

UW researcher focuses on preventing GBS infection that can cause death or neurological damage in newborn babies

A strep infection that most pregnant women are not even aware they may harbor is a major cause of illness and death in newborn babies. The bacteria—called Group B streptococci (GBS)—may have no effect on the mother, but can have devastating consequences for the infant who acquires the infection in the womb or during delivery. If the child survives the infection—and many do not—he or she may be left with lifelong neurological problems.

Although the majority of women with GBS do not experience ill effects, in addition to infection in their babies it can be the cause of premature delivery, infection of the placenta, and infection of the uterus following birth.

Before the availability of accurate lab tests for the presence of Group B strep in the mother's genitourinary and gastrointestinal tracts, and before the use of intravenous antibiotics during labor, some 12,000 babies were infected with GBS by their unsuspecting mothers in the United States every year. This figure has dropped by 75 percent with increased screening and use of antibiotics during labor. Nevertheless, GBS disease remains the most common life-threatening infection in newborn babies.

The consequences of GBS infection in infants are disastrous. Some 10 to 15 percent of infected babies die, and 20 to 40 percent suffer serious neurologic damage. The results can include blindness, hearing loss, seizure disorders, learning disabilities and spasticity disorders.

CHDD research affiliate Dr. Craig Rubens has a longstanding interest in the pathogenesis of infections that cause neurologic damage in newborns, with particular focus on GBS. He is a University of Washington professor of pediatrics, chief of the Division of Infectious Diseases, Immunology and Rheumatology, and adjunct professor of microbiology.

The goal of Rubens' lab over the last 15 years has been to gain sufficient understanding of GBS' molecular mechanisms to point the way to development of more effective antibiotics or, more importantly, development of a vaccine that would pass from the mother to protect her unborn child.



Babies with Group B streptococcus infection — especially those born prematurely — are at risk for lifelong neurological problems or death.

The Centers for Disease Control and Prevention (CDC) estimates that about 25 percent of pregnant women carry GBS in the vagina. It is not considered a sexually transmitted disease, and in many cases produces no symptoms. "It's like many of the bacteria that humans carry," said Rubens. "There is always a percentage of the population that seems to carry various bacteria—in their throats, their noses, on their skin or, in the case of GBS, in the genitourinary tract.

"The organism can colonize the birth canal without causing the mother any health problems, although she may feel ill, have a fever and experience some pain if the bacteria causes an infection of the placenta or amniotic sac surrounding the infant during birth," said Rubens. "About 30 percent of women with this infection are totally asymptomatic."

GBS infects the baby during delivery, or it can ascend into the uterus and infect the amniotic cavity prior to delivery. It can cause premature labor and delivery by infecting the placental membranes or, more commonly, the baby is infected around the time of full-term delivery as it passes through the birth canal. Premature babies are at greater risk for acquiring the infection.

GBS-infected babies are very ill. They commonly contract pneumonia by breathing in amniotic fluid infected with a large number of bacteria. From the lungs, the infection passes to the bloodstream, causing septicemia and affecting the baby's ability to control its blood pressure. GBS has the ability to pass through the

Continued on Page 2

CHDD *OUTLOOK* is published by the Center on Human Development and Disability (CHDD) at the University of Washington Health Sciences Center. An electronic version is available at <http://depts.washington.edu/chdd/OUTLOOK/OUTLOOK.html>

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service and community outreach. The Center includes the University Affiliated Program (UAP) and the Mental Retardation and Developmental Disabilities Research Center (MRDDRC).

