

C R O E T

Center for
Research on
Occupational and
Environmental
Toxicology

NEWSLETTER

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What Can Fruit Flies Tell Us About Neurodegenerative Disease?

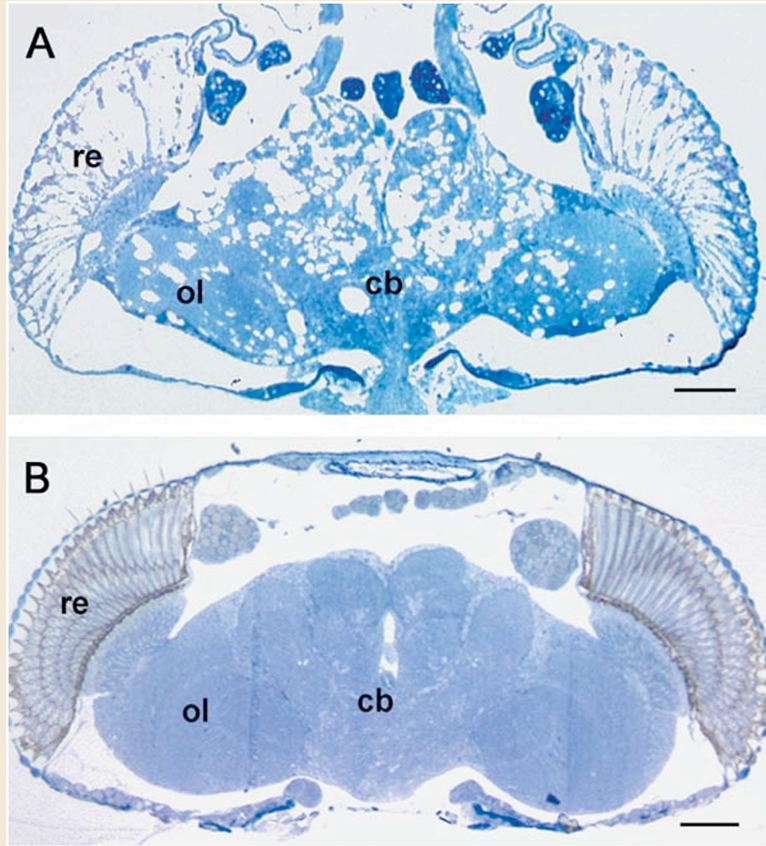
The lowly fruit fly (*Drosophila melanogaster*): scourge of the fruit bowl, but also one of the most valuable organisms in scientific research. Studied for almost a century, *Drosophila* is still used by thousands of scientists worldwide in disciplines such as genetics and developmental biology, where it is providing insights into important human health issues, including neurodegenerative disease.

One scientist studying fruit flies is Doris Kretzschmar, CROET Scientist and Assistant Professor of Molecular and Medical Genetics at OHSU. Dr. Kretzschmar is using *Drosophila melanogaster* to study basic mechanisms of neurodegeneration that are known to occur in occupational and other diseases. Her approach is to isolate and then genetically characterize *Drosophila* mutants that show premature age-dependent degeneration of the nervous system. Sorting through and observing thousands of fruit flies for signs of nervous system anomalies is a tough task that is aided by the fact that fruit flies



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are small, easy to maintain and keep in large numbers, and they develop into adults in only two weeks. These are some of the main reasons the fruit fly is such an ideal model system for biological research. Once isolated, the scientists set about the task of analyzing the fruit fly's DNA to locate any mutated genes responsible for the nervous system abnormality.



Head sections from a mutant fruit fly with a neurodegenerative phenotype (A) and from a non-mutant wild type fly (B). Abbreviations: (cb) central brain, (ol) olfactory lobe, (re) retina (eye).

One mutant *Drosophila* that has been isolated by this method is called *Swiss-cheese*, because, as it ages the neurons in its brain degenerate, forming 'holes' and producing an appearance like Swiss cheese. The gene mutant that produces the *Swiss-cheese* appearance encodes a protein similar to a human protein called Neuropathy Target Esterase (NTE). NTE is an enzyme whose function is altered by members of a class of pesticides called organophosphates. Humans who have been intoxicated by organophosphates may develop a neurodegenerative disease that can permanently

alter motor function. Other *Drosophila* isolates were found to possess mutant genes that encode proteins involved in the maintenance of nerve structure and cholesterol metabolism, processes that play an important role in Alzheimer's disease. Interestingly, these mutants influence the processing of the Amyloid Precursor Protein (APP), a key protein in the development of Alzheimer's disease in humans. To investigate APP, its function, and its role in Alzheimer's disease, Dr. Kretzschmar's lab has established a *Drosophila* model that reveals key features of Alzheimer's disease, like the formation of amyloid plaques in the brain, behavioral deficits, and neuronal cell death. This and other models are allowing Dr. Kretzschmar to investigate mechanisms underlying common neurodegen-



