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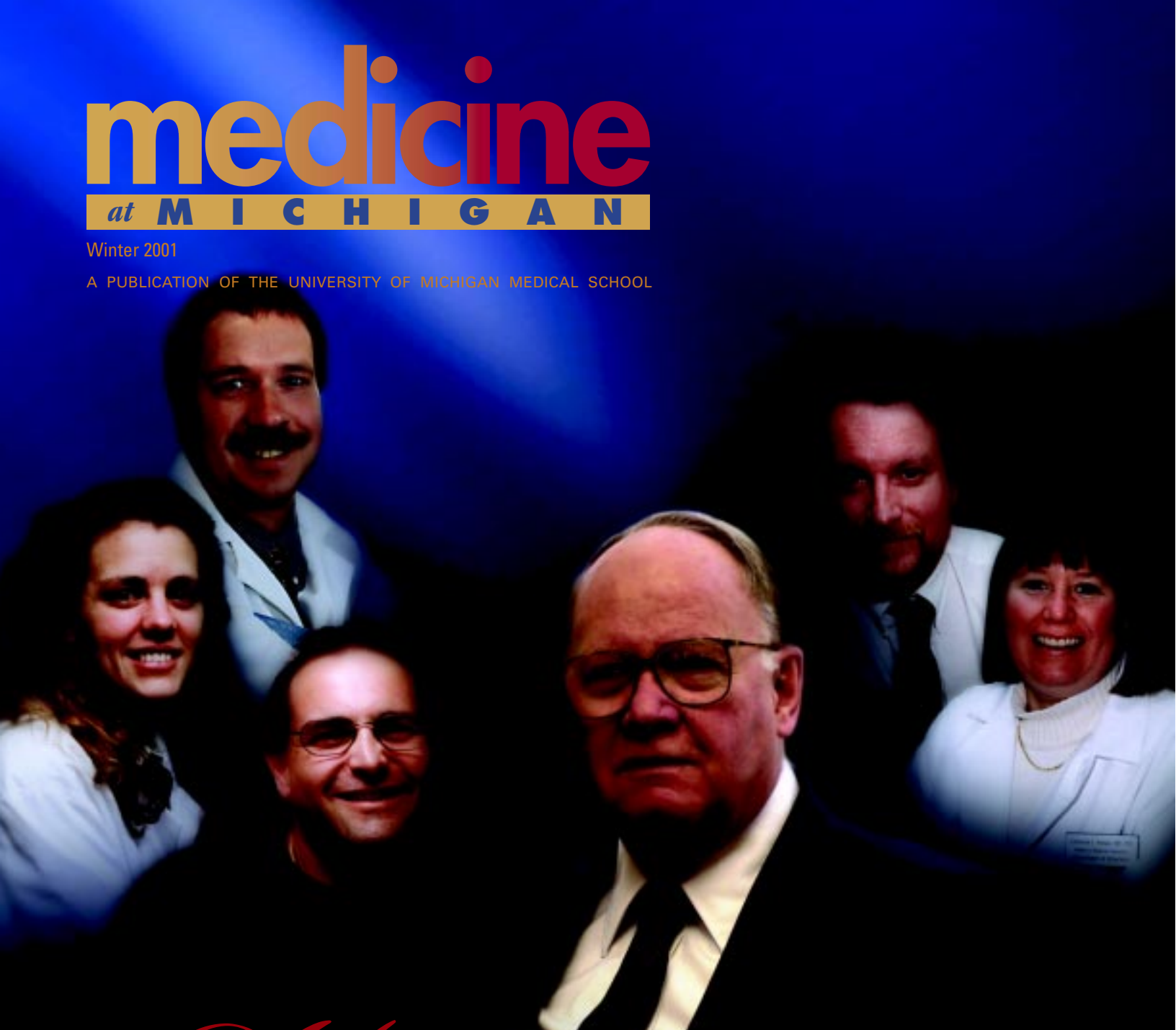

Healing and Discovering:

Michigan's Ambitious MSTP Grads Bridge the Clinic and the Laboratory

by John Barton

For Betsy Lozoff and her Research Team, 25 Years of Work Yield Important New Understandings in Child Development

Painstaking Research Reveals Long-Term Impact of Infant Iron Deficiency

After more than two decades of studying the complex relationships between nutrition and childhood development, a team of scientific investigators from the University of Michigan may finally be on the verge of learning how iron deficiency affects the human brain.

"It's exciting," says Betsy Lozoff, M.D., director of the U-M Center for Human Growth and Development. "We have finally gotten to the point where it is possible to ask brain-behavior questions more directly. It used to be that I could never say what's happening with the brain. We just had to put that aside.

