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LOW-LEVEL RADIATION HEALTH EFFECTS: DATA AND PROGRAMS

Cosponsored by the Biology and Medicine, the Environmental Sciences the Isotopes and Radiation, and the Radiation Protection and Shielding Divisions

Session Organizer: James Muckerheide (Comm Mass)

All Papers Invited

1. Wound-Healing Error Model for Radon Carcinogenesis, *Sohei Kondo (Kinki Univ-Japan)*

INTRODUCTION

Epidemiological studies of lung cancer in uranium miners exposed to radon suggest that radon is a tumor promoter.[1] I will refine this notion by applying the wound-healing error model proposed for radiation carcinogenesis in general.[2]

DATA AND MODEL

Data on Uranium Miners in Czechoslovakia

Figure 1 shows excess lung cancer deaths in miners as a function of cumulative radon exposure for three groups of workers whose average exposure extended over 14 yr (squares), 9.5 yr (triangles), and 5.6 yr (circles).[3]

Figure 2 shows that excess small-cell carcinomas plateaued after 100 working level months (WLM), while excess epidermoid carcinomas increased approximately linearly with radon exposure.[4]

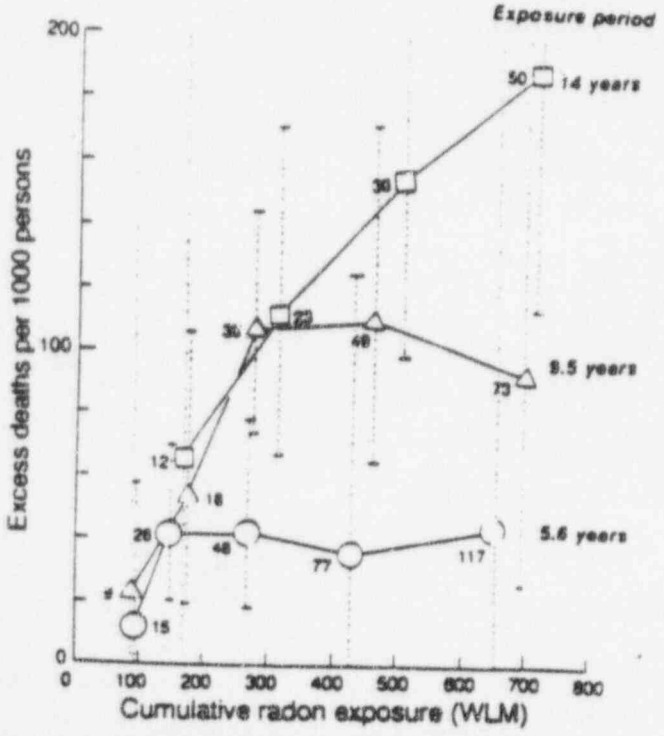

Fig. 1. Excess lung cancer deaths in miners as a function of cumulative radon exposure.

Wound-Healing Error Model for Radiation Carcinogenesis[2]

Human cancer is a genetic disease due to accumulati multiple oncomutations in a single cell. Therefore, it ta long time for a normal cell to develop into a cancerous cell, which explains the steep rise in the cancer incidence with age. I assume that oncomutations occur spontaneously, whether tissues are irradiated or not, but that cells with oncogenic mutations in a tissue moderately injured by radiation have a selective advantage for clonal expansion because the tissue damage must be repaired by cell growth, which creates the opportunity for clonal expansion. Furthermore, if the tissue damage persists for a long time, spontaneously occurring preneoplastic cells will have an increased probability for acquiring the multiple onco-

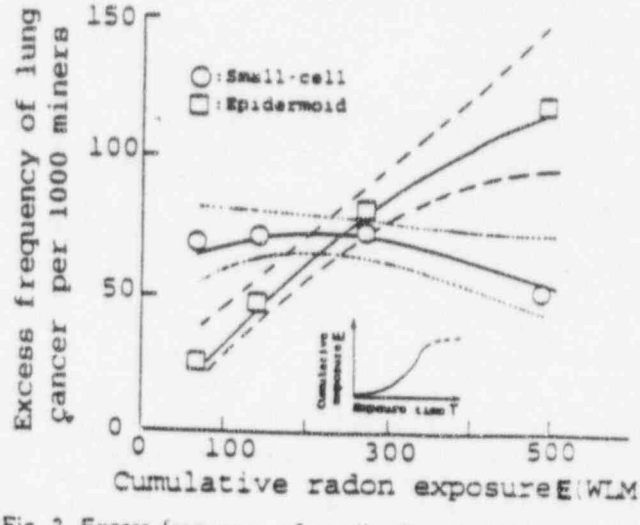

Fig. 2. Excess frequency of small-cell and epidermoid lung cancer in miners as a function of cumulative radon exposure.

mutations necessary for their progeny to produce a cancerous cell.

DISCUSSION

The wound-healing error model, in which chronic, long-term wounding after irradiation is more oncogenic than a high cumulative exposure to radon over a short time, can nicely explain the observation that workers who spread their radon exposure over more years had more lung cancers (Fig. 1). The unique shape of the dose-response curve for small-cell carcinoma, with a plateau at 100–300 WLM and diminution at 500 WLM (Fig. 2), can be explained by the wound-healing error model as follows. If the target tissue has been heavily irradiated, preneoplastic cells will have no selective advantage because cell growth may not be activated due to impairment of the tissue repair capacity. Therefore, primordial cells that produce small-cell carcinomas may be more radiosensitive than squamous cells that produce epidermoid carcinoma. The last assumption should be studied, although it seems to be the case because small-cell carcinomas are considered to be derived from neuroendocrine cells of the bronchial epithelium.

It is firmly established that the excess frequency of mutations after irradiation increases almost linearly with increasing dose and that its value at equal total exposures remains the same or decreases if exposure rates are decreased. However, uranium miners had increased lung cancer at decreased exposure rates (Fig. 1). Therefore, radon is not an oncomutagen. Mutations are the only known radiation effects that increase approximately linearly with the dose of radiation, without a threshold. Thus, no scientific evidence is available to support a linear no-threshold risk of cancer after exposure to radon. Cancer is not a problem of single cells but of cell society.

1. R. W. HORNUNG, T. J. MEINHARDT, "Quantitative Risk Assessment of Lung Cancer in U.S. Uranium Miners," *Health Phys.*, **52**, 417 (1987).

2. S. KONDO, *Health Effects of Low-Level Radiation*, Kinki University Press, Osaka, Japan, and Medical Physics Publishing, Madison, Wisconsin (1993).

3. E. KUNZ, J. SEVC, V. PLACEK, J. HORACEK, "Lung Cancer in Man in Relation to Different Time Distribution of Radiation Exposure," *Health Phys.*, **36**, 699 (1979).

4. J. SEVC, E. KUNZ, L. TOMASEK, V. PLACEK, J. HORACEK, "Cancer in Man After Exposure to Rn Daughters," *Health Phys.*, **54**, 27 (1988).

2. Test of the Linear No-Threshold Theory of Radiation-Induced Cancer, *Bernard L. Cohen (Univ of Pittsburgh)*

There is no experimental evidence supporting the linear no-threshold (LNT) dose-response relationship for radiation-induced cancer in the low-dose, low-dose-rate region of the vast majority of applications (e.g., leakage of radioactive waste, >90% of projected deaths from reactor accidents, routine emissions, clean-up of Hanford, etc.). The only basis for LNT is a very simple theory: a cancer can be initiated by a single particle of radiation, so the cancer risk is proportional to the number of these particles, which is proportional to the dose. However, this ignores the effects of radiation on repair processes, stimulation of the immune response, and timing in the cell cycle. All of these are now known to be important, and they tend to reduce the effectiveness of subsequent radiation exposure.[1] Thus, they cause LNT to overestimate the carcinogenic effects of low-level radiation. It is therefore extremely important to test LNT experimentally.

To perform this test, we compare age-adjusted lung cancer mortality rates m with mean radon exposure r in 1729 U.S. counties, constituting 90% of the U.S. population. Results are shown in Figs. 1a and 1b (see next page), where each point gives the average m-value for the group of counties within the range of r-values shown at the baseline of Fig. 1a (the figures there are the number of counties in the group). Error bars are one standard deviation (SD) of the mean, and the first and third quartiles of each group are also plotted. The solid straight line is the best fit to the data for all counties, and the dashed line is the prediction of LNT (BEIR IV version) assuming all other factors are equal. Figures 1c and 1d show these data corrected for smoking prevalence S in the various counties.

We see that, after correcting for smoking, m *decreases* by −8% per pCi/ℓ, in sharp contrast to the theory prediction of an *increase* of −7% per pCi/ℓ, a discrepancy of >20 SD. We refer to this as "our discrepancy." The principal criticism of this work is that it is an "ecological" study, dealing with groups of people (populations of counties), whereas epidemiologists much prefer to study individuals. They are very conscious of the "ecological fallacy" that the average dose to a group of people does not determine their average risk; this is obvious where a threshold is involved. However, it is easy to show that the "ecological fallacy" does not apply in testing an LNT theory—the average dose *does* determine the average risk in LNT. It is shown that other problems ascribed to ecological studies do not apply here.

Extensive studies were made of effects of uncertainties in r-values and S-values, but these can do little to explain our discrepancy. Extensive studies were also made of potential confounding by 54 different socioeconomic factors, singly or in combination, and of confounding by geography, by altitude, and by climate, but no substantial reduction in our discrepancy could be obtained. Effects of known r-S correlations—rural people have higher radon exposures and smoke less than urban people, and smokers are exposed to less radon than nonsmokers—were calculated in detail and found to have trivial effects on our discrepancy. It was shown that our discrepancy is not particular to the BEIR IV theory, but applies equally to any LNT theory based on the miner data. Properties of a hypothetical unknown confounder that could explain our discrepancy are considered, and it is concluded that its existence is far less credible than failure of the LNT theory in the low-dose region where it has never been tested.

1. B. L. COHEN, "Dose-Response Relationship for Radiation Carcinogenesis in the Low Dose Region," *Int. Arch. Occup. Environ. Health*, **66**, 71 (1994).

3. Rethinking ALARA, *Jerry J. Cohen (Cohen Consult)*

The recommendation to keep exposures to ionizing radiation "as low as reasonably achievable" (ALARA) has been a long-standing component of radiation safety programs. This recommendation is based on the assumption that there is no dose threshold below which harmful biological effects will not occur. With this assumption, it logically follows that there is no "safe" level of exposure and that any exposure, no matter how low, carries with it some risk of harm. This presumption was a departure from a previously established principle in public health that could be paraphrased "the dose makes the poison," which held that high-dose effects of harmful agents are not necessarily indicative of low-dose effects. The concept of further minimizing radiation exposures to levels well below specified dose limits originated in the 1950s with the International Commission on Radiological Protection (ICRP) rec-

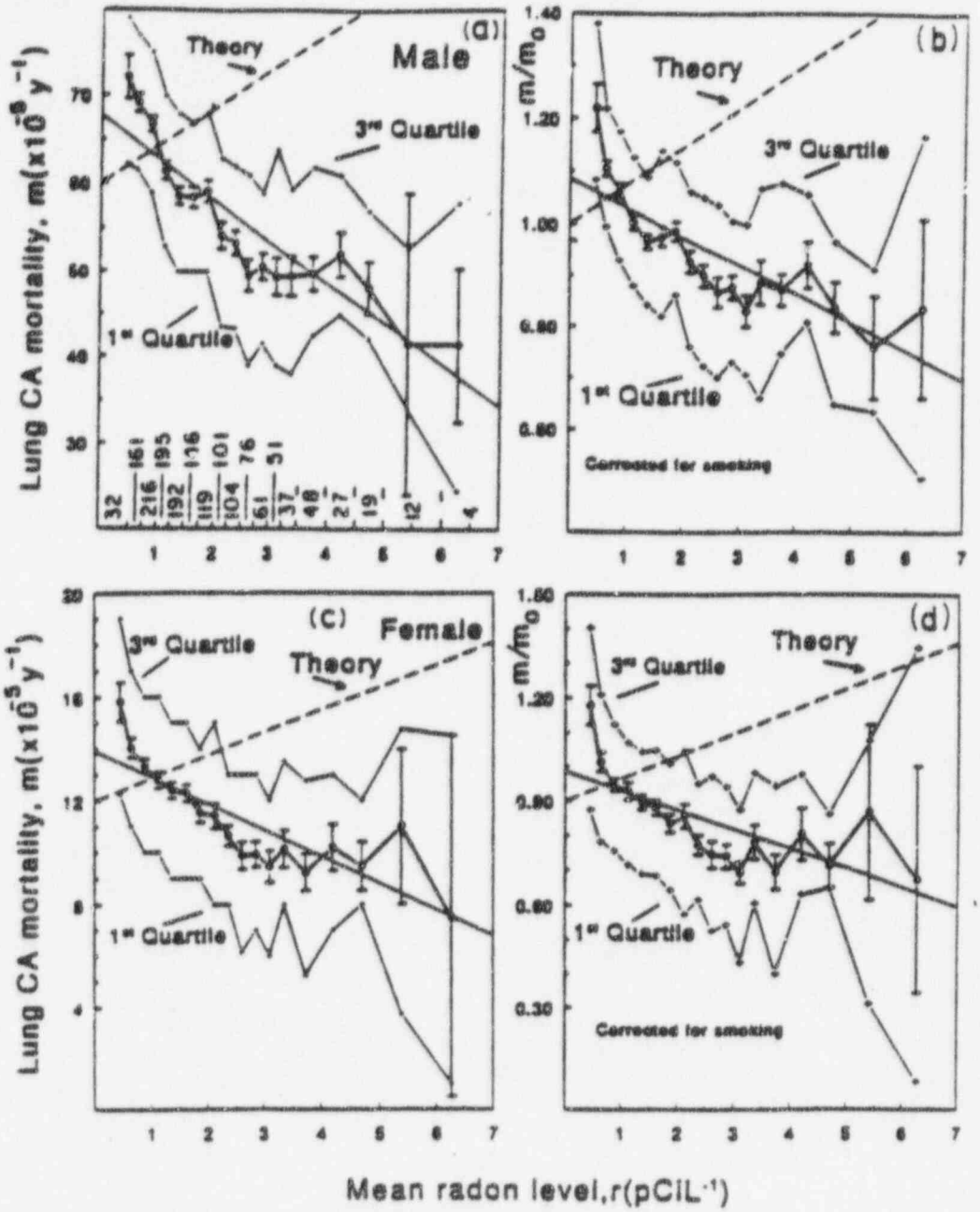

Fig. 1. Lung cancer mortality rates as a function of mean radon level in homes for U.S. counties. (Paper 2)

ommendation that doses be kept "as low as possible" (ALAP). In 1959, ICRP replaced "possible" with "practicable," and in 1973, ALAP was changed to ALARA to convey ICRP's intent to achieve dose minimization with "economic and social considerations being taken into account." To implement this guidance, ICRP recommended application of cost-benefit analysis to balance economic costs against benefits of dose reduction.

Implementation of ALARA in radiation protection programs is a regulatory requirement in the United States; however, ICRP recommendations on use of cost-benefit analysis are largely ignored. Under U.S. Nuclear Regulatory Commission (NRC) rules, required ALARA programs can essentially be defined as "dose reduction" programs. A cursory survey of nuclear installations in the United States revealed numerous instances of "ALARA horror stories" where ALARA is the cited basis for making enormous expenditures to achieve relatively trivial levels of dose reduction. This observation has led to a questioning of the basic premises upon which ALARA is founded.

ALARA is clearly predicated on the *assumption* that there is no threshold below which biological effects are nonexistent or possibly even beneficial in nature. This assumption has been used as a basis for regulatory decisions for so long now that it has come to be regarded by the public as an immutable truth. However, there is currently a considerable body of evidence indicating that the assumption is false. This evidence has been largely ignored in the regulatory decision-making process for the stated reason that it is "not convincing." Because, at very low doses, it would be statistically impossible to prove the occurrence of any effects (either harmful or beneficial), it is highly unlikely that clear, absolute proof will ever be [illegible]. However, the preponderance of direct low-dose (< 100 m[illegible]) evidence that does exist indicates that beneficial effect[illegible] be more likely.

The argument may be made that even if the no-threshold assumption is wrong, it still provides a "prudent" basis for regulatory decisions. If, in fact, low-dose radiation exposure produces no adverse effects, then accepting this assumption as a

basis for regulatory decisions is certainly *not prudent*. The resulting policies can and have caused the expenditure of vast amounts of limited resources toward meeting requirements that produce no public benefit. These resources necessarily become unavailable for other areas of public health and safety where they might actually do some good.

It may also be argued that highly restrictive regulation, as is the case with the NRC's ALARA requirements, can be justified as a reflection of inordinate public fears toward radiation. On the other hand, a strong case may also be made to the effect that such regulatory policies are a major cause for those fears, because it could logically be inferred that severe controls would be unnecessary if radiation was not extremely dangerous.

Despite the existence of scientific evidence indicating the likelihood that ALARA is technologically unfounded, one should not be optimistic that current policies will be relaxed. Considering the deep-seated public fear of radiation (regardless of dose level), such relaxation would likely prove to be politically unpopular. It is also unlikely that the idea that ALARA is an unsound policy would gain widespread acceptance among radiation protection professionals, because it is estimated that >50% of this group is gainfully employed in work that is directly or indirectly related to ALARA. Nonetheless, from a public health standpoint, ALARA is at best a highly questionable policy that should be subjected to an objective and unbiased reassessment in light of all current evidence on low-dose radiation effects. A serious problem in this regard might be the assembly of a knowledgeable group of experts to review ALARA policies, who have no vested interest in its perpetuation.

4. The Linear Hypothesis – An Idea Whose Time Has Passed, *A. N. Tschaeche (INEL/LITCO)*

The linear no-threshold hypothesis is the basis for radiation protection standards in the United States. In the words of the National Council on Radiation Protection and Measurements (NCRP), the hypothesis is: "In the interest of estimating effects in humans conservatively, it is not unreasonable to follow the assumption of a linear relationship between dose and effect in the low dose regions for which direct observational data are not available."[1] The International Commission on Radiological Protection (ICRP) stated the hypothesis in a slightly different manner: "One such basic assumption . . . is that . . . there is . . . a linear relationship without threshold between dose and the probability of an effect."[2] The hypothesis was necessary 50 yr ago when it was first enunciated because the dose-effect curve for ionizing radiation for effects in humans was not known. The ICRP and NCRP needed a model to extrapolate high-dose effects to low-dose effects. So the linear no-threshold hypothesis was born. Certain details of the history of the development and use of the linear hypothesis are presented. In particular, use of the hypothesis by the U.S. regulatory agencies is examined. Over time, the sense of the hypothesis has been corrupted. The corruption of the hypothesis into the current paradigm of "a little radiation, no matter how small, can and will harm you" is presented. The reasons the corruption occurred are proposed. The effects of the corruption are enumerated, specifically, the use of the corruption by the antinuclear forces in the United States and some of the huge costs to U.S. taxpayers due to the corruption. Examples are given of how and why those costs have been created. Players in the creation of the costs have been the regulators, Congress, the antinuclear forces, the nuclear industry itself, and the public. The interrelation and communications among those groups that resulted in creating the costs are examined. A pessimistic future for the nuclear industry and lost benefits to society are forecast if the hypothesis continues to be the basis for radiation protection standards in the United States.

