Researchers studies effects of drugs on circulation in the developing brain

Medical advances over the past quarter century have dramatically improved the survival rate of increasingly preterm infants—infants born after as few as 23 to 25 weeks of gestation, compared to the typical 39- to 40-week period. These babies are much smaller than full-term infants and their organs are much less well developed. Consequently, preterm infants often have problems that require specialized medical attention.

Neonatal intensive care units use a variety of drugs and therapeutic approaches in caring for preterm infants. According to CHDD research affiliate Dr. Christine Gleason, professor of pediatrics and head of the Division of Neonatology, most of these therapies are simply extrapolated from adult and pediatric intensive care practices. Neonatologists administer drugs and other therapies used with more mature newborns in the hope that the mechanisms for their therapeutic effects are similar, yet little is known of the actual physiological responses in these tiny infants.

In her research, which centers on neurophysiology, Gleason studies a fetal sheep model to learn how drugs and other therapies affect blood vessels and blood flow in the developing brain. She is currently investigating the immature brain's physiological responses to dopamine, a drug that is commonly used to increase blood pressure and support circulation in preterm infants. In addition, she and CHDD research affiliate Dr. Dennis Mayock, associate professor of pediatrics, are studying cerebrovascular responses to acute volume expansion, using the same model. These studies are funded by the National Institute of Neurological Disorders and Stroke (NINDS).

As a group, preterm infants are at increased risk for neurodevelopmental disorders such as mental retardation and cerebral palsy, especially when they experience a significant intracranial hemorrhage or stroke that injures brain tissue. “When preterm infants have brain injuries that we can see with ultrasound or on an MRI scan, the risk for disabilities increases,” says Gleason. “It’s not a direct line, but a bad bleed or a bad stroke is likely to have a bad outcome. So a lot of clinical attention has focused on trying to figure out what leads to these bad brain injuries.”

Though the causes are not yet well understood, clinicians try to prevent brain injuries by using drugs or volume expanders (administration of extra fluid through a vein) to raise or maintain blood pressures in preterm infants. This approach arises more from empirical correlations than a thorough understanding of how these therapeutic strategies work in the immature cerebrovascular system, explains Gleason.

Preterm infants are thought to have poor autoregulation—the physiological capability for maintaining adequate blood flow in the brain within a range of blood pressures. At birth, preterm infants tend to have lower blood pressures than full-term infants. Although blood pressure gradually rises on its own in the first few days of life, the hemorrhages and strokes that lead to brain injuries usually occur very soon after birth, often within the first day. These observations, combined with the results of studies that have shown fewer brain injuries in babies whose mean blood pressure is 30 mmHg, have led to the common...
Effects of drugs on circulation in the developing brain
continued from front page

therapeutic strategies of maintaining or raising blood pressure by infusing dopamine or by administering extra fluid.

“The rationale is reasonably sound except that we don’t really know if the reason these kids bleed is because their blood pressure is less than 30, or because of something else that is causing their blood pressure to be less than 30,” says Gleason. “I think it is very important to look at our well-intentioned therapeutic strategies, and ask if there is anything detrimental about them. If so, let’s understand what that could be and determine a better therapeutic strategy that optimizes neurologic outcome.”

Research that can increase understanding of cerebrovascular responses in the developing brain has become possible after years of work with the fetal sheep model, notes Gleason. Early studies using fetal sheep as a model for studying blood vessel responses to various drugs and low oxygen levels were done at about 130 days gestation, fairly close to the full term of 145 to 150 days. Now, Gleason and her colleagues are able to study these responses in fetal sheep at about 90 days gestation, which is comparable to 26 weeks gestation in humans.

“We are able to operate on these extremely immature fetuses to place catheters for monitoring vascular responses — the mother is healthy and carries the pregnancy right along and the fetus is healthy,” says Gleason. “We have a large body of experience and data from the sheep model so we understand a lot about its circulation.” How­ever, she points out, because these studies are conducted in utero, there are limitations to acknowledge, includ­ing the placenta’s role in metabolizing dopamine or handling rapidly administrated large amounts of extra fluid.

