CHDD OUTLOOK

News from the Center on Human Development and Disability at the University of Washington Health Sciences Center

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INSIDE

CHDD forms new research center on Joubert syndrome and other disorders of the cerebellum

Disorders of the cerebellum, such as Joubert syndrome, are an important focus of research at the Center on Human Development and Disability. While these developmental and degenerative disorders are rare and poorly understood, together they are significant contributors to neurologic disease. Their study has the potential to enhance basic understanding of the function and development of the cerebellum. Located at the base of the brain, the cerebellum controls balance and coordination and is especially important in motor learning. It is increasingly implicated in cognitive functions as well.

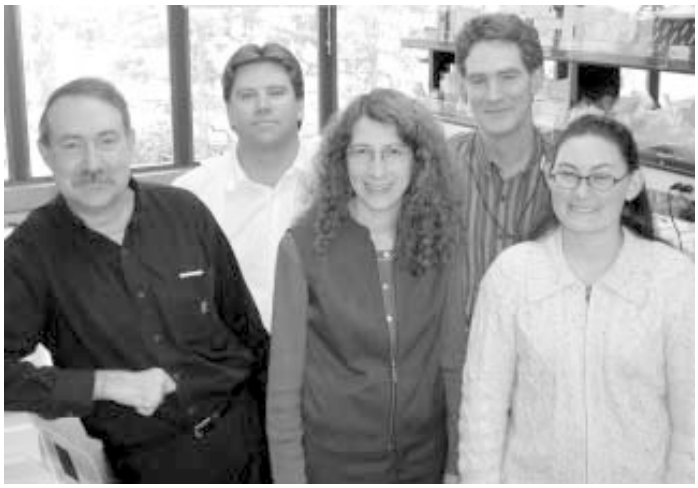
To coordinate and expand research efforts aimed at gaining a greater understanding of cerebellar disorders, CHDD has established a planning group to develop a Research Center for Developmental and Degenerative Disorders of the Cerebellum.

Principal investigators are Phillip Chance, M.D., University of Washington professor of pediatrics and neurology; Thomas Bird, M.D., professor of medicine, neurology and medical genetics; Ian Glass, M.D., associate professor of pediatrics and medical genetics; and Melissa Parisi, M.D., Ph.D., acting assistant professor of pediatrics. All are CHDD research affiliates. Chance directs CHDD's Genetics Core, heads the Division of Genetics and Development in the Department of Pediatrics, and coordinates the CHDD Research Emphasis Area (REA) on Joubert Syndrome. Bird is coordinator of the REA on Neurodegenerative Disorders.

The principal investigators will be joined by an interdisciplinary team of researchers from the UW and other institutions, with expertise in a wide range of disciplines including genetics, neurology, neuroradiology, neuropsychology, fetal pathology, ophthalmology and developmental pediatrics.

The research center will focus on various developmental and degenerative disorders of the cerebellum, including:

• Joubert syndrome, a rare autosomal recessive condition characterized by absence or underdevelopment of the cerebellar vermis with a malformed brainstem. Joubert and related syndromes are also known as the molar tooth syndromes: an MRI at the level of the brainstem shows a malformation shaped like a tooth. Characteristics vary and may include ataxia (lack of coordination), hypotonia (decreased muscle tone), an abnormal breathing pattern characterized by panting or breathing pauses, and abnormal eye movements. Kidney and liver problems, extra fingers and toes, cleft lip or palate, tongue abnormalities and seizures are also possible, as well as mild to moderate mental retardation.



From left, CHDD research affiliates Drs. Phillip Chance, Craig Bennett, Melissa Parisi and Ian Glass and CHDD Genetics Core scientist Melissa Postler are part of the team investigating Joubert syndrome and other disorders of the cerebellum.

• Dandy-Walker malformation, a heterogeneous group of disorders characterized by maldevelopment of the cerebellum and a large cyst of cerebrospinal fluid in the fourth ventricle, frequently complicated by hydrocephalus. It accounts for 1 to 4 percent of all hydrocephalus. Problems with motor coordination and balance, seizures and developmental delay are also features in some patients.

• Cerebellar hypoplasia and pontocerebellar hypoplasia, poorly understood disorders characterized by malformation or progressive atrophy of the cerebellum or the pons (which connects the beginning of the spinal cord and the midbrain). These disorders may be static or progressive. There is no molar tooth malformation.

