FPG
Child
Development
Institute
The University of North Carolina
at Chapel Hill

early developments

Summer 2004 | Volume 8 #2

Fragile X Syndrome

news

FPG project featured on CNN show

The Abecedarian Study, a long-running FPG research project, was highlighted in a recent prime-time CNN show, "The Gap—50 Years After the Brown Decision." Dr. Frances Campbell, who directs the study, was featured in the show.

The Abecedarian Project is a carefully controlled study in which 57 infants from low-income families were randomly assigned to receive early intervention in a high quality child care setting and 54 were in a non-treated control group. The treated children received full-time educational intervention in a high quality child care setting from infancy through age 5.

Investigators have now completed a young adult follow-up assessment of study participants. At age 21, cognitive functioning, academic skills, educational attainment, employment, parenthood, and social adjustment were measured. Major findings of the young adult follow-up include these:

- Young adults who received early educational intervention had significantly higher mental test scores from toddlerhood through age 21 than did untreated controls.
- Enhanced language skills in the children appears to have mediated the effects of early intervention on cognitive performance.
- Reading achievement scores were consistently higher for individuals with early intervention.
- Mathematics achievement showed a pattern similar to that for reading, with treated individuals earning higher scores.

More information about the Abecedarian Study may be found at <www.fpg.unc.edu/~ABC/>

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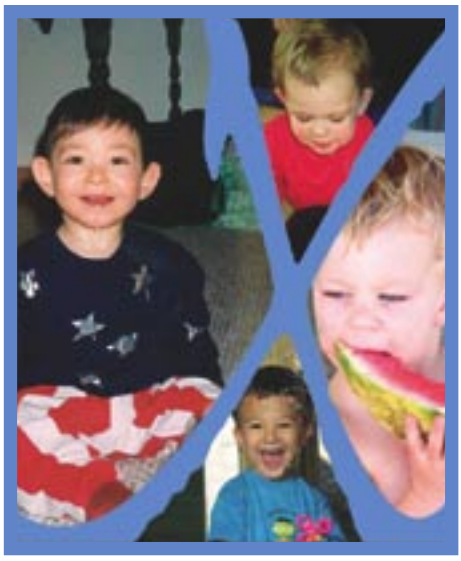
Director's Notes by Don Bailey



In 1993, some colleagues and I began a study of a little-known disorder—fragile X syndrome. The gene for fragile X had just recently been discovered, and there was lots of excitement, for many reasons. Although the disorder had been described for more than 20 years and it was almost certainly inherited, what went wrong and how it was inherited was not known. Officials at the NIH were excited because it was one of the first examples of how the Human Genome Project, a massive effort to "map" the human genome, could lead to discoveries pinpointing the causes of hundreds, if not thousands of disorders. Genetic researchers were excited because this discovery helped them to understand an unusual inheritance pattern that could not previously be explained. Many parents were excited because they finally had a better understanding of the disorder affecting their child. And the fact that fragile X is a single gene disorder gave hope to many that with the advent of gene therapy, a cure might be possible.

But of course, as with most discoveries, the answer to one question opened the door to many others. Knowing a gene flaw or "mutation" doesn't mean that you know everything about how it works. Genes, which are made up of DNA, provide instructions for making RNA, which then leads to proteins, which control all aspects of human biological function. Fragile X syndrome affects the production of a single protein (FMRP) known to be necessary for normal brain development. While much progress has been made in understanding the biology of fragile X syndrome, many mysteries remain unsolved, and a cure seems just as far away today as it did in the early 1990s.

Of course, we don't do basic biological research at FPG. But we do study children's development and behavior over time, and we are very interested in both the biological factors and the environmental factors that affect behavior and development. When we started our research in 1993, no one had studied the earliest development of children with fragile X. So we began an early childhood study, starting with children in North Carolina, South Carolina, and Virginia under the age of six. Finding nearly a hundred families of young children with fragile X was quite a challenge. But with the help of a great research team and lots of people willing to help, we did it. We have been tracking these children ever since, and some of the oldest are now getting ready to enter high school. Along the way we have involved professionals from many different disciplines and have examined the many ways in which fragile X can affect both children and families. These studies are still under way, and we are now in the midst of planning a very large study to screen 1,000,000 newborns for fragile X.

This work has been immensely gratifying. Many different people at FPG and across the university are now actively involved in fragile X research. With a strong publication record and the most comprehensive longitudinal study of fragile X ever conducted, we are well positioned to continue this work into the future. However, what we have learned from all of this goes well beyond our publications and well beyond fragile X.

- Biology is just as complicated as behavior. Compared with human development, which is enormously complicated and almost defies a "scientific" explanation, I thought biological function was relatively straightforward. In fact, genes regulate a complicated biological system with many different interactions and pathways that may never be fully understood. Although fragile X was thought to be a single gene disorder involving a single protein, in reality, it likely regulates and interacts with many other genes and many other proteins in a complex and changing pattern.
- No one person or one discipline can fully understand any phenomenon. Over the years we have worked with psychologists, neurologists, psychiatrists, special educators, genetic counselors, anthropologists, speech and language pathologists, occupational therapists, and many others who have helped to provide insights into the multifaceted aspects of this disorder.
- A focus on a single disorder still allows you to address "big" issues. For example, we now have the technology and knowledge to identify many disorders earlier than we currently are. Is it worth the investment needed to identify disorders earlier? Our work on newborn screening for fragile X will serve as a prototype for early detection of other disorders.
- You don't always know where your research will lead you. We started with a small study looking at some focused areas of development. One thing that has led to our success has been our willingness to look beyond the parameters of what we were funded to do. When we find something interesting, we study it.
- Good research takes a long time. Of course, we would all like immediate answers to questions. After more than 10 years, you would think we would have fragile X figured out. Although we know a lot more now than we did when we began, much remains to be learned. This is especially true when you do research that looks at how lives change over time.

I cannot end this column without acknowledging several groups of people. First, are all of the individuals who have worked on this project throughout the years. I hesitate to mention names, because there are too many, but you know who you are. Suffice it to say that this has been a true team effort.

Second, we appreciate the support of many different agencies and foundations. We have received funding from the Office of Special Education Programs, the National Institute for Child Health and Human Development, the FRAXA Foundation, the National Fragile X Foundation, and Ronald McDonald House Charities.

