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BIOPHYSICAL AND BIOMATHEMATICAL ADVENTURES IN RADIOBIOLOGY

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ABSTRACT

Highlights of my biophysical and biomathematical adventures in radiobiology is presented. Early adventures involved developing "state-vector models" for specific harmful effects (cell killing, life shortening) of exposure to radiation. More recent adventures led to developing "hazard-function models" for predicting biological effects (e.g., cell killing, mutations, tumor induction) of combined exposure to different toxicants. Hazard-function models were also developed for predicting harm to man from exposure to large radiation doses. Major conclusions derived from the modeling adventures are as follows: 1) synergistic effects of different genotoxic agents should not occur at low doses; 2) for exposure of the lung or bone marrow to large doses of photon radiation, low rates of exposure should be better tolerated than high rates; and 3) for some types of radiation (e.g., alpha particles and fission neutrons), moderate doses delivered at a low rate may be more harmful than the same dose given at a high rate.

I. INTRODUCTION

My interest in radiobiological research was stimulated in 1962 at Webster High School in Minden, Louisiana. Under the guidance of my biology teacher, Mr. Robert T. Tobin, a science project was initiated that involved my studying the biological effects of radiation on fruit flies. By exposing the fruit flies to beta radiation, mutant offsprings were produced, while unirradiated fruit flies demonstrated no mutations.

The project provided a valuable scientific lesson: how to conduct a test of a scientific hypothesis, using both test and control groups. The test group was made up of insects exposed to beta radiation; the control group was made up of insects of the same type, from the same source, but not exposed to beta radiation. Without use of both groups, no valid conclusions could have been drawn.

The project demonstrated that beta radiation can cause genetic harm in parents, and this harm can be passed to their offsprings. Even today, laboratory animals (mice) play an important role in estimating genetic risks in man for exposure to radiation. There are very few data on the genetic effects in humans from exposure to radiation, while there are numerous data for genetic effects in mice that can be extrapolated to man. To calculate genetic risks for a population of people exposed to radiation, very sophisticated mathematics and computer software are required today.

The high-school science project with irradiated fruit flies earned first prize in the regional science fair that was held at Grambling University. The prize I received was a cruise on a U.S. naval vessel in the Pacific Ocean off the coast of San Diego, CA. The cruise was, in part, an attempt to recruit high-school graduates into the military. However, because of the Cuban nuclear missile crisis, the vessel designated for our cruise headed toward Cuba to participate in a potential nuclear war between the Soviet Union and the United States. Fortunately, no such war occurred; however, the cruise was off.

Instead, science fair winners from all over the country toured scientific organizations in the San Diego area. A tour of General Atomics served as a major stimulus to further my interest in radiation, as I saw a nuclear reactor's intense blue light (Cerenkov radiation) that comes about when the velocity of charged particles (e.g., electrons) in the water moderator exceeds the ratio c/n, where c is the velocity of light and n is the refractive index of the medium. For water, n = 1.33. The opportunity to

see the intense blue light and to discuss with real scientists what was going on in the reactor moderator was a great experience.

In the fall of 1963, I entered Southern University and subsequently majored in physics. There, my interest in radiation continued with the scholarly lectures and laboratory experiments provided by Dr. Zoraway Singh, as well as those by others in the Physics Department (Dr. Ogba Okorie, Bholo Mehrotra, Professor Stanley Morris, and Professor James Gist, to name some). Experiments using radiation detectors and oscilloscopes were also of great value in graduate school where I used the devices to measure electrical charges on surfaces of fission fragments produced by splitting uranium-235 atoms by neutron capture. To strengthen my quantitative skills, I may have taken every course taught by Dr. Roger Newman during my stay at Southern. His teachings, as well as those by other dedicated Mathematics Department faculty members, provided a strong foundation from which I still benefit. In retrospect, I could have benefitted more from taking additional courses in biology, chemistry, and computer science, as well as a class in technical writing. In today's publish-or-perish world of scientific research, technical writing skills are very important. Research results go unpublished every day, because poor writing skills lead to their rejection by scientific journals.

My interest in radiation continued in graduate school, as my doctoral dissertation dealt with the construction of a biophysical model to describe the expected harm to biological cells from exposure to ionizing radiation. The research was conducted under the guidance of Dr. Howard S. Ducoff, a scientist recognized internationally for his research on harm to insects from irradiation. Details on my Ph.D. research and its implications are provided later.

After graduating from the University of Illinois with a M.S. in physics and a Ph.D. in biophysics, I spent 2 years as a postdoctoral participant in the Biology Division at Argonne National Laboratory, Argonne, Illinois, working in a group that studied the biological effects of neutrons and gamma radiations on mammals (mainly mice) and on mammalian cells. The head of our group was Dr. E. John Ainsworth. (He is currently the Scientific Director at the Armed Forces Radiobiology Research Institute in Bethesda, Maryland.) My research at Argonne involved development of a biomathematical model to predict life shortening in mice exposed to low doses of ionizing radiation.

