THE Physiologist MAGAZINE
NOVEMBER 2023

DETECTIVE WORK

Larissa Shimoda's lifelong curiosity led her to solving cellular mysteries.

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american physiological society®

CONTENTS

FEATURES

Cover photo by Chuck Fazio

CONTENTS

DEPARTMENTS

16

10

40

12

APPLY FOR SOCIETY AWARDS

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The American Physiological Society (APS) offers more than $1.2 million in awards and fellowships each year as part of our mission to encourage excellence in physiological research and education. These awards are a vital investment in our researchers and educators of all career levels.

Learn more about all the available opportunities and apply for the awards highlighted below at **physiology.org/awards**.

November **14**

Annual Marion J. Siegman Lectureship Award

$1,000 honorarium. Recognizes an established investigator making outstanding contributions to our understanding of muscle contraction and motility and is paving the way for new avenues of investigation in the field.

November **17**

Beverly Petterson Bishop Award for Excellence in Neuroscience

$20,000 award. Honors an early-career investigator who demonstrates outstanding promise based on their program in neuroscience and/or neurophysiology research.

November **24**

Barbara A. Horwitz and John M. Horowitz Undergraduate Research Awards

$400 or $100 honorarium. Honors undergraduate researchers submitting a first-author abstract to the APS annual meeting.

December **1**

ADInstruments Macknight Innovative Educator Award

$1,500 honorarium. Honors an early to mid-career member who incorporates innovative teaching techniques and technology resources in physiology education.

December **1**

Arthur C. Guyton Awards for Excellence in Integrative Physiology

$10,000 honorarium. Honors an independent investigator pursuing research utilizing quantitative and integrative approaches and feedback control system theory.

Calling Attention to Understudied Areas

BY MEEGHAN DE CAGNA, MSC, CAE

Happy fall!

As I write on a crisp October day with the smell of leaves, college football in season and far too much pumpkin spice everywhere, I'm astounded that summer went by so quickly. It was a busy summer at APS. We welcomed new leaders into their roles, hosting nearly 50 members at an APS Leadership Retreat. For three days they discussed critical topics around strategic planning, the future of the discipline and APS' role in shaping that future. They spoke about how to better meet the needs of members and of the changing tides in publishing that will affect both researchers and the Society.

Our staff loves interacting with APS members, and we appreciate you sharing your science, the work of your laboratory, your approach to teaching in and out of the classroom, and the challenges and opportunities you face. Through these valuable conversations, seeds are planted for stories for this magazine, and this issue is no exception. In this edition, we focus on critical unmet needs in two scientific areas that deserve greater understanding: transgender research and menopause.

I hope you enjoy the feature articles, and if there are other unmet needs in science that you'd like to see featured, please let us know.

"Our staff loves interacting with APS members, and we appreciate you sharing ... the challenges and opportunities you face. Through these valuable conversations, seeds are planted for stories for this magazine, and this issue is no exception."

OUR FEATURES

As our society at large learns more about transgender and non-binary people, so too do our research institutions—or at least they should be. On page 22, we dive into the problems of seeing research only through a "male" and "female" binary. A growing group of physiologists and other researchers are working to fill the gaps in the understanding of trans bodies. *The Physiologist Magazine* editorial team wanted to examine what scientists can do, what they're learning and what more needs to be done to help this population. And don't miss the "Inclusive Intake" box on page 27, which is an important list to help you be more inclusive with your research.

Our feature on page 28 also addresses an issue that needs more research and a broader discussion in society: menopause. Half the population will go through this transition in life and yet it's rarely talked about in public. Furthermore, scientists don't fully understand the physiological processes occurring as people go through this transition. But a growing group of physiologists are working to add to the menopause literature and call more attention to it.

Our cover article this month features Larissa Shimoda, PhD, of Johns Hopkins University. Learn how Shimoda's declared major of biomedical engineering didn't turn out to be what she was looking for—and how she found physiology instead. Shimoda enjoys the investigative process of physiology and continuing to ask more and more questions. Her story begins on page 18.

WE WANT TO HEAR FROM YOU

Remember that you, members of the APS community, are the engine that drives *The Physiologist Magazine*. Please email **tphysmag@physiology.org** to share any feedback, suggestions and story ideas. Wishing you a great fall and a successful academic year.

Meeghan De Cagna, MSc, CAE, is APS chief community and learning officer and associate publisher and editor-in-chief of *The Physiologist Magazine*. You can reach her at mdecagna@physiology.org.

center for physiology education

AN APS INITIATIVE

Elevate the way you teach.

Join us in the Center for Physiology Education, a home base for passionate scientists who are inspiring the next generation of physiology researchers.

Discover new learning modules designed by experienced educators for your modern classroom.

Access 650+ expert educator-approved resources sorted by core themes.

Make inquiries, share your experiences, attend monthly events and find opportunities to get involved.

Upcoming Community Event

Core Concepts Huddle

Share and discuss how to implement the core concepts of physiology in the classroom.

November 9, 2023, 4:30 p.m. EST

Register to attend at physiology.org/CPE.

The Physiologist MAGAZINE

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What It Means to Be the 'Scientist in the Room'

Dennis Brown, PhD, FAPS, joined the APS staff in July 2019 as the Society's first chief science officer. He is a professor of medicine at Harvard Medical School and director of the Massachusetts General Hospital Program in Membrane Biology. Brown has held several leadership positions at APS, including serving as the Society's 90th president. He talked with *The Physiologist Magazine* about his love of science and the challenges and opportunities facing the field today.

Tell us about your role as chief science officer at APS.

I oversee a team that leads APS' science policy efforts, government relations activities and the Science Policy Committee. We also deal with issues related to animal welfare. We work to protect our members' interests, to try and increase funding, change policies or to advise on policies that the National Institutes of Health (NIH) and other funding agencies want to put in place that we either agree or disagree with.

Dennis Brown, PhD, FAPS

One of the most visible things we do is meet with Congress. In June, we held 34 virtual meetings with various congressional offices to explain our point of view about aspects of science policy. In these meetings, we talk about issues that include funding for scientific research, the ethical use of animals in research and why these issues are important. (Read more on page 14.)

We want to spread the word about physiology. I work globally to create and forge relationships on behalf of APS that often yield speakers to our successful scientific webinar series and the American Physiology Summit. Through my efforts, I am always trying to maintain the scientific excellence of the Society. My job at APS is to be the scientist in the room. I am not only a scientist but also a member. I've got one foot in the member scientist community and one foot in the administration of the Society. So, I'm in a unique position to bring the two together.

How has APS changed over the years?

The average age of our members is decreasing. It used to be in the mid-50s, but the largest increase in membership is now in the 35 to 45 age group. That is good news because it means we've got a lot of beginning career and mid-career people coming up through the ranks who can be future leaders.

We are also trying to reach out more to people in what we would call non-traditional physiology fields. Many excellent scientists in different domains don't consider themselves to be physiologists, but they are doing physiological work. We need to bring these people into the Society and tell them, "Yes, you are doing physiology." This will help APS expand its horizons. We've got to open our doors to people who are doing great work but who normally would not come to our meetings.

The neurophysiology webinar series and the game-changer sessions at the American Physiology Summit are an effort to bring in unconventional lectures. They give other scientists exposure to what we do and what they can get out of our Society. So, my wish as chief science officer is that we're able to expand the scope and the breadth of the Society to take in not only physiologists but also great scientists in general.

What are you reading about right now?

I try to read as much as I can about new developments in science, both from a scientific point of view, in terms of the results of the experiments, and the methodologies. Nobel Prize winner Sydney Brenner once said, "Progress in science depends on new techniques, new discoveries and new ideas, probably in that order." Three things I find exciting right now are super-resolution microscopy, spatial transcriptomics and the CRISPR revolution.

What excites me most is to see progress. But progress can be frustrating. We got a new high-resolution microscope in my lab in April, and they

already have a new version available! These things cost half a million dollars. The machine gets delivered, and suddenly there's a better one.

What are you concerned about?

We're in the middle of a data tsunami. Every time you open a journal, you see a new paper where they've just produced masses of data. My concern is that we're getting swamped by data, and we don't have time to analyze it. For example, you see papers that advertise the discovery of 120 new genes associated with Alzheimer's disease. And you think, "Oh, that's fantastic!" But then what? We must go a step further and answer the question "So what?" And that falls squarely in the domain of physiologists to go and do the deep dive experiments.

What's your advice for the next generation of scientists?

Find something you're passionate about and that you're driven to do. This is not an easy life. You must ask for money all the time. You are judged all the time—in journals when you want to publish your work, when you're asking for grant money and when you're trying to be promoted. It is a constant life of being judged. You must be resilient enough to put up with that, to put up with the downturns, and to do that you have to have something positive come out of this. If you don't really love this, then don't do it because you're going to be disappointed.

What's your advice for working with mentors?

Find people who can help you in your career, but as importantly, allow them to help you. Don't let your ego get in the way of people helping you. I'll ask a colleague why they didn't show me their grant. They'll say, "Because I wanted to know if I could do it on my own without you." That's a laudable thing to achieve in the end. But it's not going to do you any good if the grant gets rejected. Don't think that just because I look at the grant that it's not your work. I have other people read my grants before I send them off. You need to have somebody to help you, no matter how high you are in the pecking order.

The biggest problem with mentorship is that there's no recognition for doing it. Institutions should recognize mentorship more than they do. Many institutions have something like a mentor of the year award. And that's nice, but you need more than that. You need that to be a factor in your promotion, in getting tenure, for example. Some places are doing that, but not enough are. You need to do more than just give people a plaque to put on the wall. There needs to be a concrete reward for being a good mentor. It's one of the most precious things we can do for people who work with us.

What is one of the biggest issues facing science right now?