“Right now, this is the only way that we can do these descriptive physiologic studies,” states Gleason. “We take a very stable animal, make one perturbation — study one drug or one episode of hypoxia (inadequate oxygen in the blood) — and we can be fairly confident that the responses we see are related to that perturbation and not something else. While I can’t recommend directly extrapolating my results to human infants, we still learn something about the developing brain’s physiology and about the pharmacokinetics of these drugs in the immature brain — information that we can apply in our care of human infants.”

Dr. Christine Gleason
Seizures stemming from bouts of uncoordinated electrical activity in the temporal lobe of the brain can occur at any age. Such seizures can be single episodes or they can occur repeatedly, becoming a chronic condition known as temporal lobe epilepsy. Although the tendency for a person to have recurring seizures can sometimes be traced to brain injury, in many cases no particular cause can be identified. It remains an open question why some people are more prone to repeated seizures than others.

Most research exploring the origins of epilepsy has focused on neurons, the brain cells that are the source of the erratic electrical discharges that constitute seizures. However, the focus is broadening. Glial cells, the non-neuronal brain cells that maintain the neuronal environment and respond to neuronal insult, are entering the scene. Recent research suggests that glial cells may be linked to the process of epileptogenesis—the progression from single seizures to epilepsy.

In a five-year project funded by the National Institute of Neurological Disorders and Stroke (NINDS), CHDD research affiliate Dr. Donald Born is investigating two types of glial cells and their relationship to the cause and course of temporal lobe epilepsy. Insights gained from this research may someday reduce the likelihood that a person who has one seizure will have another.

Born, acting assistant professor of pathology, is a neuropathologist who seeks answers by identifying pathological changes in brain tissue and investigating how tissue anomalies are related to changes in brain function. Some of his studies involve human brain tissue, which has been surgically removed to treat temporal lobe epilepsy that is unresponsive to drug treatment. Other studies involve brain tissue from animal models.

In much of his work, Born examines histological sections (stained thin slices of tissue) from the hippocampus, a structure of the temporal lobe that is important in learning and memory. It is also a site where seizures often begin. Born uses light microscopy to scrutinize hippocampal tissue for irregularities in neurons and glial cells. Visible neuronal degeneration is associated with much, but not all, epilepsy. Glial cell activity, which typically corresponds to neuronal damage, is also recorded in tissue changes. Some evidence suggests that, even without neuronal damage, seizures may have an affect on glial cells.

One of Born's objectives is to better understand the relationship between neuronal damage, glial cell function and seizure activity. To sort out the details, he is studying a rodent model of temporal lobe epilepsy, which mimics the spontaneous and unpredictable nature of seizures in human epilepsy. After inducing an initial prolonged seizure with a chemo-convulsant, he is evaluating how glial cells known as astrocytes and microglia react to the first seizure and contribute to continuing seizure activity.

There is delay between the initial seizure and the development of epilepsy, explains Born. "During the lag there is usually a remarkable glial response. It may be related to having a seizure or to neuronal changes that occur during a seizure. My long-term goal is learning if that response affects the propensity to have epilepsy for those animals," he says.

A growing understanding of the diversity of glial cell functions opens new avenues of investigation. "We're learning that astrocytes have electrical properties and polarized membranes like neurons, which enable them to move ions," notes Born. He is interested in determining how astrocytes handle potassium ions, electrically charged atoms thought to be important in epilepsy. "Astrocytes are gaining a much more prominent role in our thinking."

One aspect of Born's investigation focuses directly on the function of microglia, cells derived from the bone marrow that migrate to the nervous system early in development. At times of nervous system damage, resident microglia and... continued on page 7
Imagine a game in which you must work with another person to open a box of crackers. According to the rules, each of you can only use one hand. Figuring out which of you will hold the package, which of you will raise the flap and just how to open the tough wrapper inside requires clear communication—an effective two-way exchange of information.