Address all correspondence to:
CHDD *OUTLOOK*
University of Washington
Center on Human Development and Disability
Box 357920
Seattle, Washington 98195-7920

Web site — <http://depts.washington.edu/chdd/>

Editor/Writer Laurie McHale
Graphic Design Greg Owen

Center on Human Development and Disability



Michael J. Guralnick, PhD, Director
Lois Winters, Administrator

MRDD RESEARCH CENTER

Donald F. Farrell, MD,
Associate Director,
Biomedical Research
Gene P. Sackett, PhD,
Associate Director,
Behavioral Research
Phillip A. Schwartzkroin, PhD,
Associate Director,
Interdisciplinary Training

CORE SERVICES

Behavioral Science Core

Geraldine Dawson, PhD,
Co-Director
Andrew N. Meltzoff, PhD,
Co-Director

Genetics Core

Phillip E. Chance, PhD, Director

Infant Primate Research Laboratory

Thomas M. Burbacher, Ph.D.,
Director

Instrument Development Laboratory

Kirk Beach, MD, PhD, Director

Neuroscience Core

Philip Schwartzkroin, PhD,
Director

UNIVERSITY AFFILIATED PROGRAM

Adults and Elders

Doug Cook, PhD, Director

Assistive Technology

Kurt Johnson, PhD, Director

Autism

Geraldine Dawson, PhD, Director

Clinical Training

John F. McLaughlin, MD, Director

Disability Policy

Sherrie Brown, JD, EdD,
Co-Director
Doug Cook, PhD, Co-Director

Experimental Education

Richard Neel, PhD, Director

Pediatric Genetics

C. Ron Scott, MD, Director



GBS disease

Continued from Page 1

blood-brain barrier to infect the lining of the brain and cause meningitis. "These infants are very, very sick and unstable and require intensive care," said Rubens, "and a significant percentage do not survive.

"We would like to learn to prevent this disease," he said. "Prevention of such infections or decreasing the severity of response to such infections could reduce the serious developmental disabilities caused by GBS disease."

The CDC recommends that all pregnant women be screened for GBS infection between 35 and 37 weeks of pregnancy (seven to eight months), and if found to be positive, be offered antibiotics.



Craig Rubens

Although the number of infected infants is still a discouraging figure, there is good news to report in terms of screening, said Rubens. "GBS screening is now part of routine prenatal screening in most communities. Women with the bacteria can be given antibiotics at the time of delivery, and this has dropped the incidence of the disease in infants by 75 percent in the last two or three years.

"The problem is that antibiotics used in this way are a short-term solution, since their use raises the possibility of these bacteria—and others carried by the mother—becoming resistant to the particular antibiotic."

Rubens' lab is among a number of research facilities across the nation studying how Group B streptococcus causes the disease. Among the questions to be answered: How does GBS colonize pregnant women? How is GBS transmitted to the infant? What allows GBS to evade host defenses? How does GBS gain entry to the bloodstream and cross the blood-brain barrier? What factors injure host tissues and induce sepsis (blood poisoning)? Why are newborns, particularly those born prematurely, uniquely susceptible to GBS infection?

"We have set up model systems in the laboratory—both animal models and cell culture models—to help us test what traits of the bacterium are important in its ability to cause disease," Rubens said. "We have developed genetic tools for dissecting the organism and determining how the various substances it produces help it cause disease. In doing so, we hope we will identify biochemical pathways within the bacteria that can be targeted, not only for new antimicrobial therapy—antibiotics—but for preventive strategies such as vaccinations as well."

While antibiotics are efficacious if administered at the appropriate time, the most effective means of preventing GBS infection would be a vaccine.

Rubens' lab is studying particular traits of the bacteria, with special focus on the capsular polysaccharide coating on its surface. They are using molecular techniques to identify genes important for the production of the "sugar coating." By creating mutant forms of the bacteria that are defective in producing the polysaccharide capsule, they have shown that the capsule is an essential element in the virulence of GBS and its ability to evade the defenses of its human hosts.

"The polysaccharide coating could be compared to the coating on an M&M candy," said Rubens. "It protects the bacteria from the body's main defense system, the infection-fighting white blood cell. Unless the body has antibodies to the sugar coating, the white blood cells are unable to recognize the presence of the bacteria. This is where a vaccination strategy would be important."

Then, if the antibodies were present in the mother as a result of being vaccinated, she would transfer the antibodies to her unborn child, protecting it from GBS infection.

