Epidural Spinal Cord Stimulation In A Paraplegic Human

Background to the May 19, 2011 Article in *The Lancet*

**Overview**
More than 5.6 million Americans live with some form of paralysis, defined as a central nervous system disorder resulting in difficulty or inability to move the upper or lower extremities.

More than 1.275 million are spinal cord injured, and of those many are completely paralyzed in the lower extremities. In addition to total loss of motor control, this type of paralysis is also characterized by impairment or loss of bladder control, sphincter control and sexual response.

Epidural stimulation, in the context of paralysis of the lower extremities, is the application of continuous electrical current, at varying frequencies and intensities, applied to specific locations on the lumbosacral spinal cord corresponding to the dense neural bundles that largely control movement of the hips, knees, ankles and toes.

**Animal Experiments**
In a series of animal experiments beginning in the 1980s, UCLA life scientist V. Reggie Edgerton, Ph.D., Yury Gerasimenko, Ph.D., and colleagues demonstrated conclusively that, even when the spinal cord is completely disconnected from the brain, it is possible to induce stepping motions in the legs of living cats. But rats cannot step without electrical stimulation of selected regions of the lower spinal cord. Further experiments proved the animals could stand, balance and bear weight.

In their most recent animal experiments, published in *Nature Neuroscience* in 2009, Dr. Edgerton's team demonstrated that while being stimulated epidurally, the spinal cord's neural networks can initiate and sustain weight bearing and relatively coordinated stepping without cortical involvement. One of the novel findings in a series of studies by this team was that the spinal cord neural networks that can generate stepping could be controlled or directed by the sensory information from the legs. This sensory control enabled the rats to fully bear their weight, balance, step over a range of speeds and even in different directions—but only when prompted with stimulation of the spinal cord in very selected ways and at selected places.

Starting eight years ago, Joel Burdick, Ph.D. of the California Institute of Technology teamed with the Edgerton lab, to study how robotically guided physical therapy and pharmacology could be coupled in order to better recover locomotion in animal models of spinal cord injury. Building upon these studies and the earlier work of Edgerton and Gerasimenko, Dr. Burdick and Yu-Chong Tai, Ph.D. introduced the concept of high-density epidural spinal stimulation, which better pinpoints the spinal stimulating fields by the use of large numbers of stimulating electrodes.

Epidural electrical stimulation was one of three treatment modalities employed in this advanced animal research. Simultaneous with sequential patterns of electrical stimulation, the animals' legs were being precisely manipulated on a sophisticated rodent treadmill, faithfully reproducing a healthy rat's stepping patterns in real time just as the spinal circuitry was electrically stimulated. This "Locomotor Training" (LT) was found to take advantage of these neural networks' excitability and improve performance. Further performance gains were realized with use of specific serotonergic drugs.
2009 - 2010: The First Human Test

Another prominent neuroscientist, Susan Harkema, Ph.D., of the University of Louisville, was once a postgraduate student in Dr. Edgerton's UCLA lab. Dr. Harkema went on to specialize in the study and treatment of human spinal cord injuries with Locomotor Training. She also directs the Human Locomotion Research Center at Frazier Rehab Center in Louisville.

In a human LT session, the body of a paralyzed patient is suspended in a harness over a moving treadmill (a much larger and more sophisticated version of the original rodent equipment) while several specially trained therapists repeatedly help manipulate the legs in a repetitive stepping motion.

Locomotor Training is successfully employed today in clinical settings -- but without any epidural stimulation -- as a rehabilitative technique for partially paralyzed patients. Similarly, a form of epidural stimulation is used for pain relief following some incomplete spinal cord injuries. But while the combination of epidural stimulation, simultaneous LT and quipazine has indeed proved beneficial in animals with motor-complete spinal cord injuries, there had never been any human testing, which requires investigational approval from the Food and Drug Administration (FDA).

In 2009, the FDA did approve a human research protocol submitted by Drs. Edgerton, Harkema and colleagues. Experiments with epidural stimulation and Locomotor Training were authorized involving a total of five motor-complete SCI individuals.

The initial subject selected for the inaugural study, as reported in *The Lancet*, was completely paralyzed in his lower extremities following a hit and run accident in July 2006. Formerly an athlete in extraordinary physical condition, he suffered a complete motor injury at the C7/T1 level, classified ASIA B on the American Spinal Injury Association's scale as he did retain some sensation in his legs.