"But now we can ask those questions, and it is very exciting to know we are getting closer to the answers. There is a handful of investigators who are looking at the basic science side of iron and the developing brain. A number of them are now starting to work together."

Iron is required for myelin (the fatty sheath surrounding axons, which connects nerve cells and speeds nerve conduction). Iron is also required for normal functioning of the neurotransmitter dopamine. The hippocampus (a structure in the medial-temporal lobe of the brain), which is involved in memory processes, also seems to be particularly vulnerable to early iron deficiency. "These new understandings of iron's role in the developing brain make it possible for the first time to design studies to test for these effects and to understand some of the findings in iron-deficient infants," Lozoff notes.

Betsy Lozoff, M.D., professor of pediatrics and communicable diseases and director of the Center for Human Growth and Development, photographed in her North Ingalls Building office. In the background is a life-size self-portrait, done as a kindergarten class project, of Lozoff's daughter, Claudia Brittenham, now 23 and a museum curatorial assistant in Washington, D.C.
Photo by D.C. Goings, BMC Media.

Dramatic new insights regarding iron's critical role in children's development were recently revealed to Lozoff and her research team in a long-term study of 191 lower middle-class children in Costa Rica that began in 1981 in conjunction with colleagues there at National Children's Hospital in San jose. The researchers discovered that infants with an iron deficiency at the beginning of the project exhibited learning and behavior problems as teenagers — even though their original iron-deficiency anemia was corrected to normal levels through treatment.

Lozoff says the results of the study suggest there are long-lasting developmental effects among children who are afflicted with iron deficiency as infants.

The Costa Rican project was recently given a prestigious boost when Lozoff won a National Institutes of Health MERIT (Method to Extend Research in Time) grant that will allow researchers to continue studying the children after the current set of evaluations is completed.

"It's great to be able to continue the research," Lozoff says. "When I first started the project, I really thought the children would improve with iron. The fact that they didn't has led to new ways of trying to understand what's going on.

"At 12 years of age more of them have repeated a grade and have trouble with arithmetic and writing. These are problems in doing basic fundamental things that are going to make life harder for them as they go along. And then there is more anxiety and depression. When I started the work, I would never have predicted that."

In addition to the Costa Rica study, Lozoff and her colleagues are involved with a similar study of more than 1,000 children in Chile that began in 1990. In a joint project with the University of Maryland, Lozoff is working with colleagues who recently launched a new study in India that involves both iron and zinc supplements.

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— Betsy Lozoff

"And," she continues, "we are seeking funding for a program project grant to work on iron deficiency in the developing human infant, the monkey infant and the developing rodent. That's a new phase of the project for us.

"I have to say that this research area is more intriguing now than at any time in the 25 years I've been working on it.There is still only a handful of people involved, but for a long stretch there was barely anybody. With the advancements in basic neuroscience and the ability to assess young children, I can't help but be excited about the direction our research is taking."

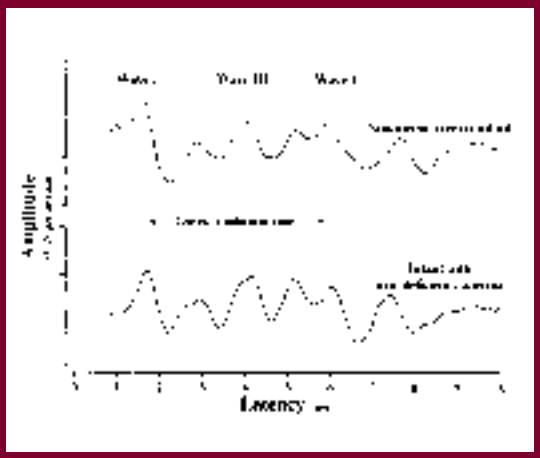
Lozoff was born in Milwaukee, grew up in Kansas and graduated from high school after her parents moved to the San Francisco Bay area. She earned degrees in social relations and computer applications at Radcliffe College in 1965, and wasn't immediately inspired to attend medical school.

Lozoff's research in Chile included a home-based intervention program to attempt to counteract the effects of early iron deficiency anemia. Here, one of the home visitors works with a mother and her baby.

Instead, she found herself involved with anthropology projects that included summer fieldwork with the Otavaleno Indians of Ecuador for Harvard University, a study of the Indians of Martinique, and a stint in India for a project dealing with childhood diarrhea.