• Hereditary cerebellar ataxias, a heterogeneous group of disorders that are individually rare but collectively more common. They cause progressive degeneration of the cerebellum, failure of muscular coordination, inarticulate speech and other neurologic findings, often resulting in a shortened lifespan. Some types are associated with cognitive deficits or mental retardation.

"Joubert syndrome has been one of several areas of research emphasis at CHDD," said Chance. "However, it was never a primary area of investigation because we didn't have a critical mass of people interested in it. The recent addition of Drs. Glass and Parisi has infused the project with a clinical and developmental focus. Historically, it's been difficult to get funding for research in this area, because it's a complex group of disorders. However, there are

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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 Mental Retardation and Developmental Disabilities Research Center.

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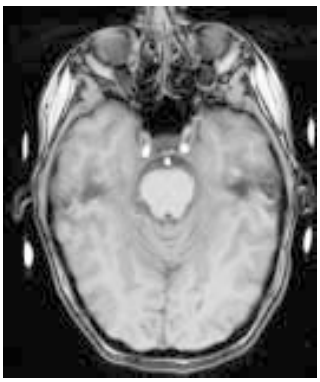
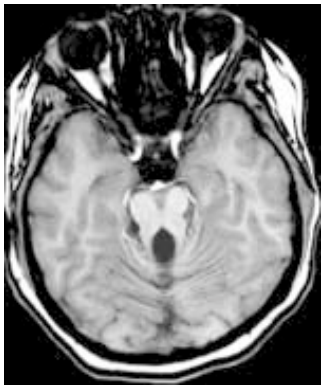
now many families and patients available for study, there's a growth of knowledge in neurobiology related to the cerebellum, and there are advances from the Human Genome Project. It becomes conceivable to apply the tools of molecular biology to gain insights, through evaluation of genes known to play a role in the development of the cerebellum, which may be potential targets for mutations."





MRI scans of a normal brain, top, and a Joubert syndrome patient, below, showing the "molar tooth" sign

Few genes have been identified for any of the developmental cerebellar disorders, said Chance. "Many are disabling conditions for which there are limited therapeutic interventions and a high burden of care. Insights into their origins may offer clues to possible therapeutic interventions and, at the very least, improve the quality of information and genetic counseling available to families."

"These malformations of the posterior fossa (the cerebellum and brainstem) were never classified in any logical way until good MR imaging became available in the 1990s," said Glass. "In 1997, the molar tooth brain malformation involved in Joubert syndrome was imaged by Dr. Bernard Maria, now at the University of Missouri. That enabled the work that Phillip Chance has done, to recruit and diagnose affected families in a much more systematic way than in the past."

A large part of the center's efforts will be directed toward Joubert syndrome. "It's been difficult to establish diagnostic criteria for Joubert and develop a homogenous pool of subjects to study because no two patients look the same," said Chance. "It's a multi-system disorder involving vital organs including the liver and kidneys. That fact hasn't been appreciated until recently."

"We're in the infancy of understanding cerebellar malformations," said Parisi. "A better understanding of Joubert syndrome will shed light on other posterior fossa malformations. People have assumed that the cerebellum is involved only in balance and coordination, not in higher thought processes and learning. That assumption is being challenged as we observe the effects of structural cerebellar abnormalities on the cognitive abilities of affected children."

The task of finding a gene for Joubert syndrome is proving complex, given the multiplicity of symptoms. The disorder was first described in 1969 by Dr. Marie Joubert. "The original family described is French Canadian," said Parisi. "It appears there may have been a family ancestor who carried a recessive mutation for a particular gene, which was then transmitted to subsequent generations." A region on chromosome 9 has been mapped in some families with symptoms of Joubert syndrome in the country of Oman. However, said Parisi, most of the families being studied are not linked in that particular chromosomal region, so clearly there must be more than one gene involved.

"We're looking for a multitude of genes," said Chance. "If we find a gene that's abnormal in a given patient and that patient has mental retardation, at this point we don't know if the gene is affecting the cerebellum directly or if it also has actions in the cerebral cortex."

