CHDD OUTLOOK

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

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Center on Infant Mental Health and Development established

To focus on the social and emotional health and well being of the youngest members of society, a new Center on Infant Mental Health and Development has been established at the University of Washington. The center will place special emphasis on vulnerable children who are at developmental risk for various reasons, including mental health issues faced by their mothers or other caregivers, an absence of social supports, conditions of poverty and homelessness, and parental substance abuse.

The new center is an interdisciplinary effort jointly sponsored by the UW's Center on Human Development and Disability (CHDD) and the UW School of Nursing, to be based at and administered by CHDD. The School of Nursing will offer a Certificate Program in Infant Mental Health to train specialists in the field, and a Zero to Five Clinic will be established at CHDD to facilitate training for the certificate program. Numerous research programs, as well as community outreach and dissemination activities, will also be a part of the new center.

A child's emotional health depends on the relationship with the primary caregiver, usually the mother.

The director is Dr. Kathryn Barnard, professor of family and child nursing and a CHDD research affiliate who has an international reputation in the field of early childhood development.

"If we are to work with the infant, we must also work with the mother or other caregiver," said Barnard. "We recognize that the majority of early caregivers are the mothers. We will offer professional training to treat not just the mother and not just the child, but rather, the relationship between them."

Dr. Michael J. Guralnick, director of CHDD, notes that CHDD has long been at the forefront of efforts to support early childhood development and early intervention programs for vulnerable children and their families in Washington state and across the country. "The new center will allow the consolidation and dramatic expansion of our early intervention programs to meet the mental health needs of infants and young children and foster their overall development," he said.

"This center came into being because of Kathryn Barnard's passion for this area," said Dr. Nancy Woods, dean of the UW School of Nursing. "Over her many years of research, she has learned that infants cannot wait. Becoming a good parent doesn't come automatically; it's learned behavior. If you wait to intervene to improve the parent-child interaction, the child pays the price. The goal is prevention, because there is good evidence that if infants are not given good nurturing care in the earliest months, they lose ground in terms of brain development. "

"We are proposing relationship therapy," said Barnard. "There may be experiences or relationships in one's past that prevent one from relating to one's new baby. For example, with a history of abuse or neglect in her own past, a young mother may be unable to get on with life. The goal is to offer infant-parent psychotherapy, to deal with these 'ghosts in the nursery'—the title of a seminal article on mother-infant relationships—and facilitate the new relationship, to help the mother promote the child's ordinary developmental needs."

Typically, said Barnard, few therapists treating depressed parents deal with the parenting role, assuming that the parenting role will straighten out if the depression is dealt with. "What we're proposing is different from adult psychotherapy, in that it provides not only psychotherapy, but relationship therapy."

Dr. Donna Weston, a developmental psychologist, has been hired to direct the new certificate program, which involves an 18-month curriculum. Ten students will commence training in January 2002, and funding will permit training of 50 students over a five-year period.

"This is an interdisciplinary program," Weston said. "We expect to enroll licensed professionals from a variety of disciplines, including social work, pediatrics, clinical psychology, developmental psychology, psychiatry, counseling and guidance, early childhood education, speech and language specialties, teaching, occupational therapy and physical therapy. In addition to diagnosing and treating mental health problems in infants and toddlers through relationship therapy, our graduates will serve as consultants to other professionals in related fields."

Dr. Marian Birch, clinical director of the certificate program who has more than 20 years of experience in relationship therapy, notes that each student will work with one to three families on problems related to emotional development. "We're using an apprenticeship model," she explained. "Students will work with families under direct supervision, developing skills and approaches to build a relationship with a family." Most contacts between student

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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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therapists and families will take place in the home, rather than in the clinic setting. In the longer term, the training program will expand into full-fledged masters and doctoral programs. The center will also serve as a site for internships and practicums.

