



# CHDD Outlook 2009 Issue #2

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## Working to Reduce Brain Damage from Stroke

by Kris Freeman

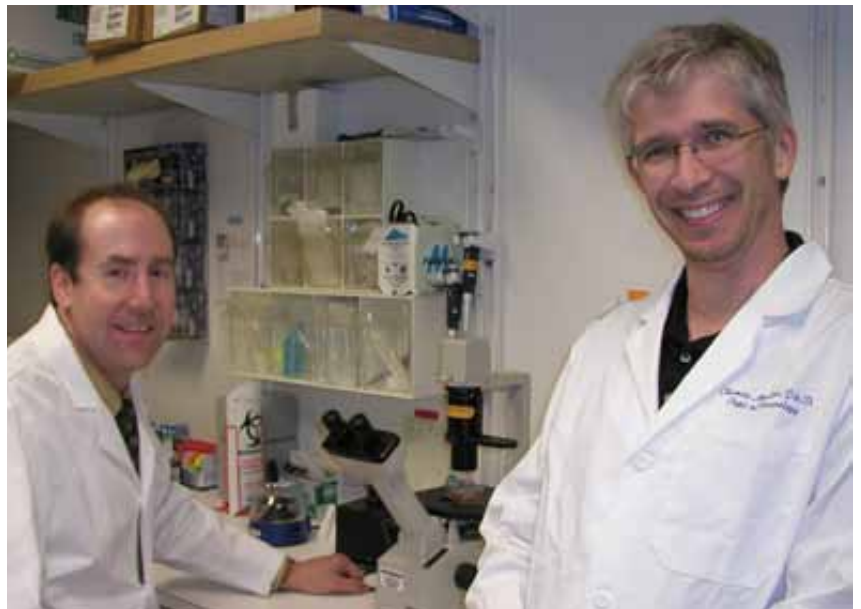
Stroke that occurs before or just after birth is a significant cause of developmental disabilities. Research affiliates at the Center on Human Development and Disability (CHDD) are researching both the basic mechanisms of inflammation caused by stroke and medications with the potential to reduce that inflammation. Their goal is to reduce brain damage.

“Stroke in infants is fairly rare, but when it does occur, it can be devastating,” said Jonathan Weinstein, M.D., Ph.D., an assistant professor of neurology and a CHDD research affiliate. Infants can be susceptible to both major types of strokes, ischemic and hemorrhagic. Ischemic stroke occurs when blood supply to the brain is reduced. Hemorrhagic stroke occurs when there is a rupture of a blood vessel. “In hemorrhagic stroke, you may still have an ischemia because flow to the brain has stopped beyond the leak. But the added complication with hemorrhagic stroke is that you get blood in the brain, which is very bad news,” said Sean Murphy, Ph.D., a professor of neurological surgery and CHDD research affiliate.

It’s estimated that about 1 in 2,300 to 5,000 newborns suffer a stroke. Risk factors for strokes in infants and children include sickle cell disease and heart disease. Other conditions associated with stroke include head and neck infections, head trauma, dehydration and autoimmune disorders. As many as 10 percent of the infants who suffer a stroke won’t survive, and many stroke survivors suffer neurological damage that can cause developmental disabilities. In addition, about a third of the survivors of infant stroke will have additional strokes, which can cause further brain damage.

Weinstein studies inflammation in the brain caused by a stroke. By determining the precise ways that inflammation causes harm, he and his colleagues are laying the groundwork for possible therapies to rescue brain tissue injured by a stroke. Some tissue is immediately killed by the stroke; this area of the injury is called the infarct core. The layer of tissue around the infarct, called the ischemic penumbra, is injured but not yet dead.

“It’s stunned or functionally inactive, sort of electrophysiologically quiescent,” said Weinstein. “Down the line, many days later, you can have cell death. But in between, in this period of days to weeks there is an inflammatory



Jonathan Weinstein (left) and Thomas Moeller, are researching the mechanisms of stroke-related brain injury, a rare but potentially devastating condition in infants.

response in the brain. In some situations inflammation can be helpful, but in the acute setting of stroke, inflammation is probably deleterious.” An over-active immune response can injure the brain by generating heat, causing swelling, and releasing compounds that trigger cell death in the injured neurons, Weinstein said.

Moderating the immune response in the ischemic penumbra could reduce the amount of injury caused by a stroke. Weinstein and his collaborator, Thomas Moeller, Ph.D., a research associate professor of neurology and a CHDD research affiliate, are currently studying microglia, a type of immune cell found only in the central nervous system. Microglia are extremely active and are constantly on the move searching for damaged neurons, plaques associated with neurodegenerative disease and infectious agents, which they mark for destruction by other immune cells. Any means to control inflammation in the ischemic penumbra will involve microglia.

Microglia are part of the innate immune system, which serves as the body’s first responder to infection. Like many innate immune cells, microglia carry an arsenal of receptors that respond to signals from dead and dying cells, as well as to types of bacteria likely to invade an injury. There is evidence that heat-shock protein, a compound released by injured cells, may trigger a specific receptor on microglia known as Toll-like receptor 4 (TLR-4). Activation of TLR-4 initiates a host of immune responses. One of Weinstein’s research aims is to characterize the role of microglial TLR-4 in the ischemic penumbra. It is possible that an antagonist of this receptor, or a pharmacological blocker of one of the signaling pathways downstream to TLR-4, could moderate the brain’s immune response in stroke and reduce brain injury.

While Moeller and Weinstein focus on the mechanisms of stroke-related brain injury, Murphy studies therapeutics that could be used to moderate inflammation. To speed their research, Murphy and his colleagues focus on existing medications that have already gone through clinical safety trials. They review the medical literature to find drugs with two characteristics: the potential to protect existing neurons from damage during a stroke and to encourage the growth of new neurons after a stroke.

“New neurons are constantly being born in the brain but at a very low rate. When you injure the brain, that rate increases dramatically. So we’re looking for drugs that will promote the development of new neurons,” said Murphy. He and his team are studying several drugs, including granulocyte colony stimulating factor (G-CSF), progesterone and progesterone metabolites, and histone deacetylase (HDAC) inhibitors.

G-CSF is a drug approved for use in persons preparing to become bone marrow donors because it promotes the proliferation of stem cells within the bone marrow. Some research indicates that in the brain G-CSF could stimulate progenitor cells that would develop into neurons. Progenitor cells can develop to replace specific types of cells lost to natural turnover or injury, although they are more restricted in their development and capabilities than stem cells. Clinical trials are currently underway to test the use of G-CSF in treating stroke and heart attack.

Progesterone is very neuroprotective. If you give male mice progesterone following a stroke injury, they do better than their counterparts who did not receive progesterone, according to Murphy. Research is underway to understand if it’s progesterone itself, or a product of progesterone metabolism, or some combination of those two that is beneficial. A clinical trial in the U.S. is currently testing the use of progesterone to treat persons with brain injuries.

HDAC inhibitors, a new category of drug, are now being used in treating certain cancers. These compounds appear to cause cell death in undifferentiated cells that are rapidly dividing, such as cancers, but also protect cells that are already differentiated. They also appear to promote the differentiation of progenitor cells in the brain to become neurons.

Clinical trials of these drugs are all focused on adults, as is much of stroke research. However, the amount of pediatric stroke research is growing, according to Weinstein. In addition, progress in stroke therapies for adults will also benefit infants and children.

“There’s a large overlap between the molecular targets in managing stroke in adults and in children,” he said.

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

#### **CHDD Outlook**

Center on Human Development and Disability, University of Washington, Box 357920, Seattle, Washington 98195-7920

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