Finally, throughout this project, we have had the privilege of getting to know a group of remarkable families. They have allowed us to study just about every aspect of their children's lives and now their families' lives as well. They have been amazingly tolerant and giving of their time and energy, hoping that this work will ultimately pay off. And they have inspired us to continue. We dedicate this work to them. |ed|

Going the Distance with Fragile X

A Fragile X Glossary

autism: a complex developmental disability that typically appears during the first three years of life

FMRP: protein necessary for brain development. Production is affected by fragile X syndrome; appears to be involved in synapse maturation and elimination

fragile X syndrome: the most common inherited form of mental retardation. Effects can vary from subtle developmental delays to major impairments

full mutation [of FXS]: is indicated by 200 or more repeats of the DNA sequence mutation; individuals will experience the impairments and delays associated with the syndrome

genotype: the genetic makeup, as distinguished from the physical appearance, of an organism or a group of organisms

hyperarousal: a tendency to become easily overstimulated and to overreact to changes in environment or routines

hyposensitivity: less than the normal ability to respond to stimuli

Individuals with Disabilities Education Act (IDEA): the law that guarantees all children with disabilities access to a free and appropriate public education, and provides services and resources to infants and toddlers with disabilities and their families

phenotypic expression: the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences. In reference to fragile X, refers to how the disorder appears in people's behavior, development, and physical features

premutation carrier [of FXS]: is indicated by 50–200 repeats of the DNA sequence mutation; individuals can transmit the disorder to their children, but may not be affected themselves

vagal tone: an index of neural control of the heart

ELEVEN YEARS AGO, FPG Child Development Institute (FPG) launched a longitudinal study of a little known form of mental retardation known as fragile X syndrome (FXS). The Carolina Fragile X Project has since grown into a multidisciplinary team studying diverse aspects of the condition, ranging from early identification to school performance. The team's research has led to wide understanding of what constitutes the condition, how it can be detected, strategies for intervention, and how to help families cope.

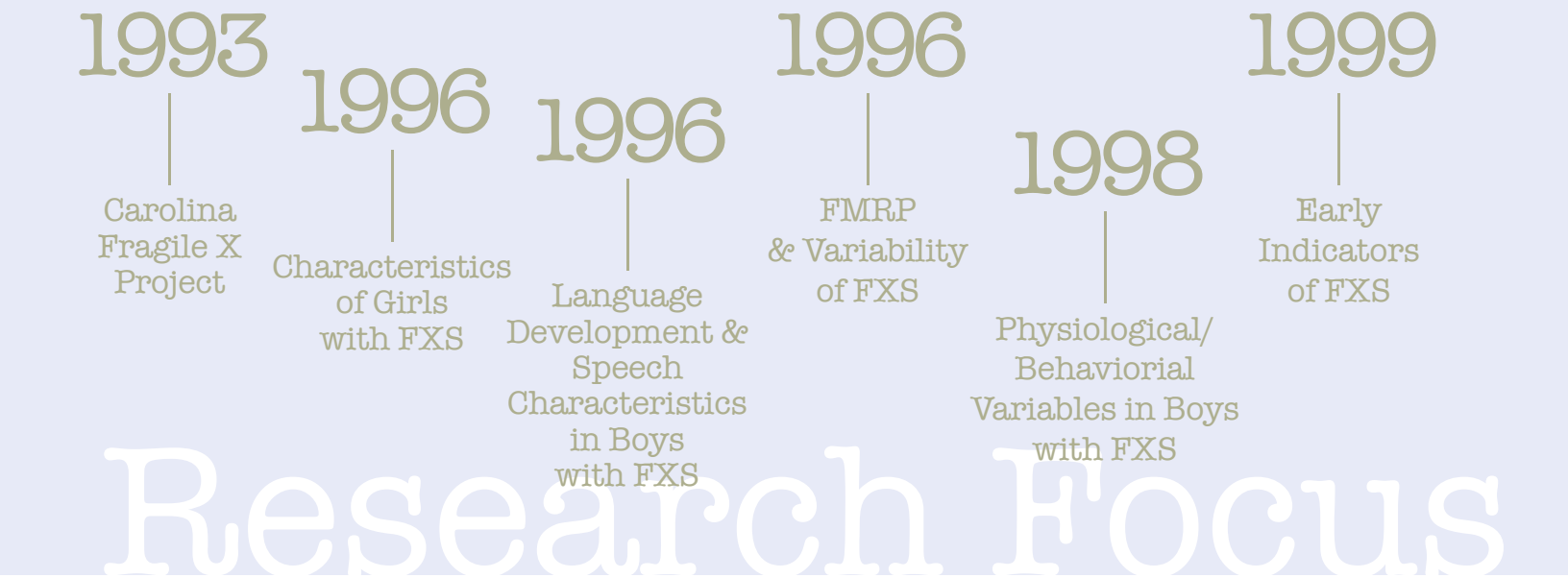
FPG researchers have published thirty-two journal articles and chapters on FXS and many more are in the works. The team is working on seven different grants totaling more than $2.2 million a year. Next spring, FPG will publish a book on early intervention for young children with FXS. FPG Director Don Bailey has written the definition of fragile X for the online version of the *World Book Encyclopedia*.

"You could say we have put fragile X on the map," Bailey says.

What is fragile X?

Fragile X syndrome is the most common inherited form of mental retardation. First described as Martin-Bell syndrome in 1943, it became known as fragile X syndrome in 1969 when Herbert Lubs discovered an unusual constriction and occasional break at the end of the X chromosome.

In 1991, scientists discovered that FXS results from a mutation known as a trinucleotide repeat expansion, in which a series of three nucleotides (CGG) in the DNA is expanded beyond its normal size. This genetic mutation disrupts



the messages sent to make FMRP, a protein necessary for normal brain development. The normal range of CGG sequences is 5–50 repeats. An individual with 50–200 repeats is a *premutation carrier* of FXS, meaning they can transmit the disorder to their children, but may not be affected themselves. Individuals with 200 or more repeats have the *full mutation* of FXS and will experience the impairments and delays associated with the syndrome.

For individuals with FXS, effects can vary from subtle developmental delays to major impairments. Males with the full mutation are more severely affected than females. Most males will have mild to severe mental retardation with cognitive and communication skills most likely to be affected. They may seem shy, anxious, and inattentive. Hyperarousal, a tendency to become easily overstimulated and to overreact to changes in environment or routines, is a common condition. Males have several distinguishing physical features, including large ears, loose joints and muscles, and an elongated face.

Females generally have milder impairments. About one third will exhibit normal development, another third will exhibit learning disabilities, and about one third will have mental retardation. Females with FXS may also be shy and exhibit social problems.