Continued on Page 8

Trinucleotide repeats: Understanding the genetics of neuromuscular and neurodegenerative diseases

In recent decades, medical researchers have increasingly come to realize that much of human disease is rooted in the genes. With many diseases, hereditary tendencies combine with environmental assaults to produce illness — as with heart disease and many cancers. If one can avoid the environmental triggers, one may be able to avoid the disease.

But for many neurological diseases, susceptibility is hardwired in the genes, and onset of the disease is inevitable if one inherits the gene. In some cases, the disease not only passes from parent to child, but increases its debilitating effects from one generation to the next.

CHDD research affiliate Dr. Albert R. La Spada is a human geneticist whose research focuses on understanding the genetic basis of neuromuscular and neurodegenerative diseases, including Huntington's disease, spinal bulbar muscular atrophy, Parkinson's disease, and spinocerebellar ataxia. An assistant professor of laboratory medicine, he came to the University of Washington in 1993. He holds an M.D. and a Ph.D. in molecular biology from the University of Pennsylvania.

As a clinical geneticist who is also an attending physician at UW Medical Center's Neurogenetics Clinic, La Spada knows the

"The timing and severity of disease is a function of how much the repeat expands in succeeding generations. We're trying to understand the molecular mechanisms behind this genetic instability, as well as the mechanisms of the neuron cell death."

Albert La Spada



frustration of treating patients to whom he can offer only counseling and palliative measures. He and his colleagues hope that research into the genetic origins of such diseases may someday allow them to offer more effective treatment, if not cures.

La Spada began his career at the University of Pennsylvania researching the genetic basis of spinal bulbar muscular atrophy (SBMA), a relatively rare disorder that affects one in about 50,000 to 100,000 persons. SBMA is a form of adult-onset spinal muscular atrophy, caused by a mutation in a gene that controls production of certain proteins in nerve and

muscle cells. It shares some of the debilitating symptoms with amyotrophic lateral sclerosis, better known as ALS or Lou Gehrig's disease. Both SBMA and ALS involve the death of motor neurons, the nerve cells that make voluntary movement possible. However, unlike ALS, SBMA is an inherited X-linked disorder: females carry the mutated gene on one of their two X chromosomes, but the disease manifests itself only in males. It is sometimes called Kennedy's disease, for William Kennedy, the neuro-

logist who first recognized it as a genetic disorder in 1968 and determined it was a sex-linked disorder, distinguishing it from other forms of spinal muscular atrophy.

"SBMA causes muscle weakness in adulthood and plays out over decades," said La Spada. "Patients become wheelchair bound, and sometimes die of the disease, usually because of swallowing difficulties."

The SBMA research produced knowledge with wider implications for other inherited diseases, including many that cause mental retardation. In 1991, while at the University of Pennsylvania, La Spada was part of the research team that discovered the cause of SBMA to be a new type of genetic mutation called "trinucleotide repeat expansion," whereby three nucleotides—in this case CAG—repeat themselves over and over again. In fact, once a family carries the mutation, the number of repeats keeps increasing from generation to generation.

Since this discovery, 14 more neurological diseases have been shown to be caused by trinucleotide repeat expansions, including Huntington's disease, myotonic dystrophy, and two forms of mental retardation. A similar trinucleotide repeat pattern has been found as the cause of fragile X syndrome, also an X-linked disorder, that in this case results in mental retardation.

"There are billions of nucleotides in the human genome," explained La Spada. "There are many cases within the genome where three nucleotides are repeated over and over, up to a certain normal threshold. However, in the case of SBMA and these other diseases, the number of repeats goes beyond that threshold, and the disease appears."

There is a relationship, although not a perfect correlation, between the number of repeats and the severity of the disease. Other genetic or environmental factors may also be involved.

Huntington's disease is caused by the same sequence of CAG repeats as SBMA. These repeats direct the cell to incorporate certain amino acids into the protein that their respective genes produce. The net result in both SBMA and Huntington's is that a run of the amino acid glutamine is expanded from a normal range of 10 to 30 repeats to more than 36 repeats, apparently the threshold for the appearance of the disease. Research has now uncovered eight of these polyglutamine repeat diseases. In addition to SBMA, this trinucleotide repeat pattern is found in Huntington's disease and five forms of spinocerebellar ataxia (SCA). Seven of the eight polyglutamine repeat diseases are autosomal dominant, meaning that each child of an affected parent has a 50/50 chance of inheriting the gene defect. SBMA is X-linked, affecting only males.