Using an interdisciplinary team approach, the center will seek to define

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CHDD fellow initiates project for immigrant children with developmental disabilities and their families

Imagine yourself as a refugee from a war-torn country, who has arrived in Seattle after making your way halfway around the world. Imagine you don't have a great deal of formal education and you speak little English. Imagine also that your child has a developmental disability, diagnosed or undiagnosed. Imagine the sense of isolation. Where would you turn for support and understanding?

This is typical of the circumstances facing many immigrant and refugee families whose children are seen at the Children and Teens Clinic at Harborview Medical Center. In 2001, Dr. Daniel A. Doherty, now a trainee at the Center on Human Development and Disability, cared for many such patients as a pediatric resident.

CHDD pediatrics fellow Dr. Dan Doherty, back right, works with family advocates assisting Somali, Vietnamese and Hispanic families who have children with developmental disabilities.

"When I imagined myself in their parents' shoes, I felt overwhelmed," he said. "I could not imagine living in a culture very different from my own, not speaking the predominant language, trying to understand my child's complex disorder that doesn't even have a name in my native country, and trying to figure out the best way to provide for my child."

Doherty is now spending three years at CHDD, continuing his study of the pediatric assessment and treatment of children with developmental disabilities as a Developmental and Behavioral Pediatrics fellow under the auspices of CHDD's LEND program—Leadership Education in Neurodevelopmental and Related Disabilities. Before his residency, he earned a Ph.D. in molecular genetics and an M.D. from the University of California at San Francisco.

Moved by the circumstances of the refugee and immigrant families he met, Doherty obtained a one-year grant through the CATCH (Community Access To Child Health) program administered by the American Academy of Pediatrics. He titled the project BRAIDD (Better Regional Access for Immigrants and Refugees with Developmental Disabilities), and pursued it in his spare time during his residency training.

The initial project identified 50 children with developmental disabilities served at the clinic, whose families spoke limited English. The focus was on Somali families, the largest immigrant population at the clinic. "We interviewed families and interpreters to explore the meaning of developmental disabilities in Somali culture, and we planned support and education groups to help families gain access to needed services and increase their ability to advocate for their children with disabilities," said Doherty.

Doherty then partnered with two advocacy agencies, The Arc of King County and the Refugee Women's Alliance, to expand the project to serve Hispanic, Vietnamese and additional Somali families. They qualified for a five-year grant from the Healthy Tomorrows Partnership for Children Program, a collaborative program between the federal Maternal and Child Health Bureau (MCHB) and the American Academy of Pediatrics. An ongoing priority is to secure funding to continue the project's work in the future, since it must attract two-for-one matching dollars from non-federal sources to renew annual funding. The opportunity for collaboration between the medical community and the advocacy organizations is another important aspect of the project.

"We want to use the support groups and one-to-one advocacy to improve the lives of children with disabilities and their families," said Doherty. "This population tends to have a history of many risk factors for health problems including poverty, poor nutrition, inadequate access to medical care, and exposure to diseases, and thus their children have a greater incidence of developmental disabilities than the general population. We want to encourage parents to improve their language skills, help them interact more effectively with health care providers, therapists, social workers, schools and government agencies, increase their ability to advocate for their children, and help them feel less isolated and better supported, both emotionally and tangibly."

Coordinated by a bilingual/bicultural family advocate, families meet every six weeks to receive practical advice and emotional support from other parents and professionals. Each meeting includes a topical presentation, discussions among family members and facilitated problem-solving. "Even though the Somali community here is fragmented because of past violence among the country's different clans, having a child with a developmental disability makes clan differences less important," said Doherty. "After they have felt so isolated, meeting other children and families with similar problems has made a huge impact on them.

"Parents want more information about their child's condition, about resources in the community, and about how they can help their children. Some of this information can be gleaned from the professional community, but much of what is needed is practical information best learned from other parents in similar circumstances."

