Infection with human immunodeficiency virus (HIV) is thought to be the most common cause of dementia in people aged 40 and younger. HIV dementia is associated with cognitive decline as well as motor dysfunction and behavioral changes.

In the early 1990s, the prevalence of HIV-associated dementia was estimated to be as high as 20 to 30 percent of patients with advanced HIV disease. While highly active antiretroviral therapy (HAART) for HIV infection has decreased the incidence of HIV dementia, HAART does not provide complete protection from or reversal of dementia. In fact, as people live longer with AIDS, the total number of cases of HIV dementia may increase.

Gwenn Garden, M.D., Ph.D., University of Washington assistant professor of neurology, research affiliate at the Center on Human Development and Disability, and coordinator of the Cellular Imaging Component of CHDD's Neuroscience Core, seeks to understand the mechanisms by which HIV infection damages the brain.

Since neurons are not directly infected by HIV and the level of virus in the brain is not strongly correlated with the degree of neurologic dysfunction, researchers believe secondary factors must be involved. “No one really understands why some HIV patients develop this neurodegeneration and others do not,” said Garden. “We think certain host factors are probably very important in determining who will suffer HIV dementia. About 10 percent of adults and up to 25 percent of children with HIV develop dementia. We don't yet understand why this is.”

Garden's current project is not asking specifically why adults are less susceptible to HIV dementia than children—which may be related to immunological factors—but rather is focused on various factors involved in susceptibility to HIV dementia. “What strain of the virus are you infected with? Even if you are infected with a more neurotropic strain (likely to infect the nervous system), how does it make its way to the brain? And once it is there, will you develop neurodegeneration and dementia? All of these steps are not particularly well understood,” said Garden.

One promising line of research is apoptosis, or programmed cell death, an essential regulatory function. Garden's lab is looking at what aspects of apoptosis are turned on in the brain by exposure to HIV. Somewhat uniquely, in HIV dementia there is not a great amount of neuronal cell death, but rather a tremendous loss of synapses (the junctions between neurons) and dendrites (the receptive surfaces of the neuron). Because several of the protein regulators of apoptosis are activated in HIV-associated dementia even though the neurons remain alive, Garden is pursuing the hypothesis that these mediators of apoptosis may also cause synapse and dendrite degeneration.

“The hope is that because the neurons are still alive, even if atrophied, dementia may be preventable or reversible if caught early.”

-- Gwenn Garden
HIV dementia . . . from Page 1

which is a central nervous system toxin capable of producing neuronal apoptosis. Her lab is seeking to determine whether HIV infection and/or exposure to the gp120 coat protein is associated with activation of caspase enzymes and apoptosis in neurons or glial cells; whether inhibition of caspase enzyme will prevent gp120 from injuring neurons; which neural cell type is the predominant target of gp120; as well as the role of gp120 in a number of other processes.

The second model in the Garden lab is a strain of live transgenic mice genetically engineered to develop a form of neurodegeneration similar to HIV dementia. “This mouse model is not infected with HIV, but expresses a protein that is part of the virus known to cause a lot of immune activation in the nervous system,” she said. “These mice develop synapse and dendrite degeneration, and their astrocytes and microglia (two forms of glial cells) react in the same way as those of HIV patients. This is not a complete model of the disease because there is no virus present, but it models the part of the disease we’re particularly interested in.”

Both in tissue cultures and in the live animal model, the caspase enzymes appear to be activated. “If we can prevent the functions of these enzymes using inhibitors, we seem to be able to prevent both the cell death in vitro and dendrite degeneration in vivo,” said Garden.

Confirming the role of caspase enzymes, the researchers were able to prevent apoptosis by crossing the HIV dementia mouse model with another mouse genetically engineered to express an inhibitor of caspase enzymes in its neurons.

“We also did a human study that showed there was caspase activation in patients who have HIV dementia,” said Garden. “The neurons are not dying, but they have the active enzyme in their dendrites, suggesting that it may play a role in addition to its role in apoptosis.”

Designing a treatment based on such findings will be difficult, said Garden. “We wouldn’t want to prevent apoptosis in general, because cells would become abnormal and form cancers or over-activate the immune system. The goal would be to find inhibitors that are specific to neurons, or that could be delivered specifically to neurons. We would be looking at some form of gene therapy or viral targeting therapy that would deliver a molecule or protein to inhibit the function of these enzymes in neurons in the central nervous system.”

