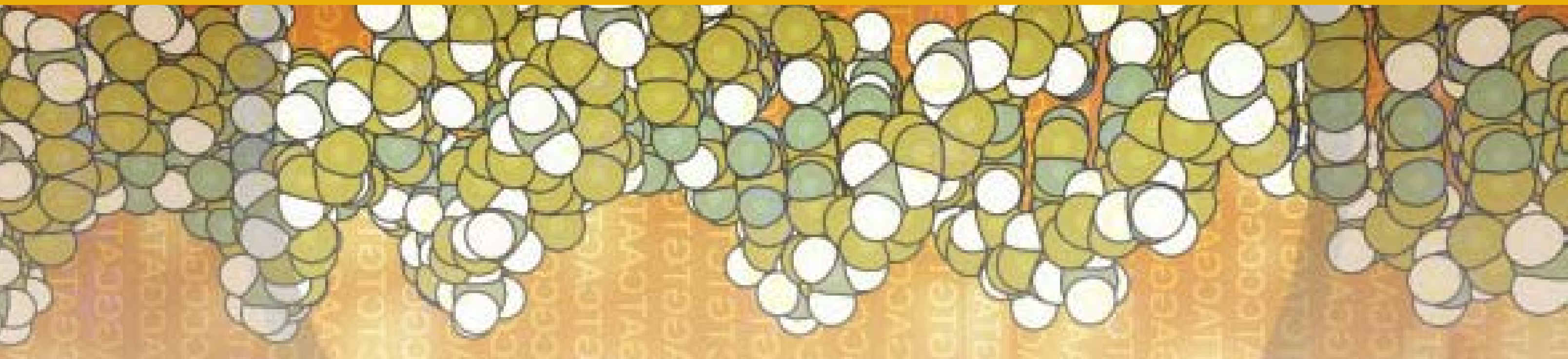

Unlocking the Mysteries of Gulf War Syndrome

Just as those hearty explorers of yesterday spent their days mapping new horizons and presenting our world with better understanding, so do the explorers of today's challenging horizons.

A dedicated team of modern-day explorers under the direction of Mariana Morris, Ph.D., and Daniel Organisciak, Ph.D., has been studying the effects of stress, and chemical interactions with stress, to try to answer more than a century of questions about one aftermath of war—misunderstood and seemingly disconnected health-related symptoms.

"Since the Civil War, similar exhibited symptoms have had different names: Soldiers Heart, Shell Shock, Battle Fatigue, Anxiety Neurosis, Post-traumatic Stress Disorder, and most recently Gulf War Syndrome," explains Dr. Organisciak, chair and professor of biochemistry and molecular biology.

Among the symptoms exhibited by soldiers and veterans through the years are headache, fatigue, respiratory illnesses, muscle and joint pain, skin rash, memory loss, sleep disturbances, gastrointestinal problems, and chest pain. Collectively these are now termed Gulf War Syndrome, the focus of a grant from the U.S. Department of Defense (DoD).

"The premise for Wright State's research team," states Dr. Morris, chair and professor of pharmacology and toxicology, "is that stress is harmful and has a wide-range of effects, that military personnel in any war zone, active or inactive, are operating under an array of physical and psychologically stressful conditions. And, soldiers are sometimes necessarily exposed to a variety of chemicals that are proven in and of themselves not to be harmful to the body."

"However," Dr. Organisciak adds, "could these same chemicals at different levels and concentrations, alone or in different mixtures with an added 'stress factor,' become toxic? Or, have deleterious effects?"

To answer these questions, simultaneous explorations into the physiology of cellular and molecular reactions to stress and chemicals, tissue metabolism using nuclear magnetic resonance spectroscopy, and probing into the genomic, proteomic, and enzymatic pieces of the puzzle are taking place.

Stress and Chemicals, a Toxic Mix

Stress protocols being used document the effects of noise on the auditory brain stem responses and the effect of emotional/physical stress on behavioral, cardiovascular, and endocrine responses. Delving into the effects of stress and chemicals on cellular, molecular, and genome function is a meticulous process of trials.

According to James Lucot, Ph.D., associate professor of pharmacology and toxicology and psychiatry, behavioral science researchers have recently developed and published a unique model for studying chronic emotional stress. This model enables the further long-term study of neuroendocrine, cardiovascular, and behavioral responses to acute or chronic stress.

Chemicals included in the various investigations include: DEET, the active ingredient in some topical insect repellents; pyridostigmine bromide (PB), a self-administered chemical provided by the military as a prophylactic against nerve gas attack; and a highly dilute form of sarin, a toxic chemical warfare agent

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Editor's note: In 2000, Wright State University School of Medicine was awarded a competitive $7.2 million grant from the Department of Defense to study Gulf War Syndrome, examining how the combination of stress and toxins might damage the body. The project received the strong support of U.S. Representative David Hobson and Mary Petticrew, a local philanthropist and community activist.

