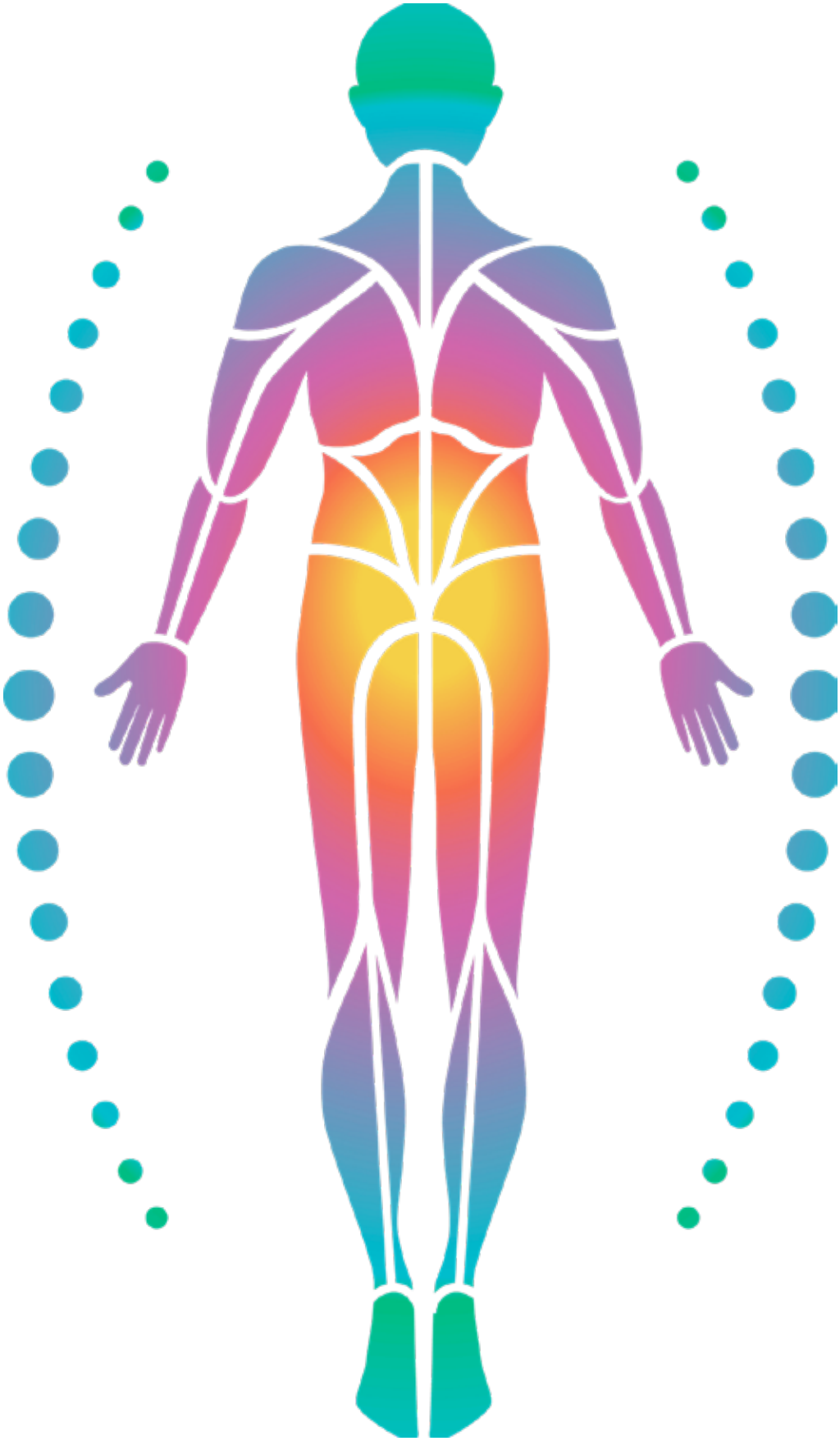
Moving Beyond Isolated Systems Symposium

July 26-28, 2022 ◆ Louisville, Kentucky



Spinal Cord Stimulation: Moving Beyond Isolated Systems Symposium

by Sam Maddox

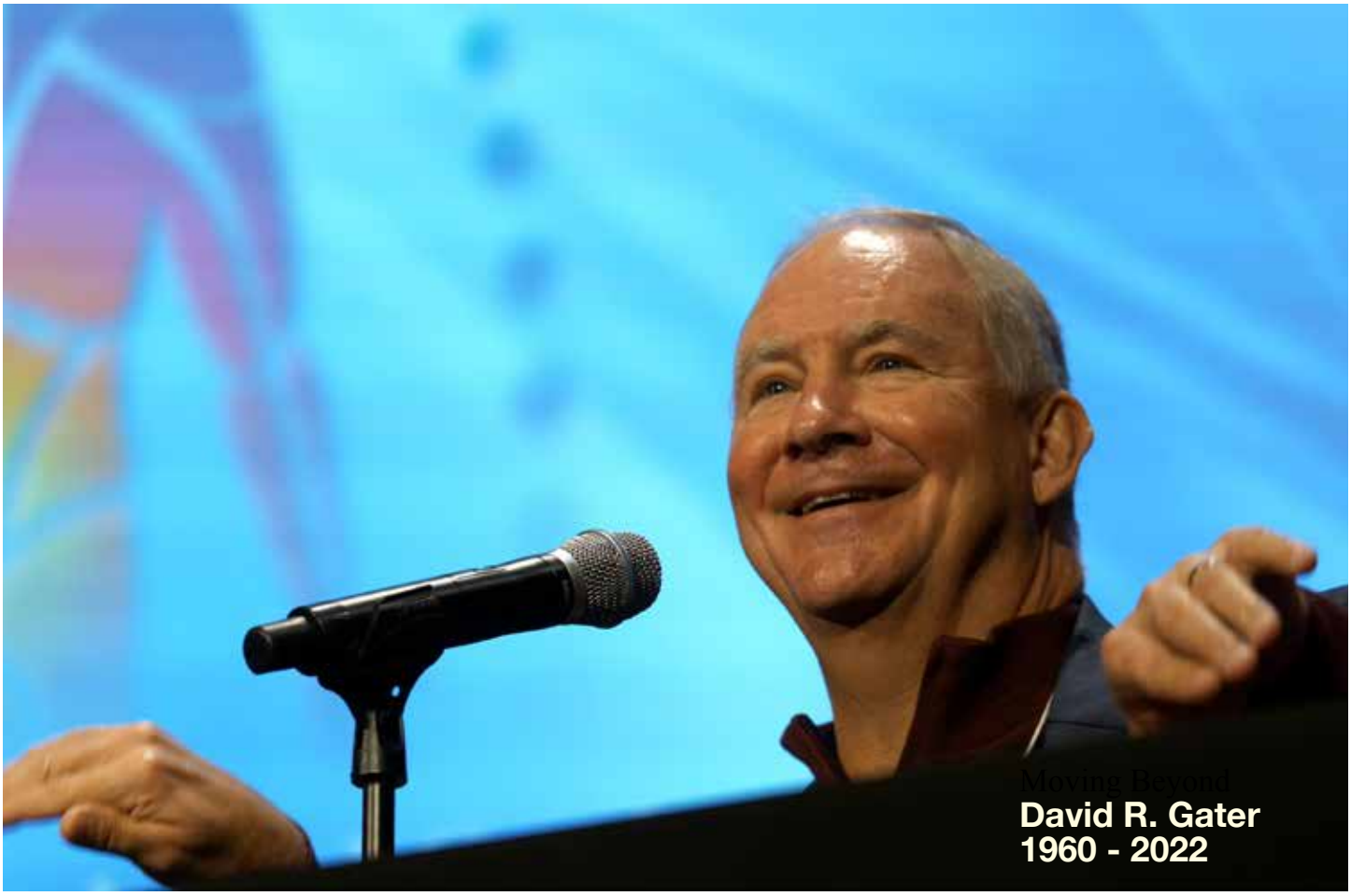
The inaugural Moving Beyond Isolated Systems Symposium was held July 26-28 in Louisville, Kentucky. The three-day event was under the direction of University of Louisville Professors David Magnuson and Susan Harkema, with help from an international program committee.

