implementation of the criteria, the Society's EDC Advisory Group established a Guidance Document Task Force, comprising experts in the science and health effects of EDCs and led by Tom Zoeller, PhD. The Task Force was charged with reviewing the draft Guidance Document and preparing a formal response to ensure that the latest endocrine science is reflected in EDC identification processes and regulatory decision-making.

Prior to the announcement of the public consultation, EFSA and ECHA revised previous versions of the draft working with European Member State experts and stakeholders from industry and non-governmental organizations (NGOs). The Society's Task Force viewed the current draft as a well-written and practical potential approach to scientific identification and regulation of EDCs. However, the Task Force emphasized several important points and potential sources of concern that EFSA and ECHA would need to clarify or address to improve the ability of agencies to identify EDCs. In our comments, we encouraged the authors of the guidance to:

- **Better define the elements of hazard characterization that are part of the identification process;**
- **Ensure chemicals that interfere with hormone action are able to be identified based on a realistic standard of scientific information, reducing the potential for false-negatives as well as false-positives;**
- **Ensure that the scope of the document incorporates all potential endpoints that are relevant to endocrine disruption, with periodic reviews to update the guidance in response to new scientific information; and**
- **Make improvements to the section on the thyroid pathway to ensure that this important pathway is properly evaluated**

We also expressed reservations about the utility of Adverse Outcome Pathways (AOPs) in the context of an identification scheme, because AOPs may not be fit for the purposes described in the guidance document, and we expect that data submitted by manufacturers and gathered from the scientific literature will be insufficient to characterize an entire pathway.

The European Commission, EFSA, ECHA, and relevant agencies will continue to conduct stakeholder outreach and hold meetings to improve the guidance document until a final version is issued. Detailed information about the guidance document can be found on the EFSA website at *www.efsa.europa.eu*. To see the Society's detailed comments, we encourage members to visit the Endocrine Society advocacy website at **https://www.endocrine.org/advocacy**.

To stay up to date on the latest congressional actions and Society advocacy, please look for updates on* Endocrine News *online and Society advocacy alerts.

Endocrine Society Advocacy Wins Expanded Access to Diabetes Technology

On January 5, the Centers for Medicare & Medicaid Services (CMS) issued guidance clarifying that Medicare Part D plan sponsors may provide coverage for newer insulin delivery devices that are not covered under Medicare Part B as part of the Part D prescription drug program. The guidance will give people with diabetes greater access to a wider range of insulin delivery devices, and allows older Americans to gain coverage for devices such as the Omnipod® Insulin Management System. Previously, people with diabetes who qualified for Medicare at age 65 had to pay out of pocket to continue using the Omnipod, and many lost access to the device.

The Society has long been a champion of improving access to and coverage for lifesaving devices for people with diabetes, and has met with numerous policy makers and regulators about this issue over the past several years. Such access gives people with diabetes the freedom to choose the device that best suits their individual needs and helps them manage the chronic condition.

Endocrine Society Hosts First Meeting of the Hypoglycemia Prevention Initiative

The Endocrine Society's Hypoglycemia Prevention Initiative took a major step toward clinical testing with the first on-site meeting of the group's steering committee at the Society's headquarters in Washington D.C. The Department of Health and Human Services has identified hypoglycemia as one of the top three preventable adverse drug events in the U.S. and the Society has been working with Avalere Health to develop strategies to address this growing clinical problem.

Led by committee chair, Jeff Boord, MD, MPH, chief quality officer, Parkview Health, Fort Wayne, Ind., the members reviewed current data regarding the prevalence, cost, and complications of hypoglycemia in people with type 2 diabetes, as well as existing strategies aimed at prevention. The discussion then turned to the specific research questions, along with the primary and secondary interventions that will be the focus of the group's pilot study.

"Through active partnership with stakeholders in the Society, primary care, and diabetes education, I believe that we can develop practical strategies and quality measures that address and mitigate hypoglycemia for at-risk patients with type 2 diabetes,"

> **“The task of improving diabetes care through reducing treatment-related hypoglycemia is a challenging one.”**

Boord says, commenting on what he hopes to accomplish as the committee's chair.

The committee chose to limit its pilot study to older patients with type 2 diabetes who are on insulin or sulfonylureas and have specific risk factors for hypoglycemia. Since most of these patients are cared for by primary care physicians, the pilot program will target that practice environment. The study will be designed to incorporate hypoglycemia assessment and possible changes in glycemic goals into existing clinic workflows.

“The task of improving diabetes care through reducing treatment-related hypoglycemia is a challenging one,” Boord says, adding “but the passion, experience, and commitment of the stakeholders on the committee makes me optimistic that we can achieve that task together.” EN

(top) The Society staff and members of the Hypoglycemia Prevention Initiative Committee spent a day collaborating in the Endocrine Society offices last month for the committee's first on-site meeting. Among the topics discussed were research issues, prevention strategies and costs, and launching a pilot study in older patients with type 2 diabetes who have specific hypoglycemia risk factors.