School of Nursing faculty associated with the certificate program—including Drs. Cathryn Booth, Jean Kelly, Diane Magyary, Colleen Huebner, Rebecca Kang, Joanne Solchany and Susan Spieker, in addition to Drs. Barnard, Weston and Birch—as well as other interdisciplinary faculty will pursue research into the social and emotional aspects of development. Core facilities will be developed to support behavioral, physiological and longitudinal studies of infant emotion, regulatory processes, interpersonal behaviors and relationships established in the early years.

"Much of our research is oriented toward the attachment issue," said Barnard. "For example, we will look at the parent's attachment history in a formal study of attachment, temperament and family cohesion. We will work with the state Health Department on nurse home visits in five counties, focusing on teenage mothers. We will do psychobiological research on basic neurological and biochemical controls for processing emotions."

Weston stresses that the new center is a training resource, not a competitor for existing agencies. "We're committed to a strong relationship with community health agencies, social service agencies, and other agencies serving high-risk infants, all of which have a common set of issues: the safety of babies, and the welfare and functional adequacy of families," she said.

The center will seek referrals from social service agencies that encounter a problem in the mother-child relationship or in the infant's own regulatory processes. Barnard noted that there is a high likelihood of referral of pre-term infants. "These tiny babies have problems with sleep rhythms, eating, startling response, and they are at risk for developmental problems. These difficult issues can become a problem in the mother's relationship with the child, especially if the mother has other challenges of her own, such as teenage motherhood."

By treating the parent-child relationship before the infant suffers long-term damage from neglect or abuse, Barnard and her colleagues believe they can make a dent in some of the unsettling statistics on the mental health of children. For example, she notes that fully 25 percent of kindergarteners enter school not ready to learn. "Of the approximately 90,000 infants born each year in the state of Washington, about 20 percent are born to parents not ready to take on the task of parenting," she said.

The center's faculty also hope to work toward changes in how the health care system reimburses for expenses of infant mental health care. "Infant mental health is not even recognized as a diagnosis," said Birch.

"This type of program can't exist within the existing system of reimbursements," said Weston. "Insurers pay to treat problems, not to prevent them from occurring in the first place. We will achieve success if we can affect these models for payment. Costs are much greater later, if you don't treat these problems in the earliest stages."

Major funding for the Center on Infant Mental Health and Development comes from local benefactors who have a strong personal and professional interest in early childhood development and have made a substantial five-year financial commitment. Support also comes from numerous grants and contracts, including student stipends provided by the Harris Foundation in Chicago. ♦

Emeritus professor and new CHDD affiliate seek to uncover the mysteries of X chromosome inactivation

Two genetic conditions—one, the most common inherited cause of mental retardation, and the other, among the rarest—are the focus of ongoing investigation by research affiliates of the Center on Human Development and Disability, as they seek to understand the molecular mechanisms that the two syndromes share, as well as how these mechanisms illuminate the processes of normal X-chromosome inactivation.

Stanley Gartler, Ph.D., a University of Washington emeritus professor of medicine and genetics and CHDD research affiliate, has focused his research on Fragile X syndrome, as part of his long career studying X-chromosome inactivation. More recently, his lab has turned its focus to ICF syndrome, a very rare autosomal recessive disorder that may shed light on related molecular processes. Gartler's colleagues include Scott Hansen, Ph.D., a UW research assistant professor of medical genetics who is a new CHDD research affiliate.

The full mutation of Fragile X, on a gene called FMR1 located on the long arm of the X chromosome, appears in approximately 1 in 2000 males and 1 in 4000 females. Since males have only one X chromosome, males with Fragile X syndrome have more severe symptoms than females, including significant intellectual disabilities. Physical features include enlarged ears, a long face, connective tissue problems and skeletal problems. Some males exhibit speech disturbances, hand biting or hand flapping, and autistic-like behaviors. Only a third to a half of females with the Fragile X mutation have significant intellectual disabilities: since females have two X chromosomes, one normally functioning gene partially compensates for the nonfunctioning one.