We've got a major workforce issue in academic science. And it's a workforce issue that's largely related to finances. Postdocs get a certain salary, but they know that they can go to industry and double it. We can barely keep technicians for more than two years. My institution has just mandated a 20% increase in all postdoc salaries. But it's an unfunded mandate. As it stands, it means I could not fund all of the people that I'm funding right now if I were to give everybody a 20% pay increase. We all agree that postdocs need more money; there's no doubt whatsoever that they do. But that will mean there will be fewer roles available until the NIH decides to increase its budget. We also need institutions to step up.

"My wish as chief science officer is that we're able to expand the scope and the breadth of the Society to take in not only physiologists but also great scientists in general."

—Dennis Brown, PhD, FAPS

What's an underrated skill scientists should develop?

The art of small talk. Sometimes at a conference people will meet someone they consider to be their scientific idol and they stand next to them and they just talk nonstop about science. You know, a person doesn't want to hear about science all the time. Instead, find out what that person's like. What drives them? What do they like doing?

There's a place to talk about science and a place to talk about just being a human. We don't have to talk about science all the time. When you go to somebody's office, look around. You'll see pictures of kids. You'll see sports medals and artwork. You'll see things that you can start a conversation about. Look around, relax and use the visual cues in the room.

Know someone we should meet?
Email **tphysmag@physiology.org**.

Whether it's teaching or interacting with colleagues, happiness is sharing your love for physiology.

Share your story with us and it may appear in the next issue of *The Physiologist Magazine*. Email your thoughts—and links to your social media posts—to tphysmag@physiology.org.

Meena Madhur
@CVimmunology

@APSPhysiology Summer Leadership Meeting Think Tank @AirlieVA!

Caroline B. Appleyard, PhD, FAPS
@appleya

Very proud of graduate student Jonathan Lopez-Carrasquillo who is one of the new @APSPhysiology Porter Physiology Development Fellows! This fellowship will help to support part of his thesis #IBD research. @PRI_PHSU @PonceHealthSU @PRicansInSTEM.

Shaunaci Stevens
linkedin.com/in/shaunaci-stevens

I'm excited to share my first blog post with iSPY Physiology, a blog site for the American Physiological Society! This post is about how diabetes can lead to cardiovascular disease, which is the overall basis of my dissertation research at Penn State. It was so fun to write, take a moment to check it out!

Prof. Farhana Sultana
@Prof_FSultana

Academic kindness costs us nothing but there is such a scarcity of it in academia. As the new academic year begins, I pray there will be less toxic fetishization of competition, hyper-productivity, mad rushing, but more compassion, care ethics, conviviality. 💚 #AcademicChatter.

Dr. Basheer Isah Waziri (MBBS, M.Sc, Ph.D)
linkedin.com/in/dr-basheer-isah-waziri-mbbs-m-sc-ph-d-355116263

Day 1 (29/08/23): First Batch Basic Life Support Training for our #physiology students at the BLS school Department of Anaesthesia Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria.

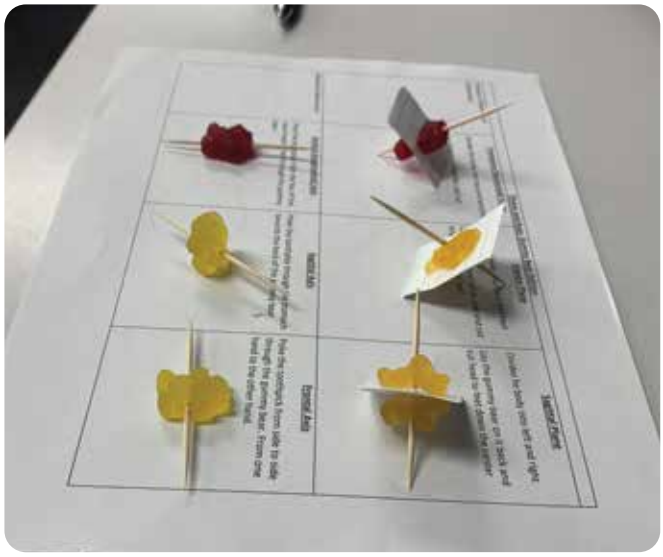
The training is organized to promote physiology #teaching by making it more practically oriented as it will help the participants to understand the practical application of the #cardiorespiratory physiology knowledge in the BLS technique.

EMaggie Morrissey-Basler, PhD
@Mag_Morrissey

My first official day as a faculty member at Providence College! @FriarHealth. I'll be teaching Anatomy & Physiology this year and my research trajectory will continue to focus on occupational heat stress and #thermalphysiology ❤️

Nigel Jiwan, MS, CISSN
@nigeljiwan

First day of lecture! Busted the gummy bears out to teach anatomical planes and axis. Highly recommend this if teaching anatomy!



Erica Dale - Lablyfe
@LabDale

Congrats to @alyssa_mickle for passing quals with honors! Now a Ph.D. candidate, she was also nominated by her thesis committee for an award cuz her presentation and proposal were so good! Proud PI here 🥲 @UFNeuroscience @UFBreathe @UFMBI

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www.youtube.com/APSPhysiology

X (Formerly Twitter): @APSPhysiology, @SciPolAPS @APSPublications

LAB NOTES

STATS & FACTS

70%

The portion of transgender or gender non-conforming people who report experiencing discrimination from a health care professional.

American Heart Association

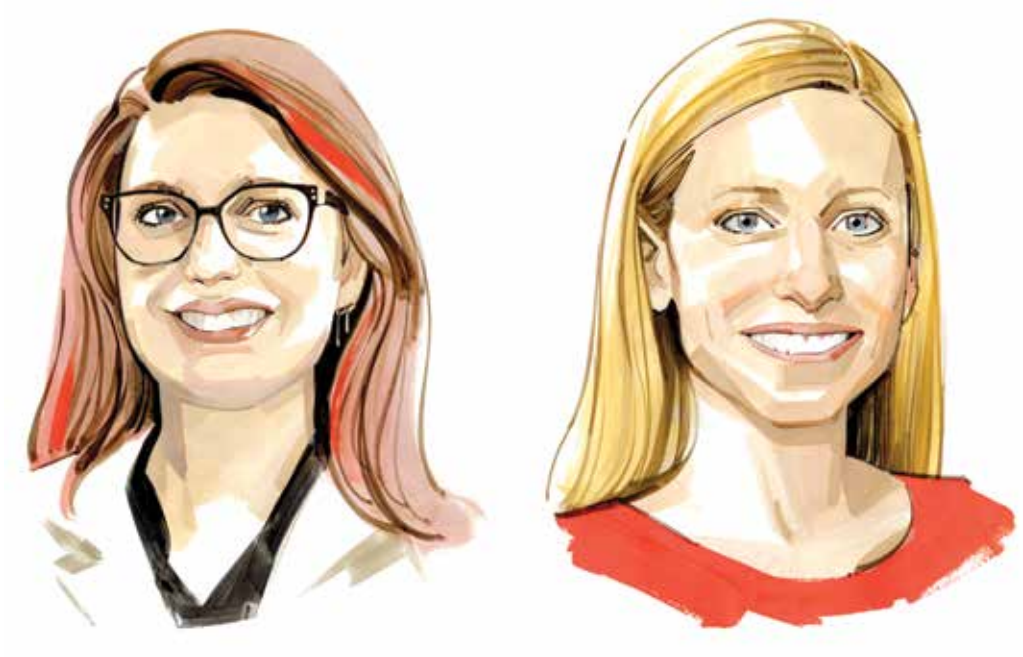
RESEARCH FIZZ

Mechanisms of mechanical overload-induced skeletal muscle hypertrophy: current understanding and future directions

This review details the history of mechanistic research into skeletal muscle hypertrophy, outlines mechanisms involved with the condition and discusses both the controversies within and future directions of such research.

***Physiological Reviews*, October 2023**

https://doi.org/10.1152/physrev.00039.2022



MENTORING Q&A | CAREER PATHS

University Life

Teaching students and a flexible schedule help make academia rewarding.

Each issue we ask a student or early-career member to pose their career questions to an established investigator and mentor. Here, Katie Anne Fopiano, a physiology PhD candidate at the Medical College of Georgia at Augusta University, asks Marni Boppart, ScD, FAPS, about her life in academia. Boppart is professor, College of Applied Health Sciences, at the Beckman Institute for Advanced Science and Technology at the University of Illinois Urbana-Champaign.

Left: iStockphoto; right: Illustrations by Kagan McLeod

Q: What experiences outside of science do you feel have best prepared you for academic research?
A: I was fortunate to be commissioned into the U.S. Air Force as an officer and aerospace physiologist right after completing my undergraduate degree. My primary job was to train pilots and aircrew members about the hazards of flying, which included hypoxia, spatial disorientation, motion sickness, visual illusions, acceleration and g-forces, human factors, circadian rhythm disruption, and fatigue.

Most of the training occurred in the classroom, which ultimately enhanced my teaching skills. However, we also were expected to fly and participate in simulations (hypobaric and hyperbaric chambers, parachute training), which was physically challenging.

These experiences inspired my lifelong fascination with human physiology, including the molecular and cellular mechanisms that promote human survival and adaptation during stressful conditions.

My current research focuses on probing the mechanistic basis for skeletal muscle growth after exercise, specifically the involvement on non-muscle stem and stromal cells. If we can address this question, perhaps we can improve human performance or develop novel cell-based therapies to rehabilitate muscle after injury and disuse.

Q: Did you always know you wanted to go into the career that you have now? Was there a turning point or defining moment that made you decide?
A: No, I never considered it throughout my training. After completing my PhD in anatomy and physiology under the supervision of Drs. Roger Fielding (previously at Boston University and now Tufts/USDA Human Nutrition Research Center on Aging) and Laurie Goodyear (Harvard Medical School/Joslin Diabetes Center), my impression of academia was that it was too challenging. The expectation to write grants, maintain an active research portfolio, and mentor students seemed overwhelming.

