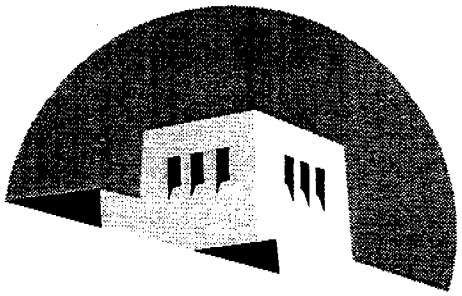

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THE UNIVERSITY OF NEW MEXICO
COLLEGE OF PHARMACY
ALBUQUERQUE, NEW MEXICO

Correspondence Continuing Education Courses for Nuclear Pharmacists

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Low Level Exposure to Ionizing Radiation: Current Concepts and Concerns for Nuclear Pharmacists

by:

Stanley M. Shaw, Ph.D.
William R. Widmer, DVM, M.S.

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Stanley M. Shaw, Ph.D.
William R. Widmer, DVM, M.S.

Editor

William B. Hladik III, M.S., R.Ph., University of New Mexico

Director of Pharmacy Continuing Education

Hugh F. Kabat, Ph.D., University of New Mexico

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LOW-LEVEL EXPOSURE TO IONIZING RADIATION: CURRENT CONCEPTS AND CONCERNS FOR NUCLEAR PHARMACISTS

STATEMENT OF OBJECTIVES

The objective of this review is to provide an overview of some of the current concepts and concerns about low-level exposure to ionizing radiation. Topics considered are mechanisms of radiation injury, assessing risk, genetic (heritable) effects, radiation carcinogenesis, and effects upon the embryo/fetus. The review is not all-inclusive as the material available is voluminous. However, upon successful completion of the course the reader should be able to:

1. Describe the initial changes in DNA brought about by radiation.
2. Discuss the concepts of repair of DNA following irradiation.
3. Understand the concept of target theory and resultant terminology.
4. Describe cell survival vs. dose relationships for single-hit, multi-hit systems.
5. Compare the concept of the "Q" theory to target theory.
6. Describe the difference between a gene (point) mutation and a chromosome mutation.
7. Understand radiation-induced injury to chromosomes.
8. Discuss the controversy regarding the shape of the dose response curve for radiation-induced genetic effects.
9. Discuss the importance of species, dose rate and dose as relevant to induction of mutations.
10. Describe two methods for assessment of the risk of genetic effects caused by ionizing radiation.
11. Understand the concept of the genetically significant dose.
12. Define the term radiogenic cancer.
13. List and explain three possible mechanisms regarding the induction of cancer by radiation.
14. Define the terms absolute risk and relative risk of radiogenic cancer.
15. Describe dose response models for cancer induction and relate the fundamental differences between models.
16. Explain the consequences of employing one dose response model for cancer induction vs. another.
17. Compare the risk of death from cancer from an acute dose to that from a fractionated dose.
18. List the potential effects of in utero exposure of the embryo/fetus to ionizing radiation.
19. Describe the risk of mental retardation from in utero exposure to radiation.
20. Discuss the concept of radiation induced life-span shortening vs. the concept of hormesis.

COURSE OUTLINE

I. INTRODUCTION

II. OVERVIEW: MECHANISM OF RADIATION INJURY

III. GENETIC (HERITABLE) EFFECTS OF RADIATION

- A. Introducton
- B. Mutagenesis
- C. Assessing the Risk

IV. RADIATION CARCINOGENESIS

- A. Introduction
- B. Mechanisms of Cancer Induction
- C. Assessing the Risk
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VI. OTHER LATE EFFECTS DUE TO LOW-LEVEL IONIZING RADIATION

VII. SUMMARY

LOW-LEVEL EXPOSURE TO IONIZING RADIATION: CURRENT CONCEPTS AND CONCERNS FOR NUCLEAR PHARMACISTS

By

Stanley M. Shaw, Ph.D.
Professor and Head
Division of Nuclear Pharmacy
Department of Medicinal Chemistry
and Pharmacognosy
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, Indiana 47907-1248

William R. Widmer, DVM, M.S.
Diplomate ACVR
Associate Professor, Diagnostic Imaging
Department of Veterinary Clinical Sciences
School of Veterinary Medicine
Purdue University
West Lafayette, Indiana 47907-1248

INTRODUCTION

Understanding the current concepts and concerns about low-level exposure to ionizing radiation is of the utmost importance to the nuclear pharmacist. It is the responsibility of the nuclear pharmacist to inform ancillary personnel about the potentially harmful effects of radiation. As new knowledge is generated, the nuclear pharmacist must be aware of changes in concepts and the implications for all personnel employed in the pharmacy.

Because of the excellent radiation protection procedures utilized in a nuclear pharmacy, the biological effects of low-level chronic exposure occurring over years of employment is the main concern for personnel in nuclear pharmacy practice. Concerns regarding low-level chronic exposure include carcinogenesis, life-span shortening, cataractogenesis, and genetic dysfunction. Of these effects, radiation carcinogenesis is considered as the single most important consequence of low level exposure to ionizing radiation (1).

Although there is an abundance of literature regarding the deleterious effects of low-level chronic exposure, considerable controversy and uncertainty

regarding the true hazard to personnel still exists. The determination of appropriate dose-response relationships for low doses based upon evidence obtained from higher dose risk assessment data continues to be a significant, controversial issue. The issue will not be resolved until mechanisms of cancer induction and expression are fully understood.

The objective of this review is to provide an overview of several aspects relative to the potential problems from low-level chronic exposure. Emphasis is placed upon low LET radiation since current radiopharmaceuticals incorporate primarily gamma-emitting radionuclides. Upon completion of the review, the pharmacists should be enhanced in the knowledge of the potential effects from low-level chronic exposure and the controversy that exists regarding this important issue.

OVERVIEW: MECHANISM OF RADIATION INJURY

Radiation injury to biologic systems is a result of damage within cellular macromolecules, principally DNA (2,3). With low LET radiation, most damage is mediated through radiolysis of intracellular water (indirect effect). Free radicals produced by radiation (Fig. 1) diffuse short distances within the nucleus and interact with DNA molecules (Fig. 2). This may result in loss or change of base(s), crosslinking of DNA strands, and single- or double- strand breakage. Initial physicochemical events occur over a period of 10^{-6} seconds (3,4). Because DNA is central to all cellular functions, and damage can be amplified many times during transcription and translation, DNA is considered as the most important cellular component regarding injury from a given dose of radiation (2-5).