Special tribute: David R. Gater, a physician scientist from the University of Miami, died unexpectedly two weeks after presenting his research at the Symposium. Dr. Gater was professor and chair of the Department of Physical Medicine and Rehabilitation and chief medical officer of the Christine E. Lynn Rehabilitation Center for The Miami Project to Cure Paralysis. Deepest condolences to his family, wife Denise, daughters Brittany and Felicia, and grandchild Levi.

Moving Beyond Isolated Systems, postponed from April 2020 due to COVID, included eight sessions with 30 presentations and three keynote addresses. Over 300 physicians, scientists, funders, businesspeople, advocates, and persons living with paralysis attended. This international, cross-stakeholder assemblage, who to this point had never all been in the same room together, was urged to see spinal cord injury from an integrated, systems biology perspective, rather than from the usual isolated organ-system view.

The Symposium agenda focused on two main themes:

The spinal cord is beautifully and maddeningly complex, and so much more dynamic than a set of nerve wires connecting brain to muscle. The cord is smart and adaptable; it's



a key part of the body's communication network that serves to balance various systemic processes including blood flow, immune response, hormones, and movement. Injury to the cord, then, limits its ability to maintain homeostasis. Leading researchers and clinicians presented data to support this multi-system, interrelated view of spinal cord injury pathology as it affects autonomic function, metabolic disease, cardiovascular health, the immune system, and movement.

There is significant and mounting evidence that neuromodulation goes beyond motor recovery; it helps the spinal cord rebalance homeostasis across body systems. The world's top experts in spinal cord stimulation presented their data from animal studies and human trials, showing how spinal cord stimulation improves health after spinal cord injury, including blood pressure regulation, breathing, bowel and bladder control, sexual function, and functional movement.

This Symposium was significant for several reasons.

First, this was the first. The field of neuromodulation is so new that there had never been a gathering with this depth of expertise across multiple disciplines and stakeholder interests. For some it felt like a family reunion – many in the room have been collaborators for many years. Many younger investigators participated, eager to push the boundaries of what is possible. Indeed, the family has expanded; many new relationships were formed.

Second, per the title, the Symposium steered the conversation about treatments or "cures" for spinal cord injury away from "paralyzed man walks" and more toward less dramatic but meaningful health and functional improvements.

Third, it was inclusive. The meeting fostered cohesion, common interest, and dialog, even among rivals and competitors, to address an unmet human need.

Next steps: a common theme during the three days of discussions was the need for collaboration and collective thinking to push spinal cord stimulation therapies across the so-called Valley of Death that separates apparent effect and commercial sustainability. In the most basic terms, this means facing the challenges of translation head-on. It also means speaking a common language about symptom and treatment, and using common ways to measure effect – not just from research data but from user experience.

What does it mean when research reports walking? There is no agreement, but efforts are already underway (e.g. the U2FP Neuromodulation Workgroup) to use common data collection language and reproducible, translatable outcome measures. More than once a participant here was heard to say, "Maybe we should trade labs so we can see how you guys do it."

The Beyond Isolated Systems meeting, which is being planned again for 2024, was never intended to unify all the various interests – research, medicine, community, funding, industry – but rather to keep all eyes on the same goal.

Note: Each Symposium session opened with a videotaped vignette from an Honorary Chair, a person living with spinal cord injury. Most had clinical experience with spinal cord stimulation and testified enthusiastically to its various benefits. These SCI community members were invited to participate during Q&A segments of the program.

Day 1
Keynote Address
Spinal Cord Injury as a Whole Body System: Biology and the Hope of Neuromodulation
The Symposium began with a keynote address from **Steven Kirshblum**, MD, an eminent physiatrist from the Kessler Institute in New Jersey, who literally wrote the book on clinical medicine for spinal cord injury. Kirshblum co-directs Kessler's Center for Spinal Stimulation, which has studies underway for both transcutaneous (skin surface) and epidural (implanted) spinal stimulation. His talk set the table for subsequent presentations diving deeper into interrelated multi-system dysfunction due to spinal cord injury.

Honorary Chair: **Natalie Barrett**, C 5/6, spinal cord injured in 2015, participant in Kessler's transcutaneous spinal stimulation trial in 2019.

Kirshblum urged the SCI field to do more to address bowel and bladder issues, pain, spasticity, and respiratory complications. "Walking is not the gold standard" in SCI treatment development, he said. A comprehensive view is needed. Moreover, treating isolated health issues often leads to a hidden problem: polypharmacy. "We write so many prescriptions. Half of people with SCI are on 10 different medications." That, he said, often leads to taking a drug to treat the side effects of another drug.

Kirshblum said he witnessed outcomes for neuromodulation across the spectrum, including Barrett, who regained some ambulation function. "Nothing is more important than the patient perspective," he said. "Patients tell me they feel better, sleep better, have more energy, feel more connected to their bodies. Some are better able to regulate body temperature or pain. Now, when patients ask me about what's new in research, I'm thrilled to give updates on neuromodulation."

