CURRENT TRENDS IN THE FIELD OF BRAIN INJURY AND BRAIN INJURY TREATMENT
Coma to Concussion; Prevention and Treatment

David S. Demarest, Ph.D.
On With Life, Ankeny, Iowa
Director of Psychology, Neuropsychology, and Clinical Counseling Services
Director of Research Affairs

OUTLINE

FACTOIDS (Neuroprostheses, electrical stimulation, Disorders of Consciousness; concussions)

STEM CELL RESEARCH

AGING AND BRAIN INJURY

FALLS/NEUROPSYCHOLOGY OF FALLS

NEUROPROSTHESES WORK CONTINUES
BRAIN-CONTROLLED WHEELCHAIR (DECODING BRAIN SIGNALS VIA A BRAIN-COMPUTER INTERFACE [BCI])
More than a decade ago, Erik Sorto, 34, was paralyzed after a gunshot wound to the neck. Now, using a robotic arm that he controls with his brain, he can pick up a drink and bring it to his lips in one smooth motion.

But unlike other experimental robotic arms, this one relies on signals sent from a device implanted in Mr. Sorto’s posterior parietal cortex—a part of the brain that plans and imagines activities.

Neural prosthetic devices are generally implanted in the motor cortex, the part of the brain responsible for executing movements. They work, but in delayed, jerky movements.

"We decode the imagined movement, and the limb executes it," said Richard Andersen, a neuroscientist at the California Institute of Technology.

### WORK WITH ELECTRICAL STIMULATION CONTINUES

(REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION [rTMS] AND TRANSCRANIAL DIRECT CURRENT STIMULATION [TDCS])

- **Title of Proposal:** Repetitive Transcranial Magnetic Stimulation (rTMS) to Restore Function After Severe Traumatic Brain Injury

- **Primary Investigator:** Theresa Pape, Dr.P.H.

- **Sponsoring Sites:**
  - Marianjoy Rehabilitation Hospital
  - Northwestern University
  - Edward Hines, Jr. Veterans Affairs Hospital

**This project**, upcoming in 2017, will involve On With Life subjects who have sustained severe traumatic brain injury and who are no more than one year post-injury, in order to examine the effect of rTMS, an innovative and “cutting-edge” treatment and intervention which has shown, and now in human subjects, greater recovery in a number of areas over time compared with a control group. Subjects will be transported to, treated, and assessed at Northwestern University/Marianjoy Rehabilitation Hospital. Follow-up assessment by On With Life staff will occur following subjects’ returns to OWL, with all follow-up data being provided to the primary researcher, Dr. Pape. This study will involve a granteehip provided to OWL through the grant funding awarded to Dr. Pape and her team.

• 2016, Journal of Pain – “Brain stimulation effective for phantom limb pain”

• 2016, Journal of Alzheimer’s Disease – “Brain stimulation slows cognitive decline in Alzheimer’s Disease”


• 2016, Stroke – “Early brain stimulation helps stroke survivors recover language function”

• Large human trials aren’t off the ground well yet; see Clinical Trial next slide through the VA
NEUROLOGIST’S OPEN LETTER TO ANNALS OF NEUROLOGY, 2016—EXPERTS WARN AGAINST DIY BRAIN STIMULATION

DISORDERS OF CONSCIOUSNESS

- Longitudinal Outcome of Patients with Disordered Consciousness in the NIDRR TBI Model Systems Programs

Few studies address the course of recovery from prolonged disorders of consciousness (DOC) after severe traumatic brain injury (TBI). This study examined acute and long-term outcomes of persons with DOC admitted to acute inpatient rehabilitation within the National Institute on Disability and Rehabilitation Research (NIDRR) TBI Model Systems Programs (TBIMS). Of 9028 persons enrolled from 1988 to 2009, 396 from 20 centers met study criteria. Participants were primarily male (73%), Caucasian (67%), injured in motor vehicle collision (66%), with a median age of 28, and emergency department Glasgow Coma Scale (GCS) score of 3. Participant status was evaluated at acute rehabilitation admission and discharge and at 1, 2, and 5 years post-injury.