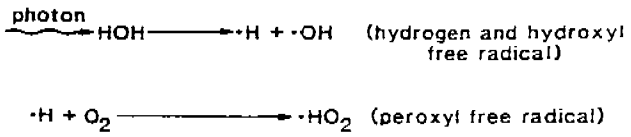

Figure 1. General reactions occurring during radiolysis of water (HOH). A photon of radiation causes splitting of the water molecule into free radicals. In the presence of oxygen, peroxy free radical, a potent reactant is produced.

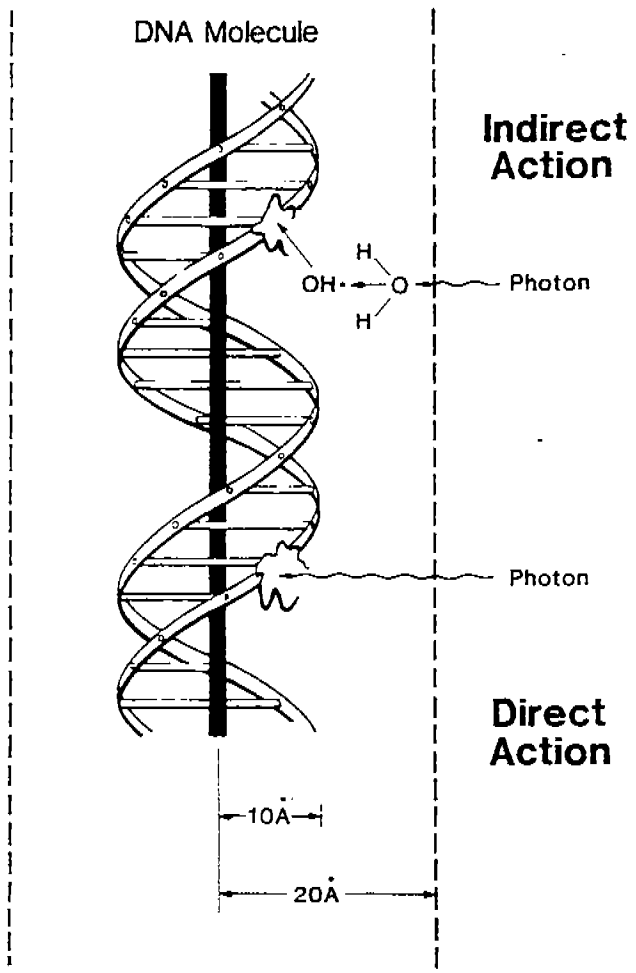

Figure 2. Direct and indirect action of radiation on DNA. With direct damage, a photon of ionizing radiation causes direct injury to DNA by altering its structure. In the living cell, a photon is more likely to first react with water, producing free radicals (see Fig 1) which attack the DNA molecule. Only free radicals produced near a DNA molecule (20 angstroms) are likely to be effective because of their short half-life. (From Hall, EJ Radiobiology for the Radiologist, ed 3, Philadelphia, Lippincott, 1988).

Repair of DNA damage is presently an area of intense research (6-7). Repair of some types of DNA damage, including single and double strand breaks, occurs in bacteria, yeast and certain mammalian cells. Repair is accomplished by a complex series of enzymatic steps wherein the damaged portions of DNA strands are excised and patched. However, mis- or inaccurate repair may lead to mutation and carcinogenesis (1,8). Mis-repair occurs when the patched portion of the DNA strand does not contain the proper base sequence. Depending on the extent and type of injury, DNA is usually repaired by cellular mechanisms within minutes to hours following exposure to ionizing radiation (7). Post-irradiation conditions, including oxygen concentration,

temperature, pH, and position in the cell cycle may affect the outcome of DNA repair (8). For instance, repair of sublethal damage is favored by physiologic pH and oxygen concentration, while repair of other forms of damage is most likely to occur when irradiated cells are under the influence of low oxygen concentration and low temperature.

The importance of position within the cell cycle, frequency of mitosis, and cellular differentiation cannot be neglected in considering the potential for repair of damage to DNA and other cellular components. For instance, cells in late G_2 and mitosis are less capable of repairing damage than are cells in G_1 or S. The so-called "Law of Bergonie and Tribondeau" still has considerable merit as cells that are radiosensitive may not have the repair capability of less sensitive cells (5).

Many approaches have been used to determine the important component(s) in a cell that is sensitive to radiation and important to function and replication. In early studies, microbeam irradiation and microsurgical techniques were used to identify the putative "target" of radiation injury. A mathematical expression of survival relationships for increased doses of radiation applied to cells *in vitro* was also used to ascertain target size. As a result of the latter approach, the concept of the target theory evolved (2,8) as a means of identifying the components(s) within a cell of importance. The target theory is a model in which it is stated that the production of ionization in or very near a structure (target) is responsible for the observed effect. The ionization in or near the structure is termed a hit. In the case of a single-hit model, it is stated that a single event in or near the target will result in the effect observed. Mathematical expression of cell survival vs. dose models led to the concepts of D_o and D_{37}. D_o is identified as the dose that will give an average of one hit per target in the cell population. The mathematical expression predicts that if a D_o dose is given, 37% of the original number of cells will survive (D_{37}).

For the single-hit theory it is stated that there is a target that must be hit once to inactivate the cell. According to the multi-hit theory, there is more than one target in the cell and each target must be hit once to inactivate the cell. A semi-log expression of survival fraction data vs. dose for a system exhibiting the characteristics of a two-hit system results in a survival curve that has a shoulder followed by a linear decrease in survival from increasing dose (Fig. 3b). The shoulder region may be considered as an area of sublethal damage where repair may occur and cells may survive. A single-hit system results in a linear decrease in survival with no indication of repairable damage (Fig. 3a).

Another approach to interpretation of cell survival vs. dose curves is that of a single-target or multi-target system. The single target theory states that the system (cell) has a single target that must be hit once to elicit the response. The multi-target theory states that the cell has two or more targets. In order to inactivate the cell, each of the targets must be hit once. The survival fraction vs. dose curve appears the same for either the single-hit, multi-hit or single-target, multi-target models. It should be noted that although DNA is considered the "target" of radiation, the exact type and amount of damage (base deletion, strand break, etc) that is sustained remains obscure.