I applied and was admitted to medical school after graduation because I thought it would be the easier road to travel. However, I quickly realized that medicine did not leave much room for raising a family or providing the opportunity to think deeply about science. I returned to academia with the attitude that I would just try my best. And I love my career choice. It is so rewarding to make discoveries and train the next generation. I have also had the chance to raise a family and travel extensively due to the flexibility it offers.

"I have found that my most creative ideas about research occur outside the office. The 'work hard, play hard' mentality has worked for me."

Q: Do you have any advice on how to keep a healthy balance in your life, in and out of work?
A: My family ensures that I keep a healthy balance. My husband and I were fortunate to be able to adopt three children at birth. I work hard during my work hours to get the job done, often eating lunch over my computer because I know I need to leave the office and get home on time. Well, most of the time! My husband, who is also a professor, and my kids know that I love my job and so they understand. Interestingly, I have found that my most creative ideas about research occur outside the office. The "work hard, play hard" mentality has worked for me.

Q: What is your biggest motivator to continue in research?
A: To be honest, I think there are more barriers than motivators to conduct basic science research in the current climate. These barriers include an increase in volume of regulatory requirements (forms, training), unfeasible expectations for publishing, length of time for peer review, and the high cost of doing business. Add to that the high expectation of administrative work and peer review at higher ranks.

A perfect day for me is one where I can just focus on science, to include reading the literature and thinking deeply about our projects. Pure curiosity about life and the human body is the primary motivator.

Q: What is your favorite aspect of being a scientist?
A: There is an excitement that comes from analyzing the results to a question that has never been addressed. But scientists also serve as mentors and teachers. It is just as thrilling to watch my graduate students develop into scientists, forming and testing their own questions. And some of my most rewarding days occur just teaching in a lecture hall, watching students' light bulbs turn on.

Got a career question you'd like to submit? Email it to tphysmag@physiology.org. We may use it in an upcoming Mentoring Q&A.

POLICY IQ | FEDERAL ADVOCACY

APS Members Take Messages to Capitol Hill

As budget negotiations ramped up in Washington, D.C., earlier this year, members from APS' Science Policy Committee (SPC) and Early Career Advocacy Fellows held virtual meetings with congressional offices to discuss the importance of robust and reliable federal funding for scientific research.

The meetings took place in June 2023, just after passage of the Fiscal Responsibility Act, which resolved the crisis over the nation's debt ceiling but also imposed new limits on future federal spending. During their meetings, APS members heard firsthand about what the legislation means for federal programs and agencies, including biomedical research at the National Institutes of Health and the National Science Foundation. (Read more about the funding increases that APS supports at **www.physiology.org/fy2024funding**.)

Congressional staff expressed concerns that the budget caps will make it harder to secure funding increases for scientific programs. Despite these challenges, it was clear that most members of Congress continue to value biomedical research and see it as a funding priority.

Personal meetings between constituents and congressional staff are an opportunity for members to tell the story of what it is like to be a working physiologist. APS members use these meetings to share their excitement for their research and passion for physiology but also the challenges they face in maintaining steady funding, complying with a myriad of federal requirements, and mentoring and preparing the next generation of researchers.

The meetings also serve as points of connection. Repeated conversations help congressional staff develop a deeper understanding of how federal funding for research benefits the state or district they represent.

To learn more about how to get involved in APS advocacy efforts, visit **www.physiology.org/career/advocacy** or email **SciencePolicy@physiology.org**.

My Advocacy Experience

"Speaking with lawmakers about the importance of scientific funding was a highlight of my summer. While I love conducting experiments and writing papers, it is extremely fulfilling to communicate the results of your studies and the struggles you face with people who are outside of the scientific community but have a large influence on our work."
—Kevin Gries, PhD

"The Capitol Hill visits are my favorite activity on the Science Policy Committee. I love interacting with my local elected officials (or their staff) because it feels like I'm making a difference for scientists. It's so important to show up and share our views as academics that seek extramural funding."
—Amanda LeBlanc, PhD

"APS Hill Day was the first time I've participated in an event advocating for scientific research. Listening to how other scientists' stories have been shaped by research and the positive impact their work has had on others' lives was an eye-opening experience."
—Morgan Zumbaugh, PhD

"Meeting with congressional representatives and their staff presented a unique opportunity to discuss the real-world impact of health-focused research, current challenges that scientists face, and the need for additional funding to support future research priorities. It also allowed me to share my expertise, voice the needs of the scientific community and practice communicating science to non-scientists."
—Steve Elmer, PhD

POLICY IQ | RESEARCH INCLUSION

APS Responds to NIH Request to Inform Women's Health Research Plan

In January 2024, the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) will release its 2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women. The plan will outline research priorities and serve as a road map for NIH institutes and centers to address research gaps and support the career development of women in the biomedical sciences. A 2022 report from the previewed five major content areas expected to be included in the plan. View the report at **https://bit.ly/ACRWHreport**.

ORWH solicited input from the research community to help guide the development of the strategic plan, and APS was one of 120 individuals and organizations to submit a response. Read the APS response at **www.physiology.org/nihplanresearchwomen**, which was prepared with input from the Women in Physiology and Science Policy committees..

APS urged NIH to include consideration of sex or gender as variables in clinical research, pointing out that sex or gender were included in only 5% of clinical studies registered in the first year of the COVID-19 pandemic. APS also identified public health gaps that must be addressed, including several that were exacerbated by COVID-19, and recommended increasing research to support transgender health. The ORWH Strategic Plan will likely address many of these disparities.

APS urged NIH to include consideration of sex or gender as variables in clinical research, pointing out that sex or gender were included in only 5% of clinical studies registered in the first year of the COVID-19 pandemic.

Established in 1990, ORWH has had many policy successes over its 33-year history. To increase support for women in research careers, the office established the Re-Entry into Biomedical Research Careers program to assist scientists who had taken a hiatus from research and the Building Interdisciplinary Research Careers in Women's Health program to connect junior faculty with career mentors.

ORWH is also charged with monitoring adherence to NIH policy on the inclusion of women in clinical studies and reports that women now account for roughly half of all participants in NIH-supported clinical research. In 2016, the NIH policy on sex as a biological variable went into effect, clarifying expectations that sex as a variable is factored into preclinical research in vertebrate animals.

The upcoming ORWH Strategic Plan follows the 2019–2023 Trans-NIH Strategic Plan for Women's Health Research (view at **https://bit.ly/ORWHStrategicPlan**). Among the advancements achieved under this plan, NIH released an R01 funding opportunity focused on studying the intersection of sex and gender influences on health and disease. The 2024–2028 strategic plan will build upon the previous plan to address the current state of women's health science, identify research gaps and establish goals based upon input from the community. NIH institutes and centers will be expected to address these goals within the context of their scientific missions.

The final version of the 2024–2028 strategic plan will be released in January 2024, with an implementation and evaluation guide to follow in the summer.

STATS & FACTS

51

The median age at which women experience menopause.

Johns Hopkins University

RESEARCH FIZZ

Advancing our understanding of bioreactors for industrial-sized cell culture: health care and cellular agriculture implications

This review explores bioreactor technology that is used to develop innovations in the biomanufacturing of therapeutic cells and cultured meat.

***American Journal of Physiology-Cell Physiology*, September 2023**

https://doi.org/10.1152/ajpcell.00408.2022

STATS & FACTS

~75%

The portion of women who experience hot flashes during menopause.

Johns Hopkins University

Far right: iStockphoto

STATS & FACTS

~90%

The portion of transgender people who wanted but did not receive puberty-delaying treatment who report lifetime suicidal ideation as adults.

Endocrine Society

RESEARCH FIZZ

Physiological responses to 9 hours of heat exposure in young and older adults. Part I: Body temperature and hemodynamic regulation

This article finds older adults maintain larger increases in heat storage and core temperature during prolonged exposure to hot, dry conditions when compared with younger adults.

***Journal of Applied Physiology*, September 2023**

https://doi.org/10.1152/japplphysiol.00227.2023

STATS & FACTS

~$1.8 billion

The cost of lost work time by menopausal women in the U.S. each year.

The New York Times

Left, Johnson and her husband, Matt, and daughter, Eliza, with a buffalo statue during a cross-country road trip. Right, Johnson with her horse, Squish. Facing page, top, Johnson at the summit of Mt. Evans in Colorado.

UNDER THE MICROSCOPE

Rapid Fire Q&A

Kathryn "Katie" M.S. Johnson, PhD, shares what scientist she would love to meet, how she spends her free time and how she feels about teaching.

Q: Ever had a "eureka" moment? Tell us about it in … 10 words or less.
A: Active learning >>> lecturing.

Q: What inspired you to become a scientist?
A: My high school chemistry teacher, Mrs. Gallup, showed me and told me I could be a scientist.

Q: How has the pandemic changed the way you work?
A: My clients became very comfortable with virtual interactions, and it really increased interest in my work.

Q: "Old school" technique you're most proud of mastering?
A: In vivo glucose clamp.

Q: Most challenging laboratory technique you've learned to use?
A: In vivo glucose clamp.

Q: Items on your lab bench that you are most possessive of?
A: Micropipettes!

Q: Best "MacGyver" moment in the lab?
A: When I did research on horses, I would take their blood samples in the field, and I used a portable centrifuge that plugged into my car.

Q: If you could meet any scientist (living or dead) who would it be and why?
A: Anthony Fauci, MD, for all the obvious reasons, but mostly for his ability to deal with all the nonscience parts of science.

Q: If you could do a sabbatical with any scientist (living or dead) who would it be and why?
A: Viji Sathy, PhD, has done such wonderful work on inclusive teaching. It would be great to spend a sabbatical working with her.

Q: What do you wish the general public understood about science or research?
A: What we know about science is always changing and that's a good thing! It means we are advancing our understanding.