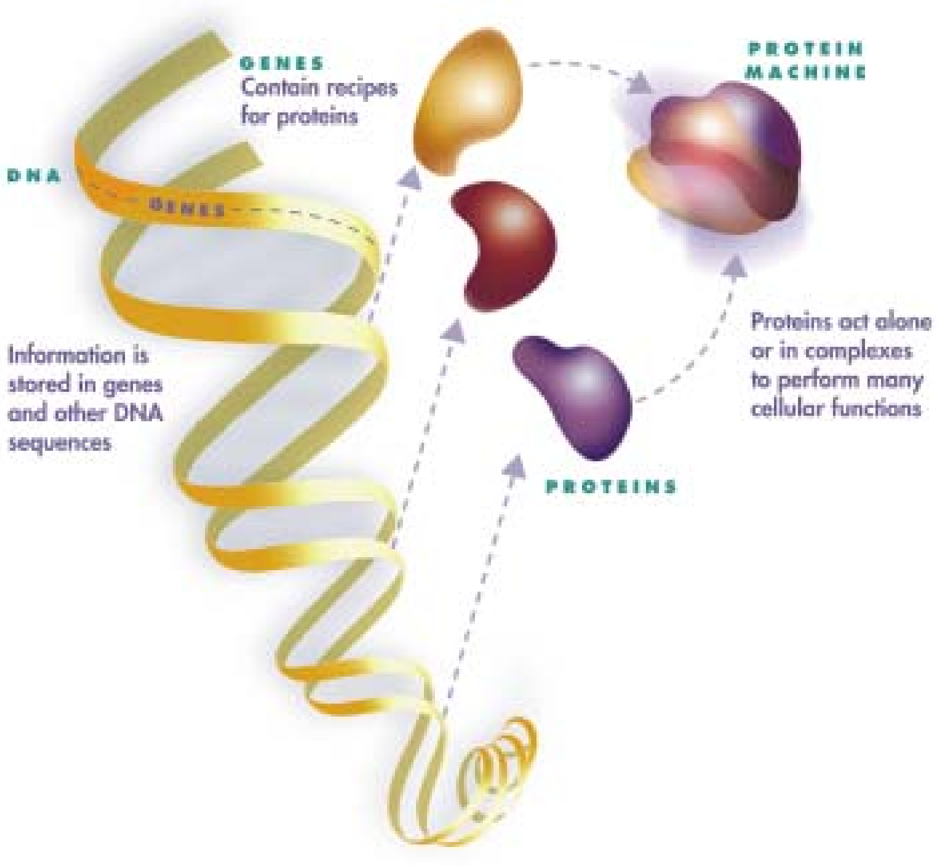
Images courtesy of U.S. Department of Energy Human Genome Program, http://www.ornl.gov/hgmis considered to be a permanent cholinesterase inhibitor. PB protects by "occupying" the cholinesterase enzyme found in blood and nerve endings. This enzyme metabolizes acetylcholine to prevent the action of chemical warfare agents and is critical in the transmission of nerve impulses and, consequently, in the control of breathing and heart rate. Some of the studies indicate there may be changes in the brain after even a low-dose PB exposure.

Nicholas Reo, Ph.D., associate professor of biochemistry and molecular biology, uses nuclear magnetic resonance (NMR) spectroscopy to study brain structures, such as the brain stem. "The NMR studies provide us with a window into tissue metabolism and enable us to evaluate the effects that chemical agents and stress may have on cellular function," states Dr. Reo.

Looking into the Genome

A portion of the examination process uses gene array technology. Led by Steven Berberich, Ph.D., associate professor of biochemistry and molecular biology, and Madhavi Kadakia, Ph.D., assistant professor of biochemistry and molecular biology, the technology in this laboratory is able to monitor changes in gene expression (the process where regions of DNA produce mRNA). Their research suggests that some chemical warfare agents reveal distinctive changes in patterns of gene expression in a small but reproducible set of genes. The research team is attempting to validate the changes and test the effects of dual exposure of these chemical warfare agents to cultured neurons, according to Dr. Berberich.