An alternative basis for radiation protection standards to assure public safety, based on the weight of scientific evidence on radiation health effects, is proposed. The basis is a numerical value for annual permissible dose. If an individual's dose remains below that value, no cost would be justified to reduce it further. If it were anticipated that the dose would significantly exceed the standard, the concept of ALAP, or keeping the dose as low as practicable, taking into account economic and social considerations and individual circumstances, would be applied. The same value is proposed for both radiation workers and the general public. It is proposed that studies of groups of individuals who are exposed near the limit be funded by the federal government to verify that no harm is observed. It is further proposed that other standards be developed to prevent the spread of radioactive material into industrial processes that are particularly sensitive to the presence of such material. Examples of such processes are photographic film and paper manufacture, computer chip manufacture, radiation measuring equipment manufacture, and research laboratories that use radioactive material. These latter standards are not safety standards. With this two-tiered set of standards, one to assure health and safety purposes, the other for industrial and research purposes, comparable to industrial "clean room" standards, members of the public would be informed that a little radiation would not hurt them, and that radioactive material may otherwise need to be controlled so that it will not be deleterious to certain manufacturing and research activities. The evils and unwarranted costs of the linear hypothesis would then be eliminated. The nuclear industry will then be able to continue to provide the enormous benefits to society that it is uniquely capable of providing.

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1. "Basic Radiation Protection Criteria," NCRP-39, p. 55 (1971).

2. "Recommendations of the International Commission on Radiological Protection," ICRP-26, Para. 27 (1977).

5. Why We Need New Approaches to Low-Dose Risk Modeling, *Joseph L. Alvarez (IT Corp, Englewood), Fritz A. Seiler (IT Corp, Albuquerque)*

The linear no-threshold model for radiation effects was introduced by the International Commission on Radiological Protection as a conservative model for the design of radiation protection programs.[1] The model has persisted not only as the basis for such programs[2,3] but has come to be treated as a dogma and is often confused with scientific fact. The pervasive use of the linear model has extended calculations of radiation risks to dose levels that cannot be measured and have risks that are much smaller than the uncertainty of the calculation. This extends the model beyond its range of applicability and requires consideration of a minimum significant risk.[4]

Examination of the model for a minimum significant risk required examination of the model and data uncertainties. In this examination a number of serious problems with the linear no-threshold model of radiation carcinogenesis were demonstrated, many of them invalidating the hypothesis. It was shown that the relative risk formalism did not approach one as the dose approaches zero. When mortality ratios were used instead, the data in the region below 0.3 Sv were systematically below the predictions of the BEIR V model. It was also shown that the data above 0.3 Sv were of little use in formulating a model at low doses. In addition, these data are valid only for doses accumulated at high dose rates, and there is no scientific justification for using the model in low-dose, low-dose-rate extrapolations for purposes of radiation protection. Figure 1 illus-

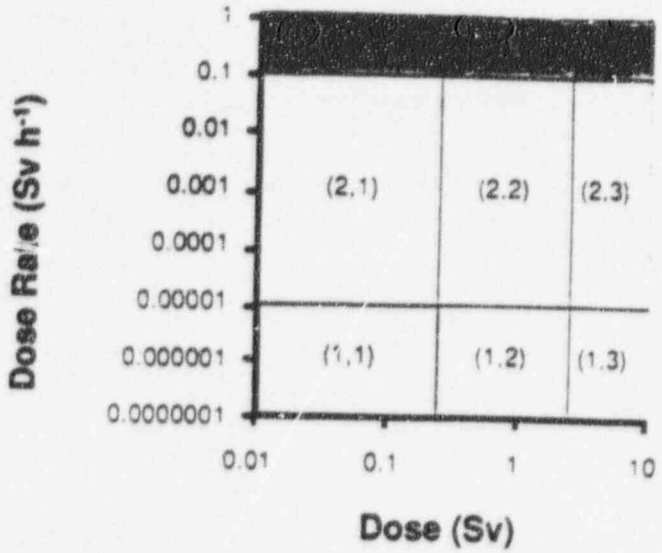

Fig. 1. [Dose/dose rate] classification chart. The Japanese bomb survivor data occupy the three top cells above 0.1 Sv/h, shown with heavy shading. Due to the sparing effect of lower dose rates, the boundaries between the three dose regions move to higher doses by somewhat uncertain factors. The predictions by a radiation protection model for routine exposures need to be made in cell (1,1), shown with light shading, and maybe in cells (2,2) and (2,3) for accidental exposures. There are large but at present ignored data sets in the middle row of cells as well as in cell (1,1), where the low-dose, low-dose-rate modeling is most needed.

trates the state of our present knowledge from the data base of the BEIR V model and the regions of dose and dose rate that are dependent on the model for interpretation. The dark shaded portion of the figure is the region of the Japanese survivors, while the light shaded portion is the low-dose and low-dose-rate region. Data exist in the intermediate region to bridge the considerable gap from the region of the n to the low-dose and low-dose-rate region. Above all, the high-dose to low-dose model ignores the copious epidemiological database that is available at low doses and dose rates, that is, exactly the region for which radiation protection models are needed. These epidemiological data also are at odds with the linear no-threshold hypothesis.

Despite these obvious errors in the model extrapolation, further examination of model fits to the Japanese survivor data were attempted. Several such models were fit to the data including an unconstrained linear, linear-square root, and Weibull, all of which fit the data better than the relative-risk, linear no-threshold model. These fits were used to demonstrate that the BEIR V model systematically overestimates the risk at low doses in the Japanese survivor data set. This systematic lack of fit hardly invites extension to low doses at low dose rates.

It is recommended that an unbiased reanalysis of the data be undertaken and the results used to construct a new model, based on all pertinent data. This model could then form the basis for managing radiation risks in the appropriate regions of dose and dose rate.

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1. "Recommendations of the International Commission on Radiological Protection," ICRP Publication 26, Pergamon Press, Oxford (1977).

2. *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V*, National Academy Press, Washington DC (1990).

3. "Recommendations of the International Commission on Radiological Protection," ICRP Publication 60, Pergamon Press, Oxford (1991).

4. F. A. SEILER, J. L. ALVAREZ, "The Definition of a Minimum Significant Risk," *Technology*, 331A, 83 (1994).

LOW-LEVEL RADIATION HEALTH EFFECTS: POLICIES AND COST/BENEFITS

Cosponsored by the Biology and Medicine, the Environmental Sciences, and the Isotopes and Radiation Divisions

Session Organizer: J. Muckerheide (Comm Mass)

All Papers Invited

1. Returning Common Sense to Regulations,

Michael R. Fox (Westinghouse Hanford)

To begin at a point of common understanding and agreement, the British philosopher C. P. Snow in 1964 wrote his short and insightful book, *Two Cultures*.[1] He described the existence of the division within society between the scientific, numerate, and quantitative on one side, and the nonscientific, nonnumerate, and nonquantitative on the other.

This division since the 1960s has flourished, deepening and expanding as technologies have advanced. The impacts of public fear among the nonscientific segment of society have been immense, since this segment represents a huge majority of the American public. What the public *perceives* as harmful, according to traditional risk data (e.g., mortality and morbidity tables), is almost inversely related to what is *actually* harmful to the public.[2]

This has led to a morass of environmental regulations that not only are extremely costly for the public to understand, comply with, and implement, in too many cases the regulations contribute precious little in the actual reduction of health risk to the same public.

The regulations regarding radiation exposures to the public are a subset, a rather large subset, of the fear-driven regulations with which we now must comply. These costs have directly affected every industry using nuclear technology and materials. The exorbitant costs of compliance, we must never forget, are almost unique to the American experience with nuclear technology.

A major contributing factor to these costs has been the Linear Theory of Harm from Radiation, which has been transformed from what was initially an administrative guideline in controlling radiation exposures to a scientific fact. It is one thing to advise a child not to go near a hot stove (instilling fear in the process). It is quite another to ask society to forego all uses of heat in domestic and industrial processes.

For the past 50 yr, the nation has been struggling with understanding nuclear technology. Even though natural radioactivity was discovered a hundred years ago, it remains substantially unknown to the American public today. Those opposed to nuclear technology have exploited this magnificently. Regrettably, in some cases people with scientific credentials have aided and abetted the critics of nuclear technology. For the most part the scientific societies remained on the sidelines during decades of public debate.

The United States has spent hundreds of billions of dollars complying with the various regulations imposed by federal and state regulators (the Environmental Protection Agency estimates $115 billion per year for compliance costs).[3] It is becoming abundantly clear that such an investment has not produ measurable reductions in health risks. In the case of radiat regulations, the reason is that at low doses of radiation ex sure, there are no significant levels of observable harm. C should not expect large and observable reductions of har regulating agents at doses not observably harmful.

The recent works by Cohen,[4] Kondo,[5] the June 1995 is of the *Health Physics Newsletter*,[6] and the efforts of the Bi ogy and Medicine Division of the American Nuclear Soci (ANS) collectively challenge (if not overthrow) the questic able underpinning of the dubious Linear No-Threshold Theo

To provide a specific example, the average resident Spokane County of the state of Washington receives >16 mrem/yr of radiation from natural sources (largely indo radon).[7] Higher individual exposures are common. There a no notable excesses of cancer mortality in Spokane Count There are many other instances of such exposures to natur radiation.

Does it make sense to set radiation exposure limits nuclear technologies and activities at levels down to 1% these natural levels? (The state of Washington is currently co sidering exposure limits of 15 mrem/yr above natural levels Hanford cleanup.) The answer is, no it doesn't, if improv public safety is the issue. Scientific societies such as the A must become active participants in these scientific debates ensure that this nation ceases squandering its financial a intellectual resources pursuing small, often immeasurable ris

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1. C. P. SNOW, *Two Cultures*, Cambridge at the Universi Press, Cambridge, England (1964).
2. P. M. SANDMAN, "Hazard Versus Outrage: Respondir to Public Concerns about the Risks of Industrial Gases presented at Int. Oxygen Manufacturers Association Annual Meeting, 1991.
3. P. ABELSON, "Pathological Growth of Regulations," *Sc ence* (June 25, 1993).
4. B. L. COHEN, "Test of the Linear-No Threshold Theor of Radiation Carcinogenesis for Inhaled Radon Decay Proc ucts," *Health Phys.*, **68**, 2, 157 (Feb. 1995).
5. S. KONDO, *Health Effects of Low-Level Radiation*, Kins University Press, Medical Physics Publishing (1993).
6. *Health Physics Newslett.*, **XXIII**, 6 (June 1995).
7. "Special Report – Radon in Washington," Washington Sta Department of Health, Environmental Health Program (June 1994).

2. Limitations on Cost-Benefit Analyses Involving Low Radiation Exposures, *Allen Brodsky (Georgetown Univ)*

The purpose of this paper is to examine some limitations on cost-benefit analyses related to activities involving individual exposures below ~0.1 to 1 Sv. Previous papers[1,2] have presented evidence showing the likelihood that there is no purely linear dose-response component at low radiation levels – that most dose-response functions where the response is the induction of an initial cancer cell are likely to be curvilinear (concave) upward at the lowest exposure levels. There is also considerable evidence that hormetic effects in this dose region, including those that can repair or kill initiated cancer cells as well as those that might provide beneficial health effects, are likely to be superimposed on any dose-response functions for the carcinogenic process alone.[3,4] These phenomena impose such large uncertainties in response at low doses that current risk factors obtained by extrapolation of linear-quadratic models fitted to human cancer data at high dose levels are inapplicable for use in low-dose cost-benefit analyses; this is true at least insofar as such analyses cannot be expected in themselves to necessarily result in optimum choices between alternative actions. The influence of these uncertainties on cost-benefit analysis has been examined using methods for such analyses as given in Ref. 5.

Limitations in ICRP-37 methods have been examined also in the usual context of deciding alternatives for a specific project. The need for a true cost-benefit analysis to provide optimum societal benefits through incorporation into a quantized framework of benefits for all projected human activities involving environmental exposure has been presented previously.[6] Thus, the variables in this examination have been restricted to those for alternatives to a specific project and include the gross benefit, production costs, radiation protection costs, and costs of detriments that include radiation health effects as well as other detriments to human life – as related only to the possible alternatives for the specific project.

We conclude from this analysis that (a) conventional methods of cost-benefit analysis can be used to help choose between alternative actions only when regulatory constraints demand specific limitations on population dose and when budget constraints have been already imposed on a project, and (b) these conventional methods do not achieve true optimization of benefit/cost for society as a whole, nor even for the exposed group.

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1. A. BRODSKY, "Are Radiation Risks Real Below 0.001 Sv per Year?" *Trans. Am. Nucl. Soc.*, **69**, 177 (Nov. 1993).

2. A. BRODSKY, "Are Radiation Risks Real Below 0.001 Sv per Year?" *Radiat. Protect. Manage.*, **12**, *3*, 61 (May/June 1995).

3. T. D. LUCKEY, *Hormesis*, 2nd ed., CRC Press, Boca Raton, Florida (1990).

4. A. BRODSKY, *Radiation Risk and Uranium Toxicology Review, with Applications to Cost-Benefit Decisions in Decommissioning*, RSA Publications, Hebron, Connecticut (1995).

5. "Cost-Benefit Analysis in the Optimization of Radiation Protection," ICRP Publication 37, International Commission on Radiological Protection, Pergamon Press, New York (1983).

6. A. BRODSKY, "Balancing Benefit vs. Risk in the Control of Consumer Items Containing Radioactive Material," *Am. J. Public Health*, **55**, 1971 (1965).

3. Cancer Risks, Risk-Cost-Benefit Analyses, and the Scientific Method, *Fritz A. Seiler (IT Corp, Albuquerque), Joseph L. Alvarez (IT Corp, Englewood)*

Two main changes in risk analysis are increasingly beginning to influence the manner in which, in the perception of scientists, low-dose modeling of radiation carcinogenesis is supposed to be done. In the past, efforts to model radiation risks have been carried out under the banner of scientific endeavors. On closer inspection, however, it has become obvious that these efforts were not guided by the scientific method and that a change in approach is needed.[1] We realize increasingly that risk analysis is not done in a vacuum and that any action taken due to the result of the analysis not only has a benefit in the form of a risk reduction but leads inevitably to an increase in cost and an increase in the risks of persons effecting the benefit. Thus, a risk-cost-benefit analysis should be done and show a clear-cut net benefit before a remedial action is taken.

These two changes will require a dramatic change in the approach to low-dose risk modeling. Some important aspects of this statement may not be directly evident, so a short analysis of the situation may be helpful. In a cost-benefit analysis, the benefit of a management action, measured in numbers of human lives saved or injuries averted, has to be compared to the cost of the action measured in dollars. Many methods, such as the Multi-Attribute-Utility Theory, have been developed to solve the obvious problem of comparing cost in human lives to cost in dollars.[2] A less obvious problem is the implicit assumption that both the reduction in risk and the increase in cost are estimated with models of roughly the same degree of sophistication and assuming that the numerical uncertainty analysis can account for the remaining differences in reliability.

In a risk-cost-benefit analysis, the costs are evaluated in a manner that is likely to yield a best possible estimate and its uncertainty. Similarly, the risk of the remedial action, often a set of different occupational risks, is based on actuarial data and is usually also done in a manner that should yield a best possible estimate. The benefit by risk reduction, however, is usually overestimated dramatically, all in the name of conservatism and the benefit of mankind. This well-meaning approach thus leads to an unacceptably biased risk and risk reduction, making these risk models completely useless for risk-cost-benefit analyses.

In the application of the scientific method to the problem of low-dose risk modeling, the most important question is, What can we as scientists honestly state about this risk? and the only acceptable procedure is one that calculates a risk using the most appropriate model available and the best possible values for the model parameters to yield the best possible risk value according to the state of the art. This is followed by an exploration of the limits of our knowledge about each one of the model parameters and, if necessary, an error propagation calculation to arrive at the total error of the risk. Again, the question is, What can we honestly say about the standard error? Then and only then should upper limits be calculated and used and statements about the low-dose risk made. Thus, from the standpoint of the scientific method, using conservative models and conservative parameter values is not acceptable. Indeed, in the new paradigm of risk assessment, conservatism is not a virtue but a sin.

An example for the application of these new rationales is the definition of a minimum significant risk.[3] It is based on the fact that some errors decrease as the risk decreases, but others do not. Thus, as the dose decreases, the risk decreases also but not all components of its standard error. There will thus be a dose for which the risk is comparable to its error, and a simple statistical test will show that the assumption that the risk

is different from zero can no longer be maintained. As with all quantities, there is a minimum scientifically meaningful risk. An inspection of the BEIR V model and its uncertainties shows that the minimum significant risk lies in the range of a few percent for a 90 to 95% confidence level. For an improved error analysis of the BEIR V data, minimum significant risks of a few times 10^{-3} might be obtained, but values near or below 1×10^{-3} are probably out of the reach of these studies. The important consequence of these evaluations is that any risk smaller than the minimum significant risk is scientifically meaningless.

1. F. A. SEILER, J. L. ALVAREZ, "The Use of the Scientific Method in Risk Analysis," *Technology*, 331A, 53 (1994).

2. R. L. KEENEY, "Decision Analysis," *Handbook of Operations Research: Foundations and Fundamentals*, J. J. MODER, S. E. ELMAGHRABY, Eds., Van Nostrand Reinhold, New York (1978).

