Head Injuries in Soldiers and Athletes May Cause Prion-like Disease

Did Lou Gehrig actually have Lou Gehrig’s disease? Or did he have a different neurodegenerative disease caused by traumatic brain injury from all those concussions he experienced playing baseball? Is this the same disease seen in a growing number of football players? Does the same kind of brain injury suffered by more than 200,000 American soldiers as a result of explosions in Iraq and Afghanistan lead to a similar disease?

And do these traumatic head injuries set off degenerative mechanisms in the brain similar to those in brain diseases ranging from Alzheimer’s to the human equivalent of mad cow disease? Dr. Daniel Perl is exploring these fascinating questions at the federal Uniformed Services University of the Health Sciences, in Bethesda, Maryland.

Degenerative brain diseases are beginning to look more alike than ever, and – unexpectedly – also like the conditions caused by some head injuries. Dr. Perl sees the same symptoms in the injured athletes and soldiers that are common to so many degenerative brain diseases: depression, personality changes, angry outbursts, and dementia. After these patients have died, he sees that the autopsied brains of former professional football players who died young can look strikingly like the brains of 85-year-old Alzheimer’s victims.

Dr. Perl described the football players’ brains as being “full of tau tangles.” Tau is a protein that misfolds and accumulates in the brains of people with Alzheimer’s and other diseases. Now that he and other scientists have begun to study the growing problem of traumatic brain injury, they’re finding it there, too.

Continued on page 11
MRI Scientists Working at India Stem Cell Institute

For MRI’s John Mercer, the upside of the growing disparity in research funding between the U.S. and other countries (see article on next page) is that those countries are spending money, and, in the case of India, they need McLaughlin’s expertise in mouse genetics and molecular motors.

As part of an international collaboration that includes MRI and Stanford University, Dr. Mercer is now in Bangalore at the new Institute for Stem Cell Biology and Regenerative Medicine, or inStem. For several years, he and his wife and colleague, Colleen Silan, will be helping to establish both a mouse genetics facility at inStem and a lab that will study inherited diseases of the heart muscle called cardiomyopathies. Cardiomyopathies are an area of focus in Dr. James Spudich’s lab at Stanford, where Dr. Mercer worked during a recent sabbatical.

Dr. Spudich (a former member of McLaughlin’s Scientific Advisory Committee) has been a key player in the development of the inStem project at the National Centre for Biological Sciences (NCBS), the leading biological research institute in India with which he has had a longstanding affiliation. “inStem is using a large spectrum of approaches” to both basic research and its clinical application, he said. An advanced technology center on campus provides technological capabilities that dramatically speed up as well as broaden the scope of the research.

“At a time of austerity in U.S. research funding, the Indian government is dramatically increasing research funding,” inStem director Dr. K. VijayRaghavan said. “They view it as economic and technological investment, not as an expense.”

Dr. Mercer will be introducing technologies to inStem developed by Dr. Spudich’s lab at Stanford for studying mutations in the molecular motors that drive the human heartbeat. These mutated motors are associated with deterioration of the heart muscle that can cause sudden death at any age, and the inherited mutations occur in one of every 500 people. “Cardiomyopathies are a huge public health problem,” according to Dr. Mercer. “A vast number of different mutations are involved, so it will take time, but the long-term goal is to develop therapies.”

“John was part of the team that made a couple of breakthroughs in my lab that enabled us to move the research into the translational or clinical realm,” Dr. Spudich said. “His extensive knowledge base of myosin motors and his enthusiasm for this application of it made him a natural partner in the project. His being in Bangalore full time makes it possible for us to carry out our work in our lab at Stanford as well as our lab in India.”

Colleen Silan, a visiting senior research associate at inStem, is also managing many aspects of the project. Additional personnel from MRI and Stanford will visit Bangalore to assist the team there, and Indian graduate students and postdoctoral fellows will visit McLaughlin for further training in mouse genetics.

Meanwhile, McLaughlin will be making mouse models for cardiomyopathy research at both inStem and Stanford. “This work depends on good mouse models, and the really exciting opportunity to connect up with all of McLaughlin’s expertise in their fine mouse facility is a very, very important element of this,” Dr. Spudich said.

MRI Director George Carlson said, “We are very pleased to be associated with this exciting project. In the context of the increasing globalization of science, the interactions with NCBS and Stanford offer our scientists in Montana the chance to be at the leading edge in international collaboration.”

Colleen Silan, Jim Spudich, John Mercer and postdoctoral fellow Tejas Gupte in the new lab.