(bottom) Participants in the Hypoglycemia Prevention Initiative meeting are (Back row, l to r): Jesse Bushman, Ken Snow, Jeffrey Boord, Lawrence Dardick, Jamie Rosenzweig, and (front row l to r): Kathleen Dungan, Hope Warshaw, and Deborah Koehn.

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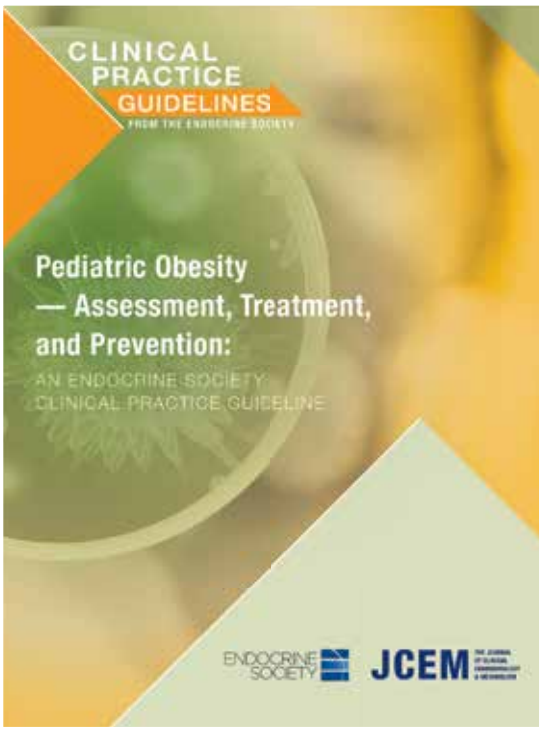

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HORMONES AND YOUR HEART
WHAT YOU NEED TO KNOW

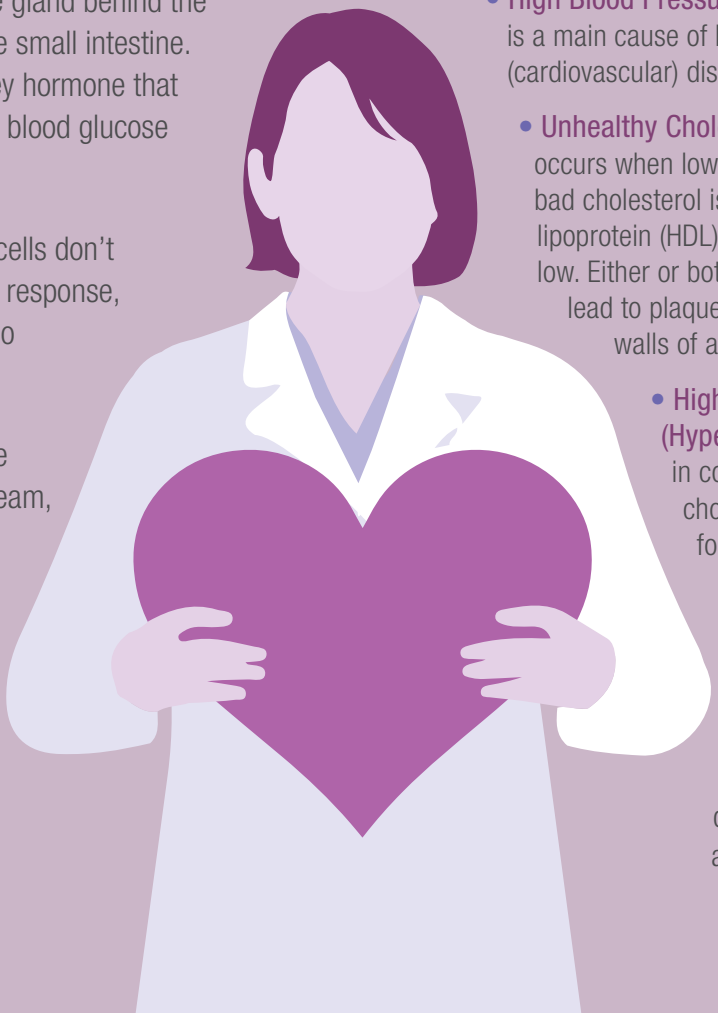
The endocrine system is a network of glands and organs that produce, store, and secrete hormones. Hormones influence many aspects of the cardiovascular system, which includes the heart and blood vessels. While hormones play a key role in maintaining cardiovascular health, high levels of some hormones can contribute to cardiovascular disease.

HORMONES AND HEART FACTS

The pancreas is a large gland behind the stomach and next to the small intestine. It produces insulin, a key hormone that "opens" cells to receive blood glucose needed for energy.