GENES, PROTEINS, AND MOLECULAR MACHINES



Current Wright State Studies

- **Low-level chemical toxicity and its relevance to chemical agent defense**
- **Studies of central nervous system neurotransmitter systems as related to the effects of PB and sarin**
- **Nuclear Magnetic Resonance (NMR) spectroscopy to determine whether chronic exposure to low levels of chemical agents combined with stress affects the normal function and metabolism of brain structures, such as the brain stem**
- **Combined stress/chemical exposure on behavioral, cardiovascular, and endocrine responses**
- **Importance of timing of the stress response—morning stress is more damaging**
- **Long term effects of PB and sarin on blood and brain cholinesterase activity**
- **Examination of the effect of PB and sarin on gene expression in brain and liver**
- **Measuring enzyme levels found in blood cells and other body tissues that could possibly be used to detoxify or degrade toxic chemicals found**
- **Biochemical analyses to assess alterations in energy metabolism in mitochondria—the energy centers of living cells**

Department of Biochemistry and Molecular Biology

Research Team

Daniel Organisciak, Ph.D., chair and professor

Gerald Alter, Ph.D., associate professor

Steven Berberich, Ph.D., associate professor

Ina Bicknell, Ph.D., assistant professor

Madhavi Kadakia, Ph.D., assistant professor

Mariana Morris, Ph.D., chair and professor

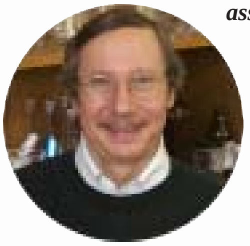
John Paietta, Ph.D., associate professor

David Cool, Ph.D., assistant professor

Robert Grubbs, Ph.D., associate professor

Lawrence Prochaska, Ph.D., professor

James McDougal, Ph.D., professor



James Lucot, Ph.D., associate professor

Nicholas Reo, Ph.D., associate professor

Department of Pharmacology and Toxicology

To monitor changes in the central nervous system, Ina Bicknell, Ph.D., assistant professor of biochemistry and molecular biology, in conjunction with Lawrence Prochaska, Ph.D., professor of biochemistry and molecular biology, and Dr. Reo, uses the auditory brain stem response, a measure of electrical activity generated in the brainstem auditory pathway in response to sound, to determine whether stress increases the permeability of the blood-brain barrier to chemicals.

"Our team also employs long-term exposure to low doses of toxin, rather than an acute exposure to high doses," says Dr. Bicknell. "Environmental toxins may have synergistic effects, that is, the action of one may enhance the action of another. So, to investigate this possibility, we are testing toxins, both individually and in combination with each other, and with a factor of stress included in some of the investigations," Dr. Bicknell explains.

"Integration in research from the genome to the whole animal is a very important aspect of our approach," Dr. Morris explains. "Wright State's unique contribution is crucial in terms of developing this methodology for now and for the future."

The DoD grant has enabled the development of a high-security facility, the founding of both a proteomic and a gene expression laboratory, and the formation of a diverse and skilled research team. Integrative research, such as the Gulf War Syndrome explorations, continues to be a crucial piece of a complex puzzle and one means toward mapping the horizons of the future.

—Nancy Harker

> **"Integration in research from the genome to the whole animal is a very important aspect of our approach."**

Supporting Researchers

Iveta Bernatova, Ph.D., visiting professor, Slovakia

Zoe Bellows, research assistant

Tina Caserta, research assistant

Michal Dubovicky, Ph.D., visiting professor, Slovakia

Vera Farah, Ph.D. visiting professor, Brazil

Luis Joaquim, M.S., visiting research scholar, Brazil

Alagamma Kalaippan, research assistant

Beth Kuczynski, Ph.D., BMS student

Mojmir Mach, M.S., visiting research scholar, Slovakia

Brena Mauch, M.A., BMS student

Andrew Neuforth, research technician

Sara Paton, Ph.D., research associate

Sam Ropp, M.S., BMS student

Sehul Shah, M.S., student

Lois Shroyer, M.S., research associate

Glossary

DNA. (deoxyribonucleic acid) The chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

Enzyme. A protein that encourages a biochemical reaction, usually speeding it up.

Gene. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Gene expression. The process by which proteins are made from the instructions encoded in DNA.

Genetic marker. A gene or group of genes used to "mark" or track the action of microbes.

Genome. The sum total of an organism's genes.

Genomics. The study of activites and functions of a cell's or an organism's genes.

Genotype. The genetic make-up of a person.

mRNA. (messenger RNA) Template for protein synthesis. Each set of three bases, called codons, specifies a certain protein in the sequence of amino acids that comprise the protein. The sequence of a strand of mRNA is based on the sequence of a complementary strand of DNA.

Microarray Technology. The study of large numbers of genes very quickly by using advanced computers and software programs connected to a scanning microscope.

Pharmacogenomics. The study of how an individual's genetic inheritance affects the body's response to drugs.

Protein. Often called the "building blocks" of tissues. A large complex molecule made up of one or more chains of amino acids.

Proteome. All of the proteins produced from all the genes of a genome.

Proteomics. The study of activities and functions of the proteins in cells and organisms.

Resource: www.genome.gov/glossary.cfm