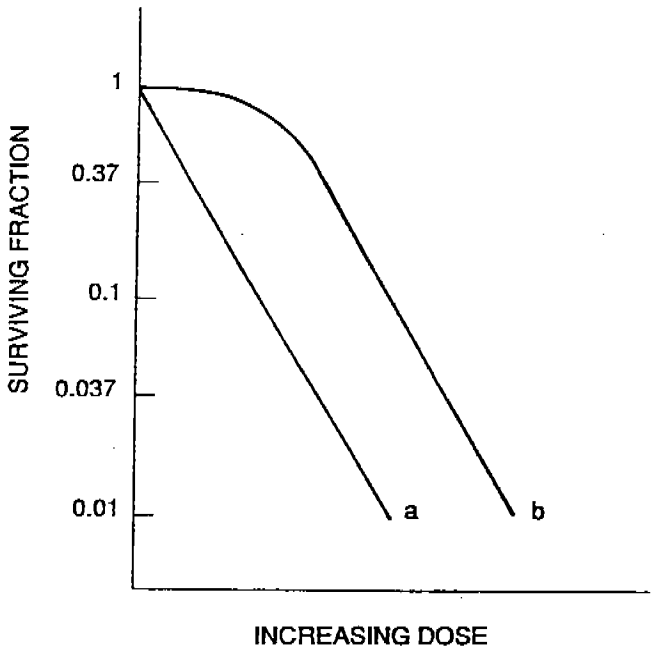

Figure 3. Dose-response model for cell killing (reproductive death) comparing single hit (a) and two hit radiation damage (b). A semi-log plot is used. The dose-response to cells with a single target for cell killing is linear (a). Note the lack of a shoulder in the first decade of cell killing. With a cell system requiring two hits for cell killing, there is a shoulder representing sublethal damage (b). The slope (D_o or D_{37}) for both dose responses is the same at higher doses.

In addition to the target theory, the "Q" theory has been offered as an explanation for observations related to cell killing. With the Q theory, cells are considered to contain a single radiosensitive site (DNA). However, cells also are thought to contain a protective "Q" substance that engenders repair of radiation damage before it can be expressed (6). Therefore, Q substance must be inactivated by

radiation before cell killing (reproductive death) occurs. The Q substance has not been conclusively identified, but may be associated with sulfhydryl-rich intracellular molecules (8). The Q theory assumes that repair of sublethal damage occurs and can be demonstrated on the dose-response curves used for the target theory. When Q is present within the cell, cell killing is typified by the shoulder of the dose-response curve. When Q has been inactivated, cell killing is represented by a straight line.

GENETIC (HERITABLE) EFFECTS OF RADIATION

Introduction

Ionizing radiation is a potent mutagen. Numerous radiation-induced gene and chromosome mutations have been documented in man and animals. Gamma and x-ray are known to increase the rate of spontaneous mutations in man and animals. Mutations caused by ionizing radiation are no different than those that occur naturally and are also the same as those caused by viruses and chemicals. Hence, their detection in human populations is a difficult task requiring sophisticated statistical methods.

Although the term "genetic effects" (mutations) usually implies injury to germ cells (reproductive tissue) causing hereditary diseases, the genome of somatic cells can also undergo mutation and the damage can be expressed in daughter cells of an organ or tissue. Therefore, exposure to ionizing radiation can result in damage to future generations, that is, hereditary, or to the parent organism. For example, squamous cell carcinoma of the hands is thought to result from genomic damage to somatic cells of an individual, while dysproteinemia that has been observed in the offspring of atomic bomb survivors is caused by geneomic damage to reproductive tissue of the parent(s). The important issue of cancer induction will be dealt with under the heading "Radiation Carcinogenesis."

While heritable effects of radiation have been extensively studied in animals, there is a paucity of data for human beings. The major source of human data stems from the continuing evaluation of data collected from offspring of survivors of the Hiroshima and Nagasaki atomic bomb detonations. Although dose rates were high and the LET varied, considerable effort has been made to normalize the data so that low dose and low dose rate extrapolations can be made for low LET radiation exposure. Although the results have been questioned repeatedly by the scientific community, atomic bomb survivors remain the best source of information regarding human genetic effects resulting from exposure to ionizing radiation. Because future generations of the survivors will be studied, these data will continue to yield meaningful conclusions in the years to come.

Mutagenesis

A gene (point) mutation is a change in the primary structure of DNA resulting from loss, gain or substitution of a base. Gene mutations can be dominant, recessive, or sex-linked and range from being nearly imperceptable to lethal. Chromosome mutations (aberrations) are more complex than gene mutations and result from radiation-induced chromosome breaks. After a chromosome has been broken, the break may be restored with no ill effect (restoration) or part of the chromosome may be lost during the next mitosis (deletion). When there are multiple breaks in a chromosome, rearrangement of sections of chromosomes may occur, changing the base sequence and the genetic code. Rejoining (restitution) of broken ends of the same chromosome results in formation of rings, and rejoining of two different chromosomes may result in formation of a dicentric; these events usually result in mitotic death.

Specific data on point mutations in human beings is lacking, but cytogenetic damage induced by gamma and x-irradiation has been studied in man and animals. A high number of chromosomal mutations (dicentric and rings) has been observed in the circulating lymphocytes of medical radiation workers and atomic bomb survivors. Although these mutations may persist for years, cytogenetic damage to lymphocytes has not been linked to an increase in cancer rate (2,9). Because they are easily sampled and are uniquely sensitive, lymphocytes have been used as a dosimeter for human exposure to gamma radiation. A linear-quadratic, no threshold dose response has been generally described (2); however, there is other evidence that a threshold clearly exists (9).

Ionizing radiation may also injure or cause dysfunction of the mitotic apparatus that either slows or impairs mitosis (8). A serious imbalance of genetic material in daughter cells may result. Damage to the centromere of a chromosome may slow migration of a chromosome (lagging) along the mitotic spindle so that it is not included in a daughter cell. The leftover chromosome becomes a micronucleus and is lost to future generations. Rearrangement following multiple breaks of

chromosomal arms may result in location of a centromere at the end of a chromosome. For unknown reasons, chromosomes do not function properly during mitosis when a terminal centromere is present. During mitosis, a chromosome with a terminal centromere is also likely to be lost. Nondisjunction occurs when a centromere damaged by ionizing radiation fails to separate at mitosis, causing an uneven chromosome number. Aneuploidy (change in the number of one or more specific chromosomes) and polyploidy (multiple sets of chromosomes) are examples of the result of nondisjunction.