Session 1
Metabolic Diseases
This part of the Symposium considered the molecular mayhem to a body after SCI, and just how profound, and often hidden, the damage can be. Session Chair was **Dana Mc-**

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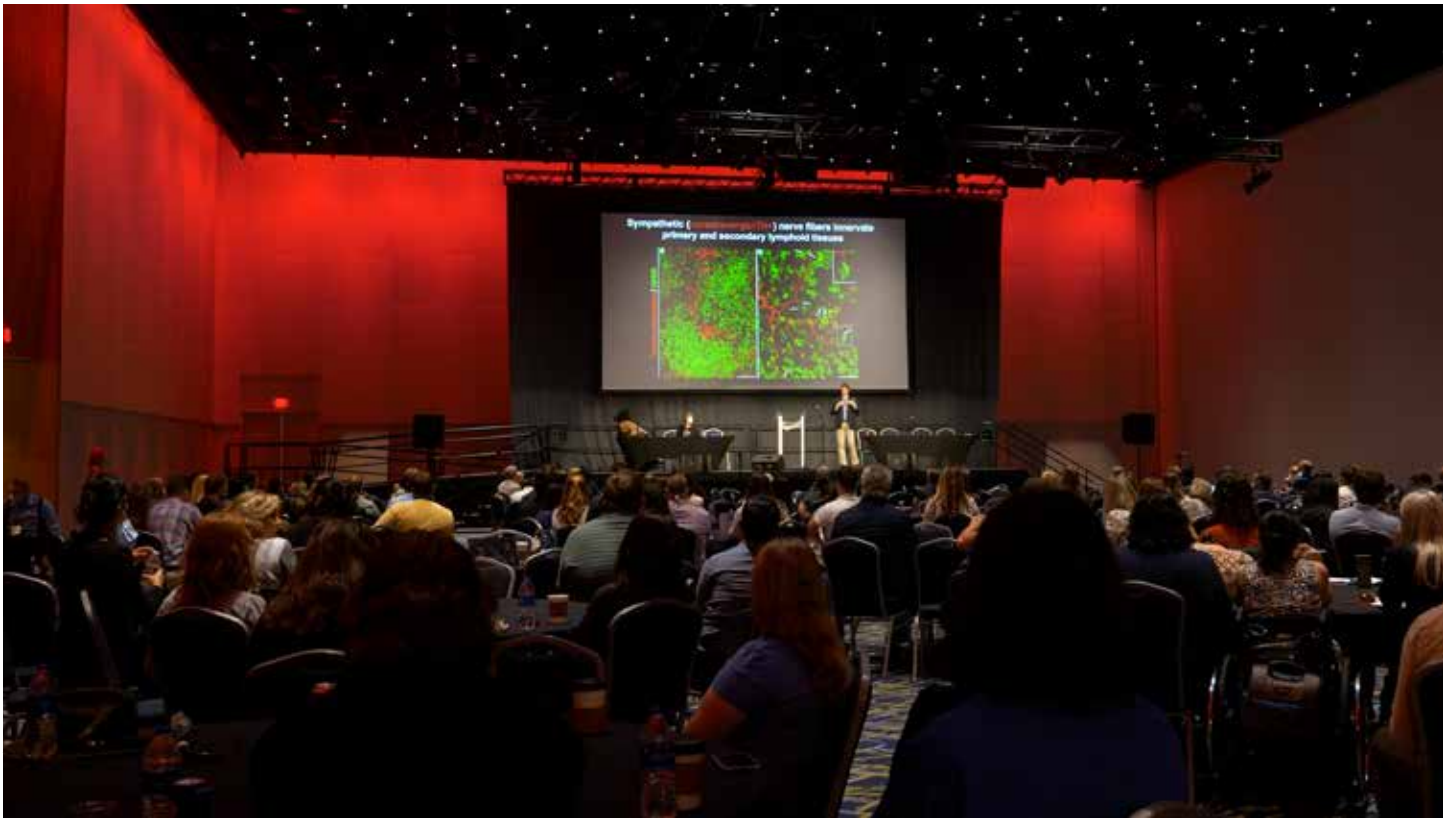

Phillip Popovich

Tigue, PhD, Ohio State University College of Medicine (married to panelist/colleague Phil Popovich). Honorary Chair: **Marissa Kirkling**, C4, a 2018 recipient of an epidural stimulator who regained blood pressure control: "I didn't realize how bad I had actually felt until I felt great. I had more energy. I felt so much more focused. It was like a new world for me."

David Gater, MD (U of Miami) described a unique pathology post-SCI he calls neurogenic obesity. This is a very common and difficult problem to manage: out of balance energy management, characterized by systemic inflammation, metabolic dysfunction, and hypertension, leading to excess body mass and its comorbidities, including cardiovascular stress, immune system inefficiency, insulin resistance, and diabetes. The question, said Gater, is whether it's even possible to achieve a negative energy balance after SCI. For many, exercise is not easily accessible, and then it only goes so far – even vigorous exercise may not be enough to burn sufficient calories. He recommended doubling the 150-minutes per week of physical exercise stipulated in current clinical practice guidelines. Dietary and lifestyle changes may be a more practical target. He recommended more education regarding risks of sedentary living, along with rigorous vigilance and bi-annual testing of the SCI population for markers of obesity and elevated blood-borne inflammation.

Phillip Popovich, PhD, who heads the Ohio State University Center for Brain and Spinal Cord Repair, described a condition called dysautonomia that often accompanies SCI. This disrupts communication between the nervous and immune systems, leading to chronic immune dysfunction and pathological changes in all organ systems. What happens is that the spinal sympathetic nervous system, a specialized part of the spinal cord that helps to keep all organs functioning normally, changes – both in structure and overall level of activity. Activity changes because after injury, communication from the brain to spinal cord, which normally serves as a brake on sympathetic function, is lost. This causes the sympathetic nervous system to become "hyperactive," resulting in overstimulation and killing of cells in the immune system. For people with SCI who are already at high risk for infections (bladder, skin, lungs, etc.), these immune changes can lead to severe medical problems. This sympathetic nervous system dysfunction is progressive, said Popovich. The body is never able to fully recover. Popovich's group hopes to target therapies to restore normal function in the sympathetic nervous system and immune system. He said that chemogenetics, using a designer drug, can effectively modulate neuronal activity in ways similar to the effect of electrical stimulation.

Session 2
Muscle as An Endocrine Organ

This session was chaired by **David Magnuson**, Kentucky Spinal Cord Injury Research Center. Honorary Chair: **Paul Erway**, spinal cord injured in 1980, pushed 50 marathons in 50 states in 50 weeks in 2013; he wrote a book series about his adventures, "50 Abilities."

David Ditor, PhD, Brock University Department of Kinesiology, also focuses on chronic inflammation due to SCI and

David Goldstein

its cascade of multi-system effects, including pain. He spoke about "high quality" weight loss – not just losing fat mass but maintaining lean mass. He's studied the role of exercise and diet in managing and reversing inflammation, including the introduction of an anti-inflammatory diet (no refined wheat products or refined sugars, no cow's milk, no hydrogenated oils, plus supplements).

Karyn Esser, PhD, University of Florida Health Department of Physiology and Functional Genomics, described the role of circadian rhythms and molecular clocks built into muscle. These rhythms are disrupted by spinal cord injury. This isn't bad for just the muscle; disruption of the molecular clock induces weakness and triggers hormonal systemic changes that affect insulin resistance, the heart, brain, and bone. Esser's lab is looking at the role of exercise in resetting the circadian clocks. Timing of activities may be an important variable for muscle clock homeostasis.