Verbal communication and negotiation are skills of social interaction often taken for granted, but they cannot be presumed in children with autism. Impairment in the ability for social interaction is one of the hallmarks of this developmental disorder, which is estimated to affect one in 1,000 individuals. However, with intervention, children with autism can develop more effective social and communication skills. The earlier in life intervention begins, the better.

The Autism Program is a clinical service recently added to CHDD’s University Affiliated Program (UAP). Under the direction of Dr. Geraldine Dawson, professor of psychology, the Autism Program provides a variety of services for children with autism spectrum disorders, their families and their community-based service providers. Two clinics make up the Autism Program—the Autism Spectrum Disorders Clinic and the Developmental Neuropsychiatry Clinic.

The Autism Spectrum Disorders Clinic, staffed by psychologists Dawson and Drs. Julie Osterling and Felice Orlich, provides diagnostic, behavior management and intervention planning services for children suspected of having autism spectrum disorders, such as autism, pervasive developmental disorder (PDD) and Asperger syndrome. In the Developmental Neuropsychiatry Clinic, psychiatrist Dr. Alan Unis provides diagnostic services and pharmacologic treatment for children, adolescents and young adults with autism spectrum disorders and other developmental disorders with co-existing psychiatric problems.

Although each clinic operates independently, they regularly interact. Sometimes they work together with one child if the child's case spans the scope of both clinics. Some children go through both clinics at the same time. The entire staff of the Autism Program meets regularly to discuss such cases and to consult on other cases in which overlapping issues arise.

A major activity for both clinics is consultation with clients' community-based service providers. “As autism specialists, we provide diagnostic and consultation services that can assist practitioners in the community in managing relatively rare and complex problems that many of them may see only once or twice in their careers,” explains Dawson. “There's a tremendous need for clinical services for children with autism and their families. By offering consultation to parents and professionals we are attempting to address the need.”

Services for children with autism spectrum disorders and their families offered by UAP clinical program

Autism Spectrum Disorders Clinic

The Autism Spectrum Disorders Clinic serves children from infancy through elementary school age who are experiencing difficulties in social interaction and communication. An evaluation begins with a detailed interview with parents as well as a diagnostic observation of the child and usually involves an assessment of cognitive and language functioning. Such an assessment is essential, Dawson explains, because a lot of decisions about whether a child shows a certain symptom must be made relative to the child's cognitive level.

Early diagnosis is a major focus for the clinic. To facilitate diagnosis at a young age staff use a standardized observational technique called the ADOS, which stands for Autism Diagnostic Observation Schedule. “The ADOS in combination with clinical observation is considered state-of-the-art, and has been shown to provide reliable diagnoses of autism in children as young as 2 years,” says Dawson.

In another area of emphasis the clinic staff consult with parents and community service providers regarding education and intervention planning. Consultations encompass a variety of situations, such as designing and supervising home behavioral intervention programs and responding to requests from school districts for advice and training. The clinic combines a number of empirically supported intervention approaches in order to design a program that best supports a child's optimal development. One area of consultation grows out of Dawson and Osterling's interest and expertise in early diagnosis and intervention. They work with families and therapists to develop intervention programs specifically for very young children. “There aren't very many places for parents to turn for services for children from birth to 3, but we have a great deal of interest in that period and we've worked with a number of infants and toddlers and their families,” says Dawson.

The transition to kindergarten from preschool is another period with limited intervention services for children with autism, according to Dawson. Parents have many questions about whether their child should go after preschool. Are they really ready to go
into a regular classroom? Are they going to have the support they need? Do they need an aide? To answer these questions, clinic staff consult with the teacher and conduct a thorough assessment of the child’s cognitive and academic skills.

The clinic also provides services related to behavior management. “Children with autism often present with challenging behaviors such as aggression and noncompliance,” explains Dawson. “One of the services we offer is to help parents and teachers develop behavior management plans.”