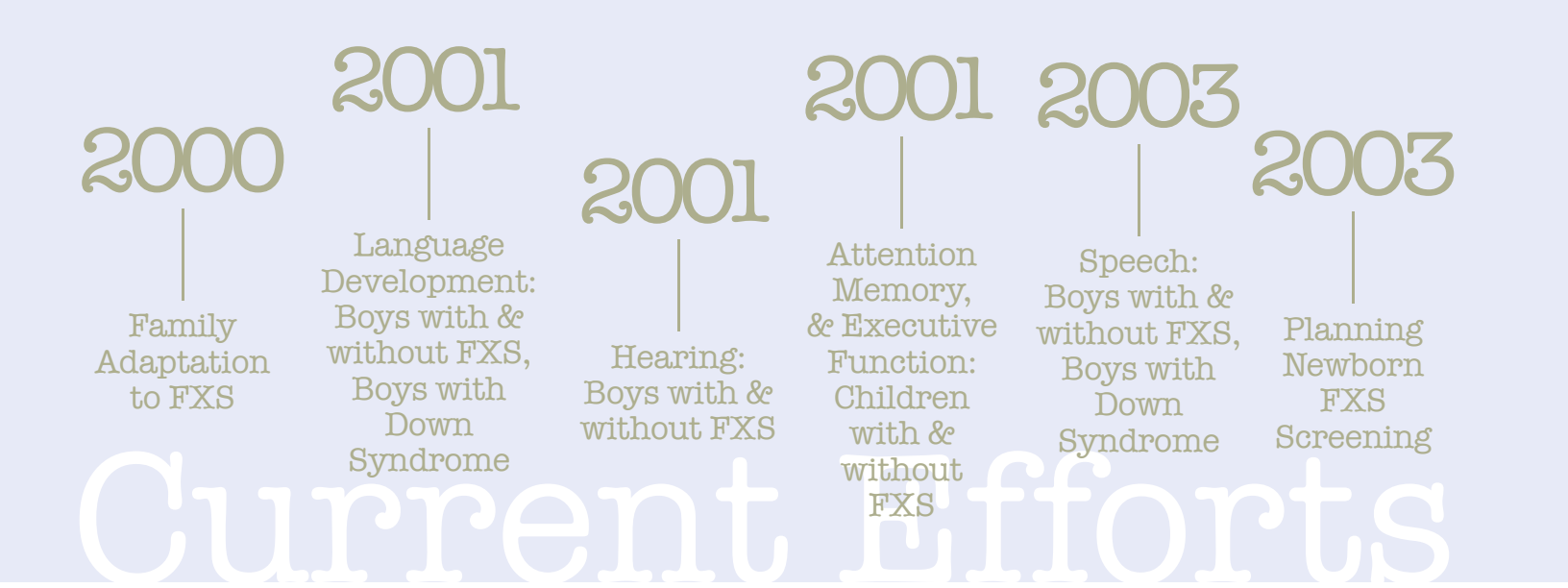
The early years

The foundation of the Carolina Fragile X Project began with a series of longitudinal studies following the development of children with FXS beginning in preschool. Initially funded by the Office of Special Education Programs in the US Department of Education, these studies have been headed by Bailey with co-investigator Deborah Hatton. The first study, begun in 1993, focused on a group of 75 preschool boys. Successive grants in 1995 and 2001 have followed this same group of boys through elementary and middle school. A separate study on young girls was initiated in 1996.

Collectively, those studies have yielded a wealth of information on FXS. They suggest that although parents usually notice problems much earlier, the typical child with FXS is not diagnosed as developmentally delayed until 21 months and not formally diagnosed with FXS until 32 months. They show considerable variability in early development, with some children progressing much faster than others. Boys have been found to have a higher activity level, to be slower to adapt to new situations, to be less persistent and more withdrawn than typical children. Roughly one quarter of boys with FXS are also classified as autistic, and experience more serious delays than children with autism or FXS alone.

Researchers also have collected information about the early intervention or educational services that children with FXS receive, as well as parental perceptions of these services. This work led to a major "synthesis" conference in 2004 where experts discussed the features of an early intervention program most likely to be successful for children with FXS. Researchers are now planning a large study to determine the effectiveness of earlier intervention.

School performance is a crucial part of the longitudinal studies. Analysis of elementary school experiences shows that by second grade, most boys are placed in self-contained classrooms that only serve children with disabilities and that by age 8, many children still experience challenges in performing basic functioning skills. Data on middle school performance are now being collected.



Further refinement and recent studies

Beginning in the mid-90s, FPG researchers began expanding the scope of their research, looking at particular aspects of FXS.

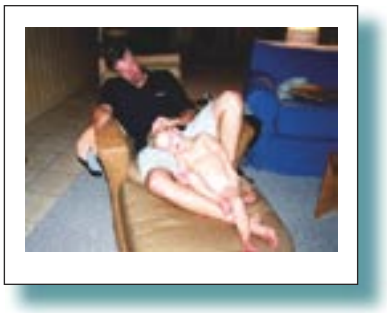
- In a 1996 study funded by the National Institute on Disability and Rehabilitation Research, Joanne Roberts and Penny Mirrett examined the language development and speech characteristics of boys with FXS.
- In another study, Bailey and co-investigators Hatton and Annette Taylor examined the relationship between levels of FMRP, the protein affected by FXS, and the variability in effects of FXS on individuals.
- Bailey and Jane Roberts investigated the relationship between physiological and behavioral variables in boys with FXS.
- In 1998, Jane Roberts received a grant from the FRAXA Foundation to examine classes of medication and their effects on the physiological and behavioral responses of boys with FXS.
- The following year, Bailey, Hatton, Roberts, and Mirrett launched an investigation of the early development of infants, identified the earliest indicators of the syndrome, examined issues related to early screening of infants, and evaluated the usefulness of screening protocols used by pediatricians and other clinicians. This study has led to a planning grant from the NIH to develop a study for newborn screening for FXS.

Since the year 2000, FPG researchers have focused much of their research on children's development and the experience of families of children with FXS.

- Joanne Roberts and co-investigator David Zajac of the School of Dentistry are continuing their research into speech and language with three studies funded by the National Institute of Child Health and Human Development and the March of Dimes. One is studying the language development of three groups of preschool and early elementary-aged boys—one group with FXS, another with Down syndrome, and one with typical development. The other two projects are examining the hearing, speech, and language development of young boys with FXS compared to young boys without the disorder.
- Bailey and co-investigators Hatton, Stephen Hooper, Peter Ornstein, Jenni Schaaf, and Martie Skinner are midway through a project on Attention, Memory, and Executive Function in FXS. This project seeks to determine how children with FXS attend to important signals in their environment, remember key events and facts, and use this information to make decisions and solve problems.
- Bailey and colleagues were awarded a major center grant from the National Institute for Child Health and Human Development. Entitled Family Adaptation to Fragile X Syndrome, this project seeks to describe and explain the variation in the extent to which parents of children with FXS experience a positive quality of life; construct environments that promote cognitive, language, academic, and adaptive development in their children; and promote social-emotional development and address challenging behaviors in their children with FXS.

