

Pediatric Audiology Clinic focuses on newborn hearing screening, early diagnosis and intervention

In years past, children with hearing loss often were not diagnosed until they were almost two years old. By that age, say speech and hearing experts Richard Folsom, Ph.D., and Lisa Mancl, M.S., of the Pediatric Audiology Clinic at the University of Washington's Center on Human Development and Disability, such children have lost months crucial to the normal development of speech and language—months that are gone forever. "Good hearing is essential for developing speech and language," said Mancl, lead certified pediatric audiologist at the clinic and clinical supervisor of graduate students.

"Newborn hearing screening and pediatric audiology are all about speech and language development," said Folsom, clinic director, professor of speech and hearing sciences and CHDD research affiliate. "That is essentially why we are involved. Our desire is to identify permanent hearing loss early in life so that we can intervene. Our long-term goal is to maximize the child's developmental outcome."

All infants in University of Washington's Medical Center's Neonatal Intensive Care Unit (NICU) have been screened for auditory function for a number of years; this spring, the screening was extended to the well-baby nursery, said Mancl. While such universal newborn screening is not yet a mandate in Washington state, it is required in many other states. In Washington, about 80 percent of hospitals with obstetric services now screen all babies.

Since babies in intensive care are more likely to have hearing



Babies with hearing loss who are promptly fitted with hearing aids have an opportunity for normal speech and language development.

loss because of prematurity and other factors that place them at higher risk, a physiological test called the brainstem auditory evoked response (BAER or ABR) is administered in the NICU. Electrodes are placed on the scalp of the sleeping infant, providing an evaluation of a substantial portion of the auditory sys-



Audiologist Lisa Mancl evaluates a toddler diagnosed with hearing loss.

tem, including brainstem activity. "We use this test in the NICU because it's sensitive to auditory problems and it may also pick up other problems that are neurologic in nature," said Folsom.

In the well-baby nursery, an evoked otoacoustic emissions test (OAE) is given to evaluate functioning of the cochlea in the inner ear. A miniature microphone is placed in the external ear canal and sound is presented. If the cochlea is normal, new sounds generated inside the cochlea come back to the external ear canal, where they are recorded.

"This happens only in people with normal hearing," said Folsom, "so it's an ideal screening test. If we don't get a response, we need to do additional testing." The OAE can be administered by non-audiologists and is thus practicable for widespread screening.

At UW Medical Center, the newborn testing program is a joint effort of the Department of Speech and Hearing Sciences and the Department of Otolaryngology. "Otolaryngology screens the babies, and the results come to us," said Mancl. "There are two parts to evaluating for hearing loss: one is screening, and the other is the follow-up. Both parts are crucial, because after hearing loss is detected, the child must be evaluated here at our clinic with complete diagnostic testing, followed by intervention."

In newborn nurseries, about four children in 1,000 are born with hearing loss ranging from mild to profound. However, the

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initial focus of screening was babies in neonatal intensive care units, since about three or four in 100 have hearing loss. "But if you looked at the medical records of 100 three-year-olds with hearing loss, only half would have been considered at risk," said Folsom. "So it's important to screen all babies, whether at risk or not."

Such universal screening is important, because if hearing loss is not detected early in life, speech and language will not develop normally. "Babies who have failed the screening test are seen in our clinic as young as one week old," said Mancl. "There is no lower age limit. Hearing aids can be custom-fit for babies' little ears. A child of 18 months who has no words to communicate is going to be well behind. There is great frustration on the part of the child and the parents. If the loss goes uncorrected into preschool and school, the child is going to have academic problems as well."

Statistics show that approximately 33 babies are born with significant hearing loss in the United States every day. Up to half of newborn hearing loss is from unknown causes, said Folsom; in fact, 90 percent of babies with hearing loss come from hearing parents. Causes that can be identified include a significant number of genetic causes, as well as various problems that would put a baby in the NICU: congenital infections such as rubella or cytomegalovirus (CMV), craniofacial abnormalities, bacterial meningitis, respiratory distress syndrome, extended use of a ventilator, low APGAR scores at birth, severe jaundice, low birth weight, and extended use of medicines that can damage the ear. "There are a number of infections that the mother might have," said Mancl. "CMV infection is an important one. Hearing loss caused by CMV starts out mildly at birth but can progress to irreversible profound hearing loss, even if caught early."