Q: No. 1 guilty pleasure?
A: Reality TV shows.

Q: Most influential scientist on your career?
A: Marion Fass, ScD, helped me find teaching and introduced me to becoming an effective educator.

Q: Biggest misconception about physiology/physiologists is … in five words?
A: No time for active learning.

Q: Favorite way to spend a free hour?
A: Get outside and be active with my husband and daughter.

Q: Most valuable quality in a colleague?
A: Willingness to use their knowledge and talents to engage in discussions and find solutions to tough issues.

Far left: iStockphoto; All photos in Rapid Fire Q&A courtesy of Kathryn M.S. "Katie" Johnson, PhD

Q: Tell us a surprising fact about you.
A: I ride my young horse, Squish, as much as I can!

Q: Favorite part of your job?
A: Working with educators from all over the world.

Q: Least favorite part of your job?
A: Editing presentations.

Q: Title you'd use on your autobiography?
A: "The Scientist that Doesn't Do Science."

Q: How would you describe your job to a child?
A: I help teachers become better teachers.

Q: One thing every researcher/scientist should try at least once in their life?
A: Teaching a topic that is not their research specialty.

Q: Next book on your reading list?
A: "How Far the Light Reaches: A Life in Ten Sea Creatures" by Sabrina Imbler.

Q: Favorite TV show, movie series or podcast to binge-watch/listen?
A: "Derry Girls."

Q: Favorite musician/musical artist/band?
A: Queen and Coldplay.

Q: Go-to snacks to get you through long days?
A: Granola bars and ginger ale.

Q: Crunchy or creamy?
A: Creamy. Not even a choice.

Q: City, suburb, country? (Favorite place to live)
A: Exurb.

Kathryn M.S. "Katie" Johnson, PhD, is a nationally recognized physiology educator who collaborates with academic institutions and professional societies to develop initiatives promoting evidence-based and inclusive learning strategies. In 2018, she founded Trail Build LLC. Her role as a consultant has included assisting APS in the development of the Center for Physiology Education.

Q: Favorite lab mishap story that you can share without incriminating the innocent?
A: Thinking about lab mishaps makes me queasy!

Far right: iStockphoto

PUBLISH WITH POLISH | KEYWORD OPTIMIZATION

How to Help Readers Find Your Research

You've written your research paper, and you're getting ready to submit it for consideration for publication. But before you do so, you need to think about how your research will make its way to readers if it's accepted. There are some fundamental steps you can take as you write your article to help readers find it when it gets published and raise the visibility of your research.

Optimizing your title and keywords for search engines can go a long way toward directing readers to your research—and increasing your article's citations and Altmetric score. Here are some things to keep in mind:

- Avoid making titles overly technical and dense. Research has shown that shorter titles generate more page views, so try to keep titles under 15 words.
- Be direct and avoid vagaries. Calling out the results of your research in the title can also generate interest.
- Be aware of current popular keywords in your field. Including some of these often-searched terms in the title is important because many search engines weigh terms in a title more heavily than words in the text itself.
- Keep it simple. Terms in the keywords section should hit a sweet spot of not too broad—such as listing scientific fields—and not too specific. Think of terms that a lay audience might consider regarding your research. Consult with an academic librarian or use tools such as Google Trends or Hashtagify (**www.hashtagify.me**) to find relevant keywords that generate page views.

Although the meat of your article will be the text, spending time on the title and keywords is an important part of getting your research into the hands of readers.

Learn more about preparing your paper for publication at **www.journals.physiology.org/author-info**.

WORK DETECTIVE

Larissa Shimoda's lifelong curiosity about how the body works has shaped her into a research scientist focused on solving cellular mysteries.

BY MEREDITH SELL

When Larissa Shimoda, PhD, leaves Johns Hopkins University after work, she drives through the streets of Baltimore, hops on the freeway and points her headlights toward the country. "As I'm driving home, everything gets quieter," the professor of medicine says. Outside, birds and frogs replace traffic and sirens as the dominant noise-makers. Twenty-five minutes later, she pulls into her driveway. She greets her husband and three dogs. It's good to be home.

Photo by Chuck Fazio

Shimoda and her sisters celebrate their father's 80th birthday in Maui.

Home is where Shimoda's interest in science and the human body began. Growing up in Seattle, where her father worked as an electrical engineer for Boeing and her mother volunteered as a school nurse, Shimoda remembers playing doctor with her three younger sisters. At age 5, her favorite TV show was "Emergency!," a medical drama that put the spotlight on paramedics. Her mom owned a collection of "Cherry Ames, Student Nurse" books—a medical mystery series in the vein of "Nancy Drew"—and 8-year-old Shimoda read them voraciously. The combination of human health, mystery-solving and plucky main character held her in rapt attention and stirred her growing curiosity in physiology.

"I was more and more interested about the body and how things worked: How do you see? How does that get into your brain?" Shimoda remembers. She'd ask her mother these questions and receive partial answers, but she always wanted to know more.

RESEARCH QUESTIONS

Her undergraduate studies at Marquette University in Milwaukee gave Shimoda the opportunity to finally figure things out. At least, that's what she thought. She wanted to eventually do medical research, so she declared a major in biomedical engineering, thinking the track would cover areas such as genetic engineering. But then she found herself in physics and calculus classes, learning how to build circuits.

"I spent the first two years hating everything I was doing," she says. "I couldn't see how all of that was going to help me do the research I wanted to do." She called her parents and tried to convince them to let her drop out and go to art school instead. "They convinced me to stick it out."

Good thing, too, because her junior year everything changed, and it only took one class. The professor gave an assignment to find and report on a scientific paper that used an engineering approach to solve a medical problem. Shimoda went to the library and flipped through the "Index Medicus," a massive reference book that listed published journal articles. Eventually, she found a paper that looked at how to address phenylketonuria patients' lack of a certain enzyme by designing artificial lipid vessels that would protect the enzyme in the bloodstream so it wouldn't be destroyed as a foreign entity.

"[The authors] went through the process of how they figured out what the [vessel] composition should be and what the pore size should be and how to calculate it—and I just thought that was the coolest thing," Shimoda says. "Everything clicked. I started going back to class. My grades, the trajectory, changed dramatically."

That was just the beginning of her evolution. In her master's studies, also in biomedical engineering, she started working with a neonatologist in the lab, looking at blood vessel constriction and dilation.

"In preterm infants, cerebral hemorrhage, at the time, was a pretty significant problem," Shimoda says, "so [the neonatologist] was trying to understand the regulation of these blood vessels."

Shimoda helped by building an electronic system to control pressure and flow in a blood vessel. She set it up with piglet cerebral vessels, which are comparable to human infant vessels. "I was taking these little blood vessels and I was increasing flow and decreasing flow and looking to see how much they dilate or constrict. And could I figure out which mechanisms were controlling that?" she says.

This project continued into Shimoda's PhD work, where she transitioned from building the electronic system to testing it and calculating what was happening in terms of stress and pressure. But she noticed that she was more interested in why the blood vessels responded the way they did than she was in figuring out the best engineered technology. The research team projected the blood vessels onto a video screen so they could watch them contracting and relaxing in real time. What she saw fascinated her.

She thought: How does this happen in the blood vessel? What are the cells doing? How does the blood vessel control flow? What does this do in the brain? What does it do in the lung with pulmonary vessels? How does that lead to disease? How can we interfere so you don't get disease? Her inquisitive nature perked up, and the questions, the mysteries, seemed endless.

FINDING ANSWERS

After finishing her PhD in 1995, Shimoda left Marquette for a three-year training program at Johns Hopkins in pulmonary medicine and pulmonary physiology. "I was excited to learn more about the lung and explore pulmonary physiology," she says. "I learned how to perform an isolated lung perfusion, which we still do … and then learned some of the more cell-based models, which I hadn't been as familiar with."

Toward the end of her fellowship and early in her work as a faculty member at Johns Hopkins, Shimoda collaborated with Gregg Semenza, MD, PhD, who received the 2019 Nobel Prize in Physiology or Medicine for work on hypoxia inducible factor, or how cells recognize and respond to low oxygen.

"Nature's not dumb, so if it can take a protein and have it have one function, why not build in a couple other functions to get more bang for your buck? That's been fun [to try] to unravel."

What she learned working with Semenza has since influenced Shimoda's work investigating how and why cells in cases of pulmonary hypertension grow out of control and what aquaporins (proteins that transport water) do beyond their most easily observable function.

"Nature's not dumb, so if it can take a protein and have it have one function, why not build in a couple other functions to get more bang for your buck?" she says. "That's been fun, trying to unravel what some of these other functions for these proteins are that maybe can lead us to therapeutic targets down the road."

Research is detective work, but solving the mystery takes much longer than it does to read a few hundred pages of "Cherry Ames" over a night or two. And discovering what a specific type of cell does in a certain experiment doesn't immediately lead to treatments for human disease.

Shimoda points to the example of endothelin, a protein that regulates blood pressure. Endothelin-1 was discovered in 1987, when Shimoda was in college, but it wasn't until 2001, nearly 15 years later, that a resulting therapy addressing pulmonary hypertension was developed. And even 15 years is somewhat fast—perhaps only possible because of how much more connected the science community has grown.

Every study Shimoda and her team publishes today joins a vast ecosystem of research, where other researchers can learn and take note, drawing inspiration and developing further questions for their own studies. The hope is that eventually something discovered in Shimoda's lab will pay off in a tangible treatment—a drug or intervention—for human disease.

In the meantime, Shimoda continues her work, not in a detective's trench coat, but the white lab coat of a scientist.

Shimoda with members of her lab at the Respiration Section banquet during the 2023 APS American Physiology Summit.

Illustration by Ancapital/Shutterstock

BEYOND THE BINARY

Researchers are expanding the understanding of the body beyond "male" and "female."

