

Center for
Research on
Occupational and
Environmental
Toxicology



This issue features the works of Douglas Russell, curator and instructor at Oregon State University's Department of Fine Art.

NEWSLETTER

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Nanobiotechnology: Developing Miniaturized Neural Prostheses, Diagnostic Devices and Drugs

In the never-ending race to make computers smaller and faster, physicists have developed remarkable tricks to manufacture devices that are very, very small - hundreds of times smaller than a human hair. In this nanometer dimension (billionths of a meter), we can now manufacture crystals, particles, spheres, wires, and tubes in a uniform and reliable manner, and at reasonable scale and cost. As scientists learn new methods to manipulate the architecture of molecules at the nanoscale, applications of unprecedented sensitivity to our internal and external environment are being developed. Naturally, this technology is being applied to biology and medicine, and CROET is playing an important role in this exciting new field called nanobiotechnology.

The potential for scientific advances that nanobiotechnology offers has convinced the National Science Foundation to sponsor the nation's first Science and Technology Center devoted to nanobiotechnology. The Center is a consortium of four institutions: Cornell, Princeton, OHSU, and the research laboratories of the New York State Department of Health. CROET was selected to



participate in this program because of its unique expertise in studying the nervous system. Two CROET scientists are currently participating in this endeavor. Gary Banker, PhD, a Senior Scientist at CROET, is using nanofabrication technology to understand the fundamental biology of nerve growth and to develop methods for promoting nerve regeneration. Dr. Banker's lab is investigating nanofabrication technology as a means of precisely controlling the interactions between neurons and signaling molecules in their immediate environment that direct how and where the neurons should grow. Bruce Patton, PhD, an assistant scientist at CROET, is using similar technology to investigate how specific proteins direct the formation of axons (the nerve cell's long connecting process) and synaptic terminals (the neuron's specialized structure for communicating with target cells).

Thus far, the Banker lab has demonstrated that neurons can be trained to grow in specific patterns on tiny etched substrates that have been treated with such signaling molecules. A movie of this feat can be viewed on CROET's website (<http://www.ohsu.edu/croet/faculty/banker/bankerlabmovies.html>).

Similarly, the Patton group has shown that a protein found on skeletal muscle nerve endings arrests the growth of axons in experimental settings that reproduce how axons stop when they reach synaptic sites in real muscles during recovery from a nerve injury. Both scientists hope that prosthetic devices coated with these proteins will someday allow a patient's nervous system to be connected to external devices, allowing the functions of medical implants and prostheses to be accurately controlled by nerves that have lost their natural targets (such as an arm) through accident, chemical exposure or disease. Dr. Banker believes that this technology will also lead to miniaturized devices that can be implanted into the brain or spinal cord to help restore function to damaged areas of the nervous system.

In addition to research, CROET also participates in a course to teach the fundamentals of nanobiotechnology to PhD students in biology and engineering. The course focuses on applications in biomedical and biological research, and is teleconferenced to seven universities around the

country. Some of the potential applications of nanobiotechnology include:

— Smart pharmacies, propelled through the human body with tiny biological motors that run on nature's energy to dispense drugs precisely where and when cells (such as cancer cells) signal the need. Such nanotherapeutics may offer the possibility of delivering drugs to specific tissues, which would reduce the dose that is required. Less drug means fewer side-effects and a reduced risk of toxicity to the patient.

— Nanofabricated surfaces with structural patterns to grow artificial pancreatic cells and reverse the effects of diabetes - or to grow "neuron repair kits" (brain-cell transplants) for those afflicted with Parkinson's or Alzheimer's disease.

— Super-small, directionally-sensitive hearing aids, based on the auditory organ of a tiny parasitic fly that homes in on the mating calls of crickets - as well as micro-robots based on the muscles of the flea.

— Improved research capabilities in the life sciences, allowing us to 'see' more directly the processes of life as they occur. These include nanoparticles (dots, bars, rods) as labels for biological molecules, as well as nanoscale assay systems that will provide more sensitive and highly specific detection and analysis capabilities.

— Improved patient diagnostic capabilities: biosensors using nanowires, nanoparticle arrays and nanofluidics systems that provide unprecedented sensitivity to our internal and external environment. For example, with the ability to detect a few protein molecules, the field of diagnostics can be brought to the level of a single cell. Instead of collecting blood, we may someday need only to sample a single breath of air.

Nanobiotechnology is an exciting new field that holds promise for improving our daily lives—in the home, the workplace, our natural environment—and CROET is at the forefront of this emerging new science.