CHDD's Pediatric Audiology Clinic provides a full range of services related to hearing loss, including hearing aids, parent education and support. Families are referred to early intervention programs and other services as needed. Children can now receive cochlear implants shortly after their first birthdays. "Research shows that children who receive implants early do better than children implanted later in life," said Folsom.

"Many families need a lot of support," said Mancl. "They are almost paralyzed by the news of the hearing loss. There can be grief, denial and shock. Other families go into action and make phone calls and go on the internet to learn everything they can. Families may have raised an older sibling without a disability, and all of a sudden they have to learn something completely different. They have to learn how to communicate with a child in a new way."

An important component at CHDD is a year-long training program for graduate students in audiology, through the center's Clinical Training Unit. Students rotate through CHDD's High-Risk Infant Follow-Up Clinic, Child Development Clinic and Pediatric Audiology Clinic. "Many students may not have considered pediatric audiology as a calling, but they see interesting and challenging populations, and find the involvement in families' lives very satisfying," said Mancl.

"They're in the room when the audiologist breaks the news that a child has a permanent sensorineural hearing loss that will change the child's and the family's life, and they're there in the next rotation when the family comes back for a re-check, and they see the positive changes made after intervention," said Folsom.



Richard Folsom

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CHDD leads effort to measure and analyze brain atrophy in individuals with Huntington's disease

Since the identification of the gene for Huntington's disease in 1993, scientific research into the devastating inherited disease has greatly increased. With expanding knowledge, there is hope for development of effective treatments and an eventual cure.

Huntington's disease, or HD, is a degenerative and ultimately fatal brain disorder that generally shows clinical symptoms in midlife, although less frequently it can manifest itself in young children or elderly persons. A mutation on the fourth chromosome inserts an excessively repeating DNA sequence called a trinucleotide repeat into the gene for HD. The gene controls the production of the huntingtin protein (spelled with an I, not an O). The diseased form of huntingtin causes the death of cells in the basal ganglia, a cluster of neurons at the base of the brain that play an important role in regulating motor function. The ensuing neuronal damage produces severe physical, cognitive and emotional impairments and in the long term leads to death.

As an autosomal dominant disease, HD afflicts everyone who inherits the gene from an affected parent. The chance of such inheritance is 50 percent. An estimated 35,000 to 50,000 Americans have the clinical symptoms of HD, and up to 250,000 more are at risk, making it one of the more common inherited disorders. It affects as many people as cystic fibrosis or muscular dystrophy.

The decision to undergo testing to determine whether one has inherited the gene is a difficult one for those at risk, since there is as yet no cure or even effective treatment. While the genetic test determines unequivocally whether one will have HD in the future, it cannot predict when symptomatic disease will commence, making planning for the future difficult, as well as living with the knowledge that one will inevitably succumb to a debilitating illness.



Dr. Elizabeth Aylward and research assistant Venu Yallapragada look at a brain scan of a study participant. They will measure basal ganglia on MRIs from 500 participants every two years for the life of the study.

Elizabeth Aylward, Ph.D., professor of radiology at the University of Washington, research affiliate at the Center on Human Development and Disability, and coordinator of experimental design and image analysis of the Brain Imaging Component of CHDD's Neuroscience Core, is co-principal investigator on a study entitled "Neurobiological Predictors of Huntington's Disease," or PREDICT-HD.

The multi-site clinical research study is sponsored by an international consortium called the Huntington Study Group, with support from the Huntington's Disease Society of America and the Hereditary Disease Foundation. It seeks methods to detect the earliest signs of HD and determine how to predict timing of the beginning clinical manifestations of the disease. The goal is to gain essential information for future trials of experimental drugs that could delay onset of HD, slow its progression, and ultimately prevent it altogether.

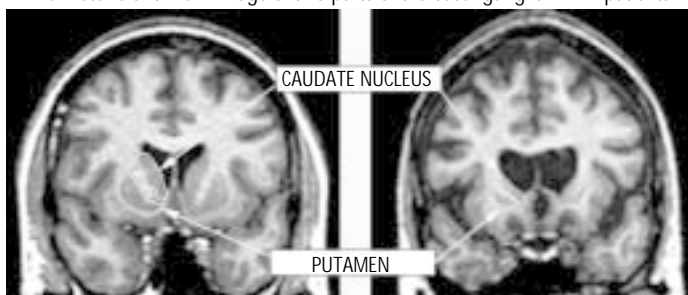
"We will track some 500 people participating in the PREDICT study at 21 sites in the United States and Canada," Aylward said. "Prior to enrollment in the study, individuals will have been genetically tested and most will have the gene for HD. A small number of individuals who have tested negative for the HD gene mutation will be included as control subjects." Participants are being recruited from a national registry of families with HD, from support groups and from other sources of patients.

