Center for Environmental Health *in Northern Manhattan*

MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

Issue #1

Newsletter produced by Columbia University's NIEHS funded Center for Environmental Health in Northern Manhattan

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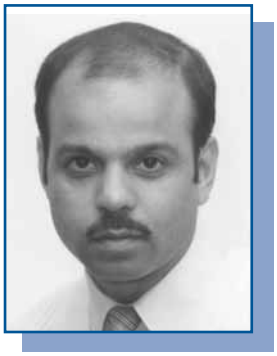
Lead Linked to Essential Tremor

Essential tremor (ET), which affects as many as one in five people over age 65, is a progressive, disabling, and incurable neurological disease that results from damage to the cerebellum and its connections in the brain. ET is characterized by an action tremor of the hands and/or head and develops in many people in middle and older age. Patients may also show signs of more widespread cerebella involvement such as ataxia, cognitive deficits, and other abnormalities of the brain and nervous system. There is no cure for ET and few attempts have been made to halt its progression with neuroprotective therapy. Medical treatment aims to lessen the severity of the tremor, which is the major symptom, and medications are ineffective in approximately 50% of patients.

Dr. Elan D. Louis, *Associate Professor of Neurology and co-Director of the Center's Neurotoxicology/ Neurological Disorder research core,* and his colleagues carried out a study to determine if environmental exposure to lead is associated with ET. Patients were matched to controls on age, sex and ethnicity. Blood lead concentrations were analyzed in the NIEHS Center's Trace Metals Facility Core laboratory. Lifetime occupational history was used to also obtain information about exposures. Blood lead concentrations were higher in essential tremor patients than those without the disorder ever after adjusting for age, sex, smoking, diet, and occupational history. "Determining whether this association is due to increased exposure to lead or a difference in how ET patients' bodies metabolize lead requires further investigation," Dr. Louis says. The paper was published in a recent issue of *Environmental Health Perspectives.*

Researchers Find Oxygen Radicals Needed for Carcinogenesis



For years, epidemiologic studies have found strong associations between estrogens and breast, endometrial, and uterine cancers. For example, women who begin menstruating early, or who start menopause late, produce more estrogen over their lifetimes and have a higher risk of breast cancer. While estrogen has long been a suspected carcinogen, in December 2003, the National Institute of Environmental Health Sciences (NIEHS) added estrogen to its list of known cancer-causing agents. Despite estrogen's new status on the NIEHS listing of known carcinogens, not all forms of the hormone are carcinogenic. And that has raised the question of the how cancer-causing estrogens stimulate tumor development.

A study by Hari Bhat, an Assistant Professor in the Department of Environmental Health Sciences and his research team, showed that more than one sequence of steps is necessary before estrogen can cause cancer. In addition to a hormone receptor-mediated process, a second process is also required. Their results suggest that blocking the second pathway could prevent estrogen-induced cancers. But the researchers also found that even non-carcinogenic estrogens can cause cancer under certain conditions. This research was published in the Proceedings of the National Academy of Sciences.

To see if cancer-causing estrogens need oxygen radicals to produce tumors, Dr. Bhat implanted estrogen pellets in hamsters that are susceptible to estrogen-induced kidney cancer. As expected, nearly all the hamsters with the pellets developed cancer within seven months. It appears that estrogen promoted an increase of cells but also produced oxygen radicals when metabolized by the cell. As expected, none of the hamsters developed kidney cancer when a non-carcinogenic form of estrogen was implanted and no oxygen radicals were produced. When a non-estrogen molecule that generates oxygen radicals was combined with the non-carcinogenic estrogen, 30 percent of the hamsters developed kidney cancer within seven months.

Dr. Bhat's results clearly suggest, "estrogen receptor activity and oxidative stress are both needed for estrogen to produce cancer." More research is needed as to how estrogen increases the risk of cancer that will hopefully lead to the development of new anti-oxidant therapies to treat or prevent cancer.

COLUMBIA AND HARVARD UNIVERSITY RESEARCHERS CONDUCT STUDY ON TOXIC EXPOSURES IN URBAN ENVIRONMENTS

Steel dust generated by New York City's subway system affects the amount of iron, manganese and chromium that commuters breathe

Columbia University researchers have found that steel dust generated in the New York City subway significantly increases the total amount of airborne iron (Fe), manganese (Mn) and chromium (Cr) that riders breathe. The airborne levels of these metals associated with fine particulate matter in the subway environment were observed to be more than 100 times greater than levels observed in home indoor or outdoor settings in New York City. Their research findings are scheduled to appear in the January 15th issue of Environmental Science & Technology, a peer-reviewed journal of the American Chemical Society, the world's largest scientific society.

