



xenobiotic metabolism: regulation, variation, and toxicogenomics

For years a scientific debate has raged about the relative role of our genes versus our environment in the development of important public health conditions such as cancer, birth defects and neurological diseases like Alzheimer's and Parkinson's. Dr. Curt Omiecinski, Professor in the Department of Environmental Health, and his laboratory have been actively investigating the interface of environmental exposure and genetics, an area termed ecogenetics. Virtually every chemical that enters our bodies- including over-the-counter and prescription drugs, environmental pollutants, and natural chemicals in our diet- are broken down, or biotransformed to usually harmless forms that are then eliminated in urine or feces. Like virtually all biological processes, the ability of an individual to detoxify such foreign chemicals varies by their genetics. Dr. Omiecinski's laboratory has focused on identifying and understanding human genetic variability in two groups of biotransformation enzymes, the cytochrome P450s (CYPs) and the hydrolytic enzymes.

Dr. Omiecinski's group has discovered and characterized human genetic variation, or polymorphism, in two different forms of epoxide hydrolase. One form of the enzyme is involved in the bioactivation of certain potentially cancer-causing chemicals present in tobacco. His lab also teamed with researchers in Medical Genetics to identify genetic polymorphisms in another hydrolytic enzyme, termed paraoxonase, that is important for its role in detoxifying widely used pesticides. These discoveries have paved the way for

a large number of follow-up studies examining the molecular epidemiological associations of enzyme variation with cancers and other environmentally associated diseases.

Unlike many enzymes in the body, most biotransformation enzymes are inducible – that is, the amount of enzyme present in the body can go up or down in response to their environment. Thus, in addition to genetic differences in the enzyme itself, the level of certain CYP enzymes in the liver can greatly increase

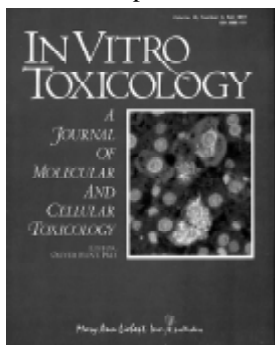
following exposure to some drugs, such as phenobarbital (PB), as well as many PB-like non-drug chemicals, such as the common environmental pollutants, PCBs, and the

pesticides, chlordane and DDT. Such enzyme induction can contribute to adverse drug-drug interactions. Recent studies have indicated that more than 2.2 million hospitalized Americans suffer adverse drug reactions each year, and approximately 100,000 die unintentionally from administration of medications, ranking as the 5th leading cause of death in the US. Although the PB induction response noted above has been recognized in humans for many years, work accomplished in Dr. Omiecinski's laboratory has contributed to the understanding of molecular mechanisms responsible for this effect. Using novel transgenic mouse models, his research was the first to localize the molecular switches (the so-called PB enhancer region) far upstream of the core promoter elements of PB responsive genes. His group also has developed a sophisticated primary liver cell culture system that has helped to identify key signaling pathways and extracellular components necessary to maintain the induction response in cells following PB treatment. Recently, his laboratory has been working on the characterization of genetic variation in a key set of nuclear receptor proteins that bind with the inducer chemicals and regulate the enzyme induction response. The identification of subtle genetic differences in nuclear hormone receptors in the population, coupled with an understanding of human genetic variation in chemical metabolizing enzymes, should lead to better predictive strategies for identifying individuals at greatest risk for adverse drug responses and/or toxicities resulting from chemical exposures.

Dr. Omiecinski serves as the deputy director of the UW/ NIEHS Center in Ecogenetics and is faculty director of that center's Molecular Biomarkers facility core. The core's staff work closely with toxicology, epidemiology, and other researchers at the UW and the FHCRC, providing genotyping services for study populations, as well as functional genomics technologies, such as the use of DNA microarrays. Ongoing projects include cancer population studies and genetic studies on the risk of Parkinson's and Alzheimer's disease.



Curt Omiecinski



Journal cover photo from an article by Dr. Omiecinski

Further reading: Omiecinski CJ, Rimmel RP, Hosagrahara VP. Concise review of the cytochrome P450s and their roles in toxicology. *Toxicological Sciences* 48: 151-156, 1999

Curt Omiecinski will deliver the Distinguished Faculty Lecture for Spring Quarter on June 7, 3:00-4:30pm, Health Sciences Center, Room T-625.