BY ISOBEL WHITCOMB

Male or female: For decades, this was the choice that patients and research participants had to make, whether they were checking in at their primary care provider's office or enrolling in a clinical trial. And for decades, this choice left out an entire group of people: the trans community.

People who identify as transgender and gender non-conforming—umbrella terms referring to people whose gender identity doesn't match the sex they were assigned at birth—tend to have very different health outcomes from their cisgender peers (people whose gender identity does match the sex they were assigned at birth).

The term "transgender" encompasses a wide swath of experiences. Every trans person has a different understanding of their gender and different goals for their body.

Transgender people experience higher rates of cardiovascular disease, mental illness, chronic illness and some cancers compared to the cisgender population. They're also less likely to have access to medical care, due to factors such as denied insurance coverage, fear of coming out to medical providers and discrimination in doctor's offices, according to the 2015 U.S. Transgender Survey from the National Center for Transgender Equality.

Until recently, the little research that did shed light on this population did so with a narrow lens, focusing on mental health or HIV/AIDS, according to a review published in the February 21, 2021, issue of *The Journal of Clinical Investigation*. That's changing, but slowly. In 2017, APS published the first animal model for gender-affirming hormone therapy in the *American Journal of Physiology–Endocrinology and Metabolism*. In 2022, the National Institutes of Health announced it would increase funding for research on gender-affirming care.

A small, growing group of researchers is working to fill the gaps in the understanding of trans bodies and the best ways to care for them—from the potential cardiovascular risks inherent to being trans to the effects of gender-affirming hormone therapy. However, there are still more questions than answers. For physiologists, it's vital to get up to date on what is known and unknown—and how to approach these gaps in research, from both a research and clinical standpoint.

A DIVERSITY OF EXPERIENCES

The term "transgender" encompasses a wide swath of experiences. Every trans person has a different understanding of their gender and different goals for their body. For example, not all trans people experience gender dysphoria, which is distress around a perceived misalignment between one's body and gender.

And to be trans doesn't necessarily involve medical transition, which is the process of aligning the body with one's understanding of their gender, usually through gender-affirming hormone therapy or surgery. Many trans people don't have access to gender-affirming health care; others may not seek it out in the first place, according to a June 2019 report published in *Translational Andrology and Urology*. For example, around three-quarters of respondents to the 2015 U.S. Transgender Survey reported wanting gender-affirming hormone therapy. A much smaller percentage—19% of trans men (men assigned female at birth) and around half of trans women (women assigned male at birth)—reported wanting gender-affirming genital surgery (labiaplasty or phalloplasty).

It's also important to understand that for those who do seek out gender-affirming care, these therapies and procedures are lifesaving. According to the Cleveland Clinic, trans people experience higher rates of mood, personality and anxiety disorders than the general population. As many as 82% of transgender people have considered suicide, and 40% have made a suicide attempt, according to the 2015 U.S. Transgender Survey. These issues are substantially lower in people who have received gender-affirming care. An observational cohort study published in February 2022 in *JAMA Network Open* found that among 104 trans youth, those who received gender-affirming care experienced a 73% decrease in suicidality and 60% decreased risk of depression compared to those who didn't. Cornell University has compiled over 50 studies that report similar trends.

The data on the benefits of gender-affirming care are unambiguous, says Jesse Moreira-Bouchard, PhD, a cardiovascular physiologist at Boston University. "All our anecdotal evidence suggests that gender-affirming care is good and that it's working," they say. But beyond the tenet that gender-affirming care saves lives, the understanding of trans health gets murkier.

MISSING THE FOREST FOR THE TREES

Take cardiovascular health. Moreira-Bouchard got their start as a cardiovascular physiologist focusing on blood pressure. It was during their postdoctoral research that they became interested in the impacts of stress on the cardiovascular health of minoritized populations, particularly trans people. More research, such as a December 2022 report in *Circulation: Cardiovascular Quality and Outcomes*, was pointing to the fact that sexual minorities (gay, lesbian or bisexual, for example) were more likely to experience hypertension than their heterosexual peers. Some initial research pointed to a similar trend

in trans people. In the U.S., trans men are four times more likely to experience a heart attack compared to cisgender women and are two times more likely compared to cisgender men, according to an April 2019 report published in *Circulation: Cardiovascular Quality and Outcomes*. But there was an important discrepancy between these two lines of inquiry. While research into the cardiovascular health of sexual minorities focused on environmental stress and experiences of discrimination and stigma, research into trans people was laser-focused on one thing: gender-affirming hormone therapy.

There is some early evidence pointing to an association between gender-affirming hormone therapy and cardiovascular risk markers. Researchers followed 470 transgender adults for up to 57 months after starting hormone therapy. Their results, published in the June 2021 issue of *Hypertension*, found that within two to four months, average systolic blood pressure was higher in the transmasculine group by 2.6 mmHg and lower in the transfeminine group by 4.0 mm Hg.

In a retrospective cohort study, Danish researchers compared 2,671 trans participants to cisgender controls. Their results, published in the September 2022 issue of the *European Journal of Endocrinology*, found that both transfeminine and transmasculine people had a higher risk of any cardiovascular diagnosis compared to cisgender people of either sex. The most notable difference was between trans men and cis men; trans men were more than twice as likely to receive a cardiovascular diagnosis. The study found that gender-affirming hormone therapy accounted for some of this difference.

Moreira-Bouchard says that with its heavy focus on gender-affirming hormone therapy, this research ignores the bigger picture of trans health. Researchers know that discrimination, housing insecurity and lifestyle factors such as smoking are all predictive of poor cardiovascular health. Researchers also know that trans people are more likely to check all of these boxes. But much of the research exploring a link between cardiovascular health and gender-affirming hormone therapy doesn't adequately parse out these potential confounding factors. "There is this hypercritical lens on trans folks," Moreira-Bouchard says.

Another key methodological flaw: Much of this research doesn't include information on dose or participants' hormone profiles. "You could be comparing apples to oranges," Moreira-Bouchard says. Collecting this information is particularly crucial; research suggests that many trans people self-administer a different dose of hormone therapy than the one prescribed to them.

Moreira-Bouchard and other experts researching trans health agree that it's important to establish the safety of gender-affirming care, but doing so will need to involve approaching research from a more comprehensive perspective. That means conducting longitudinal, rather than cross-sectional, research

Researchers know that discrimination, housing insecurity and lifestyle factors such as smoking are all predictive of poor cardiovascular health. Researchers also know that trans people are more likely to check all of these boxes.

and collecting comprehensive information on demographics, lifestyle, environmental stressors and hormone dosing along the way, Moreira-Bouchard says.

THE RIGHT MODELS

Troy Roepke, PhD, who is gender-queer, sees a similar lack of attention to the effects of chronic environmental stress on the health of trans people. According to Roepke, who is an associate professor in the Department of Animal Sciences at Rutgers University in New Jersey, scientists know very little about what happens in the brain during gender-affirming hormone therapy. And any research that looks into these effects needs to take into account social stressors. "What's the stress of being a trans, non-binary person in this society that is increasingly more transphobic and queer phobic? And what does that do to gender-affirming hormone therapy?" Roepke asks. "Gender-affirming hormone therapy can affect the response to stress; meanwhile, stress can affect how hormones are cleared from the body."

One way to address these gaps in understanding is to develop better animal models, Roepke says. For the past six years that researchers have conducted these studies, they've done so in ways that don't accurately replicate what hormone therapy looks like in trans people, Roepke adds. For example, modeling hormone therapy in a mouse often involves conducting a gonadectomy, then introducing hormones. "But that's not what happens with trans people or non-binary people," Roepke says. Much of the time, trans people receiving hormone therapy keep their gonads intact, then take some combination of hormones, androgen blockers or hormone enzyme blockers.

Roepke also sees issues with the route of administration in animal studies. Increasing evidence suggests that whether hormone therapy is given via injection, orally or topically alters the way the body metabolizes the drug. When hormones are only introduced to animals in the form of implanted pellets, another layer of inaccuracy is added. Finally, researchers can introduce chronic environmental stress into animal models to elucidate the role of this confounding factor, Roepke says.

"What's the stress of being a trans, non-binary person in this society that is increasingly more transphobic and queer phobic? And what does that do to gender-affirming hormone therapy?"

—Troy Roepke, PhD

NAVIGATING THE KNOWN AND UNKNOWN

So how can researchers and clinicians approach their work with trans patients and participants, while keeping these uncertainties in mind?

First, it's important to remember that there is strong evidence for the benefits of gender-affirming care and weak evidence for any potential risks, says Joshua Safer, MD, executive director of the Mount Sinai Center for Transgender Medicine and Surgery in New York. Research in cisgender populations further supports the safety of these therapies, he points out. A paper published in the June 2023 issue of the *New England Journal of Medicine* documented the safety of exogenous testosterone in

older cisgender men with low levels of the hormone.

The Women's Health Initiative demonstrated that older cisgender women who received hysterectomies and took pure estrogen (as opposed to estrogen-progesterone therapy) had lower risk of heart attack and breast cancer than those who did not. Although this research is not perfectly representative of the trans population, researchers should take these results into account when thinking about the safety of gender-affirming hormone therapy, experts say.

"Gender-affirming hormone therapy is very safe. Most of the so-called risks seem to be fears rather than true risks," Safer says. "So, it might be more a matter of weighing unfounded fears versus harm of not treating."

From there, clinicians can run potential risks on a patient-by-patient basis. Maybe a patient seeking gender-affirming hormone therapy has cardiovascular disease and chronic kidney disease; therefore, their doctor may consider that treatment might reduce their stress, which might benefit their heart health. Then, the clinician can monitor both heart and kidneys, Moreira-Bouchard says.

In response to interventions, trans people receiving gender-affirming care often see health markers improve beyond what is average for the population, perhaps because they are regularly engaging in health care, Safer says.