3. F. A. SEILER, J. L. ALVAREZ, "The Definition of a Minimum Significant Risk," *Technology*, 331A, 83 (1994).

Panel Discussion

Panelists: *Marvin Goldman (HPS)*
Anthony Thompson (SPP&T)
Jerry Cuttler (AECL CANDU-Canada)
Myron Pollycove (NRC)
Leonard Sagan (Sagan Consult)
John Cameron (Cameron Consult)
Carol S. Marcus (Harbor-UCLA Medical Ctr)
A. N. Tschaeche (INEL/LITCO)
Joseph L. Alvarez (IT Corp, Englewood)
Fritz A. Seiler (IT Corp, Albuquerque)
Jerry J. Cohen (Cohen Consult)
Michael R. Fox (Westinghouse Hanford)
Sohei Konoo (Kinki Univ-Japan)
Bernard L. Cohen (Univ of Pittsburgh)
Allen Brodsky (Georgetown Univ)

LOW-LEVEL RADIATION HEALTH EFFECTS: ADAPTIVE CELL REPAIR AND BENEFICIAL EFFECTS

Cosponsored by the Biology and Medicine, the Isotopes and Radiation, and the Environmental Sciences Divisions

Session Organizer: J. Muckerheide (Comm of Mass)

All Papers Invited

1. Can Low-Level Radiation Cause Cancer?

James E. Trosko (Michigan State Univ)

CANCER IS NOT "CAUSED" BY ONLY ONE THING

Health in a multicellular organism is maintained by homeostatic processes. Disruption of these homeostatic controls at the molecular, biochemical, cellular, and organ systems levels can be brought about by irreversible changes in the genetic material (mutagenesis), cell death (cytotoxicity), or reversible changes in the expression of genes at the transcriptional, translational, or posttranslational levels (epigenesis). While radiation is known to induce DNA damage/mutations, cell, death and epigenetic changes, in addition to cancers that are found in radiation-exposed animals, experimentally, and in humans, epidemiologically, the question is, At low-level exposure, what is the risk that cancers are "caused" by the radiation?

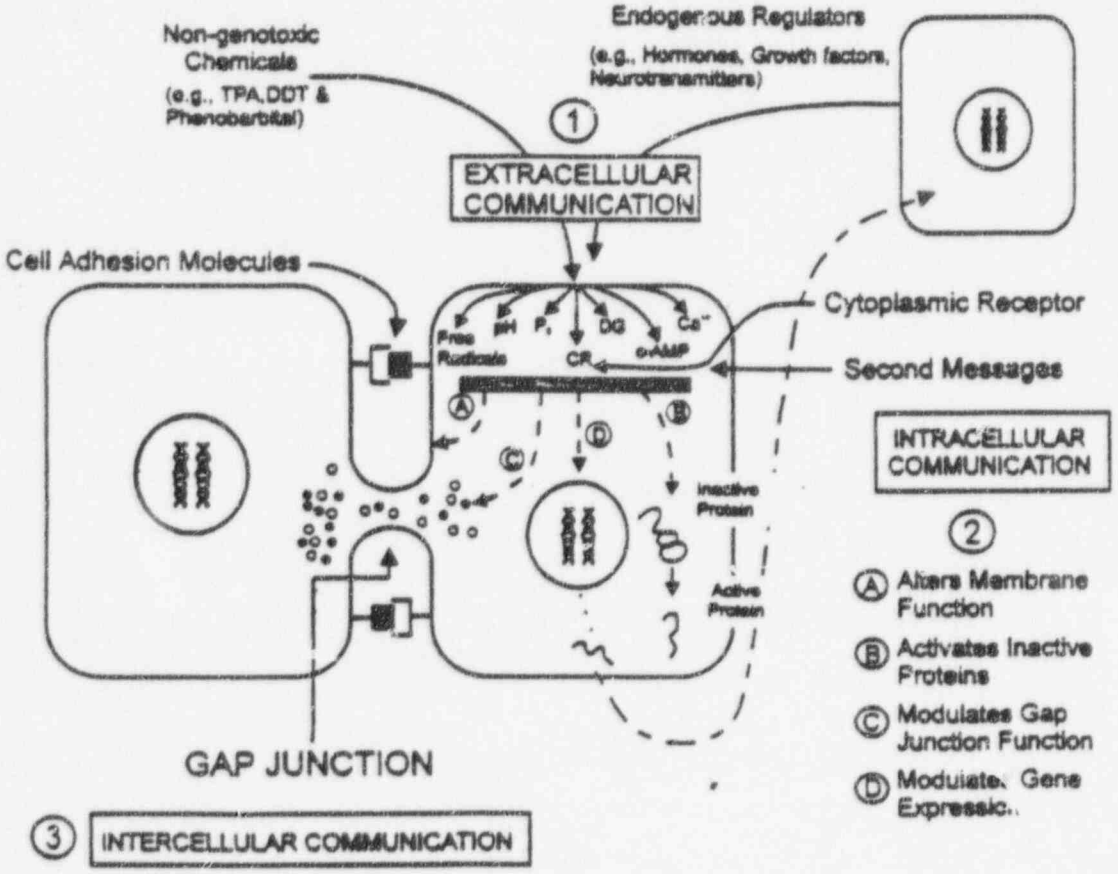

Fig. 1. This scheme characterizes the postulated link between extracellular communication and intercellular communication via various intracellular transmembrane signaling mechanisms. It provides an integrating view of how the neuroendoc. neimmune system (mind or brain/body connection) and other multisystem coordinations could occur. Although not shown here, activation or altered expression of various oncogenes also could contribute to the regulation of gap junction function.

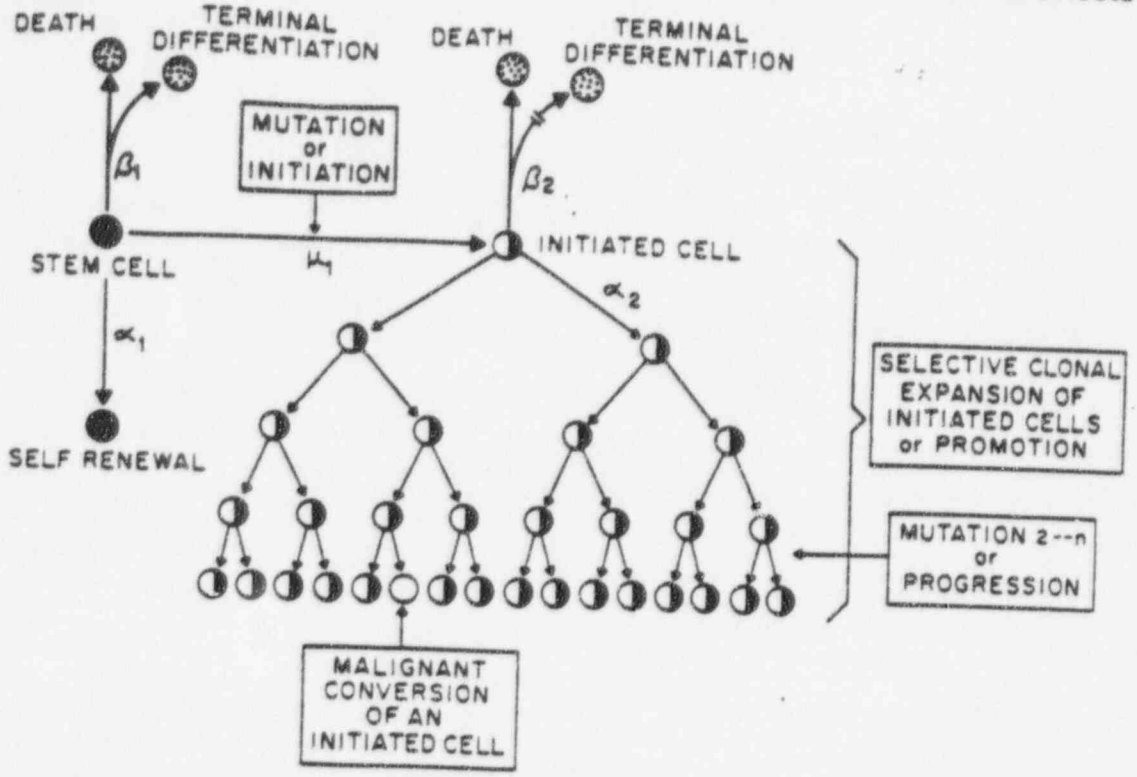

Fig. 2. The initiation-promotion-progression model of carcinogenesis: β_1, rate of terminal differentiation and death of stem cell; β_2, rate of death, but not of terminal differentiation of the initiated cell ($-||-$); α_1, rate of cell division of stem cells; α_2, rate of cell division of initiated cells; μ_1, rate of the molecular event leading to initiation (i.e., possibly mutation); and μ_2, rate at which the second event occurs within an initiated cell.

CANCER IS A MULTISTEP, MULTIMECHANISM PROCESS

Our understanding of experimental in vitro and in vivo studies, as well as epidemiological data, suggests that carcinogenesis is the result of many endogenous and exogenous factors interacting during a multistep, multimechanism process.[1] No single factor "causes" cancer.[2]

Carcinogenesis is a multistep, multimechanism process involving the irreversible conversion of a stem cell to a terminal-differentiation-resistant cell (initiation), followed by the clonal expansion of this cell (promotion) and by the acquisition of other genetic and epigenetic alterations leading to malignancy (progression) (Fig. 1).

The initiation and progression steps seem to be facilitated by mutagenesis, whereas promotion has been associated with agents that cause mitogenesis (e.g., cell killing, growth regulators, chemical mitogens). Regardless of the actual mechanisms that could lead to cancer, cancer cells are phenotypically characterized as being non-contact inhibited, blocked in their ability to terminally differentiate and having no growth control. In effect, cancer is a problem of homeostatic control within and between cells. Cancer is more than a cell problem, it is a cell-society problem.

A hypothesis had been advanced that cancer cells are the result of some dysfunction in gap junction intercellular communication (GJIC). Cell-to-cell communication, mediated by extracellular factors (growth regulators, hormones, neurotransmitters, etc.), which trigger intracellular signals (e.g., Ca^{++}, pH, phosphorylation changes), could modulate (up or down) GJIC (Fig. 2).

This integrated hypothesis postulates that chemical promoters, oncogenes coding for growth factors, receptors or transmembrane signaling elements, and transcription factors can isolate an initiated cell from the suppressing influence of surrounding normal cells by downregulating the transfer of ions and small molecules through gap junctions. Tumor-suppressor genes would be predicted to upregulate GJIC or to prevent the downregulation of GJIC by oncogenes.

Ionizing radiation, as an efficient clastogen and inducer of deletion mutations, might be affecting any of the steps (e.g., deleting regulator genes controlling oncogenes, rearranging oncogenes to have altered expression, causing cell death to promote surviving stem cells initiated by other agents, and deleting tumor-suppressor genes). The stem cell pool at the time of acute ionizing radiation, the number of initiated cells in the body, and the amount of cell killing by a given dose of ionizing radiation would all contribute to the carcinogenic risk.

It will be difficult to estimate the frequency of gene or chromosomal mutations in the few stem cells that give rise to cancer. If ionizing radiation leaves a unique fingerprint in the kind of DNA lesions/mutations found in the tumors of exposed organisms (molecular epidemiology), there might be some estimate to ionizing radiation's contributory role in carcinogenesis. Even more difficult will be the estimation of ionizing radiation's role in inducing cell death (particularly in the induction of apoptosis or in the induction of altered gene expression) because both of these end points are induced by many natural and other exogenous nonradiation factors. At low-level exposure, detecting biomarkers for ionizing radiation's effects on signal transduction, an epigenetic effect, will be difficult to assess.[3]

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1. J. E. TROSKO, "Radiation-Induced Carcinogenesis: Paradigm Considerations," *Biological Effects of Low Level Exposures: Dose-Response Relationships*, p. 205, E. J. CALABRESE, Ed., CRC Press, Boca Raton, Florida (1994).

2. J. E. TROSKO, "Does Radiation Cause Cancer?" *RERF Update*, 4, 3 (1992).

3. J. E. TROSKO, "Epigenetic Biomarkers: Potentials and Limitations," *Biomarkers and Occupational Health*, p. 264, M. MENDELSON, J. P. JEETERS, M. J. NORMANDY, Eds., Joseph Henry Press, Washington, D.C. (1995).

2. Signal Transduction Through *p53*-Dependent Pathway After Low-Dose Ionizing Radiation, *Takeo Ohnishi, Hideki Matsumoto, Xinjiang Wang (Nara Medical Univ-Japan)*

In the study of cell-cycle events, recent attention has focused on the signal transduction pathway in which a tumor-suppressor protein, wild-type (wt) *p53* protein, acts as the key protein. A major advance in recent years has been the partial elucidation of the G_1-arrest mechanism. However, the transcriptional regulation mechanisms of components of the cell-cycle machinery remain unknown. We have investigated the induction of *p53*, *WAF1*, and *cdk2* after gamma-ray irradiation using two human glioblastoma cell lines, U-87MG bearing the wt *p53* gene and the other, T98G, a mutant gene. After the cells have been irradiated with gamma rays at 3 Gy, the level of *p53* and *WAF1* mRNAs in U-87MG increased gradually for up to 10 h, whereas *these* mRNAs were overexpressed in T98G, and these levels remained relatively stable after irradiation. In an attempt to examine the induction of *cdk2* after gamma-ray irradiation, we analyzed the level of *cdk2* mRNA using the reverse transcriptase-polymerase chain reaction (RT-PCR) technique. We calculated the amounts of *cdk2* mRNA relative to that of b-*actin* mRNA in both cell lines, then plotted them against those in nonirradiated cells. After irradiation, the level of *cdk2* mRNA in U-87MG gradually increased more than twofold by 10 h after gamma-ray irradiation, whereas the level of the mRNA in T98G remained relatively stable after irradiation. This result demonstrates that wt*p53* induces the expression of not only *WAF1* but also *cdk2*.

On the other hand, we report the induction of wt *p53* protein accumulation within 12 h in various organs of rats exposed to X-ray irradiation at low dose (10, 25, or 50 cGy). The levels of *p53* in some organs of irradiated rats were increased about two- to threefold in comparison with the basal *p53* levels in nonirradiated rats. Differences in the accumulation of *p53* after low-dose X-ray irradiation were observed among the small intestine, bone marrow, brain, liver, adrenal gland, spleen, hypophysis, and skin. In contrast, there was no obvious accumulation of *p53* protein in the testis and ovary. Thus, the induction of cellular *p53* by low-dose X-ray irradiation in rats seems to be organ-specific. We consider that cell type and interactions with other signal transduction pathways of the hormone system, immune system, and nervous system may contribute to the variable induction of *p53* by low-dose X-ray irradiation. Thus, the *p53*-dependent signal transduction pathway may be important for ensuring cell-cycle progression, DNA replication, chromosome segregation, and DNA repair.

3. Programmed Cell Death for Defense Against Anomaly and Tumor Formation, *Sohei Kondo (Kinki Univ-Japan), Toshiyuki Norimura (Univ of OEH-Japan), Taisei Nomura (Osaka Univ-Japan)*

INTRODUCTION

Cell death after exposure to low-level radiation is often considered evidence that radiation is poisonous, however small the dose. Evidence has been accumulating to support the notion that cell death after low-level exposure to radiation results from activation of suicidal genes – 'programmed cell death' or 'apoptosis' – for the health of the whole body. This paper gives experimental evidence that embryos of fruit flies and mouse fetuses have potent defense mechanisms against teratogenic or tumorigenic injury caused by radiation and carcinogens, which function through programmed cell death.

DATA AND DISCUSSION

Cell Replacement Repair of Teratogenic Injury in Fruit Flies

When male genital disks of *Drosophila melanogaster* larvae at the third instar were exposed to 50 Gy, all of them developed into abnormal adult genitalia, whereas when they were transplanted into 2-day younger larvae, all of them developed into normal genitalia.[1] These results fit the model of cell replacement repair, in which cells with teratogenic injury are replaced by healthy ones within the cellular society of a target organ and in which this presumed cell replacement results in complete elimination of injured cells by programmed cell death, since otherwise the residual injured cells would give rise to abnormal portions in the adult organ.

Cell Replacement Repair of Teratogenic Injury in Mice

Experimental studies with mice have established the empirical rule that irradiation during the pre-implantation period of the embryo (0.5 to 5 days after fertilization) causes a high incidence of prenatal death but virtually no anomalies in the survivors. After the implantation stage, however, fetuses become progressively resistant to prenatal death. The sensitivity to neonatal death or to gross anomalies at term reaches a peak around days 9 and 10. Even at the stage most sensitive to the teratogenic effects of radiation, there is a threshold of ~1 Gy. We irradiated fetuses at 9.5 days with 2 Gy of X rays. Fetuses homozygous for null mutation of gene *p53*, ($p53^{-/-}$), showed

TABLE I (Paper 3)

Effects of Caffeine on Mutations, Malformations, and Tumors Induced in Mice by Exposure to Urethane or 4NQO (Ref. 3)

Agent	Biological effects	Incidence without caffeine	Incidence with caffeine
Urethane	Mutations	12.8%	16.2%
Urethane	Malformations	52.9%	7%[a]
Urethane	Lung tumors	52.5%	21.9%[b]
4NQO	Lung tumors	4.3 nodules/lung	1.8 nodules/lung[b]

[a] $p < 0.001$.
[b] $p < 0.01$.

anomaly incidence three times higher than that induced in wild type ($p53^{+/+}$) fetuses; fetal $p53^{+/+}$ cells were sensitive to radiation-induced apoptosis but fetal $p53^{-/-}$ cells were not sensitive.[2] These results support the notion that in wild-type mice exposed to below-threshold doses of radiation, cells having induced teratogenic injury commit apoptosis, and dying cells are replaced by healthy ones.

Programmed Cell Death Suppresses Tumorigenesis But Not Mutagenesis

Table I (Ref. 3) shows that when fetuses of mice pretreated with urethane or 4-nitroquinoline 1-oxide (4NQO) – an inducer of bulky adducts to purine bases of DNA reparable by excision repair – were then treated with caffeine for ~1 day at 6-h intervals, the incidence of lung tumors was significantly reduced, whereas the incidence of somatic mutations (detected by coat color mosaics) was not reduced. These results suggest that urethane and 4NQO act primarily as tumor promoters rather than oncomutagens. Evidence is available to support the notion that caffeine enhances the apoptotic activity of cells damaged by 4NQO in the G2 phase.[4]

CONCLUSION

The fact that the animal body contains cells that are highly sensitive to death by radiation indicates that animals have highly sensitive defenses against risk of low-level radiation rather than that low-level radiation is hazardous to animals, including humans.

1. S. KONDO, *Health Effects of Low-level Radiation*, Kinki University Press, Osaka, Japan, and Medical Physics Publishing, Madison, Wisconsin (1993).
2. T. NORIMURA, S. NOMOTO, M. KATSUKI, Y. GONDO, K. NAKANO, S. KONDO, "Mice Deficient for *p53* are Susceptible to Radiation-induced Teratogenesis," *Proc. 10th Int. Cong. Radiat. Res., Abstracts* (in press).
3. T. NOMURA, "Diminution of Tumorigenesis Initiated by 4-Nitroquinoline 1-Oxide by Post-Treatment with Caffeine in Mice," *Nature*, **260**, 547 (1976); see also "Comparative Inhibiting Effects of Methylxanthines on Urethane-Induced Tumors, Malformations, and Presumed Somatic Mutations in Mice," *Cancer Res.*, **43**, 1342 (1983).
4. S. KONDO, "Apoptosis by Antitumor Agents and Other Factors in Relation to Cell Cycle Checkpoints," *J. Radiat. Res.*, **36**, 56 (1995).

