The Rise and Fall of the Linear No-Threshold (LNT) Theory of Radiation Carcinogenesis

By Myron Pollycove, M.D.

Visiting Medical Fellow
US Nuclear Regulatory Commission
Professor Emeritus
Laboratory Medicine and Radiology
University of California, San Francisco

Presentation at American Institute of Physics, 1997

As a physician and physicist, I feel privileged to address physicists and engineers at this conference. Physics, together with its sister Chemistry and daughter Biology, furnish knowledge of the laws of Nature. The welfare of society depends upon a harmonious interaction of these laws of our environment and our physical body with human actions of conscience and integrity. I fully believe in the Hippocratic Oath of the physician to act "for the benefit of my patients, and abstain from whatever is deleterious." Growing together with Nuclear Medicine since 1953, I was concerned with the radiation health effects of our patients and staff. At the University of California, Berkeley, we held to the conservative threshold limits of the Atomic Energy Commission. Later at the University of California, San Francisco, we adhered strictly to further reductions of exposures to "as low as reasonably achievable," ALARA. The latter were associated with the Linear No-Threshold (LNT) theory that all radiation doses, even those close to zero, are harmful. Low doses are held to have the same effects as high doses, but with lower incidence.

Fully involved with clinical research, teaching, and the diagnosis and treatment of patients in both Nuclear Medicine and the Clinical Laboratory, it never occurred to us to question radiation regulations. These regulations are based upon recommendations of International and National Radiation Protection Committees composed of eminent radiation science specialists. Nevertheless, after 35 years of complete trustful acceptance of radiation protection policy, in the late 80's and 90's peer reviewed publications and conferences began to present data that were incompatible with LNT theory.

Upon retirement from UCSF in 1991, I accepted the position of Visiting Medical Fellow with the US Nuclear Regulatory Commission. In addition to consulting duties, I began a careful examination of some published epidemiologic low dose radiation studies. No statistically significant low-dose radiation study (<20cGy) was found to support the LNT theory of carcinogenesis and mortality risk. This was confirmed by the National Council of Radiation Protection and Measurements (NCRP) Report 121 (11/30/95) on Collective Dose that summarizes the current state of LNT theory:[1]

> "...essentially no human data, can be said to provide direct support for the concept of collective dose with its implicit uncertainties of nonthreshold, linearity and dose-rate independence with respect to risk. The best that can be said is that most studies do not provide quantitative data that, with statistical significance, contradict the concept of collective dose...
>
> Ultimately, confidence in the linear no threshold dose-response relationship at low doses is based on our understanding of the basic mechanisms involved. ...[Cancer] could result from the passage of a single charged particle, causing damage to DNA that could be expressed as a mutation or small deletion. It is a result of this type of reasoning that a linear nothreshold dose-response relationship cannot be excluded,. It is this presumption, based on biophysical concepts, which provides a basis for the use of collective dose in radiation protection activities".

Cell and tissue low-dose stimulation of the DNA damage control biosystem has been confirmed at the

level of the organism as well as the cell by the 1994 report of UNSCEAR. Why, then, aren't we aware of corresponding beneficial effects in humans who have been exposed to low-dose radiation? Regrettably, presentation of this data has been suppressed, deleted, discounted as unreasonable, and unscientifically criticized as implausible or invalid. Concurrently, efforts to present low-dose data that support the LNT theory have led to misrepresentation of their data by authors of four studies:

- The 1989 Canadian Fluoroscopy Study[2] discards the most statistically significant data demonstrating large *decreases* of breast cancer mortality at 0.15Gy and 0.25Gy cumulative exposures. The study retained insignificant higher dose data so that "The best fit for the data was provided by the linear model..."
- The 1996 revision of the Canadian Fluoroscopy Study[3] states that since low-dose data is uninformative, it is necessary to extrapolate from high-dose data. The authors then removed the low-dose categories 0.10-0.20Gy and 0.20-0.30Gy by lumping together 5 dose categories to form a single 0.01-0.49Gy dose category.
- The 1995 Cardis, et al. Study of Nuclear Industry Workers in three Countries[4] reports that non-chronic lymphocytic leukemia was significantly associated with chronic low-dose occupational exposure. The authors apply a one-sided methodology to their 7 dose categories with a total of 119 deaths in order to discard the 4 dose categories with fewer observed leukemia deaths than expected. A computer simulation of 5000 deaths was then used to simulate statistical significance for the remaining 33 deaths in the 3 dose categories selected.
- The 1996 RERF Life Span Report 12. This report was used in November 1996 to mobilize support for the LNT theory. The International