"Our major focus is to understand why extending the run of glutamines leads to the death of nerve cells," said La Spada. "We want to understand why motor neurons die in spinal bulbar mus-



Albert La Spada

Continued on Page 7



CHDD researchers train advocates to help homeless women become better parents

Put yourself in the shoes of the homeless woman with no partner, few financial resources, and a young child to raise. Ponder how you would cope with a baby, facing the challenges of street life and lacking the positive example of parenting from your own mother and father. Imagine how difficult it would be to become a good and nurturing parent.

A homeless mother has more than her share of obstacles to surmount. Learning to be a sensitive and empathetic parent is one of the most challenging, but it is of utmost importance if her young child is to thrive and grow up secure and healthy.

Dr. Jean F. Kelly, a UW research associate professor of family and child nursing, heads a research project aimed at assisting advocates for the homeless in promoting good parenting skills among their clients. Kelly is chair of the Early Intervention Task Force for CHDD's University Affiliated Program as well as a member of CHDD's Nursing Research Program. The overall goal of her research is to better understand

how early environmental factors affect children's social, emotional and cognitive behavior. She is interested in developing more effective preventive interventions to enhance healthy family functioning and more positive child outcomes.

Beginning in 1998, Kelly and her colleague, Kim Buehlman, focused on one of the most at-risk populations: homeless parents with children aged birth to 3.

"Homeless parents expend tremendous emotional resources trying to meet basic human needs, often leaving little in reserve to offer support and understanding to their young children at a time when their children need it most," said Kelly. "Studies show that a majority of homeless children suffer from developmental, emotional and learning problems. All the conditions that lead to developmental problems come together in the situation of homelessness. Research has shown that a necessary condition for a child to escape the cycle of poverty and become a productive and healthy member of society is to experience a nurturing relationship in which the child is valued and communicated with."

Kelly and Buehlman designed a training and early intervention protocol whose purpose was to train social service providers—advocates who work with homeless women—to enhance the parent-child interaction within the context of their regular meetings with their clients.

"Most service providers lack the necessary training to give positive instructional feedback to parents about the quality of the parent-child relationship. They're hesitant to intervene because they feel inadequately prepared or feel they would be intruding on this intimate relationship," she said.

According to national statistics, families with children are the fastest growing segment of the homeless population in the United States, making up possibly 40 percent of the homeless population. While there was no typical mother in the study, a common denominator was low or no income. The women were aged 19 to 40. Their education levels ranged from no high school through college educated. Most were unmarried; some were living with partners. The children in the study ranged from 6 months to 26 months of age.

The study included two 10-week phases. The researcher/trainers accompanied each of four service providers to their separate weekly meetings with two homeless clients and their babies. For the first 10 weeks, the trainers worked directly with the women, modeling the

desired parent coaching method, while the service providers observed.

For the following 10 weeks, the roles were reversed. Additional mothers and babies were recruited into the study, and the service providers then tried their hand at coaching the parents, with the trainers acting as the observers and giving feedback after each session.

"While the mother played with her baby, we gave feedback during their interaction," said Kelly. "We taught the moms to read the baby's cues, to respond sensitively, and reflect emotions. The goal is to increase the security that the baby feels with the mother, and to help the mothers learn to be sensitive and responsive."

At the end of each session, a 45-minute training session allowed service providers and researchers to discuss what they observed.

Videotaping the sessions was an important aspect of the study, as it allowed researchers, service providers and mothers to see where progress was being made, both in enhancing service providers' skills, and in fostering nurturing behavior in the mothers. Videotaping helped parents observe their own responses to their young children's behaviors and cues.