Dr. Felice Orlich specializes in the diagnosis and assessment of high-functioning children with autism spectrum disorders, including Asperger syndrome. These children often benefit from a neuropsychological assessment because they often have subtle learning problems in addition to impaired social skills.

The clinic also conducts social skills groups for such children. Osterling and intern Emily Werner are leading such a group this summer. The group is made up of 5 to 7 year olds with autism or Asperger Syndrome and children the same age with typical development. Weekly meetings consist of activities especially aimed to develop social skills in the children as well as a concurrent parent education/support group.

Children with autism tend to be more visually focused and to process visual information better than auditory information, explains Osterling. With that factor in mind, she divides pertinent skills into general rules, represents them visually through pictures and then creates activities in order to practice applying the rules.

One such activity is the two-person package-opening game described earlier, which the group plays at snack time. Another activity focuses on the concept of maintaining an appropriate distance for effective communication. Each child holds a Hula Hoop around him or herself to delineate personal space, which, according to the rule, cannot be crossed by another child. In addition to holding the Hula-Hoop, each child wears a name tag on his or her back that belongs to another child. The children are then asked to retrieve their own name tags. According to the rules, they have to do it without crossing personal spaces and thus need to exercise their verbal interaction and negotiation skills.

Developmental Neuropsychiatry Clinic

The Developmental Neuropsychiatry Clinic conducted by Dr. Unis serves young people from child- to adulthood who have developmental and psychiatric disorders. He provides a psychiatric evaluation and diagnosis focusing on any medical factors that may be contributing to behavioral symptoms.

Children with autism may have unrecognized co-existing conditions, Unis notes. “What really concerns us is that we don’t miss a kid who also has Fragile X, inborn errors of metabolism or subtle, but treatable, medical conditions.”

A specialist in the use of the latest pharmacological interventions, Unis works closely with referring primary-care physicians to select and maintain appropriate medications. Because most medications used to treat psychiatric disorders have received very little testing in children, Unis interacts a great deal with families as he closely monitors and regulates doses. “Even though an adult dosing schedule may not immediately translate into a child dosing schedule, we know that if we ‘start low and go slow’ we can minimize any negative effects,” he says.

Services of the Developmental Neuropsychiatry Clinic are in high demand. Since its inception, in early 1998, Unis has seen more than 300 families in the one-day-per-week clinic. “I don’t think that I could work this hard if it wasn’t for the parents,” says Unis. “The parents of these kids are incredibly patient with physicians and they’re incredibly good teachers. There is more to learn about autism by listening to them than any book could ever teach you.”

For more information on the Autism Spectrum Disorders Clinic, call (206) 543-5153. For more information on the Developmental Neuropsychiatry Clinic, call (206) 685-1240.
Although the project’s objective was to provide services, not to collect research data, it yielded an unexpected outcome that begs further investigation, according to Scott. Taken together, the assessments showed a much higher incidence of developmental delay in children who were in foster care than in children who were not. This finding raises a significant question about the relationship between being in foster care and having developmental delay. Is foster care a risk factor for developmental delay? If so, what strategies might be implemented to address that risk?

“It was a small mini-grant program and we’re quick to say that you can’t make too many generalizations based on 23 children,” says Scott. “But, given that it wasn’t really designed to be a research program at all, we think this finding is puzzling and intriguing.”

The project was funded by King County DDD as part of an effort to find innovative approaches for addressing the needs of under-served populations.

Thirty families responded. By the end of the project period, Scott had seen 23 of these children. Their ages ranged from 6 months to nearly 36 months. Nine of the children were in foster care. Of those nine, five children had developmental delay. Of the 14 not in foster care, one had developmental delay.

Scott used the same criterion to diagnose developmental delay that the State uses to determine eligibility for early intervention. In Washington, a child from birth to 3-years-old is eligible for services if he or she tests 1 1/2 standard deviations, or more, below the mean on a test that measures developmental functioning. Tests such as the Bayley Scales of Infant Development, which Scott used, give an infant or toddler tasks that produce an observable set of behavioral responses. By evaluating these responses, he was able to assess each child’s current level of cognitive, language, social-emotional and fine and gross motor development.