4. Low-Level Radiation Effects on Immune Cells, *Takashi Makinodan (VA Med Ctr, Los Angeles)*

INTRODUCTION

The purpose of this study was to characterize the effects of chronic low-dose ionizing radiation (LDR) on murine immune cells. Previously, it had been reported that LDR enhances the proliferative activity of T cells in vitro and delays the growth of transplantable immunogenic tumors in vivo. This suggests that LDR eliminates immune suppressor cells, which downregulates immune response and/or adaptively upregulates the responsiveness of immune effector cells. It had also been reported that human lymphocytes become refractive to high dose radiation-induced chromosomal aberrations by pretreating mitotically active lymphocytes in vitro with very low doses of ionizing radiation, and the adaptive effect can be abrogated by cycloheximide. This suggests that protein synthesis is required for lymphocytes to respond adaptively to LDR.

METHODS

Twelve-week-old C57BL/6 mice were exposed to ionizing radiation (^{60}Co facility at doses ranging from 0.01 to 0.10 Gy/exposure, at a dose rate of 0.09 Gy/min, three to five times per week, for a period of 1 to 4 weeks). Three days after the last exposure, mice were killed and their spleens were analyzed for their immune cell composition, DNA strand breaks, level of activity of a DNA repair-associated enzyme (poly [ADP-ribose] transferase), levels of heat shock protein and mRNA, and T-cell mitogen-induced proliferative response.

RESULTS

The following results were obtained:

1. An exposure dose of 0.04 Gy > 0.10 Gy > 0.0' Gy, and a total of 10 exposures > 15 exposures > 5 exposures for 2 weeks, 3 weeks, and 1 week, respectively, as judged by the proliferative response. These results suggest that the proliferation-enhancing effect of LDR is dose-dependent, the effective dosage of LDR is extremely low, and the effective dose range is very limited.

2. T cells, and not B cells, are the primary cells in the spleen that are responsive to LDR, as judged by splenocyte reconstitution studies, and thymectomy abrogates the proliferation-enhancing effect of LDR. This suggests that the thymus, which generates new T cells and modulates the maturation of immature T cells extrathymically, is a primary target organ of LDR.

3. The constitutive levels of DNA strand breaks and poly (ADP-ribose) transferase activity in splenocytes of mice exposed to LDR are lower than those of sham-irradiated control mice. This suggests that LDR promotes the repair of DNA strand breaks and/or eliminates cells with DNA damage.

4. Splenocytes, whose proliferative activity had been enhanced by LDR, possess elevated constitutive levels of heat shock protein and mRNA; these splenocytes proliferate more extensively in response to mitogenic stimulation than splenocytes of sham-irradiated control mice.

These results suggest that LDR is modulating the expression of heat shock protein genes, which, in turn, suggests that the signal transduction process of T cells could be adaptively upregulated by LDR.

The physiologic outcomes of chronic LDR were assessed by determining the effects on autoimmune-susceptible C57BL/6 *lpr/lpr* mice and mammary tumor-susceptible C3H/He mice. With the former model, the results showed that LDR eliminates abnormal double-negative ($CD4^-CD8^-$) T cells, which are responsible for the characteristically enlarged lymph nodes and spleens and delays the onset of autoimmune disease manifestations. With the latter model, LDR was ineffective in downregulating the growth of spontaneous mammary tumors in *ad libitum*-fed mice. In contrast, caloric restriction (calorically 70% of the food consumed by mice of *ad libitum*-fed diet) was effective in retarding tumor appearance; however, once the tumors appeared, they grew as rapidly as those in *ad libitum*-fed mice. A striking effect was observed when chronic LDR was combined with caloric restriction [i.e., mice were adapted to a diet calorically equivalent to 70% of the *ad libitum*-fed diet in a stepwise manner (100% → 90% → 80% → 70%) over a 3-week period, then exposed to chronic LDR (0.04 Gy/exposure on 3 alternating days per week for 4 weeks) and maintained on a calorically restricted diet throughout the study (44 weeks)]. The appearance of tumors was not only retarded, the growth rate approached 0, the incidence of tumors was drastically reduced, and the frequency of tumors undergoing regression was very high. Moreover, large clusters of $CD8^+$ T cells were found infiltrating the regressing tumors but not in tumors of calorically restricted or *ad libitum*-fed mice.

CONCLUSION

These results show that chronic LDR is effective in enhancing the immune responsiveness of T cells, and the enhanced immune responsiveness is associated with elevated constitutive levels of heat shock proteins and mRNA and reduced constitutive levels of DNA strand breaks. The biologic significance of chronic LDR is reflected by the retardation of disease in autoimmune-susceptible mice and by the downregulation of spontaneous mammary tumors, when combined with caloric restriction. Further studies are in order to provide insight into the mechanism of adaptive upregulation of chronic LDR on immune-responsive T cells.

5. Radiation Hormesis: Radioactive Waste for Health, *T. D. Luckey (Oralu Corp)*

Hormesis is the stimulation of any system by low doses of any agent. The hormesis model is particularly applicable to radioactive waste management. Radiation hormesis encompasses the beneficial effects of low-dose irradiation in both animals and humans.[1] The radiation hormesis model comprises statistically significant (χ^2 test) results that compare total death rates and cancer death rates in exposed and unexposed nuclear workers.[2] The usual "healthy worker effect" is negated because both groups were in the same plants. These data invalidate all linear (no-threshold) models. This dramatic change in concepts about the effects of low-dose irradiation transforms problems about radioactive waste into solutions for improved health.

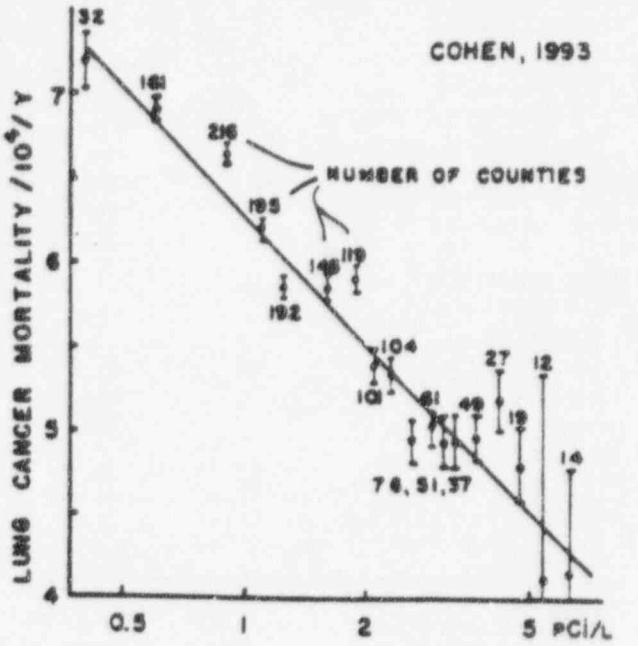

Fig. 1. The inverse correlation between lung cancer mortality and radon concentration in the United States. The vertical lines give one standard deviation for the number of counties indicated for each value. (Used with permission of *Journal of Occupational Medicine and Toxicology*.)

TABLE I

Background Levels of Ionizing Radiation

	mGy/y
PLACE	
UNITED STATES	2.6
NILE DELTA	3.5
EXPOSED WORKERS[a]	3.6
PROPOSED PERSON ALLOWANCE	5.0
JET AIR FLYERS[b]	5
KERALA, INDIA	4-23
GUAPARA, BRAZIL	10-18
MEAIPE, BRAZIL	22
GERAIS, BRAZIL	23
ARAXI, BRAZIL	35
OPTIMUM[c]	100
RAMASARI, IRAN	243
GUARAPARI BEACH	263
MAXIMUM SAFE LEVEL[c]	10,000

[a]This includes both natural and industrial exposures.
[b]Earth exposure plus 1000 h/yr at 11-km altitude.
[c]See Ref. 1.

Total deaths were 24% lower in 28 542 nuclear shipyard workers exposed to >5 mSv (lifetime dose) than in 33 352 unexposed and minimally exposed workers.[3] Obviously, recommendations to lower background radiation to levels which are as low as reasonably attainable (ALARA) are counterproductive to health. The data suggest that if background exposures were safely increased to that of frequent fliers (Table I), the United States would have ~10 000 *fewer premature deaths* each week (260 million people × 0.85% death rate yr^{-1} × 0.24 = 530 000 fewer deaths per year).

The importance of radiation hormesis was amply confirmed by comparing cancer death rates in exposed (a lifetime dose >7 cSv) and unexposed nuclear workers (Table II). These results based on observations of almost 8 million person-yr show that low-dose irradiation will decrease cancer mortality rates. The decreased cancer mortality rate following low-dose irradiation has been attributed to increased immune competence.[8]

TABLE II

Low-Dose Exposures Decrease Cancer Deaths in Nuclear Workers

PLANT	NUMBER OF WORKERS		CANCER DEATHS/1000		P
	UNEXPOSED	EXPOSED	UNEXPOSED	EXPOSED	
SHIPBUILDERS[4]	111,757	40,777	27.6	23.7	<0.01
U. S. WEAPONS[5]	20,619	15,318	34.8	20.8	<0.01
CANADA ENERGY[6]	21,000	4,000	22	2	<0.01
BRITISH WEAPONS[7]	58,945	36,272	9.9	2.6	<0.01

Several populations have lived for many generations in areas with unusually high natural background radiation[1] (Table I). These populations have no unusual health problems. This concept is validated by the inverse correlation between radon in homes and lung cancer mortality rates for 1600 of the most populous counties of the United States[9] (Fig. 1). The inverse correlation shows *radon is not a major cause of lung cancer deaths*.

Use of the hormesis model would greatly reduce the cost of radioactive waste cleanup.[10] The amount removed would be reduced. Also, radioactive waste could be used to safely double our nonmedical level of background radiation (Table I). This would decrease both cancer mortality and premature total death rates. Savings from radioactive waste management, industry sick leaves, premature deaths, and national health care should be used for (a) research on low-dose irradiation and (b) training health physicists, nurses, and physicians in the techniques of radiation supplementation.

Our national wealth would be increased by allowing industrial workers 26 mGy/yr. This exposure is equivalent to that of healthy populations in other parts of the world (Table I) and considerably less than the suggested optimum.

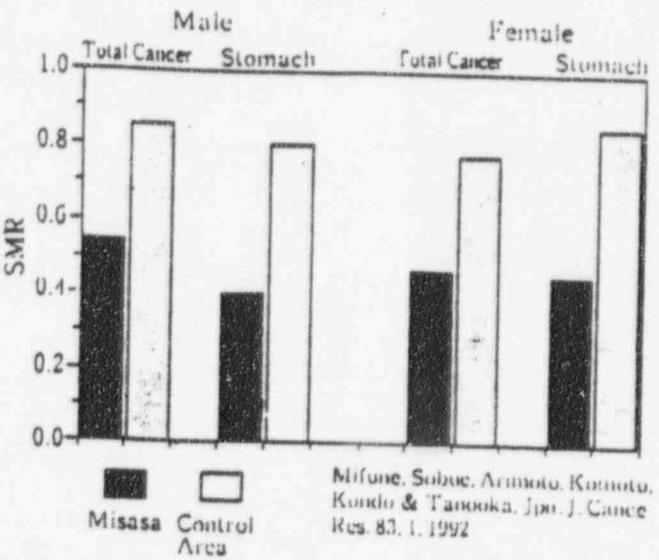

Fig. 1. Comparison of standardized mortality ratio, Misasa/control area.[4]

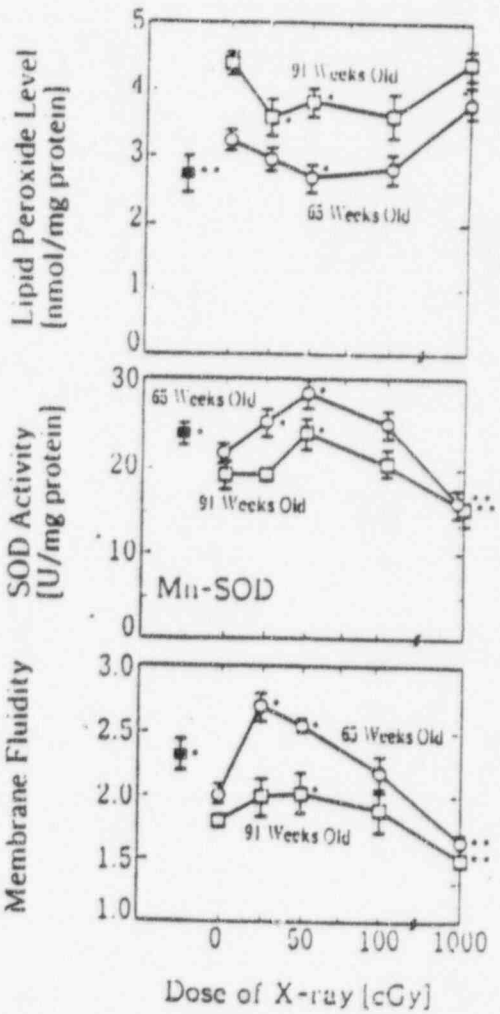

Fig. 2. Dose and aging-dependent changes in lipid peroxide level, SOD activity, and membrane fluidity of rat's brain cortex by X-ray irradiation.[5] Membrane fluidity as determined by spin-label method using ESR spectrometer. '■' shows the data from sham-irradiated 7-weeks-old control. The number of rats per experimental point is 10 to 15. $^{*}P < 0.05$ and $^{**}P > 0.01$ versus sham-irradiated 65- or 91-weeks-old control (t test).

1. T. D. LUCKEY, *Radiation Hormesis*, CRC Press, Boca Raton, Florida (1991); see also *Hormesis with Ionizing Radiation*, CRC Press, Boca Raton, Florida (1980).
2. T. D. LUCKEY, "Radiation Hormesis in Cancer Mortality," *Int. J. Occup. Med. Toxicol.*, 3, 175 (1994).
3. G. M. MATANOSKI, "Health Effects of Low-Level Radiation in Shipyard Workers," U.S. Department of Energy (1991).
4. G. M. MATANOSKI, "Cancer Risks in Radiologists and Radiation Workers," *Radiation Carcinogenesis: Epidemiology and Biological Significance, Progress in Cancer Research and Therapy*, Vol. 26, p. 83, J. D. BOICE, J. F. FRAUMENI, Eds., Raven Press, New York (1984).
5. E. S. GILBERT, S. A. FRY, L. D. WIGGS, G. L. VOELZ, D. L. CRAIGLE, G. R. PETERSEN, "Analysis of Combined Mortality Data of Workers at the Hanford Site, Oak Ridge National Laboratory and Rocky Flats Nuclear Weapons Plant," *Radiat. Res.*, 120, 19 (1989).
6. J. D. ABBATT, T. R. HAMILTON, J. D. WEEKS, "Epidemiological Studies in Three Corporations Covering the Nuclear Fuel Cycle, *Biological Effects of Low Level Radiation*, IAEA-STI/PUB. 646, p. 351, International Atomic Energy Agency (1983).
7. G. M. KENDALL, C. R. MUIRHEAD, B. H. MACGIBBON, et al., "Mortality and Occupational Exposure to Radiation: First Analysis by the National Registry for Radiation Workers," *Brit. Med. J.*, 194, 220 (1992).
8. S.-Z. LIU, "Multilevel Mechanisms of Stimulatory Effect of Low Dose Radiation on Immunity," *Low Dose Irradiation and Biological Defense Mechanisms*, p. 225, T. SUGAHARA, L. A. SAGAN, T. AOYAMA, Eds., Excerpta Medica, Amsterdam (1992).
9. B. L. COHEN, "Compilation and Integration of Studies of Radon Levels in U.S. Homes by State and Counties," *Crit. Rev. Environment/Control*, 22, 243 (1992).
10. T. D. LUCKEY, "Radioactive Waste Management for Health," *Rad. Protect. Manage.*, 12, 53 (1995).

6. State of Research on Radiation Hormesis by CRIEPI, *Sadao Hattori (CRIEPI-Japan)*

In 1982, Luckey of the University of Missouri published a paper in the journal *Health Physics* describing radiation hor-

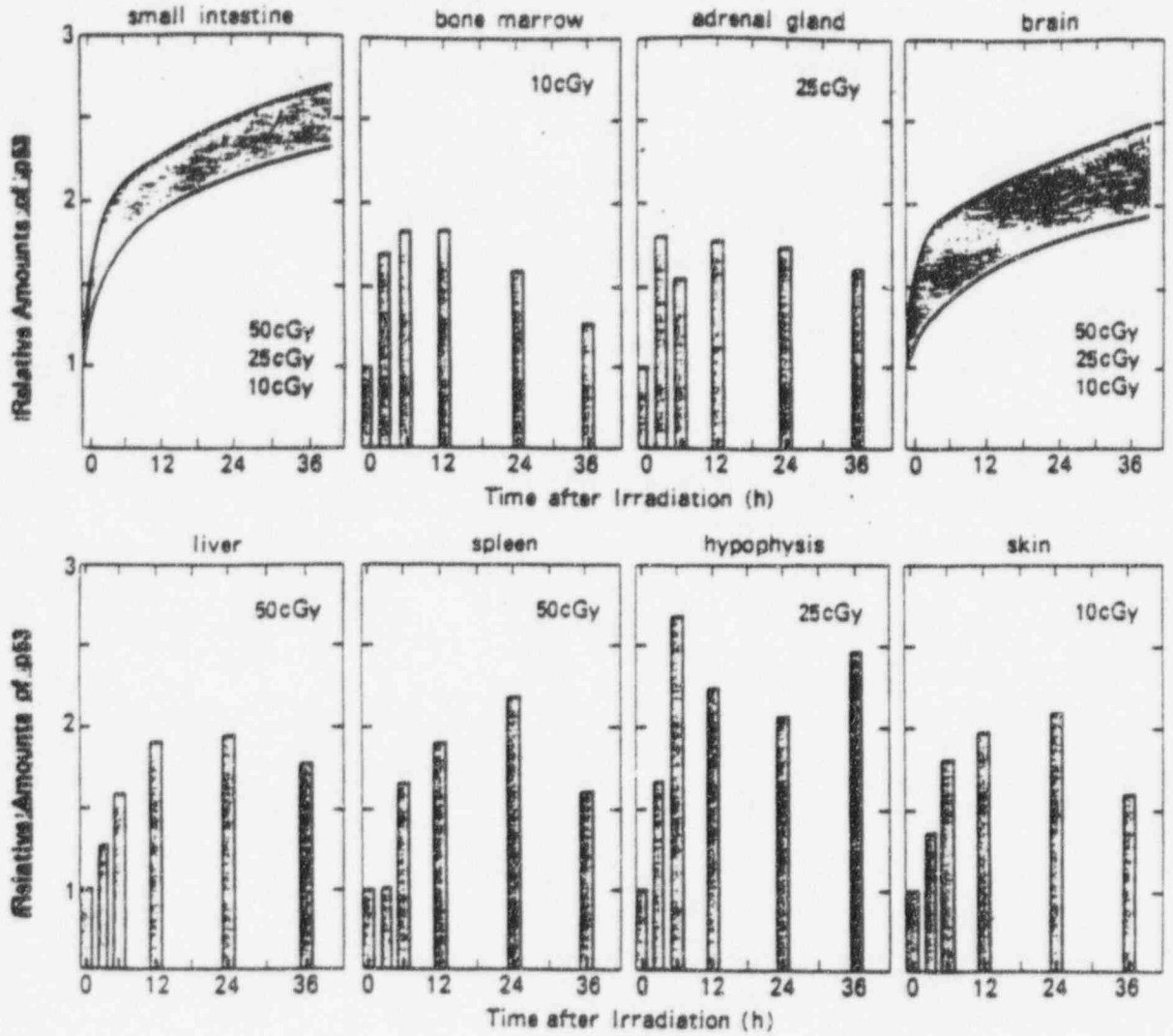

Fig. 3. The *p53* protein accumulation in organs of rats after low-dose X rays.

mesis with many references. His assertion was that there is a beneficial effect of low-dose radiation on the human body, contributing to a healthy body, longer life, and vitalization.[1,2]

The radiation hormesis research by the Central Research Institute of Electric Power Industry was initiated on the rationale that if Luckey's claim were to be true, radiation management in Japan is extremely erroneous and that we have to find the truth.