Participants receive neuropsychological testing, clinical evaluation and brain scanning using magnetic resonance imaging (MRI). In an important component of the study, all MRIs are sent to Aylward and her UW colleagues for measurement and analysis. Her research assistant, Venu Yallapragada, is measuring the basal ganglia on all 500 scans. This part of the brain shows the most atrophy in HD, and the atrophy can be observed before clinical symptoms appear.

MRIs will be repeated every two years for comparison. "We have funding for four years, but we hope to continue this study for the long term," said Aylward. "We would like to be able to follow everyone to conversion, that is, to symptomatic diagnosis with the unequivocal presence of motor symptoms."

Utilizing data from many research subjects that show how neuropsychological and MRI measures change over the long term and how far in advance of the appearance of symptoms the changes occur, the investigators hope to be able to predict when clinical onset of disease would take place in a new population of people who carry the gene but who do not yet have symptoms.

Brain scans show shrinkage of two parts of the basal ganglia in HD patients



Adult without Huntington's disease

Adult with Huntington's disease

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Medical Genetics Clinic offers diagnosis, counseling for individuals and families with inherited disorders

The clinic waiting room at the University of Washington's Center on Human Development and Disability is frequently filled, usually with parents seeking help for their young children who have developmental disabilities. But on some clinic days, multiple generations of extended families gather to meet with experts in the center's Medical Genetics Clinic and learn how an inherited disorder has affected members of their family.

'Genetic conditions frequently affect multiple systems in the body, so people are seen by an interdisciplinary team with a wide range of expertise....we take care of the whole person.'

Robin Bennett

staff are genetic counselors Corrine Smith, M.S., CGC, Whitney Neufeld-Kaiser, M.S., CGC, and Mercy Laurino, M.S.; social worker Catherine Kendall, MSW, and program coordinator Debra Olson, B.S.

The clinic has seen marked growth since the advent of genetic testing for many inherited disorders, said Bennett, who joined the clinic in 1984 and is now president of the National Society of Genetic Counselors. "For many years we saw 200 to 300 patients a year. Now, we see more than 1,200 people a year in our two loca-

"Our waiting rooms are often full," said Robin Bennett, M.S., CGC, clinic manager and senior genetic counselor. "As a genetic counselor, you see a whole family and you recognize the spectrum of their particular disorder, where some are moderately affected and some more severely." Also on

tions at CHDD and University of Washington Medical Center."

Last year the clinic saw people from all over the Northwest with almost 200 different genetic diseases, with a focus on neurogenetics, connective tissue disorders, hereditary skin disorders and cancer genetics. Among the disorders more commonly seen are Huntington's disease, Turner syndrome, the hereditary ataxias such as spinocerebellar ataxia, Marfan syndrome, Ehlers-Danlos syndrome, neurofibromatosis and Von Hippel Lindau disease. The UW has been named a National Center of Excellence for many of these disorders.

While many genetic conditions can be confirmed by testing at UW laboratories, often blood or tissue samples must be sent away for analysis. "Some diseases we see are so rare that only one laboratory in the world is equipped to do the test," said Bennett.

During an initial visit, a genetic counselor takes an extensive family history, usually involving three or four generations, to determine who in the family has the disorder and who does not, and how it manifests itself. Medical records are collected to document the condition in various family members. A family tree called a pedigree is drawn up, to illustrate the presence of the malfunctioning gene in family members through the generations. Genetic diseases are inherited in various ways: some manifest themselves in every generation; others affect only males in the family, coming down, for example, through unaffected mothers to their sons.

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Robin Bennett, MS, CGC

National practice guidelines for counseling individuals with fragile X syndrome

Robin Bennett has been a leader of national efforts to write genetic counseling practice guidelines for inherited disorders, including fragile X syndrome, the most common inherited cause of mental retardation. The guidelines are published on the website of the National Guideline Clearinghouse, www.ngc.gov.