Everyone is exposed to small radiation doses from the environment and from radioactive elements incorporated into their body. For this and other reasons, we looked to animals to tell us about possible harm to man from exposure to low radiation doses, especially for protracted or fractionated exposure over a long time. With fractionation, the total dose is separated into smaller fractions spread over time. Details on some of the results of this research are discussed later.

After leaving Argonne, I went to the Inhalation Toxicology Research Institute (ITRI), Albuquerque, New Mexico, where I have worked since 1977. My research at the ITRI has mainly dealt with developing biomathematical models for health effects of large radiation doses to people.

The remainder of this manuscript focuses on some of my contributions to radiobiological research. Background information is provided on radiobiological concepts and terminology.

II. RADIOBIOLOGICAL CONCEPTS AND TERMINOLOGY

A. Ionizing and Nonionizing Radiations and Radioactivity

The term **radiation represents the emission of any type of ray or particle from a source.** If the radiation has enough energy to produce ions by either direct or indirect means, then it is called **ionizing radiation.** The research to be described here deals with radiobiological effects of ionizing radiation in mammals or on mammalian cells. What are some examples of ionizing radiation, and why is there interest in mammals? Examples of ionizing radiation are alpha particles, beta particles (i.e., negative electrons), positrons (i.e., positive electrons), X rays, gamma rays, negative pions, and accelerated charged heavy ions. The interest in mammals stems from the fact that all humans are mammals.

B. Radiation-Induced Harm to Humans

Because all humans are made up of many different types of cells, radiation doses that harm cells could lead to observable harm to people. While radiation-induced harm to one cell may not be a problem, the same harm to many of our cells could lead to big problems. Examples of harm resulting from damage to many cells are hypothyroidism; skin erythema (i.e., reddening of the skin); suppression of sperm count in

males and suppression of ovulation in females, thus reducing their ability to have children; loss of unborn babies by pregnant women; babies with major birth defects caused by irradiation during pregnancy; children that do not grow to a normal size (i.e., growth retardation); and children who are mentally retarded because of improper development of the brain due to irradiation *in utero*. In some cases, harm to a single cell may lead to problems e.g., mutation and cancer (Scott, 1981).

C. The Dose Makes the Poison

Whether or not a specific radiobiological effect is caused by exposure to radiation depends on the total kinetic energy deposited by the radiation into cells. The more energy deposited in tissue, the larger the dose, and the more harm that can be produced to a person (Lea, 1955; Sacher and Grahn, 1964). The **absorbed dose**, a macroscopic concept, is the **amount** of **energy deposited in biological tissue (or cells), divided by the mass irradiated.** Units for absorbed radiation dose are numerous (e.g., rad, Gy, cGy). Throughout this manuscript the International System (SI) unit, the Gray (abbreviated as Gy), is used and represents the deposition of 1 joule/kg. One-one-hundredths of a Gy is called a cGy (centi-Gray) and corresponds to what is called the rad (i.e., 100 ergs/g). The rad, which preceded the Gy, is not an SI unit.

D. Linear Energy Transfer

The concept **linear-energy transfer (LET)**, is used to distinguish between different kinds or classes of radiation (e.g., high-LET vs. low-LET). **Linear energy transfer is the average rate at which energy is lost by charged particles as they penetrate matter.** Typical units are keV per micrometer. An LET equal to 100 keV per micrometer represents, on the average, a loss of 100 keV per micrometer of distance traveled. When energy is lost at a rapid rate like 100 keV per micrometer, the charged particle does not penetrate very far. Alpha particles are an example of high-LET radiation. Alpha particles from Pu-239 have an LET of approximately 100 keV per micrometer in water. As a result, they lose energy at such a rapid rate that they can be stopped by the thin layer of dead skin on the back of your hand. Beta particles are mostly low-LET radiation and do not lose their energy as rapidly as do alpha particles, so they can pass through the layer of dead skin on the surface of the body and reach critical cells whose damage can lead to skin cancer.

E. Hot Beta Particles

Radioactive, beta-emitting particles resulting from the nuclear accident that occurred on April 26, 1986, at the Chernobyl nuclear power plant in the Soviet Union, are a major concern. A large research effort sponsored, in part, by the International Atomic Energy Agency is underway to study the biological effects of hot beta particles from Chernobyl. **Hot beta particles are highly radioactive, single particles.** One concern related to these hot beta particles is the risk of skin cancer from a hot particle deposited on the skin.

F. Stochastic and Nonstochastic Effects

Both the frequency and severity of biological effects can increase as the radiation dose increases. Two types of biological effects can be distinguished depending on their response to increasing dose: Stochastic effects and nonstochastic (or deterministic) effects.