ICF syndrome, whose acronym stands for the major features of the syndrome— Immunodeficiency, Centromeric decondensation and Facial anomalies—is an extremely rare disorder, having been diagnosed in only about 40 individuals since it was first recognized in 1988. Males and females are similarly affected. They have growth and developmental abnormalities, including mental retardation. Lymphocytes (infection-fighting white blood cells) in ICF patients do not produce the normal complement of immunoglobulins; they leave patients open to severe, life-threatening infections.

In Gartler's current study, funded by the National Institute of Child Health and Human Development and entitled "Dosage Compensation in Mammals: X Inactivation," he and his colleagues first concentrated on cloning the defective gene that produces ICF syndrome, to shed light on a number of molecular mechanisms, both normal and abnormal. "The ICF syndrome appears to be a model for the differential analysis of the various repressive factors that maintain the silence of the inactive X," says Gartler.

Dr. Stanley Gartler

One of these repressive factors is DNA methylation, a normal process that occurs throughout the human genome. It involves the addition of methyl groups (carbon and hydrogen) to DNA, which shuts down the activity, or expression, of a gene. In most cases, this shutdown is precisely what is needed for normal functioning, as in the inactivation of the second X-chromosome in females. However, when methylation takes place inappropriately, genes that should be expressed are not, leading to problems. In fragile X syndrome, hypermethylation (excess methylation) of the FMR1 gene leads to abnormal silencing of the gene.

In ICF syndrome, hypomethylation, or failure to add methyl groups to specific sections of DNA, produces unstable chromosomes. ICF is the only genetic disorder known to involve abnormalities of genomic methylation patterns. Hansen, of the Gartler lab, demonstrated that the mutant gene underlying ICF syndrome is a DNA methyltransferase (DNMT3B), a gene whose protein methylates certain types of heterochromatic DNA.

Another focus of the study is replication timing. Every time a cell divides, its genes must double, or replicate themselves. The timing of replication happens in a highly ordered way: some genes replicate early in the cycle of cell division, some replicate late. "Normally, expressed genes replicate themselves early, whereas silenced (inactive) genes replicate later," explains Gartler. Abnormally late replication may disallow the gene from being "proofread" for errors in replication, or it may prevent completion of the replication process before the cell divides.

The Gartler lab has discovered that in ICF syndrome, there is a difference in replication timing in certain genes found in fibroblasts (cells that form connective tissue) as compared to the same genes found in lymphoblasts (cells that form blood). In a preliminary study of one female ICF patient, they found marked undermethylation of inactive X-linked genes, and variable advances in their time

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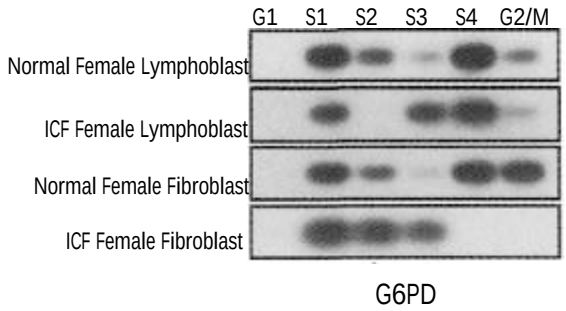

This graphic illustrates the timing of replication of the G6PD gene in lymphoblast and fibroblast cells from a normal female compared to replication timing in cells from a female with ICF syndrome. Letters across the top represent phases of cell division from early (G1) to late (G2/M). Darker blots indicate areas of greatest DNA synthesis. Replication of the inactive X in ICF fibroblasts is dramatically advanced.

CHDD research affiliate confronts craniofacial disorders in the research lab and in the clinic

Among the many potential causes of neurocognitive difficulties is a group of inherited syndromes that have in common a condition known as craniosynostosis: the premature fusion of the calvaria, the bones of the infant's head.

In the typically developing infant, the sutures—the fibrous joints separating the five bony plates that make up the skull—stay open for nine months to two years to accommodate the rapid growth of the young brain. In fact, most of the sutures may not fully fuse until the mid-twenties.