In addition to mental retardation, fragile X syndrome often includes emotional and behavioral problems and seizures, as well as characteristic physical features: a long face, large ears, flat feet and hyperextensible joints. Individuals with fragile X syndrome have a mutation of the FMR1 gene on the X chromosome, a "fragile site" where there is an expanded DNA sequence (a triplet repeat). Since it is an X-linked disorder, males are affected more severely than females, who have a gene on their other X chromosome that functions normally.

The Center on Human Development and Disability is es-

tablishing a national center of research into the molecular mechanisms of fragile X syndrome, with the goal of contributing knowledge that could lead to effective treatment. Research-oriented clinicians will increase the clinical presence at CHDD of patients with fragile X, work collaboratively with laboratory scientists, and interact with colleagues at other sites.

The genetic counseling guidelines of which Bennett is an author state that working with individuals and families with fragile X syndrome requires a long-term commitment on the part of the genetic counselor. Counseling includes taking a family history of three or more generations, a detailed medical history and a pregnancy history of carriers at risk, as well as educating the family, assessing risk for other family members, testing for the gene, addressing psychological and ethical issues, and following up with education, referrals to professionals and support groups.

Neurogenetics Clinic counsels people at risk for inherited neurological disorders

The Neurogenetics Clinic, a subspecialty clinic of the Medical Genetics Clinic, offers genetic diagnosis for neurodevelopmental and neurodegenerative disorders. Established in 1974, it was the first neurogenetics clinic for adults in the United States. The medical director is Thomas Bird, M.D., professor of medicine, neurology and medical genetics, CHDD research affiliate and coordinator of CHDD's Research Emphasis Area on Neurodegenerative Disorders.

The clinic focus is on inherited neurological disorders as they affect adolescents and adults, including Huntington's disease, Charcot-Marie-Tooth disease (a common inherited neurological disorder in which those affected gradually lose sensation and use of their limbs as nerves in the extremities degenerate), some forms of muscular dystrophy, and the hereditary ataxias (which involve degeneration of the cerebellum, a part of the brain that governs coordination), as well as disorders that may have a genetic component, such as Alzheimer's disease, Parkinson's disease and ALS (Lou Gehrig's disease).

The disorder seen most frequently at the Neurogenetics Clinic is Huntington's disease (HD). HD is an autosomal dominant disease: each child of a parent who carries the gene for the disease has a 50/50 chance of inheriting it. "Some people have the test for HD because they are having symptoms, and they are confirming the diagnosis," Bennett said. "Others are not symptomatic and want to know whether they inherited the gene."

People at risk for HD meet with a genetic counselor before testing. "We talk about the pros and cons of testing, and how the knowledge of their status will impact their lives, as well as the lives of their family," said Bennett. "They talk about life decisions they might make differently based on the test results."

The decision to be tested for HD is often excruciatingly difficult, since there is no treatment as yet for this progressive and ultimately fatal neurodegenerative disorder. Those at risk because HD runs through their family must decide whether it is preferable to live with uncertainty or to know one's future, positive or negative. The decision to be tested is sometimes made in the context of whether to have children, since HD symptoms may not appear until after the prime child-bearing years. After counseling, those who decide to be tested make a return visit to the clinic for a neurological exam with Dr. Bird and more counseling. They return once more to receive the laboratory results.

"While you would think there is a great sense of relief to learn that one has not inherited HD, many people have a hard time with the good news," said Bennett, "because it doesn't take away the disease in the family. There is 'survivor's guilt' that can be very strong. Some people have lived their lives as if there is no tomorrow, because they think it's almost literally true. Then, when they have their futures given back to them, they have a hard time dealing with it. They may regret past decisions about personal relationships or having chosen not to have children. As genetic counselors, we help them to deal with these issues."

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"People come to our clinics because they're not sure whether they have inherited a disorder that they might pass on to a child," Bennett said. "Perhaps they have a brother or sister with a developmental disability, and they wonder whether there is a genetic cause. We need to evaluate the sibling to know what genetic test should be done." While the clinic assists people in making general decisions about childbearing, the UW has a separate prenatal diagnosis clinic for couples expecting a child.