Stochastic effects are effects whose **probability of occurrence in an exposed population** (rather than severity in an affected individual) **is a direct function of dose** (BEIR V, 1990); such effects are commonly regarded as not having a threshold. Hereditary effects are considered stochastic; some somatic effects, especially cancer, are considered stochastic. The larger the dose, the greater the probability of harm (Sacher and Trucco, 1962). However, because cancer is a stochastic effect of irradiation, we cannot say whether or not a chest X-ray will lead to cancer. We can only evaluate the probability that it will cause cancer. By the way, this probability is too small to be concerned about.

Nonstochastic effects are those effects **whose frequency and severity are related to the dose.** For doses above a threshold, the frequency and severity can increase. Examples are death from injury to the sensitive cells in the bone marrow (hematopoietic death), hypothyroidism resulting from irradiation of the thyroid, and erythema resulting from irradiation of the skin. Years ago, after radiation was just discovered, physicists measured radiation dose by irradiating the skin on the back of their hands. The radiation dose was determined by how red the skin was. Of course, we would not do this today, as skin cancer was discovered to be a major risk of such a practice.

III. STATE-VECTOR MODELS

A. State-Vector Model for Cell Killing

My dissertation research involved developing a mathematical model to predict harm (death) to cells exposed to different types of ionizing radiation. A mechanistic state-vector model (MSV model) for cell killing by exposure to ionizing radiation (Scott, 1977) resulted from this research.

The MSV model for cell killing incorporated important concepts such as repair or intracellular damage to DNA; differing sensitivities for cells with different ages relative to the biological cell cycle; and greater damage from high-LET radiation (e.g., alpha particles) than from low-LET radiation (e.g., X rays). A special case of the model is presented in Figure 1, which is specific for cells trapped in the same stage of the cell cycle (i.e., synchronized cells). For cells distributed over multiple stages of the cell cycle, the model is much more complicated.

Time-related changes are modeled in two separate regimes (t and t'). The t-regime relates to changes that take place during irradiation. The t'-regime relates to changes that continue for a short time after the irradiation stops: lethal misrepair or correct repair of intracellular damage.

The state X(0) represents undamaged cells. The state X(1) represents cells with sublethal damage that could be repaired. The state L represents cells that have lethal damage. The product $\emptyset(0)s$ gives the rate at which cells with irreparable lethal injury are directly produced from cells in X(0); s is the dose rate; $e(0,1)s$ is the rate at which cells with potentially repairable damage are produced from cells in X(0); $\eta(1)$ gives the rate at which cells return from the damaged state X(1) to the undamaged state X(0) due to correct repair of sublethal damage; $\emptyset(1)s$ is the rate at which cells in damaged state X(1) are converted to cells in the lethal damage state L due to direct effects; and $\beta(1)$ is the rate at which cells enter L from X(1) due to lethal misrepair (i.e., indirect effects).

The fraction of cells in the states X(0) and X(1) can be represented by variables x(0;t;t') and x(1;t;t'), respectively. The fraction of the irradiated cells in L can therefore be calculated as 1-x(0;t;t')-x(1;t;t'), so long as cell division does not occur during irradiation.

The temporal changes associated with Figure 1 can be represented using a vector differential equation with vector elements x(0;t;t') and x(1;t;t'). The vector differential equation and its solution is the basis for the term state-vector model.

At some time during the t' regime, steady state levels will be achieved for cells in X(0) and L. For the steady state, the fraction of the cells in X(0) then determines the survival fraction; the fraction of cells in L determines the fraction of cells killed. Note that variability in cell killing is not addressed by this method of modeling. However, when lethal cellular damage has a Poisson distribution over the irradiated cells, the average number of lethal lesions per cell is given by

$$h = -\log[x(0;t;\infty)] \ , \qquad (1)$$

where log represents the Naperian (or natural) logarithm. The symbol ∞ indicates a steady-state value. In such cases, the probability of j lethal lesions can be calculated for a Poisson distribution with expectation value h. The variance of h will then be equal to h.

Recent theoretical calculations suggest that departure from a Poisson distribution of lethal lesions may occur. While the number of charged particles interacting with DNA in the nuclear target has a Poisson distribution, there is a second distribution of the number of interactions with DNA, given traversal of the nuclear target. The convolution of these two distributions leads to departure from the Poisson distribution of lesions.

With the MSV model, positive curvature (Figure 2) in the dose-response curve for the fraction of cells killed at low and moderate doses, delivered at high dose rates, was found to indicate that normal dose-rate effects should occur when the dose rate is varied. By normal dose-rate effects, it is meant that low rates are less effective than high rates, because of more efficient repair of damage at low rates (Figure 3). However, a negative curvature dose-response curve (Figure 2) in similar circumstances was found to indicate an inverse dose-rate effect. With inverse dose-rate effects, low rates are more effective (Figure 4) in producing biological effects than high rates (Rossi and Kellerer, 1986; Balcer-Kubiczek *et al.*, 1988; Miller *et al.*, 1988).