In a child with craniosynostosis, one or more of the sutures close early, forcing the brain to expand where the bones are not resisting growth, causing the skull to become distorted. The abnormal skull growth may be associated with increased intracranial pressure, impaired cerebral blood flow, airway obstruction, impaired vision and hearing, and learning difficulties. Surgical intervention is required.

Dr. Cunningham coordinates the care of little Catherine Vaughn, 13 months, who has Crouzon syndrome. She has had numerous surgeries.

The causes and potential treatments for craniosynostosis are the research focus as well as the clinical interest of Dr. Michael Cunningham, University of Washington associate professor of pediatrics in the Division of Genetics and Development. A research affiliate at the Center on Human Development and Disability, he is also director of the Children's Craniofacial Center at Children's Hospital and Regional Medical Center in Seattle and an affiliate of the UW's Molecular and Cellular Biology Program and the Center for Ecogenetics and Environmental Health.

Sporadic non-hereditary craniosynostosis is fairly common, occurring in about one in 2,500 births. The current emphasis in the Cunningham research lab, however, is on a group of less frequently seen hereditary syndromes that occur in about 1/25,000 to 1/250,000 births, although research results may have implications for all forms of craniosynostosis.

Syndromic craniosynostoses are caused by mutations that can be passed from generation to generation; the child of a parent with most forms of hereditary craniosynostosis has a 50 percent chance of inheriting the disorder. Many craniosynostosis syndromes are caused by mutations of genes called fibroblast growth factor receptors (FGFRs), found on three different chromosomes. Other craniosynostosis disorders are caused by mutations on genes of transcription factors, the TWIST and the MSX2 genes, whose proteins function to turn on other genes.

One of the syndromes under scrutiny in the Cunningham lab is Apert syndrome, caused by a mutation on FGFR2, a gene on chromosome 10. In a child with Apert syndrome, one tiny chemical building block in one copy of the FGFR2 gene is exchanged for another. This single change causes the physical features of Apert syndrome: the skull is prematurely fused, the midface is sunken, and the fingers and toes are fused. The lab is also working on Crouzon syndrome, caused by a different mutation of FGFR2.

While there is a large body of research on causes of craniosynostosis syndromes, Cunningham, who has a Ph.D. from the UW Department of Biological Structure as well as a medical degree, is taking a new tack in his investigations. "I decided to stop thinking about the identification of the initial molecular changes, and focus on how these molecular changes lead to craniosynostosis," he said.

Cunningham began archiving bone samples from children undergoing craniofacial surgery to correct the shape of their skulls and faces; bone that would otherwise be discarded. The bone cells containing the mutations were used to produce living cell lines, useful for a series of experiments. The Cunningham lab has produced cell lines from 15 children with Apert syndrome, all patients at Children's Hospital.

Although they are unique syndromes, all of the diseases caused by FGFR mutations have a similar pathogenesis, said Cunningham. His lab is working on the intracellular signaling cascade, on how the cell responds to the abnormal FGFR2 protein which constantly signals from the cell surface. Several ongoing studies are geared to understanding the function of these receptors and transcription factors in cell development and why derangement of their function leads to craniosynostosis.

"We're looking for the cellular responses to these mutations," he said. "How does the cell respond to the introduction of a change in the function of one of these receptors? When we transplant these human cells underneath the coronal sutures of laboratory rats, it looks as though we may induce craniosynostosis." More research is needed to confirm this finding.

For Pfeiffer syndrome, caused by a mutation of the FGFR1 gene, Cunningham's lab has acquired a colony of transgenic mice.

"This mouse has exactly the same mutation as the human Pfeiffer mutation," said Cunningham. "It causes abnormal suture fusion, as well as severe deficiencies in the mid-face. We are using the mouse as a model to study both processes of syndromic craniosynostosis in humans."

