Issue Number 1

INTERFACE: GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI WINTER 1994

Daniel W. Nebert, MD, Director

Susan McGrath and Marian L. Miller, PhD, Assistants to the Director

Welcome to our Newsletter

The focus of our new Center for Environmental Genetics (CEG) is to investigate the interplay between genes and the environment. The 25 members of the CEG, derived from five departments around campus are examining the impact of genetic diversity on the ***response of the individual*** to toxic environmental agents—from sunlight to chemical pollutants—in species as varied as human, mouse, rat, fruit fly, yeast and bacteria. Identification of the underlying causes of genetic differences—in an individual or in a subgroup of the human population—in response to a toxic agent will provide an important foothold into our understanding of the basic mechanisms of toxicity. This knowledge will aid the individual in making more informed decisions about lifestyle changes, as well as increasing his/her awareness about potentially hazardous environmental exposures.

How can we help educate the public to make the most rational choice about their lifestyle, as it relates to their genetic make-up? The answer to this question is found in some of our future plans for the CEG's Public Outreach Program: **(i)** to educate the public through general lectures; **(ii)** to initiate a rigorous, yet friendly, interactive science program for children in grades K through 12; and **(iii)** to develop a Ph.D. training program in Medical Genetics Counseling, which will focus on genes and the environment.

IN THIS ISSUE

An article in the 30 November 1993 ***New York Times Science Section*** about Francis S. Collins, the new director of the National Center for Human Genome Research, underscores the extremely urgent need during the next decade for a new breed of genetics counseling and education of our children, as well as their parents. Our goal is to make the individual and the public more aware of such concepts as Mendelian genetics, risk assessment and probabilities.

We in the CEG are looking forward to providing an important resource to the entire environmental research community. We welcome all suggestions about improvements in format for this NewsLetter in the future. We will also be happy to consider all contributions (serious, provocative or humorous) submitted.

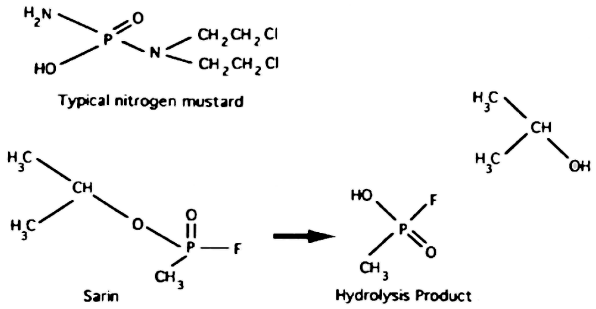
The Gulf War Syndrome

At 3 a.m. on 20 January 1991, 3 days after the Gulf War had begun, U.S. soldiers at a construction battalion camp in Saudi Arabia (more than 100 miles from the Kuwaiti border) were awakened by an exploding Scud missile. Before many of them could apply their gas masks, they sensed the acrid smell of ammonia and saw a whitish gray cloud drift over the camp. Soon afterwards, some of those exposed started getting sick while others exposed did not. Military personnel in other locations have reiterated similar experiences. The U.S. government remains uncertain about the reliability of these phenomena, perhaps in part because some soldiers were affected while others were not.

First came the large red blotches on their hands and arms. Within a week, some felt tired almost all of the time. Other symptoms—persisting up to the present time—have included chronic diarrhea, confusion and difficulty sleeping, painful joints, headaches, runny nose, tightness in the chest and intermittent difficulty breathing.

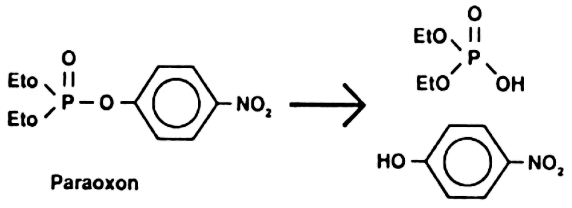
One theory has focused on heavy industrial pollution around the Saudi city of Jubail, where many of the ailing troops had been deployed. The Pentagon

has accepted a recent report from the Czech military, however, indicating that some of its chemical sensors detected trace amounts of ***mustard gas*** and the nerve poison ***sarin*** (Fig. 1) in Saudi Arabia during the Gulf War. Experts are uncertain as to where the toxins came from. Whatever the exposure was, there appear to be approximately 8,000 military personnel that have become sensitized to the degree that their bodies can no longer tolerate minute amounts of environmental chemicals that are normally harmless. The closest medical disease to what is being described is "multiple chemical sensitivity," but even this syndrome appears not to account for all the symptoms that have been registered by veterans of this war. Nobel Laureate Joshua Lederberg (Rockefeller University) has been asked to head a board of inquiry about this rare or emerging new environmental disease.



As noted above, some soldiers became affected while others did not, even in situations that looked like the exposure was similar or identical. Might there be a genetic component to this toxic response?