Christopher Cardozo, MD, Icahn School of Medicine at Mount Sinai, studies myokines, molecules produced and secreted by skeletal muscle to initiate crosstalk with other tissues and organs in order to regulate metabolic homeostasis. His talk asked the question, does exercise correct the unwanted effects of impaired hormone circuits in mice with spinal cord injuries? Specifically, Cardozo noted that SCI lowers certain hormones (FGF2 and adiponectin), thus impairing fat metabolism and insulin action. These effects, he said, can be reversed. Exercise could be therapeutic by normalizing levels of these hormones. Cardozo noted that drugs could be developed to balance these hormonal signals.

Session 3
Autonomic Cardiovascular Dysfunction in SCI

This section was chaired by **Andrei Krassioukov**, University of British Columbia Division of Physical Medicine and Rehabilitation. Honorary Chair: **Rob Wudlick**, spinal cord injured in 2011, Clinical Research Project Manager at the University of Minnesota Department of Rehabilitation Medicine, co-founder, North American Spinal Cord Injury Consortium, co-founder, Get Up Stand Up to Cure Paralysis.

Autonomic issues are an important area of study in the neuromodulation field. The benefits of spinal cord stimulation on such autonomic functions as blood pressure, bowel and bladder management and sexual function have been surprising and significant. Indeed, the first clinical approvals for epidural spinal cord stimulation are likely to address autonomic issues.

David Goldstein, MD, PhD, from the Autonomic Medicine Section at the National Institute of Neurological Disorders and Stroke, presented a broadened view of the autonomic nervous system. He noted that many current studies, including some discussed at this very Symposium, described autonomic physiology first presented by John Langley 100 years ago. Goldstein extends the three-part sympathetic, parasympathetic and enteric nervous systems to include neuroendocrine and neuroimmune systems. This "extended autonomic system" is central to the overall homeostasis of the body and is dramatically affected by spinal cord trauma. Goldstein's "homeostatic theory" lends itself to computer modeling and deeper knowledge, expanding opportunities for the "biocy-

Andrei Krassioukov

bernetic treatments" being discussed at the Symposium to exploit homeostasis. "Our understanding of the autonomic nervous system," said Goldstein, "is in its infancy."

Andrei Krassioukov, MD, PhD, addressed clinical applications of neuromodulation to restore autonomic function. His group was the first to show that skin-surface spinal cord stimulation restored autonomic cardiovascular control in people with SCI, completely normalizing blood pressure and eliminating symptoms of orthostatic hypotension (the dizziness and nausea experienced when sitting or standing up too fast) within 60 seconds of application. Krassioukov described current studies using transcutaneous stimulation to reduce bowel function time (from 2 hours to 25 minutes). He is also exploring changes in sexual function in an epidural stimulation study (ESTAND, University of Minnesota, principal investigator David Darrow appearing later in the Symposium program).

Jill Wecht, EdD, James J. Peters VAMC and Icahn School of Medicine, Mount Sinai, studies autonomic cardiovascular function, in particular orthostatic hypotension and autonomic dysreflexia. Here she described the destructive and often unknown impacts that unsteady blood pressure (BP) management has on daily function and quality of life for individuals with SCI – including potential cognitive dysfunction. SCI folk either don't report symptoms or consider them "no big deal." But clearly, Wecht said, BP is a big deal. Wecht's research has shown a relationship between premature cognitive aging in the SCI population with impaired autonomic cardiovascular control. "It is untenable to ignore blood pressure instability in the SCI population simply because individuals remain without symptoms," she said. "We need to do better." There are drugs that may help. And there is neuromodulation and its exciting potential to restore blood pressure control.

Keynote Address 2

The Intrinsic Capacity of the Spinal Cord to Coordinate Movements, and its Control From Brainstem and Forebrain

This talk by **Sten Grillner**, PhD, Karolinska Institute Department of Neuroscience, Stockholm, was prefaced by Honorary Chair **Rob Summers**, the first spinal cord injured person to receive a multichannel epidural implant, a project that launched the modern neuromodulation era in 2011 here in Louisville under the direction of Reggie Edgerton, Susan Harkema, et al. "Everyone can have a better quality of life because of this technology," said Summers. "Let's make it happen."

Grillner was introduced by Edgerton, who honed his spinal cord physiology skills with Grillner in Sweden in the late 1980s while taking a sabbatical from UCLA. "Sten's lab planted the seeds for all the papers and work we are hearing about now," said Edgerton.

Grillner presented an overview of the spinal cord circuitry that coordinates movement and sensory control of the different phases of the step cycle (e.g., lift, swing, touch down). He summarized the many complex ways the brainstem and the forebrain control the spinal cord. In executing motor control, Grillner noted, the task of determining which muscles are to be activated, how intensely, and for how long, has been as-

Sten Grillner

signed to neural circuits located within the spinal cord. The spinal motor system comprises a set of local interneurons assembled into ordered networks, central pattern generators, to control the activity and output of spinal motor neurons.

Grillner, still busy in the lab at age 81, continues to study spinal networks and the notion that the spinal cord is "smart." His current work is mainly in the lamprey. He explained that this ancient animal, which can be traced back 560 million years, embodies all the essential building blocks of the mammalian brain – forebrain, cortex, basal ganglia, and the dopamine system. New functions have been added over the millennia to accommodate limbs and independent hand and finger movements, language, and cognitive functions, but the essential blueprint of our nervous system evolved at the dawn of vertebrate evolution.

Day 2
Keynote Address
History and Overview of Epidural and Transcutaneous Spinal Cord Stimulation Strategies for Motor Recovery Treatments
Karen Minassian, Medical University of Vienna. Honorary Chair: **Henry G. Stifel, III**. Stifel sustained a cervical spinal cord injury 40 years ago; his family created the Stifel Paralysis Research Foundation, which merged with the American Paralysis Association and eventually became the Reeve Foundation, for which Stifel has long been a board director. In 2020 he moved from New York to Louisville to join the epidural stimulator implant program.

Minassian provided a detailed history of epidural and transcutaneous spinal cord stimulation. In 1973, just four years after the first human implants (2-electrode fixed systems) were performed to address pain, motor function recovery was surprisingly observed in a woman with partial paralysis being treated for pain due to multiple sclerosis. (Cook and Weinstein.) Surprisingly, she also regained volitional control of her upper and lower extremities, as well as sitting, standing, and ambulation function during stimulation. This led to a number of investigational studies of spinal cord stimulation for motor control; improvements in motor, sensory, and bladder function were reported.

The first implanted stimulation study targeting spinal cord injury (for spasticity) took place in 1978 in Chicago (Richardson and McLone). The stimulation alleviated spasticity and offered unexpected secondary benefits: bowel regulation, sweating below lesion level, penile erections. These results kickstarted many more spasticity related clinical trials for spinal cord stimulation. Results were generally favorable in MS and SCI.

Minassian noted the first report of epidural spinal cord stimulation in chronic spinal cord injury came in 1986. Milan Dimitrijevic, an early pioneer then working in Houston, reported that the stimulation "markedly or moderately" reduced spasticity in 63 percent of 59 spinal cord injury patients in his study.