The results are part of the TEACH (Toxic Exposure Assessment, a Columbia and Harvard) study to understand pathways and levels of personal exposures to potentially toxic air pollutants in inner city areas of New York City and Los Angeles. This research was funded by the Mickey Leland National Urban Air Toxics Research Center and the NIEHS Center for Environmental Health in Northern Manhattan, at Columbia University's Mailman School of Public Health.

"This study in no way suggests that people should avoid riding the subway. There are no known health effects at the levels that we observed in the NYC subway system. Furthermore, reducing subway ridership would just increase surface traffic emissions," says Dr. Chillrud, a geochemist with the Lamont-Doherty Earth Observatory and co-director of the Exposure Assessment Facilities Core of the NIEHS Center for Environmental Health in Northern Manhattan.

For the NYC field research, a total of forty-one students attending the A. Philip Randolph Academy, a public high school in Harlem with enrollment from four of the five NYC boroughs, participated during the winter and summer of 1999. Air samples were collected over 48 hour time periods from rooftop sites in Harlem and Rockland County, New York and from inside and outside of each student's home. At the same time, students carried a specially designed backpack with a battery-operated pump to collect what were called personal samples as they went about their normal daily routines.

A Profile of the Exposure Assessment Facility Core

Directors: Patrick Kinney, Sc.D. and Steve Chillrud, Ph.D.

The overall goals of the Exposure Assessment Facility Core are to design exposure assessments in support of research by Center investigators and to provide sampling and/or analytical capabilities for a wide range of environmental samples. This Core facility combines study design, methods development, environmental sampling, and analytical capabilities at the Mailman School of Public Health (MSPH) and the Lamont Doherty Earth Observatory (LDEO). It currently has the ability to collect integrated personal and area air samples for analysis of total suspended particulates (TSP), PM10, PM2.5, black carbon, polycyclic aromatic hydrocarbons, airborne allergens, and a long list of particle-associated metals and elements. Capabilities for real-time area sampling exist for particle mass using beta attenuation; particle counts between 0.3 and 5-µm aerodynamic diameter, and for black carbon. The Core also analyzes several indoor allergens (including those from house dust mites, cockroaches, mice, cats, and some fungi) collected in house dust. Additional analytical facilities are available at LDEO and include the ability to measure stable isotopes. The Core can also measure indoor air ventilation rates or water movement by following a tracer, sulfur hexafluoride (SF6).

Additional facilities include a white light reflectometer for making black carbon measurements on filters, sample preparation laboratories including clean rooms and laminar flow hoods, and a wide array of instruments such as Scanning Electron Microscopes. Furthermore, the LDEO lab has supported the design and development of air monitoring systems, ranging from multi-pump boxes for measuring multiple air contaminants at fixed indoor and outdoor locations to a range of hi-tech personal air monitoring packs that are worn by study participants.

A number of projects are currently underway. Air measurements and analyses for PM2.5, black carbon, NO2, and airborne allergens are being carried out in Dr. Perera's Columbia Children's Center cohort study. Measurements are also being made for Dr. Kinney's study, "Traffic-related particle exposures in NYC adolescents," to investigate exposures to diesel exhaust and associated respiratory health impacts among high school students in the South Bronx and northern Manhattan. The Core provided assistance in developing dust sampling protocols, questionnaires, and electronic databases for study participants and laboratory analysis information for Dr. Chew's study of allergic sensitization among Puerto Rican children. Drs. Simpson and Chillrud together with their colleague Dr. Stute have been using SF6 it as a purposeful tracer for understanding groundwater flow in complex aquifers that are being studied to understand arsenic mobilization and transport processes. Center-funded pilot projects that are being supported include personal

2003-2004 Pilot Projects Awarded

In July 2003, the Center awarded five pilot projects to Columbia University investigators through the Center's Pilot Grant Program under the leadership of Deputy Director, Dr. Paul Brandt-Rauf. The goals of the pilot projects are to enhance and promote research and training in environmental health sciences. A broad range of research activities are eligible for funding consideration, ranging from studies of basic molecular mechanisms of disease to epidemiological research. Priority is given to research proposals that are relevant, innovative and experimentally sound. Linked proposals or proposals demonstrating collaborative efforts are given preference. The following pilot projects were awarded in 2003:

Air Concentrations of Heavy Metals in NYC Subway and Their Potential Health Impact.