The Children's Craniofacialy Center, headed by Cunningham, treats patients from a wide geographic area, including Europe, Russia, Ukraine, Korea and Hawaii, in addition to the five states of the WWAMI region (Washington, Wyoming, Alaska, Montana and Idaho) served by the UW School of Medicine. More than 40 people are members of the team caring for patients and their families. Craniofacial pediatricians coordinate care by specialists in the field of audiology, dental medicine/orthodontics, genetics, neuroradiology, neurosurgery, nursing, nutrition, occupational and physical therapy, ophthalmology, oral and maxillofacial surgery, orthopedic hand surgery, otolaryngology, plastic and reconstructive surgery, psychiatry, social work and speech pathology. Adult patients are treated at UW Medical Center or Harborview Craniofacial Center, usually by the same surgeons.

One unique patient seen at Children's is a young girl who, incredibly, was found by the Cunningham lab to have two independent mutations: the FGFR2/Apert mutation as well as a mutation in the TWIST gene, which causes Saethre-Chotzen syndrome. "We thought the initial sample might be contaminated, so we did the assay three times on three different cell lines from her. When she had additional surgery I retrieved a fresh bone sample and isolated it," said Cunningham. "Indeed, she has both mutations, something never been before." The likelihood of this occurring by chance is infinitesimally small, about 1/250,000 x 1/25,000, and it is not known why these two mutations occurred in this patient. Although he cannot be sure because she was adopted from an orphanage, Cunningham speculates that perhaps the father had the milder TWIST mutation and, because of his advanced age when he fathered the child (a risk factor for spontaneous appearance of Apert), also gave her the FGFR mutation.

"As the clinical world becomes more adept at treating these patients, we're finding that outcomes are much better," he said. "The first surgery for almost all syndromic synostosis now is by nine to 12 months of age. Our team reconstructs the skull to allow the brain to expand in a more normal configuration. However, many children still have cognitive problems."

While surgery to reshape skulls and faces is increasingly successful, the goal of Cunningham's research is to identify molecular targets that might be amenable to intervention, to prevent craniosynostosis from occurring in the first place, or to ameliorate it once it does occur. It may be possible to develop medical techniques to alter the pathogenesis, or natural history of the disease as the result of basic discoveries made in labs such as Cunningham's; for example, by interfering with the function of the protein that inhibits cells from dying, which seems to be part of the pathogenesis of craniosynostosis.

"It might be theoretically possible to intervene in utero, but realistically it's more likely to be after the baby is born," said Cunningham. "If we could make a gel strip containing inhibitory proteins that would prevent the suture from closing, we might be able to go in with a very minimal surgical procedure and place the strip. We would maintain the suture for as long as needed to let the brain grow. Then we could go back in and do another minimal procedure to remove the strip and let the sutures close."

Cunningham realizes that this is speculative, but he hopes that as he and others uncover the biologic basis of craniosynostosis, more targeted treatments may become available.

Research just getting underway will ultimately give Cunningham's lab access to bone samples from some 285 patients with non-syndromic craniosynostosis. Dr. Matthew Speltz is principal investigator on a forthcoming study of neurocognitive outcomes in children with non-hereditary forms of craniosynostosis. He is an associate professor of psychiatry and behavioral sciences who is also a CHDD research affiliate and a clinical psychologist in the Children's Craniofacial Center. Cunningham is the clinical coordinator and co-principal investigator on the three-year study, which will involve four medical centers across the country.

"While surgery to reshape skulls and faces is increasingly successful, the goal of research is to identify molecular targets that might be amenable to intervention, to prevent craniosynostosis from occurring in the first place, or to ameliorate it once it does occur."

Dr. Michael Cunningham

CT imaging before surgery will show the severity of fusion and amount of brain compression in each patient. The goal of the research is to answer a number of questions about the value of surgery, the importance of its timing, and whether neurocognitive outcomes can be predicted by clinical means.