Dr. Jim Stout, medical director at Odesa Brown, and Kathy Jones, a graduate student in the Maternal and Child Health Program in the School of Public Health and Community Medicine worked with Scott on the assessment project. Based upon the correlation they found between developmental delay and foster care, they hope to undertake a research project to determine whether foster care is actually a risk factor for delay. “Since we were not setting out to look at foster care, we need to see if we can replicate this finding,” says Scott.

Scott and his colleagues surmise that in many cases an initial factor probably exists that leads both to foster care and developmental delay. However, Scott sees the identification of such causal factors as a difficult research question that should be deferred for
Understanding epilepsy in non-neuronal cell
continued from page 3

newly derived cells from the blood with similar properties come to the site of damage to remove debris and products of cell death. Transformed to macrophages, these cells take on roles as phagocytes and in effect garbage collectors, becoming part of the inflammatory response to injury.

As part of the debris removal system, microglia are small factories for several bioactive molecules, points out Born. Some of these molecules are inflammatory mediators that trigger biological processes such as signaling mobilization of astrocytes and additional microglia to stabilize the situation or form a scar.

"If we find that an aspect of the glial response influences the propensity to have chronic epilepsy, we may be able to identify something that we could give at the time of the first seizure to provide protection against future events."

Dr. Donald Born

a while. First, he would like to undertake a replication study that would establish whether there is a risk that can be minimized and what kind of medical care children in foster care should be receiving. "Does foster placement signal a risk of developmental delay that is so high that there ought to be special developmental surveillance for those children?" he asks.

The American Academy of Pediatrics recommends that children in foster care receive developmental assessment from their primary health care provider, says Scott. "But we don't know how that recommendation is implemented in busy pediatric practices," he notes. "There is some evidence to suggest that test instruments used in such settings may be less sensitive to mild and borderline developmental delays than instruments such as the Bayley. It may be that some children who would qualify for birth-to-3 programs aren't identified by some of the briefer developmental screens in use in pediatric practices."

Families of children diagnosed with developmental delay through the assessment project were referred to the county family resources coordinator for assistance in gaining access to appropriate services. The project's spotlight on developmental assessment also generated additional requests for assessments. "Word of mouth spread pretty rapidly, especially in families who have more than one foster child," says Scott. "We'll be seeing these children either as part of the High Risk Clinic at CHDD or, for families who have difficulties with transportation, at Odessa Brown."

"If we find that an aspect of the glial response influences the propensity to have chronic epilepsy, we may be able to identify something that we could give at the time of the first seizure to provide protection against future events. Based on current technology, one choice might be an anti-inflammatory agent to slow down the whole inflammatory response."

Dr. David Scott

Dr. David Scott
Effects of drugs on circulation in the developing brain
continued from page two

development of blood vessels and cerebral circulation. This work is funded by the UW Alcohol and Drug Abuse Institute and the Arc of Washington Trust Fund.

Gleason has found a marked difference in vascular responses to episodes of hypoxia in lambs exposed to alcohol as fetuses, compared with lambs not exposed to alcohol. This finding suggests that prenatal exposure to alcohol may have an effect on vascular development. She hypothesizes that part of the brain damage associated with fetal alcohol syndrome (FAS) may be related to disrupted development of cerebral blood vessels. This disruption may alter the ability of blood vessels to respond appropriately to stresses such as changes in blood oxygen or carbon dioxide levels. In a pilot study with the preterm fetal sheep model, Gleason is looking at vascular responses at an earlier point in development to determine the effects of chronic maternal alcohol exposure early in pregnancy. The ultimate goal of this work is to gain a clearer understanding of the mechanisms associated with alcohol-related fetal brain injury, which may someday lead to interventions for preventing FAS.