During inpatient rehabilitation, 268 of 396 (68%) regained consciousness and 91 (23%) emerged from post-traumatic amnesia (PTA). Participants demonstrated significant improvements on GCS (z = 16.135, p ≤ 0.001) and Functional Independence Measure (FIM) (z = 15.584, p≤0.001) from rehabilitation admission (median GCS=9; FIM=18) to discharge (median GCS=14; FIM=43). Of 337 with at least one follow-up visit, 28 (8%) had died by 2.1 years (mean) after discharge. Among survivors, 64 (19%) improved in Functional Recovery of Persons with Traumatic Brain Injury (FUTURE) GCS Score by 5 or more points after discharge. Participants with follow-up data at 1, 2, and 5 years post-injury (n=108) demonstrated significant improvements on the FIM-Motor (p<0.01) and Disability Rating Scale (p=0.1). Significant improvements were observed on the DRS and FIM Motor at 1 and 2 years post-injury (p<0.01). Persons with DOC at the discharge admission at 1, 2, and 5 years post-injury showed significant improvements throughout initial recovery and in years post-injury.

CONCUSSIONS FINDINGS... LOTS GOING ON, WITH MUCH MONEY PUT INTO THE GAME

- 9/2-16 NEW YORK TIMES – “POP WARNER IS FACING A CLASS-ACTION LAWSUIT OVER CONCUSSIONS”
- 2016, ORTHOPAEDIC JOURNAL OF SPORTS MEDICINE – “CONCUSSION RATES RISING SIGNIFICANTLY IN ADOLESCENTS”
- 2016, AMERICAN ACADEMY OF NEUROLOGY – “EVIDENCE ATHLETES HAVE WHITE MATTER BRAIN CHANGES SIX MONTHS AFTER A CONCUSSION”
- 2016, FRONTIERS IN NEUROLOGY – “IN FIRST-EVER SURVEY, 36 PERCENT OF WATER POLO PLAYERS REPORT CONCUSSIONS”
• BIAIA IS PARTNERING WITH ST. LUKE’S HOSPITAL IN CEDAR RAPIDS AS TO CONCUSSION TRAINING/PROGRAM?

• CHILDSERVE IN JOHNSTON HAS A CONCUSSION CLINIC, INCLUDING ADVERTISING BASELINE SCREENING/EVALUATION

• UNIVERSITY OF IOWA SPORTS MEDICINE/UNIVERSITY OF IOWA CONCUSSION CLINIC

• 2016, DES MOINES REGISTER – “IOWA’S YOUTH SOCCER LEAGUES ENACT HEADING CHANGES TO PREVENT CONCUSSIONS”

• The number of high school football players in the U.S. has declined by 25,000 over the past five years. Last year, five high school players died playing football. That is more deaths than in college, semi-pro, or professional levels according to the National Center for Catastrophic Sports Injuries.

• 2016, JOURNAL OF NEUROTRAUMA – “HEAD IMPACTS FROM SINGLE SEASON OF HIGH SCHOOL FOOTBALL PRODUCE MEASURABLE CHANGES IN BRAIN CELLS”

• 2016, AMERICAN ACADEMY OF NEUROLOGY – “MORE THAN 40% OF RETIRED NFL PLAYERS HAVE BRAIN INJURY”

• 2016, SCIENCE DAILY – “PITUITARY INSUFFICIENCY IS PREVALENT AFTER BLAST CONCUSSION IN MILITARY VETERANS” (SLEEP DISTURBANCE, FATIGUE, DEPRESSION)
WHAT IS A STEM CELL ANYWAY?

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

What do stem cells do, including but not limited to CNS conditions?