Commission on Radiation Protection (ICRP) under Chairman Roger Clark and the French Society for Radiation Protection reviewed this Life Span Study of Atomic Bomb Sutrvivors which includes the 1985-1990 mortality data.[5,6] The ICRP claimed that analysis of this new data shows a statistically significant increased solid cancer mortality at doses as low as 5cSv. According to Warren Sinclair, President Emeritus of the NCRP and Chairman of the ICRP Committee 1 which analyzes results of health-effects studies, the new results "vindicate" previous recommendations to lower permissible dose limits to 2 rem/year for occupational workers and to 0.1 rem/yr for the general public. "The combination of more data points and a more precise analysis," Sinclair said, "allowed the RERF researchers to state with confidence that excess cancer risk due to radiation was observed at doses as low as 50mSv."[6] The "more precise analysis" does not use the *observed* excess solid cancer deaths but substitutes *estimated* excess deaths derived from a model fit to high doses that assumes linearity.

The report omits statistical analysis of the observed excess solid cancer deaths following exposures of 5 rem (P=0.25) and 15 rem (P=0.56) that demonstrates they are not statistically significant; the lowest significant DS86 dose for increased solid cancer mortality is 35 rem (P=0.03). The correct dose for this increased cancer mortality is considerably greater than 35 rem. The revised DS86 dosimetry used gives estimates for neutron radiation from the Hiroshima atomic bomb that are lower by an order of magnitude than both the original T65D dosimetry and the experimental values obtained from neutron activation measurements at the hypocenter that correspond to low-dose exposures.[7]

While no statistically significant data support the assumption of monotonic increased risk of cancer with increased low-dose radiation, in recent decades a considerable body of contradictory scientific epidemiologic data has accumulated.

Increased longevity and decreased cancer death rates have been observed in populations of the U.S., China, India, Austtria, and the United Kingdom exposed to high natural background radiation. Several recent epidemiologic studies with high statistical significance have reported that exposure to low or intermediate levels of radiation are associated with *decreased* mortality and/or *decreased* incidence of cancer:

- Cancer Mortality in an Irradiated Eastern Urals Population (1994).[8]
- This study reports statistically significant 28% and 39% decreases of cancer mortality in the 50cSv and 12cSv dose groups.
- Atomic Bomb Survivor Mortality from All Causes (1993)[7]
- Longevity is significantly greater in the exposed survivors than in the unexposed.
- University of Pittsburgh Residential Radon Study (1995)[9] Figure 1

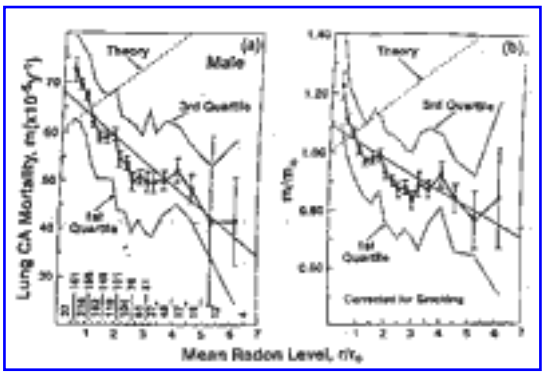

Figure 1

- A comprehensive survey that includes the effect of smoking and more than 60 other confounding factors, analyzes 89% of the U.S. population, many exposed to high residential radon concentrations, shows with very high

statistical significance, the strong tendency for lung cancer mortality to decrease as radon exposures increase, in sharp contrast to the increasing mortality expected from the LNT theory.