To enable families to attend the meetings, the project provides childcare and transportation assistance. It also offers some one-to-one advocacy, acts as a clearinghouse for information on services,

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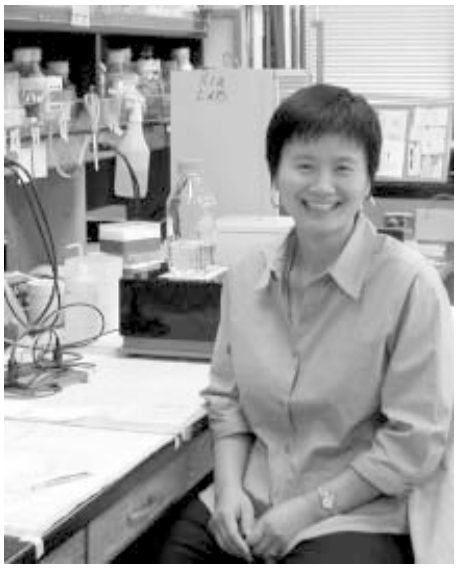
Apoptosis: Lab studies normal and abnormal forms of programmed cell death in neurons of the CNS

For an organism to maintain health, its cells, ironically, must be programmed to die. This process is called programmed cell death. Apoptosis, a form of programmed cell death, plays a vital role in helping to maintain a healthy organism. In the developing human fetus, for example, apoptosis removes the cells that form the webbing between the developing fingers, transforming them into normal human digits. In the young child's brain during early development, apoptosis eliminates surplus cells and fosters the proper synaptic connections between neurons. Apoptosis destroys cells damaged by viruses or toxins, cells that have suffered genetic damage, and immune system cells no longer fulfilling their function. Chemotherapy and radiation therapy may effect a cure by inducing apoptosis in some types of cancer cells, where natural apoptosis has failed.

Apoptosis plays an important role in the development of the nervous system. While normal apoptosis serves to promote the health, development and homeostasis of the organism, inappropriate apoptosis in human neuronal cells may contribute to a variety of neurodevelopmental and neurodegenerative conditions, including Down syndrome, stroke, epilepsy, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease), and Alzheimer's disease.



Dr. Zhengui Xia is working to identify signaling pathways that regulate apoptosis in neurons.

To solve the mysteries of these and other diseases, science must gain an understanding of the mechanisms that regulate neuronal apoptosis, issues of fundamental importance for neurobiology. At the University of Washington, Zhengui Xia, Ph.D., associate professor of environmental health and a research affiliate at the Center on Human Development and Disability, is seeking to advance scientific understanding of neuronal apoptosis.

"Neuronal activities and neurotrophins are critical for the differentiation, survival and adaptive responses of neurons, both during development and in the adult brain. During development, apoptosis serves as a prominent force in sculpting tissues," said Xia, "to remove cells that are produced in excess or have developed improperly, and to eliminate cells that are no longer needed. During neuronal development, up to 50 percent of neurons and oligodendrocytes (glial cells in the central nervous system that myelinate axons) are eliminated."

The overall objective of Xia's and colleagues' research is to identify the signaling pathways that regulate neuronal apoptosis induced by various disease models, as well as by environmental toxicants. "Many environmental toxicants exert their effects by inducing apoptosis, and they may contribute to the development of neurodegenerative disorders," said Xia. "Although genetic studies have linked some neurodegenerative disorders to genetic predisposition, most cases arise sporadically, and their causes and origins remain largely undefined. Environmental factors and gene-environmental interactions may play a large role."

Xia's lab is focused specifically on the role of various kinase signaling pathways on neuronal survival and apoptosis. One line of research involves the study of the possible role of environmental toxicants, including pesticides. While studying mechanisms for neuronal cell death, Xia and colleagues discovered that several pesticides, including chlorpyrifos and rotenone, stimulate apoptosis in normal cells. "This suggests the interesting possibility that pesticide-induced apoptosis may play a role in neurodegeneration and cause defects in learning and memory during childhood development," said Xia.

Chlorpyrifos, the most widely used pesticide in the United States, is used on more than 40 food crops, as well as in homes as a treatment for termites, on lawns and ornamental plants, and in pet flea collars. Its use is being increasingly restricted. Rotenone is a selective pesticide derived from several tropical plants, commonly used in farming and gardening as well as in managing problem species of fish in lakes and streams. Recent studies show that rats treated with rotenone reproduce all the features of Parkinson's disease.

"Pesticide exposure may cause neurotoxicity in many regions of the CNS and contribute to many forms of neurodegeneration in addition to Parkinson's disease," said Xia. "Our data show that cortical neurons are sensitive to rotenone and chlorpyrifos treatment by inducing apoptosis. The data suggest that chronic exposure to pesticides may cause general neurotoxicity. We are seeking to understand the underlying mechanisms."