The shape of the dose-response curve for radiation-induced genetic effects has been debated for years (10). The results of various *in vitro* studies are confounding. Because limited human data is available, the basis for estimation of genetic risk and dose-response has been estimated from animal studies. Much of the controversy exists because the dose-response curve for genetic effects caused by low-level exposure to radiation has been extrapolated from high dose animal experiments [doses greater than 10 rem (10)]. Moreover, many of these extrapolations were made from high dose rate data where a variety of mutagenic endpoints were studied (11), necessitating additional extrapolations to account for the "dose rate effect" [for a given dose of radiation, high dose rate is generally considered 3-4 times as effective as low dose rate radiation as occurs in chronic low-level exposure (11)].

Early work with *Drosophila* (fruit fly) gene mutations indicated gamma radiation caused a linear, no threshold response (Fig. 4) (3,10). This model, e.g., the linear hypothesis, implied that the frequency of gene mutations was directly proportional to dose and was independent of dose rate (fractionation). Therefore, genetic effects were considered to be cumulative, adding up over a period of time and suggesting that chronic, low-level exposure to radiation resulted in a serious hazard to radiation workers. From these experiments, it was concluded that the dose required to double the spontaneous mutation rate (doubling dose) in *Drosophila* was in the range of 5-150 rem. The maximum permissible dose (MPD) concept evolved from these data. The MPD may be considered conservative because it assumes no repair and is considered to err on the "safe" side.

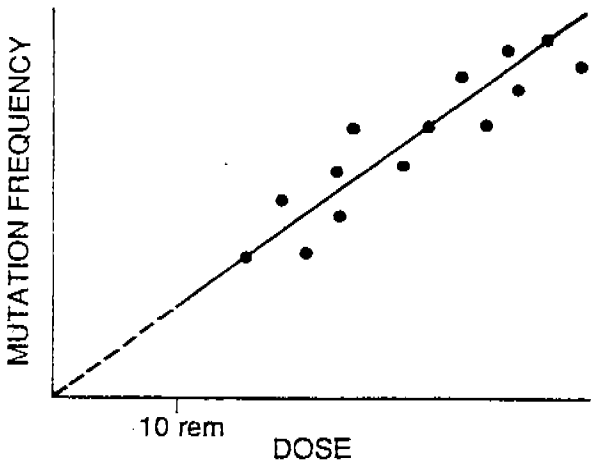

Figure 4. Linear dose-response model derived from experimental data on radiation-induced gene mutations in Drosophila. No threshold was identified; however, the low dose (dotted line) region has been extrapolated from the high-dose data.

Subsequent work, including the "megamouse*" project (10) of the 1960's and 1970's, revealed a variety of dose responses depending on the mutation and the germ cell line studied (in the megamouse project, the radiosensitivity of different mutations varied by a factor of 20). Mutation frequency was also affected by the quality factor of the radiation (LET), the dose given, and the dose rate. In the megamouse project, a dose-rate sparing effect was found with low LET radiation. This important conclusion suggested that, unlike *Drosophila*, spreading a given dose over time (fractionation) reduced the number of mutations observed in mice (Fig. 5). This suggested that genetic damage could be repaired and that it was not uniformly cumulative. In these experiments, the number of mutations induced by high LET radiation was not affected by dose rate. Also, high LET radiation produced more mutations (steeper slope) per unit dose than low LET radiation (12). The doubling dose in mice ranged from 50 to 250 rem, considerably greater than for *Drosophila*, leading to the belief that mammalian species may be less sensitive to induction of mutations. Because many of the mouse studies were performed with high dose rates, application of mutation risk to low-level human exposure is difficult. It has been estimated that low dose rate exposure may decrease the mutation rate by a factor of 5 or more (11).

The main source of data on human genetic effects of radiation has been the continuing study of atomic bomb survivors. Limited data is also available from survivors of nuclear accidents, including the Chernobyl disaster. The results of these studies, in conjunction with many *in vitro* studies on human cell populations, have suggested that the probability of

mutations within a human population increases with *any* increase in radiation dose. The Committee on Biological Effects of Ionizing Radiation (BEIR IV) (11) reported that although there is evidence of repair of genetic damage at the molecular level, the majority of present data suggest frequency of damage induced by low-level ionizing radiation best fits the linear, no threshold dose response hypothesis.

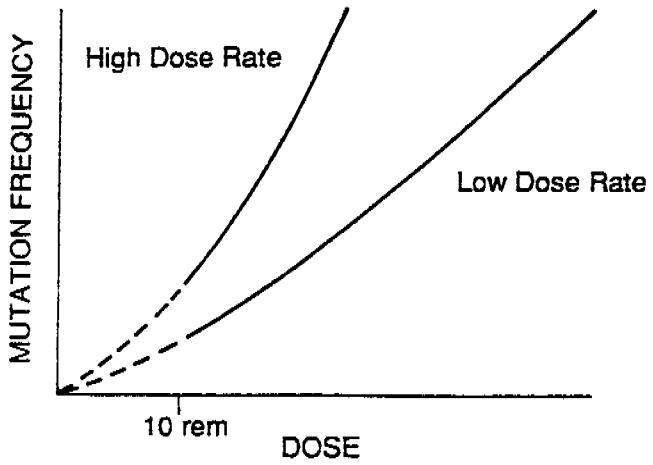

Figure 5. Dose response model derived from the results of the "Megamouse" experiments. Specific mutations were studied and mutation frequency was higher Note the strong quadratic function at higher doses. The dotted lines represent extrapolation from high-dose data.

Assessing the Risk

Two methods are generally used to assess the risk for genetic effects caused by ionizing radiation: absolute risk and doubling dose. A third method, the genetically significant dose, is used to chart the impact of ionizing radiation on the human population, particularly regarding medical exposure. The absolute risk of genetic effects is expressed as the number of mutations per rem or rad of ionizing radiation. With absolute risk, the incidence of spontaneous mutation is ignored and the incidence of mutation is quoted as a function of dose. Estimates in man, based on animal experimentation suggest that the absolute risk of mutation is approximately 10^{-7} per rem per gene (8). Because the spontaneous mutation rate in man is 10^{-5} per gene per generation, detection of absolute changes in radiation-induced mutations is problematic and requires large populations and long-term study. Therefore, it is often easier to use the doubling dose method to assess the relative genetic risk.