- U.S. Nuclear Shipyard Worker Study (1991) [10] Table 1
- The UN Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1994 reports, "The statistically significant decrease in standardized mortality ratio for deaths form all causes [0.76±0.015] cannot be due to the healthy worker effect alone, since the non-nuclear workers and the nuclear workers were similarly selected for employment and were afforded the same health care thereafter." "The type of work carried out by the three groups wsa identical, except that the nuclear workers were exposed additionally to ^{60}Co gamma-radiation."[11]
- The Canadian Fluoroscopy Study (1989) [2] Figure 2

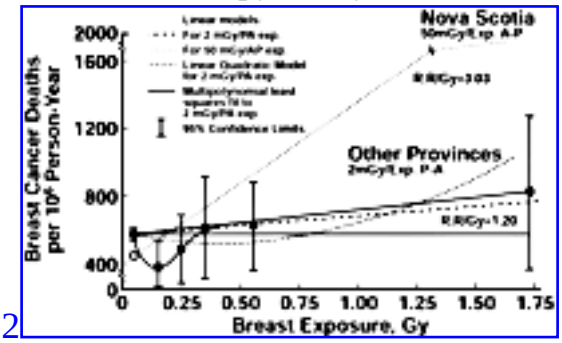

Figure 2

- Breast cancer mortality is statistically significantly decreased to 0.66 in women exposed to cumulative doses of 10-20 cGy and is decreased to 0.84 in women exposed in the 20-30 cGy dose range.

Despite almost 40 years of intensive search, the LNT theory is not supported by *any* statistically significant quantitative low-dose (e.g. <20cGy) data. On the other hand, this "presumption, based on biophysical concepts," is contradicted by the emergence during the past two decades of significant data demonstrating

risks *decrements* in response to low-dose radiation exposures. Risk *increments* response to high doses (e. g. > 1 Gy) are well documented. The matter is clearly more complex than a simplistic biophysical presumption of linearity. These observations require careful realistic scientific and public policy discussion based upon current epidemiology and molecular biology.

The complex cell circuitry signaling for growth, division, and death includes both extracellular factors and transcription factors. "...the extraordinary detail and duplicate functions of these circuits are designed so that single disruptions here and there do not create malignant growth. A cell divides without restraint only when its circuitry has been disrupted at a number of key points: multiple [persistent] mutations are required."[12]

Mis/unrepaired DNA alterations in an environment free of mutagens, occur with very high frequency. "... by fundamental limitations on the accuracy of DNA replication and repair, ...in a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being..."[13] The additional relentless continual damage of DNA by reactive oxygen metabolites (O_2^-, ^-OH, H_2O_2), comprising 2-3 percent of all oxygen consumed, and thermal instability, increases this number to about 10^{14} mutations per gene.[14,15]

"From this point of view, the problem of cancer seems to be not why it occurs, but why it occurs so infrequently. Evidently, the survival of mammals must depend on some form of double-or more than double insurance in the mechanisms that protect us from being overrun by mutant clones of cells that have a selective advantage over our healthy normal cells; if a single mutation in some particular gene were enough to convert a typical healthy cell into a cancer cell, we would not be viable organisms."[13]

Our survival depends on effective defense mechanisms that prevent (anti-oxidants, cell cycle control) and repair (DNA repair enzymes) DNA damage, and *remove* about 10^{16} potential mutations *daily* by cell cycle control, programmed cell death (apoptosis), necrosis, and the immune system (Figure 3).[11,14,15] Low dose radiation stimulates and increases the effectiveness of this DNA damage control biosystem (Figure 4).