CROET Surveys GOSH Conference Attendees

One of the fun perks of occupational safety and health conferences, aside from the great health and safety information that is provided, is all the goodies offered by vendors – just for showing up at their booths – and the 2003 Oregon Governor’s Occupational Safety and Health (GOSH) Conference was definitely no exception.



This year, visitors to CROET’s information booth had to work for their ‘swag’ by filling out a questionnaire. This informal survey was designed to assess how well we are performing at getting the message out about CROET and the services we provide. Three questions were asked: Have you heard of CROET at OHSU? If so, have you ever used the CROET Website or contacted a CROET staff person directly? Do you need information on.....? This latter question was followed by a long list of possible information topics, of which up to five could be checked off.



The results were as follows:

Of the one hundred eighteen people who responded to our questionnaire, 58% said they had heard of CROET - and of these, 63% had either used the CROET website, contacted CROET personnel directly, or both. The information from this part of the survey is encouraging in that it demonstrates success at getting the word out to the Oregon



workforce. Because 42% of respondents were not yet aware of CROET and the services we offer, however, the survey also tells us that we must continue to find new and innovative ways of reaching out to the people of Oregon. Occupational safety and health conferences continue to be our primary means of access to Oregon workers—but other methods, including spots on Oregon Public Radio, are being used and evaluated for their effectiveness.

The final survey question, about the information needs of respondents, was designed to inform us about new topics we could address on our website or at future CROET-sponsored occupational health and safety education seminars. Two topics, ergonomics and health and safety training, stood out as the most popular choices, followed by chemical safety and toxicology, personal health and safety, risk assessment, health and safety regulations and material safety data sheets (MSDS), respectively. The least requested information needs were in the areas of training for management, environmental concerns, and risk/hazard communication. Overall, comments that respondents made echoed their

expressed informational needs. CROET will co-sponsor a seminar on ergonomics in health care in summer, 2004.

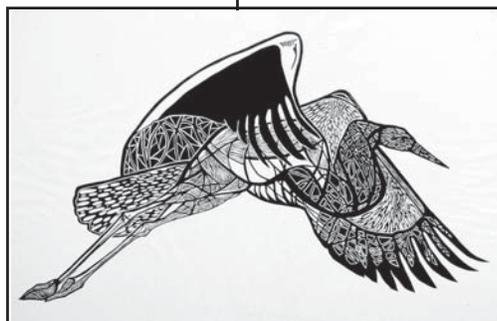
Manganese, Welders, and Parkinson's Disease

Paracelsus (1493-1541), regarded by many as the father of modern toxicology, said that “all substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy”. This statement can certainly be applied to manganese. Manganese (Mn) is an essential trace element in the cellular metabolism of all living organisms and can be found naturally in high concentrations in many foods, including nuts, grains, and beverages such as tea. It is the twelfth most abundant element in the Earth's crust. As a dietary nutrient, humans have evolved mechanisms that allow us to absorb Mn, retain what we need, and to excrete the rest. It wasn't until Mn found use in industry that Paracelsus' maxim was again proven true. Only 20 years after Parkinson published his classic 1817 paper *An Essay on Shaking Palsy*, a peculiar syndrome called “manganese crusher's disease” was reported in five French miners working at a Mn ore-crushing plant. Their illness manifested as limb tremor, muscle weakness, whispering speech, salivation, and a bent posture while walking. Manganism has since been identified in hundreds of cases, most notably in miners, smelters and workers involved in the manufacture of dry-cell batteries. The disorder begins gradually, often with psychiatric disturbances (“manganese madness”), including hallucinations, emotional instability, and compulsive and aberrant behavior. In a later stage, motor disturbances similar to those of Parkinson's disease (PD) emerge. Sometimes patients develop motor symptoms without experiencing a phase of manganese madness.

Although environmental controls have largely reduced or eliminated the risk for development of occupational manganism, the issue re-emerged in October when a jury awarded compensation to a Missouri man for his claim that he had developed a Parkinson's-like illness from occupational exposure to welding fumes. It is well known that welding rods, as well as steel, contain varying amounts of Mn. This raises several questions — does Mn cause PD or a closely related syndrome? Can manganism be differentiated from PD? And, perhaps most importantly, can manganese exposure increase the risk of

developing PD in those who are at risk through genetic predisposition or other reasons? The answers to these questions are not entirely clear, but recent research has provided some insight.