One glance at the chemical structures in Figure 1 brings to mind the human paraoxonase deficiency polymorphism. Human serum paraoxonase/arylesterase catalyzes the hydrolysis of organophosphates, aromatic carboxylic esters, and carbamates. The physiological function of paraoxonase remains unknown. The human metabolism of organophosphates, such as the insecticide parathion, has been known for more than 40 years—almost from the time that these toxicants came into widespread use. Parathion is converted to paraoxon, via oxidative desulfurization by a cytochrome P450 system in liver and other tissues. Hydrolysis of paraoxon is catalyzed by serum paraoxonase activity (Fig. 2).



There are 10- to 40-fold differences in serum paraoxonase activity between individuals. The polymorphism was first carefully investigated in 1976 by Playfer ***et al.*** High and low paraoxonase activities are controlled by two alleles at a single autosomal locus located on the long arm of chromosome 7. Europeans exhibit about 50% homozygotes for ***low activity***, 10% homozygotes for ***high activity***, and 40% heterozygotes with intermediate activity. The human paraoxonase ***PON*** gene has been cloned, and genotypes can now be readily detected (arginine at position 192 in the high-activity enzyme is changed to glutamic acid in the low-activity enzyme).

What is it about sarin that makes it so toxic? Using the orbital calculations in the HyperChem software program, we find that fluoride is a good leaving group, which would render the P-F bond labile to something that is more electronegative than F and which can attack the extremely electropositive P. Such an attacking nucleophile could be a cysteinyl sulfur of a protein or perhaps an O or N of a nucleic acid. The charge distributions on sarin and its hydrolysis product are about the same. However, sarin has the large, bulky 3-carbon blocking group that probably creates a lot of steric hindrance for any attacking nucleophile. On the other hand, the hydrolysis product has a large opening for attack on the P (Fig. 1). We conclude that this hydrolysis product is an extremely potent electrophile and would be very toxic. Is sarin metabolized by paraoxonase to this reactive hydrolysis product? If so, this would suggest that sarin would be more toxic in individuals having high paraoxonase activity than those having low activity. Given identical exposures during Desert Storm, could it be that those soldiers having the Gulf War Syndrome might be homozygotes for the high paraoxonase allele?

Mustard gases are known to possess the unique property of rapid absorption into tissues and poisoning the acetylcholinesterase at the neuromuscular junctions. Yet, the Gulf War Syndrome remind us more of the "Sick Building Syndrome," in which numerous symptoms occur throughout the body, and which is reminiscent of either **(i)** an ***allergic*** reaction or **(ii)** activation of an ***inflammatory*** response. Symptoms of the Sick Building Syndrome include headaches, mental confusion and sleepiness, temporal arteritis, conjunctivitis, rhinitis, bronchial wheezing, heart arrhythmias, intestinal cramping and diarrhea or constipation, and joint pains. In a disease where systems like these throughout the body can become involved, the most likely common target would be the mast cell or the macrophage. An ***allergic*** reaction might occur via activation of the immunoglobulin E (IgE) pathway. Activation of an ***inflammatory*** response, on the other hand, might represent an extremely electrophilic reactive intermediate (such as the sarin hydrolysis product), capable of binding covalently to cellular proteins and nucleic acids, and activating the inflammatory response transduction pathway by way of an "oxidative stress" signal—not unlike that seen for many reactive environmental toxicants.

—Contributed by Howard G. Shertzer and Daniel W. Nebert

CEG Members in the News

We appreciate all the faculty who provided information about what they have done in recent months. Please continue to do so, and any members who have not participated in this issue, please do so in the following issues.

Eula Bingham was appointed to serve on the Board of Environmental Science and Technology for the National Research Council, National Academy of Sciences.

Ralph Buncher has received a grant for $15,000 from the American Academy of Allergy and immunology for the biostatistical analysis of data on asthma immunotherapy.

Iain Cartwright was invited to talk at the Institute of Molecular Medicine, Imperial Cancer Research Fund Laboratories, University of Oxford, U.K., July 1993.

Lloyd Hastings was an invited speaker for a Mini-Symposium entitled "Models for sustainable human development," at the 11th Annual Science Symposium, Central State University, Wilberforce, OH, May 1993.

Gordon K. Livingston attended the thirty-first Hanford Symposium in Richland, Washington, on Health and the Environment and presented the paper, "The effect of in vivo exposure to ^{131}Iodine on the frequency and persistence of micronuclei in human lymphocytes."

George Leikauf gave a platform presentation, "Airway epithelial cells activation in response to oxidants" at the American Lung Association/American Thoracic Society International Conference, San Francisco, May 1993.

John C. Loper was an invited speaker for the 2nd International Symposium on Cytochrome P450 of Microorganisms and plants, Tokyo, June 1993.

Dan Nebert was an invited speaker at the 86th Nobel Symposium entitled "Toward a Molecular Basis of Alcohol Use and Abuse," Karolinska Institute, Stockholm, Sweden.

Charlotte Paquin attended the Gordon Conference on Extrachromosomal Elements, Plymouth, New Hampshire, July 1993.