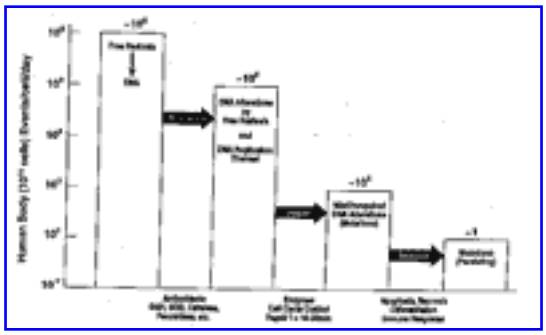

Figure 3

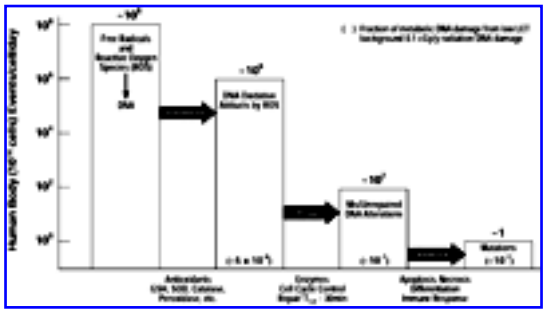

Figure 4

The progressive age-related decline of biosystem effectiveness and accumulation of mutations in stem cells is associated with an increase in the incidence of cancer with the third to the fifth power of age.[13,16-20] The low incidence of cancer under the age of 50 is

usually associated with genetic defects of the biosystem controlling DNA damage.

A whole body radiation background of 1mGy/year would produce about 10^{-7} mutations per day.[15,21] Exposure to 20cGy/year would produce $2x10^{-5}$ mutations/cell/day[15], a very small linear incremental risk of cancer would result theoretically, *assuming that the effectiveness of the biosystem controlling DNA damage remains constant*. During the past 15 years studies have shown that biosystem control of DNA damage does *not* remain constant, but adaptively responds with beneficial activity to low-dose (e.g.<20cGy), low-dose-rate (e.g. <1cGy/min) radiation as well as to low-dose toxic chemical agents.[11,16,22] As the dose increased to high dose (e.g. >1cGy) radiation levels, the DNA damage control biosystem is progressively suppressed and fails with corresponding increase of metabolic mutations.

LNT theory applied to the risk of cancer is based on two assumptions: 1) the biological response of cancer to radiation dose montonically increases, and 2) all mutations, whether induced by ionizing radiation or other agents, produce a corresponding increase in the risk of cancer, assuming the fraction of DNA damage repaired is constant with dose. These assumptions are not valid. They are contradicted, with no support, by *all* statistically significant low-dose epidemiological data and they ignore *the operative effect of ionizing radiation on the DNA damage control biosystem*. Emphasis is placed on the relative difficulty of repairing infrequent double strand breaks (0.4/cell/cSv low-LET radiation),[21] DSB produced by 0.1cSv/y gamma radiation are 1/5000 of metabolic DSB, while ignoring the daily *removal* and control of the unrepaired breaks, together with trillions of other environmental and spontaneous mutations, by the adaptive responses of cell cycle control, self programmed cell death (apoptosis), necrosis and the immune system. Disregarded are the extremely high

background of spontaneous metabolic mutations and the adaptive responses to radiation that, until they diminish with age, very effectively prevent, repair and *remove* both the spontaneous and the relatively few low-dose, low-dose-rate environmental mutations.

Contrary to the increased risks associated with injury to the DNA damage-control biosystem by high-dose radiation, this biosystem is stimulated by low-dose radiation to control even more effectively the relentless metabolic DNA damage and decrease mortality rate and the risk of cancer. These observations of fundamental *biologic* cellular functions and corresponding epidemiologic studies contradict the theoretical assumptions based on *biophysical* concepts and *exclude* a LNT dose-response relationship.

Nevertheless, since 1959 the LNT theory has remained the basic principle of all radiation protection policy. This theory is used to generate collective dose calculations of the number of deaths produced by background radiation. The increase of public fear through repeated statements of deaths caused by "deadly" radiation has engendered an enormous increase in expenditures now required to protect the public from all applications of nuclear technology: medical, research, energy, disposal and cleanup remediation. These funds are allocated to appointed committees, the research they support, and to multiple environmental and regulatory agencies. The LNT theory and multibillion dollar radiation activities have now become a symbiotic self-sustaining powerful political and economic force.

Scientific 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 adhering to non-scientific influences on radiation protection standards and practice23 that impair health care, research and other benefits of nuclear technology and waste many billions of dollars annually for protection

against theoretical risks, these resources could be used productively for effective health measures and many other benefits to society.