Nina Stachenfeld, PhD, FAPS, has noticed this trend in her own research on the effects of testosterone therapy on people assigned female at birth. Stachenfeld, a fellow at the John B. Pierce Laboratory and a senior research scientist in obstetrics, gynecology and reproductive sciences at Yale School of Medicine in New Haven, Connecticut, clearly remembers meeting a young trans man as part of one of her studies. When a preliminary test revealed that he had endothelial dysfunction and dyslipidemia (risk factors for cardiovascular disease), he asked what he could do. Stachenfeld suggested an exercise program might turn his health around. She didn't meet with him again but heard through his health care provider that the young man had formed an all-trans exercise support group.

"If a doctor were to say, 'I'm supportive of you, I want to help you get hormonal treatment, we're going to work on this together, but to be safe, I'll need you to start an exercise program, or get on a statin,' many would be receptive of that," Stachenfeld says. "This is a promising and exciting population to work with. They're making a decision about their lives and how they want them to change."

Inclusive Intake

One important way to expand research beyond the gender binary is intake that's more inclusive of the trans community. Not only does gender-inclusive intake return more granular data, it might help gender and sexual minorities, who are more likely to be distrustful of medicine and research, feel safer, says Jesse Moreira-Bouchard, PhD, a cardiovascular physiologist at Boston University. "People shouldn't feel marginalized by an intake form," they say. "That's the first thing you do. That sets the tone." *The Physiologist Magazine* spoke to experts about where to begin:

- **Avoid the word "other."** When asking someone's sex or gender, including only three categories—male, female and "other"—automatically frames anyone who doesn't fit the gender binary as an outsider. Include a wide spectrum of gender descriptors, from "agender" (a person who doesn't identify with any gender or who has no gender to express) to "Two-Spirit" (a term used by some Indigenous people who have characteristics of both men and women). List them in alphabetical order. Don't list man or women first, followed by gender minorities.
- **Transgender isn't a gender.** Transgender is an umbrella term that encompasses a wide range of genders. Many non-binary and genderqueer people don't identify as transgender. Some transmasculine people might identify their gender as simply "man" rather than "trans man." Instead, ask if participants or patients are transgender in a separate question. Define the term "trans" and include language that clarifies why you are asking.
- **Take an organ inventory.** Gender isn't a reliable predictor of anatomy, nor is being trans. For example, many trans people choose gender-affirming chest surgery (breast augmentation or removal) but not gender-affirming genital surgery (labiaplasty or phalloplasty).
- **Get clarity about hormones.** Similarly, only about half of trans people undergo gender-affirming hormone therapy; those that do take a wide range of doses. (Many self-administer a dose other than the one prescribed by their physician.) Ask whether participants or patients are taking gender-affirming hormone therapy, then ask them about their dose.

For more on this topic, check out the APS podcast episode "Inclusive Demography in Medical Research" at **https://bit.ly/inclusivedemography.**

Breaking the Silence

Menopause is often spoken about in hushed terms. But physiologists are advancing our understanding of this natural life shift.

BY JENNIFER L.W. FINK

Anyone with ovaries who lives long enough will eventually experience a decrease in production of estrogen. Menstrual cycles will cease, and their physiology will change, as the body no longer produces regular, predictable quantities of hormones that affect the functioning of nearly every organ system.

Some people will have a tough time falling or staying asleep. They may struggle with "brain fog" and feel frustration because once simple cognitive tasks require extra effort. Occasional bursts of internal heat may trigger sweating and discomfort. Urinary dysfunction may occur, sexual functioning is affected, and a person's risk of osteoporosis, bone fractures, heart disease, high blood pressure and Alzheimer's dementia increases significantly.

Illustration by Mariam Arsaliaa

Yet, even though menopause is a universal experience for half of the human population, scientists and clinicians still understand little about the physiological process of it.

"We don't really know the underlying biological changes that are occurring as women are going through menopause," says Kerrie Moreau, PhD, professor of medicine in the Geriatrics Division at the University of Colorado Anschutz Medical Campus. Scientists don't know precisely what causes hot flashes, a vasomotor symptom that affects as many as 75% of North American women as they go through the menopausal transition. And very little is known about women's metabolism after menopause, says Virginia Miller, PhD, FAPS, professor emerita and former director of the Women's Health Research Center at the Mayo Clinic in Rochester, Minnesota.

Although massive gaps in knowledge remain, scientific understanding of menopause has increased greatly over the past 20 years or so, largely due to the work of resolute physiologists.

"We now have more women in science, and many of us want to study the female physiology and diseases that impact us directly and may have been ignored in the past," says Heddwen Brooks, PhD, professor chair of the Department of Physiology at Tulane University School of Medicine in New Orleans. "This is why having more diverse scientists is really important. We women spend a third of our lives in menopause, if we are lucky, and understanding how menopause changes our physiology is important."

FLAWED STUDIES HINDER RESEARCH

Scientists and clinicians have long known that the risk of heart disease, osteoporosis and some cancers increases after menopause. So, in 1991, the National Heart, Lung and Blood Institute launched the Women's Health Initiative (WHI) to better understand how diet, hormone therapy (HT), and calcium and vitamin D supplementation impacted the health of postmenopausal women. These studies were not intended to elucidate the physiology of menopause or to outline the typical progression of the menopausal transition. Rather, the intent was to determine the effectiveness of possible treatments for health conditions that commonly affect older women.

However, the WHI was stopped abruptly in 2002 after researchers

Timeline of Menopausal Transition

A person's physiology, health and well-being are greatly influenced by their menopausal transition. Although this process can vary greatly—some, for instance, continue having regular menstrual cycles until their menstrual period suddenly stops—most people progress through predictable stages as they age. Early perimenopause to menopause timeline: approximately 3–9 years.

Early Perimenopause

(average age at start of menopausal transition: 44–55)

- Variable menstrual cycle length
- Increasing follicle stimulating hormone (FSH) levels
- Fluctuating estrogen levels, trending toward decrease

Late Perimenopause

- Occasional skipped periods/amenorrhea of at least 60 days
- FSH levels dramatically increase
- Decreasing estrogen
- Decreasing bone mineral density of spine

SYMPTOMS THAT SPAN EARLY AND LATE PERIMENOPAUSE

- Hot flashes and night sweats
- Increasing fat mass and decreasing lean mass
- Increasing BMI
- Cognitive changes or "brain fog"
- Dry skin

> **"We now have more women in science, and many of us want to study the female physiology and diseases that impact us directly and may have been ignored in the past."**
>
> **—Heddwen Brooks, PhD**

noted a statistical increase in breast cancer and stroke—and no apparent benefit for reducing cardiovascular risk—among women taking HT. HT prescriptions and usage plummeted, and science was stifled.

"We had to temporarily suspend research," says Moreau, who was studying the effect of different types of hormone therapy alone and combined with aerobic exercise training on vascular aging at the time. The National Institutes of Health required her (and other researchers) to inform all potential research subjects of the increased risk of cardiovascular disease with hormone therapy, and it became "a recruiting nightmare to try to get women into the study," she says.

Reanalysis of the WHI data revealed several flaws: The study combined women from a large age range, 50 to 75, so it included women well past menopause. Many women in the study received HT for the first time a decade or so after their last menstrual period—a choice that didn't reflect clinical practice at the time. Plus, previous observational studies had noted reduced coronary artery disease among women who took hormones at the time of menopause.

The WHI study used orally administered conjugated equine estrogen—which contains some estrogen but

Menopause

(Average age: 51)

Pinpoint in time—occurs 12 months after last menstrual period

Early Postmenopause

- Increasing fat mass and decreasing lean mass
- Decreasing hip bone mineral density
- Increasing blood pressure
- Estrogen levels may continue to decline
- FSH levels continue to increase before stabilizing about two years after menopause

(Individuals may experience menopausal symptoms up to a decade after menopause.)

Late Postmenopause

- Symptoms stabilize
- Bone loss continues

SYMPTOMS THAT SPAN LATE PERI/MENOPAUSE

- Urinary frequency
- Increased likelihood of urinary infections and urinary incontinence
- Vaginal dryness and atrophy

SYMPTOMS THAT SPAN MENOPAUSE/ EARLY POST/LATE POST

- Increased risk of cardiovascular disease
- Increased risk of fractures
- Increased risk of Alzheimer's dementia

"After the Women's Health Initiative was halted, "we had to temporarily suspend research ... and [it became] a recruiting nightmare to try to get women into [our] study."

—Kerrie Moreau, PhD

is mostly estrogen metabolites such as estrone sulfate—in combination with a synthetic progestin. This was different from the natural hormone 17β estradiol, which is what's used in laboratory settings and can be delivered transdermally. The transdermal approach is closer to how bodies naturally get estrogen.

The much-publicized increase in breast cancer risk didn't apply across the board, and an updated analysis of the breast cancer findings of the WHI Estrogen-Alone Trial found that estrogen-alone HT does not increase the risk of breast cancer in postmenopausal women. (That analysis was published in the April 12, 2006, issue of the *Journal of the American Medical Association*.)

When the data from the WHI study were stratified by age, those women who were given estrogen early in menopause saw some protective effects. The incidence of diabetes was reduced, Brooks says, and no detrimental impact was seen on the cardiovascular system.

Nevertheless, after 2002, there was a sharp decline in menopause-related studies. To this day, many women are hesitant to take hormones to relieve menopausal symptoms and many clinicians are reluctant to prescribe HT to postmenopausal women, even though HT is approved by the U.S. Food and Drug Administration to treat symptoms and prevent bone loss after menopause.

"It has become a problem for many women to find a physician who will prescribe them [hormone replacement therapy] as many have not kept up to date on the science following the initial release of the WHI data," says Brooks, who's been studying the molecular signaling pathways involved in postmenopausal hypertension for decades. "We need to educate women and physicians to consider that not all HT is the same. The route of delivery—oral versus transdermally—matters."