There seemed to be great momentum 30 and 40 years ago. What happened? Minassian suggested that the studies were observational and that no one understood the mechanism. It was difficult to compare papers; some suggested motor recovery was the result of unmasking spasticity. Patient follow-up was lacking. There was not yet any data showing that

Karen Minassion

spinal cord epidural stimulation could increase plasticity in the spinal circuits after injury.

(Also, missing from the scenario four and five decades ago: public awareness, commercial development, and marketing. Contrast that with today's higher media visibility for some clinical trials, plus a much better informed and more engaged SCI community pushing for treatment development.)

While human trials slowed, work continued through the 1990s and early 2000s, including studies of locomotor (treadmill) training and rehab to promote recovery and enhance the effect of stimulation. In 1998 Dimitrijevic and Gerasimienko reported evidence of a spinal central pattern generator in humans. Tonic spinal cord stimulation elicited rhythmic, alternating stance and swing phases of lower limbs, suggesting that spinal circuitry in humans could generate stepping-like activity even when isolated from brain control.

In 2002 a paper from R. Herman *et al* reported recovery of functional gait in a quadriplegic, ASIA C (incomplete) spinal cord injured man who received a spinal cord stimulation implant along with intensive rehab training (stepping with partial weight bearing). He reportedly recovered enough to ambulate at home and in the community.

In 2004, Minassian co-authored a study with Dimitrijevic reporting that stepping-like movements in humans with complete spinal cord injury could be induced by epidural stimulation of the lumbar cord.

2011, the UCLA/Louisville group reported that a complete paraplegic (Summers) could stand with epidural lumbosacral spinal cord stimulation switched on. In 2018 this group reported overground walking in two chronic motor complete SCI individuals. This was also reported at the same time by Megan Gill and the Mayo clinic team in one motor and sensory complete individual. In addition, the Courtine group (supervised by Minassian at the Swiss Federal Institute of Technology) reported overground walking recovery in three men with incomplete SCI using next-generation implantable technologies.

Minassian and his group in Vienna are now mainly focused on transcutaneous stimulation of human locomotor networks. Earlier this year Minassian and colleague Ursula S. Hofstoetter (see below) co-edited a special edition of the *Journal of Clinical Medicine*, 16 contributions from 92 peers, "Transcutaneous Spinal Cord Stimulation: Advances in an Emerging Non-Invasive Strategy for Neuromodulation." Skin surface stimulation has a lot of upside, they report, but its acceptance in clinical practice will hinge on safety and effect, and also on better understanding of its physiological mechanism. There is much more to learn.

Reggie Edgerton

Session 4
Transcutaneous Stimulation: Motor Systems.
Chair: **Karen Minassian**, Honorary Chair: **Mike Nichols**, C5, injured in a high school hockey game in 2014.

Yury Gerasimenko, PhD, speaking by remote video feed. He's clearly one of the most widely published and oft-cited experts in the field, having contributed to work in his native Russian, in Europe and in the U.S., in particular at UCLA and in the human studies in Louisville (where he now holds an academic position). Gerasimenko also contributed to the science and intellectual property groundwork for many commercial spinal cord stimulation efforts internationally. He is scientific director for a Russian company, Cosyma, also pursuing transcutaneous therapies for SCI. Here Gerasimenko discussed a new skin-surface stimulation strategy, using multi-segmental electrode placement at the cervical, thoracic, and coccygeal segments. He showed data that this technique enabled independent stepping recovery after motor complete paraplegia.

Ursula Hofstöetter, PhD, part of the Medical University of Vienna group, has deep experience with clinical studies using transcutaneous spinal cord stimulation to boost residual locomotor function and to control spinal spasticity. Here she described studies using a simple, $250 stimulation unit. "Nothing fancy is necessary," she said, for significant benefits without side effects. She cited the effect of transcutaneous stimulation on spasticity and on "little things," such as handwriting/texting improvement and speed of ascending stairs. She too is looking at synergistic effects of multi-segmental stimulation.

Reggie Edgerton, PhD, like his old friend Grillner, is in his 80s and still remains active in the lab after more than 50 years. He's linked to the University of Southern California now but has long been associated with UCLA's Brain Research Institute and is considered the paterfamilias of the spinal cord stimulation field. He began his talk with his conflicts of interest slide. He has a stake in the neuromodulation companies SpineX and Onward, which are both currently running spinal cord stimulation clinical trials.

Edgerton's presentation title is based on a quote: "It is what we think we know already that often prevents us from learning." This is by 18th Century French physiologist Claude Bernard, whose work helped establish the concept that the body maintains a stable internal environment amidst changing external conditions — e.g., homeostasis: The point, said Edgerton, is that things we think we know become embedded in the assumptions that we "unknowingly" make, particularly the case in designing or performing an experiment or in interpreting the data from experiments.

He discussed a series of SCI focused experiments demonstrating "that what we thought we knew, was clearly wrong."

Symposium attendees, l to r, Laura Kenney, Jennifer Thompson, Andrea Behrman, Kylee Hoelscher, Linda Kenney.

In one study, rats were trained to kick a hind leg when hearing an auditory cue. Then the animals were spinal cord injured. A month later, the animals recovered stepping but no response to the sound. But after two months, after getting spinal cord stimulation, the auditory trigger was recovered. What this means, said Edgerton, is that not only did a novel connectivity form but that it was not, as might be expected, due to the recovery of the circuitry that generated stepping.

"How did the signal get from the ear to the spinal cord," Edgerton asked. "There's more basic physiology than we appreciated." He suggested that there is a "supraspinal connectome" that integrates inputs from hearing, smell, sight, taste, and touch. This system has built-in redundancies and emphasizes the central role of the dorsal spinal cord as it continuously monitors the position of the lower body throughout life. "It scares me to make any generalizations on how this works. I'm less and less sure – there is very important physiology we don't even know about."

Plenary Lecture
Mechanism-driven Technologies and Therapies for Spinal Cord Injury
Grégoire Courtine, Swiss Federal Institute of Technology. Honorary Chair, **Trisha Taylor**, mother of Davis Taylor who was spinal cord injured at age 14 in 2021 and participated in transcutaneous spinal cord stimulation research at the University of Louisville.

Courtine knows previous panelist Edgerton well, having completed his post-doctoral training under the guidance of the senior scientist at UCLA. Courtine has a lab now in Lausanne and is chief science officer for Onward. Courtine's presentation reviewed the past two decades of preclinical research, clinical trial innovations, and commercial momentum – in particular he noted the "Swiss precision" of Onward's approach – validating neuroprosthetics as a means to improve motor and autonomic functions in people with spinal cord injury.

Courtine described recent work with a "biomimetic" stimulation system. The implanted 16-electrode array is longer and broader than what's been used previously. The team used a computational framework and spinal cord atlas for optimal electrode positioning. The stimulation in this study was not continuous or static, as is the usual case. Courtine's group developed dynamic, spatiotemporal software to program a library of specific motor neuron firing patterns underlying walking, swimming, rowing, and biking. (*A discussion of spatiotemporal vs. static continued on Day 3, see below.*)

In three clinically complete (ASIA A) participants, Courtine's group reported earlier this year that biomimetic stimulation restored trunk and leg motor functions within 1 day and provided recovery of some independence after lengthy rehabilitation. The participants could stand and walk with the help of a front-wheel walker for stability.