After many test results were obtained, some from human data, as shown in Fig. 1 (Ref. 3), and others from various animal experiments, that support the radiation hormesis hypothesis,[4] we initiated a collaborative research and testing program with more than ten universities on more than ten experimental subjects.

The subjects in which we are currently interested are as follows:

1. effects of free radicals produced by low-dose radiation
2. molecular biological response to low-dose radiation
3. radiation effects on neurotransmitting systems
4. stimulative effects of low-dose radiation on immune systems
5. expansion of the vivid life span, as shown in Fig. 2 (Ref. 5).

Results and findings obtained through the research program include cell rejuvenation, radiation adaptation, stimulation of the tumor suppressor genes, and the recovery of diabetics.

Professor Sakamoto of Tohoku University Hospital is achieving great success in therapy for non-Hodgkins lymphoma. He applies 10 cGy of X rays three times per week, for 5 weeks for a whole-body irradiation of 150 cGy. He succeeded in therapy for intermediate-stage patients with non-Hodgkins lymphoma. He has obtained a drastic increase in the survival rate, from 36% at 5 yr after treatment (from only local high dose therapy without whole-body dose irradiation), to 90% after 5 yr (from local high-dose irradiation combined with whole-body low-dose irradiation).

He also succeeded, with whole-body low-dose irradiation, in achieving the recovery of a patient with terminal liver cancer.

Professor Ohnishi of Nara Medical University has tried to find a clear reason for this. He found that the tumor-suppressor gene *p53* response was stimulated by a 10- to 25-cGy dose to rats as shown in Fig. 3 (Ref. 6).

Many kinds of stimulative responses are being found at molecular levels in organisms by low-dose radiation, as are other various biophysical responses.[7,8] This suggests to us that this is an unknown and extremely comprehensive and meaningful field of research and possible human health benefit.

1. T. D. LUCKEY, "Physiological Benefits from Low Levels of Ionizing Radiation," *Health Phys.*, 43, 6 (1982).

2. T. D. LUCKEY, *Hormesis with Ionizing Radiation*, CRC Press, Boca Raton, Florida (1980).

3. *Proc. Int. Conf. Low Dose Irradiation and Biological Defense Mechanisms*, Kyoto, Japan, 1992.

4. M. MIFUNE, S. KONDO, H. TANOOKA, et al., "Cancer Mortality Survey in a Spa Area (Misasa Japan) with a High Radon Background," *J. Jpn. Cancer Res.*, 83 (1992).

5. K. YAMAOKA, "Increased SOD Activities and Decreased Lipid Peroxide Level in Rat Organs Induced by Low Dose X-Ray Irradiation," *Free Radical Biol. Med.*, 11, 3 (1991).

6. T. OHNISHI et al., "Accumulation of Wild-Type p53 Protein in Various Organs of Rats After Whole Body Exposure to Low-Dose X-Ray Irradiation" (in press).

7. S. KONDO, *Health Effects of Low Level Radiation*, Kinki University Press, Medical Physics Publishing, Wisconsin (1993).

8. S. HATTORI, "State of Research and Perspective on Radiation Hormesis in Japan," *Int. J. Occ. Med. Toxicol.*, 3, 2 (1994).

Actual scientific data on health effects from low-to-moderate doses of ionizing radiation contradict the presumed "linear, no-threshold" dose-response "model." Use of the linear model as a basis for regulations and standards has resulted in high public costs with negligible or zero health benefit to society, and in the potential loss of nuclear science and technology contributions to humanity.

The health effects of low-level radiation: Science, data, and corrective action

by Jim Muckerheide

At the American Nuclear Society's 1994 Winter Meeting in Washington, D.C., two special sessions were held on "Low-Level Radiation Health Effects," covering actual dose-response data and applicable research programs. Two additional sessions, on these topics plus "Policies and Cost/Benefits," were held at the 1995 ANS Meeting in Philadelphia, Pa. Representatives of the Health Physics Society (HPS) and the National Council on Radiation Protection and Measurements (NCRP) were among the presenters at these sessions. At the October 29–November 2, 1995, ANS Winter Meeting in San Francisco, Calif., four additional sessions, on this topic plus "Biology Research and Beneficial Effects," and a panel on "Needs for Research, Organization and Corrective Actions," are to be held.

Also planned is the ANS "Radiology Centennial Award and Lecture," with Myron Pollycove, professor emeritus in nuclear medicine at the University of California at San Francisco, honored as the ANS Wilhelm Roentgen Radiology Centennial Orator.

Papers and panel discussions at these ANS meetings have addressed and will address actual low-to-moderate dose-response data with respect to the scientific bases for the "linear, no-threshold model." These substantial but little-known data generally contradict the linear model or its application, and are not appropriately considered by the government agencies and their funded studies, which are driven by the radiation protection mission. The fact that policies and cost/benefits of applying the linear model cause unwarranted public fears and large public costs, with negligible public health benefit (and even potentially significant public detriment), will also be addressed.

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Comprehensive, applicable data

There are voluminous relevant dose-response data, organized into significantly exposed populations. Significant radiation effects data on nonhuman populations, and on cellular and molecular biology and genetic effects research data, have been and will be presented in the ANS sessions.

The significantly exposed populations are:

- Japanese survivors of the atomic bombings of Hiroshima and Nagasaki.
- Occupationally exposed populations (including radiologists and other medical practitioners).
- Medically exposed patient populations.
- Radium body-burden populations.
- Weapons and facilities releases populations (with military weapons tests observers).
- High natural background radiation–exposed populations.

In brief summary, data on health effects from low-to-moderate radiation doses show no adverse health effects at doses below about 20 cGy (1 cGy equals 1 rad). (The exception is for moderate doses, above about 5 cGy, of high dose rate X rays to the fetus at cell differentiation during the second trimester of development.) In addition, data show that adverse health effects are small for doses in the range of 200–400 cGy at low dose rates and for fractionated high dose rate exposures.

Statistically significant data show below-normal adverse health effects (i.e., health *benefits*) at low-to-moderate doses compared with unexposed populations. These data, however, are effectively obscured when linear relationships are arbitrarily imposed on these nonlinear data, thus misrepresenting low-to-moderate dose effects. When relationships are not artificially forced to conform to the linear model, scientific fitting of the data shows that polynomial relationships generally are the "best-fit" to the actual low-to-moderate dose data.

This article briefly summarizes a substantial compilation of the scientific data primar-

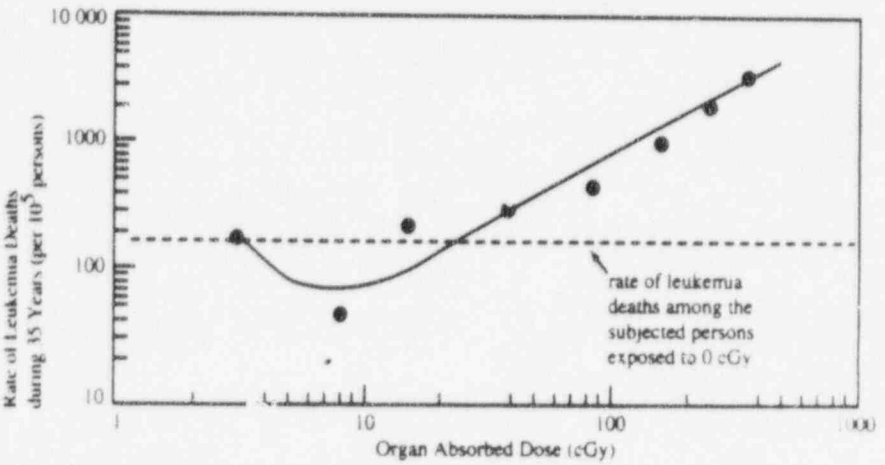

Fig. 1. Dose response for leukemia in Japanese survivors

cancers, however, were found in radiologists who started practice after 1921, when enhanced radiation protection practices were adopted. This result contradicts the linear model, which would show adverse dose effects in this population if it were valid.

• *No excess cancers were found in U.S. Army radiologic technicians, with estimated 50-cGy doses.* Yalow noted that these approximately 6500 radiological technicians received an estimated 50-cGy dose in training. (After classroom work in the morning, they practiced making X rays in the various positions on each other in the afternoon.) This was followed by an average two years of service. A 29-year follow-up compared them with other Army medical, laboratory, and pharmacy technicians. The linear model predicts an increase in cancers at these doses, which should be readily detected in this population.

• *Mortality and cancer rates are lower in higher exposed nuclear shipyard workers.* John Cameron, professor emeritus of the University of Wisconsin and a member of the Technical Advisory Panel for the $10-million 1978–1987 Nuclear Shipyard Worker Study (NSWS) that followed about 70 000 of the approximately 700 000 U.S. nuclear shipyard workers, reports that the 28 542 nuclear workers with doses greater than 5 mSv have 24 percent *lower* total mortality (statistically significant) than the 33 352 non-nuclear workers, and those with doses less than 5 mSv have 19 percent *lower* mortality (also statistically significant).

This large group has exceptional dosimetry compared with most high-dose early workers. Their exposure was primarily from external gamma doses, with low confounding effects (except asbestos, which appears in increased mesothelioma rates) with higher doses than later similarly well-monitored groups. The Department of Energy, however, has not published the report, the data are not in the literature, and the contractor report was minimalized when it was eventually released in 1991. Cameron noted that had the study found 24 percent *higher* mortality or increased cancer in the nuclear worker population, the treatment it received from the bureaucracy and the media would have been significantly different.

• *No excess cancers nor noncancer health effects were found in the high-dose DOE worker population group.* Shirley Fry, of the Oak Ridge Institute for Science and Education, presents these results from a study of 3145 white male early nuclear workers who were exposed to more than 5 cGy in any one year, though with data only through 1984, since the follow-up programs were defunded. The only significant health effects are *fewer* total deaths (ascribed to a presumed "healthy worker effect"—a population bias that exists due to the "screening-out" of the less healthy, or unemployable, population), and *fewer* deaths from circulatory and digestive diseases than the general population. All-cancer deaths are slightly higher, but are not statistically significant. Since this group received higher doses than the general radiation worker populations, all above 5 cGy and 70 percent above 10 cGy, the linear model predicts significant increases that would be evident.

TABLE II
IARC OBSERVED/EXPECTED LEUKEMIA (EXCEPT CHRONIC LYMPHOCYTIC LEUKEMIA) MORTALITY (119 DEATHS IN 15 825 TOTAL DEATHS)

Cumulative dose (cSv)	Deaths (Observed/Expected)
0–1	60/62.0
1–2	19/17.2*
2–5	14/17.4
5–10	8/9.0
10–20	8/6.4*
20–40	4/4.7
>40	6/2.3*

*Greater-than-expected leukemias. Note, for this table, 11 dose categories were collapsed to 7.

Early nuclear workers have generally *lower* cancer rates than the general population. A "healthy worker effect" is used to discount these significant data. Although it could readily be determined, the effect has not been quantified. Applying the healthy worker effect to cancers, however, has been questioned, since screening-out of the infirm in employment, especially in the time frame of interest, does not have an evident relationship to the likelihood of later development of cancer. It also conflicts with contrary health research arguments that consider the industrial/chemical workplace to be a major *cause* of cancer incidence.

The early nuclear worker exposure data, however, are generally poor. Compared with the NSWS data, the dosimetry is questionable, with many confounding effects, especially from internal exposures, with relatively poor work and dose histories, and inconsistent wearing of badges. Study results are often poor, with effects that are not dose-response related, that are often negative (showing greater effects at lower doses), or in which dose effects are not considered.

Myron Pollycove notes that a recent report by the International Association for Research on Cancer (IARC) similarly misrepresents dose-response data to report a linear model result. The IARC report chooses to ignore data that show lower risk, i.e., a risk decrement. First, in this combined occupational exposure group, it chooses to ignore the most accurate data, the NSWS, compared with the early weapons facility workers with their questionable dosimetry and confounding factors. Then, in a population of 15 825 total deaths, IARC reports on 119 leukemia deaths, excluding nonradiogenic leukemia. The data show that there are 60 deaths observed with 62.0 expected for doses of less than 1 cSv, and 59 deaths observed, with 57.0 expected for doses greater than 1.0 cSv (see Table II). Clearly, there is no excess leukemia found in these data.

Pollycove notes that the IARC report states explicitly in the "Statistical Methods" section that they applied (they presumed) the linear model across 11 dose categories, and that "As there was no reason to suspect that exposure to radiation would be associated with a decrease in risk . . . one-sided tests are presented throughout." This states that they explicitly ignore all negative data. For the table, the 11 dose categories were collapsed to 7, resulting in greater-than-expected leukemias in three of the seven dose groups (the * in Table II). Since only positive data are allowed to be considered, only the data from the three greater-than-expected dose groups are used, even though these dose groups are not even contiguous. Since the selected data are not significant, the IARC performs a Monte Carlo calculation on 5000 trials (effectively multiplying the data by roughly a factor of 100) to "find" that the results show a "significant" linear dose-response "trend."

This "result" was then the subject of a worldwide media campaign, reasonably reported even in *Nuclear News*, that the linear model is confirmed. This report was widely distributed long before the data and analysis were published and available for review.

IARC also reports that the 44 multiple myeloma deaths are similarly found "significant," noting that this is "attributable primarily to the associations reported previously . . . in the Hanford and Sellafield cohorts." This note indicates that they are aware, without so stating, that this "association" is not found in other cohorts and is generally considered to be erroneous in these studies, consistent with the weakness in the dosimetry and the confounding effects. (The study reports that cancer relative risk is 0.99 and leukemia is 1.22 at 10 cSv.)

Clearly, if all data were considered by IARC without arbitrarily excluding the contrary data, and presuming the linear model, the mortality data in these combined populations do not support the linear model. As Don Luckey, emeritus professor of biochemistry at the University of Missouri, has found, objectively examining all the data in each of the cohorts indicates positive/beneficial effects for the exposed populations, a result that would be reasonably expected to result in a positive (beneficial) effect in the combined populations. The IARC, consistent with BEIR, the NCRP, and other government data presentations, capriciously misrepresents the data to conform to the linear model.

Medical patient exposures

Various medical procedures expose patients to low-to-moderate whole-body doses, often associated with high doses to specific organs, that exceed public or radiation worker doses. These exposures include moderately high doses to relatively young and otherwise healthy patients. Early procedures (until the 1970s) exposed many patients to relatively high doses compared with current practices. U.S. research to follow medical patient radiation exposure data has not been supported, and some data that fail to show adverse effects have not been published (e.g., a follow-up of childhood iodine-131 procedures). Some significant medical follow-up data, however, do exist.

tual MIT data is less than 1/200 million (where a goodness-of-fit of 1/2 is considered poor); and the "full-range" model is less than 1/220 000, with "BEIR in between." (BEIR V is now more equivalent to the Gofman-Tamplin model.) The Center for Human Radiobiology (CHR) at Argonne National Laboratory, established in 1970 to be an "immortal organization" for the life of the radium-burden population, consolidated all U.S. cases.

Evans' invited summary at the 1981 International Conference on Radiobiology of Radium and the Actinides in Man (published in the *Health Physics Journal* in 1983), with then more than 4000 U.S. cases and from other international studies, stated that the scientific evidence "... has continued to show no radiogenic tumors, or other effects, in hundreds of persons whose effective initial body burden was less than about 50 μCi of Ra-226, and whose cumulative skeletal average dose is less than about 1000 rad."

Maletskos reports on his recent analyses, with Evans and others, and in another independent analysis by Otto Raabe, that a 1000–1100-cGy threshold is again confirmed now, another decade later. Also, Robert Thomas, a former director of the CHR, presents background on program termination and the lack of resolution for disposition and availability of the radium-burden population records. After the 1981 international conference and Evans' summary, the CHR was incrementally constrained and defunded by the DOE, beginning in 1983, when annual reports were stopped, to 1986, when new cases and case follow-up were stopped. Finally, in 1992, the program was terminated, even though more than 1000 cases are still alive.

• *A log-normal distribution of all tumors versus dose in the dial painters projects a minimum threshold of about 400 cGy.* Thomas reports on the 65 tumors in 1545 cases in the homogeneous group of young women luminizers/dial-painters. These 65 tumors are shown to be log-normally distributed only in the 154 cases with doses greater than 1000 cGy. This highly conservative evaluation does not weigh the evidence of the 1391 cases below a 1000-cGy dose that have no adverse health effects. These results again refute the presumed use of the linear model for radium doses.

• *There is significantly lower mortality from all causes in young U.S. and U.K. female dial painters.* Thomas also shows that only breast cancer is minimally elevated in the then-young female luminizers. They worked directly exposed to radium with substantial, unknown external chest, neck, and head doses in addition to their internal doses. Excepting the 65 bone and head tumors found in cases with extremely high doses, there is no increase in all-cancer deaths for this population. Substantially *lower* circulatory/cerebrovascular diseases are the most significant health effects. The luminizer data shows very low noncancer mortality compared with the general population, with dramatically *reduced* mortality for 20 years following the initial exposure.