Steven N. Chillrud, Ph.D., Lamont-Doherty Earth Observatory; and Paul W. Brandt-Rauf, M.D., Dr.P.H., Environmental Health Sciences ($25,000)

This pilot project will test the hypothesis that train operation in the subway system is responsible for the elevated air concentrations of Mn, Fe, and Cr in the NYC subway. Additionally, the researchers will compare the concentrations of these metals in urine and blood samples of tested subjects with levels in samples collected from subjects who live nearby but infrequently ride the subway. They will investigate the correlation between metal exposure and subtle changes of these metals and/or their biological indicators in human body fluids. The ultimate goal of this study is to evaluate air quality in the NYC subway system and assess the potential for human exposure consequences through investigation of useful biological indicators (i.e., biomarkers) for metal exposure.

Hus1: A Suppressor of Mutagenesis and Carcinogenesis?

Haiying Hang, Ph.D., Center for Radiation Research ($25,000)

Most known cell cycle checkpoint genes are suppressors of mutagenesis and tumorigenesis. Hus1, Rad1 and Rad9 are a novel group of cell cycle checkpoint genes, and their protein products form a ring-shape trimer complex. The complex can be loaded onto and slide along double strand DNA. It is not known if the proteins play roles in suppressing mutation and tumor development. In this pilot study, Dr. Hang is challenging Hus1-null cells with two environmental genotoxins benzo[a]pyrene and ultraviolet (UV) light, and examining if Hus1-null cells have higher mutation and transformation rates than wild type cells. This is the first step in determining if this gene is a DNA mutation/tumor suppressor.

Th2 Differentiation and Gene Expression Following Environmental Diesel Exposure.

Rachel Miller, M.D., Department of Medicine/Pulmonary ($25,000)

Living near areas with increased motorized traffic volume, or where diesel exhaust emissions are known to be elevated, is associated with decreased pulmonary function among inner-city children with asthma. However, the mechanisms by which diesel exposure induces airway inflammation and triggers asthma are not entirely clear. Nonetheless, multiple studies have suggested that diesel may augment immune pathways associated with the induction of allergy, such as the upregulation of the T cell interleukin 4 promoter. Another unanswered research question concerns which genes are differentially expressed following exposure to diesel. This question is important because it may help discern the critical mechanisms or immune pathways.

Dr. Miller hypothesizes that diesel preferentially upregulates the differentiation of naïve T helper cells and/or dendritic immune cells to a more allergic phenotype (e.g. production of cytokines such as IL-4 important to allergy). She also hypothesizes that diesel exposure alters gene expression in human T cells or dendritic cells, including genes important to immune pathways that ultimately may contribute to asthma. The second hypothesis will be addressed by using microarray technology that can assess the expression of thousands of genes simultaneously. The hope is that this work will enable a better understanding of the mechanisms and genes involved in diesel-induced inflammation critical to asthma, and ultimately to a better understanding of potential modes of intervention.

Exposure to Air Pollution from Biomass Fuel Combustion Among Women in a Rural Bangladesh Population.

Habibul Ahsan, M.D., Faruque Parvez, Patrick Kinney, Sc.D., Regina M. Santella, Ph.D., Depts. of Epidemiology and Environmental Health Sciences, MSPH ($25,000)

About 3 billion people worldwide use biomass fuel (wood, charcoal, agricultural residues and dung, etc.) for cooking and household energy. Due to incomplete combustion, biomass fuel produces a number of toxic and carcinogenic elements and particulate matter that have been associated with many adverse health effects including acute respiratory illnesses (ARI), chronic obstructive pulmonary diseases (COPD), tuberculosis and asthma, especially among women and children. Pollutants from biomass fuel combustion have also been linked with adverse pregnancy outcomes, low birth weight babies and risk for lung cancer. However, the association between particulate air pollution and health effects has been less conclusive mainly due to lack of individual-based data.

Exposure to air pollution from biomass fuel combustion among rural women in Bangladesh will be determined by measuring fine air particles (known as PM2.5). This data will be related to ARI and COPD. Personal air samples will be collected over 8 hours from women while they cook and do other household chores. Questionnaire and clinical data will also be collected. A spot urine sample will be used to determine the association between exposure to biomass fuel combustion and a biomarker (1-hydroxypyrene) of polycyclic aromatic hydrocarbon exposure.

Glypican 3: A Lung Tumor Suppressor Associated with Cigarette Smoking.