Dorris Kretzschmar, Ph.D.

erative diseases that affect humans. Now that gene mutations involved in neurodegeneration have been located, Dr. Kretzschmar's lab is using genetic and molecular techniques in an attempt to isolate other genes and proteins that interact with the mutant genes. Locating these "interaction partners" will help to reveal the molecular and metabolic pathways that lead to neurodegeneration in Dr. Kretzschmar's fruit fly model system. By gaining a more complete understanding of the mechanisms of neurodegeneration in the fruit fly, it will be possible to transfer that knowledge from insects to vertebrates, which will ultimately lead to a fuller understanding of human neurodegenerative disease.

CROET Faculty Member Joins Prestigious NIH Review Panel

CROET's Show-Ling Shyng, PhD, has accepted an invitation to serve on a National Institutes of Health (NIH) Center for Scientific Review panel, the Cellular Aspects of Diabetes and Obesity Study Section. Scientific review panel members are selected on the basis of their demonstrated competence and achievement in their scientific discipline as evidenced by the quality of research accomplishments, publications in scientific journals, and other significant scientific activities, achievements and honors.

Dr. Shyng is a CROET faculty member and Assistant Professor in the Physiology and Pharmacology Department, the School of Medicine at OHSU. She received her B.S. in Zoology in 1984 from the National Taiwan University and her PhD in Neurobiology and Behavior in 1990 from Cornell University. After spending a year as a postdoctoral fellow at the California Institute of Technology, Dr. Shyng moved to Washington University where she was a research associate, and then a research assistant professor in the Department of Cell Biology and Physiology. She joined CROET as an Assistant Scientist in 1999.

Study section members review grant applications submitted to the NIH, make recommendations on these applications to the appropriate NIH national advisory council or board, and survey the status of research in their fields of science. These functions are of great value to medical and allied research in the United States. Membership in a study section represents a major commitment of professional time and energy as well as a unique opportunity to contribute to the national biomedical research effort.

To learn more about Dr. Shyng's research, please visit: <http://www.ohsu.edu/croet/faculty/shyng/>

CROET Toxicology Information Center (TIC) Moves to New Location

The Toxicology Information Center has moved up — from the CROET first floor to the third, or — “ground” floor, immediately adjacent to the courtyard with its landmark marble head sculpture.



Toxicology Information Center Entryway and Marble Head Sculpture

This new location provides a more inviting space for those seeking access to the TIC's electronic, print and other information resources, and gives enhanced visibility to CROET outreach, which offers occupational safety and health information and education to the community. A new feature of the TIC is the entry foyer, where a variety of informational materials from CROET, allied OHSU health and safety groups, and the Oregon Poison Center, will be available and on display. The new TIC is also directly connected to a seminar room that will allow outreach personnel greater flexibility to provide resources and space to groups concerned with enhancing safety in the Oregon workforce. The next time you're in the neighborhood, please drop in and see what the TIC has to offer.

Area Occupational Medical Association Meets in New TIC

The Northwest Association of Occupational and Environmental Medicine held its bi-monthly meeting recently at the new CROET Toxicology Information Center library. Doctor Chris Morgan, MD, presented the evening's talk titled "Do you see what I see?" in which he reviewed the fine

