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In This Issue

The Return of the ORISE Cytogenetic Biodosimetry Laboratory

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Why would a laboratory that was established in the 1960s and closed in the 1990s be reestablished now? In large part because of 9/11. Due to the increased threat of a radiological event, a population of people who do not routinely wear personal dosimeters may be exposed to ionizing radiation.

> *. . . a biological method to estimate the radiation dose . . . when physical dosimetry methods either require verification or are unavailable.*

The Oak Ridge Institute for Science and Education (ORISE) Cytogenetic Biodosimetry Laboratory (CBL), which was opened and dedicated in March 2007, has the capability to help assess the dose of radiation exposure received by victims of both accidental occupational exposures and nuclear terrorism.

"The widespread use of ionizing radiation for medical, industrial, military, and research purposes has increased the risk of accidental occupational exposures," explained CBL Technical Director Dr. Gordon K. Livingston. "However, the four terrorist attacks on the United States which occurred on 9/11 brought about a new and greater concern for radiation exposure, namely, the threat of nuclear terrorism. Several terrorist threat scenarios could result in segments of the population being exposed to ionizing radiation. The Cytogenetic Biodosimetry Laboratory was developed as an integral part of a national emergency response plan to have the necessary medical countermeasures in place in the event of mass radiation casualties. Accurate radiation dose estimates are essential for physicians providing medical care and making life-saving decisions for patients exposed to ionizing radiation. Cytogenetic biodosimetry could play an important role in providing the necessary dose estimates."

To bring *Health Physics News* readers up to date on this exciting technology, Livingston explained cytogenetic biodosimetry and discussed its origins and uses.

What is cytogenetic biodosimetry?

Livingston: Cytogenetic biodosimetry is a biological method to estimate the radiation dose received by a person when physical dosimetry methods either require verification or are unavailable. The method is based on ionizing

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radiation's capacity to induce DNA strand breaks as it passes through a cell's nucleus (typically a circulating lymphocyte). The extent of DNA damage is then measured by counting the number of broken and rearranged chromosomes in a sample of cells after they have been induced to divide in culture. The measurement of the chromosomal/DNA damage can be quantified microscopically and compared to a standard calibration curve in order to derive a dose estimate.

How is cytogenetic biodosimetry used to estimate radiation exposure?

Livingston: Once the chromosomal/DNA damage is quantified by scoring several hundred cells using a microscope, the frequency of broken and rearranged chromosomes (indicated by dicentrics—chromosomes with two centromeres) can be compared to a calibration curve in order to calculate a dose estimate. Such a comparative analysis for dose estimation is valid because it has been shown that the response of human lymphocytes to ionizing radiation is qualitatively and quantitatively the same whether the radiation exposure occurs when the lymphocytes are in the body (in vivo) or out of the body (in vitro).

How long does it take to figure out the exposure using cytogenetic biodosimetry?

Livingston: Lymphocytes in peripheral blood require 48 hours to culture before they can be harvested, processed onto slides, and then stained and mounted with coverslips and are ready for microscopic analysis. The earliest time in which a result can be obtained is sometime during the third day (72 hours) when several hundred cells must be screened visually to count the frequency of dicentric chromosomes, which are known to correlate with the radiation dose.

Can other things cause the same type of damage to the chromosomes or is the damage radiation-specific?

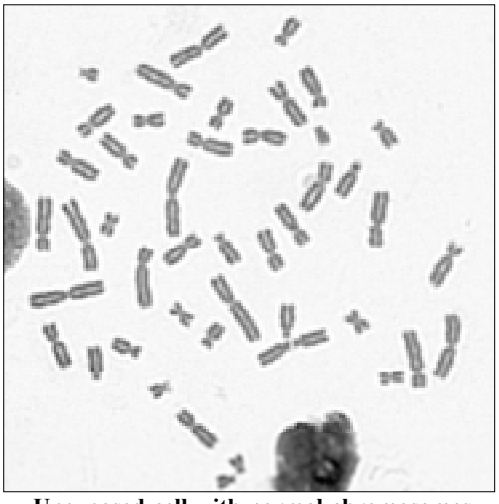
Livingston: For the most part the chromosome aberrations known as dicentrics are quite radiation-specific. There are some radiomimetic chemicals (typically represented by alkylating agents used in chemotherapy) that can mimic radiation effects, but they are not likely to present a confounding exposure.

When did the field of cytogenetic biodosimetry start?

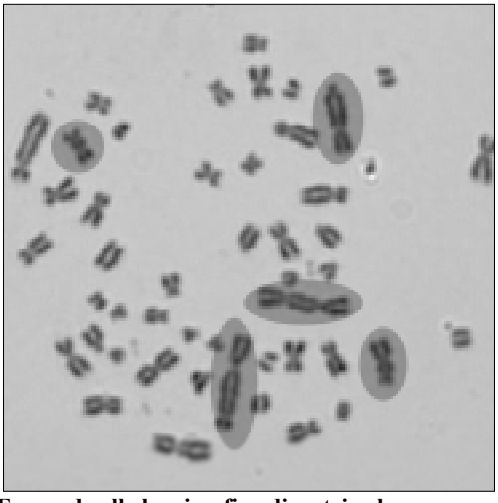
Livingston: The origin of cytogenetic biodosimetry can be traced back to the mid-1960s when chromosome aberrations were first observed by Michael Bender in patients undergoing radiation therapy treatments. This observation led to the idea that such effects might serve as biological markers of radiation exposure. In vitro lymphocyte calibration curves were established (though not without controversy). Later in the 1960s, the technique became firmly established when tested in a number of cases of accidental human exposure to radiation where physical data allowed dose reconstructions to provide a test of the cytogenetic dosimeter's usefulness.