In addition to studying the molecular pathogenesis of HIV dementia, Garden’s lab is studying the basic cellular biology of programmed cell death in the central nervous system. “We continue to be concerned with glial responses—both astrocytes and microglia—to neuronal injury and apoptosis,” said Garden, “to add to our understanding of how the brain responds to a variety of injurious stimuli that promote an inflammatory or excitotoxic reaction in the central nervous system.

“Even though our work is focused on HIV dementia, the results may also shed light on important cellular interactions that occur in many other settings, including stroke, traumatic brain injury, seizures, inherited neurodegenerative diseases and mitochondrial disease.”

"We think certain host factors are probably very important in determining who will suffer HIV dementia. About 10 percent of adults and up to 25 percent of children with HIV develop dementia. We don’t yet understand why this is.”

-- Dr. Gwenn Garden
People with developmental disabilities and their families confront huge obstacles in obtaining basic health care services that most people take for granted. They receive fewer routine health examinations, less mental health care, less oral health care, and have fewer opportunities for exercise. They are at greater risk for poor nutrition, overmedication, injury and abuse. Too few health care providers receive adequate training in treating individuals with developmental disabilities.

To address the formidable challenge of adequate access to health care and health promotion for adults with developmental disabilities, the Center on Human Development and Disability, in conjunction with the Washington State Developmental Disabilities Council, has undertaken a multi-year project to provide training to caregivers, family members and others who advocate for adults with mental retardation, as well as to health care professionals. The project began three years ago, and has now been extended.

The challenge was recently highlighted in JAMA, the Journal of the American Medical Association. “Poor health care for people with mental retardation has been the rule rather than the exception.... The barriers are many, and they are complex. Inadequate physician training is partly the cause; threadbare reimbursement rates through Medicaid exacerbate the problem.” (JAMA, Medical News and Perspectives, July 17, 2002)

“The goal of our project is to give advocates—both family members and residential care providers—a better understanding of the needs of adults with developmental disabilities,” said Douglas Cook, Ph.D., director of CHDD’s Adults and Elders Program, who heads the project and conducts the training sessions. “We want to give them strategies for dealing with health care professionals to ensure good care for their relative or client, and to improve their skills at dealing with behavioral issues that prevent good health choices.”

-- Dr. Doug Cook

Prior to designing and conducting the training sessions for family members and advocates, Cook and colleagues surveyed health care providers and advocates across the state to determine what they considered the greatest barriers to adequate care for adults with developmental disabilities. Issues most frequently cited were the family’s comfort and satisfaction with the health care provider, the physician’s ability to communicate with the patient, and the family’s difficulties in explaining issues to the physician. “There is a need for ongoing training to better understand and serve clients,” said one respondent.

In response to survey results, Cook has offered half-day and all-day workshops to advocates in a number of counties. The half-day sessions focus on resources available to provide good health care, and the full-day sessions include training in methods of health promotion for adults and elders with disabilities. Case studies help participants confront concrete examples and think about how to change behaviors and intervene to promote health.

The project is continuing on a smaller scale to provide training to advocates in counties across the state not included in the first phase of training, and to include underrepresented and diverse populations of caregivers.

“While some obstacles to care are matters of national policy

See ‘Access to health care’ on page 7
CHDD investigator researches the role of glial cell reactivity in traumatic brain injury and epilepsy

Traumatic brain injury causes more than 50,000 deaths in the United States each year. Another 50,000 people annually survive severe head injuries and are left with significant neurological problems. Among the estimated 200,000 people who suffer minor head injuries every year, many experience ongoing problems ranging from headaches to seizures, intellectual impairment, memory impairment, decreased ability to concentrate and emotional instability.

Immediately after head injury, there may be little evidence of brain trauma. But in the minutes, hours and days that follow, additional brain damage can ensue, including hematoma, brain swelling, increased intracranial pressure and infection. Months and even years after the initial traumatic event, epilepsy may appear, further complicating the lives of posttraumatic patients.

Medical scientists are seeking to understand the cascade of biochemical events that occur following brain injury in order to devise effective methods of intervening—most likely drug treatments—to prevent or minimize further damage.

While most investigators concentrate their research on the response of neurons and synapses to brain injury, Raimondo D’Ambrosio, Ph.D., focuses on the role of a different type of brain cells—the glia—in exacerbating the damage to the brain after a blow to the head. He is a University of Washington assistant professor of neurological surgery and a research affiliate at the Center on Human Development and Disability.

In his laboratory at Harborview Medical Center in Seattle, D’Ambrosio studies brain-injured rats that have incurred a moderate loss of neurons in the hippocampus, the portion of the mammalian brain involved in memory formation. The rodents lose their capability to store short-term memories, as evidenced by difficulties in learning and remembering a specific location in a maze. The lab also uses various techniques to study the electrophysiology of individual glial cells.