The doubling dose is the dose of radiation required to cause twice the number of spontaneous mutations (2,8). Because this method takes into account the natural, or spontaneous mutation rate, it is known as the "relative" mutation risk. Although extremely controversial, early evidence from atomic bomb survivors set the acute doubling dose for human beings at 156 rem (13). By calculation, the doubling dose for chronic low-level exposure was estimated to be 468 rem. These doses were calculated from three genetic effects studied in the children of the survivors. In contrast, the BEIR V report states that the results of atomic bomb data suggest the median doubling dose is 100 rem. This is in agreement with the results of animal studies using various genetic endpoints, where the median doubling dose for low-level, low LET radiation was found to be approximately 100 rem (11). These estimates fall within the 50-250 range originally suggested by the megamouse project.

The genetically significant dose (GSD) is an index used to assess the presumed impact of gonadal exposure to ionizing radiation on whole populations. The GSD is expressed in rems and relates to a population and not the individual or the number of mutations produced. Only radiation doses to the gonads of the members of the population that will reproduce are considered genetically significant. In other words, the GSD merely determines the gonadal dose that is received by those that will likely bear children and averages it over the entire population (gene pool). Therefore, people that receive gonadal radiation, but are not considered likely to have children, do not contribute a genetically significant dose. Similarly, a gonadal dose absorbed by young, healthy individuals contributes to the GSD. Finally, the GSD attempts to average the impact of presumed genetic effects for the entire population. Thus, the GSD is the dose that if given to each member of the population would result in the same genetic impact (effect on total gene pool) that actually results from doses received by those producing offspring.

In summary, current evidence implies that any increase in the amount of radiation exposure is expected to cause a proportional increase in the frequency of mutations and there is some "risk" for occupational workers (9,11). It has been suggested that a dose of 1 rem per generation might raise the spontaneous mutation rate by 1% (10). Thus, for chronic low-level, low LET exposure, the increase in mutation frequency may be undetectable in the human population (8). Although human data is sparse, it appears that human beings are no more sensitive to heritable effects of radiation than

animals; possibly, human beings are less sensitive (10). Ionizing radiation is known to cause mutation, but a statistically significant increase in heritable effects has not been documented when occpational exposure has remained within dose limits recommended by the NCRP.

"Megamouse" refers to the fact that over 7 million mice were used, not giant mice from mutation.

RADIATION CARCINOGENESIS

Introduction

The potential for cancer induction is considered the most important concern resulting from chronic, low-level exposure to ionizing radiation (8,9). Although studied extensively, the mechanism, the dose-response curve and the absolute risk of radiation carcinogenesis remain poorly understood. Because carcinogenesis is a late effect that occurs years after exposure to radiation and because radiation-induced cancers are no different than cancer caused by other agents, the epidemiological investigation of radiogenic cancer has progressed slowly. Perhaps the most practical approach to the study of radiogenic cancer involves the assessment of absolute risk of cancer from medical and background radiation sources. Quantization of the risk of chronic low-level radiation exposure is a major endeavor of organizations such as the International Commission on Radiation Protection (IRCP) and the National Commission on Radiation Protection (NCRP).

Unlike heritable effects, there is ample data on radiation-induced cancer in human beings. Many of the early workers in the field of radiation, including Mme. Curie and her daughter, suffered from radiogenic cancer. Historically, high doses of ionizing radiation have been associated with skin, lung, thyroid, breast, bone and lymphatic tumors (1,8). In addition, radiation is known to induce leukemia and other hematopoietic neoplasms. Various cancers have been documented in people exposed to large doses of gamma radiation at Chernobyl and atom bomb explosions. Scientists generally concede that exposure to any dose of ionizing radiation carries *some* risk (probability) of cancer induction, although it may be imperceptible at low doses (8,10,11). Unfortunately, few data are available for assessing the risk of human cancer in the low dose range (< 10 rem). The majority of risk assessments for low-dose, low-level exposure have been extrapolated from high dose data. Risk for cancer at many sites including leukemia, breast and thyroid cancers associated with low-level exposure have been estimated (11). Regarding radiogenic cancer, the bone marrow, thyroid gland, breast, and to a lesser extent, bone are considered the more sensitive organs of the human body.

Mechanisms of Cancer Induction

While the exact mechanism of radiogenic cancer is unknown, there is an unequivocal association of radiation exposure and cancer. Several theories have been proposed; three will be described here. The first is the *two-step initiation-promotion theory*. It is believed that most cancers are a two step process (8). First, the genome of the cell is injured in some way by a carcinogen (initiation). This injury, followed by a latent period, is usually inapparent and cannot be measured by routine medical tests. However, cell injury can be enhanced by an additional insult (promotion) which results in tumorigenesis. Ionizing radiation is thought to be a carcinogen that causes initiation. Chemicals, viruses, mutation and free radicals are other examples of initiators. Promoters include hormones and some carcinogens as well as the event of cell division.

A second theory regarding the mechanism of radiogenic cancer is the mutational theory. The *mutational theory* is supported by evidence that radiation alone may cause somatic mutations which result in cancer induction. While the exact genetic change associated with mutation is unknown, the altered genome results in malignant transformation that establishes a clone of cancer cells. Portions of the cells genome that down-regulate cell division are possibly altered by mutagenesis. Chromosomal aberrations are frequently observed in cancer cells (8).

The *oncogene theory* proposes that all cells contain oncogenes that are normally suppressed by a regulator gene. If chromosomes are broken by radiation and rejoined, rearrangement (translocation) may result so that the oncogene is no longer located near a regulator gene. Thus, the oncogene can be turned-on, expressing a malignancy. However, there is no direct evidence that oncogenes are activated by ionizing radiation (2).

Assessing the Risk

As with genetic effects, the risk of radiogenic cancer can be expressed in absolute and relative terms (8,10). *Absolute* risk is the number of excess cancers per unit of time in a specific population per

unit of dose. Absolute risk is usually derived by comparing irradiated versus nonirradiated populations. *Relative* risk is the ratio between the risk of cancer induction for a population receiving a given mean dose and an unexposed population (similar to the doubling dose concept). The relative risk may be expressed as a multiple or fraction of the spontaneous cancer rate for a population. Because the spontaneous rate of cancer is low, expressing risk in this way may be quite misleading. For instance, if the spontaneous cancer rate is 2%, doubling the risk would give a cancer rate of 4%, only representing a few cases. Therefore, risk is best expressed in absolute terms.

