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Project Title: Biological Effects of LLIR and Normal Oxidative Damage: The Same or Different?

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Number of Graduate Students Actively Involved in Project: 1 (Susan Bailey)

Specific DOE Problems That Are Being Addressed and Potential Practical Relevance:

Epidemiology alone is insufficient to estimate risks associated with low-level ionizing radiation (LLIR) with confidence. Yet much of the concern in mitigating environmental effects of the "cold war legacy" of radiation contamination involves LLIR. For example, a question arises as to how clean a contaminated site needs to be in order to be considered adequately restored. The answer depends in part on the risk associated with residual contamination. Incorporation of radiobiological principles offers policy makers a means to improve LLIR risk assessment. However, these principles must be established under realistic exposure conditions to be defensible. Typically in vitro radiobiological experimentation is conducted under normal atmospheric conditions. The oxygen content of the atmosphere, which exceeds the physiological oxygen concentration by several fold, may affect the results of radiation experiments. Therefore it is the goal of this newly funded project to examine genetic damage, and cellular responses to that damage, induced by LLIR under physiological O<sub>2</sub>. One important question to be answered: Does LLIR produce biological effects that are fundamentally different from those caused by endogenous oxidative damage? If it does, then there is a firm rationale for radiation protection concepts that seek to limit radiation exposure to the lowest reasonably achievable level. Alternatively, genetic damage induced by LLIR may be essentially the same as endogenous oxidative damage. If so, then LLIR would impose a small, and often temporary, increase in the overall burden of genetic damage. This condition would not differ qualitatively from variations in endogenous oxidative damage that occur naturally in response to stimuli such as exercise, dietary change, or infection. In this case, radiation protection standards for LLIR might justifiably be relaxed.

#### Research Objective:

Low LET radiation produces most of its effects through the generation of reactive oxygen species (ROS), i.e. the so-called "indirect effect". These ROS are not unique to radiation exposure, but are also produced continuously during the course of aerobic metabolism. In vitro radiobiological experiments are conducted almost exclusively under normal atmospheric oxygen, a value that exceeds the in vivo physiological oxygen concentration by about six fold at sea level. Thus the true cellular response to LLIR may be masked or distorted by an unnaturally high level of oxidative lesions imposed by non-physiological O<sub>2</sub>. This situation calls into question the soundness of currently accepted radiobiological experimental methods, especially as they relate to science-based risk assessment.

We propose to establish an oxidative stress laboratory where experiments can be conducted on cells grown in gas mixtures containing from 2.5 to 95% O<sub>2</sub>. This 38-fold difference will result in dissolved O<sub>2</sub> concentrations ranging from slightly hypoxic, to physiological (4.3% O<sub>2</sub> at the elevation of Los Alamos), through "normal" atmospheric cell culture conditions (19% O<sub>2</sub>), to clearly hyperoxic. Taking the physiological O<sub>2</sub> concentration as the appropriate control condition, we will examine and compare the consequences of inducing genetic damage either by LLIR or by temporary exposure to elevated O<sub>2</sub>. We will determine if transient oxidative stress induces the same genetic effects, such as DNA base damage, chromosome aberrations, HPRT mutation, and transformation, as exposure to ionizing radiation. Furthermore, we will determine if important cellular responses, such as bystander effects, the adaptive response, and genomic instability, can be induced by LLIR without the additional oxidative stress imposed by atmospheric O<sub>2</sub>, or if the threshold dose for initiating these effects changes.

#### Research Progress and Implications:

This report summarizes work after approximately 5 months of a three year project. Thus the project is still in an early stage. We are in the process of setting up an oxidative stress laboratory and establishing the cell culture procedures for the biological assays that will be used routinely. Experiments are in progress that are designed to investigate reported beneficial effects of low radiation doses. This phenomenon has been named "hormesis". The experiments will test the hypothesis that hormesis results from a triggering of an antioxidant defense mechanism by low doses of radiation.

The PI attended and presented a poster at the Low Dose Radiation Research Meeting that was held in Washington, DC on November 10-12, 1999. Several potential collaborations with other DOE low-dose investigators were identified and will be pursued in the near future.

#### Planned Activities:

We have identified radiation hormesis as a research subject that is likely to have a significant impact on risk analysis in the short term. We will investigate the mechanistic basis of this phenomenon in the coming year.

Information Access: No publications have as yet resulted from this project.