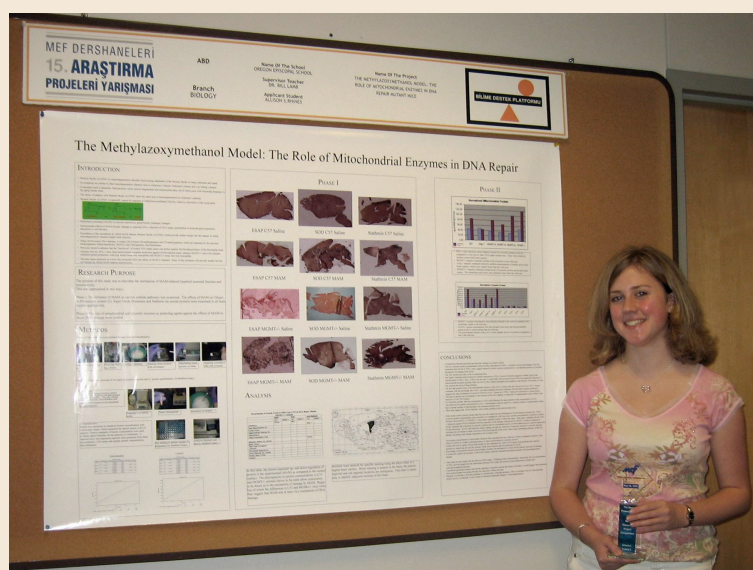


Doctors congregate prior to their meeting at CROET's TIC

points of interpreting MRI images of the shoulder. His primary focus was on the various types of rotator cuff injuries that are typically seen in his practice. These types of injuries are a common occurrence among Oregon workers. Dr. Morgan is Medical Director for Open Advanced Imaging in the Portland area. He is board certified in Radiology, has fellowship training in CT and ultrasound imaging, and is well known for his expertise in musculoskeletal radiology. By the end of the evening, conference attendees had been given a much better understanding of the anatomy and pathophysiology of the shoulder.

Student Intern Earns Award at International Science Competition

Former Oregon Episcopal School senior and CROET intern Allison Rhines has earned another science award, this time at an international science competition held in May 2006, in Istanbul, Turkey. You may remember Allison, who as a junior in 2005 earned a second place science award at the Intel International Science and Engineering Fair in Phoenix, Arizona. This year, she, along with other high school students from 14 countries in the Middle East and Eastern and Western Europe,



Allison Rhines poses with her research presentation and trophy

presented research at this one-week conference, called the MEF Dershaneleri 15 Arastirma Projeleri Yarismasi (The 15th MEF Research Projects Competition). Allison had the opportunity to discuss her work with professors from some of Istanbul's most prestigious universities. There were two categories in the competition: Turkish student projects and international student projects. Allison's project was awarded "best project" in the international category, which was the only prize awarded in that division. Allison conducted her research under the supervision of CROET's Dr. Glen Kisby. The title of her project was "The Methylazoxymethanol Model: The Role of Mitochondrial Enzymes in DNA Repair."

Chelation Challenge: Is this an appropriate way to diagnose mercury poisoning?

Most physicians are inexperienced in the diagnosis and treatment of mercury poisoning. This is because mercury toxicity is rarely seen today, even in industrial settings that involve the use of mercury, where workers may be at increased risk for exposure. Nevertheless, media publicity about mercury in fish and controversy surrounding the dental profession's use of mercury-containing amalgam restorations (which have not been shown to cause mercury poisoning in the general population) has increased the public's concern about mercury in our environment. Consequently, more people are asking health care professionals to test for mercury, often in the hope that an explanation for unresolved health complaints will be found. Once testing is initiated, physicians are often at a loss as to how to interpret the lab reports, as well as what to do, especially when non-standard testing protocols such as chelation challenge are employed.

What is chelation challenge?

In general, the standard protocol for mercury testing involves the collection of blood, urine, or less commonly, hair, which is then assayed for mercury by a certified medical lab. Whole blood and hair are the preferred materials to assess exposure to organic mercury compounds, such as methyl mercury, whereas urine is preferred to assess inorganic (e.g. mercuric chloride) mercury exposure. Chelation challenge, as practiced by some, is a urine test in which a chemical that binds to metals (e.g. EDTA, DMPS or DMSA) is administered intravenously or orally prior to urine collection and laboratory analysis. The theory behind chelation challenge is that the chelating agent binds to mercury within the body, increases its excretion into the urine, and thereby unmasks the 'actual' body burden of mercury. But, while this may sound logical, the reality is not so simple, as will be discussed.

What is a 'normal' concentration of mercury in blood or urine?