“One line of research in my lab is the physiology, or basic functioning, of glial cells,” said D’Ambrosio. “In the past, they were thought merely to provide nutrients and scaffolding for the neurons, which were considered responsible for the brain’s actual functioning. In the last 10 to 15 years, however, glial cells have been found to possess a much more complicated and important role. They have been found to express virtually all the receptors and ion channels that were thought to be an exclusive feature of neurons, and have been shown to affect neuronal and synaptic excitability and function. Therefore, they can no longer be considered passive cells, but are actually an active component of the brain.” While the brain contains an estimated 100 billion neurons, it has 10 to 50 times as many glial cells.

D’Ambrosio’s other line of research is the pathophysiology of glial cells, i.e., their functioning following trauma or other damage to the central nervous system. “Every insult to the central nervous system results in a common pathological feature called glial reactivity. There are very few laboratories working on the pathophysiological changes in glial cells following traumatic brain injury, and therefore there is a dramatic lack of data.”

In response to central nervous system damage, glial cells become “reactive.” They alter their normal activity and undertake to repair the damaged area of the brain. They remove cellular debris, kill damaged neurons, control inflammation and release cytokines and neurotropic factors.

However, in taking on this new role in response to injury, they may lose their ability to perform their normal function of exerting appropriate control over the firing of the neurons. “The data we have collected so far suggest that glial cells cannot perform two functions—the repair function and the normal control function,” said D’Ambrosio. “If they do not, their reactivity itself may be a factor in delayed neuronal death and in the onset of epilepsy.”

Further complicating the problem, the area of glial cells that becomes reactive often exceeds the region of the brain initially traumatized. The lab seeks to determine whether reactive glia are capable of promoting pathological changes in neurons undamaged by the original injury, and secondly, whether an injury in one area of the brain induces reactive glia to cause problems elsewhere in the brain.

The focus is on glial cells’ regulation of the brain’s extracellular space, which surrounds all brain cells. “The excitability of the neurons and synapses depends on the regulation of certain chem-
icals and ions in the extracellular space, primarily potassium and glutamate," D'Ambrosio explains. "Glial cells are predominantly responsible for maintaining homeostasis (equilibrium) in the extracellular space, a crucial factor in neuronal excitability. We are asking whether post-traumatic reactive glial cells properly regulate extracellular space."

The lab has found that, although glial cells are activated to repair neuronal damage, they have a decreased capability of regulating the concentration of potassium in the extracellular space. Using various electrophysiological techniques, D'Ambrosio's lab has data showing there is an abnormal accumulation of potassium in the post-traumatic brain, from the date of injury until at least a month after. More distant time intervals from injury are now under study.

Abnormal accumulation of potassium or glutamate in the extracellular space would cause otherwise normal neurons to discharge, synchronize and provoke epileptic seizures. "The finding that post-traumatic glial cells have an impaired ability to regulate the extracellular space is important. It shows that glial cells in becoming reactive may be a pro-epileptogenic factor that is totally independent of the neurons," said D'Ambrosio.

The goal is to gain sufficient knowledge to point the way to more effective treatments for both traumatic brain injury and epilepsy. "The hope would be for a drug treatment that targets glial cells, to be paired with currently available drugs that target neurons," he said. The lab has received a grant to study drugs that would help post-traumatic reactive glial cells regulate extracellular potassium.

Another way to approach the problem would be to control reactivity itself," said D'Ambrosio. "If we can characterize the bad things about reactive glial cells, we could design therapies to ameliorate the negative aspects of reactivity while maintaining the cells' ability to repair the damaged tissue."

Another focus of research in the D'Ambrosio lab is post-traumatic edema. Following a severe brain injury, people die because intracranial pressure increases and the brain ceases to function. "The major cause of death following brain trauma is increased intracranial pressure. Patients seem to be fine, and then three days or so after injury they die," said D'Ambrosio. One of the important causes is cytotoxic edema, caused by swelling of the glial cells. As the cells react to repair the damage, they load too much water and swell. (Another form of edema, vasogenic, occurs when the blood-brain barrier breaks down and water moves from the bloodstream to the brain.)

"The mechanisms by which glial cells swell following traumatic brain injury are not well understood," said D'Ambrosio. "We are trying to see if we can ameliorate this phenomenon by targeting the pathophysiological changes in the electrophysiology of the glial cells. These changes were not known until 1999, when we published our original findings."