- They get injected into animals... and in a nonregulated way in persons more and more
- They help
- They die or they don’t integrate properly
- They cause tumors (Safety...)
- They do things other than they were hypothesized to do, good or bad (e.g., “Diabetes” study in mice – target was pancreas; increased blood flow)
Stem cell work in animals continues to show great promise. The work has focused primarily on spinal cord injury.

We have discovered neuronal stem cells in the adult brain. “Many questions remain before we adequately understand how to control these cells to repair anything, including a damaged brain” (Laurence Katz, M.D., Director, UNC School of Medicine Carolina Resuscitation Research Group).

---

STEM CELL RESEARCH/FINDINGS

**Cord Blood Stem Cells Give New Hope to Brain Damage**

---

U of California, Irvine, 2008 – researchers have identified a gene that is specifically responsible for generating the cerebral cortex – this “creator” gene instructs stem cells in the developing brain to form the cortex (which is where higher cognitive functions are more likely to exist).

U of Pennsylvania School of Medicine 2008; *Journal of Neurosurgery* – Have figured out how to grow neurons in culture in systems – a neural network – which still maintain the ability to generate electrical signals, and have transplanted the network into animals. They’ve induced axons to actually grow. They’ve “created the first engineered living human nervous tissue constructs.”
• James Fallon mobilized existing stem cells, causing them to proliferate, migrate and eventually differentiate into new cells (shown by the red area back left) that fill in the damaged animal’s brain, returning function to the stroke victim. (Credit: Photo by Daniel A. Anderson/University Communications)
• (2011)

(2011)
• More animal studies, including ones implanting human neural stem cells into mice, are showing both that the cells are growing in the animals’ brain, but also that doing so can improve cognitive and physical function in the animals. “Stem Cells Help Irradiated Mice Grow New Brain Cells.”

(2011) Fascinating growth of organs with stem cells! “First permanent artificial organ via stem cells” – A lab-grown windpipe:

IT’S A PLASTIC POLYMER MATRIX “DIPPED IN THE CELL BROTH, COATING IT AND AT THE SAME TIME EXPOSING THE LIVING CELLS TO OXYGEN”
• Stem cells are being used to grow a number of different human body parts in the lab, such as a vein, a windpipe, and a urethra. Kidneys, lungs and livers are thought to be the next round of major structures that may be grown with stem cells!

(2011)

• Too many stem cell studies have “poor donor cell survival and functionality.” “The ongoing tissue inflammation and scarring at the lesion site, in addition to the lack of supportive tissue structure within the cavity, present a hostile environment that jeopardized the survival of transplanted cells.”

• 2010 – First human trial of neural stem cell therapy for a stroke survivor

• World’s First Procedure to Repair Brain Damage from Stroke
  Performed at the University of Pittsburgh Medical Center

• PITTSBURGH, — Doctors at the University of Pittsburgh Medical Center (UPMC) performed the world’s first cell transplant to reverse brain damage from stroke on an 82-year-old woman with paralysis of the right leg and arm and loss of most speech.
(2013) STEM CELL RESEARCH UPDATE

- American Academy of Neurology Conference January 2013
- In an animal model of ALS (progressive, neurodegenerative disorder characterized by loss of motor neurons), a minimally invasive method of reprogrammed adult cells into stem cells extended lifespan and improved neuromuscular function — "the neural stem cells expressed all the neural stem cell markers and had neural stem cell-specific markers." 

- Scientists removed the cells from a rat kidney, leaving only its collagen scaffolding, then reseeded the scaffolding with neonatal stem kidney cells, producing a manmade kidney which, transplanted into rats, filters waste and produces urine. Research is moving to pigs, then humans.

(2013) STEM CELL RESEARCH UPDATE CONTINUED...

- Using an immune-suppressing medication and adult mouse stem cells, researchers at U of M–Columbia have cured type 1 diabetes in mice. The stem cells turned into endothelial cells that generated the development of new blood vessels to supply existing beta cells with the nourishment they needed to regenerate and thrive.
• We’re still growing organs. Youngest patient ever to be given a grown organ – 2 and ½ year old girl who had a windpipe grown using plastic fibers/matrix and stem cells taken from her bone marrow. Previous youngest was a 4 year old with spina bifida who had a bladder grown.