The MSV model was demonstrated to predict normal dose-rate effects for cell killing by low-LET X and gamma irradiation (Scott, 1977). Fitting the MSV model to available data for survival of spermatogonia type B cells irradiated with 400 MeV neutrons (a type of high-LET radiation), led to a negative-curvature dose-response curve, while a positive curvature dose-response curve was obtained for the same cells for low-LET irradiation. This indicated that inverse dose-rate effects should arise for the high-LET irradiation when the dose rate is varied (Scott, 1977). However, no data were available at the time to validate model predictions of an inverse dose-rate effect.

Inverse dose-rate effects were predicted to arise from two possible ways: (1) from competing modes of cellular lethality (direct and indirect) when the direct mode (transitions directly from X(0) to L) is favored over the indirect mode (transition from X(0) to X(1) and then to L) and (2) when lethal misrepair is favored over correct repair.

The prediction of an inverse dose-rate effect for cell killing by high-LET radiation did not win the approval of other scientists in the field. Their general view was that for high-LET irradiation, cells would be inactivated via a "one-hit" mechanism that should not depend on dose rate. With a one-hit mechanism, all cells that develop lethal injury would go directly from state X(0) to state L without any intermediate state being involved. In this case, the fraction of cells killed by low and moderate doses would be a linear function of dose and independent of dose rate (Figure 5).

I rechecked my calculations for possible error. None were found. The calculations indicated a small inverse dose-rate effect for cell killing at moderate doses. Because the predicted effect was small, whether or not it occurred would not make a big difference either way, so that there was no excitement about the predicted inverse dose rate effect for some high-LET radiations.

B. State-Vector Model for Life Shortening

Subsequent research as a post-doctoral participant at Argonne National Laboratory led to development of a similar state-vector model for life shortening in mice exposed to neutrons from a nuclear reactor (i.e., fission neutrons) (Scott and Ainsworth, 1980). The model was specific for low-to-moderate radiation doses (few Gy) that mainly produced life shortening through the induction of leukemias and fatal tumors.

Before pointing out model predictions, it is useful to discuss briefly the views of other scientists at the time on what the life-shortening, dose-response curves should look like (conventional models). For low-LET irradiation, their view was that the dose-response curve should be curvilinear, showing positive curvature (Figure 2), with low dose-rate (or fractionated exposure) not as effective as high dose rate single exposure, because repair of damage occurs more efficiently at low rates, or between small dose fractions than for a single dose given at a high rate. For high-LET irradiation, the conventional model was one of a linear dose-response curve for days of life lost, independent of dose rate or fractionation.

Based on the conventional models for days of life lost, each irradiated animal suffered the same amount of life shortening from unspecified causes. None was untouched. For the conventional linear model for high-LET radiation, if a dose D caused loss of 1 day of life, then every irradiated individual exposed to D lost 1 day of life. A dose 2D then caused each individual to lose 2 days of life. Thus, with the conventional high-LET model, severity of the effect increased as the dose increased, not the frequency, because every individual was affected. Similarly, for the conventional low-LET model, the dose-response curve has positive curvature. If a dose D causes one to lose 1 day of life, then a dose 2D will lead to more than 2 days of life being lost. Each individual exposed to a dose D would lose the same amount of life. Everyone was equally affected.

The state-vector for life shortening that I developed was a marked departure from the conventional models, in that only those individuals that have radiation-induced tumors experience life-shortening (i.e., lose days of life). The state-vector model is probabilistic, depending indirectly on the probability of life-shortening tumors being induced. With this model, the frequency of affected individuals changed with dose, so not every individual is necessarily affected. At very low doses, only a few individuals are affected, if any. Because life shortening at low doses is thought to be mainly due to tumors, and because tumor induction is viewed as a stochastic effect, this modeling approach seemed plausible.

As with the conventional model for low-LET radiation, the state-vector model for life shortening led to normal dose rate effects for days of life lost with low

dose rates being less effective than high rates, because of repair of damage. However, for high-LET, fission neutron irradiation of mice, it led to a curvilinear dose-response curve showing negative curvature, instead of a linear dose-response as indicated by the conventional model. The state-vector model predicted an inverse dose-rate effect for life shortening in mice exposed to fission neutrons. However, unlike the small inverse dose-rate effects predicted with the cell killing model developed in my Ph.D. research, this predicted effect was more dramatic and should be detectable from studies that were planned at the time. Subsequent research by others validated model predictions of an inverse-dose-rate effect (Fry, 1990).