D'Ambrosio has also proposed a study of glial cells following hypoxia, or stroke. "It is known, for example, that stroke causes massive glial reactivity. All the findings we have on brain trauma can be applied to the hypoxic brain. A drug that works on the post-traumatic brain could potentially also work in the brain following stroke, if the problem is the same."

While D'Ambrosio is currently focused on traumatic brain injury, the next logical step is to look at other insults to the central nervous system. "It is conceivable that all of these pathologies of the brain—trauma, stroke, meningitis and hypoxia—have a feature in common, which is glial reactivity. All may have at least one component related to the loss of function of glial cells that become reactive."
A primary activity of the University Center for Excellence in Developmental Disabilities (UCEDD) is interdisciplinary training. In a major expansion of its training activities, our UCEDD is embarking on a multi-year initiative to establish a comprehensive web-based curriculum in the field of developmental disabilities. Heading the effort to coordinate training across the UCEDD’s various programs and expand online training is Mark Harniss, Ph.D., director of interdisciplinary training and evaluation, assisted by instructional designer Marie Kotowski, M.S.

One of two major components of the Center on Human Development and Disability, the UCEDD offers training across disciplines to students preparing for careers in the field of developmental disabilities and to professionals seeking further expertise in the field, in addition to providing information to family members, caregivers and others who advocate for children and adults with developmental disabilities.

"Our goal is to design a modular curriculum that is both comprehensive and flexible. Our initiative will target in-house trainees, as well as professionals in the community, families and caregivers of persons with developmental disabilities, and individuals with developmental disabilities."

-- Dr. Mark Harniss

The UCEDD consists of eight organizational components providing interdisciplinary training, model clinical services, community outreach, clinical and applied research, and dissemination of information. The units include the Adults and Elders Program, the Autism Center, the Center on Infant Mental Health and Development, the Center for Technology and Disability Studies, the Clinical Training Unit, the Community Disability Policy Initiative, the Experimental Education Unit and the Genetics Program.

About 250 pre-professional trainees annually prepare for leadership roles in the field of developmental disabilities through classroom work and hands-on training at CHDD and in schools, clinics, service agencies and other community sites that serve persons with developmental disabilities.

"There is an incredible diversity of students in the programs that make up the UCEDD," said Harniss. "Our goal is to design a modular curriculum that is both comprehensive and flexible. We envision offerings on three levels of expertise: orientation, for those new to their profession or to the field of developmental disabilities; intermediate, for those working in a related profession and seeking to learn more about developmental disabilities or develop a specialty; and advanced, for experts in the field interested in expanding their knowledge and moving into leadership roles."

Harniss emphasizes that he will not determine the curriculum or decide who receives training. "These decisions are made by each program. I will work with the programs to identify what materials can be put online, what commonalities exist among the programs, and what resources can be shared throughout CHDD."

While clinical training and face-to-face instruction will continue to be very important modes of training at CHDD, online training will be greatly expanded. The projected web-based core curriculum in developmental disabilities will be broad, and will enhance the learning opportunities already available at CHDD in the fields of developmental pediatrics, occupational and physical therapy, psychology, nursing, nutrition, social work, pediatric dentistry, speech and language pathology, audiology, adaptive technology, genetics, special education, and related fields.

The objective in placing materials online, said Harniss, is that students will not only receive training in specialized areas, but also will be given a comprehensive overview of the complex and challenging field of developmental disabilities. "Many of our trainees specialize, but it's important that they also gain an appreciation of the field of developmental disabilities as a whole, including such issues as funding and legal matters. Offering the basic content of the core curriculum through web-based modules will allow faculty to explore more advanced topics in the weekly core seminars that all pre-professional trainees attend."

Since the material being developed will be freely accessible on CHDD's web site, families, advocates and people with developmental disabilities will also be able to access web-based topics of interest, such as information about the latest research on a particular disability. Web content will be designed to be accessible to learners with sensory disabilities.

Harniss, whose background is instructional technology and...
special education, notes that there is an urgent need for everyone involved in the field of developmental disabilities to have access to good, reliable sources of information. “Our initiative will target in-house trainees enrolled at the University of Washington, as well as professionals in the community, families and caregivers of persons with developmental disabilities, and individuals with developmental disabilities. The field is changing rapidly, and many professionals are not prepared to deal with the needs of individuals with developmental disabilities.”

Kotowski, whose background is in instructional design, will assist Harniss in designing web-based training modules for distance learning. She will work with faculty, gather course content and prepare it for the web, and design and administer assessment tools. “Marie will transform information into instruction and implement it online,” said Harniss. “Face-to-face training can then be used more effectively.