• 2013 Scientists Fabricate Rudimentary Human Livers
• Use of human stem cells, created from human skin cells, to make a functioning solid, small, organ, which, when transplanted into mice, grew in size, made human liver proteins, and metabolized drugs as human livers do. The liver buds also developed blood supplies, attaching themselves to the blood vessels of the mice.

• Cell transplantation, 2015
• Transplanted human umbilical stem cells into mice “modeled with Alzheimer’s Disease”, just through iv injection, to investigate how the cells distributed and stayed in the system (our imaging techniques are getting better), and found that the cells migrated to brain tissue as well (as elsewhere), were retained there for up to 30 days, and did not promote the growth of tumors.
• They’re going to inject the cells intracerebrally next.

• For a minimum of $15K, professional athletes are not getting a “soup” of human cells that includes stem cells derived from a patient’s own fat – knees, elbows, hips, necks, and it will be going into brains soon. IntelliCell Corporation. There are individuals who say that it’s helping them…

• James Andrews, perhaps the most prominent sports doctor in America, agree to serve as a consultant and was issued 18 million shares in the company.

• New York Times article in last month – “Here’s the catch. Nobody knows if this type of treatment really works or if it’s even legal under FDA rules.” Complicated issue.

• Stem cell clinics in the USA have quadrupled in the last five years to 200.
• June, 2015 University of Connecticut Health Center, ImStem Biotechnology, and Advanced Cell Technology — showed that mice with an MS-like disease “could be restored to near normal by injecting them with a different type of stem cell... mesenchymal stem cells derived from human embryonic stem cells.” Those cells crossed the blood-brain barrier and migrated to damaged cells in the nervous system, reducing symptoms and appearing to “repair the damaged sheathing around nerves cells that is the hallmark of MS”

• In addition to the organs that have been grown with stem cells, the latest is a skin substitute developed from a patient’s cells to treat complex burns and soft tissue injuries – US Army Institute of Surgical Research in San Antonio. In grafts, it lowered the rate of infection, resulting in less need for immunosuppressants and reducing the number of surgeries required.

• Nature, January 2015 – RIKEN Center for Developmental Biology in Kobe, Japan
• Researchers turn adult cells back into stem cells — “just squeezing or bathing cells in acidic conditions can readily reprogram them into an embryonic state.”
• Cells were able to be made “pluripotent” stem cells though stress (stimulus-triggered acquisition of pluripotency)
• Dr. Haruku Obokata has already reprogrammed a dozen cell types, including those from the brain, blood, lung, skin, and liver. 25% of the cells survive the stress and 30% of those convert to the pluripotent cells.
• In theory, a doctor could, say, scrape some cells off the arm of a heart attack patient and turn them into stem cells, which could then become healthy heart cells.
• “Stem cell transplantation will be a promising stroke therapy in the future.” USF College of Medicine Department of Neurosurgery and Brain Repair, October, 2015. Stem Cells

• Rats modeled with stroke had a newly discovered type of skin-derived stem cell – MUSE (multilineage-differentiating stress-enduring) transplanted, with significant improvements in neurological and motor functions.

• The cells “attained neuronal characteristics… readily differentiated into neural-lineage cells after integration into the stroke brain,” and did not cause tumors.

Don’t have the clinical trials specific to humans and brain injuries – yet

• UTHealth and Children’s Memorial Hermann Hospital study cord blood stem cells for pediatric traumatic brain injury

• HOUSTON, TX (January 05, 2011) – Discontinued the study; IDK why

• Cord Blood Registry Center for Regenerative Medicine is partner in trial

Don’t have the clinical trials specific to humans and brain injuries – yet. But...