Nuclear weapons/facility releases

• *No adverse health effects are found in the 46 186 "atomic veterans" exposed to above-ground nuclear tests.* Yalow notes that while the 3200 participants in the "Operation Smoky" nuclear bomb test had 10 leukemia deaths compared with 3.97 statistically expected, only one leukemia case had a dose greater than 3 cGy. Contrasting to that data, the 3000 participants in "Operation Greenhouse" experienced only one leukemia death, compared with 4.43 expected. Both of these results are typical in applying statistics to small populations. Other similar studies found: No increased cancers or increases in all-cause mortality in 22 347 British weapons tests participants, and no difference in mortality, nor trends by dose, in 954 exposed Canadian military personnel.

High natural background radiation

• *Cancer mortality in the seven U.S. Colorado Plateau states is about 15 percent less than the U.S. average at background doses about three times the U.S. average (excluding radon lung doses).* Yalow notes the substantial data in this study, and addresses potential confounding effects. The results refute the linear model. The dose differences, with the size of the populations and the death statistics, are sufficient for the linear model to show increases in adverse health effects.

• *No adverse effects are found between stable, equivalent, Chinese populations in a province with a factor of three difference in natural background doses.* Yalow presents these results from the study of two Han peasant populations of roughly 70 000 persons each, who have lived in their respective regions for up to six generations. Uranium and radium and other decay products are more than four times higher (about 8 ppm compared with about 2 ppm) in the High Background Area (HBA) compared with the Control Area (CA). Thorium and its decay products are about six times higher (about 50 ppm compared with about 8 ppm). Extensive area radiation monitoring and personnel dosimetry of this population were conducted for more than 10 years.

Extensive health monitoring for about 20 years shows slightly lower mortality in the HBA for all cancers (including leukemia), with equivalent hereditary diseases and congenital defects, except somewhat higher rates of Down's syndrome, which is shown to be primarily due to an abnormally low incidence in the CA (compared with the larger region and China as a whole), plus a significantly higher birth rate to women who are more than 35 years old in the HBA. (The mother's age is a known association with higher rates of Down's syndrome). These data dramatically contradict the linear model. The population size and the accuracy of the dosimetry, and detailed health data over many years, establish that increases in adverse health effects would be readily detected by the linear model.

• *There are no discernible health effects in other high-background-radiation dose populations.* Yalow observes that studies of the population of 12 918 people in Kerala, India, who were exposed to four times the dose rate of a neighboring town with a control population of 5938, found no adverse effects, except 12 cases of Down's syndrome compared with none (an abnormal low rate) in the control population. She notes that Down's syndrome in Kerala is slightly *lower* than the rate in India. She also notes that in Guarapari, Brazil, with six times the background dose rate, no adverse health effects are found. Also, studies of numerous other small populations that live at relatively high natural radiation dose rates have found no adverse health effects associated with significant increases in radiation doses. Such natural high-background sources of radioactivity are thousands of times greater than the radioactivity from releases from nuclear facilities or from radioactive waste disposal sites.

• *No increased lung cancer is associated with indoor radon.* Yalow notes that nonsmoker lung cancer incidence is 2–3/100 000. In 1985, male lung cancer rates were 75/100 000, and female lung cancer rates were 27/100 000. She observes that 95 percent of lung cancer is associated with smoking, contradicting EPA predictions that 15 percent of U.S. lung cancer is associated with radon (20 000 of 140 000 deaths per year) using linear projections from a few early uranium miner cases of lung cancer.

Yalow observes that there is no lung cancer in nonsmoking uranium miners who have less than 1000 times the average 70-year indoor radon levels. She notes that EPA erroneously predicts 1000–5000 lung cancer deaths/100 000 persons (1–5 deaths/100) in persons so exposed. She adds that the lack of lung cancer in the miners at these high radon doses scientifically discounts radon as a potential cause of lung cancer for the very much lower indoor radon levels. Yalow also shows that the significant and well-documented China HBA population has 2.7/100 000 lung cancer deaths compared with a higher rate, 2.9/100 000, in the low-dose CA. These results clearly contradict the linear model.

Yalow also observes that uranium miners and smokers have different lung cancer types

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Continued from previous page

with the loss of his jaw and other disfiguring effects and complications. The U.S. Food and Drug Administration used this case to achieve the authority it had been seeking over radiation and radioactivity. However, FDA then did not study the consequences to the many thousands of people who had been using radiation and radioactivity (400 000 to 500 000 vials of Radithor alone were estimated to have been sold), nor did it assess the benefits, or the long-term risks. Robley Evans, of the Massachusetts Institute of Technology, collected data on more than 600 radium-burden cases, mostly dial painters, from the 1950s to 1969, with more than 4000 cases eventually identified at the Center for Human Radiobiology at Argonne National Laboratory. The radium cases, now with more than 50 years of follow-up, showed a threshold of approximately 1000 cGy (20 000 cSv) average dose to the skeleton.

In the June 1995 ANS sessions, the author noted that these results were ignored in setting ingestion standards (i.e., Byers, whose death led to creation of public fear and rejection of radiation use, ingested 5 million–10-million nCi; the radium-burden case cancer ingestion threshold is about 250 000 nCi; but U.S. drinking water standards are about 2 nCi/yr [a significant public cost for unjustified regulation]).

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gan, organism, population), to the total mass, is scientifically related to effects, both mathematically and empirically. He shows that this is consistent with other toxicological results, and with macro events (e.g., vehicular accidents) that relate discrete energy events to damage. A "hit size effectiveness function" is derived in units with both coordinates at the same biological "level," which results in an effective threshold. He shows that in the Japanese population, a linear relationship with known cancer effects shows that about 3000 joules of energy are required to produce one cancer effect. In radiation biology, increasing the number of cells to improve "statistics" for measuring effects, is actually an increase in the mass and total imparted energy. These analyses disprove the possibility of a linear relationship of the "energy concentration" dose to cell, organ, organism, or population effects.

Viewing the data

From the time of Eben Byers' death in 1932, radiation protection policies and research have increasingly fostered public fears and supported costly government regulations and programs. These costs have been largely borne, with minimal questioning, directly by the general public, due to the ability of affected governments, utilities, and private corporations to readily pass these costs through in medical and utility bills with small adverse competitive costs. These large costs might have been wasteful, but were moderate compared with the primary costs of nuclear technology operations and the cost of providing necessary protection for workers and the public from hazardous radiation exposure.

Recently, however, these radiation protection excesses have resulted in large incremental public costs, with even more proposed, with no accompanying public health benefit. Currently, these policies especially affect radioactive waste management and site decommissioning costs, to the benefit only of government bureaucracies and contractors. The immense costs incurred are reducing the viability and public benefits of many radiation and nuclear technology applications, and humanity is losing major advances and contributions to human health and well-being, without benefit to public health.

Current work in Japan, and similar work in China, with the beginnings of small efforts in Europe and elsewhere, along with some U.S. work in biology performed in cancer and genetics research, may be the hope of the future. Again, the world is responding to U.S. data and initiatives, especially as compiled and confirmed by the singular work of Luckey and the research and reporting of many others, including those who have participated in the ANS sessions mentioned earlier, while U.S. policy and public progress in the use and reasonable control of radiation and nuclear technology applications stagnate in favor of fostering public fear and unjustified public costs.

EPA and Nuclear Regulatory Commission rulemakings propose to still further reduce public radiation dose limits and increase public costs, for no public health benefits. This is true even when arbitrarily applying the linear model dose-response, since the proposed regulations would reduce exposures that are "less than 1 percent" of public radiation doses to limits that are "much less than 1 percent" of public doses; and to "protect" individuals from doses that are small compared with natural variations in daily living (e.g., much less difference than living above the second floor of a building instead of on the first floor, working in a granite building, or getting water from a well instead of a reservoir).

ANS and other nuclear science, medicine, and technology-based organizations must change past organization policies and participate in these rulemakings and other public policy proceedings. There is a need to require the federal agencies to address the factual evidence on radiation dose-response health effects that are necessary to establish valid regulatory standards to assure public health and safety; and to constrain ever-increasing regulatory and program costs that provide no public health and safety benefit, and that cost society the loss of the benefits of nuclear science and technology applications to human health and welfare.

Current radiation protection limits are estimated to cost in the range of $23 billion per life-year saved, as reported by a Harvard School of Public Health study. Even these values are taken from regulatory analyses, based on the linear model, which are likely to understate the cost/benefit. Simply reflecting null health effects data by using a conservative no-threshold sigmoidal dose-response model would result in increasing these reported costs by factors of tens to thousands (e.g., considering the radium-burden population data). Of course, recognizing an actual threshold as shown by the radiation dose-response data makes these incremental costs infinite, before considering the data that demonstrate beneficial effects for moderate doses in many populations.

Nuclear technologies bear these highly biased public health and environmental protection costs, adding tens of millions of dollars in both capital and annual costs to nuclear power operations, when the baseline already shows much lower adverse public health and environmental effects than those from alternative technologies. The historical

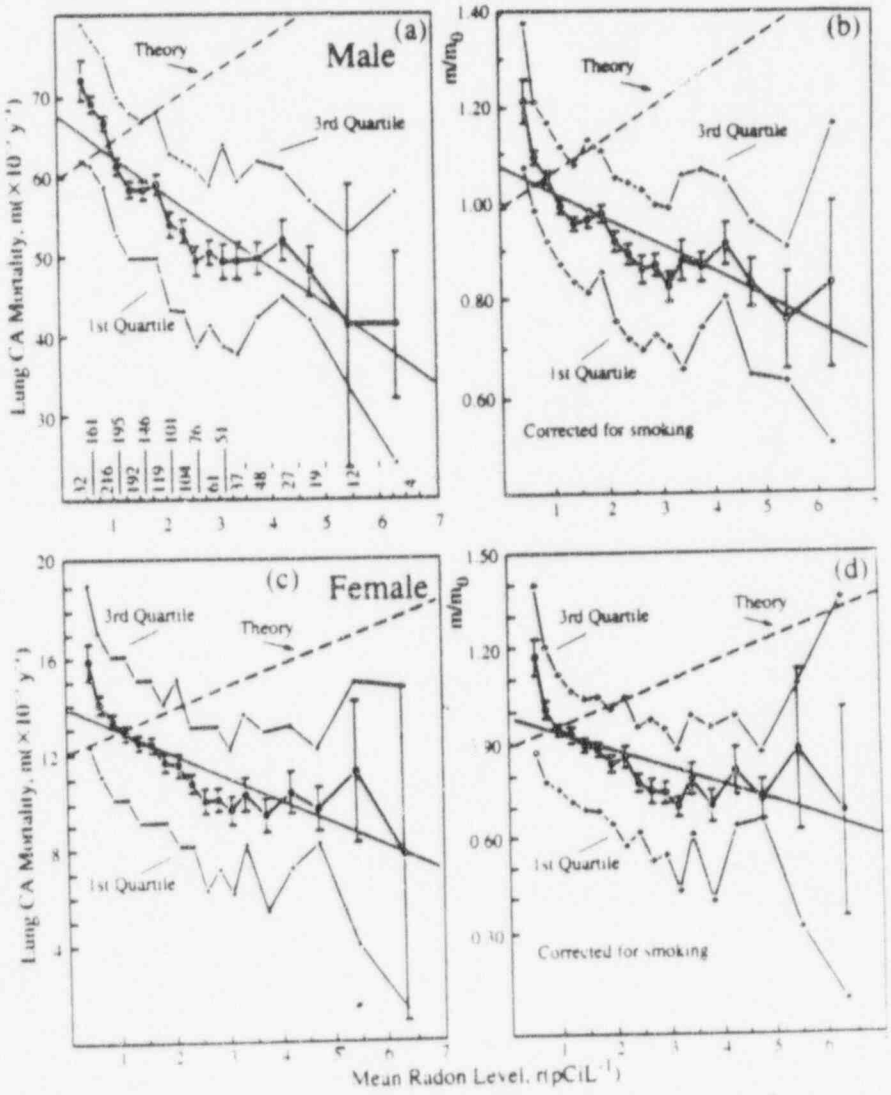

Fig. 6. Lung cancer mortality rates compared with mean home radon levels by U.S. county and comparison with presumed linear model by BEIR IV.

Preface

The Committee on Interagency Radiation Research and Policy Coordination asked the National Council on Radiation Protection and Measurements (NCRP) to provide advice on the use of collective dose in radiation protection, particularly as it should pertain to radiation exposures of the United States public.

In response to this request, NCRP Scientific Committee 1-3, Collective Dose, was established. Serving on Scientific Committee 1-3 were:

Ronald L. Kathren, *Chairman*
Washington State University
Richland, Washington

Members

John R. Johnson
Battelle, Pacific Northwest Laboratories
Richland, Washington

Dade W. Moeller
Dade Moeller & Associates, Inc.
New Bern, North Carolina

Roy E. Shore
New York University Medical Center
New York, New York

Barbara J. McNeil
Harvard Medical School
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Keith J. Schiager
University of Utah
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Robert Ullrich
University of Texas
Galveston, Texas

David A. Waite
Ebasco Environmental
Bellevue, Washington

Scientific Committee 1 Liaison

Eric J. Hall
Columbia University
New York, New York

NCRP REPORT No. 121

PRINCIPLES AND APPLICATION OF COLLECTIVE DOSE IN RADIATION PROTECTION

Recommendations of the
NATIONAL COUNCIL ON RADIATION
PROTECTION AND MEASUREMENTS

Issued November 30, 1995

National Council on Radiation Protection and Measurements
7910 Woodmont Avenue / Bethesda, MD 20814-3095

The app. n of the conversion factor, *alpha*, requires that the loss of future human resources (life expectancy) per unit collective dose be quantified. The ICRP and NCRP (ICRP, 1991; NCRP, 1993) provides nominal probability coefficients for stochastic effects, weighted for the detriment from nonfatal cancers and severe hereditary effects, of 5.6 percent Sv^{-1} for adult workers and 7.3 percent Sv^{-1} for the general population. For the multiplicative model, the loss of life per fatal cancer is 13 to 15 y (ICRP, 1991). As a first approximation for the purpose of illustration, the amount of life lost or impaired may be taken as the total detriment multiplied by the amount of life lost per fatal cancer. The estimated loss of life is then calculated to be approximately 0.8 y Sv^{-1} for workers and 1.0 y Sv^{-1} for the general population. One method for calculation of years of life lost per unit dose, which also considers age at the time of irradiation and organs irradiated, has been published (Maillie *et al.*, 1993).

An important question then is: "How much of current human resources (time and effort) are we willing and able to trade for future human resources?" As a society, we appear to be willing to spend extraordinary sums to save or prolong the life of identified individuals and we are willing to spend large sums as long as the number of individuals at risk is small. The amount we are willing to spend to improve life expectancy or quality of life for people we do not know and cannot identify is less clear, but the available funds are clearly limited. The principles and problems associated with evaluation of dose have been discussed in ICRP Publication 37 (ICRP, 1983).

6. Conclusions and Recommendations

It is clear that the concept of collective dose has, over the years, found increasing application in radiation protection, both as an operational tool for controlling radiation exposures to radiation workers and to the general public, and as a means of estimating the prospective risks to populations from real or potential radiation exposures. The application of the concept of collective dose for these purposes, however, is subject to certain limitations and qualifications, and the Council therefore cautions against inappropriate usage of this potentially valuable but limited tool.

Implicit in the concept of collective dose is the assumption of a direct proportionality between the risk incurred and the radiation dose, over the range of doses and dose rates of concern, *i.e.*, the response to radiation is both linear and time independent, and that any incremental dose above background, no matter how small, carries with it a proportionate risk of a specific stochastic effect or group of effects. The absence of a threshold is not essential to the use of collective dose, provided its magnitude is smaller than the natural background. The assumption of linearity without threshold is justified for radiation protection purposes. It should be recognized, however, that at low levels of individual exposure the risk estimates are uncertain by a factor of two or more in either direction and a threshold in the dose response can not be excluded, nor can the possibility that the risks are underestimated at low doses be excluded.

Modern radiation protection practice is based on three tenets: *Justification* of a practice to ensure that it, in fact, provides a net positive benefit; *ALARA*, taking into account social and economic factors; and *dose limits* which are established to ensure that the procedures for justification and ALARA do not result in excessive risk to individuals or to groups of individuals. The first two of these tenets—justification and ALARA—imply consideration of the total practice, and therefore collective dose may be the only reasonable quantity on which a suitable evaluation may be based. Dose limits normally apply to the individual, but constraints on the collective dose may also be applicable, albeit with important restrictions.

Given the foregoing discussion of the underlying bases and limitations of collective dose, the Council recommends the following:

1. The concept of collective dose should be considered as one of the means for assessing the acceptability of a facility or practice. However, because collective dose depends upon demographic variables as well as radiation doses, it is recommended that regulatory limits not be set in terms of collective dose.
2. Collective dose is most useful when applied to populations with known characteristics such as size, age, sex, etc. Where population characteristics are poorly defined or highly uncertain or subject to significant temporal change, collective dose should be applied with appropriate caution.
3. When the uncertainty in the number of individuals summed in the population component of collective dose is large (*e.g.*, one or more orders of magnitude), collective dose should not be used as a surrogate for risk even at relatively high levels of individual radiation doses.
4. Application of collective dose should be limited to stochastic effects (deterministic effects are not included) and to the dose range in which risk is assumed to be proportional to dose and independent of dose rate.
5. Assessing risk from collective exposures in medicine must reflect the great uncertainty in applying population based risk estimates to patients due to specific age distributions, health status and, possibly, shorter life expectancy.
6. All doses should be included in calculations of collective dose; there is no conceptual basis for excluding any individual doses, however small, from the collective dose calculation. There may, however, be practical limitations [see recommendations (2), (3) and (4)].
7. When the range of individual doses spans several orders of magnitude, the distribution should be characterized by dividing it into several ranges of individual doses, each covering no more than two to three orders of magnitude, with the population size, mean individual dose, collective dose and uncertainty being considered separately for each range.
8. Projection of collective committed doses to future populations and situations should be done with care and situations must recognize the large uncertainties introduced by unpredictable changes in relevant parameters, *e.g.*, less than about 10 percent.
9. When the collective dose is smaller than the reciprocal of the relevant risk coefficient, the risk assessment should note that the most likely number of excess cancer deaths is zero.

In the future, broader application of collective dose may be appropriate, but extension will necessitate a greater knowledge and understanding of the parameters used in the determination and calculation of collective dose and its attendant risks.