MENOPAUSE IS MORE THAN ESTROGEN LOSS

Because estrogen levels decrease dramatically as women go through menopause—with women in their 60s having lower estrogen levels than men of the same age—much research has focused on understanding estrogen's impact on the cardiovascular and other organ systems.

Miller has examined the vascular function of estrogen, showing that estrogen affects vascular responsiveness and enhances production of nitric oxide in the vascular endothelium. It also affects regulation of intracellular calcium. These functions may explain, at least in part, women's increased risk of cardiovascular disease after menopause. Other effects of estrogen include modulation of beta-adrenergic receptors on vascular smooth muscle and regulation of the renin angiotensin system, all of which contribute to an increased risk for hypertension, stroke and heart attack.

"We're just beginning to understand that there are sex differences in the way sex steroids work to control blood pressure," says Jane F. Reckelhoff, PhD, FAPS, professor of pharmacology at the University of Mississippi Medical Center and APS past president. Large studies have shown that women's blood pressure, pre-menopause, is generally lower than men's. However, between the ages of 40 and 60, when most women are undergoing the menopausal transition, there's a significant increase in women's blood pressure, and after age 75, women are more likely to be hypertensive than men, Reckelhoff says.

Researchers have learned, via animal studies, that boosting estrogen levels does not decrease blood pressure. "There's a point where animals stop responding after a certain age," Reckelhoff says, which may be why some human studies have found that estrogen replacement does not lower blood pressure or reduce risk of hypertension in women. Reckelhoff suspects there may be "some change that occurs with aging to the estrogen receptors, so that the response to estrogen isn't the same as it was prior to menopause."

Research by Brooks and others suggests increased T cell-mediated

Although nearly 1 in 3 women said menopause symptoms interfered with daily life, only 44% discussed potential treatments with their health care providers.

inflammation during postmenopausal hypertension. Pre-menopause, females have more regulatory T cells than males, but females' T-regulatory cell populations decrease during the menopausal transition. "We're trying to understand, if we restore regulatory T cells, can we protect cardiovascular disease?" Brooks says. "We have data to show that we can."

Increased systemic inflammation may play a role in the development of menopause-associated asthma, an under-recognized sub-type of asthma that is physiologically different than asthma in children or adult males. While researchers are still working to understand the biologic mechanisms at play, they've learned that menopausal status, not age, increases the risk of new-onset asthma.

Additional research into the immunologic impact of menopause may point the way to new treatments. Although immunotherapy is now commonly used to treat cancers and some autoimmune diseases, "people don't think about immunotherapy for cardiovascular disease. But I think it's quite feasible, perhaps in the next 20 years," Brooks says.

An increased understanding of the role of follicle-stimulating hormone (FSH) during the menopausal transition may also lead to new therapeutics. Although scientists and clinicians once thought that estrogen deficiency caused dyslipidemia in menopausal women, high FSH levels are more closely correlated with total and LDL cholesterol postmenopause.

Increased FSH levels also appear to trigger increased adiposity, abdominal weight gain and bone loss and may negatively affect cognitive function. One study noted an association between elevated FSH levels and a reduction in bilateral subcortical volume of the amygdala; other studies showed neurofibrillary tangles and impaired cognitive activity as FSH levels increased in ovariectomized mice. A 2022 in vivo study showed that administering an FSH-blocking antibody reduces tangle formation in the brains of mice and improves cognitive function. Other mouse studies have found that blocking FSH reduces body fat, lowers serum cholesterol and increases bone mass.

Moreau and colleagues are actively working to learn more about the role of FSH in postmenopausal changes in body composition and vascular function. "We're giving postmenopausal women GnRH antagonists to lower FSH levels. Then we'll see if there are changes in adiposity and vascular function," she says. "We'll have a group that also gets estrogen, so we can look at these different paradigms and try to pinpoint what's more important, estrogen or FSH. It may turn out that both are playing a role."

Researchers at Johns Hopkins University in Baltimore have developed a first-in-class FSH-blocking antibody that has been shown to prevent and treat osteoporosis in mice. They hope it may one day be used to prevent and treat human obesity, osteoporosis, dyslipidemia and neurodegeneration.

SHIFTING MENOPAUSE MANAGEMENT

Although scientific understanding of menopause has advanced, clinical management of menopause-related symptoms and health conditions hasn't shifted much. At present, most females do not receive treatment for troublesome menopause symptoms. Although nearly 1 in 3 women said their symptoms interfered with daily life, only 44% discussed potential treatments with their health care providers, according to the 2022 National Poll on Healthy Aging.

The American Medical Association recommends an individualized approach to menopause management, with HT used to alleviate bothersome symptoms. The American College of Obstetricians and Gynecologists says that "menopausal hormone therapy should not be used for the primary or secondary prevention of coronary heart disease at the present time," while supporting the use of HT for relief of menopausal symptoms in women who are in early menopause and good cardiovascular health.

By studying the physiologic changes related to menopause, researchers are paving the way for more targeted treatments that may ultimately improve the health and quality of life of women worldwide.

Contemplating graduate school as the next step in your education and career?

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MEMBERSHIP

Members Can Now Affiliate with More Sections

In addition to affiliating with a primary section, APS members can now opt in and affiliate with any sections or interest groups they want to receive updates and information about. There are no limits on the number of affiliations members may hold, but they will still select a primary section affiliation where they can vote and hold office. To affiliate with other sections, update your membership profile at **www.physiology.org** or email the APS Membership Department at **members@physiology.org**.

JOURNALS

Short on Time? Check Out the New Micropodcasts

In just 10 minutes or less, you can catch up on the latest research from the *American Journal of Physiology-Gastrointestinal and Liver Physiology* through micropodcasts. In these short episodes, authors give a brief overview of their research findings and the potential impact of their work. After listening, you can also read the related articles. Visit **www.ajpgi.podbean.com** to hear the latest.

CENTER FOR PHYSIOLOGY EDUCATION

New Graduate School Curriculum Resources

Check out the new Center for Physiology Education Graduate Resources library to provide your graduate physiology students with foundational and transferable research skills and trainee development. Educators and mentors

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- design, revise and assess physiology graduate programs;
- enhance graduate student research training and mentoring; and
- support trainee development in research design, communicating science and teaching.

View the library at **www.physiology.org/gradeducation**.

BLOGS

Write for I Spy Physiology Blog

If you enjoy talking about your work, we invite you to write for the award-winning I Spy Physiology blog. Here, our members explain physiological concepts—and some cool science—to a nonscientist audience. We endeavor to answer the questions "What is physiology?", "Where is physiology?" and "Why does it matter to you?" through current news, health articles and research snippets. Recent posts include:

- "Sweating to Keep Cool"
- "Feeling queasy? Try Some Ginger!"
- "Spotlight On: Heart Attack"

To learn more about how you can contribute, email the APS Communications Office at **communications@phyisology.org**.

Joyner Receives American College of Sports Medicine Honor Award

Michael Joyner, MD, is the 2023 recipient of the American College of Sports Medicine Honor Award. The award recognizes "a distinguished career of outstanding scientific and scholarly contributions to sports medicine and/or the exercise sciences." Joyner is the Frank R. and Shari Caywood Professor of Anesthesiology and departmental vice chair for research at the Mayo Clinic in Rochester, Minnesota. His research interests range from investigating the effect of high altitude on exercise performance to the role of convalescent plasma in treating COVID-19. Joyner has been an APS member since 1986.

AWARDS

**Award deadlines may be subject to change*

Arthur C. Guyton Distinguished Educator Award (November 10)

Cardiovascular Section Clinical Science Young Investigator Award (November 10)

Cardiovascular Section New Investigator Award (November 10)

Cardiovascular Section Outstanding Graduate Student Trainee Award (November 10)

Cardiovascular Section Outstanding Postdoctoral Trainee Award (November 10)

Cardiovascular Section Research Recognition Award (November 10)

Cell & Molecular Physiology Section New Investigator Award (November 10)

Cell & Molecular Physiology Section Research Recognition Awards (November 10)

Cell & Molecular Physiology Section Robert Gunn Student Awards (November 10)

Central Nervous System Section New Investigator Award (November 10)

Central Nervous System Section Research Recognition Award (November 10)

Central Nervous System Section Van Harreveld Memorial Award (November 10)

Charles Tipton Postdoctoral Research Award (November 10)

Charles Tipton Predoctoral Research Award (November 10)

Endocrinology & Metabolism Section New Investigator Award (November 10)

Endocrinology & Metabolism Section Research Recognition Award (November 10)

Environmental & Exercise Physiology Section CANTROL Environmental Systems New Investigator Research Award (November 10)

Environmental & Exercise Physiology Section CANTROL Environmental Systems Postdoctoral Research Award (November 10)

Environmental & Exercise Physiology Section CANTROL Environmental Systems Predoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Early-career Research Award (November 10)

Environmental & Exercise Physiology Section Gatorade Sport Science Institute Postdoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Gatorade Sport Science Institute Predoctoral Research Award (November 10)

Environmental & Exercise Physiology Section New Investigator Award (November 10)

Environmental & Exercise Physiology Section Nike Loren G. Myhre Postdoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Nike Loren G. Myhre Predoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Partnership for Clean Competition Anti-doping Postdoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Partnership for Clean Competition Anti-doping Predoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Steven M. Horvath Research Recognition Award (November 10)

Environmental & Exercise Physiology Section Women in Physiology Postdoctoral Research Award (November 10)

Environmental & Exercise Physiology Section Women in Physiology Predoctoral Research Award (November 10)

The Janet and Robert Speth Undergraduate Researcher Award (November 10)

Juan Carlos Romero and Water & Electrolyte Homeostasis Section Postdoctoral Research Award (November 10)