The new NCBS building in Bangalore, “the Silicon Valley of India.”
One scientific institute in China now has more genome sequencers than does the entire United States. And China’s not the only country that threatens America’s lead in science. Many countries are ramping up their investments in medical research, following the model that took the U.S. to the top of the field. Ironically, the U.S. is now heading in the opposite direction by making funding for research a lower priority, ceding ground to its competitors. The President of Research!America brought this message to MRI in August.

"Medical research has a history of success," Mary Woolley said. "It’s not by accident that it’s been a priority in this country." That success proves we can find solutions for the many diseases our families face, if we continue to support research at a competitive level, she said.

And there’s a big economic bonus to funding research: “Not only is it saving lives and helping people live longer, more productive lives,” she said, “but it’s saving money by driving the economy and by reducing health care costs over the long haul.”

“Other countries know research creates new sectors in their economies and lots of new, good jobs. They’ve learned to treat it as an investment, not an expense.” Yet, in the U.S., the National Institutes of Health (NIH) budget is not keeping up with inflation. NIH used to fund the proposals of 1 in 3 scientists; now it’s 1 in 6. One result is that American scientists are being lured overseas by funding for their projects. (See article on facing page.)

The NIH is a great example of a federal agency where tax dollars do not stay in Washington but are reallocated to the states, to places like MRI, according to Woolley. In 2010, $54 million in NIH funding supported approximately 1,000 jobs in Montana.

“Research does matter to Montana,” she said, and the state’s congressional delegation is well-positioned right now to make a difference in the level of funding that goes to research as Congress sets its priorities for a tighter budget.

“If you think research should be a priority, let your representatives know that,” she told the group. While Research!America polls show Americans strongly support funding for research, Congress doesn’t tend to hear a lot about support for science, which makes it easier for them to cut back on funding. And that puts America’s future on the line.

“It’s an important time for our country,” Woolley said. “Americans want an economy powered by innovation, and we want to support the future of health, otherwise known as research.”

The total budget to fund “the future of health” is roughly $30 billion. Most of this budget goes to support researchers and those who work for them all over the country, including more than 1,000 in Montana.

NIH is one of the best bargains for our tax dollars.

It costs around $100/per person per year in the U.S. to research every disease and disability.

That’s a lot of research, and it adds up to significantly less than 1% of the total federal budget.

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New York Times foreign affairs columnist Thomas Friedman’s new book, That Used to Be Us, lists government-funded research as one of the “5 pillars of American success from Lincoln, on.”

Mary Woolley spoke to MRI’s National Development Council. Research!America is a nonpartisan, nonprofit alliance working to make research for health a higher national priority. MRI is one of its 400-plus member organizations.
Science, by its very nature, is a slow process of rigorous investigation over time. But with a major boost from its recently completed fund drive, scientists at MRI are quickly advancing their research in exciting directions. In addition to the expanded animal resource center completed last year, the new funds have brought in a new principal investigator, several postdoctoral fellows, and some high level equipment that is already making a difference in the scientists’ ability to make discoveries about diseases like Alzheimer’s and Parkinson’s.

A major gift from the Oakland family of Great Falls topped off McLaughlin’s multi-year fund drive in time to meet last summer’s deadline for matching the Montana Department of Commerce’s 2009 grant of $2 million. The match was met through donations, pledges, and bequests from individuals, as well as private and federal grants, including two grants from the American Recovery and Reinvestment Act.

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New postdoc Brenda Canine is applying her pharmaceutical background to Dr. Carlson’s lab’s efforts to find genetic targets for drug development for Alzheimer’s and prion diseases. Using the new in vivo imaging system, she is able to monitor the course of a brain disease over time in the same live mouse, helping her to identify genetic markers early on in the disease process.

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With the good jobs it’s helped provide, the partnership also gives Montana an economic boost. That’s why the State of Montana made the project possible by providing a total of $4 million over the course of its two phases. MRI matched that with another $4 million. The economic downturn that came during the fund drive resulted in some cutbacks at MRI, and the funds brought in also helped minimize the impact of those cuts.

McLaughlin’s ongoing efforts to recruit another new investigator with some of the funds raised are focused on finding a physician-scientist who would translate the Institute’s basic research into its clinical applications with patients. This will usher the Institute into an exciting new era where the time for translation of basic research like ours to patient care will be dramatically shortened.

We’ve pictured some of the personnel and equipment covered by these funds below and on the following pages.