The discussion of Onward's ambitions continued at lunch with the next speaker, company CEO **Dave Marver.** He said a trial of 65 patients had recently been completed for the company's transcutaneous stimulation device. *(Note: Top line data was released in September. The company said its primary endpoint was met: "Statistically significant, clinically meaningful improvement in upper extremity strength and function.")*

If all goes as planned, Marver says the noninvasive stimulation device will be clinically approved by mid-2023 to address arm and hand function in people with SCI. Onward's implantable system, described above by Courtine, is further down the road; trials have just begun. Marver said the likely clinical indication would be orthostatic hypotension, in a perfect scenario, hitting a 2025 target.

Session Five
Epidural Stimulation: Motor Systems
Chair, **Kristin Zhao**, Mayo Clinic Department of Physical Medicine and Rehabilitation. Honorary Chair: **Devina Robles**, cervical spinal cord injury in 2012, recipient of epidural stimulation implant in Louisville.

This part of the program featured four talks and a panel:

- **Marco Capogrosso**, University of Pittsburgh Department of Neurological Surgery; computer modeling and animal testing.
- **Igor Lavrov** of the Mayo Clinic Departments of Neurology and Biomedical Engineering; merging neuromodulation with neuroregeneration.
- **Enrico Rejc**, Assistant Professor and Director of the Metabolic, Neuromuscular and Skeletal Research Core, Kentucky Spinal Cord Injury Research Center; promoting standing function.
- **Claudia Angeli**, Kentucky Spinal Cord Injury Research Center; crossing the threshold from modulation to recovery.
- **Megan Gill**, PT, DPT. Assistive and Restorative Technology Laboratory at the Mayo Clinic, in discussion with Angeli; performance focused neuromodulation.

Capogrosso came to Pittsburgh via Switzerland where he completed his doctorate in the Courtine lab. In 2018 Capogrosso was co-author for the group's news-making epidural spinal cord stimulation study, using timed stimulation (spatiotemporal) pulses to enable voluntary control of walking in individuals with permanent motor deficits. Capogrosso takes a theoretical approach to translational neuroscience with computational neuro-biomechanical models of the spinal circuits, while at the same time testing the models in animal experiments. He described recent work (published in July) showing that targeted and timed epidural stimulation bursts restored voluntary arm and hand control in three monkeys with spinal cord injury. He's also studying spinal cord stimulation in a clinical trial for stroke.

Photo by Susan Howley

Sten Grillner and Rob Summers

Lavrov is a physician and scientist who trained in Russia under Gerasimenko and got his neuromodulation training at UCLA under Edgerton and the continued tutelage of his Russian mentor. Here he described his current work at Mayo, linking neuromodulation to neuroregeneration. He spoke of evidence that newly regenerated axons (via scaffolds seeded with Schwann cells) combined with spinal cord stimulation reorganized spinal circuitry to improve motor recovery after complete SCI. It may not be necessary to regenerate the long axons from the brain; in Lavrov's study, motor control and improved gait appeared to be achieved by regenerating short spinal tracts, thus forming detours.

Rejc, who also trained at UCLA, was a co-author on the groundbreaking 2011 Lancet paper (with Harkema, Edgerton, Gerasimenko and Angeli, all here) reporting standing in a motor complete paraplegic with spinal cord stimulation. Here Rejc presented recent work on standing and upright postural control. During stimulation and using a robotic upright stand trainer, he measured the standing performance of SCI participants as the device delivered postural perturbations. Arm and trunk movements were compared using hands on handlebars for self-balance and hands off (free hands). Free hands body control resulted in greater trunk displacement and muscle activation compared to hands on, and therefore this strategy might lead to better training methods and outcomes.

Angeli, born in Argentina, trained at Michigan State, has been involved in the dozens of epidural implants done in Louisville from the beginning for recovery of motor and autonomic dysfunction. She described recent studies from the Louisville group, including clinical trials that enabled volitional lower extremity movements in people with chronic, motor complete SCI with no clinically detectable brain connection. She reported "surprising data" regarding restoring voluntary movement as it relates to the participant's intent to take steps. "Turns out one has to be in the present for the right information to get to the spinal cord. Walking after chronic motor complete spinal cord injury took place only with combined epidural stimulation and the participant's intention to engage in walking." She was first author on a 2018 NEJM paper that demonstrated overground walking with epidural stimulation in clinically complete individuals.

Gill transitioned full-time from clinical work into research in 2018. She was involved in clinical trials at Mayo replicating epidural stimulation outcomes from the Louisville group. She was first author on the 2018 paper reporting recovery of a completely paralyzed man; he could take bilateral steps on a treadmill, independent from trainer assistance. That result, she said, depended upon several variables, including optimization of proprioceptive input during training, stimulation parameters, and the degree to which the participant attempted to intentionally control motor activity during each step cycle. Intention could be engaged using visual feedback with mirrors and verbal feedback between clinicians and participants. The best stepping performances leading to the greatest independence occurred with minimal trainer assistance, which only happened when the participant was mindfully stepping. When the participant was stepping more passively, the level of assistance increased during the stance to swing transition.

Day 3
SPECIAL PRESENTATION
How to Stimulate: Tonic-integrated Network Focused? Spatial Temporal Dorsal Root Focused?

The final day of the Symposium began with a discussion of tonic vs. spatiotemporal stimulation, featuring Claudia Angeli, Grégoire Courtine, Reggie Edgerton, Susan Harkema, Marco Capogrosso, Karen Minassian and Igor Lavrov. Tonic stimulation means that epidurally placed electrodes, when engaged, are continuously so. Spatiotemporal means electrode firing is timed to specific body positions and sequenced in pre-set stimulation patterns; stimulation bursts are applied at the exact time when the participant attempts to perform the associated movement.

There isn't yet a qualitative choice of stimulation style. Tonic is the basis of the 16-channel paddles made to treat pain; this is what got the SCI neuromod field to where it is. It is the basis for the work in Louisville, Mayo Clinic and University of Minnesota that enables the spinal circuitry to function more as it did pre-injury. The Minassian and Courtine groups innovated spatiotemporal techniques mainly to improve motor activity – e.g. walking function – in recent high-profile studies.

Important points made during the discussion:
- Motor systems may not be the clinical starting point for epidural stimulation. It is much more likely spinal cord stimulation will be approved for autonomic function, in particular blood pressure management.
- Data for spatiotemporal stimulation for autonomic, non-motor systems is just emerging.
- Is the central autonomic network hard wired to the motor cortex, and would motor output affect autonomic function? Unknown.
- Is one method superior for increasing plasticity of spinal networks? Unknown.
- The simplest, safest universal system is what clinicians will need.