"We videotaped mother and child as they played together, as well as when the mother taught her child a new skill," said Kelly. "We showed the tape to the mom, and asked her to tell us what she



A homeless mother views a videotape of her interactions with her baby, with positive instructive feedback from a social service provider, right.

liked about her interaction with the baby, and what she would like to work on. Then, we assigned goals for the next nine weeks.”

The playtime was structured according to a mother-child interaction protocol developed by the National Institute of Child Health & Human Development’s (NICHD) Early Childcare Research Network. The teaching episode was structured using a Teaching Task Protocol developed through NCAST, the Nursing Child Assessment Satellite Training, by CHDD research affiliate Dr. Kathryn Barnard, a UW professor of nursing. NCAST conducts training in research methods for assessing behaviors of children and parents. Barnard demonstrated the importance of parent-child interaction as a predictor of later cognitive and language development.

The first videotape was also a pre-test to be compared with a post-training videotape, to determine whether the intervention had been effective. By the end of the training, there were positive results both in the service providers’ ability to foster positive behavior in the mothers’ interactions with their young children, and in the mothers’ responsiveness to their children.

“Before the training sessions,” said Kelly, “the advocates didn’t know how to structure the sessions to encourage the mother to interact with her child. Instead, they discussed issues with the mother while the child played nearby. They were hesitant to intervene in the parent-child relationship because of their own lack of knowledge and the concern that their feedback would seem intrusive.”

“Homeless parents expend tremendous emotional resources to meet basic human needs, leaving little reserve to offer support to their young children when they need it most.”

Dr. Jean Kelly

The advocates observed that the parents liked the non-judgmental, positive feedback, and they gained confidence in their ability to help parents recognize and respond sensitively to their children.

“We pick up on what the mom does that’s positive, in order to encourage that behavior,” said Kelly. “We use an approach where we’re building on the positive things the mothers do, in order to increase their sensitivity and responsiveness.”

Not only was the feedback positive, it was also instructive and immediate, to give the parent information on why her behavior is important to child development. At the beginning of the training sessions, there was almost none of this type of instructive feedback on the part of the advocates.

Examples of positive instructive feedback might be: “You followed your baby’s lead so nicely when she reached for the jack-in-the-box. Following her lead lets her know you understand her needs and wants.” “It’s really nice the way you let him mouth the toy. Even though he is getting better at using his fingers, his mouth still gives him lots of information.”



A homeless mother plays with her twins while a project trainer observes and gives positive feedback.

“Positive instructive feedback points out to the mother the important behaviors to employ with her child,” said Kelly. “She’s showing sensitivity, picking up on cues, and letting the baby know that what he’s communicating is very important. There’s a give-and-take to the relationship and he’s picking up on it. That’s the beginning of language. With the intervention, we significantly increased the responsiveness of the mother to individual actions of the child. We also significantly increased the amount of stimulation the mother provided and the amount of positive regard she showed for her child.”

Kelly, who has a doctorate in special education from the University of Washington, used a similar training approach for her doctoral dissertation, focusing on young children with disabilities. In the future, she hopes to use the same approach in other settings. “We hope we can use this protocol for service providers who work with children with disabilities and their parents, as well as in training childcare providers for typically developing children and for children with special needs,” she said.

The results of the study are being published in the fall 2000 issue of *Topics in Family Childhood and Special Education*. Kelly also presented results last spring at the National Health Care for the Homeless Conference. She would like to see longitudinal studies to determine whether such interventions produce long-term positive effects in children. She recommends that people who work with young children and their parents be taught such strategies as part of their training, so that they become competent facilitators of positive parent-child interactions.

Funding for the first year of study came from the University of Washington’s Royalty Research Fund, which encourages faculty members to go in new directions in practice or research. Funding for a second year came from Health Care for the Homeless, a program of the King County Department of Public Health. ♦

The ketogenic diet: high-fat regimen relieves seizures in many children with intractable epilepsy

If a medical expert told you that a diet deriving up to 90 percent of its calories from fat could be medically beneficial to a young child, you might be tempted to question the researcher's credentials—if not sanity.