PD is one of the most common adult neurodegenerative diseases, but its causes in most cases remain unknown. Although there is evidence for both genetic and environmental factors, the majority of PD cases are classified as idiopathic (of unknown cause). What is known for certain, however, is that PD results from the loss of dopamine-producing brain cells located within a part of the brain known as the substantia nigra. A pathological hallmark of the disease is the presence of



red-staining bodies within the neurons, called Lewy bodies. In contrast to PD, the majority of pathological changes in manganism are seen in a brain area called the pallidum, and Lewy bodies are usually absent. Some of these pathological differences can be seen with a brain scanning technique called positron emission tomography

(PET). Fluorodopa PET provides an index of the integrity of the nigrostriatal projection, which is abnormal in PD. In manganism, the fluorodopa PET scan is normal, indicating that the nigrostriatal connection is intact. Thus, at the pathological level, it is apparent that PD and manganism affect different parts of the brain.

PD and manganism are further differentiated by a careful analysis of clinical symptoms. It has been reported that the clinical features of manganism differ from PD by the more frequent presence of dystonia (abnormal muscle tone), a propensity to fall backward, less frequent resting tremor, and a failure to sustain a therapeutic response to drugs used in the treatment of PD. Thus, based on clinical presentation and pathological analysis, manganism and PD are related, but distinct clinical syndromes.

It is not yet known whether Mn exposure increases the incidence of PD in predisposed individuals. However, recent findings have been provocative. In an epidemiological study of welders with PD published in the January, 2001 issue of the journal *Neurology*, Recette et. al. found that welders had a younger average age at

onset (46 years) of PD compared with a control population of non-welders (63 years average age of onset). All other factors, such as clinical symptoms, family history, response to therapy, and fluorodopa PET were identical between welders and controls, indicating that the welders had typical PD and not manganism. These findings suggest that welding might be a risk factor for PD, but do not provide information about the cause (since welding involves exposure to multiple chemicals and environments). Nor do these results support the hypothesis that Mn toxicity from welding exposure may lead to delayed and progressive typical PD. Thus, at this time, there is no solid evidence that exposure to manganese causes or enhances the development of PD in welders or the general population.

Use CROETweb.com’s Advanced Search tool to quickly find the resources you need.

CROETweb’s advanced search tool helps you search over 1100 workplace safety and health resources. You can limit your search to Oregon-specific information or Spanish language materials only. Or, you can search just for information that comes from certain types of sources, such as state governments or professional societies.

Try these searches for practice.

1. Choose the topic “Restaurant & Kitchen”, then click the “Oregon-specific” checkbox. This shows all of the Oregon-specific restaurant and kitchen safety links on the website.
2. Choose the topic “Pesticides” and click the Spanish-language button. This shows all of the Spanish-language pesticide information links on the website.
3. Type the keyword **dental** in the Keywords box, then choose Source Type “Professional Society/ Organization”. This will return links related to “dental”, but only those from professional organizations. Try it again, but choose the source type “Government, national.”

The screenshot shows the CROETweb.com Advanced Search page. The browser window title is "CROETweb.com Advanced Search - Microsoft Internet Explorer". The address bar shows "http://www.croetweb.com/advsearch.cfm". The page header includes "OHSU Oregon Health & Science University" and "Center for Research on Occupational and Environmental Toxicology". The main content area is titled "Advanced Search" and contains the following search criteria table:

Keyword(s): <i>(Optional)</i>	<input type="text"/>	Any word in the link name, url, or description. Search tips
Topic:	Any/All Topics	Limit to a specific topic.
Source Type:	Any/All Source Types	Type of source.
Language:	<input checked="" type="radio"/> English <input type="radio"/> Spanish	
Oregon-specific?	<input type="checkbox"/> I want to search for Oregon information only	Limit results to Oregon-based information.

Below the table are "Clear" and "Search" buttons. At the bottom of the page, there is contact information for CROET at OHSU and a copyright notice for 2001-2003.

Find the Advanced Search tool by clicking on [Advanced Search](#) in the SEARCH THE SITE box at the bottom of our homepage: www.croetweb.com

The image shows a simplified "SEARCH THE SITE" box. It has a blue header with the text "SEARCH THE SITE:". Below the header is a white search input field with a "Go" button to its right. Underneath the input field is a blue link labeled "Advanced Search".

CROET welcomes three new faculty members

CROET is pleased to welcome its three newest faculty members: Steven Lloyd, Ph.D., Amanda McCullough, Ph.D., and Pamela Lein, Ph.D.