"The amazing thing about this research is the many directions it has led us over the years," says Bailey. "We have learned so much from the children, from families, and from other researchers that has caused us to keep asking new questions and seeking new answers. Our ultimate goal is to do research that helps to shape future policy decisions about early identification and early intervention that provides appropriate support for both children and families." |ed|

All in the Family



MUCH RESEARCH HAS BEEN CONDUCTED on the underlying biology of fragile X syndrome. Investigators are also well on their way to understanding and describing how FXS affects behavior and development. By comparison, little attention has been paid to the family consequences of fragile X. With the funding of FPG's Fragile X Research Center, that is beginning to change.

The Fragile X Research Center is a joint effort between The University of North Carolina at Chapel Hill and the University of Kansas. Its aim is to understand how families cope with FXS and what might be done to help support families. Eleven investigators from six disciplines—anthropology, developmental psychology, special education, speech and hearing sciences, quantitative psychology, and psychiatry—are collaborating in this effort.

... although a child's learning problems can be hard for families, it is the behavioral problems that are more likely related to serious family stress ...

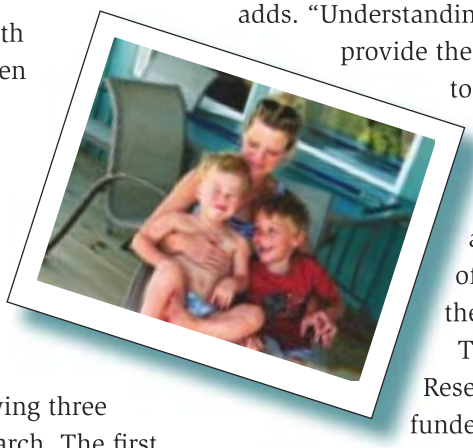
Why bother to study the family consequences of FXS? "In some respects, the challenges that families of children with FXS face are similar to those of children with other disabilities," says Don Bailey, FPG director and head of the Fragile X Research Center. "But in many ways, the family dimensions of FXS are unique. This is particularly true in the areas of children's learning, their behavior problems, and the inherited aspects of the disease."

Most children with FXS have significant developmental delays that impact school performance and independent functioning. Families must constantly work to organize their home and find specialized services to help their child learn language, cognitive, and academic skills.

Children with FXS may also exhibit a wide range of behavioral and emotional problems, including social anxiety, self-injury, autistic behavior, and other challenging behaviors. Parents must deal with the stress and burden of regulating emotion and problem behavior to help their child adapt to the larger world.

"We've found that although a child's learning problems can be hard for families, it is the behavioral problems that are more likely related to serious family stress," Bailey says. "Families of children with FXS may not be able to take their child out to a restaurant or the mall without that child acting out in some fashion. That can dramatically alter the family's life."

Bailey says FXS is also unique for families in that it is inherited. Usually parents give birth without realizing they have the gene that carries the disease. Individuals who carry the gene must decide when and how to tell other family members and encourage them to get genetic testing. Women with the gene must consider that they risk having additional children with FXS. Mothers of children with FXS may feel guilty and suffer from depression. Mothers who have the full mutation themselves may face challenges in caring for their children.



The Center is following three broad aims in its research. The first is to describe and explain the extent to which parents of children with FXS experience a positive quality of life, are hopeful for the future, and are protected from adverse mental health outcomes (such as anxiety or depression). The second is to describe and explain the extent to which parents are able to provide environments that promote their children's cognitive, language, academic, and adaptive development. The third aim is to describe and explain the extent to which parents are able to promote social-emotional development and deal with challenging behaviors.

Center investigators are collaborating on three projects involving a total of one hundred families. Data are being collected using a range of methods, including surveys, semi-structured interviews, ethnographic interviews, and direct observation.

"We aren't just looking at the negative consequences for families," Bailey says. "Many families have rallied together, finding a common purpose in helping their child cope with this disease. In fact, we have met many remarkable families who inspire all of us with the amazing things they have done."

"Ultimately, we are trying to understand why some families do well and others are more challenged," he adds. "Understanding this will help us provide the proper supports to families that need them. The bottom line is helping them achieve the quality of life for which they hope."

The Fragile X Research Center is funded by the National Institute of Child Health and Human Development. The Center was awarded $6 million for a five-year period beginning in July of 2003. |ed|

Acknowledgment: We are grateful to the Hamilton family for sharing photos from their family vacation album for this article.

Screening Newborns for Fragile X

KATHY MAY noticed there was a problem with her son, Sam, within weeks of his birth. He was not easy to console and always seemed to keep his hands clasped. At 6 weeks, she tried unsuccessfully to get Sam to look at her when she clapped her hands. At 15 months, Kathy's doctor expressed concern that Sam's language development was behind. She took Sam to an early intervention service provider who, suspecting he was autistic, recommended that he be tested at the local children's hospital. At 20 months, the diagnosis was confirmed—Sam had fragile X syndrome.

Compared to most families of children with FXS, the Mays were fortunate. Sam was diagnosed with FXS earlier than most children. According to a recent FPG study, the average boy with FXS is not diagnosed with FXS until nearly 3 years of age, and many are only identified much later. Had these children been identified earlier, they would have been immediately eligible for early intervention services under the Individuals with Disabilities Education Act.

FPG's study revealed another consequence of the late determination of FXS—more than half of the families surveyed had additional children without knowledge of the reproductive risk. Of the 191 children who were born to these families after the birth of their first child with FXS but before the FXS diagnosis, 109 (57%) also had FXS. Thus, a substantial proportion of the families ended up with two children with the disorder, imposing additional caregiving demands and stress.

"Our study showed that parents perceive the discovery of FXS as a process that takes too long," says Don Bailey, director of FPG. "One alternative is to establish a program of newborn screening."

With the discovery that FXS is a genetic disorder and the subsequent development of accurate DNA testing, it is now possible to genetically screen the population for FXS. Possible approaches include screening the following groups: women of childbearing age, pregnant women, newborns, and children at the first sign of developmental delay. FPG researchers have concluded that newborn screening provides distinct advantages over the other options. Whether that policy will become widespread remains to be seen.

In the US, states determine whether to screen newborns for genetic disorders, which disorders to screen for, how to finance screening, and what follow-up mechanisms are in place to provide for treatment and support. Currently, all states mandate screening of newborns for phenylketonuria (PKU) and congenital hypothyroidism, and all states but one screen for galactosemia and sickle cell disease. Beyond that, there is wide variability among the states as to what they screen for.

