

Nature Report: Genetically Altered Mosquitoes Impair Malaria Transmission

Malaria kills about 2 million people annually, mostly African children under the age of 5. While conventional approaches to controlling the disease have been ineffective, CWRU School of Medicine researchers have developed a genetically altered mosquito that one day could be added to the arsenal in the war against the disease.

The May 23 issue of the journal *Nature* features a paper by a team of CWRU Department of Genetics scientists, led by Professor of

Genetics Marcelo Jacobs-Lorena, Ph.D., that reports about transgenic – or genetically altered – mosquitoes that prevent the passage of malaria from one individual to the next. The paper is titled “Transgenic Anopheline Mosquitoes Impaired in Transmission of a Malaria Parasite.”

There are thousands of types of mosquitoes, but very few carry the malaria parasite, *continued on page 2*



Marcelo Jacobs-Lorena, Ph.D.



Cleveland Clinic College of Medicine of Case Western Reserve University Announced

CWRU and the Cleveland Clinic Foundation announced May 14 a landmark agreement to form a new medical education and research program. The new

Cleveland Clinic College of Medicine of Case Western Reserve University will enroll its first entering class in 2004 and will prepare physician-investigators and scientists dedicated to advancing

biomedical research and practice. The college will admit an entering class of

up to 40 students from a national and international pool of applicants, and will not duplicate the existing M.D. program of the CWRU School of Medicine.

This agreement creates the infrastructure for physicians and scientists at CWRU and CCF to work together to develop a pioneering curriculum that prepares high-powered students for

careers as clinical investigators and physician-scientists.

Less than 2 percent of physicians in the United States are prepared to perform clinical research, according to an article in the *New England Journal of Medicine* (Ley T. J., Rosenberg L. E., Jan 31, 2002).

“This joint venture brings together one of the nation’s leading hospitals with the research university that 50 years ago forged the curriculum that is today the world standard for medical education,” said James W. Wagner, interim president of CWRU. “We are delighted to have achieved this new partnership, which will mean so much for this community and the nation in

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“This historic partnership will have a significant impact on medicine, research and education. Together, The Cleveland Clinic and Case Western Reserve University will raise the visibility and scale of these activities.”
-Floyd D. Loop, M.D.

At 2 Years, Cocaine Babies Suffer Cognitive Development Effects

Researchers Also Find Tobacco Has Negative Effects On Motor Development

Scientists know the effects of cocaine on the adult brain and cardiovascular systems. Now there is a growing body of research documenting the effects of prenatal cocaine exposure on infants, which is raising public health concerns about the long-term cognitive and developmental outcomes for these children.

A study published by the CWRU School of Medicine, MetroHealth Medical Center, and University Hospitals of Cleveland researchers in the April 17 issue of the *Journal of the American Medical Association*, "Cognitive and Motor Outcomes of Cocaine-Exposed Infants," looks at how

This study is the first to document the negative effects on cognitive development in a scientifically rigorous manner.

prenatal cocaine exposure affects child developmental outcomes. The study was conducted by Lynn T. Singer, Ph.D., Robert Arendt, Ph.D., Sonia Minnes, Ph.D., Ann Salvator, M.S., and H. Lester Kirchner, Ph.D., all of the CWRU School of Medicine, Department of Pediatrics; Kathleen Farkas, Ph.D.,

CWRU Mandel School of Applied Social Sciences; and Robert Kliegman, M.D., Medical College of Wisconsin, Milwaukee, Wis.

CWRU researchers followed 415 cocaine-exposed infants born at MetroHealth Medical Center in Cleveland to determine how prenatal cocaine exposure affects child developmental outcomes. They were compared to non-exposed infants on cognitive and motor development until age 2. What they found, according to Singer, was that prenatal cocaine exposure does affect a child's cognitive development, but not motor development. However, tobacco exposure had negative effects on motor development.

There have been previous studies in this area, but their findings are contra-

dictory. While some studies have found generalized developmental delays in cocaine-exposed infants, other studies have not demonstrated differences or found only subtle cognitive effects. Those studies, CWRU researchers say, are flawed for several reasons, including high dropout rates, small sample sizes, ignored negative environmental factors, lack of biologic measures revealing exposure severity, incorrect sample populations and outdated development scales.

This study is the first to document the negative effects on cognitive development in a scientifically rigorous manner. Singer, professor of pediatrics and psychiatry, and interim provost and CWRU vice president, said the study was unique because it had measures of both the mothers' self-report of their drug use prenatally, as well as infant meconium, which provided a physical measure of the amount of drug exposure. The study also controlled for many more factors in the environment than prior studies, including stimulation levels in the home, mothers' vocabulary and mental health status and characteristics of foster caregivers. The team used newly standardized versions of the major infancy development tests. And they were able to maintain more than 90 percent of the participants during the study, and at two years, 100 percent of the sample had at least one follow-up visit.

Mothers and infants were recruited between 1994 and 1996 from a high-risk population screened for drug use. Urine samples were obtained immediately before or after labor and delivery, and analyzed for the presence of cocaine metabolites, cannabinoids, opiates, PCP and amphetamines. Urine tests for drugs were performed by the hospital on all women who received no prenatal care, appeared to be intoxi-

cated or taking drugs, had a history with the Department of Human Services in previous pregnancies, or self-admitted or appeared to be high risk for drug use after interview by hospital staff. Meconium was collected in the hospital from infants' diapers and screened for drugs.