Dr. Lloyd, a Senior Scientist at CROET, earned his Ph.D. in Molecular Biology from the University of Texas Graduate School of Biomedical Sciences in Houston, TX. He comes to OHSU from the University of Texas Medical Branch in Galveston. Dr. Lloyd is interested in the molecular mechanisms of DNA repair and mutagenesis. One of his many research projects involves creating lines of transgenic mice that contain altered DNA repair enzymes. One line of mice possesses novel DNA repair enzymes that have an enhanced ability to repair damage caused by ultraviolet light, while another line lacks a crucial DNA repair enzyme. Ultimately, Dr. Lloyd's research will help to better understand the body's ability to repair damage caused by occupational and environmental stressors.

Dr. McCullough is an Assistant Scientist at CROET and an Assistant Professor in the Department of Molecular and Medical Genetics at OHSU. She received her doctoral degree in Cellular and Molecular Biology from the University of Vermont. Prior to coming to OHSU, she was an Assistant Professor in the Department of Human Biological Chemistry

and Genetics at the University of Texas. Dr. McCullough's research interests are focused on the biochemical mechanisms of DNA repair systems and the role of DNA repair in the cellular responses to environmental stress. The ultimate goal of her research is to correlate alterations in DNA repair systems with human cancers, aging, and other disease states.

Dr. Lein is an Assistant Scientist at CROET. She received her Ph.D. from the State University of New York at Buffalo and her M.S. in Environmental Health from East Tennessee State University. Before coming to OHSU, Dr. Lein was an Assistant Professor in Toxicological Sciences at the Johns Hopkins University Bloomberg School of Public Health. Dr. Lein's research is in the field of developmental neurotoxicity. She is interested in understanding the cellular and molecular mechanisms that regulate the development of the nervous system, and how toxic chemicals affect the development of nerve cells. Her work will help address public health concerns about the vulnerability of the developing nervous system to occupational and environmental factors.

CROET welcomes these three distinguished scientists, each of whom brings new, funded research programs to Oregon.

Dr. Linda McCauley Accepts Position at the University of Pennsylvania

CROET Scientist Linda McCauley, PhD, RN, FAAN, has accepted a chair position, Nightingale Professor of Nursing, and the Associate Dean for Nursing Research in the School of Nursing at the University of Pennsylvania. Her many friends and colleagues gathered at a luncheon in December to wish her well, and she received a plaque honoring her many accomplishments at CROET from Director Peter Spencer. We congratulate Linda on her new appointment beginning in January, 2004. We know she will do well in Pennsylvania.

Dr. McCauley joined CROET in 1994 as a Scientist, assuming the role of epidemiologist in a major research project on Gulf War veterans. She was also a Professor in OHSU's School of Nursing. Linda came from the University of Cincinnati where she earned her Ph.D. in Environmental Health and Epidemiology and remained there to become Professor and Director of Occupational Health Nursing. While at CROET, Linda received the prestigious Mary Louise Brown National Research Recognition Award from the American Association of Occupational Health Nurses.

What most marked Linda's 9 years at CROET was the creation of strong research programs in migrant worker and family health and in surveillance. Linda's skills at bringing people together led her to

multidisciplinary research with diverse collaborators in industry, government, labor and public organizations. Her most extensive program was research on exposures to organophosphate pesticides in migrant workers. Her work centered on monitoring exposures in workers' and growers' homes (near orchards), developing improved measures of exposure, determining if intensive cleaning could reduce exposures in homes, and investigating possible neurobehavioral effects of pesticide exposures. A prevention outcome of this project was a Spanish-language videotape that showed how to reduce pesticide exposures in the home and workplace. This videotape was distributed in Oregon and the supporting agency purchased copies to distribute in other agricultural areas of the US.

On a recent visit to Hood River, CROET Associate Director Kent Anger spoke with the father of an Advisory Board member for Linda's study of pesticide exposures in migrant workers and their families. He said that he had seen many other studies come and go in Hood River and the leaders had come with their conclusions already formed. But, his daughter and orchard owner in Hood River told him that Linda McCauley's research was "straight" because she had no pre-conceived conclusions, which was the highest compliment they could give. We couldn't agree more.

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 includes approximately 100 scientists and research staff exploring 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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Artwork by Douglas Russell

OUTREACH

CROET will provide exhibits at the following conferences.

Cascade Occupational Safety & Health Conference

Hilton Eugene & Conference Center
Eugene, Oregon
March 9-11, 2004

Healthcare Ergonomics Conference 2004

Doubletree Hotel Portland - Lloyd Center
Portland Oregon,
July 26-28, 2004

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