Over the years, evidence of inverse dose-rate effects of high-LET irradiation has gradually surfaced, and today many, but not all scientists, acknowledge the existence of these effects. Inverse dose-rate effects of high-LET irradiation have been reported for life shortening in mice (Fry, 1990; Ainsworth *et al.*, 1976, 1977; Thomson *et al.*, 1983; Thomson and Grahn, 1988; Storer *et al.*, 1979; Ulrich, 1984), for *in vitro* transformation of cells (Miller *et al.*, 1990; Hill *et al.*, 1982, 1984, 1985; Jones *et al.*, 1989; Yang, 1986; Brenner and Hall, 1990), for lung and bone cancer in humans (Darby 1990; Howe *et al.*, 1986, 1987; Hornung and Meinhardt, 1987; Sevc *et al.*, 1988; Lubin et al, 1990), and animals (Lundgren *et al.*, 1987; Humphreys *et al.*, 1990; Muller *et al.*, 1983, 1989), and for lymphoma (Muller *et al.*, 1988) and cataracts in animals (Medvedovsky and Worgul, 1990).

IV. OTHER MODELING ADVENTURES

A. Models for Effects of Combined Exposure to Different Toxicants

Predictive biomathematical models have also been developed for the combined effects of different agents, including cell killing, mutagenesis, and tumor induction by combined exposure to different radiations or radiation plus a genotoxic chemical (i.e., chemical that damages DNA) (Scott, 1983, 1984, 1986). The models allow one to predict the combined effects of different toxicants from knowledge of the agent-specific, dose-response functions. The approach used is called a hazard-function approach, because the probability of producing the biological effects of interest is obtained indirectly from the cumulative hazard function that arises in probability theory.

The cited references (Scott, 1983, 1984, 1986) provide a way to calculate the hazard function h for a given combined exposure. The risk (or probability) of the stochastic effects of interest is then related to h through the equation

$$\text{Risk} = 1 - \exp(-h) . \tag{2}$$

The hazard function h can be thought of as representing the cumulative rate of production of critical damage, with critical damage being the damage required to produce the biological effect of interest. In the very special case where the critical damage induced by the combined exposure has a Poisson distribution, h would then correspond to the average amount of critical damage per biological target (e.g., cell, tissue, organ). For example, in the case where activation of a specific proto-oncogene (a process related to initiation of certain cancers) is scored among cells and has a Poisson distribution, then h would represent the average number of the specific oncogenes activated per cell.

The hazard-function model (Scott, 1983, 1984) was used to predict the cell killing by combined sequential exposure of L5 cells to 180-kVp X-rays and 14-Mev neutrons, based on data of Masuda (1970). The X rays represent low-LET radiation and the neutrons, high-LET radiation. With the model, one can partition cell killing into three parts: that due only to X-ray damage; that due only to neutron damage; and that due to interaction effects. The percentage of the total cell killing that is attributable to synergistic interaction effects can then be calculated. Results of this calculation are shown in the response surfaces in Figures 6 and 7 and lead to the prediction of greater synergistic effects for cell killing when the neutron dose precedes the X-ray dose than for reversing the ordering of the exposures. This predicted asymmetry in the interaction effect has been validated by data (Scott 1983, 1984).

In those cases where the different agents act independently, h will be given by the sum of the agent-specific hazard functions. In the very-low-dose region, independent action can be assumed for combined exposure to different radiations, for effects arising from damage to DNA (e.g., cell killing, mutations, tumors). Independent action would be

expected, because it is unlikely that two or more radiations would hit the same cell at very low doses. The radiation dose to the nucleus of a cell (i.e., nuclear dose) is a stochastic quantity.

B. Specific Energy z and Lineal Energy Density y

The stochastic nuclear dose is called the **specific energy z**. The stochastic dose z has the same type of units as macroscopic absorbed dose (e.g., Gy). The distribution of z over biological targets from different cells (e.g., cell nucleus) depends on the size of the target, the type of radiation, and other variables, e.g., primary or secondary charged particle energy. The microscopic correlate to the LET (a macroscopic concept) is the **lineal energy** y which represents the energy deposited by a charged particle in passing through a microscopic target divided by the average chord length of the target. When either z or y is known, the other can be calculated because they are related. Special types of radiation counters are used to measure z and y spectra (i.e., their distributions).

C. Relationship Between z and Absorbed Dose D

The average value for z corresponds to the **macroscopic absorbed dose D**, which is the total energy deposited in tissue divided by the mass of the tissue irradiated. Some biophysical models attempt to explain radiobiological effects on cells based on the stochastic dose z, instead of on the absorbed dose D (Kellerer and Rossi, 1972, 1978; Zaider *et al.*, 1983; Brenner and Zaider, 1984). Other models have been based on lineal energy y (Bond *et al.*, 1985). In addition to z and y being stochastic, effects such as mutations, tumors, and cell killing are also stochastic, so that doubly stochastic models are required when they are based on z or y. The stochastic biological effect can be modeled as a probability that depends on z or y. Convolutions of z or y spectra with conditional probabilities lead to calculation of expected biological harm.