Insulin Resistance — cells don't "open" normally and, in response, the pancreas creates too much insulin.

When too much glucose remains in the bloodstream, you can develop type 2 diabetes and cardiovascular problems, including unhealthy cholesterol levels, high blood pressure, and heart disease.



CARDIOMETABOLIC RISK FACTORS

- High Blood Pressure (Hypertension) is a main cause of heart and blood vessel (cardiovascular) disease
- Unhealthy Cholesterol (Hyperlipidemia) occurs when low density lipoprotein (LDL) or bad cholesterol is too high and/or high density lipoprotein (HDL) or good cholesterol is too low. Either or both of these changes may lead to plaque accumulation on the inner walls of arteries
- High Triglycerides (Hypertriglyceridemia) in combination with unhealthy cholesterol may add to plaque formation on the walls of arteries
- Metabolic Syndrome is a cluster of risk factors (high blood pressure, high blood triglycerides, low HDL, increased abdominal fat) that increase the chances of developing heart disease, stroke, and diabetes

Visit hormone.org for more information.

Additional Editing by Robert M. Carey, MD, MACP, *University of Virginia*
Sources: American Heart Association

Hormone Health NETWORK®
FROM THE ENDOCRINE SOCIETY

YOUR DOCTOR CAN DETECT RISK FACTORS BY TAKING KEY MEASURES OF YOUR OVERALL HEALTH. HERE ARE HEALTHY RANGES:

Measure	Healthy Range
Waist circumference	under 40” (men); under 35” (women)
Triglycerides level	under 150 mg/dL
Fasting blood glucose level	under 100 mg/dL
Blood pressure	under 120 mm Hg (systolic) and 80 mm Hg (diastolic)
High-density lipoprotein (HDL) cholesterol	over 40 mg/dL (men); over 50 mg/dL (women)
Low-density lipoprotein (LDL) cholesterol	under 100 mg/dL

DID YOU KNOW?

Cardiometabolic problems often come from low activity levels and the foods we eat, but other factors — your genes, hormonal diseases, and certain medications — can also contribute to these conditions.

At least **68%** of people age 65 or older with diabetes die from some form of heart disease and **16%** die of stroke.

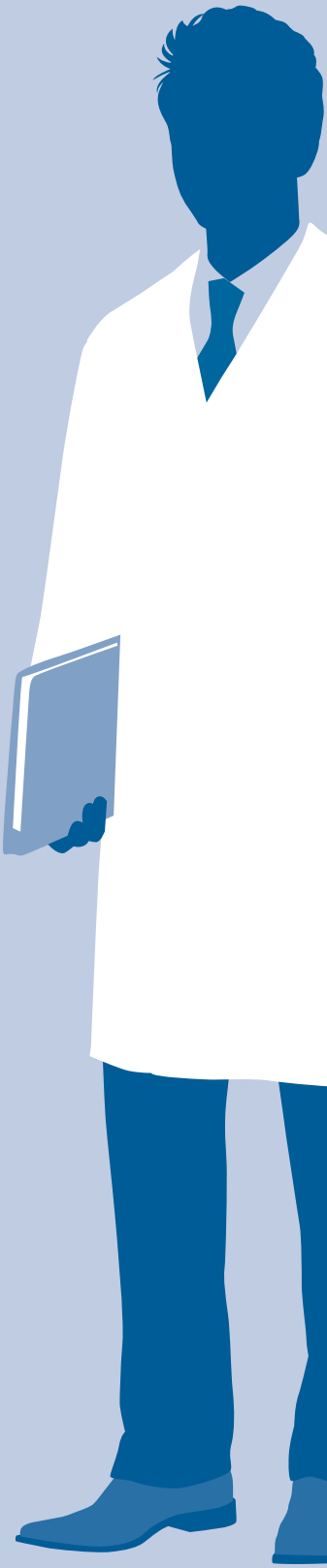
Adults with diabetes are **2-4** times more likely to have heart disease.

Diabetes is **1 of 7** major controllable risk factors for cardiovascular disease.

KNOW YOUR RISKS FOR HEART DISEASE:

- 2 to 4 times more likely to have heart disease or stroke if you have diabetes
- 1.8 times more likely to be hospitalized for a heart attack if you have diabetes
- 3 times more likely to have a heart attack if you are a woman with diabetes
- 2 times more likely to have a heart attack if you smoke

Source: American Heart Association



TREATMENT

A heart-healthy diet and brisk physical activity are nearly always part of a treatment plan for cardiometabolic risk factors. For many, medications will also be part of the plan. Be sure to follow your treatment plan exactly as your doctor prescribes so you can control your cardiovascular risk factors.