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Editorial

The issue of the decade: hormesis

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The Wyngaarden and Pauwels review of hormesis in this issue is most timely. Despite an exponential increase in data supporting hormesis during the past 15 years, there has also been a parallel increase in restrictive regulations of radiation that cripple medical research, diagnosis, and therapy, inhibit the development of nuclear energy, and impose enormous financial burdens upon society. Until recently, the "H" word has been ridiculed and taboo in authoritative scientific committees. In 1994, after 12 years of deliberation, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the most distinguished international authority on this subject, decided to publish its report on radiation hormesis, "Adaptive responses to radiation in cells and organisms" [1].

Why have scientific circles discounted or ignored evidence supporting hormesis for more than 50 years? Initially, the main scientific evidence of human radiation effects came from epidemiologic studies of atomic bomb survivors in Hiroshima and Nagasaki. These studies demonstrated a roughly linear relationship between extremely high single doses of radiation and the induction of cancer. In the absence of comparable low dose effects it was prudent to adopt the no-threshold hypothesis that extrapolates linearly from effects observed at very high doses to the same effects at very low doses, even those approaching zero. This hypothesis also implies that effects unobserved at high doses do not occur at low doses. It was accepted in 1959 by the International Commission on Radiological Protection (ICRP) [2] to guide rules for the protection of occupationally exposed workers following the original tentative acceptance of the hypothesis by UNSCEAR in 1958 [3]. This UNSCEAR report states: "Present knowledge ... does not permit us to evaluate with any precision the possible consequence to man of exposure to low radiation levels. Many effects of irradiation are delayed; often they cannot be distinguished from effects of other agents; *many will only develop once a threshold dose has been exceeded* some may be cumulative and others not; and individuals in large populations, or particular groups such as children and fetuses, may have special sensitivity. Those facts render it very difficult to accumulate reliable information about the correlation between small doses and their effects either in individuals or in large populations .... Such a situation requires that mankind proceed with great caution in view of a possible underestimation. At the same time, the possibility cannot be excluded that our present estimates exaggerate the hazards of chronic exposure to low levels of radiation. Only further intensive research can establish the true position."

Despite the absence of any supportive evidence of predicted low-level radiation effects, this no-threshold working hypothesis came to be regarded as a scientifically documented fact by many scientists. The tendency to neglect or reject epidemiologic human studies and experimental studies of cells and organisms that contradict the linear-no threshold theory of radiation carcinogenesis is supported by the widely accepted view that chromosome aberration and gene mutation can be produced by a single particle of ionizing radiation and so initiate a malignancy. However, no consideration is given to biological defense mechanisms that could be stimulated further by low-level increments of radiation above background. Stimulated defense mechanisms could also decrease carcinogenesis by chemical and other nonionizing agents as well as ionizing radiation.

The operation of these defense mechanisms in response to low-level radiation is examined critically in the recently published UNSCEAR report [1].

Adaptive processes to low-level radiation were demonstrated in human lymphocytes, mouse cells, and fibroblasts from various species, with evidence of cross-adaption between toxic chemical agents and low-dose radiation. These mechanisms of adaptive response include:

1. The up-regulation of genes and protein synthesis influencing cell cycle kinetics
2. The identification of activated genes and their enzyme products specifically involved in radiation-induced DNA repair
3. The relationship between radiation-induced repair genes and those activated by other mutagens
4. The ability of cells to remove toxic radicals
5. The activation of membrane receptors and the release of growth factors
6. The effects of radiation on the proliferative response to mutagens
7. Enhanced immunosurveilance by T-cell ontogeny, apoptosis and radiation-induced interphase death, and signalling processes in thymocytes.

The DNA repair enzyme was heralded by *Science*, 23 December 1994, as the "molecule of the year" [4]. The

convergence in 1994 of many decades of research in various repair pathways has firmly established that DNA repair enzymes, once thought to be important only in rare forms of human disease or radiation damage, occupy the central role in the life of the cell. These enzymes are grouped in pathways that specialize in three types of repair: mismatch repair of errors made when DNA is copied; base excision repair of DNA injury by oxidation and other common reactions; and nucleotide excision repair of large, bulky DNA lesions caused by outside agents such as ultraviolet light and chemicals. Defects in the mismatch repair gene hMSH2 are present in a large proportion of patients with the common cancer, hereditary nonpolyposis colorectal cancer. Patients with the rare genetic disease xeroderma pigmentosum lack a nucleotide excision repair enzyme with resultant extreme sensitivity to sunlight and frequent development of skin cancer before age 10. Another repair enzyme defect occurs in patients with ataxia telangiectasia, a rare disease with extreme sensitivity to ionizing radiation. Current research is testing the theory that declining DNA repair is a significant component of aging. If so, this would explain the progressive increased incidence of cancer with aging. Current research discloses that the development of cancer is much more dependent upon the functional status of repair mechanisms than the extent of DNA injury. Very high doses of radiation result in marked impairment of repair function. As David Koshland Jr. states in his *Science* editorial, "Moreover, the new understanding of repair systems may bring about a reexamination of the postulated linear extrapolation for pesticides and radiation and allow more realistic assessments of environmental risk. Evaluation based on such knowledge would not depend on the opinions of partisan protagonists, but on good, solid scientific evidence" [5].

Three recent reports are significant additions to the epidemiological evidence suggesting beneficial effects of radiation reviewed by Wyngaarden and Pauwels. Dr. Zbigniew Jaworowski, past chairman of UNSCEAR, in his current review of hormesis cites very recent data showing hormetic effects in humans from the former Soviet Union [6]. After high radiation exposure from a thermal explosion in 1957, 7852 persons living in 22 villages in the Eastern Urals were divided into three exposure groups averaging 49.6 cGy, 12.0 cGy, and 4.0 cGy and followed for 30 years. Tumor-related mortality was 28%, 39%, and 27% lower in the 49.6-cGy, 12.0-cGy, and 4.0-cGy groups, respectively, than in the nonirradiated control population in the same region. In the 49.6-cGy and 12.0-cGy groups the difference from the controls was statistically significant. Epidemiologic studies showing beneficial effects of low doses of radiation in atomic bomb survivors and other populations were reviewed recently by Sohei Kondo, Professor of Radiation Biology, Atomic Energy Research Institute, Kinki University, Osaka, Japan [7]. Included are the apparently beneficial effects of low doses of external gamma rays on the life span of radium-dial pointers and the low mortality rates of plutonium-exposed workers on the Manhattan Project. B.L. Cohen's completed monumental 12-year study that relates the incidence of lung cancer to radon exposure in nearly 90% of the population of the United States was published in the February 1995 issue of *Health Physics* [8]. This enlargement of earlier surveys to 1722 counties from which 1601 were selected for adequate permanence of residence provides extremely high-power statistical analysis. After applying the BEIR IV 1988 correction for variations in smoking frequency, there is a very strong tendency for lung cancer mortality to decrease with increasing mean radon level in homes, in sharp contrast to the BEIR IV theoretical increased mortality derived by linear-no-threshold extrapolation of effects in uranium miners exposed to very high radon concentrations. The discrepancy between theoretical and measured slopes is by 20 standard deviations. Rigorous statistical analysis of 54 socioeconomic, seven altitude and weather, and multiple geographic variables as possible confounding factors, both single and in combination, demonstrates no significant decrease in the discrepancy. The multiple independent requirements that a possible unknown confounding factor must meet make its existence highly improbable. A reasonable explanation is that stimulated biological mechanisms more than compensate for the radiation "insult" and are protective against cancer in a low-dose, low-dose-rate range.

The repeated criticisms of Cohen's studies, while maintaining the validity of the poor epidemiologic evidence of the uranium mine worker studies, exemplifies the need to observe the admonition of John D. Graham, Center for Risk Analysis, School of Public Health, Harvard University, "Finally, and most importantly, we need to be acutely sensitive to the construction of asymmetric burdens of proof in the scientific literature and the process of consensus formation. The papers by Drs. Schaffner and Sagan warned us of the generic danger: proponents of a prevailing paradigm will tend to ignore, suppress, and censor evidence that seems to be incompatible with or threatening to the status quo. ...I would like to conclude....[with] what I believe is the most critical concept in the conference: the "optimum dose." When background doses (from all sources) exceed the optimum dose, the hormesis concept is irrelevant to social policy. When the optimum dose exceeds the background dose (from all sources), the hormesis hypothesis has profound implications for social policy" [9].

Recent high statistical power epidemiologic studies of low-level radiation and studies of adaptive responses to low-level radiation are bringing about a reexamination of the "no-threshold hypothesis" based upon the hypothetical linear extrapolation of high-dose effects to effects of very low doses approaching zero. The 1994 UNSCEAR report documents that multiple defense mechanisms at molecular, cellular, organ, and systemic levels are currently being demonstrated and confirmed by numerous investigators. Stimulation of these adaptive re-

sponses by low-level radiation involves gene activation, repair enzyme synthesis, DNA repair, protein synthesis, stress-response protein production, activation of membrane receptors, detoxification of free radicals, proliferation of thymocytes and splenocytes, and stimulation of the immune system.

Mounting reproducible evidence of the operation of various defense mechanisms and their stimulation by low-dose ionizing radiation provides further details of how biological defense mechanisms, nonoperative at high doses, are stimulated and enhanced by low-level radiation damage so as to overcorrect and predominate. These investigations demonstrate why the negative health effects observed at high levels of radiation that overwhelm these defense mechanisms cannot be extrapolated to the low levels at which these stimulated defense mechanisms predominate with decreased cancer induction, decreased mortality, and other observed positive health effects.

An understanding of the positive health effects produced by adaptive responses to low-level radiation would result in a realistic assessment of the environmental risk of radiation. Instead of wasting many billions of dollars annually for protection against hypothetical risks of low-level radiation exposure, the resource could be used productively for effective health measures.

References

1. UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Adaptive responses to radiation in cells and organisms*. Document A/AC.82/R.542, approved 11 March 1994.
2. ICRP (International Commission on Radiological Protection). *Recommendations of the International Commission on Radiological Protection*. ICRP Publication No. 1. London: Pergamon Press, 1959.
3. UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*. United Nations General Assembly, Official Records, Thirteenth Session, Supplement No. 17 (A/3838), 1958.
4. Koshland DE, Szostak A, Hanawalt PC, Modrich P. DNA repair enzymes and mechanisms. *Science* 1994; 266:1925–1927, 1954–1960.
5. Koshland DE. Molecule of the year: the DNA repair enzyme. *Science* 1994; 266:1925.
6. Jaworowski Z. Hormesis: the beneficial effects of radiation. *21st Century Sci Tech* 1994; 7:22–27.
7. Kondo S. *Health effects of low-level radiation*. Osaka: Kinki University Press; Madison, Wisc: Medical Physics Publishing, 1993.
8. Cohen BL. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys* 1995; 68:157–174.
9. Graham JD. Synopsis of the BELLE conference on chemicals and radiation. In: Calabrese EJ, ed. *Biological effects of low level exposures: dose-response relationships*. Boca Raton, Fl: E.J. Lewis, 1994.

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Review article

Hormesis: are low doses of ionizing radiation harmful or beneficial?

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Abstract. A review is provided of the literature on radiation hormesis, hormesis being any physiological effect that occurs at low doses and which cannot be anticipated by extrapolating from toxic effects noted at high doses. Epidemiological studies suggesting beneficial effects are considered, and experimental evidence for the existence of hormesis is then appraised. In the latter context, there are possible low-dose effects at the molecular level, at the cellular level and on the organism as a whole. It is concluded that while it is difficult to analyse the effects of low-dose radiation with statistical significance, the concept does permit the reconsideration of the validity of currently accepted notions.

Key words: Hormesis – Ionizing radiation – Epidemiological studies – Experimental studies

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Introduction

Since its discovery ionizing radiation has captured the imagination of the public. Initially it was thought to be healthy in all doses, leading to unusual applications such as ladies corsets containing radium and radium drinking cups. But as time passed it became clear that there was an upper limit to the presumed beneficial effects. Undesired side-effects caused by relatively high doses of radiation led to the belief that radiation was harmful at all doses. Later, the concept of the threshold dose was introduced to explain the fact that negative effects were observed only above certain dose levels. Furthermore, it was suggested that low doses of radiation might actually have beneficial effects on organisms. Results of experiments that pointed in this direction were attributed to a process named "hormesis" [1].

Hormesis is *any physiological effect that occurs at low doses and which cannot be anticipated by extrapolating from toxic effects noted at high doses* [2]. Hormetic effects are normally beneficial but may co-exist with toxic effects. Hormesis may be characterized as a process whereby low doses of an otherwise harmful agent may result in stimulatory or otherwise beneficial effects. The word originates from the Greek word *hormaein*, which means "to excite", and refers to a much broader spectrum of phenomena including many toxicological observations. According to Stebbing [3] the term was probably first coined in a publication dating from 1942 describing the growth stimulation of fungi by a naturally occurring antibiotic, which at higher concentrations suppressed fungal growth. There are many examples in nature of processes that follow a hormetic model. A striking example is vitamins, widely accepted to be very beneficial at certain doses, but known to be toxic at higher doses. Hormetic models of ionizing radiation suggest that it behaves in a similar way. A schematic representation of the models illustrating the presumed beneficial and harmful effects of ionizing radiation is shown in Fig. 1. The hormetic model is clarified in Fig. 1C, which illustrates the concept that at lower doses the effects of radiation are beneficial. In the diagrams effects are shown to be either harmful or beneficial as the radiation dose is increased. The point at which the radiation has no overall effects is referred to as the "zero equivalent point" [cf. 24].

In this article we shall review the literature that has appeared on this subject. Subsequently epidemiological and experimental evidence will be brought forward to elucidate the arguments in favour of radiation hormesis. This paper will be concluded by highlighting some criticisms raised against hormetic models.

Epidemiological evidence suggesting beneficial effects of radiation

Literature data on radiation hormesis describe the observed beneficial effects at dose levels between 1 and 50 cGy [cf. 18]. Many epidemiological studies have been performed to investigate whether threshold dose of ionizing radiation exists. Obviously, it is difficult to find a situation in which a large group of subjects is exposed to

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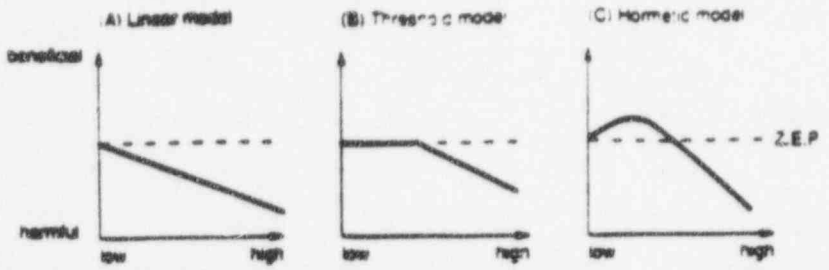

Fig. 1A–C. Representation of the effects of low-level ionizing radiation on living organisms. On the x-axis the overall effect of the radiation is represented, on the y-axis the level of radiation received is represented. A shows the established linear model, in which it is presumed that the effects of radiation are unfavourable at all doses above zero. B shows a threshold model, in which the adverse effects start at some point above zero. The hormetic model is demonstrated in C, in this model the effects of radiation at lower doses are beneficial. *Z.E.P.* Zero equivalent point at which radiation has no overall effect

ionizing radiation, allowing accurate assessment of the dose. As a consequence of this, beneficial effects may be difficult to quantify. Nevertheless, several epidemiological studies have come to the conclusion that such beneficial effects really exist. These reports are summarized in the following paragraphs.

In a Canadian study [4] the mortality due to cancer at nuclear power stations was reported to be 58% lower than the national average. One reason for this could be the strict medical tests that the nuclear power workers are subjected to before being offered a job. However, workers in the non-nuclear power industry who underwent comparable medical tests have a mortality due to cancer which amounts to 97% of the national average. It is therefore unlikely that this marked drop in cancer mortality is due to "the healthy worker effect" alone, as equally "healthy" workers in the non-nuclear power industry do not have this lower mortality. An epidemiological study of cancer frequency and mortality in nuclear power workers has also been carried out in Britain [5]. Also in this study it was found that cancer frequency amongst nuclear power workers was lower than the national average, but no definite conclusions were reached.

In a Chinese study [6], two groups of people were epidemiologically compared. The first (74.000 people) lived in an area with a relatively high background radiation (2.28 mGy per year), while a second (control) group (78.000 people) lived in an area with less radiation (0.95 mGy per year). The first group had a lower mortality due to cancer. Cancer mortality in the first group was 48.8×10^{-5} (±2.3) per person per year. Cancer mortality in the control group was higher 51.1×10^{-5} (±2.2). The difference is not statistically significant, but if only an older age category is compared (40–70 year olds) a significant difference is observed. The cancer mortality in the first group is 144×10^{-5} (±8.0) per person per year, whereas the control (lower background radiation) group shows the higher rate of 168×10^{-5} (±9.0) per person per year. The justification for only comparing these higher age groups is that this part of the population has received a higher total life radiation dose, causing enough difference in dose between the groups for a hormetic effect to be observed. The chance that this difference would occur at random is 2.3%. One must, of course, be aware that other factors such as dietary habits may have caused this difference in cancer mortality.

In an U.S. energy department study [7], the workers at three facilities were exposed to plutonium and other radioactive substances. The purpose of the study was to measure adverse health effects caused by the exposure. The plutonium exposure was mainly by inhalation. It appeared that the standard mortality ratio due to lung cancer was only 14% of the national level and all cancers in general appeared to be 70% of the national level. These figures are too extreme to be caused only by "the healthy worker effect". It was also observed that the number of smokers amongst the studied group was comparable with the national average, eliminating this factor as a source of error.

In a study looking at the effects of a high background radiation in various cities in India [8] it was observed that in areas with a high background radiation level the cancer incidence/mortality was significantly less. Five cities were studied and the higher the level of radiation, the lower the rate of various forms of cancer. Bombay, Nagpur, Bangalore, Pune and Madras were chosen for this investigation. Whereas the radiation levels in Bombay and Pune were much lower (<400 μSv/year, compared to 600–800 μSv/year in Bangalore and Madras), cancer incidence and mortality were higher. The reduction occurs at the rate of 0.03 per μSv/year (per 100000 people) in the Indian population. In the United States, Hickey et al. [9] have also measured the effects of differing levels of background radiation in different areas. From this study it was concluded that total cancer mortality is inversely correlated with background radiation dose with a statistical significance level of 0.05, but the Indian data are based on a larger population. In addition the authors mention that due to a low degree of industrialization, carcinogenesis is less influenced by the environment than in other countries.

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A Japanese study looking at cancer incidence/mortality in atomic bomb survivors looked at the dose response within the low dose range [10]. In this study it was difficult to evaluate the data and not really possible to establish the existence of hormesis by statistical analysis. Another Japanese study [11] looked at 290 male A-bomb survivors who had been exposed to 50–149 cGy of radiation. These showed significantly lower mortality from non-cancerous diseases than unexposed males but higher rates of cancer. It is evident that epidemiological studies amongst atomic bomb survivors are difficult to carry out, as received doses are difficult to ascertain. To date no really conclusive evidence for hormesis has been found in this type of study.