But an old dietary regimen, first popularized in the 1920s as a treatment for intractable childhood epilepsy and largely abandoned a few years later in favor of new medications, has found new adherents in the last decade.

Scientists across the country are once again examining the ketogenic diet—a stringent high-fat, low-protein, low-carbohydrate regimen—to determine how it quiets the storm of errant electrical impulses in the brains of a significant number of children whose epilepsy does not respond to other therapies.

Dr. Jong M. Rho is investigating the mechanisms by which the ketogenic diet exerts its effects on the brain. Rho is a research affiliate at the Center on Human Development and Disability, a University of Washington assistant professor of neurology and pediatrics, the co-director for translational research at the UW's Pediatric Epilepsy Research Center (PERC), and a clinician at Children's Hospital and Regional Medical Center, where he sees young patients with epilepsy.



Jong Rho

Rho and his colleague, CHDD research affiliate Dr. Philip Schwartzkroin, UW professor of neurological surgery and PERC's director of research, were guest editors of a recent special issue of *Epilepsy Research* devoted entirely to "The Ketogenic Diet: Mechanisms and Models."

"Epilepsy is more common in children than diabetes or cancer," said Rho. "Of the nearly 200,000 new cases of epilepsy each year in the United States, about 75 percent begin in childhood. Uncontrolled epilepsy affects intelligence, memory, concentration, motor skills, problem solving, school performance and behavior."

Epilepsy often co-exists with other disabilities, such as autism and mental retardation, making the search for methods of prevention and effective treatment of special interest to the CHDD, said Dr. Michael J. Guralnick, director of the CHDD.

"The ketogenic diet stems back to the historic observation that fasting can result in seizure control," said Rho. In 1921, investigators at Presbyterian Hospital in New York and at the Mayo Clinic reported that epilepsy could be controlled when ketosis was induced through fasting or diet. But when new drugs became available to treat epilepsy in the 1930s, the diet fell out of use. Until the 1990s, it was rarely prescribed.

After a 1994 "Dateline NBC" program featured a boy who became seizure-free and medication-free after a month on the diet,

inquiries deluged epilepsy centers across the country. The boy, Charlie Abrahams, was later the focus of a 1997 television movie with Meryl Streep, "First Do No Harm." A number of centers have since initiated programs incorporating the diet.

The ketogenic diet mimics the biochemical changes that occur with starvation. It produces ketones, which give the breath and urine the characteristic acetone smell of ketosis. Ketosis occurs when the body burns fat instead of glucose, the body's usual energy supply, which is largely lacking in the diet. Ketones—the products left after fat is burned, most notably beta-hydroxybutyrate—build up in the blood.

The question is, do ketones have any direct role in modulating the excitability of the brain? Or does some other aspect of the diet—caloric restriction, high levels of fatty acids, lack of glucose, or altered hormonal levels—cause the reduction in seizures? The diet has been called "a therapy in search of an explanation."

About two-thirds of children on the ketogenic diet respond positively, with mild to marked reduction in seizure activity; about 10 percent become seizure-free. For many children, the positive effects last even after a normal diet is gradually reintroduced. Typically, children stay on the diet for about two years.

"We have treated dozens of patients with good efficacy since the program was introduced at Children's in 1995," said Rho. "The ketogenic diet is a viable alternative for patients who don't respond to conventional anticonvulsant drugs, and who are not candidates for epilepsy surgery. There is a potential with this diet to avoid some of the side effects of the antiepileptic drugs, as well as to obtain cognitive and behavioral benefits.

"However, staying with the diet requires a strong commitment on the part of the parents, as well as meticulous vigilance to avoid foods and even supplements that might contain hidden sugars."

Children are normally hospitalized for an initial period of fasting and fluid restriction. They are then placed on a daily regimen that supplies about 90 percent of their total calorie intake from fat—but a total of only 75 percent of normal daily calories. Protein and carbohydrate levels are kept very low, and fluids may also be restricted. They are given vitamin and mineral supplements.