Xia's lab is testing the hypothesis that the two pesticides induce apoptosis by activating stress-activated protein kinase pathways known as the c-Jun NH2-terminal protein kinase (JNK) pathway and p38 mitogen-activated protein (MAP) kinase pathway.

In a study entitled "Neuronal Function of JNK," funded by the National Institute of Neurological Disorders and Stroke (NINDS), Xia and colleagues are beginning to uncover the differences among the activities of three JNK genes, JNK1, JNK2 and JNK3. The JNK family of MAP kinases has been implicated in several physiological functions, including regulation of cell death; but their molecular and cellular mechanisms remain undefined. Of the three genes, only JNK3 is activated by an environmental toxicant called sodium arsenite; Xia is testing the hypothesis that it

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PKU Clinic at CHDD provides vital support to families

Within hours of birth, a blood sample is drawn from almost every newborn baby in the United States to screen for a rare genetic condition of which most parents are unaware: phenylketonuria or PKU. The metabolic disorder affects about 200 to 300 babies born in the United States each year, or about one in every 12,000 to 15,000 births.

While adjusting to the typical challenges of life with a new baby, families receiving the diagnosis of PKU for their child face the daunting prospect of a stringent lifelong dietary regimen. Unless a special diet low in the amino acid phenylalanine is instituted within days of birth and maintained throughout life, the missing enzyme that characterizes PKU leads to mental retardation and other neurological problems.

To assist families in understanding and adhering to the diet, nutritional clinics have been established in every U.S. state to educate and provide support. At the Center on Human Development at Disability, a multifaceted program led by Cristine Trahms, M.S., R.D., serves families in Washington state whose lives are impacted by PKU. The multidisciplinary team includes PKU Clinic director C. Ronald Scott, M.D., nutritionists Beth Ogata, M.S., R.D. and Janie Heffernan, M.S., R.D., psychologist Steve Sulzbacher, Ph.D., social worker Jan Garretson, MSW, genetic counselor Lisa Sniderman-King, M.Sc., CGC, and program coordinator Vicki Frasher.

"Generally, we can expect four or five new babies in clinic each year from across the state of Washington," said Trahms. "We spend an incredible amount of time with new families, to get them the information they need, educate them about the significance of the disorder, and make sure they're able to make a commitment to the rigorous diet."

PKU is an autosomal recessive disorder: When both parents carry the non-functioning gene, there is one chance in four that any child they conceive will inherit two copies of the gene and thus be born with the disorder. Individuals with PKU lack a liver enzyme that metabolizes phenylalanine, one of many amino acids that make up protein. The buildup of excess phenylalanine in the blood can lead to severe and irreversible brain damage.

In order to keep "phe" levels as low as possible and protect the brain from its damaging effects, the diet for PKU eliminates virtually all sources of natural protein, including meats, fish, poultry, eggs, milk, cheese, nuts and beans, as well as foods that most of us consider carbohydrates but which in fact also contain protein, such as breads, cereals, pasta, potatoes, and rice.

The basis of the diet for PKU, supplying up to 80 percent of daily nutritional needs, is a medical formula manufactured to contain phenylalanine-free protein, vitamins and minerals. One such formula is called Phenyl-Free. Low-protein breads and pasta, fruits, vegetables and juices can be eaten in moderation.

Trahms stresses that adherence to the diet is a lifelong commitment. "Our motto is 'A Member Forever,'" she said. "Phenylketonuria affects cognitive development. People with PKU who are not treated are unable to live independently. Those diagnosed early who stay on the diet can go to college and hold a job. Our goals are that these children will be diagnosed and begin treatment as soon as possible, their phenylalanine blood levels will be exquisite, and their intellectual capacities will be unaffected."

There are generally no physical signs when blood levels of the amino acid are elevated. "Brain damage may occur without physical manifestations," said Trahms. "To ensure normal cognitive development, blood levels must be monitored monthly or even more frequently when there are problems adhering to the diet. The bottom line is to keep blood phenylalanine levels below 6 mg per deciliter. We can only achieve these goals with family-centered resources and guidance."