Charles Powell, M.D., Department of Medicine/Pulmonary ($25,000)

The single most important causal factor associated with lung cancer is cigarette smoking. Despite the clear association between cigarette smoking and lung cancer, only a small percentage of smokers develop lung cancer and approximately ten percent of lung cancer cases occur in individuals who have never smoked cigarettes. While current lung carcinogenesis paradigms suggest an orderly progression from cigarette smoke exposure to DNA adduct formation to genetic alterations in tumor suppressor genes (p53) and oncogenes (Kras) to lung tumor formation, current research suggests that other biochemical and molecular pathways may be required for lung carcinogenesis. In previous work, Dr. Powell examined lung tissue specimens from smokers and nonsmokers with lung cancer. Subsequent studies demonstrated that expression of Glypican 3 (GPC3), a heparan sulfate proteoglycan, was low in lung tumors from both smokers and nonsmokers and was decreased in the normal tissue of cigarette smokers compared with the normal tissue of nonsmokers. In addition, expression of GPC3 was associated with growth inhibition of lung cancer cells implanted in nude mice.

This pilot proposal will further examine whether or not GPC3 expression is directly associated with exposure to cigarette smoke carcinogens. It will also focus on how GPC3 functions as a tumor suppressor gene. The study will attempt to determine if GPC3 null mice exposed to cigarette smoke carcinogens have increased numbers of tumors.

Special Awards

Peggy M. Shepard, environmental advocate, community leader, author and founder and Executive Director of our community partner, West Harlem Environmental Action (WE ACT), recently received a prestigious Heinz Award of $250,000 for her outstanding achievements and life's work as an environmentalist. The Heinz Awards were established in 1993 through the Heinz Family Foundation of Pittsburgh to honor and sustain the legacy of U.S. Senator John Heinz who died two years earlier. The awards recognize exceptional leadership and accomplishments in areas of particular interest to Senator Heinz including the Arts and Humanities, the Environment, Public Policy, the Human Condition, and Technology, the Economy and Employment. Peggy received the Heinz award for her work as a passionate crusader for protecting the environmental health of our nation's inner cities.

Congratulations to Peggy and WE ACT!

Websites

For more information about our Center, please visit our website at:
http://www.cumc.columbia.edu/dept/niehs/index.html

A Profile of the Exposure... continued from page 3

air monitoring in Bangladesh and the bioavailability of steel dust in NYC subway workers.

In the aftermath of 9/11, the Core began work on collecting air and dust samples as part of an extensive collaboration with the Johns Hopkins NIEHS Center on their study of teamsters transporting debris. This involved support in the field as well as analyses of a limited number of particulate samples for a suite of 28 elements and metals measured by High Resolution ICP-MS and for polyaromatic hydrocarbons and chlorinated and brominated organic compounds measured by High Resolution Gas Chromatography Mass Spectrometry. The goals of this study include measuring area samples and personal exposure of individuals working in and around ground zero; providing exposure information to these workers; developing a database of personal exposures and area concentrations for use in future health assessment studies; and identifying "signatures" of World Trade Center (WTC) emissions that can be used at off-site locations.

A central theme of the WTC exposure work was to help put exposures into perspective by putting contaminant compositions and levels into context from a historical perspective. Recent work by various Center investigators has generated a wide array of air pollutant data (outdoors, indoors, and personal) for NYC that is being used to provide estimates for background levels of volatile organic compounds, aldehydes and particle-associated elements that could be measured in NYC prior to September 11, 2001.

About the Center . . .

Columbia's Center for Environmental Health is dedicated to improving the environment and health of everyone. The different programs were created to make collaboration, communication and research more effective.

Research Cores: The three main areas of concentration are:

Cancer Core *- Trying to find answers to complex issues. The main goals of the Cancer Core are to facilitate research on cancer causation around different racial/ethnic groups, to understand the mechanisms of environmental carcinogenesis and to develop methods for assessing human exposure to carcinogens in the environment.*

Neurotoxicology/Neurodegenerative Diseases *- Determining the role of the environment in Essential Tremor and Parkinson's disease and other neurologic disorders. Exposures to heavy metals and pesticides may play a role in various neurologic diseases. Investigators are studying both the mechanisms by which this may occur and humans who may be exposed.*

Respiratory Disorders *- Uniting community concerns and research. Researchers studying respiratory diseases such as asthma need to interact with each other and with the local community to better understand the causes as well as to develop prevention strategies.*

Community Outreach and Education Program: *This program is uniquely designed to fill communication voids among community residents and environmental health researchers who live and work in local neighborhoods by providing: training for community residents around environmental health issues; public forums and environment and health conferences; increased active participation of community residents on academic and civic advisory boards; and training sessions for health care providers on environmental exposures.*