Cunningham will look at the study subjects to examine the possibility of genetic anomalies. "We will do mutational analysis on all 285 patients, because some of these children may have hereditary syndromes that have been overlooked. We will have all these bone samples for which we can assess potential biologic differences. If we can show there are biologic differences in a patient's bone cells, perhaps even related to the specific type of fusion, then perhaps we can come up with causal mechanisms. There's a lot of suspicion that these children have issues other than just their cranial problems. The question is, are their neurocognitive problems induced by their fusion, or related to their underlying condition?"

Cunningham clearly relishes the opportunity to pursue his keen interest in these children who face so many challenges. "It's extremely satisfying to be able to pursue both my clinical interests and my research focus," he said. "Our work in the lab complements our work in the clinic. We are taking our findings from the bench to the bedside, and back." ♦

Law fellowship pilot program at CHDD gives new emphasis to legal rights of people with disabilities

While people with developmental disabilities are entitled to the same wide array of civil rights that all Americans enjoy, the legal resources to ensure those rights may be difficult to access. Families are faced with a host of challenges as they deal not only with the day-to-day emotional and social impacts of their child's disability, but also with the financial burdens of medical care and care-giving, with the ins and outs of dealing with the school system, and with making their way through the intricacies of state funding agencies.

At the Center on Human Development and Disability at the University of Washington, efforts are underway to assist families of persons with developmental disabilities with legal issues, and to train professionals in the legal rights of their clients so that they can be more effective advocates within their practices.

Dr. Sherrie Brown, a research associate professor of education and an attorney with a long history of work in disability rights, directs CHDD's Community Disability Policy Initiative and one of its components, the Legal Advocacy and Disability Policy Task Force.

Brown also teaches in the law schools at the UW and Seattle University and in the UW College of Education's Educational Leadership and Policy Studies area. She chairs a committee of faculty, students, administrators and community representatives whose mission is to introduce disability studies into undergraduate and graduate curricula at the UW's three campuses.

Jim Levy is a law fellow working with Sherrie Brown, director

"Discrimination based on a belief that disability makes one an inferior person is pervasive in our society," Brown says. "Changing the belief requires efforts at many levels. My primary interest has been in educating lawyers in disability law so that individuals with disabilities can find legal advocates with the skills to address civil rights violations. For many years, I have wanted to develop a training program in disability law for law students as well as others who work with people with disabilities—teachers and health care providers in particular."

As an initial step, Brown obtained funding for a pilot project at the CHDD to enable law fellows to work with families of children with disabilities, as well as clinicians and trainees, on legal issues related to disability. "We're not providing legal representation to families," she explains. "We're providing training to help individuals advocate for themselves and to help professionals better understand the legal issues so that they can act as advocates for families. When necessary, we can provide referrals to legal professionals in the community."

CHDD's first law fellow is James Levy, an attorney who is working with families and staff at CHDD's Child Development Clinic and its High Risk Infant Follow-Up Clinic. Levy's focus is on legal issues related to access to assistive or adaptive technology (AT), since funding for the pilot program comes from CHDD's Center for Technology and Disability Studies. He also receives logistic support from CHDD's Clinical Training Unit. If the law fellowship program is funded in the future, Brown's vision is that it will expand to include additional fellows and a focus beyond the area of assistive technology.

Levy, who came to CHDD in the fall of 2000, spent much of the first year of his two-year fellowship observing activities in the clinics, talking to families, consulting with clinic staff, and following families through the process of obtaining needed services for their children.

"The goal is to see the big picture, to give me an idea of the issues families face when they have a child with a disability," Levy says. "They're dealing with a variety of disabilities, many government agencies, the Department of Social and Health Services, school districts—there are a huge number of legal issues.

"I have a strong civil rights interest in relation to disabilities," he adds. "Disability rights have not really been satisfactorily addressed. There are barriers to full participation in society for people with disabilities. There is a movement for equality, but there is still a need for legal assistance, public benefits, civil rights law—affirmative action in the broad sense. This program can provide tools for people to resolve problems themselves."