Cristine Trahms weighs one of the children attending the monthly PKU Clinic at CHDD.

CHDD offers support on many levels for families and individuals with PKU. A monthly clinic offers medical assessment, nutritional assessment and nutrition education. As children grow, they meet in groups with a nutritionist to work on a nutrition education project and interact with peers, while their parents discuss issues related to rearing a child with PKU. Periodic meetings with all age groups, including a yearly picnic, provide the opportunity for families to mingle with other children and adults with PKU. A food co-op allows families to sample and purchase specially formulated low-protein products, such as pasta, crackers and baking mixes.

During the clinics, special age-appropriate activities are aimed at preschoolers, elementary students, and middle and high school students, to foster skill-building, self-esteem and support for making healthy eating choices. Transition to adulthood decision-making and full independence is supported through an adult PKU clinic. Special support is offered to women with PKU who are pregnant or considering pregnancy, since a mother's elevated phenylalanine levels can cause severe harm to the fetus.

In addition to the clinics, a comprehensive web site offers information and support at http://depts.washington.edu/pku/. The entire education curriculum is gradually being placed on the web site. Families with a new diagnosis of PKU receive the "PKU Pal," a thick binder filled with information and support materials,

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and an informational video, "Really Living with PKU," developed by the PKU Action Group, a non-profit parent board that supports the activities of the PKU clinic.

The clinic works with about 200 families in Washington state. The main clinic site is at the CHDD in Seattle, and a satellite clinic in Spokane serves families on the east side of the state. "Because some live at a distance, we make individual contracts with some families," said Trahms. "But it's clear that families who actively participate in educational sessions are the ones who really internalize the treatment into family life."

"We work with families and children on nutrition education to make sure they have the skills to make reasonable food choices. These kids have always been on this diet. They don't know any other way, so they're less prone to make bad choices. The whole secret is to develop patterns of choice so you almost don't have to think about it; it's just the way you live your life. You get up in the morning, you drink your formula, you eat your low-protein cereal, you have a certain kind of lunch. It's just part of the pattern."

A young participant in the monthly PKU Clinic learns to prepare a phenylalanine-free stir-fry dish.

Trahms contrasts the dietary compliance of children with PKU with those who develop a condition such as diabetes later in childhood, who may have difficulties adhering to a newly restrictive diet. "That's a struggle, compared to children diagnosed with PKU at four days of age, for whom the special diet is a way of life."

It was once thought that people with PKU could safely stop the low-phe diet as they grew older. However, many who went off the diet began to experience problems with concentration and memory, and many have returned to the diet in hopes of regaining some of their cognitive skills. Clinicians now recommend that people with PKU remain on the diet for life. "Certainly, to stop using the formula and eat high-protein foods can cause cognitive damage," said Trahms.

Statistics from the PKU Clinic show that compliance figures—those who maintain excellent blood levels of phenylalanine—run between 80 and 85 percent. "These numbers are a tribute to the families and their concern for their child's healthy development," said Trahms. "Some families that are poorly organized and in crisis are unable to comply. We try to put supports in place for those who can't comply: home health aides, transportation services and extra resources."

Trahms and her team are testing a new family-centered support model based on the Bright Futures health supervision outcomes, a national initiative that starts with a therapeutic alliance and ends with an independent adult. "It's like a business model," she explains. "The parent starts out as the CEO of care, and as the child matures and grows, he or she gradually takes charge of care. Families have said that this business model, which uses words like CEO, manager, supervisor and consultant, helps them understand that maintaining the diet is a job that needs to be done. It gives them a little emotional distance so they can look at progress. The child is always moving forward and becoming more competent. The parents adjust their intervention based on the child's growing skill. The focus of our nutrition education curriculum has evolved into shared management."

The CHDD clinic's focus on shared management was described in an award-winning article by Trahms and Gail Kieckhefer, Ph.D., in the journal *Pediatric Nursing* in 2000. In recognition of her work, Trahms received the American Dietetic Association's National Award for Excellence in Clinical Nutrition in 2001.

"Our emphasis is on tools to support knowledge, skills and independence," she said. "You have to offer step-by-step support if you want families and kids to be compliant, because you're asking them to do a lot. You're asking them to change their lives, but the stakes are so very high. It's a situation where how smart your child is depends entirely on what you do on a day-to-day basis. That's a big responsibility." ♦

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may be a target for pharmaceutical therapy to block inappropriate neuronal apoptosis.

