Stroke=Cerebrovascular Accident (CVA)

Brain receives 20% of the blood flow
Contains 400 miles of blood vessels!
Stroke occurs when blood flow to parts of the brain is blocked or when blood vessels break and bleeding occurs

- Damage ranges from minor/undetectable to major/complete loss of function depending on the type, size and location of the stroke.
- Loss of brain function usually occurs suddenly; Bostonians called it “a shock”!

<table>
<thead>
<tr>
<th>Ischemic Stroke on MRI or CT scan</th>
<th>Hemorrhagic stroke on CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Ischemic Stroke MRI" /> <img src="image2" alt="Ischemic Stroke CT" /></td>
<td><img src="image3" alt="Hemorrhagic Stroke CT A" /> <img src="image4" alt="Hemorrhagic Stroke CT B" /></td>
</tr>
<tr>
<td><img src="image5" alt="Ischemic Stroke MRI" /> <img src="image6" alt="Ischemic Stroke CT" /></td>
<td><img src="image7" alt="Hemorrhagic Stroke CT C" /> <img src="image8" alt="Hemorrhagic Stroke CT D" /></td>
</tr>
</tbody>
</table>
Public health burden of stroke

By the numbers:

- **Fourth leading cause of death in US.**
- **6.8 million Americans** have had a known stroke (overall prevalence 2007 – 2010 was 2.8%); almost **800,000 new strokes** each year (~23% are recurrent strokes). In those >50 y.o. stroke risk increases exponentially with age.
- **Hypertension and Atherosclerosis** are the most common causal risk factors for stroke and are **treatable**; also the most prominent treatable risk factors for cognitive decline and dementia.
- Despite the **steady decline in one’s annual risk of stroke**, the aging of the US population is on course to lead to a **21.9% increase in prevalence by 2030**.
- **“Silent strokes”** are even more prevalent, 6% - 28% in elderly; associated with cognitive decline, dementia.
- **White matter disease** is very prevalent- 40-80% in elderly, associated with hypertension and risk of cognitive decline and dementia.
- Stroke costs the US **$38.6 billion** in 2009
- Mean **lifetime cost** of ischemic stroke - **$140,048**
- 6 months after an ischemic stroke (≥65y.o.) – half have some **paresis**, 30% are **unable to walk** without assistance, and nearly half had **cognitive deficits**
A global issue

• According to the World Health Organization, high blood pressure is responsible for 9.4 million deaths worldwide every year, and 51% of stroke deaths

• Cardiovascular disease (heart disease and stroke) accounts for ~18% of deaths worldwide, which is higher than cancer (~8%) and HIV/AIDS (~2%).

• Stroke is 3rd leading global cause of death (#1 in China) and growing fastest in underdeveloped world.
The NIH investment in stroke research

NIH funded $310 million on Stroke Research in FY 2012

Primary NIH Institutes supporting stroke research:

- National Institute of Neurological Disorders and Stroke (NINDS)- *stroke and cerebrovascular biology*
- National Heart Lung and Blood Institute (NHLBI)- *heart disease and vascular biology*
- National Institute on Child Health and Human Development (NICHD) / National Center for Medical Rehabilitation (NCMRR) – *stroke rehabilitation*
- National Institute of Aging (NIA)- *vascular cognitive impairment*
NINDS is the lead institute for Stroke research at NIH
$217 M in FY 2010

$97 M other basic and translational research
$24 M Phase 1/2 trials
$64 M Phase 3 trials
$13 M Translational program and SBIR/STTR
$13 M Training and career development
$7 M Epidemiology and genetics U01s

~ 17% NINDS solicited
~ $30 M program project and center grants
NIH supports research in stroke prevention, treatment, and recovery. This includes:

- Cerebrovascular biology
- Athero research
- Hemostasis
- Genetics
- Prevention
- Behavior change
- Epidemiology
- Neuroplasticity
- Biology of repair after injury
- Neural regeneration
- Neuroprotection
- Acute treatment
- Reperfusion
- Recovery
Prevention

• 50-70% of stroke is considered preventable by fairly simple measures but....
• Stroke is not a disease, it is the consequence of disease of the blood vessels
• The major blood vessels diseases, hypertensive vascular disease and atherosclerosis, worsen for decades before they cause stroke.
• Blood pressure control and healthy lifestyle need to begin younger in life.