- workers' compensation health care.....inside ▶▶
- HIV-1 infected mothers and infantsinside ▶▶
- national alzheimer's coordinating center....inside ▶▶

improving the quality of workers' compensation health care in washington state

Health care delivered through the workers' compensation system has been plagued by problems of poor quality, high levels of patient and provider dissatisfaction, and high costs. Washington State has become a nationally recognized leader among states for its efforts to improve the quality of workers' compensation health care delivery. Over the past several years, the Department of Labor and Industries (L&I), the agency responsible for administering the workers' compensation program in Washington State, has worked closely with senior faculty in the School of Public Health and Community Medicine to pursue a research agenda aimed at improving workers' compensation health care delivery. This work has been done under the leadership of two of the School's faculty, Dr. Gary Franklin, Research Professor in the Department of Environmental Health and Medical Director of L&I, and Dr. Thomas Wickizer, the Rohm and Haas Distinguished Professor of Public Health Sciences and Professor of Health Services. Drs. Wickizer and Franklin have also established a training program, with a five-year grant from the National Institute of Occupational and Health Safety, to train health services researchers in the field of occupational health.

Drs. Wickizer and Franklin's first collaborative research study was the Washington State Managed Care Pilot (MCP) evaluation. The MCP was initiated in 1995 to assess the effects of managed care on health outcomes, patient satisfaction, employer satisfaction and medical and disability costs. The MCP evaluation was the first major prospective study of managed care within the field of workers' compensation. It involved 120 employers whose injured workers were treated through managed care physician networks. Health outcomes, costs, and satisfaction among workers who were injured during a 12-month period starting in April 1995 and who received treatment through managed care were assessed in relation to injured workers in a comparison group that received traditional fee-for-service care. The MCP evaluation found no difference in health outcomes but substantially lower medical and disability costs (disability costs represent wage replacement payments for workers who lose four or more days of work due to a work-related injury).

What's interesting about these findings is that disability payments were not subject to capitation. In other words, the managed care plans were not at risk for disability costs; L&I made these payments in the usual way. Thus, the managed care plans had no financial incentive to minimize disability costs. Because disability costs account for approximately 60% of all workers' compensation costs, this finding has

important implications. Data indicate that injured workers who are out of work from three to six months have a dramatically reduced chance of going back to productive full time work. Thus, there is the need to intervene early in a workers' compensation case to prevent long-term disability.

What accounted for the lower disability costs among managed care patients? We believe the explanation lies in the way that care was reorganized in the MCP. The MCP clinics used an occupational-medicine model that emphasized better care coordination, enhanced integration of treatment activities, improved communication between providers and employers, integrated case management, and enhanced efforts to improve return to work. By delivering care through this model, the managed care occupational health clinics participating in the MCP were able to prevent disability and get workers back to work sooner.

The findings of the MCP evaluation led L&I to sponsor

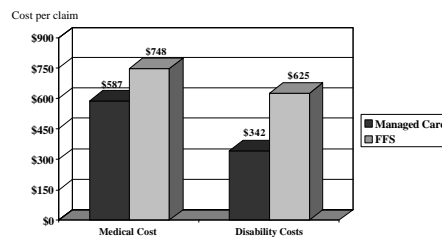
a follow-up policy study, which was conducted by Dr. Wickizer. The recommendations of this policy study then led to the decision by L&I to sponsor a major quality improvement project, known as the Occupational Health Services (OHS) project, which is now ongoing. The major focus of this project is to improve quality, health outcomes, and satisfaction among

injured workers by improving the organization of care delivery, by developing financial and non-financial incentives for providers, and by strengthening the capacity of the local systems to deliver high quality occupational health care based upon explicit quality indicators. The OHS project is currently in the design phase and will be implemented in two Washington pilot communities in early 2002. Formal process and outcome evaluations of the OHS will be performed under the leadership of Drs. Franklin and Wickizer.

The MCP evaluation and the current OHS quality improvement project demonstrate the value of collaborative partnerships to conduct health policy research. L&I's close association with the School of Public Health, its relationship to key stakeholder organizations, such as the Washington State Medical and Chiropractic Associations, and to business and labor leaders, and the collaboration between faculty in the Departments of Environmental Health and Health Services have all contributed to the success of this research effort.