Levy sees the law fellow program as part of a proactive, preventive practice of law. "It's a pre-litigation approach," he says. "People can learn the law and be advocates for themselves."

In the second year of his fellowship, Levy is moving from information-gathering to working with individual families, school districts, insurance providers and public benefits agencies on issues related to assistive technology. "The goal is to meet the needs of families that come to CHDD by referring them to appropriate community resources, including legal advocates. We want to address their legal needs as a whole, even if not directly related to their child."

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New research affiliates bring their expertise to CHDD

Dr. Theodore P. Beauchaine, assistant professor of psychology, holds a Ph.D. in clinical psychology from the State University of New York at Stony Brook. His research is focused on the development of autonomic nervous system functioning in impulsive children and adolescents, including those with ADHD, and on environmental influences on regulation of emotion and on impulsivity. He is concerned with family interaction patterns that reinforce behavioral dysregulation and negative affect, and with the role these patterns play in children's social and emotional development. He sees childhood as a period in which developing autonomic systems may be vulnerable to long-term changes in functioning. He hopes to extend his psychophysiological studies to include functional magnetic resonance imaging (fMRI) assessments of central nervous system substrates of impulsivity.


Beauchaine

Dr. Robert L. Davis is an associate professor of pediatrics and epidemiology at the UW. He received an M.D. from the University of California at San Diego in 1989, and a Masters in Public Health (Epidemiology) from the UW in 1993. He was formerly an epidemiologist with the Washington State Department of Health, and serves as the senior advisor for vaccine safety to the Vaccine Safety Datalink Project, a multi-HMO collaborative project run by the Centers for Disease Control (CDC). Dr. Davis' research focus is on the safety of vaccine use in children. His research interests include the health effects of thimerosal (ethyl mercury preservative used in some vaccines) on neurodevelopment and the possible association between thimerosal and development of autism. He is also involved in assessing a possible relationship between the measles mumps rubella (MMR) vaccine and autism.


Davis

Dr. Adriana Emmi is a research assistant professor in the Department of Neurological Surgery. She received an M.D. in medicine and surgery in 1992, and a Ph.D. in neuroscience in 1996, both from the University of Palermo, Italy. She is engaged in research to further understand the mechanisms, cellular changes and genetic alterations underlying control of electrical rhythm in the brain, to ultimately develop a preventive or more focused therapy for epilepsy. Her research includes a project using the Eker rat to study tuberous sclerosis (TSC), which is highly correlated with early-onset seizure syndrome, to understand how TSC gene mutations give rise to cortical tubers and epilepsy. Other studies focus on the role of glial cells in controlling electrical rhythms in the developing and mature brain.


Emmi

Dr. Anne Hing is an acting assistant professor of pediatrics. She received a medical degree from Washington University School of Medicine in St. Louis, Mo., in 1985, and joined the University of Washington School of Medicine in 1999. Dr. Hing is studying the molecular basis of genetic disorders known as preaxial polydactyly and frontonasal dysplasia. Individuals with these disorders may have significant developmental delays in association with their craniofacial malformations. Information on the molecular basis of these conditions may provide insight into both limb and craniofacial development. Hing is also participating in a study of the molecular basis for congenital heart defects associated with deletions of human chromosome 8p23.1. Patients have mild developmental delays, microcephaly and congenital heart disease.

Dr. David Jardine is an associate professor of anesthesiology and pediatrics based at Children's Hospital and Regional Medical Center. He received an M.D. in 1980 from Johns Hopkins University School of Medicine and joined the UW faculty in 1987. He is working with Dr. Philip Mirkes to determine whether over-expression of the 70-kilodalton heat shock protein (HSP70) in a transgenic mouse can prevent neuronal apoptosis following cerebral ischemia. He is also beginning another project using a DNA microarray to examine the expression of multiple heat shock genes in children who are victims of sudden infant death syndrome (SIDS). This may lead to a better understanding of an illness called hemorrhagic shock and encephalopathy syndrome. Some 75 percent of infants who survive hemorrhagic shock and encephalopathy syndrome suffer permanent developmental disabilities.