Session 6
Neurosurgical Approaches and the Clinical Future of Neuromodulation
Chair, **James Guest**, University of Miami Miller School of Medicine. Honorary Chair, **Jerod Nieder**, who sustained a cervical spinal cord injury in 2011 and received an epidural stimulation implant in Louisville in 2018. His greatest benefit: being able to get a full night's sleep.

This session presented three neurosurgeon scientists, **James Guest**, Miami Project to Cure Paralysis; **Maxwell Boakye**, Chief of Spinal Neurosurgery and Director of Quality Improvement and Clinical Director of Kentucky Spinal Cord Injury Center; and **David Darrow**, University of Minnesota.

Guest, a physician/researcher, is very familiar with neuromodulation; he was PI for the Miami Project's involvement in Onward's transcutaneous clinical trial. Guest's talk here considered the effect of deep brain stimulation, alone or in combination with epidural spinal cord stimulation, on movement recovery. Guest cited 2013 work from the Martin Schwab lab in Switzerland reporting that stimulation of the mesencephalic locomotor region (MLR) of the brain markedly improved hindlimb function in rats with chronic, severe, but incomplete spinal cord injuries. What if DBS is combined with spinal cord stimulation? In animals with moderately severe SCI, DBS evokes stepping and improved weight support. Adding epidural stimulation improves weight support and gait quality.

Boakye, who came from Ghana to the U.S. as a teenager, is a half-time neurosurgeon and half-time neuroscientist. (He also has an MBA and a Masters in Public Health). Boakye was the primary neurosurgeon in almost all of the 45 epidural implants for SCI in the Louisville group. Here he discussed surgical technique and risk mitigation. Stimulator placement is a fairly easy outpatient procedure, he said. Pa-

Maxwell Boakye, James Guest, David Darrow

tient selection has been carefully managed: it's not possible to know how an individual will respond to neuromodulation from functional tests, MRI or other scans. Boakye and his team avoid people with an infection history (UTI is the most common pre-op issue) and rule out people with depression or substance abuse issues. Also important: careful surgical technique, doing it the same way every time.

Darrow started a clinical trial (E-STAND) in 2017 for epidural spinal cord stimulation while completing his residency in neurosurgery. The trial has enrolled 18 of a projected 100 participants and is seeing very positive results, similar to the work in other trials (significant autonomic recovery, some volitional movement when stimulation is off). Darrow's group implants a 16-electrode paddle (made by Abbott rather than the Medtronic unit used in the Louisville and Mayo studies. Representatives for both Abbott and Medtronic attended the Symposium).

There are significant differences between E-STAND and all other spinal cord stimulation trials: no rehab or training is required before or after implantation, therefore no team of experts is needed for follow-up, no time commitment or relocation necessary. Participants are sent home with a handheld device to dial-in their own stimulation parameters, with data recorded remotely. Here, Darrow described his experience so far with "patient-in-the-loop optimization." The idea was to separate the effect of spinal cord stimulation from the effect of training. Darrow said patterns are emerging with more participant input but admitted the huge volume of data reflects the heterogeneity of the patient mix and is useful but suboptimal. "Still kind of a mess," he said. "But patient feedback is critical to understanding optimization."

Session 7
Intersystems, Health, and Community Integration of Neuromodulation
Chair **Susan Harkema**, PhD, University of Louisville. Honorary Chair: **Denna Laing**, spinal cord injured former Boston Pride professional hockey player and 2020 recipient of an epidural stimulation implant in Louisville.

Aaron Phillips, PhD, a self-described "hemodynamic nerd," started his own laboratory at the University of Calgary in 2017 with a focus on the physiology and neuroscience of autonomic and cardiovascular function. He collaborates with many labs, including the UCLA group, the Courtine lab, and the Darrow group. Phillips is a member of the E-STAND trial team and is Scientific Director for Stimsherpa Neuromodulation, an optimization company Darrow started. Here he discussed efforts to clinically address cardiovascular instability, in particular orthostatic hypotension (lightheaded-

Susan Harkema

ness while sitting or standing up) using spinal cord stimulation. Cardiovascular dysfunction is chronically linked to heart disease after SCI. Philips said he is working with Onward, the Courtine lab and several other research groups on a multicenter $26 million Bridging the Gap study, a program of the Defense Advanced Research Projects Agency (DARPA). Phillips is tasked with developing a clinical biomimetic stimulator system to target hypotension "hotspots" in the spinal cord. Meanwhile, Phillips is currently enrolling participants with chronic cervical or high-thoracic injuries in a clinical trial to activate circuits in the spinal cord responsible for blood pressure control.

Onward sponsored a lunch discussion free-for-all in a convention center breakout room on the Symposium's final day. Members of the SCI community, their families and caregivers were invited, a turnout of about 50 people. **Scott Chesney** hosted; he's a 35-year veteran wheelchair user/spinal stroke survivor who is now a spokesman for Onward. Here are several points made by the community:

- The Symposium exposes a hard truth: the stimulation field is in its infancy; there is much more work ahead.
- Is spinal cord stimulation good enough now or should people wait for better paddles and perhaps a combination therapy to boost the effect?
- The doctors and researchers are not always aware of the patient perspective; despite the Honorary Chair concept, the same is true at this meeting.
- Walking may be sexy for companies and investors but that is not what most folks are looking for.
- Keep bladder/bowel/sexual function in the conversation.
- The group was urged to get involved in the research, clinical and translational processes that affect them, to be sitting at the decision-making table.

Charles Hubscher, PhD, Kentucky Spinal Cord Injury Research Center, spoke about his work in Louisville to integrate cardiovascular and bladder health in patients with spinal cord injuries. He and Harkema are currently directing a clinical trial measuring symptomatic autonomic dysreflexia and cardiovascular changes during bladder filling and bowel stimulation (full bladder = high blood pressure). Ultimately the goal is to regulate cardiovascular function therapeutically as part of bladder and bowel management using spinal cord epidural stimulation to normalize blood pressure. Experimentally spinal cord epidural stimulation keeps blood pressure steady, reduces incontinence and prevents autonomic dysreflexia. Said Hubscher, lower bladder pressure may mean greater storage capacity, less frequent catheterization and better quality of life.

Ona Bloom, PhD, Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Hofstra/Northwell Health, reviewed aspects of immune dysfunction related to SCI and described ways that might improve the body's defense system to improve life expectancy (infection remains the leading cause of death -- people with SCI are 80 times more likely to die of sepsis than uninjured people, said Bloom). Intraspinal and systemic inflammation appear to impede neurological recovery, she said, both acutely and chronically, leading to the list of medical consequences presented here on Day 1: autonomic dysreflexia, poor immune response, chronic inflammation, hypertension, blood pressure instability, obesity and metabolic disorders, elevated risk of heart disease, stroke, pain, and depression.

It may be possible to develop drug therapies to counter pro-inflammatory molecules affecting immune activity. Bloom said neuromodulation seems to improve immune response, as does physical activity. Vagus nerve stimulation combined with rehab is another promising area of study. "Does improved function equal improved immunity? We hope to know."