“We hope to have full implementation of a comprehensive core curriculum in developmental disabilities within five years, and the first course online by next year. When this web initiative is fully implemented, we believe that CHDD will be in a position to play a leadership role in online training in the field of developmental disabilities.”

Information on training is available on the CHDD website at http://depts.washington.edu/chdd/.

Access to health care . . . from page 3

and budget issues, we believe these workshops address the barriers posed by communication and comfort issues between health care providers and family members,” said Cook. “I want families and other caregivers to have the ability to become more effective advocates for people with developmental disabilities. People can achieve much more than they realize.”

Another goal of the project was to provide training to health care professionals—primary care physicians, physicians’ assistants, nurse practitioners and occupational therapists—through a series of training modules and workshops. Acknowledging the challenge of attracting health care providers to in-person workshops, the professional training component of the project was re-focused as online training, at http://depts.washington.edu/aedd/.

“There is a clear need for improving access to health care for adults with developmental disabilities,” said John F. Mclaughlin, M.D., director of CHDD’s Clinical Training Unit. “There is a sense on the part of physicians that patients with developmental disabilities are difficult to deal with. Our message is that, as a health care provider, you are already taking care of adults with mild developmental disabilities and may not realize it. You are already competent to provide this care. In fact, the problem is not unique to developmental disabilities, but exists for a breadth of chronic medical conditions where special health care needs extend from childhood into adulthood.”

File photo

CHDD is working on a project to see that more adults with developmental disabilities have access to good health care.

A sample case study from a workshop for advocates for persons with disabilities

Linda is a 60-year-old woman with moderate mental retardation who has congestive heart failure. Her doctor has recommended that she lose weight, get regular exercise and eat a low-sodium, low-cholesterol diet. She lives in an intensive tenant-support arrangement.

Linda works at a sheltered workshop. She brings her lunch every day: a bologna and cheese sandwich, pretzels and chocolate chip cookie. During her break, she gets a Coke and potato chips from the vending machine. She has eaten this diet for 25 years and is very resistant to the idea of changing. On weekends, she likes to go to a fast-food restaurant for a cheeseburger and french fries.

She has support with grocery shopping, but insists on buying pretzels and potato chips. She becomes very angry when staff suggest she leave the store without the two items.

Linda does not get any regular exercise, and has trouble climbing stairs. A staff member recently tried to take her for a hour’s walk at a nearby park. She returned home after 15 minutes because she was exhausted and declared she would never go walking again.

Linda is fascinated by machines. A staff member noted she watches infomercials on TV about treadmills, rowing machines and other types of exercise equipment.

Possible discussion items for workshop participants: How could staff at Linda’s sheltered workshop and at her residence be involved in helping her make changes that would improve her diet? How might Linda be motivated to begin making changes in her dietary habits and increase her level of exercise?
CHDD welcomes three new research affiliates

Dr. Paul D. Connor holds a Ph.D. in clinical psychology/neuropsychology from Brigham Young University. He is an acting instructor in the Department of Psychiatry and Behavioral Sciences. His research centers on the neuropsychological and neuroimaging assessment of the effects of prenatal alcohol exposure, especially where fetal alcohol syndrome (FAS) or fetal alcohol effect (FAE) has been clinically diagnosed. Research projects include a functional magnetic resonance imaging (fMRI) study of cognitive activation in FAS/FAE and a longitudinal neuropsychological and mental health follow-up from birth of a large group of subjects, now adults, who were prenatally exposed to alcohol.

Dr. Nancy L. Haigwood holds a Ph.D. in bacteriology and immunology from the University of North Carolina, and did postdoctoral studies in virology at the Johns Hopkins University. She is an associate professor of pathobiology and microbiology, and principal investigator on a research study of perinatal transmission of simian HIV, the primate form of the virus that causes AIDS. The goal of her research is to increase understanding of what factors increase or decrease the likelihood of transmitting HIV infection from mother to fetus or infant. Perinatal transmission of HIV in humans is associated with delays in cognitive, motor, language and social development.

Dr. Elizabeth C. Oesterle holds a Ph.D. in auditory physiology from Purdue University and also has degrees in music and psychoacoustics. A research associate professor of otolaryngology/head and neck surgery, her research focus is the inner ear, its development and ability to repair itself after damage. Specifically, her focus is inner ear hair-cell regeneration, with the long-term goal of developing therapies to alleviate sensorineural hearing disorders. She also studies the development of the inner ear sensory epithelia.

Visit the CHDD website at http://depts.washington.edu/chdd