Prior to implantation of the epidural stimulator, the subject underwent 170 Locomotor Training sessions with no stimulation over a period of 26 months -- with no measurable effect -- in order to ensure that LT alone was not responsible for any subsequent improvements.

Key Research Findings

In the initial phase of the research experiment, the subject has been able to reach a standing position, supplying the muscular push himself while his spinal cord was being stimulated electrically. He can stand independently, bearing full weight, for up to four minutes at a time (up to an hour with periodic assistance when he weakened). He also developed the capacity to voluntarily move his toes, ankles, knees and hips while being stimulated. In addition, he experienced improved temperature regulation and some recovery of autonomic function. Potential Limitations: Human, Equipment and Drugs.

"While these results are obviously encouraging, we need to be cautious, and there is much work to be done," says Dr. Edgerton.

To begin with, only one subject has been studied; the results need to be replicated. (The second of five subjects authorized by the FDA has now been selected). In addition, the first subject, while completely motor-injured below the C7 spinal section, did retain some feeling below the lesion level. It is not yet known how these interventions will work with those who have no conscious sensation below the injury.

Yet another issue is the equipment involved, which, although highly effective for pain relief, was never designed for this purpose. Substantial research and development investment by the medical device industry, government or scientific entrepreneurs will likely be required to further advance the state of the art.
Finally, the drug compounds used in animal testing are not suitable for human use; it is likely a large investment in further pharmacological research will also be needed.

Nonetheless, Drs. Harkema, Edgerton and their colleagues envision a day when at least some individuals with complete spinal cord injuries will be able to use a portable stimulation unit and, with the assistance of a walker, stand independently, maintain balance and execute some effective stepping. Possibly even more importantly, the secondary complications associated with spinal cord injury may be greatly affected, improving the quality of life of these individuals.

"This is a significant breakthrough," notes Dr. Harkema. "It opens up a huge potential to improve the daily functioning of individuals." "We now have proof of concept," adds Susan Howley, Executive Vice President for Research at the Christopher & Dana Reeve Foundation "It's an exciting development. Where it leads to from here is fundamentally a matter of time and money."

**Lead Investigators**

*Susan Harkema, Ph.D.* is a leading researcher in the field of neurological rehabilitation. She is Professor in the Department of Neurological Surgery at the University of Louisville; Rehabilitation Research Director at the Kentucky Spinal Cord Injury Research Center; Director of Research at the Frazier Rehab Institute in Louisville; and Director of the Christopher & Dana Reeve Foundation's NeuroRecovery Network.

Dr. Harkema is lead author of [*The Lancet*](https://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.7391713/k.A66/Epidural_Spinal...) article. Her primary focus is the study of the plasticity of the human lumbosacral spinal cord in individuals with spinal cord injury during Locomotor Training.

*V. Reggie Edgerton, Ph.D.* is a leading researcher in the field of neuromuscular plasticity. He is a Distinguished Professor in the Departments of Integrative Biology and Physiology and of Neurobiology and is a member of the Brain Research Institute at The University of California, Los Angeles.

Dr. Edgerton's laboratory focuses on two main research questions. One is, how, and to what extent, does the nervous system control protein expression in skeletal muscle fibers? A second, general question is how the neural networks in the lumbar spinal cord of mammals, including humans, control stepping and how this stepping pattern becomes modified by chronically imposing specific motor tasks on the limbs after complete spinal cord injury. Dr. Edgerton has worked with NASA in studying strategies to preserve the ability to perform movements safely during prolonged weightlessness, where crewmembers must maintain a critical level of locomotion control when returning from microgravity and returning to 1G.

*Yury Gerasimenko, Ph.D.* is a Professor and Director of the Laboratory of Movement Physiology, Pavlov Institute of Physiology in St. Petersburg, Russia and Researcher in the Department of Integrative Biology and Physiology at the University of California, Los Angeles. Dr. Gerasimenko is a pioneer in the use of epidural spinal cord stimulation for regulation of locomotor behavior in spinal animals, as well as subjects with injured spinal cords. He has performed extensive studies to develop an effective rehabilitative strategy for recovery of injured spinal cord by using a combined therapy including epidural spinal cord
stimulation, pharmacological intervention and locomotor training.