Normal blood pressure, Exercise, Normal body weight,, Diet of fruits and vegetables, Low salt, Abstinence from tobacco, moderate alcohol intake.
Stroke Deaths

Note: Stroke deaths are defined by ICD-10 codes I60-I69. Data are age adjusted to the 2000 standard population.
Source: Vital Statistics System—Mortality (NVSS-M), NCHS, CDC.
Acute Stroke Treatment

• Time is Brain!
  – Tissue plasminogen activator dissolves clots that cause stroke and improves outcome in ischemic stroke if given within 3 hours of stroke onset.
  – Defective blood vessel that bleeds into head must be fixed.
  – Transient stroke symptoms are a warning that stroke is probable in next hours-days.

• The development of stroke centers based on tPA administration has improved US stroke care for all.
Examples of Current NIH Stroke Projects

Basic and translational research:
- Lots of projects focused on understanding cellular/molecular mechanisms of disease and repair processes, identifying and developing potential prevention/treatment/rehab strategies

Population/genetic studies:
- International Stroke Genetics Consortium and ICH ethnic/racial study.
- Reasons for Geographic and Racial Differences in Stroke (REGARDS)
- Stroke Prevention-Intervention Program (SPIRP)

Clinical trials:
- Aggressive blood pressure prevention trial (SPRINT)
- tPA in Childhood Stroke
- ICARE upper extremity rehab trial
- Insulin in acute stroke
- Magnesium in acute stroke (FAST-MAG)
- Network for phase 2 & 3 stroke trials (New!)
NINDS Stroke Branch (intramural)

• Basic / translational investigations of immunological approaches to preventing stroke in hypertensive animals, and endogenous neuroprotection strategies to mitigate stroke damage

• Clinical research to expand and improve the use, safety and efficacy of clot-busting medicines such as tPA in collaboration with Washington Hospital Center and Suburban Hospital
  – Advanced brain imaging methods to study strokes in progress; discovered new MRI markers of early brain injury.
  – The MR WITNESS trial to identify patients with unknown time of stroke who may be safely and effectively treated with tPA.
Impact of NINDS Clinical Research

- **Epidemiology/Disparities** - REGARDS, NOMASS, Cincinnati-Ky

- **Prevention** - major discoveries from several trials, including AF studies, WARS, WASID, ISAT, NASCET, ACASS, COSS, CREST, SAMMPRIS and many others. Stroke Risk continues to decline.

- **t-PA Reperfusion in acute stroke** - revolutionized acute stroke management

- **Hemorrhagic stroke** - ISAT (endovascular coiling as alternative to aneurysm surgery in specified subgroups).

- **Rehabilitation** - Recent Phase III RCTs showed benefit of intensive rehabilitation: Constraint therapy (EXCITE), Home-based rehab and treadmill rehab (LEAPS).

- **Networks** - New North American Stroke Treatment Trials Network (US and Canada) to test new interventions in prevention, treatment and rehabilitation.
Stroke Recovery Research

• Even with improved prevention and treatment of stroke, highly effective recovery strategies are needed to help the millions of surviving stroke victims regain function.

• Understanding how to harness the processes that govern the brain’s ability to recover should allow development of new therapeutic strategies.

• Rehabilitation care received by patients is highly variable, and evidence for which practices work best is needed. Recent evidence from the EXCITE and LEAPS trials indicates that more intensive therapy is better than current standard of care.
The General Rule is that Stroke Victims Recover Function over Weeks to Months

Severely Disabled Strokes – defined by FIM score < 77

On admission to Spaulding Rehab, almost three-quarters of our strokes were severely disabled

On discharge from Rehab, only about a third remained severely disabled

Age is a major determinant of the degree of recovery after stroke.
Setting the Stage for Recovery Trials

- Recovery happens!
- Process is easily measured
- Occurs 1-6 months post stroke.
- First 3 months is fastest phase, slower 3-6
- Plateau seen after 6 months.
- Recovery occurs as a function of age

Studies of the upper extremity motor system after stroke illustrate a number of forms of brain plasticity.

Spaulding

If they cannot speak,
Encourage them to sing, and
If they cannot walk, teach them to dance!!
Brain reorganization after stroke

The results of ICMS mapping of the PMV hand area before and 3 mo after the ischemic infarct in 4 monkeys.