The views expressed in this paper are those of the author and do not necessarily reflect the views or policies of the U.S. Nuclear Regulatory Commission. The U.S. Government has the right to retain a nonexclusive royalty-free license in and in any copyright covering this article.

References

1. National Council on Radiation Protection and Measurements. *Principles and Application of Collective Dose in Radiation Protection*. NCRP Report No. **121**. Bethesda, MD. NCRP, 1995;45
2. Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, Risch HA, Preston DL. *Mortality from breast cancer after irradiation during fluroscopic examination in patients being treated for tuberculosis*. N Engl J Med **321**:1285-1289 (1989).
3. Howe GR, McLaughlin J. *Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study*. Radiat Res **149**: 694-707 (1996).
4. Cardis E., et al., *Effects of low doses and low dose rates of external ionizing radiation: Cancer mortality among nuclear industry workers in three countries*. Radiat Res **142**: 117-132 (1995).
5. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. *Studies of the mortality of the atom bomb survivors*. Report 12, Part I. Cancer: 1950-1990. Radiat. Res. 1996;**146**: 1-27.
6. Nucleonics Week. *Linear nonthreshold model said vindicated by new data*. McGraw-Hill:

1996: **37** (46): 1-3.
7. Kondo S. *Health Effects of Low-Level Radiation*. Osaka, Japan: Kinki University Press. Madison, WI: Medical Physics Publishing, 1993.
8. Jawarowski Z. *Beneficial radiation.* Nukleonika **40**:3-12 (1995).
9. Cohen BL. *Test of the Linear No-Threshold theory of radiation carcinogenesis in the low dose, low dose rate region*. Health Phys **68**:157-174 (1995).
10. Matanoski GM. Health effects of low-level radiation in the shipyard workers final report. Report No. DOE DE-AC02-79 EV10095. Washington: US Department of Energy, 1991.
11. United Nations Scientific Committee on the effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes*. New York, 1994; **Annex B**. Adaptive Reponses to Radiation in Cells and Organisms: 185-272.
12. Varmus H, Weinberg RA. *Genes and the Biology of Cancer*. New York, NY: Scientific American Library; 1993: **153**.
13. Bishop JM, Cairns J, Ellman R, Land H, Ponder B. *Cancer, Chapt. 21*. In: Molecular Biology of the Cell (Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD, eds). New York, NY: Garland Publishing, 1989: 1187-1218.
14. Billen D. Spontaneous *DNA damage and its significance for the "negligible dose" controversy in radiation protection*. Radiat Res **124**: 242-245 (1990).
15. Pollycove M, Feinendegen L. *Quantification of human total and mis/unrepaired DNA alterations: intrinsic and radiation induced*. Unpublished data.
16. Yamaoka K. *Increased SOD activities and decreased lipid peroxide in rat organs induced by low X-radiation*. Free Radical Biol Med **11**: 3-7 (1991).

17. Sohal RS, Weindruch R. *Oxidative stress, caloric restriction, and aging*. Science **273**: 59-63 (1996).
18. Lithgow GJ, Kirkwood TBL. *Mechanisms and evolution of aging*. Science **273**: 80 (1996).
19. Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. *DNA repair and aging in basal cell carcinoma: a molecular epidemilogy study*. Proc Natl Acad Sci USA **90**: 1614-1618 (1993).
20. Miller RA. *The aging immune system: primer and prospectus*. Science **273**: 70-74 (1996).
21. Ward JF. *Radiation chemical methods of cell death*. In Fielden EM, Fowler JF, Hendry JH, Scott D, eds, Proceedings of the 8th International Congress of Radiation Research, Vol II. London, England; Taylor & Francis; 1987; 162-168.
22. Makinodan T, James SJ. *T cell potentiation by low dose ionizing radiation: possible mechanisms*. Health Phys **59(1)**: 29-34 (1990).
23. Taylor LS. *Some non-scientific influences on radiation protection standards and practice*. Health Phys **39**: 851-874 (1980).

RSH > **Documents** > **Pollycove 97**

For more information please contact the RSH President and CNTS Director:
Jim Muckerheide jmuckerheide@cnts.wpi.edu

For website problems please contact the Webmaster @ CNTS

10/03/02