Since we are all exposed daily to very small amounts of mercury, primarily organic (methyl) mercury from fish or elemental mercury from the atmosphere or dental amalgams, we all have measurable amounts of mercury in our blood and urine. Therefore, a large body of data exists regarding the average levels of mercury found in healthy human populations using standard mercury testing protocols. In whole blood, 2 micrograms per liter ($\mu\text{g/L}$) approximates the average background mercury level in people who do not eat fish; but for most people, blood mercury averages between 5 and 20 $\mu\text{g/L}$. In communities with very high rates of fish consumption, blood mercury has been documented to be as high as 200 $\mu\text{g/L}$ without overt signs of toxicity. In urine, normal population values average about 4-5 μg mercury per gram creatinine ($\mu\text{g/g Crt}$), but can range to as high as 20 $\mu\text{g/g Crt}$ in non-occupationally exposed individuals (Urine mercury is often reported in units of $\mu\text{g/g Crt}$, which normalizes for variations in urine concentration, because creatinine excretion occurs independent of urine production). Workers occupationally exposed to inorganic mercury have had urinary mercury levels in excess of 100 $\mu\text{g/g Crt}$ without adverse health effect.

So what's the problem with chelation challenge testing?

When a chelating agent is administered, urine mercury levels almost always increase, even in people who do not have health problems. The testing laboratory will report the urine mercury level as high, because the reference values, or healthy population norms to which the patient's urine is being compared, are based on urine from non-chelated patients. No laboratory has established normative values for post-chelation

urinary mercury concentrations, making the significance of such results unclear. Yet, patients often ask or are encouraged to undergo expensive treatments based on these confusing or misleading laboratory results.

An obvious question is where does the chelated mercury come from? One source is mercury that has been temporarily immobilized within the kidneys by the body's own protective chelating proteins. These proteins naturally protect against cellular damage as the kidneys slowly excrete mercury, as well as other heavy metals. Another source is contained in an otherwise inert form within dental amalgams. Chelating agents can pass through the saliva and pull mercury from exposed amalgam surfaces, where it is then swallowed, absorbed and excreted in urine. Thus, chelation challenge elevates urinary mercury, often to levels not all that high, but provides no indication of whether a patient is being overexposed. Moreover, chelation challenge by itself provides little useful information that mercury is the likely cause of an adverse health complaint. Furthermore, chelation itself carries health risks, but is valuable in the treatment of those patients with overt heavy metal poisoning.

The toxicological effects of mercury, as well as the amount of mercury required to produce those effects, are well documented in the medical literature. Therefore, it is probably unwise to seek a diagnosis of mercury poisoning unless such diagnosis is founded on a history of exposure, such as through occupation or accident, as well as attendant adverse health effects that are consistent with mercury exposure. Without such a foundation, the use of chelation challenge to make a medical diagnosis of mercury toxicity will likely create only uncertainty and expense for patients who may already be concerned about their good health.

For more information on mercury, please visit our website at <http://www.croetweb.com>

Local Industrial Hygiene Group Meets at CROET

CROET's Toxicology Information Center hosted a recent meeting of the Pacific Northwest Section of the American Industrial Hygiene Association (AIHA), sponsored by the Portland local education committee. The group, which includes Industrial Hygienists working in the Portland Metro/Salem area, meets monthly and is currently headed by



Dr. Kent Anger addresses local industrial hygienists.

Annie Moorman, Loss Control Consultant for SAIF. Guest speaker for this session was CROET Assistant Director Kent Anger, who gave a slide presentation on his recent trip to Egypt, where he and colleagues are conducting research into pesticide exposures among cotton farm workers. Dr. Anger's talk was both educational and entertaining, as he described agricultural work practices along the Nile River and his efforts to set up and make functional a portable "suitcase" laboratory. The trip was funded by federal indirect cost funds, and the purpose of the trip was to obtain preliminary data on major pesticide exposures for a grant application that will help us develop methods to measure and reduce pesticide exposures in Northwest farm workers. Overall, the meeting was well attended, and meeting planners hope to return to CROET for future meetings.

C R O E T Center for Research on Occupational and Environmental Toxicology

CROET, the Center for Research on Occupational and Environmental Toxicology at Oregon Health & Science University, conducts research, provides consultations and offers information on hazardous chemicals and their health effects. CROET's 100+ scientists and research staff explore a range of questions relating to health and the prevention of injury and disease in the workforce of Oregon and beyond. CROET's Toxicology Information Center is open to the public and is staffed to answer Oregonians' questions about hazardous substances in the workplace and elsewhere. CROET's Web site also provides answers to questions about industries found in Oregon through links on a series of pages devoted to industry-specific topics.

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OUTREACH

CROET will exhibit at the following conferences.

Oregon Governor's Occupational Safety & Health Conference

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March 12 - 15, 2007

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