• The University of Texas Health Science Center at Houston (UTHealth) has begun enrollment for the first Phase I safety study approved by the Food and Drug Administration to investigate the use of a child’s own umbilical cord blood stem cells for traumatic brain injury in children. The study is being performed in conjunction with Children’s Memorial Hermann Hospital, UTHealth’s primary children’s teaching hospital.

• The innovative study, which builds on UTHealth’s growing portfolio of research using stem cell-based therapies for neurological damage, is led by principal investigator Charles S. Cox, the Children’s Fund Distinguished Professor of Pediatric Surgery and Pediatrics at The University of Texas Medical School at Houston, part of UTHealth, and director of the pediatric trauma program at Children’s Memorial Hermann Hospital. It will enroll 10 children ages 18 months to 17 years who have umbilical cord blood banked with Cord Blood Registry (CBR) and have suffered moderate to severe traumatic brain injury (TBI). The study is not designed for acute care and will only enroll participants within 6-18 months of their injury.
BRAIN INJURY ACROSS THE LIFE SPAN – LONG-TERM PLANNING

BRAIN INJURY ASSOCIATION OF AMERICA

Conceptualizing Brain Injury as a Chronic Disease
Brain Injury Association of America, 2009

A position paper of the Brain Injury Association of America

AGING AND BI

• Aging and BI, and the continued trend to think of BI as a long-term health problem/process, even as to the point of arguing for the terms “patient” and “disease”

• Aging issues encompass those individuals who sustain injuries when younger and are living into older age, as well as older individuals sustaining injuries
BRENT MAZEL, M.D. –
“BRAIN INJURY AS A DISEASE”

• "Brain injury disease should be reimbursed and managed on a par with other diseases. It’s not now.
• Only then will they (Ps) get the medical surveillance, support and treatment they need and deserve.
• Only then will TBI research receive the funding it deserves and requires.
• Only then will we be able to truly speak of a cure!

DR. MAZEL

• Brain injury is not an event!
• It never ever ever goes away!
• It’s not a static process
• It impacts organ systems
• It is ‘disease causative and disease accelerative’

• Event: “The final outcome”
• Disease: “A condition of ill-health or malfunctioning in a living organism”

EVIDENCE TO USE THE TERM DISEASE:

• Life expectancy reduction (7 years as average)
• Increased problems with
  • Seizures
  • Septicemia (infection)
  • Pneumonia
• 1.5 times more post-injury hospitalizations (at 10-year mark; Brain Injury, 2008)
• 2.2 times more post-injury days in the hospital
• 1.4 times more post-injury physician claims
• Increased incidence of neurologic problems, visual disturbance, sleep disturbance, neuroendocrine dysfunction, growth hormone dysfunction, and more—dysfunction with thyroid, gonadal hormone, sexual, musculoskeletal, incontinence, psychological problems, Alzheimer’s...
MEDICAL PROBLEMS FOUND WITH TBI

• Balance
• Sleep
• Headaches
• Seizures
• Spasticity

Loss of Urinary Control
Body Temperature Changes
Arthritic Conditions
Risk of Stroke

Mt. Sinai School of Medicine, 2006

• HO can continue to be longer-term risk factor, especially with severe TBI
• Immune system may be associated with higher prevalence of infection ('posttraumatic immune paralysis'
• 1.5-17 (depends on severity) more likely to develop seizures. Yasseen et. Al, 2008 found 9% of TBI group 24 years post-injury were being treated for Szs.
• From injury to time of seizure can be as long as 12 years (Aarabi et. al., 2000)

254 individuals, 2 and 5 years post-injury, 42% continued to report visual disturbance at 5 years (Oliver et. al., 2000)
• Sleep complaints are common, up to 70% in TBI outpatient group (Chesnut et. al., 1999)
• The National Highway Traffic Safety Administration showed 56K auto crashes annually cited by officer as driver drowsiness being evident/a factor, 2003)
• Hypopituitarism is found in 30% over a year post-injury, mod-to-severe injury. Interestingly, 5% had normal pituitary (Agha & Thompson, 2006) functioning at 3 months but developed the condition at one year
• 5% of persons still incontinent at one year follow-up (Safaz et. al., 2008)
WITHIN THE REALM OF FALLS:

- Balance and gait issues associated with aging
- Cognitive impairment
- Alcohol intoxication
- Medication side effects
- Adverse drug reactions

Are all associated as major risk factors for fall-related traumatic brain injury in older adults

(AT THE SAME TIME), THOSE WITH TBI ARE NOT PREDESTINED TO MEDICAL & PSYCHOLOGICAL CONDITIONS

BRAIN INJURY & DEMENTIA

- Dementia of the Alzheimer’s type (DAT) – the most common dementia
  
  **Symptoms of DAT**
  - short-term memory loss
  - arithmetic
  - naming
  - wandering
  - disinhibition
  - insomnia

- Vascular Dementia – second most common form of dementia
BRAIN INJURY & DEMENTIA
RELATIVE RISK (RR) OF ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>TBI Severity</th>
<th>No TBI</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Plassmon & Evans, 2006

PSYCHOLOGICAL ISSUES
Depression in individuals over 65 is “a major public health problem.”
National Institute of Mental Health

Holsinger 2002 – Lifetime prevalence of major depression in the TBI group was 18.5% vs. 13.4% in those without TBI
Risk of depression increased with severity of TBI
Chemtob 1998 – Combat veterans – among those with PTSD, 77% had sustained a previous TBI
Depression is an increased risk factor for death
3.5% of persons over 65 have clinical depression; the figure is rising
If a person has a “medical illness,” the rate of depression is 40%

MEDICATIONS AND ELDERS
Aging and illness lead to more drugs
Elders consume 30% of all medications prescribed
2/3 of elders take 5-12 medications daily
Psychological medications are the 3rd most common in elders after cardiac and pain medications
Elders typically require smaller doses of drugs than other ages
• persons with TBI, even less
IS BRAIN INJURY A CHRONIC CONDITION/DISEASE?

Now I know!!!

Leading Causes of Traumatic Brain Injury

- 35% Falls
- 16.5% Struck by or against
- 12% Struck
- 17% Traffic incidents
- 10% Assault
- 9% Other

Source: www.cdc.gov/traumaticbraininjury/downloads

CENTERS FOR DISEASE CONTROL, 2013

[Bar chart showing age groups and causes of traumatic brain injury]
NEUROPSYCHOLOGY AND FALLS

- Gait and cognition are interrelated in older adults – declines in attention, psychomotor processing, problem-solving, and spatial awareness can have significant impacts on fall probability
- Gauchard et al. (2006); persons with cognitive deficits mildly beyond normal aging were twice as likely to have fallen in the past and showed twice as many falls
- Depression correlates with the incidence of falls (Delbaere et al., 2010), and severity of depression correlates with greater incidence rates (Eggermont et al., 2012)
  - Depression is related to a higher chance of recurrent falls – 1.3 to 2.2 times more likely (Stalenhoef et al., 2002)
• Even in healthy adults, there is significant loss in gray and white matter, especially in the frontal, and next, in the parietal lobe.

• What does the parietal lobe do? Visual-spatial/visual perceptual skills are primary, navigation/pathfinding, spatial sense/spatial awareness.

• Taken overall, deteriorations in the frontal regions with resulting declines in frontal functions are most likely to contribute to the increased risk of falling in aging adults.
• Brain aging is strongly associated with (or is even a predictor of) an increased incidence of falling.
• Gray and white brain matter changes are associated with change in function and increased incidence of falls.
• Cognitive training in the aging population is showing promising results in reducing fall risk – “Neuropsychological mechanisms of falls in older adults,” Liu, Chan, and Yan, 2014.
• In one study, benefits lasted even 5 years after the cessation of the intervention (Willis et al., 2006).

• Questions?
• Thanks – I love this stuff.