Jardine

Dr. Sandra Juul holds an M.D. from the University of Washington and a Ph.D. in Developmental Biology from the Pritzker School of Medicine, University of Chicago. An assistant professor of pediatrics in the Division of Neonatology, she is principal investigator on a study of the effects of erythropoietin (Epo) in neurodevelopment and neuroprotection. She has identified Epo and its receptor in the developing human brain and spinal cord, and has measured Epo in the spinal fluid of newborns and older children, and in healthy and diseased children. Her research shows that Epo has protective effects on neurons when these cells are exposed to damaging conditions such as hypoxia or toxic cytokines. Using a variety of molecular biology, cell and tissue culture techniques, she is working to identify how Epo might influence neurodevelopment and protect from brain injury.


Juul

Additional new research affiliates already named will be profiled in the next issue of CHDD Outlook. ♦

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of replication. One such gene, an X-linked gene called G6PD, escapes X inactivation in ICF fibroblasts, but not in ICF lymphoblasts. In fibroblasts, the gene on the inactive X replicates at about the same time as the gene on the active X, while the same gene in lymphoblasts replicates late. "Our lymphoblast data indicate that gene repression can occur in the absence of promoter methylation and suggest that late replication may be sufficient for repression," says Gartler. "We now know that the inactive X is silenced by many factors."

Gartler and colleagues are also investigating replication timing in fragile X syndrome. In studying an area of the X chromosome called Xq27, where the FMR1 gene is located, they have found that Xq27 is a late-replicating band, and represents the unusual situation of a late replicating gene being expressed. The regions adjacent to Xq27 replicate earlier in cell division and the boundary regions between the areas may replicate late in one cell type and early in another. "It seems possible that such genes may be located in such boundary regions to facilitate replication-associated gene regulation," says Gartler. "We have now found other examples of late-replicating genes that are expressed, contrary to the general rule for such genes. We are interested in whether these may represent a special class of genes that require late replication for proper functioning."

While Gartler and colleagues are focused on a basic understanding of normal genetic and molecular processes in the light of the abnormal function demonstrated by Fragile X syndrome and ICF syndrome, there may be hope for clinical interventions sometime in the future. An existing drug known to inhibit methylation could theoretically be used to treat patients with fragile X syndrome. However, its actions are not specific, and could cause problems in other genes. Perhaps further research will allow targeting of a drug. When Gartler's colleague, Scott Hansen, fused ICF cells to normal hamster cell lines, it produced methylation of the regions usually undermethylated in ICF cells. The finding that hypomethlyation can be reversed suggests a future treatment. ♦

Law fellowship . . . from page 6

"I'm not aware of any other center that offers a legal fellowship," says Brown. (Every state has centers similar to CHDD's, known as University Centers for Excellence in Developmental Disabilities, formerly as University Affiliated Programs.) "It's a way to begin to meet a huge need in the community for lawyers with an understanding and knowledge of disability law. I hope eventually the law fellow will be able to also provide education in the community: to the state bar, to state agencies, to legislative bodies, as well as providing legal information to practitioners and clinicians, for example, on such issues as eligibility for public benefits or for insurance coverage of a particular therapy.

"Our first task is to have the concept of the law fellow accepted as a component of the comprehensive team approach to service for children and families," she adds. "This is a long-term systems change effort that will take some time to develop. CHDD's Clinical Training Unit has given Jim a great amount of support during this first year, and I think that we have established the need for legal advocacy as one of the services available for those families that need assistance in legal matters."

The goal is to have funding for two fellows on two-year fellowships. In addition to the disability law fellowship, Brown hopes that the next step may be establishment of another fellowship in the area of special education law.

"I think changing society's perception of disability is in part a legal issue," she says. "I became a lawyer in order to work for equal rights for people with disabilities and although there is a long way to go, there has been progress." ♦

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

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