Steve Potter was an invited lecturer on "Mouse homeobox genes: some expression patterns, target blind sequence and knockout phenotypes," McGill Cancer Center, Montreal, Canada.

Carol Rice was invited to participate in the Second International Symposium on Silica, Silicosis, and Cancer in San Francisco, California, October 1993. She gave a review of silica exposure measurements issues and chaired a session.

Peter J. Stambrook has been selected to be a member of the NIEHS Scientific Review Committee 1993-1997.

James R. Stringer was the co-author of a paper in ***Transgenic Research*** entitled "Expression of the *lacZ* gene targeted to the *HPRT* locus in embryonic stem cells and their derivatives."

Wilson Tabor was a lecturer on "The role of the laboratory in the verification process," a 3-day Training Workshop for the Environmental and Occupational Health Inspectors, Instituto Nacional de Salud Publica, Cuernavaca, Mexico, July 1993.

David Warshawsky was invited to present a talk on the "Detection of polycyclic aromatic hydrocarbon metabolites in aquatic organisms," at the 7th International Bioindicators Symposium and Workshop on Environmental Health, Kuopio, Finland, in autumn of 1992.

Jonathan Wispe has been awarded the Clinician Teacher Award for the Newborn Division, University of Cincinnati for 1992. He also won the award in 1990 and 1991.

Destiny, Fate and Genes--- Portuguese Style

When we attended a scientific meeting several weeks ago in Lisbon, Portugal, we were reminded of ***things within and things not within our control.*** Several old-style restaurants in Lisbon offer a fascinating atmosphere during dinner, characterized by singing of the ***Fado,*** a Portuguese folk song which renders the soul of these people into music with a powerful overflowing feeling. ***Fado***, loosely translated as "fate," is the actual personification of an unpredictable Being to whom we relinquish our fate. The lyrics of the ***fado*** express our surrender into the hands of this Being, with a mixed feeling of pleasure and pain. The mighty voice of the ***fadista*** stirs the audience into a mood best characterized in Portuguese by the term ***Saudade***, a longing for lost or wished-for well-being. The origin of ***fado*** has been lost in the mist of time, but its cathartic effect continues strong in the tradition of the Portuguese people.

Most of us think of genes as if they were ***fados***, unpredictable bearers of pleasure and pain that demand our total surrender, because their workings are beyond our control. The general feeling about

genetics is that our genes are something from which we cannot escape; we are born with a particular set of genetic determinants and we are ***fated*** to the outcome that they have reserved for us.

Many ***environmental and lifestyle factors***, however, can be within our control. The focus of our new Center for Environmental Genetics (CEG) is to investigate the interrelationships between genes and the environment. As we gain knowledge about our genes and an understanding of how they function and interact with environmental and lifestyle factors, we will begin to master their workings so that we can delay, or totally prevent, numerous environmentally-based diseases. Gaining more knowledge about ***genetic factors***, the theme of the CEG, will therefore help us greatly in this task.

The National Institute of Environmental Health Sciences (NIEHS)—based in Research Triangle Park, North Carolina—conducts and supports research and training aimed at understanding how environmental and lifestyle factors might cause human disease and disability. This mission of the NIEHS is important because, of all the causes of disease, environmental and lifestyle factors are the ones most within our control. **—Submitted by Daniel W. Nebert and Alvaro Puga**

RECENT CEG-PONSORED SPEAKERS for the 1993-94 Academic Year at the University of Cincinnati

NOVEMBER 3, 1993
Paul B. Watkins, M.D.
Director, General Clinical Research Center
The University of Michigan Medical Center
Ann Arbor, MI 48109-0108
" The importance of CYP3A enzymes in health and disease"

DECEMBER 1, 1993
Heinz Baumann, Ph.D.
Department of Molecular and Cell Biology
Roswell Park Memorial Institute
Buffalo, NY 14263-0001
"Cytokine-specific regulation of acute phase plasma protein genes"

JANUARY 5, 1994
Richard D. Irons, Ph.D.
Director, Molecular Toxicology and Environmental Health Sciences Program
"Of mice and men: Studies on the mechanisms of chemical leukemogenesis"

APRIL 13-14, 1994
Irwin Fridovich, Ph.D.
James B. Duke Professor
Department of Biochemistry
Duke University Medical Center
Durham, NC 27710
"The two faces of oxygen"
"Problems imposed by redox-cycling compounds and the adaptive responses thereto"

MAY 11-12, 1994
Arno G. Motulsky, M.D.
Professor of Medicine and Genetics
Department of Medicine
University of Washington
Seattle, WA 98195
"Genetics and environmental disease"
"Pharmacogenetics and ecogenetics: Models for genetic susceptibility to common diseases"

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Fax 513-558-0925 and 513-821-4664

E-mail DAN.NEBERT@UC.EDU

INTERFACE
Center for Environmental Genetics
University of Cincinnati
PO Box 670056
Cincinnati, Ohio 45267-0056

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