"Genetic conditions frequently affect multiple systems in the body, so people are seen by an interdisciplinary team with a wide range of expertise," said Bennett. "Genetic counselors are always present, because we are experts at giving information to people in an understandable way, getting them into support groups, doing follow-up, and helping with any genetic testing. We take care of the whole person, and we work with the individual's health care provider in their home community. We're a consultative service, as well as a multidisciplinary management site.

"For some people, there is a sense of relief to finally have a diagnosis for a condition that may have affected their family for generations," said Bennett. "They are gratified that we know the name of their disorder, we can spell and pronounce it, and we can refer them to support groups and other services. At the same time, it may be a shock to learn that others in their family are at risk. There can be a lot of grief, which is one of the reasons that this special field of genetic counseling exists. We counsel and support the whole family." ♦

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Folsom and Mancl are hopeful that Washington state, like a number of other states, will soon mandate universal newborn screening for hearing. "There is research showing that it makes a difference," said Folsom. "We have always screened children at kindergarten age, but it makes a difference if you identify and intervene early. In years past, we saw few infants at our clinic. We were more likely to see children at 18 months or two years or even older. Parents often suspect a problem for a long time before they arrive for a hearing test. By then, we've lost crucial years of language development. We're trying to capture those years."

"Our targets are that every child will be screened at birth, diagnosed by three months, and provided with intervention, including hearing aids, by six months," said Mancl. "It's not easy to hit those target ages, and it can't be done without newborn screening."

Both acknowledge that newborn screening can produce some false positives, because the tests are highly sensitive. Parents may suffer anxious moments before follow-up testing reveals that the child has normal hearing. "But research shows that false negatives from the screening tests are very rare," said Folsom. "Among the group that fails are all the babies with hearing loss."

"Identifying hearing loss is a crucial first step, but it's the easy part," said Mancl. "The hard work for families and professionals comes after the loss is diagnosed, hearing aids are fitted, and early speech and language intervention is initiated." ♦

Taking advantage of neural plasticity to help the brain reorganize and repair itself after injury

Science once thought the brain was incapable of development beyond the first few years of life. It was believed that once the neurons of the brain formed connections during the early years of development, the nerve connections were then fixed. If the brain were later damaged by an event such as a blow to the head or a stroke, the conventional wisdom was that nerve cells, neural connections and functions under control of the affected brain region would be irretrievably lost.

However, more recent research has shown that the brain has a remarkable ability to reorganize itself throughout the lifespan, not just during the developmental period. This phenomenon—called neural plasticity—enables neurons to compensate for injury as well as respond to environmental stimuli that result in learning. Scientists now know that by continually reorganizing connections between neurons, the brain has the ability to repair itself and even recover lost function.

Some two million people suffer head injuries annually in the United States. Approximately 100,000 die and another 100,000—predominantly young people in the 15-25 age range—are left with significant lifelong cognitive and physical disabilities. Given the large number of traumatic brain injuries, researchers are eager to find ways to enhance recovery processes.

Ramona Hicks, Ph.D., associate professor of rehabilitation medicine at the University of Washington and a research affiliate of the Center on Human Development and Disability (CHDD), focuses her research on the role of neural plasticity in recovery and regeneration following traumatic brain injury.

Other investigators in CHDD's Research Emphasis Area in Neural Plasticity, which Hicks coordinates, are focused on neural responses to injury inflicted by diseases and disorders such as stroke, epilepsy and HIV infection, as well as changes associated with development. The goal is to understand the neurobiological processes that control injury, and to determine the mechanisms of interventions aimed at enhancing recovery. Still other researchers are investigating the role of activity-dependent processes and signaling in the development of neural function, especially issues related to gene-environment interactions in the development of hearing, language and cognition.

In her earlier career as a physical therapist, Hicks worked with children with brain damage from various causes, especially cerebral palsy, as well as with stroke patients. "There are commonalities in the brain's response after various injuries," she said. "While the



Dr. Ramona Hicks studies the role of neural plasticity in recovery and regeneration following brain trauma.

causes may be different, the result is that people have some measure of disability after brain injury." Her clinical experience with brain-damaged patients led to her research pursuits, working with a rodent model of traumatic brain injury, and examining the role of exercise and environmental stimulation in repairing brain damage.