D. Models for Toxicity to Normal Tissue

Hazard-function models have also been developed for damage to normal tissue of the body arising from brief or protracted exposure to ionizing radiations. Dose-response models have been published for acute lethality from injury to the bone marrow (hematopoietic death), gastrointestinal tract (gastrointestinal death) or lung (pulmonary

death) (Scott and Hahn, 1980; Scott, 1988a, 1988b; Scott *et al.*, 1988; Scott and Hahn, 1989; Scott *et al.*, 1990).

The hazard-function model for hematopoietic death has been adapted for application to radioimmunotherapy (RIT) (Scott and Dillehay, 1990). RIT is a relatively new therapy for cancer in which a specific radionuclide (usually a beta emitter, e.g., I-131 or Y-90) is attached to an antibody (e.g., antiferitin). The antibody is designed to attach to cancer cells (based on antigens on their surface such as feritin) and thereby allows their destruction by local irradiation. This approach spares normal tissue from damage. However, some of the normal tissue (e.g., bone marrow) can also be irradiated and toxicity to normal tissue can limit the success of the therapy.

Hazard-function models have also been developed for morbidity effects of irradiation, including severe mental retardation from *in utero* exposure, skin erythema, cataracts, hypothyroidism, respiratory dysfunction and fetal death (Scott and Hahn, 1989). A nonparametric method for estimating hazard functions for stochastic and nonstochastic effects of chronic exposure to a toxicant has also been developed (Scott, 1982).

V. SUMMARY

Highlights of my biophysical and biomathematical adventures in radiobiology was presented. Early research dealt with developing state-vector models for the effects of ionizing radiation on cells and on laboratory animals with emphasis on cell killing and life shortening in rodents. The research provided a theoretical basis for inverse dose-rate effects of some high-LET irradiations of cells and animals. While there were no data to support the theoretical predictions at the time they were developed, subsequent experimental and epidemiological research of other scientists on effects of high-LET radiations has demonstrated inverse dose-rate effects for a number of endpoints including mutations and transformations in cells, cancer in man and life shortening in animals.

More recent research has developed models for predicting stochastic and nonstochastic effects of combined exposure to different radiations and for stochastic effects of combined exposure to radiation plus a genotoxic chemical. Research results indicate that synergistic interaction effects are basically a moderate- and high-dose

phenomena. For low doses, the different agents would be expected to act independently, for endpoints such as cell killing, cell transformation, and mutations.

Dose-rate-dependent models have also been developed for nonstochastic effects of irradiation of man. The results indicate that man can tolerate considerably larger doses of low-LET radiation when delivered at low rates than can be tolerated when delivered at high rates. Dose-rate-dependent and other models that I developed for nonstochastic effects of irradiation are used by the U.S. Nuclear Regulatory Commission and by the U.S. Department of Energy for assessing potential health effects of nuclear accidents. The National Radiological Protection Board in the United Kingdom uses some of the models for assessing the consequences of nuclear disasters (e.g., nuclear war), and the U.S. National Aeronautics and Space Administration is incorporating some of the models into their computer software for assessing harm to astronauts from exposure to radiation in space.

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FIGURE LEGENDS

Fig. 1. State vector model for cell killing by ionizing radiation, for cells of the same age with respect to the cell cycle. A. Transitions that take place during irradiation. B. Transitions that take place after irradiation.

Fig. 2. Hypothetical linear, positive-curvature, and negative-curvature dose response curves for stochastic radiobiological effects of exposure at high dose rates of ionizing radiation.

Fig. 3. Hypothetical dose-response curves demonstrating normal dose-rate effects for typical stochastic effects of low-LET irradiation. With normal dose-rate effects, low rates of exposure are less damaging than high rates, because repair of damage is more efficiently carried out when the radiation dose is given at a low rate.

Fig. 4. Hypothetical dose-response curves for stochastic radiobiological effects that demonstrate an inverse dose-rate effect. With an inverse dose-rate effect, low rates of exposure are more damaging than high rates.

Fig. 5. Hypothetical linear dose-response curve for one-hit stochastic effect. The linear shape is limited to low and moderate doses. For one-hit effects, high- and low-dose rates produce the same amount of damage, for the same dose.

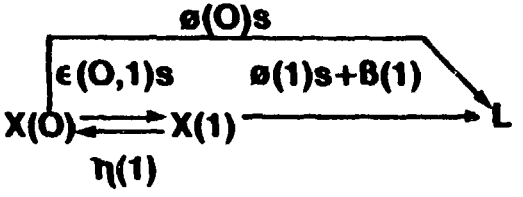
Fig. 6. Response surface for predicted contribution (%) to cell killing arising from synergistic effects of sequential exposure of L5 cells to low-LET X-rays followed by high-LET neutrons.

Fig. 7. Response surface for predicted contribution (%) to cell killing arising from synergistic effects of sequential exposure of L5 cell to high-LET neutrons followed by low-LET X-rays.