The dose-response relationships for induction of radiogenic cancer is very complex and controversial (1,8,11,12,14,15). In most animal and cell culture models there is a dose-dependent increase in tumorigenesis (steep) portion followed by a dose-dependent decrease when there is "saturation" at higher doses (>300 rem). Data from human cancer resulting from high doses (atomic bomb detonations and nuclear accidents) of radiation also fit a similar dose-response curve. Establishing the exact shape of the curve below 100 rem is problematic because extrapolation from high dose data is needed (limited human or animal data is available for low-dose exposure.) It is even more difficult to set the 0-10 rem region of the curve, the range of low-level exposures. Compounding the issue, most high-dose data was associated with a high dose rate. Therefore, extrapolation of high dose animal data and the available human data is one of the most controversial issues in the field of radiobiology. Because of the complexity of the issue at hand, only the dose response for low-level, low-LET radiation will be presented.

The BEIR V Report

The subject of dose-response and assessment of risk for radiogenic cancer was addressed in the BEIR V report in 1990. The Committee used three general methods of extrapolation from the high dose region of the dose-response curve (Fig.6). The linear model, used for the MPD concept, assumes no threshold and that the effectiveness of radiation per unit of dose is the same at high and low doses. This, again, is consistent with the concept that any radiation exposure is harmful. Animal data suggest otherwise; that the low part of the dose-effect curve bends downward, hence the "below linear model" (Fig 6). With this model, the risk per dose unit is less at low doses and some degree of repair or threshold effect is implied. An "above linear model" was proposed, which has a rapidly rising dose response rate (slope) at low-levels. The above linear assumption was used to fit data from occupationally exposed workers at nuclear power plants and the Portsmouth Naval shipyard and from soldiers exposed to nuclear weapons tests (8,15). The model has been debated, and was refuted by the 1980 BEIR III report. Many scientists question the above linear model because the population sample was too small and may have been at a higher risk for cancer induction in the first place. The possibility that this model is correct is alarming; the increased sensitivity to low-level radiation would imply that 50-70% of all human cancer would be due to natural background radiation**, rather than the present estimate of 1% (8).

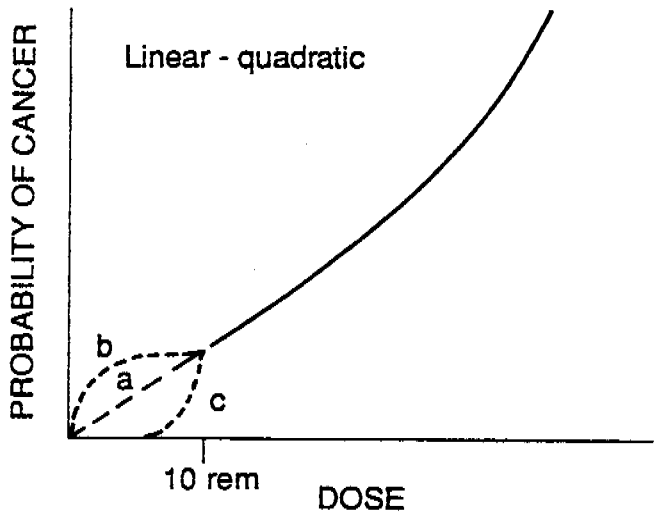

Figure 6. Generalized dose response model for induction of radiogenic cancer. At doses greater than 10 rem the incidence of cancer is usually a quadratic function of dose. Below 10 rem, the shape of the curve is unknown. There is data to suggest that the low dose region may be (a) linear, (b) above linear or (c) below linear. The BIER V report considers the below 10 rem portion of the curve to be linear. Dose response curves for specific radiogenic cancers are available (11).

For doses below 10 rem, the BEIR V Committee concluded that the frequency of cancer induction, like heritable effects, is best represented by the linear-quadratic model with no threshold. The BEIR V Committee adopted this position after careful review of the life-span study of Japanese atomic bomb survivors, people that received therapeutic x-rays for ankylosing spondylosis, tuberculosis, dermatophytosis (tinea capitis) and cancer of the cervix. The Committee determined that the risk of radiogenic cancer was 3 times higher for solid

tumors and 4-5 times higher for leukemia than was given in the BEIR III Report. The estimated absolute lifetime risk of death from cancer following a 10 rem **acute whole body dose** was stated to be 0.8%. For chronic (fractionated) exposure the risk decreased by a factor of 2, implying repair may occur. Compared to previous reports, the committee stated that the risk for leukemia was also increased for those subjected to *in utero* irradiation.

The principal conclusion of the BEIR V Committee is that if 100,000 people of all ages receive a whole-body dose of 0.1 Gy low LET radiation in a single brief exposure, 800 extra cancer deaths are expected over their remaining lifetimes in addition to the nearly 20,000 cancer deaths in the absence of the radiation. The BEIR V Report also lists the expected types of cancer and differences in risks due to sex and age at time of exposure. Furthermore, it provides estimates of risk for chronic continuous low dose rate exposures to all radiation qualities. For example, estimates of lifetime excess cancer mortality per 100,000 exposed persons are listed below:

a. continuous lifetime exposure to 1mSv/y (100 mrem/y)

	Total	% of normal *	leukemia	nonleukemia
male	520	2.5	70	450
female	600	3.4	60	540

b. continuous exposure to 0.01 Sv/y from age 18y to 65y

	Total	% of normal *	leukemia	nonleukemia
male	2880	14	400	2480
female	3070	17	310	2760

(*) "normal" refers to those individuals normally expected to die from cancer, from all causes

As stated previously, the natural cancer death rate in the USA is 20,000 per 100,000 persons (given in terms of risk over a lifetime).

A linear dose-response model was preferred by the BEIR V Committee. The Committee stated that departure from linearity could not be excluded at low doses beyond the range of observation. They also reasoned that the departures could be in either direction, i.e, increased or decreased risk. Moreover, the Committee noted that epidemiologic data cannot rigorously exclude the existence of a threshold in the millisievert dose range.