"By that time, I was particularly interested in children's behavior and development, and I was interested in situations that were common from a world-wide perspective, not just in the United States. I went into medical school thinking that I wanted to be involved with developing-country issues in some way or another. I didn't know about pediatrics or behavior and development, but somehow I knew I was going to have something to do with developing countries."

She graduated from Case Western Reserve University in 1971, then spent three years at nearby Rainbow Babies and Childrens Hospital in Cleveland, Ohio, followed by nearly 20 years on the faculty of Case Western. Lozoff came to the Department of Pediatrics in the U-M Medical School in 1993, and was named, later that year, director of the U-M Center for Human Growth and Development, a multidisciplinary collaboration among biomedical, behavioral and social scientists to further the understanding of the complex processes by which human beings develop and grow. The



Naptime in Santiago — In the Sleep and Functional Neurobiology Laboratory at the Institute of Nutrition and Food Technology of the University of Chile, infant subjects 6-18 months of age come into the lab, accompanied by their mothers, for their afternoon naps. While napping, the babies are measured for a variety of things such as auditory responses, sleep-wake pattern, motor activity, heart rate and respiration to determine their neurophysiologic development as it relates to iron deficiency. Infant health is generally excellent in Chile, but dietary iron deficiency is common.

The accompanying example of auditory brainstem response in two infants six months of age illustrates what Lozoff and her colleagues have discovered. When the response of nonanemic control infants (top wave) and infants with iron deficiency (bottom wave) are compared, the response time of anemic infants is longer. While differences were slight at six months, they got bigger at 12 and 18 months — a clear indication of slower development in the auditory pathway of the nervous system in infants with iron-deficiency anemia.

"The central nervous system used to be mostly a big black box about the effects of early iron deficiency," says Lozoff. Today Lozoff and colleagues around the world, including Vietnam where she will be speaking at the International Nutritional Anemia Consultative Group Symposium in Hanoi in February, know that a variety of factors, ranging from poverty and family disadvantages to the infant's biochemistry and behavior, influence the development of a child's brain.

long-range goal of the Center is to optimize children's physical, cognitive and socioemotional development.

"It was in the 1970s," she recalls, "that I had the chance to hear Frank Oski, who was a wonderful hematologist, talk about his pilot study on iron deficiency. I listened to him and told myself, 'That's it!'"

It has been estimated that 20 to 25 percent of children throughout the world have anemia — a reduction in oxygen-carrying hemoglobin in the blood — due to severe iron deficiency. Although the problem is less common in this country, recent estimates indicate about five percent of poor African-American and 18 percent of Mexican-American infants and toddlers are iron deficient.

Dramatic new insights were recently revealed to Lozoff and her research team in a long-term study of 191 lower middle-class children in Costa Rica that began in 1981 in conjunction with colleagues there at National Children's Hospital in San Jose. The researchers discovered that infants with an iron deficiency at the beginning of the project exhibited learning and behavior problems as teen-agers — even though their original lack of iron was corrected to normal levels through treatment.

"In the U.S. we put iron in baby formula and cereals," Lozoff explains. "We've also put ascorbic acid in certain foods to help the body absorb iron, and we've encouraged breast feeding. All of those things have helped reduce iron deficiency in the United States.

"But there isn't a good way to prevent iron deficiency in most parts of the world. You've got areas where there are no safe water supplies and that means you're feeding babies unsafe formula. You also see more iron deficiency in European infants than we have in the United States because many European countries have not endorsed the same iron supplementation recommendations as we have in this country."

The Costa Rican government made a national recommendation to supplement children's diets with iron as a result of the findings of Lozoff and her research team.

Lozoff says that as she began to become interested in iron deficiency, she was attracted to Central and South America as potential areas for research.

"I was looking for places where there was not generalized malnutrition," she explains. "I wanted places where there weren't problems with abnormal hemoglobins on a genetic basis, where there wasn't malaria and where there weren't a lot of parasites.

"I wanted a place where I would be able to focus on iron deficiency. That's what took me into Central and South America. There are countries there where they have very good health and have wiped out generalized malnutrition. Lead and parasites are not major problems."

The Costa Rican government made a national recommendation to supplement children's diets with iron as a result of the findings of Lozoff and her research team.

"My colleagues in Chile," she says, "have also moved toward a national fortification program. The initiatives to try to reduce micronutrient deficiencies have taken off around the world. At the World Bank and UNICEF, it's not only iron. It's also zinc deficiency and vitamin A deficiency.

"It's gratifying to be able to look back and say there is certainly a very different level of attention being paid to these issues than when we started." m

The **interdisciplinary research team** participating in Betsy Lozoff's iron deficiency studies includes the following U-M scientists and faculty:

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