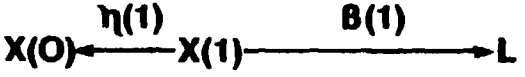
Fig. 1

MODEL FOR CELL KILLING BY IONIZING RADIATION

A. t-regime transitions



B. t'-regime transitions



Similar model also developed for life shortening in small mammals.

Fig. 2

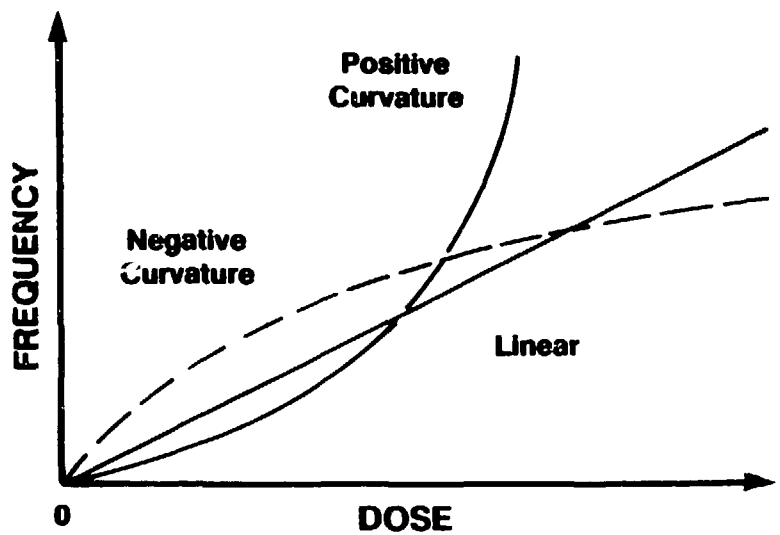

Positive
Curvature
Negative