Cohen and Colditz [12] looked at the effects of radon exposure on cancer risk in U.S. homes. It has been suggested that radon in U.S. homes is responsible for about 10000 fatal lung cancers each year (BEIR 1988) [13]. This number is, however, based on extrapolations of data on miners who have been subjected to high radon concentrations. This study found that lung cancer rates decreased with an increase in radon levels. Smoking prevalence may have influenced the results, but this was corrected for. Many other confounding factors are considered and dealt with, such as socio-economic variables and geography. Nonetheless, a very strong negative correlation was found between lung cancer mortality rates and mean radon levels. A British study came to similar conclusions [14]. Both these studies support hormetic models for lung cancer mortality.

A study involving 700,000 shipyard workers (108,000 of whom were nuclear shipyard workers) by the Johns Hopkins Department of Epidemiology, School of Public Health and Hygiene [15] concluded that both the nuclear workers receiving more than 500 mR and those receiving less than 500 mR had significantly lower mortality (0.76 and 0.81, respectively) from all causes of death than the non-nuclear workers. Non-nuclear shipyard workers' mortality rates were similar to non-shipyard workers, therefore eliminating the healthy worker effect as a bias. This is consistents with other studies of populations in states with higher background radiation (approximately 1 mGy per year more than states with lower background radiation) that demonstrated increased longevity and a 15% reduction in overall mortality [16–19].

A study of 31,710 Canadian female tuberculosis patients who underwent fluoroscopy [20] concluded that the breast cancer risk increased with received radiation dose. According to this report, which comprised examinations performed in the period between 1930 and 1952, a theoretical lifetime excess of 900 deaths due to breast cancer would occur in a hypothetical group of one million women having received 0.15 Gy. The report used a linear model to calculate the hypothetical increased risk at this low dose of radiation. A more recent analysis of the data by Pollycove [21] applying an empirical polynomial function demonstrated that for this dose, 10,000 deaths per million would be prevented rather than 900 excess deaths being induced (better than 99% confidence limit).

Experimental evidence

Further evidence for the existence of hormesis has been obtained from results emanating from experiments designed to demonstrate low-dose effects at the molecular level, the cellular level and on an organism as a whole [22].

Effects at the molecular level

At the molecular level hormesis has been explained by both DNA repair and detoxification of free radicals.

DNA repair. It is an established fact that the extent of DNA damage is proportional to the radiation dose received [23]. However some experiments indicate that this relationship may not be totally linear. Low-dose radiation might cause an adaptation whereby cells become resistant to the mutagenic effects of subsequent high-dose exposures. These low doses may induce the production of proteins that are involved in DNA repair. Experiments showing the induction of adaptation to ionizing radiation have been carried out on human lymphocytes using low levels of radiation-incorporated tritiated thymine followed by higher doses of X-rays [24]. It was found that the number of chromatid breaks induced by the X-rays was lower than expected. It was later found that this adaptive effect could also be induced by exposure to very low doses of X-rays before the higher doses were given [25]. Another interesting observation was that the effects could only be induced using a fairly narrow range of doses [19]. This may be an explanation for the fact that hormetic models have not come to light earlier. In this laboratory test it appeared that, once the effect was induced, it lasted for the relatively long duration of three cell cycles. It was also found that these phenomena were only fully existent after 4–6 h, suggesting the involvement of a repair enzyme. Electrophoresis experiments reinforce this idea that proteins (enzymes) are involved and have determined the presence of a 30- to 35-kDa protein, thought to be responsible for DNA repair [26].

Free radical detoxification. Free radicals are known to cause DNA damage. Ionizing radiation causes a temporary increase in intracellular free radical concentration. It is suggested that protective mechanisms are activated, leading to longer term protection against DNA damage. Feinendegen et al. [27] have investigated the effect of low-level radiation and the subsequent increase in intracellular free radical concentration on DNA synthesis. It was found that DNA synthesis was temporarily inhibited, this inhibition reaching its maximum in 5 h. The

decrease in DNA synthesis was accompanied by an increase in the concentration of the free radical scavenger gluthionine. This temporary inhibition of DNA synthesis gives the cell time to carry out the DNA repair process. By temporarily inhibiting crucial intracellular activities and inducing the production of free radical scavengers, the low-level radiation has the effect of inducing a degree of protection against the harmful effects of further exposures to radiation and the detrimental effects of subsequent free radical attacks.

Effects at the cellular level

At the cellular level hormetic effects include immunostimulation and fertility enhancement. Some authors believe that radiation is essential for life and the preservation of the species. Luckey [28] hypothesized that a base amount of radiation is essential for cell growth. Several studies have been carried out to look at effects on the cell, as detailed below.

Immunostimulation. High doses of radiation are known to suppress the immune system, but at low levels radiation may induce the generation of a haematopoietic growth factors. In a Chinese study [29] the effects of low dose radiation on the immune system were studied using mice. The reactivity of thymocytes to interleukin-1 was shown to be depressed at radiation doses ranging from 0.025 to 0.25 Gy, but there was an increase in cell number in the thymus between 0.025 and 0.10 Gy, resulting in an improvement of the reaction of the whole organ. In these experiments the reaction of the organ to interleukin-1 was measured by counting cells in thymocyte suspensions made after exposure to varying degrees of radiation: the greater the cell count, the better the reactivity [30, 31]. Studies of the immune system of A-bomb survivors [32] showed some results which may not rule out hormetic enhancement of the immune system but failed to come up with conclusive evidence for immunostimulation.

Fertility enhancement. In a Belgian/French study [33] male and female mice were exposed to 10 mrad/h for different lengths of time. Female fertility was decreased and male fertility increased relative to a control group. This increase in male fertility may be an example of radiation hormesis. Female fertility was reduced due to the high sensitivity of the oocytes to radiation. Cytological and histological studies of the testes did not reveal any difference between the exposed and unexposed organs, suggesting that the increase in fertility occurs in an indirect way via physiological effects. Human studies also suggest an increase in fertility as a result of low levels of radiation [34].

Experiments at the cellular level. At the cellular level experiments have been performed using unicellular organisms. Background and chronic low levels of radiation have been found to increase the growth rate of the aquatic protozoans, *Paramecium caudatum* and *Paramecium tetraurelia* [35]. Using groups that were shielded from background radiation, groups exposed to low levels of gamma radiation and control groups, it was found that radiation could stimulate proliferation of these single-cell organisms. The stimulatory effect occurred only in a limited range of doses and disappeared at doses above 50 mGy/year. Experiments were also done in space onboard the space shuttle Challenger [36] to measure the effects of cosmic radiation on paramecia; however, results were inconclusive due to the combined influence of cosmic radiation and low gravity.

Cellular experiments were also done by Fabrikant [37]. His experiments demonstrated changes in the proliferative characteristics of tissues under continuous low-dose radiation. Cell population kinetics were measured for rapidly and slowly dividing cell types. Data were collected on immunohaematopoietic tissues, regenerating liver tissue, intestinal epithelium and seminiferous epithelium. Adaptive changes to the irradiation were observed in the cell populations, the cell cycle being accelerated so as to replace damaged cells. Cells that normally divide more rapidly showed a better response, replacing damaged cells at a higher rate.

Effect on the organism as a whole

In animals and humans low-level radiation presumably leads to an increase in life span. This increased longevity has been attributed to two factors: (1) an initial production of free radicals (which are thought to be involved in ageing [38]) as a result of low-level radiation leading to a feedback reduction of intracellular free radical levels; (2) the fact that these phenomena resemble caloric intake restriction effects [39] (caloric intake restriction has been found to increase life span [40]). Low-level radiation is known to produce oxygen radicals, which affect endocrine balance. This is interpreted by the body as an increased food intake, thus lowering appetite and therefore caloric intake, which in turn increases longevity.

Animal experiments. Theories on hormesis have been tested by performing experiments on mammals. Congdon [41] reviewed some of these with interesting results. Starting in the 1940s, experiments at the National Cancer Institute (USA) led by Lorenz exposed mice, guinea pigs and rabbits to varying degrees of radiation. A group of mice was exposed to 0.11 R per 8-h day until natural death. The experimental group had a longer mean survival rate (nearly 2 months compared to the control group). There was also an increased body weight in the irradiated animals: animals exposed to 0.11 R had an average weight increase of 50% over the controls after approximately 69 weeks of exposure.

In another study [42] young adult beagles were injected with graded activities of radioactive substances and were observed for the entire remaining portion of

their life. The main part of the radiactive dose was due to α particles. The rate at which bone sarcoma appeared in these animals increased fairly linearly with dose and no evidence for hormesis whatsoever was found.

Observations in humans. In 1987 Matanoski etal. [43] published a study on the mortality amongst radiologists in comparison to other medical practitioners. Radiologists who started practising before 1940 experienced an increased rate of death due to cancer as well as other diseases. This is in contrast to the mortality found in a group of radiologists who started practising after 1940: amongst younger radiologists the mortality appeared to be lower than that among other medical specialists of the same age group. This observation has been attributed to the fact that the younger radiologists received a lower overall dose of radiation and that due to greater precautionary measures in more recent years the average yearly radiation dose received by radiologists is less. The authors suggest a protective effect, which disappears in later life when the cumulative dose becomes too high.

Concluding remarks

Although the issue of radiation hormesis has been investigated by a number of authors, it appears that relatively few articles have been published on this subject since its so-called discovery. This is surprising as radiation hormesis is undoubtedly of interest from a scientific standpoint and may even have social consequences. It is obvious that many radiobiological studies have concentrated on the effects of high doses of radiation and that the reports on hormesis with low doses have often led to the passionate exchange of views [44, 45, 46]. Criticism comes down to general recognition that it is difficult to analyse the effects of low-dose radiation with statistical significance [47]. The cumulative results as expressed in this article may not really prove the existence of hormesis but they do allow one to challenge the paradigms. On the other hand it should be noted that some authors are undesirably enthusiastic to prove the theory and unintentional selective scientific blindness may occur. In science, self-fulfilling prophesies are not uncommon and often negative results are not published and create false ideas.

After reading through the existing literature on radiation hormesis, however, we believe that one should not necessarily agree or disagree with the concept. It rather opens the possibility to reconsider the validity of currently accepted notions.

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References

1. Lorenz E. Some biological effects of long continued irradiation. *Am J Roentgenol* 1950; 63: 176.
2. Sagan L.A. What is hormesis and why haven't we heard about it before? *Health Phys* 1987; 52: 521–525.
3. Stebbing A. Hormesis, the stimulation of growth by low levels of inhibitors. *Sci Total Environ* 1982; 22: 213.
4. Abbot JD. Hamilton TR. Weeks JL. Epidemiological studies in three corporations covering the Canadian nuclear fuel cycle. *Biological effects of low level radiation.* IAEA: Vienna. 1983: 351.
5. Kendall GM. Muirhead CR. Macgibbon BH. O'Hagan JA. Conquest AJ. Goodhill AA. Butland BK. Fell TP. Jackson DA. Webb MA. Haylock RGE. Thomas JM. Silk TJ. *First analysis of the national registry for radiation workers. Occupational exposure to ionizing radiation and mortality.* NRPB: Chilton. Didcot. UK: 1992: NRPB-R251.
6. Luxin W. etal. Epidemiological investigation of radiological effects in high background radiation areas of Yangjiang, China. *J Radiat Res* 1990; 31: 119–136.
7. Tietjen GL. Plutonium and lung cancer. *Health Phys* 1987; 52: 625–628.
8. Nambi KSV. Soman SD. Environmental radiation and cancer in India. *Health Phys* 1987; 52: 653–657.
9. Hickey RJ. Bowers EJ. Spence DE. Zemel BS. Clelland AB. Clelland RC. Low level ionizing radiation and human mortality: multiregional epidemiological studies. *Health Phys* 1981; 40: 207–219.
10. Kato H. Schull WJ. Awa A. Akiyama M. Otake M. Dose-response analyses among atomic bomb survivors exposed to low level radiation. *Health Phys* 1987; 52: 645–652.
11. Mine M. Okumura Y. Ichimaru M. Nakamura T. Kondo S. Apparently beneficial effect of low to intermediate doses of A-bomb radiation on human life span. *Int J Radiat Biol* 1990; 58: 1035–1043.
12. Cohen BL. Colditz GA. Tests of the linear-threshold theory for lung cancer induced by exposure to radon. *Environ Res* 1994; 64: 65–89.
13. BEIR. Report. US National Academy of Sciences Committee on Biological Effects of Ionizing Radiation. Washington D.C. *Health risks of radon and other internally deposited alpha emitters* (BEIR-IV). Washington D.C.: National Academy Press. 1988.
14. Haynes RM. The distribution of domestic radon concentrations and lung cancer mortality in England and Wales. *Radiat Prot Dosim* 1988; 25: 93–96.
15. Cameron J. The good news about low level radiation exposure: health effects of low level radiation in shipyard workers. *Health Phys Soc Newsletter* 1992; 20: 9.
16. Craig L. Seidman H. Leukemia and Lymphoma mortality in relation to cosmic radiation. *Blood* 1961; 17:319.
17. Frigerio NA. Stowe RS. Carcinogenic and genetic hazard from background radiation. *Biological and environmental effects of low level radiation.* International Atomic Energy Agency. Vienna. 1976; 2: 285.
18. Cohen JJ. Natural Background as indicator of radiation induced cancer. *Proc. 5th Int. Radiat. Assoc.* Jerusalem. 1980
19. Webster EW. The effects of low doses of ionizing radiation. *J Tenn. Med. Assoc.* 1983; 76: 499.
20. Miller AB. Howe GR. Sherman GJ. Lindsay JP. Yaffe MJ. Dinner PJ. Risch HA. Preston DL. Mortality from breast cancer after irradiation during fluoroscopic examinations in pa-

ients being treated for tuberculosis. *N Engl J Med* 1989; 321: 1285–1289.

21. Pollycove M. Positive effects of low level radiation in human populations. In: Calabrese EJ (ed) *Biological effects of low level exposures: dose-response relationships*. London: CRC Press; 1994: 171–187.
22. Macklis RM. Burresford B. Radiation hormesis. *J Nucl Med* 1991; 32: 390–399.
23. Wolff S. Are radiation-induced effects hormetic? *Science* 1989; 245: 575, 621.
24. Olivieri G. Bodycote J. Wolff S. Adaptive response of human lymphocytes to low concentrations of radioactive thymine. *Science* 1984; 233: 594–597.
25. Shadley JD. Wolff S. Very low doses of X-rays can cause human lymphocytes to become less susceptible to ionizing radiation. *Mutagenesis* 1987; 2: 95–96.
26. Wolff S. Wiencke JK. Afzal V. Youngblom J. Cortes F. The adaptive response of human lymphocytes to very low doses of ionizing radiation: a case of induced chromosomal repair with the induction of specific proteins. In: Beversnock KM. Stather JW. (eds) *Low dose radiation: biological bases of risk assessment*. London: Taylor and Francis; 1989: 446–454.
27. Feinendegen LE. Muhlensiepen H. Bond VP. Sondhaus CA. Intracellular stimulation of biochemical control mechanisms. *Health Phys* 1987; 52: 663–669.
28. Luckey TD. Physiological benefits from low levels of ionizing radiation. *Health Phys* 1982; 43: 771–789.
29. Liu SZ. Liu WH. Sun JB. Radiation hormesis: its expression in the immune system. *Health Phys* 1987; 52: 579–584.
30. He WH. Feng RL. Liang JY. Chen MZ. Chen L. Li RB. Zhang GH. Survey of cancer mortality rate among inhabitants of high background area in Guangdong. *Chinese J Radiol Med Protection* 1985; 5: 109–115.
31. Zhai SJ. Liu XJ. Pan TM. He WH. Feng RL. Chen MZ. Li SH. Chen L. Li RB. Yie HX. A preliminary report on the survey of cancer mortality in high background area 1970–1980. *Chinese J Radiol Med Protection* 1982; 2: 48–56.
32. Bloom ET. Akiyama M. Kusunoki Y. Makinodan T. Delayed effects of low-dose radiation on cellular immunity in atomic bomb survivors residing in the United States. *Health Phys* 1987; 52: 585–591.
33. Lennard A. Delpeux M. Meyer R. Decat G. Leonard ED. Effect of an enhanced natural radioactivity on mammal fertility. *Sci Total Environ* 1985; 45: 535–542.
34. Meyer MB. Tonascia J. Long term effects of prenatal X-ray on human females. II. Growth and development. *Am J Epidemiol* 1981; 114: 317–336.
35. Planel H. Soleilhavoup JP. Tixador R. Richoilley A. Conner A. Croute F. Carnero C. Gaubin Y. Influence on cell proliferation of background radiation or exposure to very low, chronic γ radiation. *Health Phys* 1987; 52: 571–578.
36. Richoilley G. Tixador R. Gasset G. Templier J. Planel H. Preliminary results of the "paramecium" experiment. *Naturwissenschaften* 1986; 73: 404.
37. Pelnikan JI. Adaptation of cell renewal systems under continuous irradiation. *Health Phys* 1987; 52: 561–571.
38. Harman D. Free radical theory of aging. In: Johnson JE Jr. Walford R. Harman D. Miquel J. (eds) *Free radicals, aging, and degenerative diseases*. New York: Alan R. Liss; 1986: 3–49.
39. Toner JR. Physiology of the hormetic effect. *Health Phys* 1987; 52: 549–551.
40. Toner JR. Food restriction, ionizing radiation, and natural selection. *Mech Ageing Dev* 1985; 30:261.
41. Congdon CC. A review of certain low level ionizing radiation studies in mice and guinea pigs. *Health Phys* 1987; 52: 593–597.
42. Mays CW. Lloyd RD. Taylor GN. Wrenn ME. Cancer incidence and life span vs α-particle dose in beagles. *Health Phys* 1987; 52: 617–625.
43. Matanoski GM. Sternberg A. Elliot EA. Does radiation exposure produce a protective effect among radiologists? *Health Phys* 1987; 52: 637–644.
44. Moghissi AA. Ray DL. Radiation and cancer risk. Letter. *Health Phys* 1988; 54: 473.
45. Gofman JW. Health effects of ionizing radiation: Dr Sagan's paradigms [letter]. *Health Phys* 1987; 52: 679.
46. Sagan LA. Reply to Dr. Gofman's comments on the health effects of ionizing radiation [letter]. *Health Phys* 1987; 52: 680.
47. Hart G. Why is zero radiation considered good? [letter]. *Nucl Med Commun* 1993; 14: 506–507.