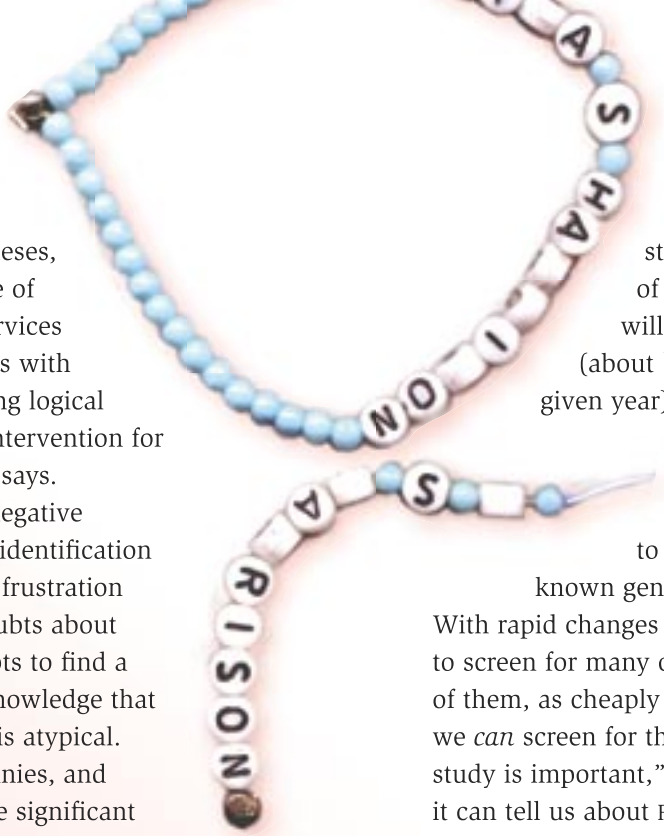
The question of which disorders to screen for remains the subject of considerable debate among policymakers, medical professionals, and the general public. Currently accepted guidelines rest on three fundamental criteria: 1) the disorder must be a significant public health problem that has major consequences for affected individuals, 2) an accurate, acceptable, and cost-effective procedure for screening the disorder must be available, and 3) a treatment must exist which, if provided early, can significantly alter the course of the disease or disorder.

Bailey contends that FXS clearly meets the first of these criteria and could soon meet the second and third. "A recent review estimates that at least 1 in 4000 males are born with the full-mutation FXS, and 1 in 270 females may be a carrier. FXS exerts a clear and devastating effect on affected individuals, especially males, resulting in moderate to severe mental retardation, high levels of anxiety and arousal, and frequent instances of autism and self-injurious behavior. On that basis, I would contend that FXS presents a significant public health problem."

With respect to the second criterion, Bailey finds that while DNA testing for FXS is virtually 100% accurate, it is expensive, averaging between $200–$300 per test. However, new technologies may soon lower costs considerably. "It is quite likely that the cost of screening could be reduced to $10–$20 per child in the next 2–3 years, and other methods could be even cheaper," he says.

Currently, there are no medical treatments available for FXS, thus, this disorder does not appear to meet the third criterion (a treatment is available) using traditional standards. However, nonmedical treatment by early intervention programs may improve development among individuals with FXS and thus could be considered to alter the course of the disorder. "Recent research suggests that FMRP, the protein disrupted by FXS, appears to be involved in synapse maturation and elimination," Bailey says. "If so, the most powerful interventions may be those that could be provided early in life during the period of rapid proliferation and pruning of neural connections.

... at least 1 in 4000 males are born with the full-mutation FXS, and 1 in 270 females may be a carrier.



"These facts and hypotheses, coupled with the existence of a nationwide system of services readily available for infants with disabilities, provide a strong logical basis in support of early intervention for children with FXS," Bailey says.

There are a number of negative consequences for delayed identification of FXS. Parents experience frustration with professionals and doubts about themselves in their attempts to find a professional who will acknowledge that their child's development is atypical. Families, insurance companies, and the health care system face significant financial costs for the repeated visits that often happen before a diagnosis is made. Children and families miss out on the access to early intervention services provided by the Individuals with Disabilities Education Act (IDEA). Finally, families do not have access to information about carrier status of parents and thus may make future reproductive decisions without knowledge of the risk that a child will have FXS.

Nonetheless, routine screening for FXS will not likely happen in the next 3–5 years since it does not fully meet the existing criteria for newborn screening, and also due to concerns about negative consequences for children (e.g., stigmatization), and controversies over issues related to reproductive decision-making and screening for carrier status.

To help make decisions about the desirability of newborn screening, Bailey has embarked on an ambitious project. With planning grants from the National Institute of Health, the Maternal and Child Health Bureau, the Centers for Disease Control and Prevention, and the National Fragile X Foundation, he and his colleagues are developing plans for a massive research project. The goal is to conduct a study to determine the costs and benefits of newborn screening for FXS. To do so will require screening 1,000,000 newborns (about $^1/_4$ of all children born in the US in a given year) and conducting follow-up monitoring and intervention studies with those who have FXS.

The Human Genome Project has led to a dramatic increase in the number of known genetic causes of developmental disability. With rapid changes in technology, soon it will be possible to screen for many of these conditions, perhaps hundreds of them, as cheaply and easily as one. But just because we *can* screen for them, does that mean we *should*? "This study is important," says Bailey, "not only because of what it can tell us about FXS, but also about newborn screening for other disorders. We're about to enter a new era of genetic information, and research is desperately needed so that when policy decisions are made, they can be informed by solid research." |ed|

The Behavioral Challenge

When 3-year-old Jason was presented with a new child care provider, he began to bite the back of his own hand. He would not look at the woman, despite his mother's attempts to introduce them. At one point, Jason swung at his mother, hitting her on the leg with his tiny fist.

"I don't know what to do with him when he gets like this," Jason's mother said. "It's making my life really difficult."

According to FPG research, behavior, rather than cognitive delays, may be the greatest concern of parents and teachers of children with fragile X syndrome. Not every child with FXS exhibits serious problems, but many do, and that has prompted the research community to examine how a child's genetics, brain, behavior, and environment act as a result of this single gene disorder.

Deborah Hatton, co-principal investigator of the Carolina Fragile X Project, has been conducting longitudinal studies of temperament and behavior of children with FXS since 1994. Temperament reflects biologically-based individual differences, while behavior reflects how a child acts out his or her feelings. "Temperament and behavior challenges of children with FXS range from shyness to aggression toward others or self, and are more common among boys with the condition than among girls," Hatton says.

Hatton's early studies, based on parent questionnaires completed annually over a 5–year time period, revealed that 3- to 8-year-old boys with FXS are significantly more active and less adaptable, approachable, persistent and intense than typically developing boys of the same age.

"Parents noticed the same behaviors in their boys that we observed during our study: high activity, attention problems, and withdrawing behaviors," Hatton says. "We also found considerable variability in the behavior of boys in the study."

More recently, Hatton's research on boys between the ages of 4 and 12 showed that nearly half (49%) scored within the borderline or clinically significant range on total behavior problems, while more than half (57%) scored in that range on the attention and thought problems. Boys with autistic behavior were more likely to have high scores on thought problems and social problems. Studies show that 25–47% of boys with FXS display autistic behavior.