While these findings indicate that the risk of radiogenic cancer is greater than previously thought, the BEIR V Report has been questioned by leading radiobiologists and physicians (16). Much of the controversy stems from the use of data gleaned from the atomic bomb survivors, who received acute (microsecond) doses. No adjustment was made by the BEIR V Committee for the difference in dose rate effect when extrapolating the data to represent the response to low-level irradiation. Because repair is known to occur at lower dose rates, the frequency of dose related effects is usually considered to be reduced by a factor of 2-3 (16).

What practical conclusions can be drawn from these studies? First, risk assessments for low-level exposure are really estimates, extrapolated from high dose data. High-dose data are available to health scientists for studying dose-response. Data on low-level exposures, suitable for epidemiologic analysis, are not available. This includes the 0.1-0.5 rem range used in nuclear medicine patients. This is because the difference between the incidence of spontaneous and radiogenic cancers is so small that a sample population of millions would be needed to conduct a meaningful study (16). Second, the entire issue of risk due to low-level exposure must be placed into perspective when people residing in areas of high natural background radiation do *not* have a higher rate of solid tumors or leukemia when compared to other populations. Third, if the recommended MPD were to be reduced by one-half, nuclear medicine workers would likely be unaffected because most exposures are <2.5 rem per year (16).

*****The estimated dose from natural background radiation is approximately 80-250 mrem/year depending on geographic location. This is well below the 10 rad range that is considered to be low-level.***

EFFECTS OF IONIZING RADIATION ON THE EMBRYO AND THE FETUS

Excessive exposure of the embryo or the fetus to ionizing radiation may cause a classic triad of embryonic death, congenital malformation or growth retardation in mammals (8,17). Exposure of the developing embryo to ionizing radiation may cause major congenital defects, embryonic death or perinatal death. During the period of preimplantation (0-9 days in man), the conceptus is particularly sensitive to radiation. Based on

extrapolation from experimental animals, *in utero* doses of 10-25 rad may be lethal during preimplantation. However, surviving embryos are at a low risk for congenital abnormalities and perinatal death.

Ionizing radiation is teratogenic and may cause major congenital malformations, including microcephaly, microphthalmia, cerebral hypoplasia, and skeletal and dental defects. These malformations are most common when exposure occurs during the period of organogenesis (10-50 days). Irradiation at this time has been associated with a high incidence of growth retardation and perinatal death (8,11).

With *in utero* exposure to ionizing radiation during the period of the fetus (51 days-term), the most likely deleterious effects are fetal growth and mental retardation, and maldevelopment of the central nervous system. Although differentiation of most human tissues has ceased by 51 days post-conception, the central nervous system continues to develop, even postnatally. The developing embryo/fetus is sensitive to radiation-induced mental retardation, and there is little if any threshold for this effect between 48 and 112 days of gestation. This unique sensitivity can be explained by intense neuronal stem cell proliferation during organogenesis. Analysis of data from atomic bomb survivors implies that the risk of severe mental retardation at 48-112 days is 40-45% per seivert (100 rem) (9,11). Exposure after 112 days of gestation may also cause mental retardation, but the risk is reduced by a factor of 4 because neuronal proliferation has peaked. The occurrence of radiation-induced mental retardation often correlates with microcephaly (17).

The incidence of childhood leukemia might be increased by *in utero* exposure to ionizing radiation at anytime during gestation (8,9,17). There is data both for and against this concept. Studies in the USA and England claim an association between childhood malignancy and *in utero* irradiation, while results from animal experiments and data from atomic bomb survivors do not (8).

OTHER LATE EFFECTS DUE TO LOW-LEVEL IONIZING RADIATION

Life-span shortening, and cataractogenesis are other effects that may be linked to chronic exposure to low doses of ionizing radiation. While there is abundant literature regarding these effects, their importance is considered less than those effects previously described in this paper.

Although studies have suggested that low-level exposure to radiation causes life-span shortening, this issue remains in doubt. In many of these studies, the decrease in life span was actually a secondary effect resulting from cancer induction (1,18). Life span shortening attributed solely to chronic radiation exposure in people has not been conclusively demonstrated.

The lens of the eye is sensitive to ionizing radiation. In atomic bomb survivors, single doses in the range of 60-150 rad of gamma radiation was considered the threshold for cataractogenesis. With highly fractionated exposure, the threshold was 5000 rad (11). These doses are clearly beyond the occupational limit.

The mammalian gonads are also sensitive to the effects of ionizing radiation (11). In the human testis, an acute dose of 15 rad is sufficient to cause temporary infertility. The human ovary is less radiosensitive than the testis, where the threshold for acute exposure is approximately 65 rad. Fractionation increases the tolerance to infertility (11). It should be stressed that the major risk to the gonads for low-level exposure to ionizing radiation is mutation, as described under "Genetic Effects of Radiation."

Paradoxically, there is scientific evidence that in some instances, chronic low-level exposure to ionizing radiation causes a beneficial effect. These beneficial effects include enhanced resistance to disease, improved viability, and increased life-span. Studies have shown that laboratory animals exposed to chronic low doses of ionizing radiation may outlive control animals. At the cellular level, it has been suggested that beneficial radiation-induced mutations may result in hormesis. Mechanisms are unclear, but may include enhanced repair of DNA damage, improved scavenging of free radicals, stimulation of the immune response, and improved maintenance of cell populations (19,20). Although the concept of radiation hormesis is fascinating, it has not gained widespread acceptance in the scientific community. However the issue cannot be avoided and merits further investigative efforts.

CONCLUSION

Knowledge of the biological effects of ionizing radiation is of contemporary importance to nuclear pharmacists for three main reasons. First, it is

necessary for nuclear pharmacy practitioners to ntain adequate radiation safety practices in the work place. Second, nuclear pharmacists are often the main source of expertise regarding biological effects of radiation in laboratories where radiopharmaceuticals are used. Lastly, those occupationally exposed to chronic low doses of ionizing radiation should be kept abreast of new theories and concepts generated by research in radiobiology.

As expected, the jury is still out in regard to the true risk from low-level chronic exposure to ionizing radiation. The data included herein are not intended to bring forth fear for personnel employed in a nuclear pharmacy, but to reinforce the attitude of a healthy respect for the potential harm from overexposure to radiation. However, the nuclear pharmacist must maintain a proper perspective. For example, the author of an article in a health physics newsletter (21) presented comparisons of risk to nuclear power plant workers to other occupations and situations. He cited an overall radiation risk coefficient of $3x10^{-4}$ per rem for nuclear power plant workers as compared to an annual risk for crew members being involved in an aircraft accident with a fatality as $4.5x10^{-4}$ for scheduled commercial carriers and $7.7x10^{-3}$ for scheduled commuter carriers. Also, we accept a per capita annual risk greater than $2x10^{-4}$ for the privilege, convenience and advantages of automobiles and trucks.