Road to a Cure Committee Members: Irv Weissman, Shannon Anderson, Edy Thogerson, Kathy Rice, Leslie Oakdall, Randy Gray, Nancy O’Brien, Nancy Davidson and Paul Eichwald. (Not pictured: David Cameron, Cindy Poett, Gina Reilly, Gerald Molin, and Andy Miller.)
According to Dr. John Bermingham, the Typhoon imaging system’s superior sensitivity and quantitation capabilities are saving the researchers much labor and shortening the duration of their experiments.

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We Appreciate our Road to a Cure Fund Drive Donors

Major gifts from Anderson Steel Supply, Nancy and Ian Davidson, the M. J. Murdock Charitable Trust, the Oakland family, Sletten Construction Company, Gene Thayer, and Irving Weissman helped make it possible for us to meet our goal. Cindy Poett, Dave Cameron and Nancy Davidson were instrumental in securing a grant from The Charles Engelhard Foundation.

Our deep gratitude goes to all who made contributions of any size to help support MRI’s research on diseases that plague our families. Thanks to the following donors, McLaughlin was able to match $4 million in grants from the Montana Department of Commerce. In addition to those who contributed specifically to the Road to a Cure campaign, unrestricted donations were also applied to the match, so those individuals helped us meet our goal, and their gifts were doubled in value.

The advanced equipment the Institute purchased with Road to a Cure funds has already enabled new research findings. The new confocal microscope has revealed to Dr. Deborah Cabin’s lab an intriguing relationship between the Parkinson’s disease gene she studies and the Alzheimer’s plaques that Dr. George Carlson’s lab studies. The microscope’s capacity for 3-D reconstructions and for precisely identifying the intracellular locations of proteins is having a major impact on research at the Institute.

Below left is a 3-D reconstruction side view of a 10 micron mouse brain section. At right, the same section is tilted and opens up to reveal more dimension and detail. In both images, red represents Alzheimer’s plaque, Parkinson’s disease protein is shown in green, and blue represents cell nuclei.

The National Development Council works to support funding of MRI. At this summer’s annual meeting, Irv Weissman (far left) spoke about the impacts on MRI of the decline in NIH funding and NDC members met in small groups to discuss potential sources of non-federal support. 

You deserve proper recognition for your gifts. While we make every effort to accurately name each individual and organization, occasional errors occur. Please check your name for accuracy and let us know if we omitted or misspelled your name. Thank you again for your gift and, if necessary, your forbearance.

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Opening Doors to a Future in Science

University of Montana student Garrett Morrill is one step closer to his dream career in biological engineering after spending his summer exploring the interactions of two genes associated with brain disease. While he fantasizes about one day building organisms that clean up oil spills and the like, some of his fellow student interns at McLauglin Research Institute are moving toward more traditional careers in research or medicine.

The dynamic group of high school and college students who spent their summer at MRI alongside local science teachers was a bright presence amid darkening reports that science education in the U.S. is failing to keep the country in the lead. 

Alekses Clifton is a senior at Great Falls High, but she sounded like a pro when she presented her research findings at summer’s end. Alekses teamed up with Great Falls High Honors Biology teacher Rob Truax to study a gene associated with Parkinson’s disease in Deborah Cabin’s lab. She was inspired by the fact that their project will contribute to the understanding of the disease. “It really helped that I might one day help give them more information about these diseases so they can treat people medically.”

Her teacher/lab partner agreed. “This is not a science summer camp,” Rob Truax said. “We’re doing science that a real scientist intends to use— they don’t give you a project to occupy your time but one that will actually help them.”

“People don’t realize that here in Great Falls we have world class science, always on the verge of discovering a major breakthrough that will help find cures for Alzheimer’s, Parkinson’s, and other neurodegenerative diseases,” he said. “This is something you’d expect at MIT, not in Great Falls, Montana.”

Howard Hughes Medical Institute

The Howard Hughes Medical Institute (HHMI) funds the high school student and teacher program. Four students teamed up with four teachers to work in four different labs.

Students

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<thead>
<tr>
<th>Name</th>
<th>School</th>
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<tbody>
<tr>
<td>Hallie Bronc</td>
<td>Geraldine High School</td>
</tr>
<tr>
<td>Alekses Clifton</td>
<td>Great Falls High School</td>
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<td>Jeremy Kerr</td>
<td>Central Catholic High School</td>
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<td>Sarah LaPierre</td>
<td>CM Russell High School</td>
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Teachers

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<tbody>
<tr>
<td>Mike Hodges</td>
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</tr>
<tr>
<td>Ben Jaques</td>
<td>East Middle School</td>
</tr>
<tr>
<td>Dan Rediske</td>
<td>CM Russell High School</td>
</tr>
<tr>
<td>Rob Truax</td>
<td>Great Falls High School</td>
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Teacher Cohort

Teachers who have worked in the labs in previous years were part of the Teacher Cohort this year, working to translate what they’ve learned in the labs into lessons for classrooms across Great Falls.