Xia's lab is also undertaking another study of apoptosis, titled "Regulation and Function of ERK5 in CNS Neurons," funded by the National Institute on Aging. This research focuses on another family of MAP kinases known as ERK or extracellular signal regulated kinases, especially on a recently found gene, ERK5. They are seeking to define the signal transduction pathway for ERK5 activation in neurons of the cortex, specifically, whether it is activated by neurotrophins (factors that support the survival of neurons). They will also determine whether ERK5 protects cortical neurons from various forms of damage and promotes survival of neurons.

Xia's lab has recently launched a new area of research into signal transduction mechanisms that regulate neurogenesis (the production of neurons). "That is, what makes a neuron progenitor cell proliferate and differentiate during development? A better understanding of neurogenesis during early development may provide insights into neuronal stem cell proliferation in adult animals. This is an area of research that also offers hope for treating neurodegenerative disorders," she said.

"The balance between survival pathways and cell-death pathways in neurons of the central nervous system is very complex. It is our hope that we might gain insights into the relationships between environmental toxicants and neurodegenerative disorders, in addition to pointing the way to development of drug interventions and treatment strategies." ♦

CHDD welcomes eight new research affiliates

Dr. Nigel Bamford, assistant professor of neurology and pediatrics, holds an M.D. from the University of Utah Medical School. He completed post-graduate training in pediatrics at Columbia-Presbyterian Medical Center, New York, and in neurology at the Neurological Institute, New York. His research focus is on the effects of dopamine on synaptic function, whose disruption is implicated in numerous disorders, including cerebral palsy, dystonia, juvenile Parkinson's disease, Huntington's disease and drug addiction. To gain insights into mechanisms underlying various neurodevelopmental and neurodegenerative disorders, Bamford has recently used multiphoton microscopy and other methods to observe corticalstriatal presynaptic terminal response patterns to synaptic dopamine.

Dr. Craig Bennett, research assistant professor of pediatrics in the Division of Genetics and Development, holds a Ph.D. from the University of Sydney. His research focus is genetic diseases of the peripheral nervous system and developmental disorders of the cerebellum. He is interested in identifying genes that may restrict expression in the early developing cerebellum and in prioritizing candidate loci in a large number of families with Joubert syndrome. He was involved in identifying a new gene for Charcot-Marie-Tooth disease, mutations of which result in CMT type 1C. Other studies focus on isolating a gene for ALS4, a chronic juvenile form of amyotrophic lateral sclerosis.

Dr. Sybil Carrere, research assistant professor of family and child nursing and adjunct research assistant professor of psychology, holds a Ph.D. in social ecology from the University of California, Irvine. Her primary research interest is in assessing the influence of parenting on children's emotional development and psychological health during the transition from middle childhood to adolescence, within a developmental psychopathology framework. Assessments include psychophysiological measures, emotional communication, behavioral observation, and self-reports. A related research interest is the impact of maternal stress during pregnancy on a child's later ability to regulate emotions.

Dr. Ian Glass is an associate professor of pediatrics with an adjunct appointment in medical genetics. He is director of medical genetics at Children's Hospital and Regional Medical Center. A native of New Zealand, he holds an M.D. from the University of Otago Medical School and completed post-graduate training in pediatrics and genetics at Mt. Sinai School of Medicine, the University of California San Francisco, Birmingham (U.K.) Maternity Hospital, and the Royal Hospital for Sick Children, Glasgow. His research focus is the molecular and developmental basis of inherited neurological disease, including genes for Joubert syndrome and other posterior fossa malformations.

Dr. Melissa Parisi, acting assistant professor of pediatrics in the Division of Genetics and Development, holds a Ph.D. in developmental biology and an M.D. from Stanford University. Her postgraduate training in pediatrics and medical genetics was at the University of Washington and Children's Hospital and Regional Medical Center. Her primary research interest is developmental disorders of the cerebellum, particularly Joubert syndrome, an autosomal-recessive condition whose features include hypotonia, developmental delay, and abnormal breathing pattern and/or eye movements. She is involved in efforts to understand the genetic and molecular basis of Joubert and related cerebello-oculo-renal conditions, and to explore the biologic basis of cerebellar development.