Tom Wickizer



Washington State managed care pilot project: differences in medical and disability costs between managed care and FFS patients.

Further reading: Wickizer T, et al. Improving the Quality of Workers' Compensation Health Care Delivery: The Washington State Occupational Health Services Project. *Milbank Quarterly*, 2001, 79(1), 5-33.

effect of breastfeeding on HIV-1 infected mothers and their infants

The prevention of transmission of HIV-1 from mothers to their infants in the United States is a success story. With routine HIV-1 serologic testing during pregnancy, use of antiretrovirals, and avoidance of breastfeeding, transmission rates have been dramatically reduced. Unfortunately, this is not the case in less developed countries, and particularly in subSaharan Africa where the problem is greatest.

For the past 15 years, Joan Kreiss, Professor in the Departments of Epidemiology and Medicine, has been studying mother to child transmission of HIV-1 in Nairobi, Kenya. In conjunction with Ruth Nduati, formerly an MPH student in the School of Public Health, and currently a Senior Lecturer in the Department of Pediatrics at the University of Nairobi, she planned and conducted a unique and challenging randomized clinical trial of breastfeeding and formula feeding among HIV-1 infected mothers. HIV-1 infection rates among children were 36.7% in the breastfeeding group and 20.5% in the formula feeding group at 2 years of follow-up. Thus, the frequency of breastmilk transmission was 16.2%. Among children in the breastfeeding group, 44% of all HIV-1 infections were attributable to breastmilk exposure.

There are a number of impediments to the use of breastmilk substitutes in resource-poor areas. These include the absence of antenatal HIV-1 testing programs to identify infected women, the cost of formula, and the fear of stigmatization associated with HIV-1. In addition, there is concern that the gains achieved by preventing HIV-1 transmission might be offset by increased mortality caused by diarrhea and other infectious diseases associated with formula use. In the Nairobi trial, morbidity and mortality among children were closely monitored. Formula use was not associated with increased incidence of diarrhea, pneumonia, or death. Children in the formula group had a significantly better

outcome than those in the breastfeeding group, since they were more likely to be alive and free of HIV-1 disease at two years (70% vs 58%).

The issue of breastfeeding and HIV-1 has focused exclusively on the risks that breastfeeding imposes on the infant. Drs. Kreiss and Nduati were also concerned that the metabolic and nutritional demands of breastfeeding might have an adverse impact on the HIV-1 infected mother. They found that women who were randomized to the breastfeeding group had a 3-fold higher mortality rate at 2 years than women randomized to formula. The 2 year mortality rates were 10.5% and 3.8%, respectively. In addition, children were much more likely to die if they lost their mother, even if they themselves

had escaped HIV-1 infection. Thus, breastfeeding in the Nairobi trial was associated with serious adverse consequences for both mother and child.

The perinatal HIV-1 research group in Nairobi continues to focus on breastmilk transmission with a new study led by Grace John, Assistant Professor in the Departments of Medicine and Epidemiology, and Dorothy Mbori-Ngacha, former MPH student in the School of Public Health, and currently Senior Lecturer in the

Department of Pediatrics at the University of Nairobi. The goal of the study is to determine whether the presence of HIV-1 specific cytotoxic T-lymphocytes in infants of infected mothers is protective with regard to ongoing HIV-1 exposure through breastfeeding. The results of this study will have direct relevance to HIV-1 vaccine development.

The results of the Nairobi studies have contributed greatly to knowledge about breastfeeding and HIV-1, but the challenge remains to put knowledge into practice. The goal should be to enable HIV-1 infected mothers throughout the world to choose the infant feeding method that will minimize risks to themselves and their children.

The goal should be to enable HIV-1 infected mothers throughout the world to choose the infant feeding method that will minimize risks to themselves and their children.

Further reading: Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, Ndinya-Achola J, Bwayo J, Onyango FE, Hughes J, Kreiss J. Effect of breastfeeding and formula feeding on transmission of HIV-1: A randomized clinical trial. JAMA 2000; 283:1167-74.