In her research, Hatton looked for a correlation between maternal education and reported problem behavior. Interestingly, mothers with higher education reported more problem behavior, and thought and attention problems, than did their less educated peers. Boys who were taking medication had more total problem behavior, more internalizing problems, and more social problems. Attention seemed to be an area of particular concern.

Other research found that 73% of boys with FXS met diagnosed criteria for attention deficit hyperactivity disorder (ADHD) compared to 33% of their age and IQ matched peers. Boys with FXS are also likely to engage in self-injurious behavior at some point in their lives. Hatton's colleague Frank Symons found that hand biting is a common form of self-injury in children with FXS, and most likely to be evidenced when the child's preferred routines were disrupted, when requests were made of the child, or when the child was faced with a difficult task.

FPG's research suggests there is an underlying physiological basis for the emotional and self-regulation problems of children with FXS. FPG investigator Jane Roberts has examined the relationships between physiological arousal, as indexed by heart rate variability, and vagal tone (an index of neural control of the heart) in boys with FXS compared to a control group of typically developing boys. Results suggest that boys with FXS have higher heart rates, even when resting. Furthermore, they did not display expected patterns of heart activity in response to phases of increasing challenge. Other researchers have reported that children with FXS displayed elevated levels of electrodermal activity (perspiration measured on finger tips) during a variety of sensory tasks and that they may have higher levels of the stress hormone cortisol. All of this evidence suggests that there may be an underlying physiological basis for the behaviors observed in children with FXS.

FPG's recent work indicates that the temperament and behavior of children with FXS may change radically between infancy and 12 years of age. According to Hatton, infants appear to be *under-responsive* to sensory stimuli, while preschool aged children are *overly responsive*. "In our studies of preschool children, we were struck by their high activity, low attention and adaptability, impulsivity, hypersensitivity to sensory stimuli, and reluctance to approach new people or situations," she says. "In contrast, our clinical impressions of infants with FXS at 9, 12, and 18 months suggests a general hyposensitivity (lack of response) in longitudinal observational protocols of temperament, development, and sensory function."

Families face particular parenting challenges in dealing with children with FXS. Research suggests that parental characteristics and child temperament interact to influence family adaptation and child outcome over time. Positive outcomes occur when families adapt levels of environmental demand to meet the temperamental characteristics of the child, a concept known as "goodness-of-fit." Unresponsive or poor parenting can exacerbate challenging behaviors and the temperamental characteristics of irritability, distress, and negativity.

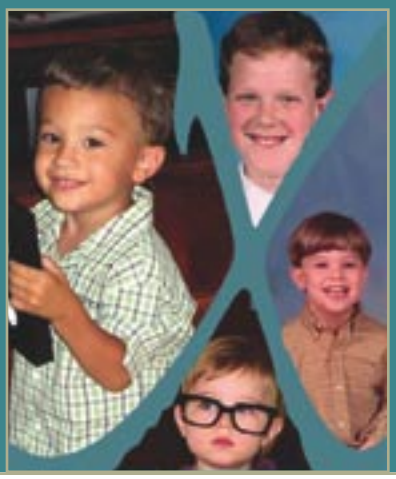
"A parent who is laid back and calm and who has little structure to daily routines may be well suited to a fussy and highly sensitive infant," Hatton explains. "A parent who is rigid, highly structured, and anxious may find such an infant more challenging."

Recently, FPG has been awarded a grant to study Family Adaptation to Temperament and Challenging Behavior in FXS. Hatton is principal investigator of this project and Steve Reznick is co-principal investigator. Jane Roberts is examining physiology in the children in the study to see how it relates to temperament and behavior.

Positive outcomes occur when families adapt levels of environmental demand to meet the temperamental characteristics of the child, a concept known as "goodness-of-fit."

"The behavior of children with fragile X syndrome is intriguing—particularly the changes that we have observed clinically over time," Hatton says. "The possibility of linking behavior to physiological characteristics, such as heart rate, and to genetic variables, is exciting. While learning more about the behavior of children with FXS, we will also be searching for strategies that families and teachers can use to promote positive behavior in these children. If behavioral problems are controlled, children will be more likely to experience success developmentally and academically, and parents and teachers will experience less stress. This research has the potential to improve the lives of children and families and the professionals who work with them." |ed|

Speech, Language, and FXS



Ask five-year-old Damon a question and his response is likely to be difficult to understand. When he meets new people, he becomes very quiet and avoids eye contact. Seven-year-old Tim answers questions in short sentences, but often is not on the topic being discussed. Tim and Damon's speech characteristics are typical of boys with fragile X syndrome (FXS)—girls who carry this genetic mutation are considerably less affected. By identifying these characteristics early in childhood, researchers at FPG hope to aid in the assessment of children with FXS and prescribe intervention strategies that will improve the speech and language of these children as they mature into adults.

Research into speech and language difficulties among young boys with FXS began at FPG in 2001 under the direction of Joanne Roberts, FPG senior scientist and professor of pediatrics and speech and hearing sciences at the University of North Carolina at Chapel Hill. Roberts and co-investigators David Zajac and Jack Roush are assisted by two post-doctoral fellows, Elizabeth Hennon and Beth Barnes, project coordinator Kathleen Anderson, and research staff Anne Edwards, Cheryl Malkin, Julia Jurgens, Lauren Moskowitz, and Siara Cowan.

Funded by the National Institute of Child Health and Human Development (NICHD) and the March of Dimes, the studies are examining the language of young boys with FXS in comparison to boys with Down syndrome and typically developing boys; and whether young boys with FXS have atypical hearing and auditory processing. The studies are also investigating the factors affecting poor speech intelligibility in conversational speech of young boys with FXS.

Photo: Don Trull, FPG

Assessing speech and language skills involves pointing to pictures with verbal directions.

Roberts says most males with FXS will show moderate-to-severe delays in communication skills. "Phonological difficulties are common, including consonant substitutions and omissions, which is characteristic of developmentally younger children," she says. "Conversational speech is often unintelligible, although single-word utterances often are understandable."

Other speech characteristics of some males with FXS include a rapid and fluctuating rate, and repetitive speech. Males may also have trouble repeating multisyllabic sequences and may demonstrate oral motor difficulties.

With respect to language, boys with FXS often have delays in grammatical and vocabulary development. Some boys may have atypical pragmatic language, including frequent repetition of words, sentences, and topics, poor topic maintenance in conversation, difficulty answering direct questions, and gaze aversion.

"The cause for these pragmatic impairments has often been attributed to hyperarousal, although word retrieval difficulties, syntactic difficulties, and executive function deficits also have been cited as possible causes," Roberts says.