Susan Harkema, Symposium co-organizer, gave the meeting's last talk. She got her start at UCLA, studying locomotion and SCI recovery strategies, completing her neurophysiology post-doctoral fellowship under Reggie Edgerton. She was recruited to the University of Louisville 2005 to continue neuromodulation studies and was named associate director of the Kentucky Spinal Cord Injury Research Center. Harkema spoke here about her interdisciplinary team's emphasis on whole body systems and the serendipitous finding that epidural spinal cord stimulation of the lumbosacral spinal cord didn't just wake up spinal networks for motor function; stimulation also had a profound effect on autonomic function and therefore multiple body systems. Harkema is currently involved in four active clinical trials for epidural stimulation, targeting standing and stepping, bladder function, bowel motility, and cardiovascular health.

The Louisville group has done 45 epidural implants in 11 years, 2 to 1 male, 76 percent cervical injury and all but one AIS A and B (motor complete injuries). The center averages about two implants a month.

Session 8
Stakeholder Roundtable

The final presentation of the Symposium featured a lively dialog between representatives of science, clinical medicine, industry, funding, and the SCI community. The panel was chaired by **Linda Bambrick**, PhD, Program Director, National Institute of Neurological Disorders and Stroke (NINDS); she manages the portfolio of grants for spinal cord injury and axonal regeneration.

Honorary Chair and Roundtable panelist, **Denna Laing**, who has experienced both spinal cord injury and epidural stimulation.

Other panelists included

- **Camilo Castillo**, MD, a spinal cord injury physician and Program Director for the Spinal Cord Injury (SCI) Program at Frazier Neuroscience and Rehabilitation Centers.
- **Naomi Kleitman**, PhD, Senior Vice President for Grants & Research at Craig H. Neilsen Foundation.
- **Dave Marver**, CEO of Onward.
- **Mary Schmidt Read**, PT, DPT, Spinal Cord Injury Program Director, Research Coordinator, Magee Rehabilitation Hospital.
- **Nate Torgerson**, Senior Systems Engineer, Medtronic.

Here are some of the points discussed by the panel and audience, within the context that neuromodulation is a medical device technology maturing into a marketable, reimbursable therapy for spinal cord injury:

- We don't fully understand how neuromodulation or neuroplasticity works. Yet while most agree it is a necessary pursuit to investigate mechanisms, there is seen to be little incentive for researchers to do so.
- Do we have to completely understand the mechanism(s) before using spinal cord stimulation? Most people here would say no.
- Clinicians face a prescription black box; those who would apply a putative spinal cord stimulation therapy to their patients will need training – so many individuals with SCI have a primary care doctor who may know nothing about basic SCI care, imagine now adding this technology into the mix.
- Clinicians will also certainly require some sort of algorithm to predict device placement, dosage, timing, contraindications, etc.
- When does neuromodulation become "medical necessity," a key pathway to insurance reimbursement?
- What does patient care look like outside of large SCI clinical centers? It is likely spinal cord stimulation will occur in the higher volume clinics, e.g. Model Systems Centers, and filter down from there to smaller clinics.
- What do caregivers need to know about working with stimulation device settings and parameters?
- Off-label prescribing of spinal cord stimulation will happen. What could go wrong?
- Castillo: How can doctors in today's broken medical system be expected to deal with patient demand for spinal cord neuromodulation when they are not able in many ways to take care of basic SCI care?
- Kleitman: It's one thing to say isn't this technology wonderful but what are its limits? What are the safety issues?
- What happens when a battery fails, or programming becomes glitchy or outdated? What are the ethical questions related to industry support and follow-up for long-term implantation of an electro-medical device?
- Bambrick: The FDA will want a standardized approach from device companies, likely meaning regulatory approval for a narrow clinical indication just to get to market and importantly, so doctors learn how to deploy it.
- The day after the implant, insurance payors need to know

David Magnuson

what is the transition strategy, what does aftercare look like, what is the person going to be able to do at home?

- Torgerson: Companies must make a profit. Payors must make sure the device makes a real difference.
- Marver: Industry needs to get something approved, therefore the plan is to start with transcutaneous stimulation, not a high-risk device, and for which there is little or no rehabilitation reimbursement burden.
- But what exactly is the rehabilitation component going to amount to?
- What are the cost consequences to the healthcare system? Does this have potential to save money, for example, by preventing urinary tract infections, or reducing use of catheters? By reducing blood pressure issues, the health benefits would be enormous, as would the savings if cardiovascular disease or diabetes are prevented.
- Published data is not the only means of quantifying data. How and where will user experience information be kept, and shared? How about an open-source repository?
- Going forward: Panelist Laing asked, can someone please take the lead?
- Schmidt-Read suggested forming an interdisciplinary focus group.
- From the floor, the Symposium's final comment framed the next-steps discussion: Said Matthew Rodreick, Executive Director for Unite 2 Fight Paralysis, everyone in the room is a member of a research to clinical development ecosystem, with each segment of the pipeline represented on the panel. "I don't trust myself to determine what the next steps should be. I don't trust any of you individually, science, clinical medicine, industry, funding, and the SCI community, to fully represent the problem or solution. I only trust all of us together. I suggest there needs to be a platform or process that includes all our perspectives, held in an effective tension to deliver that solution."

In Conclusion:
As a final précis of the 2022 Moving Beyond Isolated Systems Symposium, program co-director and U of L Professor **David Magnuson** offers this assessment and perspective:

With the help of an outstanding program committee, we set out to organize a meeting that would address four goals. First of all, to foster dialogue and information exchange between and among several generations of world-class scientists that have contributed to the field of spinal cord stimulation and spinal cord injury. We were thrilled to include among our speakers the seasoned veterans along with early-career investigators. Attendees ranged from undergraduates to post-docs to principal investigators to professors emeriti.

Secondly, we sought to expand the conversation about spinal cord injury from the cell, tissue or motor function focus to a whole-body, systems-biology view and to bring that expanded perspective to the burgeoning field of spinal neuromodulation via transcutaneous or epidural stimulation. We assembled a team of speakers for the first day of the meeting to highlight aspects of the whole-body response to spinal cord injury, and to dig into a few important examples.

Our third goal was to focus on the state of SCI neuromodulation: Where we are now, how we got here and potentially, what are the next steps. This goal was addressed by a fantastic group of speakers that represented the major groups and centers that are focused on SCI neuromodulation. A keynote address from Karen Minassian beautifully handled the "how we got here" component.

Finally, our fourth and perhaps most important goal was to bring together several key SCI neuromodulation stakeholders including consumers, caregivers, clinicians, representatives from industry and funding agencies to exchange ideas on the further development and future deployment of SCI neuromodulation to those who will benefit. This was addressed by the final session, chaired by Linda Bambrick and including representatives of the key stakeholder groups. This session resulted in several important ideas and suggestions, including the need for smaller focus groups, a larger, perhaps NIH-sponsored workshop, and future iterations of this meeting.

On behalf of the organizing committee, and the many people involved both behind and in front of the microphones, we thank you.