©2003 by American Physiological Society
Basic research on the brain’s ability to change

**Neuroplasticity** -- ability of the nervous system to reorganize its structure, function, connections in response to internal and external stimuli

• described at many levels, from molecular to cellular to neural circuits, to behavior;

• occurs most robustly in *childhood* brain development and in *response to brain injury* in which case it is enhanced by *practice*.

• Also underlies lifelong learning and memory formation.

• Determined by neural activity ← practice.
Representative reconstructions of layer V pyramidal cells respective of treatment condition (IE, IS, and SE).


©2001 by Society for Neuroscience
Time-lapse imaging of apical dendrites reveals heightened levels of spine formation in peri-infarct cortex.

Understanding the biology of repair

Basic research provides promising therapeutic targets.

- The immune system and inflammation can affect stroke recovery - immune response may exacerbate brain injury early after ischemia, however it is a mediator of brain rewiring and recovery.

- Intrinsic repair processes involve developmental programs that turn on after stroke, such as generation of new brain cells, axonal outgrowth to deinnervated regions, new connections (synapses) between neurons.

- Key molecular signaling pathways in recovery process identified.

- Neuro progenitor cells are important for biology of repair and enhancement of such stem cell response may enhance recovery.

*In order to harness neuroplasticity for clinical applications, behavioral improvements must be demonstrated in human studies.*
NIH Stroke Rehabilitation Trials Focus on “Practice”

- Locomoter Experience Applied Post Stroke (LEAPS) Trial - intensive home-based therapy improved walking ability as well as a more complex rehabilitation program involving a body weight-supported treadmill. Showed potential for improved walking with intensive treadmill therapy even 6 months after stroke.

- Extremity Constraint Induced Therapy Evaluation (EXCITE) – constraint-induced therapy is effective early (3-9 mo) and late (15-21 mo) after stroke

- Interdisciplinary Study of Arm Rehabilitation after Stroke (ICARE) - testing experimental arm therapy which combines intensive practice of tasks of the participant's choice, compared to two standard types of therapy
DARPA ARM (autonomous robotic manipulation)

Andy Schwartz
Non-human primate motor control with DARPA JHU/APL arm
NINDS/DARPA

Michael Boninger Jen Collinger
Inter-cortical electrode motor control in SCI
DARPA/VA

Doug Weber
Sensory feedback
NINDS/DARPA/VA

Wei Wang
ECoG motor control in SCI with DARPA DEKA arm
NIH CTSI/DARPA
Robotic systems for stroke rehabilitation

- Robots provide promise for effective rehab treatment offering structured therapy and precise measurement of performance.

- Robotic rehab may provide long-term intensive treatment, potentially at lower cost.
Brain-Machine-Interface of Therapeutic Exoskeleton

- A physical human-robot interface is augmented with a non-invasive brain-machine interface to engage the patient in rehabilitation tasks.

- Capitalizes on known benefits of patient intent in movement initiation and on the beneficial effects of BMI use on cortical plasticity.

- To increase upper limb function, innovate rehabilitation
The promise of robotic applications for stroke rehabilitation

• While mechanisms remain unclear, repetitive training with active concentration are believed to promote skill acquisition and motor relearning through neuroplasticity and cortical reorganization.

• Engineered devices work best when there is a strong scientific foundation and high clinical relevance.

• Multidisciplinary collaborations are essential for successful development and testing of such devices.

• Added value of generating new insight for basic science studies.

• Technical and translational hurdles will need to be overcome before clinical application can be realized.
President Obama is calling on the science community to join him in pursuing a grand challenge.

BRAIN Initiative

Brain Research Through Advancing Innovative Neurotechnologies
People have been electrochemically probing cell membranes for many years.

Signal levels that makes optics weep.
1 pA = 6,200,000 e\textsuperscript{-}/second

(Hamill et al, European J. of Physiology 1981)

Electronics hasn’t changed in 30 years!
New technologies to enable recording from large number of neurons
The BRAIN initiative – what does it mean for stroke recovery research?


• Tool development to allow us to “listen in” to the electrical signals that form the language of the brain has the potential to revolutionize our understanding of neuroplasticity.

• Potential to enhance our understanding of how neural circuits in the brain “learn” to recover after stroke and then allow us to manipulate them to maximize functional outcome for the patient.

• *If they can’t speak encourage them to sing; if they can’t walk teach them to dance.*
NIH Transforming medicine and health through discovery