Tom Cubbage (lead teacher) .... CM Russell High School
Brittany Deflinbaugh .... CM Russell High School
Sara Farr ............. North Middle School
Carolyn Pill ............... Central Catholic High School

McLaughlin’s partnership with the Howard Hughes Medical Institute (HHMI) made it possible for MRI to bring Dr. Carroll to speak in Great Falls. HHMI is a national leader in science education and has supported MRI’s summer education program with a multi-year grant. The K-12 Science Initiative grant, which runs through 2012, also enables MRI to host public lectures by scientists from around the country to improve scientific literacy, foster critical thinking skills, and enhance support for science education in the schools.

Storytelling Evolutionary Biologist Packs the House

For many years following his famous voyage on the Beagle, Charles Darwin kept his heretical theory of evolution a secret. During that time, an amateur naturalist named Alfred Wallace spent more than a decade exploring the far reaches of the Amazon and Asia. He independently arrived at the same conclusion Darwin had—that species are not immutable but adapt to their ever-changing environments. Wallace published his findings, unintentionally forcing Darwin out of hiding. With the publication of On The Origin of Species in 1859, Darwin dramatically upstaged his younger colleague.

In November, 200 people packed a hall in Great Falls to hear award-winning scientist and author Sean B. Carroll tell the captivating story of these globetrotting adventurers and how their revolutionary ideas grew out of their explorations. A third naturalist, Henry Walter Bates, played a supporting role in the story.

Before the adventures of these three young Englishmen, most of the earth was an unexplored wilderness with animals, plants, and humans unknown to the Western world. Driven by their passion for discovery, they persevered through many dangers and hardships, risking their lives and ultimately unearthing “the history of life.”

“Their achievements sparked a revolution that changed, profoundly and forever, our perception of the living world and our place within it.”

Dr. Carroll told the audience. He claimed that, while these three great voyages made up the first Golden Age of evolutionary biology, the field is now enjoying a second Golden Age. Now that scientists are able to collect the DNA of the creatures these 19th-century naturalists collected specimens of, an abundance of genetic data is confirming the findings of these early explorers beyond their wildest dreams.

Dr. Carroll is Vice President of science education at the Howard Hughes Medical Institute and Professor of Molecular Biology and Genetics at the University of Wisconsin. Among Dr. Carroll’s numerous awards is the 2010 Stephen Jay Gould Prize for his work to advance public understanding of evolutionary science and its importance in biology and everyday life.

Dr. Carroll is also writing and starring in HHMI’s engaging new series of educational films. These fascinating short films are available online at hhmi.org/bio/interactive/shortfilms.

On the same day as the evening lecture, Dr. Carroll presented his recent research findings to MRI scientists and a group of nearly eighty advanced placement high school biology students. 

Dr. Carroll’s lecture was titled Remarkable Creatures: Epic Adventures in the Search for the Origins of Species. After his book of the same name. The book was a finalist for the 2009 National Book Award and many came forward to get a copy signed by the charismatic author.
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Hood Envisions Radical Change for Institutions & Medicine

Leroy Hood is unstoppable. Just as he did as quarterback on the Shelby High School football team during the 1950s, he refuses to let obstacles stand in his way or block his vision. As he moves toward his ambitious goal of changing the world through science, he isn’t deterred by the fact that technology—or society, for that matter—has not yet caught up to his ideas.

The world Dr. Hood envisions is one in which practically every institution is revolutionized from health care to technology to K-12 education, he has an active strategy for radically changing our institutions to better serve us.

When mapping the human genome appeared too cumbersome a project to tackle, he invented the high speed DNA sequencer that made it possible. In recognition of this “bioengineering achievement that has improved the human condition,” Dr. Hood was awarded the 2011 Fritz J. and Dolores H. Russ Prize, sometimes known as “the Nobel Prize of Engineering.”

His current focus is using the genetic information made available by the Human Genome Project to transform medicine from a reactive to a proactive discipline. P4 medicine, as he calls it, will be based on predictive, preventive, personalized, and participatory health care. Within five years, he told a Great Falls audience in April, people will have access to a wellness blueprint based on their genome and will be able to catch potential diseases before they become a problem. “P4 medicine will turn around the sharply escalating costs of health care,” he said.