Researchers initially identified 647 mothers and infants for the study, excluding 232 for various reasons. Infants were seen at the research laboratory at 6.5, 12 and 24 months and administered the widely used Bayley Mental and Motor Scales of Infant Development (BSID II) standardized assessments. The scales assigned infants a standard score reflecting memory, language and problem-solving abilities, as well as measurements of gross and fine motor control and coordination.

Researchers found that for all trimesters, cocaine-using women used alcohol, marijuana and tobacco more frequently and in higher amounts than non-users. Cocaine-using women were found to be older, had more children and were less likely to have had prenatal care. They also were less likely to be married; had lower vocabulary, block design- and picture-completion scores; and higher psychological distress scores.

The study also found that cocaine-exposed infants had lower gestational age, birthweight, head circumference and length than non-exposed infants. There were more preterm, low birthweight and small-for-gestational-age infants in the exposed group.

Researchers also found that the rate of mental retardation in cocaine-exposed children at age 2 (13.7 percent v. 7.1 percent in the non-exposed group) is 4.89 times higher than expected in the general population. And the percentage of children with mild delays (37.6 percent in the exposed group v. 20.9 percent in the non-exposed



Colitis Study Calls for Different Therapies

group) requiring intervention was almost double the rate of the high-risk, non-cocaine group. Researchers speculate it is likely that these children will continue to have learning problems and an increased need for special educational services at school age.

Another important note from the study is that cognitive delays could not be attributed to exposure to other drugs or a large number of other variables, including inadequate prenatal care, caregiver or birth mother intelligence, psychological distress, postnatal drug exposure or a low-quality home environment.

Singer said the team is concerned that the study data will be misinterpreted and used to punish women or to remove children from their families.

“Prosecution of women will not address the problems of alcohol and drug abuse,” Singer said. “In fact, our study indicates that tobacco exposure also has significant negative effects on infant development. Our findings also indicate that the quality of stimulation and environmental intervention can have a large effect on children’s mental development independent of cocaine or other drug exposure.”

About one million children have been born after fetal cocaine exposure since the mid-1980s, when the “crack epidemic” emerged with the marketing of a cheap, potent, easily available, smokeable form of cocaine.

“We hope that this study will convince public policy and health providers that there needs to be a major emphasis on the provision of drug treatment, including smoking cessation, and mental health services for women – especially poor women who are currently underserved,” Singer said.

This study was supported by grants from the National Institute on Drug Abuse and the General Clinical Research Center.

Researchers at the CWRU School of Medicine and University Hospitals of Cleveland have discovered that colitis patients’ conditions may fall into two distinct phases of the disease, and should not be treated with a “shotgun approach” to therapy. Instead, this study clearly suggests that doctors need to pinpoint the progress of colitis, a form of Inflammatory Bowel Disease (IBD), from the early to the late phases, and to then treat individual patients accordingly.

This study may advance scientists’ understanding of IBD by introducing the concept of two phases, and emphasizing the importance of preventing the disease from reaching a chronic condition. Both phases produce small ulcers, tissue damage, and abscesses on the inner lining of the colon, yet the immunological mediators critical to the disease process are different between the phases. Chronic inflammation increases the patient’s risk of colon cancer.

Researchers hope that, based on their findings, doctors will learn to treat IBD patients at a younger age and more appropriately.

“The disease is most prevalent in industrialized nations, where it has gained the strongest foothold. If we broaden our therapeutic approaches to immunological targets in IBD, at least we should be able to treat teenagers so effectively that the inflammation may never enter the adult population,” Alan D. Levine, Ph.D., associate professor of medicine, gastroenterology division, pathology, and pharmacology and a member of the CWRU/UHC comprehensive cancer center.

Researchers studied IBD by using mice that lack a particular cytokine, known as Interleukin-10, and therefore cannot suppress the activity of inflammatory cells. In essence, these Interleukin-10 deficient mice develop similar health problems as humans with colitis.

Researchers suspect that the cause of colitis is tied to an immune system defect that “kicks in” when a bacterial antigen enters the intestine. The defective immune system produces an inflammation that damages healthy tissues, resulting in abdominal cramps and bloody diarrhea.

“By being aggressive and attacking the early phase of the disease, as we do in children for example, it is possible to disrupt the underlying cause of the disease,” Levine said. “Think of it this way... when you treat symptoms instead of the biological problem, the patient may feel better while the underlying metabolic problem continues to undermine the patient’s immune system.”

The researchers contend that the traditional approach to colitis—using the same kind of therapeutic modalities for all patients regardless of disease progression—can be improved. “Eventually, secondary problems develop and doctors are hard-pressed to treat them all effectively,” Levine continued. “If, instead, we fix the first problem at a young age, then there will be no secondary problems.”

The study, reported in the January 2002 issue of *Gastroenterology*, was supported by the Crohn’s and Colitis Foundation of America, National Institutes of Health, and the Research Institute of UHC.

– Eric Sandstrom, UHC Corporate Communications