While Hicks' research concentrates on the attempt to repair damage once brain injury has occurred, she notes that there are strategies that can be applied earlier, aimed at preventing or mitigating damage. "The first line of defense is prevention; for example, through the use of such safety equipment as bicycle helmets, or through lifestyle changes to decrease the chance of stroke. Even the administration of the drug tPA (tissue plasminogen activator given within three hours of ischemic stroke to dissolve a blood clot in the brain) can be consid-

ered a measure aimed at preventing irreversible cell damage."

The second line of defense is neuroprotection through the use of various drugs, to minimize the succession of degenerative processes that ensue after brain or spinal cord injury. "The goal of pharmacological intervention is to reduce that cascade of events and provide protection to the neurons," she said.

The third group of strategies, if brain injury occurs when efforts at earlier intervention have been absent or unsuccessful, attempts to induce the brain to repair itself and replace dead or injured neurons and neural connections. Such measures may involve drugs or other therapies. "Drug interventions are very important, but this is not my emphasis," Hicks said. "I am looking at non-pharmacological approaches, trying to take advantage of neural plasticity through interventions involving enrichment of the environment, exercise, and learning activities.

"There are three broad hypotheses as to why there is functional recovery after brain injury," said Hicks. "One is attributable to learning compensatory skills: for example, learning to write with the non-dominant hand. A second is attributable to adaptations in surviving neural networks, enabling them to take over the functions of damaged areas of the brain.

"A third and emerging hypothesis is that neural stem cells may replace neurons and neural networks. This is my focus: I am interested in whether endogenous neural stem cells (those produced in the patient's own brain) can be induced to replace lost cells and contribute to recovery of function after brain injury."

Neural stem cells, or neural progenitors as they are also called, were discovered in 1962. These immature cells exist primarily in



Dr. Hicks is investigating whether moderately brain-injured rats exposed to an enriched environment show greater recovery than those in a deprived environment. She seeks to determine which aspects of enrichment are most important in inducing formation of new neural connections.

two areas of the brain: around the ventricle in an area called the forebrain subventricular zone, and in the hippocampus. Hicks' research focuses on whether the brain can be induced to increase the number of stem cells it produces, a process called neurogenesis. While an embryonic stem cell transplant would also increase the number of stem cells, Hicks is working to advance knowledge of how the brain itself can be persuaded to create and utilize more stem cells.

Her premise is that environmental enrichment can increase neurogenesis. "For example, in brain-injured laboratory rats, we find that access to an exercise wheel produces a big increase in stem cells. We don't know why the stem cells are concentrated in the hippocampus, but we know they decrease with age, and they increase with exercise. I believe my work has relevance for recovery from brain injury at all ages."

Hicks' research subjects are adult laboratory rats that have been painlessly administered a controlled moderate head injury under anesthesia, with resulting damage to the hippocampus producing persistent cognitive deficits that do not resolve. The hippocampus includes an area of the brain called the dentate gyrus, where the neural stem cells reside. The goal is to see whether any of various forms of environmental stimulation will induce the stem cells to proliferate, migrate the short distance to the damaged area, and replace dead and dying cells.

After injury, there is typically a large surge of neural progenitor cells, apparently in response to the injury. The surge peaks about three days after injury. However, most of these progenitor cells do not survive to become mature cells. The neurons themselves seem to exert a regulatory function that inhibits this process of neurogenesis. "We're trying to determine whether it's possible to overcome this regulatory function and sustain neurogenesis by enriching the animal's environment," said Hicks.

She notes that a laboratory rat's caged environment, analogous to that of a typical hospital setting, is one of relative deprivation. "Hospitals do all they can, but many such environments are not very stimulating. Typically, patients are only actively engaged in therapy a few hours a day, and we don't know whether this is op-

timal. We have to figure out what type of environmental enrichment encourages the production and maturing of neural cells, first in rats and ultimately in humans. Is it social enrichment? A learning event? Physical activity? Visual stimulation?"

Preliminary results with brain-injured rats indicate that the essential component in encouraging production of neural stem cells is an environment that provides the opportunity for active engagement. "Mere physical activity, whether voluntary or forced, and mere social activity (interaction with other rats) does not seem to be adequate," she said. "In normal animals, we know exercise does good things for the brain. But what are the mechanisms that produce these positive effects? Should the exercise be aerobic, such as forced running on a treadmill, or should it be voluntary, such as access to a wheel? Should it be acrobatic, to improve coordination? Or is motor learning the important issue?"