Males with FXS often have prominent ears, although they do not appear to have hearing difficulties, Roberts says.

FPG's studies are among the first in the nation to examine the communication development of young children with FXS. Roberts hopes that her findings will aid both in the assessment of children with FXS and in developing appropriate intervention strategies. Because physical characteristics associated with FXS are not present in early childhood, language impairments may offer the first sign of the condition. Roberts hopes that her research will lead to increased awareness of these speech and language impairments and, thus, earlier detection.

The cause of an individual's speech and language difficulties and the particular domains affected will have important implications for intervention, although the specific contributing factors may be difficult to define. For example, if unintelligible speech is due to difficulties with sound patterns, then intervention should focus on particular sounds or suppression of specific phonological processes. However, if difficulties relate to such things as rate of speech, then slowing the rate of speech would be useful. For children whose communication difficulties are particularly evident in conversation, using scripts and routines in more structured environments and transitioning to more naturalistic environments with peers, teachers, and family members whenever possible would be more useful.

"Our ultimate goal is to identify the types of intervention that are most appropriate for children with FXS," Roberts says. "We want to know if there are specific strategies, different from those used with individuals with other forms of mental retardation, that we can recommend to help a child with FXS." |**ed**|

FPG's studies are among the first in the nation to examine the communication development of young children with FXS.

Finding Clues in Family Videos

Home videos are a great tool for preserving a family record, and especially for capturing those phases of early childhood that seem to pass so quickly. Now, FPG researchers are using retrospective analysis of home videos as a way of detecting previously unnoticed signs of fragile X syndrome among children aged 9 to 12 months.

Signs of FXS are often very subtle among infants and toddlers and may not become obvious for months or even years. Even if parents suspect something may be wrong with their child, physicians may downplay their fears, believing that the child is at the late end of normal development, and defer developmental evaluations until later in the second year of life. The result is that FXS is typically not diagnosed (in children without a family history of developmental delays) until children reach two years of age. Valuable time is lost during which intervention strategies could have been used. Clearly, there is a need for better methods of early detection. But since children with FXS are rarely identified during the first year of life, studying their earliest development has been virtually impossible.

Grace Baranek, FPG researcher and associate professor in UNC's Department of Allied Health Sciences, has used an innovative strategy—retrospective video analysis—to address this issue. This approach involves collecting home videos of children later diagnosed with developmental problems and analyzing them to see if unusual behaviors or delays can be detected. Raters are trained to view the videos and code a variety of social and sensory-motor behaviors in the context of natural daily activities. Her first study using this technique showed that by 9 to 12 months of age, the behaviors of children later diagnosed with autism were markedly different from those of children with delayed or typical development.

Baranek has just completed video analysis research on FXS conducted in a similar fashion to her autism research. She coded the same behavioral markers at 9 to 12 months, plus a few additional features such as repetitive movements that may reflect hyperarousal common to children with FXS. Findings so far confirm that even at this young age, children with FXS do exhibit markedly different behaviors than their normally developing peers, and can also be differentiated from children with autism.

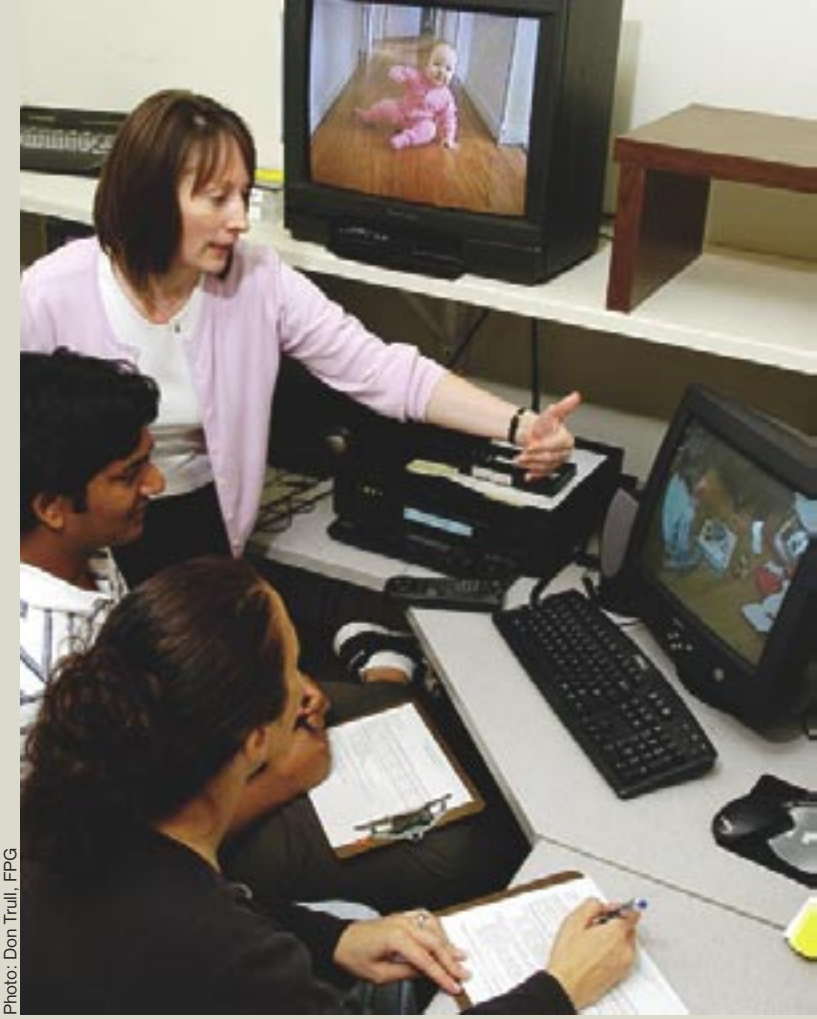


Photo: Don Trull, FPG

Grace Baranek (upper left) examines home videos of infants at her laboratory with team members Fabian David and Cassandra Danko.

"Infants with FXS were showing significant delays in the way they played with toys," Baranek says. "We also observed a high level of unusual postures, reflecting motor difficulties."

Baranek says her findings may not be practical yet. Although she has proved that early signs of developmental problems are evident during the first year of life, they may not be obvious to pediatricians or other professionals who don't have the advantage of watching, rewatching, and coding videotapes. However, these findings provide important clues about how FXS is expressed in infancy and hopefully will stimulate other research on early development.

Furthermore, "awareness of these early features of FXS may help a clinician to select evaluation methods and interventions that target the family's specific needs," Baranek says. "For example, activities designed to promote play skills, or environmental modifications that support engagement in daily activities would be recommended." ■

Fragile X Info Center

PARENTS AND PROFESSIONALS SEEKING MORE INFORMATION ON FRAGILE X will want to access FPG's new website for the Fragile X Information Center (www.fpg.unc.edu/~fxic). The website provides a wealth of information, including the effects of FXS on young children, summaries of research findings, family experiences and intervention strategies, services available for children with disabilities, and how to advocate for those services. Lists of publications, personnel, and resources related to FXS are also included.