When was the ORISE Cytogenetic Biodosimetry Laboratory first begun and why?

Livingston: In 1976 the US Department of Energy (DOE) established the Radiation Emergency Assistance Center/Training Site (REAC/TS) to provide expertise in the medical management of radiation accidents. Dr. L. Gayle Littlefield and members of her Oak Ridge Associated Universities cytogenetics research group joined with REAC/TS staff in setting up a cytogenetics



Unexposed cell with normal chromosomes



Exposed cell showing five dicentric chromosomes

biodosimety laboratory for providing "biological dose estimates" for persons involved in real or suspected radiation accidents. In addition to providing biological dosimetry, Littlefield's group conducted basic research in cytogenetics and studies of the long-term persistence of radiation-induced chromosome aberrations in irradiated patients.

When was the CBL discontinued and why?
Livingston: The CBL was discontinued in 1998 at the time the DOE began closure, dismantling, and clean-up work of a number of nuclear plant sites throughout the United States.

Why has the CBL been reestablished?
Livingston: The reemergence of the CBL has come about due to the growing threat of nuclear and radiological terrorism in the United States and throughout the world. The risk of deliberate use of radiological materials to harm unsuspecting civilian populations has increased dramatically. Physicians, hospitals, and other health care institutions will assume primary responsibility for providing care to individuals injured by a terrorist act involving nuclear materials. Dose assessments are critical for guidance of health care professionals in the diagnosis and treatment of victims. In addition to providing dose estimates to physicians, the CBL will research, develop, and validate new and innovative biodosimeters that will provide results in the shortest turnaround time possible.


Livingston demonstrating the cell culture harvesting process.

In what ways does the CBL use cytogenetic biodosimetry?
Livingston: The primary function of the CBL is to support the REAC/TS at ORISE in its role as an emergency response asset for DOE-NNSA (National Nuclear Security Administration). The CBL will serve as a triage tool to assess victims during a response to a radiological or nuclear event. Numerous casualties could quickly overwhelm medical facilities; therefore, it will be essential to distinguish individuals with little or no absorbed dose from those with mild, moderate, or severe doses so that medical resources are allocated to the best possible advantage.


Livingston analyzing samples on the automated cytogenetic biodosimetry workstation developed by MetaSystems.

Have there been new developments in the field that make cytogenetic biodosimetry more applicable for practical use than it used to be?
Livingston: Yes, many innovations and new developments with motorized microscopes, automated slide-scanning workstations, digital imaging, and the associated computer software programs have made the cytogenetic biodosimetry process more efficient and less time consuming. For example, automated systems can quickly scan a microscope slide and locate the scoreable cells in minutes compared to the hours required using manual methods. The screening of metaphase cells for evidence of radiation damage, however, still occurs visually by a well-trained cytogeneticist on the computer monitor.

Is there anything you would like to add about cytogenetic biodosimetry?
Livingston: Since the laboratory became operational and was dedicated on 30 March 2007, radiation calibration curves have been established for gamma rays, x rays, and neutrons. The CBL also participated in an international biodosimetry network along with four other laboratories (including the Armed Forces Radiobiology Research Institute and similar laboratories in Germany, Japan, and Canada) in the construction of a gamma-ray calibration curve and multiple "blind" dose assessment studies.

A critical component in reestablishing the CBL has been the support of the DOE-NNSA Emergency Response group headed by Admiral Joseph Krol. Without this primary source of funding and encouragement the CBL would not exist. Additional support was provided by the Nuclear Regulatory Commission and the DOE Office of Environment, Safety, and Health.

Gordon K. Livingston, PhD, works at the Radiation Emergency Assistance Center/Training Site (REAC/TS) in Oak Ridge, which is a program of the U.S. Department of Energy's Oak Ridge Institute for Science and Education (ORISE).

Livingston obtained degrees from Utah State and Oregon State Universities and a PhD in genetics from the University of Washington in Seattle, followed by a post-doctoral fellowship in radiobiology at the University of Nijmegen in the Netherlands. He has held faculty positions in environmental and occupational health at the University of Cincinnati and the University of Utah, where he also served four years as the technical director of the clinical cytogenetics laboratory in the Department of Pediatrics.

His research has focused on human cytogenetic responses to environmental adversity including environmental, occupational, and medical exposures to ionizing radiation. Examples include a radiobiological evaluation of families living near Chernobyl at the time of the accident in 1986. Eighty individuals who immigrated to Ohio over a two-year period (1989-1991) were tested for radiocesium uptake using a whole-body counter at the University of Cincinnati Medical Center along with a study of gene and chromosomal mutations. Results were positive for some individuals both for the presence of radiocesium and increases in gene and chromosomal mutations in blood cells. Another study involved occupational exposure to alpha radiation and its effect on chromosome aberration rates in former nuclear workers. A chromosome "painting" method was used to screen for translocations as a biomarker of past radiation exposure. Elevated rates of translocations, adjusted per genome equivalent, were found in former nuclear workers many years after plutonium intakes and were shown to correlate with bone marrow dose. Other studies focused on radiation therapy patients treated with radioiodine for thyroid cancer as well as patients treated with external radiation for lung and colon cancer. Medical irradiation studies are particularly useful since blood can be collected before and immediately after treatment and the cytogenetic response related to the treatment dose.

Before coming to ORISE, Livingston held a National Research Council Senior Research Associateship sponsored by the National Institute for Occupational Safety and Health in Cincinnati, Ohio.

Coming in the November *Health Physics News*
—A continuation of our discussion on cytogenetic biodosimetry—
Dr. Pataje Prasanna talks about the
Armed Forces Radiobiology Research Institute's (AFRRI)
work in cytogenetic biodosimetry.