P4 medicine is a byproduct of the field of systems biology Dr. Hood has pioneered, which approaches diagnostics and therapeutics with a combination of biology and technology that illuminates the body’s intricate networks. MRI has collaborated with his Institute for Systems Biology for many years.

“McLaughlin played a really critical role in proving, with us, that disease arises from disease-perturbed networks,” Dr. Hood told the audience. “Our collaborative study of prion disease with George Carlson showed the pathology of the disease and opened up ideas for therapy and how to reengineer the networks. This gave us an insight into how to make blood a window into health and disease.” The collaboration is now applying these insights to a study of Alzheimer’s disease.

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Dr. Hood is a longtime member of the Institute for Systems Biology. MRI’s public lecture series, sponsored by the Howard Hughes Medical Institute.

Dr. Hood is a longtime member of McLaughlin’s Scientific Advisory Committee.

Dr. Perl worked previously.

Daniel Perl spoke to MRI’s National Development Council in August 2011.

Former NFL player Duane Durerson was a well-educated, successful businessman whose life unraveled in a tragic tale of bankruptcy, foreclosure, domestic violence, and divorce. In 2011 he shot himself in the chest, preserving his brain, which his suicide note requested be donated to the TBI brain bank at Boston University, where Dr. Perl worked previously.

Surprisingly, Dr. Perl said, the tau tangles in the brains of people with traumatic brain injury seem to spread through the brain like prions do—along neuronal pathways, from neuron to neuron. This finding was unexpected because prions are a distinct class of misfolded proteins that act as highly unusual infectious agents in the brain, causing rare transmissible diseases in humans and animals, including mad cow disease. Now, though, Dr. Perl said, “The concept has begun to spring up that all neurodegeneration could be forms of prion disease.”

MRI Director George Carlson has been a longtime key player in the study of prion disease, as well as Alzheimer’s and other diseases associated with tau tangles. His lab’s latest research reveals this increasing convergence of the science of these two forms of brain disease. “We have excellent mouse models to look at the fundamental mechanisms by which these diseases spread,” he said.

Dr. Perl is optimistic that his newest area of research will help shed light on the diseases he has studied throughout his career, including Alzheimer’s.

“These studies should be very instructive in neurodegeneration in general, in looking at what initiates this cascade [of dying neurons].”

About the tremendous problem of traumatic brain injury itself, he said, “The scope of this is huge,” and predicted that the war veterans’ “silent epidemic” and the NFL’s highly publicized “concussion crisis” will have serious consequences for the U.S.

Senator Jon Tester spoke at the event:
“I won’t support cuts at the expense of life-saving research.”

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Senator Max Baucus

Congressman Dennis Rehberg

Senator Jon Tester

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Dr. Perl is optimistic that his newest area of research will help shed light on the diseases he has studied throughout his career, including Alzheimer’s. “These studies should be very instructive in neurodegeneration in general, in looking at what initiates this cascade [of dying neurons].”

About the tremendous problem of traumatic brain injury itself, he said, “The scope of this is huge,” and predicted that the war veterans’ “silent epidemic” and the NFL’s highly publicized “concussion crisis” will have serious consequences for the U.S.

Former NFL player Duane Duerson was a well-educated, successful businessman whose life unraveled in a tragic tale of bankruptcy, foreclosure, domestic violence, and divorce. In 2011 he shot himself in the chest, preserving his brain, which his suicide note requested be donated to the TBI brain bank at Boston University, where Dr. Perl worked previously.

“The concept has begun to spring up . . . that all neurodegeneration could be forms of prion disease.”

Research Funding Update

A month after Mary Woolley’s lecture at MRI, Montana Congressman Dennis Rehberg, Chairman of the House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies, included a $1 billion increase for the National Institutes of Health’s FY 2012 budget in the House appropriations bill. The Senate’s appropriations bill currently includes a cut of $190 million.

Field representatives for Congressman Rehberg and Senator Max Baucus attended the MRI lecture and spoke in support of funding for research.

Senator Jon Tester spoke at the event: “I won’t support cuts at the expense of life-saving research.”

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Best Wishes for the Season from all of us at McLaughlin Research Institute

A Note from the Director

We think you’ll enjoy reading about some exciting developments at MRI during the past year. All of our work is made possible with support from others, so we’re grateful for your gifts during the year.

Look for our annual report at a new time, in the early spring.

Best wishes,

Dr. George A. Carlson, MRI Director