Jane Roberts, manager of the information center, says FPG's website is geared toward those who want detailed and objective information on FXS and related disabilities with references to specific studies. The website content is written by a team of authors and reviewed by a panel of parents and professionals.

Parents who have previewed the site have given it positive reviews. "The fragile X website is an essential tool for educators and parents alike," says Nichole Tooz, parent and educator. "Its friendly format provides relevant information that is not overwhelming or foreign, even to those new to fragile X. It addresses the most pertinent topics with a simple, yet thorough style. I personally have used information from this website in public presentations and with my son's teachers and therapists. It has become an on-going resource, as the site is frequently updated with contributions from parents and professionals."

In the future, FPG plans to add content in the areas of temperament, academic achievement, educational transitions, educational services, toilet training, social skills, sibling issues, disability laws, alternative therapies, effects in permutation carriers, mental health issues, and communication skills.

FPG's Fragile X Information Center has been funded by a grant from the Ronald McDonald House Charities. Other funding sources include the Office of Special Education programs of the US Department of Education, the FRAXA Research Foundation, and the National Fragile X Foundation. Other websites available include those of the National Fragile X Foundation (www.fragilex.org) and the FRAXA Foundation (www.fraxa.org). |ed|

Jane Roberts, manager of the Fragile X Info Center, monitors the website.

Photo: John Cotter, FPG

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FPG Fragile X Websites

Carolina Fragile X Project
www.fpg.unc.edu/~fx/

Communication of Young Males with Fragile X Syndrome
www.fpg.unc.edu/~carolinacommunicationproject/

Fragile X Information Center
www.fpg.unc.edu/~fxic/

National Fragile X Awareness Day

US Senator John Edwards (NC-Dem) joined researchers at FPG to declare July 21, 2000, as National Fragile X Awareness Day. The goal of the declaration was to increase public awareness of the need for research, early diagnosis, and treatment of FXS, a disease that Edwards said "remains unknown to the vast majority of the public and even to many physicians."

Photo: Don Trull, FPG

Don Bailey (left) accepts the declaration from Senator John Edwards.

Referring to the announcement at FPG, Edwards said, "I am proud of the efforts that the Carolina Fragile X Project has undertaken. It is fitting that our commemoration is being held at one of the leading facilities in the nation for the treatment of those who inherited the syndrome."

In 1999, Edwards and Sen. Chuck Hagel of Nebraska introduced a bill that would dedicate funds to establish research centers on FXS. The bill was incorporated and passed into law as part of the Children's Health Act. The National Institutes of Health subsequently held a competition and funded three centers, including the one at FPG.

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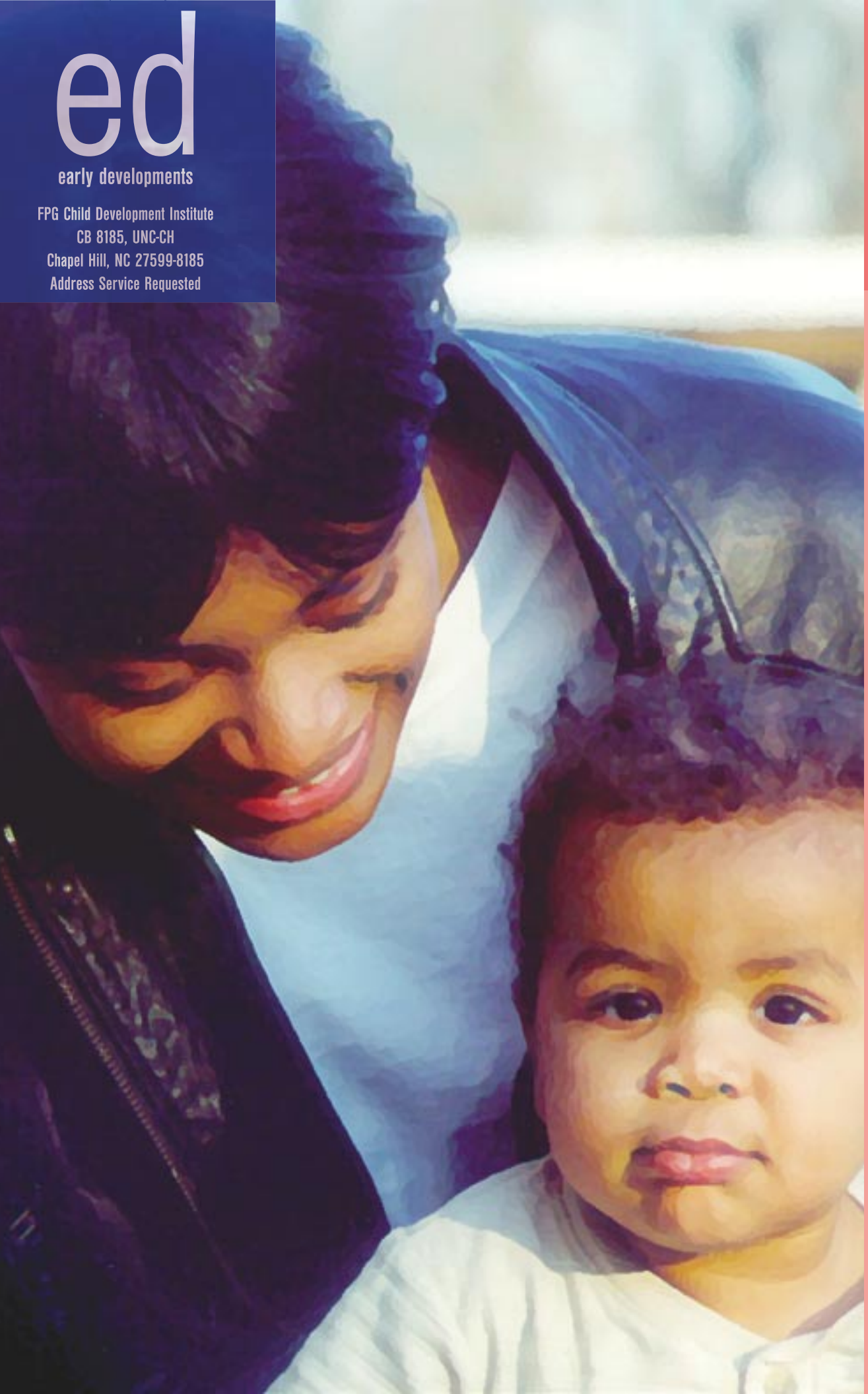

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