Studies show that some interventions can actually exacerbate brain damage. For example, animal studies have shown that forced use of a limb controlled by a damaged area of the brain increases the area of damage. "This raises questions with regard to physical therapy, since we do not know whether some interventions may have positive or negative consequences. For example, is it better to start walking right away, or to delay? What should the intensity of exercise be? What is the best strategy for inducing the brain to repair itself? Our results may assist in designing the best strategies for physical and occupational therapy after brain injury."

While the primary goal of physical therapy after traumatic brain injury is to improve motor function, recent studies suggest that physical activity may also influence cognitive function in a positive way. "Various studies support a role for exercise in improving or maintaining cognitive function in healthy humans and animals," said Hicks. "We don't know whether the cognitive improvements associated with environmental enrichment are attributable to physical activity, social interaction, novel environmental stimuli, or a combination of factors. Our studies should help shed some light." ♦

New research affiliate appointed

Dr. Carolyn Crockett holds a Ph.D. in animal behavior from the University of Washington. An affiliate assistant professor of psychology and anthropology, she is a research scientist with the Washington National Primate Research Center and coordinator of its Psychological Well-Being Program, focusing on factors promoting the psychological well-being of laboratory monkeys. She works to understand factors that can prevent abnormal behavior from developing and develops therapeutic methods for the treatment of behavior disorders in non-human primates. Dr. Crockett has a special interest in understanding individual, species, and sex differences in response to laboratory experiences and enrichment techniques. ♦



Crockett

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“It’s important to be able to predict time of conversion to symptoms using these neuropsychological and MRI measures,” says Aylward, “Initial clinical trials of drug treatments would use subjects who already show symptoms of HD, but a further goal would be to test treatments in people who have tested positive for the HD gene mutation but who don’t yet exhibit symptoms.

“A common outcome measure in treatment trials is delay of onset of symptoms. If that is your measure of effectiveness of treatment, you need research subjects who are pretty close to onset, unless you want your study to last for 20 or more years. So it would be valuable to be able to predict onset in an individual using neuropsychological and MRI measures, and then recruit your research sample from among those who are likely to become symptomatic in, say, the next two years. Then you could test an investigational drug’s efficacy by determining whether more untreated subjects become symptomatic during a two-year clinical trial, compared to those treated.”

The PREDICT trial will also measure the rate of brain atrophy during the presymptomatic stage. “It would be useful to know what the normal rate of atrophy is,” said Aylward, “so that in future trials we will know whether an experimental treatment slows it down. We also want to know when brain atrophy begins so we could determine when to begin treatment. When a drug treatment becomes available, do we give it to everyone right after their gene test? Do we give it to a three-year-old? We don’t know. A drug may be expensive and it may have side effects, and we probably wouldn’t want to give it until there is some brain atrophy or mild dysfunction. We think atrophy begins about 10 years before the onset of symptoms, but we would like to know this more precisely.

We will need more research subjects to determine this.”

While there are no results yet from the PREDICT study, Aylward is also working on another HD research project underway at Johns Hopkins University, where she was formerly a faculty member. Funded by the National Institute of Neurological Disorders and Stroke (NINDS), this study follows both pre-symptomatic and symptomatic persons with HD, with MRI scans every two years. “From this study, we know that the basal ganglia shrink in symptomatic patients at the rate of about five percent per year,” she said. “In the presymptomatic phase, the rate of atrophy depends on how far one is from onset of symptoms.”

Another study sponsored by the Huntington Study Group is PHAROS, the Prospective Huntington At Risk Study, for which the University of Washington is a research site. This study is recruiting 1,000 people ages 26 to 55 who are at risk because they have a parent with HD, but who have not been tested for the gene. The study will address important questions including: What are the earliest signs of HD and when do they start? How accurate are the measures used in detecting onset? What factors influence the age at which illness develops? In a group of people at risk, how many will develop signs of illness over a minimum three-year period of observation?

While these studies do not provide immediate benefit to current participants, said Aylward, “We do find that families are generally very eager to participate, more so than with other disorders, because they experience the inevitable debilitating effects of HD in generation after generation. With many other genetic disorders, you may know you are at some risk, but you don’t know how much at risk. People want to participate because these studies may help provide information important for understanding the onset of Huntington’s disease, and in the longer term, contribute to efforts to find an effective treatment and ultimately, a cure.” ♦



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