There are concerns about the long-term effects of the ketogenic diet, since children must stay on it for months or years. Potential side effects include possible growth retardation from protein deprivation, effects on cholesterol and triglyceride levels, vitamin and mineral deficiencies, constipation, kidney stones and elevated uric acid, possible impaired immune defenses, metabolic acidosis, and even liver failure.

The diet is challenging for families to follow, as children must be deprived of many of the foods they love. A couple of cookies contain enough sugar to switch the body over to using glucose for fuel rather than the ketone bodies, compromising its effectiveness. "Compliance is a major problem," said Rho.

The UW investigators, who have been researching the diet since 1997, are exploring a number of avenues to learn how it inhibits seizures. "The diet is a window into the mechanisms of the brain," said Rho. "If we can figure out how the diet exerts its effect, then we can begin to design a medication to take its place, or perhaps design a better diet. My goal is to find developmental animal models that are relevant to the pediatric situation."

Animal models are useful because it is possible to precisely control and evaluate factors such as components of the diet, types of seizures, and various biochemical and neurologic parameters. Rho points out that existing drugs used for epilepsy are not specific to children: they were tested in the mature, normal animal model.

Rho and colleagues believe they have identified a highly relevant animal model on which they can perform a number of studies relevant to pediatric epilepsy, including studies of the ketogenic diet, and why some infants and children develop epilepsy in response to brain injury, whereas others do not. The studies are designed to explore the complex relationship between genetic susceptibility to epilepsy and environmental factors. Their research is funded by the National Institutes of Health and the UW's Pedi-

"There is a potential with this diet to avoid some of the side effects of anti-epileptic drugs and obtain cognitive and behavioral benefits. However, staying with the diet requires a strong commitment on the part of parents."

Jong Rho

atric Epilepsy Research Foundation,

Rho's animal model is a transgenic mouse, the Kv1.1 potassium channel knockout mouse, bred to lack a gene that is also missing in some humans with epilepsy. This breed of mice is produced in the laboratory of the UW's Dr. Bruce L. Tempel, also a CHDD affiliate.

In this mouse, the genetic mutation leads to spontaneous seizures in the early stages of development. Studies are underway to understand the cellular electrophysiology of neurons from these epileptic mice.

When these mice are treated with a ketogenic diet, they develop elevated levels of GABA (gamma-aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system. The investigators are studying whether beta hydroxybutyrate, a major ketone body produced as a result of the diet, may act to raise GABA levels that are too low, and reduce the number of seizures.

Rho points out that certain anticonvulsant medications also increase the levels of GABA in the brain. Such medications presumably control seizures by a mechanism similar to that of the ketogenic diet, by enhancing the inhibition of neurotransmissions in the brain pathways that respond to GABA.

The researchers are also using the transgenic mouse to examine gene dosing: the difference in effects on brain activity of inheriting the gene from one parent versus both parents.

"We hope our basic research efforts will spur clinical research," said Rho. "The UW's Pediatric Epilepsy Research Center plans to embark on a clinical research program in 2001, when we put together a program project application to the National Institutes of Health. The goal is to bring research findings rapidly from 'the bench to the bedside.' " ♦

Trinucleotide repeats

Continued from Page 3

cular atrophy, and why cells in the brain stem, cerebellum and retina die in the case of another disease, spinocerebellar ataxia type 7 (SCA7). We're focusing on these two disorders, but the same mechanism applies to all eight polyglutamine repeat diseases.

"The immediate goal is to understand which molecules, genes and proteins are conspiring with these polyglutamines to kill nerve cells," he said. "We hope there will be obvious targets for therapeutic intervention."

La Spada points out that SCA7 shows very strong "anticipation," a term that describes the increasingly severe manifestations of the disease. From one generation to the next, the age of onset becomes lower and the disease progresses more rapidly.

"I met a brother and sister affected with SCA7," he remembers. "Their grandmother didn't show signs of the disease until she was 60. Their father didn't develop the disease until after he had three children. The brother and sister showed symptoms in their 30s, but their younger sister showed symptoms at age 6, was blind by age 9, and died at age 15.

