MICE, MYTHS AND MEN

Lauriston S. Taylor Lectures in Radiation Protection and Measurement (Lecture No. 18). R.J. Michael Fry. Bethesda, MD: N.C.R.P.; 1995, 50 pp, $20.00.

This paperback publication is a transcript of the eighteenth NCRP Lauriston S. Taylor Lecture in Radiation Protection and Measurement entitled *Mice, Myths, and Men*. The author, R.J. Michael Fry, MD, of Oak Ridge National Laboratory, is an extraordinary radiobiologist and a world leader in the field of radiation carcinogenesis.

This lecture addresses questions about the effects of ionizing and ultraviolet radiation on genes and how these changes may be linked to cancer production. Dr. Fry begins by justifying the use of various animal models to study radiation carcinogenesis in man by drawing attention to the marked conservation of gene composition across phyla. A major concern about extrapolating estimates of risks of radiation-induced cancer across species has been the assumption that the mechanisms of carcinogenesis are quite different among species. However, the more that we learn about how genes are involved in cancer, especially those changes related to the initial events in carcinogenesis, the greater the similarities are noted to be among species. This homology of DNA has made experimental mammalian and other systems valid models for addressing many biological questions.

The incidence of susceptibility for a particular cancer in humans is related to differences in lifestyle, diet and exposure to environmental factors that in turn are related to ethnic and geographic differences. Therefore, it is difficult to determine just how and to what degree cancer susceptibility is related to inherited factors. Dr. Fry presents many animal models which demonstrate large differences in susceptibility to cancer ranging from the familiar laboratory mouse to the common domestic burro. In the case of solid cancers, the susceptibility to radiation induction appears to be related to the incidence of the naturally occurring tumors for that species.

The lecture continues with a presentation of various theories of carcinogenesis. Most models assume that carcinogenesis is a multistage process similar to that observed during embryogenesis. Researchers also assume that the initial cancer causing event(s) at the gene level is associated with a defective repair mechanism(s) and/or a germ-line mutation. There is mounting evidence to suggest that the tissue environment or the influence of the community of cells surrounding a mutated cell is important for the expression or development of cancer in an organism. Investigators have found a large differential in the number of initiated or mutated cells that have the potential to develop into a cancer and the number of cancers that are expressed. We now know that a tissue can suppress the expression of malignant growth and this observation has stimulated a whole new area of investigation.

A model for the carcinogenic process in colorectal tissues in humans is presented in some detail. The model assumes that colorectal carcinomas develop from benign lesions. The sequential nature of the histological changes from adenoma to carcinoma are described along with the suggestion that certain corresponding changes at the molecular and cellular levels also occur. These mutations involve both oncogenes and tumor suppressor genes. Deletions of alleles on chromosomes 5, 17 and 18 have been identified, as well as at least three tumor suppressor genes. Loss of alleles from chromosome 17p is a common finding in colorectal cancer. This region contains the p53 gene, thus resulting in the loss of a functioning tumor suppressor gene. A complicated discussion of how multiple gene mutations in a tissue supportive of a malignant process may occur from one low dose of radiation then follows.

As the mechanisms of carcinogenesis are revealed and more fully understood, there appear to be three universal changes that must occur for a life-threatening cancer to develop. These changes are altered control of cell proliferation, accelerated angiogenesis, and the development of the ability of a tumor to invade neighboring tissues and to metastasize. Little is known about the role of radiation in the stimulation of angiogenesis and metastases.

Dr. Fry completes his lecture with a review of cancer induction and the cell cycle, along with the extrapolation of risk of radiation-induced cancers across species. Perhaps the most singular change associated with neoplasia is altered control of cell proliferation; cell production exceeds cell loss. This is associated with a well-characterized alteration in the cell cycle. Important to radiation-induced neoplasia is the observation that p53 deficient mice are extremely susceptible to tumorigenesis. The mechanism(s) of how the p53 tumor suppressor gene and its place in the cell cycle affects cancer susceptibility is being actively investigated. This gene is clearly involved with controlling the cell cycle, enhancing DNA repair and influencing malignant progression.

In general, Dr. Fry's lecture is a brilliant and concise discussion of the most common and current theories of radiation carcinogenesis derived from various animal models. The author was quick to explain these theories in the context of traditional teachings and to point out their implications for human medicine. Organizing and presenting a review of such a large number of studies is a tremendous task and therein lies its great value. I highly recommend *Mice, Myths, and Men* to those who have special interests in cancer research and radiation carcinogenesis. This manuscript should be essential reading for graduate students studying radiation biology, as well as residents and practicing physicians in the fields of nuclear medicine, radiology and radiation oncology. Nuclear medicine technologists may also find this interesting reading.

Michael J. Blend, PhD, DO
Section of Nuclear Medicine
University of Illinois at Chicago
Chicago, Illinois