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**'Epigenetics' Means What We Eat, How We Live And Love, Alters How Our Genes Behave**

*Randy L. Jirtle, Ph.D. (Image courtesy of Duke University Medical Center)*

ScienceDaily (Oct. 26, 2005) — DURHAM, N.C. – A mother rat withholds nurturing licks from its pup and elicits a brain change that impairs the pup's response to stress as an adult, researchers in Canada found. A pregnant woman's dietary deficits increase her offspring's risk of diabetes, stroke and heart disease later in life, researchers in England have shown.

These startling scientific discoveries illuminate the emerging field of epigenetics, in which single nutrients, toxins, behaviors or environmental exposures of any sort can silence or activate a gene without altering its genetic code in any way.

Rather, the environmental exposure triggers a chemical change in the body or brain that mobilizes a group of molecules – called a methyl group. The methyl group attaches to the control segment of a gene and either silences – or alternately activates – the gene. Either way, the gene veers off its intended course of activity.

Duke scientists describe methylation as putting gum on a light switch. The switch isn't broken, but the gum blocks its function.

"We can no longer argue whether genes or environment has a greater impact on our health and development, because both are inextricably linked," said Randy Jirtle, Ph.D., a genetics researcher in Duke's Department of Radiation Oncology and initiator of the upcoming epigenetics conference. Co-initiator of the conference is Fred Tyson, Ph.D., at the National Institute of Environmental Health Sciences (NIEHS). "Each nutrient, each interaction, each experience can manifest itself through biochemical changes that ultimately dictate gene expression, whether at birth or 40 years down the road."

Such stealth changes often occur in embryonic or fetal development, but they set the stage for an adult's susceptibility to a host of diseases and behavioral responses, the data suggest. Moreover, epigenetic changes – so named because they sit on top of the gene and leave its sequence unchanged – can also be passed down from one generation to the next, said Jirtle.

The good news is that methylation is potentially reversible, he said. Unlike defective genes, which are damaged for life, methylated genes can be demethylated. And, methyl tags that are knocked off can be regained via nutrients, drugs, and enriching experiences.

The fact that gene behavior is far more malleable than once believed has critically shifted the scientific community's course in mining the human genome, said Jirtle. No longer are mutant genes sought as the sole cause of disease. The dramatic rise in obesity, heart disease, diabetes and other conditions of prosperous nations are increasingly pegged as epigenetic in nature, and may well claim their origins in faulty embryonic development, he said.

In one example, Jirtle showed that four common nutritional supplements – B12, folic acid, choline and betaine from sugar beets – fed to pregnant mice actually altered the coat colors of their offspring. One or several of the nutrients methlyated the mouse agouti gene and gave rise to mice with brown coats instead of yellow coats. More importantly, he said, the supplements lowered the offspring's adult susceptibility to obesity, diabetes and cancer as compared to the unsupplemented offspring.

"Nutrition isn't a fleeting affair," said Jirtle. "We are, quite literally, what we eat as well as what our parents and even grandparents ate.

"In countries like India and China, undernutrition in one generation is followed by fat-laden fast foods the next," said Jirtle. "Children are set up in utero to experience an environment of low nutrition and find themselves in the land of plenty. The epigenetic software is programmed for one scenario but encounters another, often with disastrous results."

Seismic shifts in food sources, geographic locations, chemical exposures and even weather patterns can alter gene expression through epigenetic changes, he said.

In Finland, researchers have linked an infant's low birth weight to the adult prevalence of coronary heart disease, diabetes, hypertension, stroke and even osteoporosis. David Barker's longitudinal studies have shown that low-weight newborns are biologically different for life than their bulkier counterparts. Smaller infants have fewer kidney nephrons, altered metabolism, and are more insulin resistant, said Barker, M.D., Ph.D., professor of medicine at Oregon Health and Sciences University. These deficits reflect a fetus' response to being undernourished, and they wire their genes to respond differently to the environment that follows outside the womb.

"The notion that heart disease is solely about middle-aged men's behavior is obsolete," said Barker, one of 70 speakers presenting data at the upcoming conference. "A huge body of evidence now supports the notion that these diseases are linked to poor fetal growth followed by adequate or even an excess of food in childhood. While we are not doomed by our prenatal and early nutritional exposures, they do make us more vulnerable to disease," said Barker, whose latest results will be published in the October 27, 2005, issue of the New England Journal of Medicine.

Nutrition is only one player in the epigenetic repertoire. Behaviors have a direct impact on brain wiring, said Moshe Szyf, Ph.D., Professor of Pharmacology and Therapeutics at McGill University in Montreal and a presenter at the conference. Maternal care, for example, has long been known to affect behavioral outcomes of children, as exemplified by orphans who grow up neglected or impoverished. But Szyf and his collaborator Michael Meaney at McGill University have linked maternal grooming behaviors in rats to a specific brain change in the glucocorticoid receptor, which controls the level of stress hormone released by the adrenal glands. Rats that were not properly licked -- a rodent's form of nurturing -- produce more stress hormones as adults. Syzf identified the mechanism behind this effect as a loss of methylation in the part of the glucocorticoid receptor gene that controls its expression.

"We're showing that it's the maternal behavior that counts, not just the genetic baggage," he said. "Behavior can clearly affect the chemistry of DNA."

Szyf's team was able to remethylate the glucocorticoid receptor gene by injecting an essential amino acid, methionone, into the brains of well nurtured rats. The scientists successfully turned the good stress responders into less healthy stress responders, and vice versa by injecting a different compound into the brains of poor responders.

The reversible nature of epigenetic changes has its down sides, as well. Exposures to pesticides, toxins and synthetic compounds can methylate genes in adulthood and give rise to a host of diseases – such as cancer and asthma -- whose prevalence has soared in recent decades, said H. Kim Lyerly, M.D., director of the Duke Comprehensive Cancer Center. Pesticides encountered in utero might be dormant in the fetus, only to cause cancer ten, 20 or 50 years later, he said.

Even the lowest detectable limits of a chemical can have dire effects on a living organism, added William Schlesinger, Ph.D., Dean of the Nicholas School of the Environment and Earth Sciences at Duke. Atrizine is a prime example. Less than one part per billion of this widely used corn herbicide de-masculinizes developing frogs or causes dual male-female genitalia. Yet often the Environmental Protection Agency's instrumentation doesn't record such minute levels of chemical exposure, he said.

"If Atrizine is having this effect in animals, we question its effects on humans," said Schlesinger. "Are the current standards of exposure high enough to protect the organisms exposed to select chemicals? Our role as environmental scientists is to assess the potential impact of each compound on native organisms and develop models that physician scientists can apply to humans."

At the NIEHS, scientists have embraced epigenetics as a major frontier in their scientific exploration of the environment, said David Schwartz, Ph.D., the institute's director.

"Epigenetics represents a huge opportunity to study an alternative pathway that explains why individuals respond differently to environmental cues," said Schwartz. "This field provides the missing link between the environment and the development of diseases that goes beyond many of the subtle changes in DNA that explain only a fraction of the diseases humans develop."