"The timing and severity of the disease is a function of how much the repeat expands in succeeding generations," said La Spa-

da. "We're trying to understand the molecular mechanisms behind this genetic instability, as well as the mechanisms of the neuron cell death. These are two separate research endeavors linked by the fact that they characterize these mutations."

For many hereditary neurological diseases, genetic testing is now available, either for persons at risk or after symptoms appear. But since few therapies are yet available, the knowledge that one has developed or will develop the disease allows the patient mainly to make plans for the future and to make childbearing decisions.

"For both SCA1 and Huntington's, we may have some rational therapeutic approaches in the future," said La Spada. "For now, we can offer only relief of symptoms. As yet, there is no treatment modality specifically directed at the chain of events involved in the polyglutamine repeat diseases. If we can answer the question of why repeats expand, it may impact our understanding of the genetics underlying mental retardation. We hope to learn enough to figure out where to intervene to break the links."

La Spada is the principal investigator at the UW on the trinucleotide repeat studies, with funding from the National Institutes of Health. His colleagues include CHDD research affiliates Drs. Richard Morrison, Philip Schwartzkroin and Phillip Chance, and Dr. Carol Ware. ♦

New research affiliate

Dr. Joseph Pinter received a medical degree in 1990 from the University of California at Los Angeles, where he was a Regents' Scholar. His postgraduate training in pediatrics took place at the University of Washington and Cedars-Sinai Medical Center in Los Angeles, and he did residency and research fellowships in pediatric neurology at Harvard and the University of California, San Francisco (UCSF). Pinter joined the UW in 1999 as an assistant professor of neurology and director of the Pediatric Neurology Residency Training Program. He is board-certified in pediatrics and neurology.



Joseph Pinter

Pinter's research focus is on the use of structural and functional MRI to better understand the cognitive deficits involved in Down syndrome and other developmental disorders. He is UW project director of a research study to develop functional MRI as a means of better understanding the language and memory deficits of children with Down syndrome, in collaboration with Dr. Allan Reiss at Stanford University and Dr. Donna Ferriero of UCSF. They hope to better understand the anatomic and functional bases of mental retardation associated with Down syndrome, and possibly learn more about development of Alzheimer's disease. Pinter's interests also include epilepsy and congenital brain malformations.

He is involved in a clinical study at Children's Hospital and Regional Medical Center of intravenous immunoglobulin as a treatment for epileptic spasms, a particularly intractable type of seizure. With Dr. James Barkovich of UCSF, he has an ongoing neuroimaging project analyzing patterns of abnormality in holoprosencephaly, a birth defect in which the fetal brain does not grow forward and divide as it is supposed to during early pregnancy. ♦

GBS disease

Continued from Page 2

Rubens and his colleagues have a broader goal as well. "Our hope is to understand how GBS and other bacteria cause infections in women and infants during pregnancy, labor and delivery," he said. "Our understanding of how the reproductive system deals with infections is not very mature. A lot of study is needed on how bacteria interact with the placental membrane, the placenta and the baby in the uterus, to try and prevent prematurity as well as the devastating consequences of these infections."

Joining Rubens at the UW in his work on Group B streptococcus are Dr. Glen S. Tamura, clinical assistant professor of pediatrics, and Dr. Amanda Jones. He also collaborates with CHDD research affiliate Dr. Christopher Wilson, professor and chair of the UW Department of Immunology. Across the country, others—notably Dr. Dennis Kasper and Dr. Michael Wessels at Harvard and Dr. Pat Ferrieri at the University of Minnesota—are focusing on different traits of the bacteria.

Information on GBS is available from the CDC web site at <http://www.cdc.gov/ncidod/dbmd/gbs/index.htm> and from the Group B Strep Association web site at <http://www.groupbstrep.org/> ♦

Visit the CHDD Web site:
<http://depts.washington.edu/chdd/>



University of Washington
Center on Human Development and Disability
Box 357920
Seattle, Washington 98195-7920

Nonprofit Organization
U.S. POSTAGE
PAID
Seattle, WA
Permit No. 62