Curvature
Linear
FREQUENCY
0
DOSE

Fig. 3

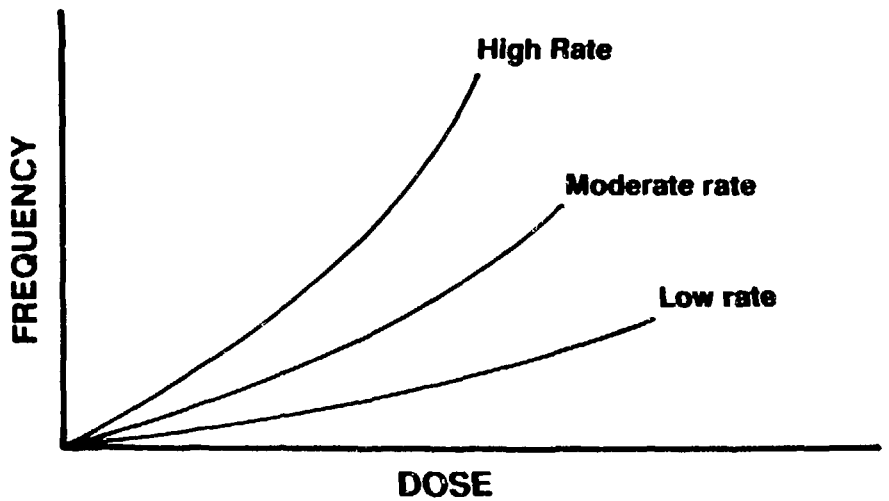


Fig. 4

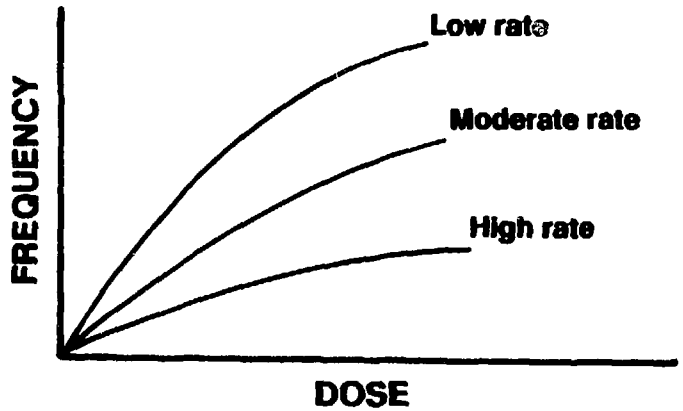


Fig. 5

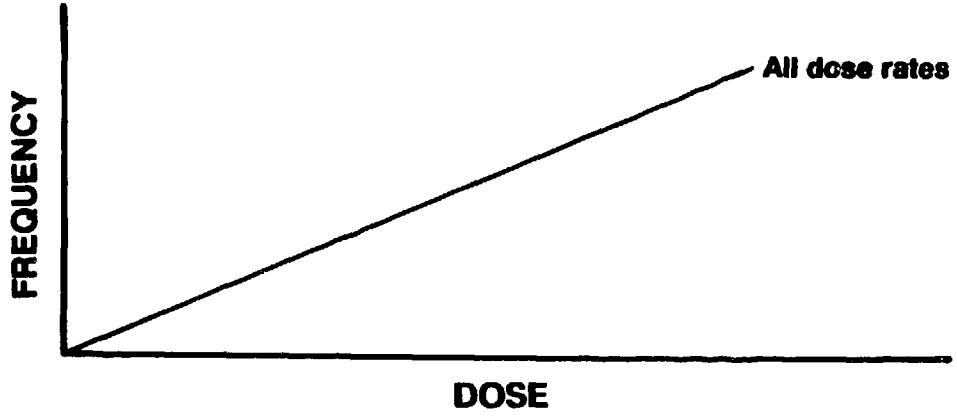


Fig. 6

X RAYS FOLLOWED BY NEUTRONS

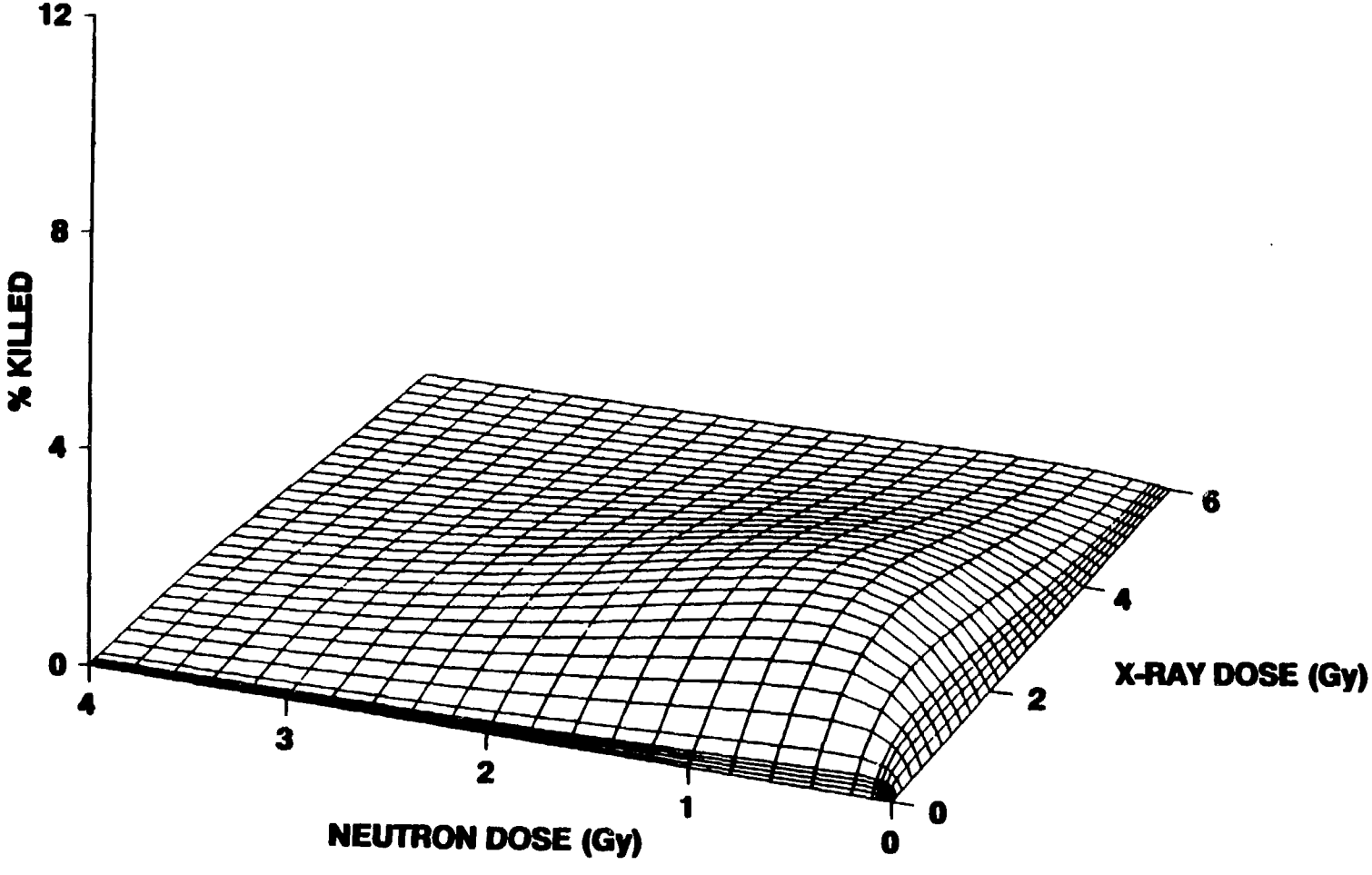


Fig. 7

NEUTRONS FOLLOWED BY X RAYS