LITTLE KNOWN FACT :

The School of Public Health and Community Medicine ranked fifth in the nation in the most recent U.S. News & World Report graduate school survey.

the national alzheimer's coordinating center: fostering collaboration between alzheimer's disease centers nationwide

An estimated 5% of all persons aged 65 or over are affected by Alzheimer's disease. Moreover, the disease occurrence and its prevalence increase dramatically with age. Some researchers estimate that as many as 47% of persons over age 85 may be suffering from the disease. In the United States, as life expectancy increases, the number of persons living with Alzheimer's disease will create an unprecedented burden on healthcare and public health.

The National Institute on Aging (NIA) began funding Alzheimer's Disease Research/Clinical Centers in 1984. The University of Washington's Alzheimer's Disease Center began in 1985 and was one of the first 10 centers of its kind. At present there are 30 Alzheimer's Disease Centers across the United States. Each Center may focus on a particular aspect of Alzheimer's disease research, such as genetics, behavioral factors, neuropathology, or clinical indications which led to dramatic variation of how subjects were enrolled and data were collected. Initially there was no common database that could provide aggregate data about subjects enrolled in the Centers; there was also little collaboration between Centers.

NIA encouraged the Centers to formulate a common database to aid collaboration and ensure accurate administrative reporting. Years passed with little agreement concerning the structure and content of such a

database. Finally in 1996, the Centers' Directors agreed on a minimum database of about 50 data elements. To include previously enrolled subjects, data had to be resurrected and abstracted into the minimum data set; the process was not ideal nor was the data collection completely standardized. The fledgling database was nonetheless a significant accomplishment. Rush University Medical Center began this work and was the interim home for the minimum database until 1999.

In 1998, the NIA issued a request for applications for an Alzheimer's disease data coordinating center to assume the maintenance of the minimum data, foster collaboration among Centers and perform a variety of other duties. In response Walter Kukull, Professor in the Department of Epidemiology, and Gerald van Belle, Professor in the Department of Environmental Health, assembled a group of highly skilled UW professionals to compete for the coordinating center. Despite intense competition, the UW's application emerged victorious and the National Alzheimer's Coordinating Center (NACC) began in July, 1999. The Minimum Data Set was

moved to NACC almost immediately. It required substantial work and reconstruction to meet modern database standards. This could not have been accomplished without Mr. Duane Beekly, the computing systems manager for NACC.

To foster collaboration between all Centers, Dr. Kukull established a new program that used pooled NACC funds to support investigator-initiated collaborative projects from the Centers. After rigorous peer-review by a scientific review committee, to date the NACC has funded 8 active collaborative

projects that involve 29 of the 30 Centers. Approximately 3 new projects will be added in July of this year. For example, one NACC-funded project supports 16 Alzheimer's Disease

Centers in a longitudinal neuropsychological and diagnostic study of nearly 5,000 normal individuals with mild cognitive impairment. The project is collecting and evaluating data on specific medications, vitamins and supplements that may show promise in preventing cognitive decline and Alzheimer's disease. Such studies require thousands

of participants (currently the database contains records on 51,000 subjects) and many years of follow-up, and can be completed only through collaborations among many different Alzheimer's Disease Centers. These awards will play a key role in finding new and better diagnostic tools, prevention strategies, and treatments for Alzheimer's Disease.

In addition to providing financial support for collaborative studies, NACC provides proactive and continuing consultation concerning project design, analysis and database management for the collaborative projects. Dr. Roger Higdon is the designated staff biostatistician. A Faculty Advisory Committee consisting of School of Public Health faculty, Drs. W. T. Longstreth, Thomas Lumley, Ron DiGiacomo, Harvey Checkoway and Stephanie Monks, provides additional methodologic consultation and support through NACC to the many centers. The National Alzheimer's Coordinating Center is dedicated to fostering constructive criticism, clean data, collaborative studies, and careful science across all the Alzheimer's Disease Centers in the US.



Bud Kukull

An estimated 5% of all persons aged 65 or over are affected by Alzheimer's disease.

Further reading: Additional information is available on the NACC website, <http://www.alz.washington.edu>

Visit the School of Public Health online at:
<http://depts.washington.edu/sphcm/>

Associate Dean for Research: David L. Eaton, PhD
Designer & Co-Editor: Nancy D. Meenen



The soulcatcher logo is a Northwest Coast Indian symbol of physical and mental well-being. Artist: Marvin Oliver

School of Public Health and Community Medicine
University of Washington
1959 NE Pacific Street
Health Sciences Center, F-350
Box 357230
Seattle, WA 98195
206/543-1144