7 SIMPLE STEPS TO PREVENTION

- Control cholesterol
- Manage blood pressure
- Reduce blood sugar
- Eat right
- Lose weight
- Get moving
- Stop smoking

Source: American Heart Association

Hackensack University Medical Center

One of the nation's foremost leaders in diabetes care and research

A recipient of four Joint Commission awards for advanced inpatient diabetes care, Hackensack University Medical Center is at the forefront of diabetes research and treatment.

Certified by the ADA, our inpatient program upholds the highest standards of care with a less than 2% incidence of hypoglycemia. Our stem cell research has led to Stem Cell Educator therapy where cord blood stem cells from a healthy donor "educate" damaged cells how to once again create insulin. And, working together with our bariatric surgery program, we've helped 60% of obese patients achieve remission of diabetes, including normal A1C levels and elimination of medication.

To learn more about our program, visit
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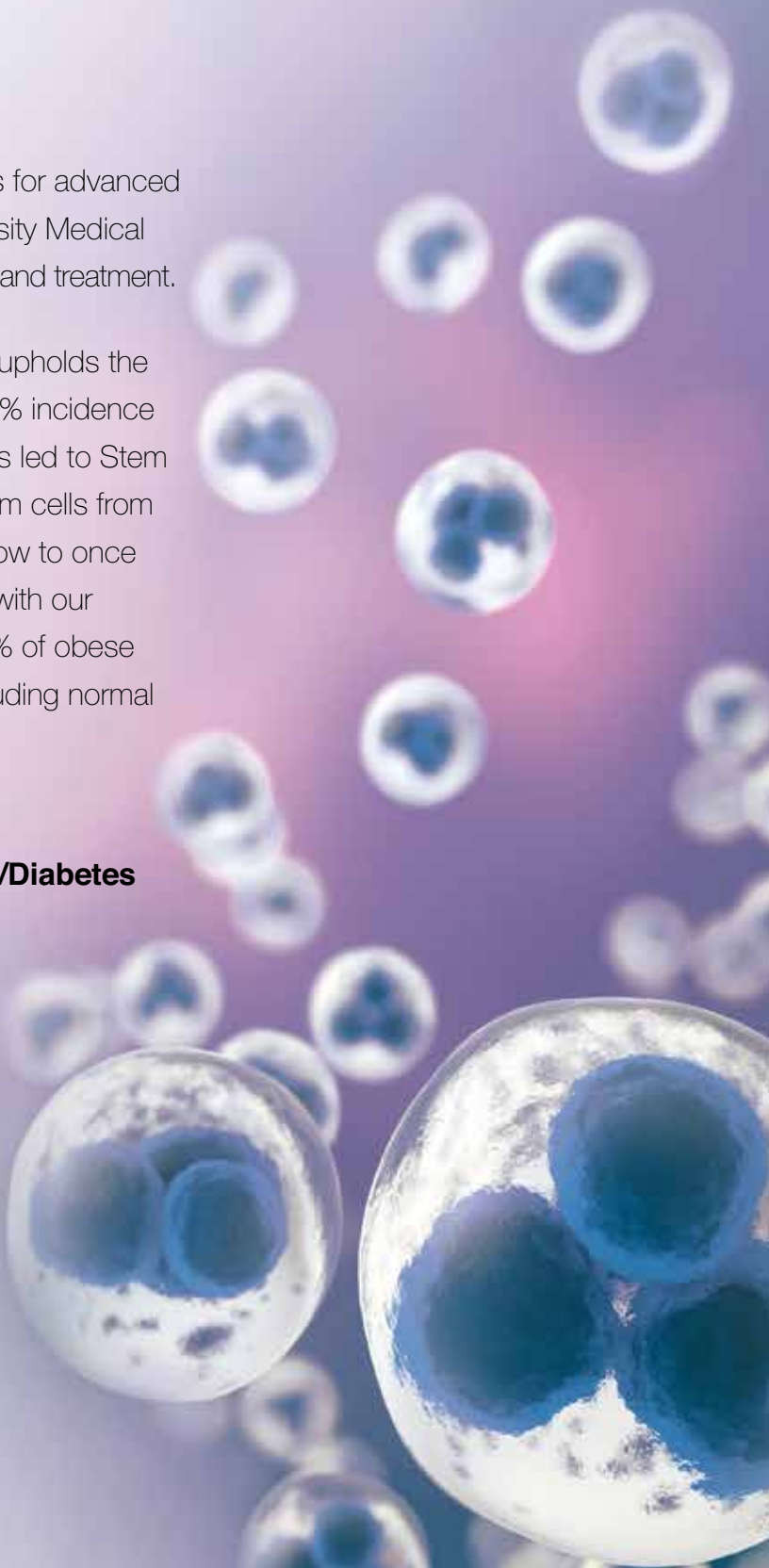

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