Leonard Share Award of the APS Water & Electrolyte Homeostasis Section (November 10)

NCARnation Trainee Presentation Award (November 10)

Linda F. Hayward Achievement Award of the APS Neural Control & Autonomic Regulation Section (November 10)

Neural Control & Autonomic Regulation Section American Physiology Summit Trainee Award (November 10)

Neural Control & Autonomic Regulation Section Michael J. Brody Young Investigator Award (November 10)

Neural Control & Autonomic Regulation Section Outstanding Graduate Student Award (November 10)

Neural Control & Autonomic Regulation Section New Investigator Award (November 10)

DATES & DEADLINES

AWARDS (CONTINUED)

Neural Control & Autonomic Regulation Section Research Recognition Awards (November 10)

Renal Section Research Recognition Award (November 10)

Respiration Section Outstanding Trainee Award (November 10)

Respiration Section Research Recognition Award (November 10)

Respiration Section Trainee Poster Presentation Awards (November 10)

Respiration Section The Usha Awards (November 10)

Teaching of Physiology Section New Investigator Award (November 10)

Teaching of Physiology Section Research Recognition Award (November 10)

Virendra B. Mahesh Award of Excellence in Endocrinology & Metabolism (November 10)

Water & Electrolyte Homeostasis Section New Investigator Award (November 10)

Water & Electrolyte Homeostasis Section Predoctoral Research Award (November 10)

Water & Electrolyte Homeostasis Section Research Recognition Award (November 10)

William Galey Scholarship Award (November 10)

Annual Marion J. Siegman Lectureship Award (November 14**)**

Beverly Petterson Bishop Award for Excellence in Neuroscience (November 17)

ADInstruments Macknight Innovative Educator Award (December 1)

Arthur C. Guyton Awards for Excellence in Integrative Physiology (December 1)

Dean Franklin Young Investigator Award (December 1)

Early-career Advocacy Fellowship (December 1)

Giles F. Filley Memorial Awards for Excellence in Respiratory Physiology & Medicine (December 1)

International Early-career Physiologist Travel Awards (December 1)

Lazaro J. Mandel Young Investigator Award (December 1)

Shih-Chun Wang Young Investigator Award (December 1)

Comparative & Evolutionary Physiology Section New Investigator Award (December 7)

Comparative & Evolutionary Physiology Section Research Recognition Award (December 7)

Comparative & Evolutionary Physiology Section Scholander Award (December 7)

Comparative & Evolutionary Physiology Section Travel Award (December 7)

Martin Frank Diversity Travel Award (December 8)

Translational Research Award (December 8)

Gastrointestinal & Liver Physiology Section Horace W. Davenport Distinguished Lectureship (December 15)

Gastrointestinal & Liver Physiology Section New Investigator Award (December 15)

Gastrointestinal & Liver Physiology Section Research Recognition Awards (December 15)

Gastrointestinal & Liver Physiology Section Trainee Poster Awards (December 15)

John S. Fordtran Gastrointestinal & Liver Section Distinguished Research Award (December 15)

Physiological -Omics Group Distinguished Lectureship Award (December 15)

Raj and Prem Goyal Lectureship in Pathophysiology of the Gastrointestinal and Liver Diseases (December 15)

Raj and Prem Goyal Translational Research Award of the American Physiological Society Gastrointestinal & Liver Section (December 15)

The Charlie Bates Research Award (January 5)

Dale J. Benos Early Career Professional Service Award (January 5)

Dependent Support Travel Award (January 5)

Porter Physiology Development Fellowship (January 15)

Teaching of Physiology Section Labfront Mid-career Educator Award (January 15)

Graduate Student Ambassador (January 24)

Local Undergraduate Research Awards in Physiology (Applications accepted on an ongoing, year-round basis)

More details: www.physiology.org/awards

CALLS FOR PAPERS

American Journal of Physiology-Cell Physiology (December 31, 2023)
- The Extracellular Matrix and its Derived Effector Molecules in Aging: Regulators and Therapeutic Targets
- Cellular and Molecular Effects of Antidiabetics Beyond Glycemic Control
- Decoding Fibrosis
- Ketones in Cellular Physiology: Metabolic, Signaling and Therapeutic Advances
- Musculoskeletal Biology and Bioengineering

American Journal of Physiology-Heart and Circulatory Physiology (December 31, 2023)
- Cardiovascular Complications of Pregnancy
- Molecular and Cellular Physiology of Heart Failure and Cardiomyopathy
- Sleep, Circadian Rhythm and Cardiovascular Health

American Journal of Physiology-Lung Cellular and Molecular Physiology (December 31, 2023)
- Alveolar Biology, Pulmonary Surfactant and Beyond: A Tribute to Dr. John Allen Clements on His 100th Birthday
- In It for the Long Haul: Understanding the Lasting Impact of COVID-19 on Lung Health and Disease
- Targeting Airway Immunity in Lung Disease

American Journal of Physiology-Regulatory, Integrative and Comparative Physiology (December 31, 2023)
- Visualizing Physiology: Using Novel Microscopy Methods to Investigate the Mechanisms Underlying Physiology and Pathophysiology

American Journal of Physiology-Renal Physiology (December 31, 2023)
- Exercise and the Kidney in Health and Disease
- Podocyte Physiology and Pathophysiology
- Sex Differences in Renal Function, Transport and Hypertension

Journal of Applied Physiology (December 31, 2023)
- Physical Activity, Mitochondria and Disease
- The Physiology of Obesity

Journal of Neurophysiology (January 31, 2024)
- Sleep Disorders

Physiological Genomics (January 31, 2024)
- Cancer 'Omics
- Integrative Physiology and Translational -Omics of Exercise and Physical Activity
- Methods and Approaches in 'Omics Research
- The Microbiome in Health and Disease
- The Physiology of Obesity

Physiological Reports (December 31, 2023)
- The Physiology of Obesity

More details: www.journals.physiology.org/calls

MEETINGS & EVENTS

American Physiology Summit
April 4–7, 2024
Long Beach, California
- Abstract submission deadline: November 3, 2023
- Registration opens: December 11, 2023
- Late-breaking abstract submissions: January 2–31, 2024
- Early registration deadline: January 17, 2024

More details: www.physiology.org/summit

WEBINARS

An In-depth View of Health Disparities through Chronic Disease Research November 7, 2023

Knowledge Base and Mapping Tools for Integrative Physiological Modeling Using SPARC December 12, 2023

NEUROPHYSIOLOGY: EXPLORING BASIC RESEARCH AND CLINICAL CONSEQUENCES WEBINAR SERIES

Unveiling the Primate Brain: Advanced Insights through Ultra-dense Electrophysiology November 1, 2023

Cellular Brain Repair for Parkinson's Disease: Is the Answer in the (Biomaterial) Matrix? November 8, 2023

Measuring Neuronal Activity and Vascular Physiology in the Human Brain Using High-resolution Functional Magnetic Resonance Imaging December 6, 2023

Compensatory Mechanisms in Parkinson's Disease January 17, 2024

More details: www.physiology.org/webinars

Connecting the Dots of Life and Disease

BY JEREMY W. PROKOP, PHD

I hear statements criticizing my scientific perspective weekly: "You should focus your research for the sake of your career." "Your science is all over the place." "Your research lacks a hypothesis and therefore is not a valid approach." Over the past decade, while not easy, I have learned to look past these statements, resulting in the most fruitful discoveries of my career.

Every individual has a different philosophy of learning and thinking. Some, such as I, are stimulated by ever-changing science and knowledge to find connections through the vast scientific overlap. While many think of us as those who get bored quickly or lack attention, I see this as the new normal of a fast-paced, data-heavy world in which research is a part.

"I am stimulated by ever-changing science and knowledge to find connections through the vast scientific overlap. While many think of us as those who get bored quickly or lack attention, I see this as the new normal of a fast-paced, data-heavy world in which research is a part."

I remember taking a jewelry-making class in high school and learning about what I always thought of as a hobby. Years later, I connected that knowledge with 3D printers to develop educational materials for understanding patients' unique genetic variants, which has now brought smiles to thousands of people who have one of our science keychains.

In my PhD training in integrated biosciences, I remember meetings with professors and students in philosophy, biophysics, chemistry and engineering that all pushed my experiments to the next level. Since high school, I have worked with labs to bring scientific communication and collaboration to the forefront of what makes me a scientist, with my mentors encouraging my collaborative skills. I have learned that combining data and communication skills can connect the dots of life and disease applicable to so many fields of medicine.

In my current role at Corewell Health, one of the nation's largest health care systems, I spend every day working with clinicians to pair their incredible ideas for improving patients' lives with already-known data. Every day, I grow the tools to do this, learning new resources that may benefit my collaborators. I aim to integrate knowledge from often divergent fields to help clinicians find the edge of knowledge and propose subsequent logical experiments. Throughout the years, I have learned that connecting knowledge is more critical than any wet lab experiment one can plan. Yet, it has become evident that our current scientific environment requires expansion into observational science and training of those with the ability to apply these observational science approaches through collaboration.

I am glad as a scientist I did not listen to so many people who told me to focus on my science and apply only hypothesis-centric research. Many of the scientists I looked up to often told me this. It was not easy to push forward. It was always tough to keep my eye on the bigger prize, the knowledge built by exploring whatever data I could access. I worry for the next generation, who grow up around so much data, yet their mentors often make similar statements I heard throughout my training and early career.

I hope trainees reading this are encouraged never to give up the quest for "connecting the dots of life and disease," no matter what others tell you.

Jeremy W. Prokop, PhD, is the data science adviser within the Office of Research at Corewell Health and an assistant professor at Michigan State University College of Human Medicine. He leads research into genomics and data integration for human health, ranging from rare diseases to the physiological response of infectious agents.

Illustration by Brett Affrunti

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