Jonathan E. Hodes, M.D., F.A.C.S. is a clinician, scientist and leading neurosurgeon in minimally invasive and microsurgical techniques of the brain and spine. He is Chairman of the Department of Neurological Surgery at The University of Louisville. Dr. Hodes has particular interests in clinical and translational research in spinal cord injury and in neurovascular disease, including brain aneurysms and minimally invasive neurosurgery. Dr. Hodes performed the implantation of the epidural stimulator, a series of 16 electrodes, on the spinal cord of the subject in *The Lancet* article. He serves as Clinical Research Director at the Kentucky Spinal Cord Injury Research Center.

Joel W. Burdick, Ph.D. is an expert in robotics, computer algorithms and neural prosthetics. He is Professor of Mechanical Engineering and Bioengineering at the California Institute for Technology, and former Executive Officer for Bioengineering and Deputy Director of the Center for Neuromorphic Systems Engineering. Dr. Burdick has worked with the Edgerton team for more than eight years developing new electromechanical technologies and computer algorithms to aid in locomotion recovery in spinal cord injured patients.

Claudia Angeli, Ph.D. manages the Human Locomotion Research Center at Frazier Rehab Institute. She holds adjunct appointments in the Departments of Neurological Surgery and Mechanical Engineering at the University of Louisville. She has 12 years' experience studying human gait and function; five studying recovery of function following spinal cord injury.

**Funding**

Funding for the epidural stimulation human research project was provided by the Christopher & Dana Reeve Foundation and the National Institutes of Health (NIBIB).

The Reeve Foundation is a national, nonprofit organization dedicated to curing spinal cord injury and improving the quality of life for people living with paralysis, by funding innovative research and through grants, information and advocacy.
The Foundation has provided grants to investigators around the world to explore spinal cord injury, repair and regeneration for three decades.

**Epidural Stimulation Research Advisory Panel**
The Reeve Foundation, with input from the investigators, established this panel to provide scientific and medical guidance; independently assess the project; and deliver thorough project assessments annually.

- Fred H. Gage, Ph.D., The Salk Institute, La Jolla, California
- Sten Grillner, Ph.D., Karolinska Institute, Stockholm, Sweden
- Robert G. Grossman, M.D., The Methodist Hospital, Houston, Texas
- P. Hunter Peckham, Ph.D., Case Western Reserve University, Cleveland, Ohio
- Arnold Snider, Vice Chairman, Christopher & Dana Reeve Foundation

**Participating Institutions**

**The Christopher & Dana Reeve Foundation** is dedicated to curing spinal cord injury by funding innovative research and improving the quality of life for people living with paralysis through grants, information and advocacy.

**UCLA** is California's largest university. The UCLA College of Letters and Science and the university's 11 professional schools offer 328 degree programs and majors. UCLA is a national and international leader in the breadth and quality of its academic, research, health care, cultural, continuing education and athletic programs. Six alumni and five faculty have been awarded the Nobel Prize.

**The University of Louisville** is Kentucky's metropolitan research university, with 22,000 students attending classes at 11 colleges and schools on three campuses. Bordered by its many medical partners, UofL's downtown Health Sciences Center is home to more than 3,000 students pursuing degrees in health-related fields with the Schools of Dentistry, Medicine, Nursing and Public Health and Information Sciences, as well as 17 interdisciplinary centers and institutes.

**Frazier Rehab Institute** is a comprehensive rehabilitation system with more than 20 locations throughout Kentucky and southern Indiana, providing therapy in acute care settings for inpatient and outpatient rehab needs. Comprehensive rehab programs, highly skilled therapists, state-of-the-facilities and innovative therapeutic techniques have earned Frazier Rehab national recognition. From infancy to geriatrics, a wide variety of diagnoses are treated including neurologic (spinal cord injury, brain injury and stroke), amputations, multiple trauma, orthopedic, arthritis, cardiopulmonary, congenital, developmental, degenerative and general medical cases.

**The California Institute of Technology** is recognized for its highly select student body of 900 undergraduates and 1,200 graduate students, and for its outstanding faculty. Since 1923, Caltech faculty and alumni have garnered 32 Nobel Prizes and five Crafoord Prizes. In addition to its prestigious on-campus research programs, Caltech operates the Jet Propulsion Laboratory (JPL), the W. M. Keck Observatory in Mauna Kea, the Palomar Observatory, and the Laser Interferometer Gravitational-Wave Observatory (LIGO). Caltech is a private university in Pasadena, California.