Dr. Laurence Shields, associate professor of obstetrics and gynecology, holds an M.D. from the University of Texas School of Medicine, San Antonio. At the University of Washington, he is co-director of Perinatal Genetics and Fetal Therapy, co-director of the Obstetric Imaging Center, and director of the Maternal Fetal Medicine Fellowship Program. His research focus is on strategies to improve neonatal outcomes where fetal conditions result in long-term morbidity or mortality. He is currently researching in-utero stem cell transplantation. The goal is to provide therapy to the fetus to correct disorders that result in significant injury if not corrected before birth.

Dr. Jennifer Stone is a research assistant professor of otolaryngology/head and neck surgery. She holds a PhD in anatomy and neurobiology from Boston University School of Medicine, and completed a postdoctoral fellowship at the UW. Her research interests are the cellular and molecular processes leading to the production of sensory hair cells. In humans and other mammals, production of sensory hair cells is limited to the gestational period. Birds have the ability to regenerate sensory hair cells following noise- or drug-induced hearing loss. Stone studies these processes in chickens during normal development and following post-embryonic hair cell damage. The goal is to extend the capacity for regeneration to the mammalian inner ear.

Dr. Raymond Sze, assistant professor of radiology and a pediatric radiologist at Children's Hospital and Regional Medical Center, holds an M.D. from Robert Wood Johnson Medical School. He completed postgraduate training at New England Deaconess Medical Center, Stanford Health Services, and Cincinnati Children's Hospital. His research interests include the development of molecular imaging techniques to study animal models of human craniofacial developmental diseases, quantitative imaging assessment of skull deformation in children with developmental skull malformations, and development of imaging techniques to guide treatment decisions in patients with developmental central nervous system or craniofacial malformations. ♦

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inheritance patterns and refine understanding of the clinical features of the various cerebellar disorders. Blood samples will be taken from patients, their parents and unaffected siblings. Permanent cell lines will be established from patient samples, in order to isolate DNA for genetic studies.

To facilitate the search for a genetic marker, a large number of affected families must be recruited. While such a marker could be used for prenatal decisions if so elected by a family, it would help to uncover the basic cause of Joubert, and offer the potential for developing gene-specific management or therapies.

Some 80 families have already been recruited for Joubert research, and additional families will be enrolled. "In particular," said Parisi, "larger families with multiply affected children are the most helpful in performing genetic linkage analysis."

Parisi recently gave a lecture at the Joubert Syndrome Foundation's patient family conference, where there was an opportunity to talk to affected families. "It's rewarding to see so many families at one time, because that's how we start to get a real sense of the condition and its challenges," she said.

"As an individual clinician," said Glass, "it's very hard to get a collective overview of the disorder, because you see only a few cases; there may be five to 10 affected families locally. But for our research, we are now able to draw families from all over the world."

"This is an area of tremendous need," said Chance. "There are many families dealing with these disorders on a day-to-day basis, and they have no explanation at a fundamental level for their children's problems. We don't know whether our research will point the way to genetic therapy, but there may be implications for behavioral therapies or drug therapies that might improve neurological function." ♦

Immigrant children . . . from Page 3

and works to broaden awareness of developmental disabilities to reach immigrant and refugee families who have not sought needed care for their children.

There is a great need for more information and culturally appropriate advocacy and referral services, said Doherty. While the total number of immigrant children in the Seattle area with developmental disabilities is unknown, he notes that special education programs in Seattle public schools serve approximately 770 children with limited English proficiency.

"We are working to increase families' understanding of how our medical system works," he said. "The terminology involved in their child's diagnosis and treatment may have no relevance to them, even in their language. We try to help them integrate medical and educational information into their own cultural understanding. At the same time, we try to provide insights into why it is important to arrive at appointments on time and to know the names of their child's doctors, medicines and diagnosis in English.

"The project is also trying to reduce the frustration that many medical providers feel when they are unable to communicate effectively with their patients and provide excellent care. We would like to figure out how all of us can effectively serve this population and promote understanding of each other's worldviews in ways that will lead to improved health outcomes for all children with developmental disabilities." ♦

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