In summary, there is a risk from radiation of which occupational workers must be aware. However, the harmful effects attributed to ionizing radiation at doses below the maximum permissible dose level (5 rem/yr) may never be truly resolved even by statistical methodology with large populations. Utilization of a good practice technique and adherence to safety guidelines remain the best approach to assuring a safe environment and attaining conformity to the ALARA concept.

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QUESTIONS

1. In regard to low-level chronic exposure, the single most important consequence is:

   a. radiation carcinogenesis
   b. life-span shortening
   c. cataractogenesis
   d. organ fibrosis

2. In determining the true risk of low-level exposure the greatest controversy continues over:

   a. the length of time necessary to develop cataracts
   b. the risk of high doses
   c. the dose-response relationship for low doses
   d. the lack of high dose data to aid in drawing conclusions

3. With low LET radiation, initial damage to the DNA is mediated by:

   a. the direct hit on a single strand
   b. ionization on purine bases
   c. enzyme mediated reactions
   d. radiolysis of intracellular water (indirect effect)

4. For the single-hit dose-response model the Do for a cell population is the dose that:

   a. will give an average of one hit per target in the population
   b. will result in the death of each cell
   c. can be tolerated and repaired
   d. will result in the death of 37% of the cells in the population

5. For a two-target dose response model for a cell population, the shoulder on the dose-response curve indicates:

   a. cells cannot be repaired
   b. that both targets have been hit once
   c. a region of sub-lethal damage
   d. nothing regarding effects upon targets within the cell

6. Prior to the Chernobyl disaster the best source of human data for determining genetic (heritable) effects of radiation has been:

   a. patients exposed to diagnostic x-rays
   b. survivors of the Hiroshima and Nagasaki atomic bombs
   c. radiologists from the 1920s
   d. radium dial painters

7. Gene mutations from early work with Drosophila (fruit fly) indicated that gamma radiation:

   a. caused genetic effects that were not cumulative from doses received over time
   b. caused gene mutations that were dependent upon dose rate
   c. caused gene mutations directly proportional to dose
   d. caused a non-linear, threshold response

8. The results of the megamouse project regarding radiation induced mutations indicated that:

   a. the degree of low LET radiation damage was not influence by dose rate
   b. genetic damage could be repaired
   c. there was little difference in mutations produced by high LET compared to low LET radiation
   d. the doubling dose for mice was the same as for fruit flies

9. Absolute risk is a method used to assess the risk for genetic effects caused by radiation. In absolute risk:

   a. the incidence of spontaneous mutation is considered
   b. the risk of mutation is approximately 10^{-1} per gene
   c. the determination of radiation-induced mutations can be accomplished in a few months
   d. the genetic effects are expressed as the number of mutations per rem

10. The doubling dose of radiation is stated as the dose to cause twice the number of spontaneous mutations. The acute doubling dose for humans based upon atomic bomb survivors is _____ rems.

    a. 6
    b. 156
    c. 256
    d. 456

11. The calculated doubling dose for humans based upon the atomic bomb survivors for chronic low-level exposure is estimated to be _____ rems.

    a. 68
    b. 168
    c. 368
    d. 468

12. In the calculation of genetically significant dose, radiation doses _____ are considered.

a. to the entire population
b. to children
c. to members of the population that will reproduce
d. to nuclear medicine/nuclear pharmacy personnel only

13. Radiation-induced cancers:

a. are common in low-level exposure situations
b. occur rather quickly after acute exposure
c. differ from cancers produced by other agents
d. cannot be clearly identified as radiation-induced

14. Regarding radiation-induced cancers, the _____ are considered as more radiosensitive.

a. skin and liver
b. eyes and skin
c. colon and eyes
d. breast and thyroid

15. In the two-step initiation-promotion theory for cancer induction:

a. radiation is considered as an initiator
b. radiation is considered to be a promoter
c. the genome of the cell is not injured initially by the radiation
d. the initial radiation injury to the cell can be measured by routine medical tests

16. In the oncogene theory for cancer induction it is proposed that:

a. cells have regulator genes normally suppressed by an oncogene
b. radiation acts by activating the regulator genes
c. chromosomes are broken by radiation
d. this is the main method of cancer induction by radiation

17. Relative risk for expressing the risk of radiogenic cancer:

a. is the number of excess cancers per unit of time in a specific population per unit of dose
b. may provide rather misleading risk numbers when compared to the spontaneous cancer rate
c. is the ratio between the risk to medical exposure and reactor personnel
d. is the best way to express radiation-induced cancer risk

18. The dose-response relationship for induction of radiogenic cancer in humans is:

a. well established and accepted
b. the same for low dose and high dose data
c. based upon animal data
d. very complex and controversial

19. The MPD concept is based upon a _____ dose-response model.

a. linear at all doses
b. below linear at low doses
c. above linear at low doses
d. a linear-quadratic

20. For doses below 10 rem, the BEIR V Committee concluded that the frequency of cancer induction is best represented by:

a. a linear model
b. a below linear model at low doses
c. an above linear model at low doses
d. a linear quadratic model

21. The BEIR V Committee determined that the risk of radiogenic cancer was _____ times higher for solid tumors than given in the BEIR III report.

a. one
b. two
c. three
d. four

22. In the BEIR V Committee report the absolute lifetime risk of death from cancer following a 10 rem acute whole-body dose was stated as _____ percent.

a. 0.1
b. 0.5
c. 0.8
d. 1.0

23. Ionizing radiation is a teratogenic agent:

a. producing congenital malformations that differ from other teratogenic agents
b. when applied to the mothers arm
c. when given between days 1-9 of gestation
d. when sufficient exposure is given to the embryo during organogenesis

24. Sufficient radiation exposure to the fetus may result in:

a. skeletal defects
b. small eyes
c. mental retardation
d. dental defects

25. Radiation hormesis:

a. is proposed as a possibility for higher doses given over a long period
b. is an accepted concept by radiation scientists
c. is a concept that indicates the exceptional danger from radiation
d. indicates a potential beneficial affect from radiation