Regarding LNT: Scientifically Worthless and Increasingly Indefensible

TO THE NEWSLINE EDITOR: I am delighted with the commentary by Siegel, Sacks, and Greenspan in the November issue of *JNM* Newsline (2021;62[11]:17N–18N, 22N) regarding my petition and those of 2 others asking the Nuclear Regulatory Commission (NRC) to cease using the linear no-threshold (LNT) theory as the basis for radiation safety regulation. The authors did an excellent job in this commentary as part of a continuing effort over the years to refute LNT. It is shameful that government regulators have hoodwinked the entire nation with nearly 70 years of LNT-based regulations, including the corollary "as low as reasonably achievable" (ALARA) principle. The NRC-required public dose limit is set at 1 mSv, despite the fact that credible evidence of imaging-related low-dose (<100 mSv) carcinogenic risk is nonexistent. As pointed out in the commentary, NRC lacks necessary in-house expertise and therefore relies on recommendations from the equally misguided International Commission on Radiological Protection (ICRP) and National Council on Radiation Protection and Measurements (NCRP). NRC pays the NCRP for its opinion, and NCRP conveniently gives NRC the opinion it bought and paid for. (One might question the value of the NRC if it lacks the in-house expertise to evaluate radiation science.)

The LNT theory of radiation carcinogenesis is based on 4 assumptions, each of which is obviously incorrect and which together rely on illogical and circular reasoning: (1) The first assumption is that there is no such thing as repair of radiation damage. However, more than 150 genes have been found to be involved in gene repair, and in 2015 the Nobel Prize in Chemistry went to scientists who for more than 40 years had been elucidating the mechanisms of DNA repair. (2) The second assumption (which actually follows from the first) is that LNT is applicable whether a specific dose of radiation is delivered slowly over time or all at once—the putative effect is the same. We know, however, that a given quantity of radiation delivered slowly is much less damaging than the same quantity delivered all at once. Patients in radiation oncology routinely receive high doses given gradually, often over a 6-week period. If the total dose were delivered all at once, repair mechanisms would be overwhelmed and damage to normal tissue would be much greater. (3) The third assumption is that a single radiation interaction causing 1 DNA mutation can cause a fatal cancer. However, stem cells that give rise to cancer contain thousands of mutations, including numerous essential driver mutations. According to J. Michael Bishop, MD, 1989 Nobel laureate discoverer of the oncogene, "A single mutation is not enough to cause cancer. In a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being. The problem of cancer seems to be not why it occurs, but why it occurs so infrequently." (4) The fourth assumption is that no processes exist at low radiation doses that do not exist at high doses. However, at high doses repair enzymes that exist at low doses are often inhibited from being synthesized.

Let us focus on radiation hormesis at low doses: Low doses of radiation result in stimulation of enzymes that not only repair radiation damage but repair damage caused by other mutagens, the most important being oxygen—yes, oxygen. The cost of being an aerobic organism is huge. According to the late Myron Pollycove, MD, breathing oxygen causes 10,000 DNA mutations/cell/hour. One rem causes 20 DNA mutations/cell/*year*. Oxygen therefore causes 4.4 million times as many mutations per year as 1 rem. Low-dose radiation hormesis is pervasive, having been found in microorganisms, algae, plants, insects, invertebrates, vertebrates, and humans. Unlike low-dose carcinogenic risk, radiation hormesis has been demonstrated to exist.

So why have radiation professionals accepted LNT and not condemned this demonstrably false theory? Ignorance? Laziness? Fear? LNT has become an illogical religion among scientists who need to recognize their problem. It is time to stand up to the regulators, challenge the scientific organizations, and demand change. We should all better educate residents and other physicians, as well as patients, on this issue. LNT is scientifically worthless and indefensible.

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Regarding LNT: NRC Wrongfully Rejects Petitions to End LNT Model Use

TO THE NEWSLINE EDITOR: I would like to offer a historical perspective on the commentary by Siegel, Sacks, and Greenspan in the November issue of *JNM* Newsline (2021;62[11]:17N–18N, 22N) on the Nuclear Regulatory Commission (NRC) rejection of three 6-year-old petitions requesting repudiation of the linear no-threshold (LNT) model. First, I am reminded of a 1980 speech by Lauriston Taylor, who said that studies "calculating the numbers of people who will die as a result of having been subjected to diagnostic X-ray procedures [by applying the LNT model] … are deeply immoral uses of our scientific knowledge" (*1*).

In 1954, soon after President Eisenhower's Atoms for Peace Speech to the United Nations, the Rockefeller Foundation mobilized and managed a National Academy of Sciences (NAS) study of radiation effects "with particular attention to the possible danger to the genetic heritage of man" (*2*,*3*). The 10-year study, by Neel and Schull, on 75,000 children of atomic bomb survivors, showed no evidence of hereditary damage (*2*,*4*). Nevertheless, the NAS rejected these data and in 1956 recommended use of the LNT model to assess the risk of radiation-induced mutations, based largely on controversial studies that irradiated fruit flies.

I previously reviewed the 1957 study by Lewis that linked the incidence of leukemia in atomic bomb survivors to their radiation exposures (*5*). The study was flawed because it combined data in the low-dose Zone D with data in the control Zone E. This concealed the high 1.1-Gy threshold for inducing leukemia, shown in Figure 1 (*6*–*8*).

Discussions in the NCRP about this cancer risk controversy led to a compromise and the NCRP decision in 1960 to adopt policies

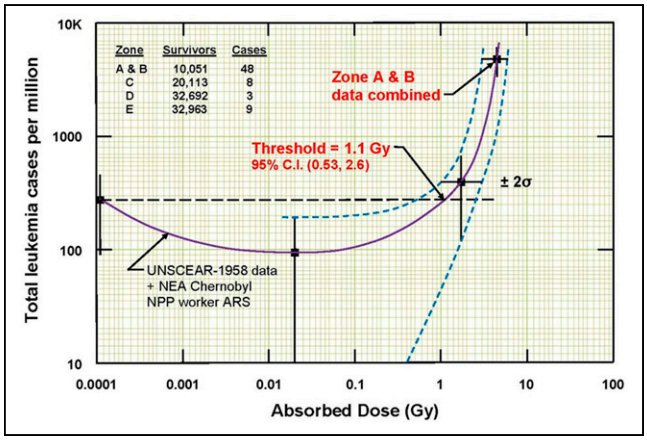

Figure 1. Graph of incidence of leukemia in 95,819 Hiroshima atomic bomb survivors versus absorbed dose, from 1950 to 1957, showing evidence of the threshold at 1.1 Gy for radiation-induced leukemia (*7*). UNSCEAR = United Nations Scientific Committee on the Effects of Atomic Radiation; NEA = OECD Nuclear Energy Agency; NPP = nuclear power plant; ARS = acute radiation syndrome. Blue broken lines show 2-σ error band.

governed by the precautionary principle and the "as low as reasonably achievable" (ALARA) benchmark. This policy included using the LNT model to estimate the risk of radiation-induced cancer (*9*). The NCRP decision was based on widespread public concern over the effects of radiation from fallout and the possibility of new information regarding effects on humans (*10*). The United States and other countries followed the NCRP policy.

This policy has not changed in more than 61 years, despite evidence in 1960 and much more evidence today that contradicts the LNT model and demonstrates that low doses of radiation benefit health (*7*). It was wrong for the NRC to reject the petitions that requested amendment of 10 CFR Part 20 to protect people based on scientific evidence that contradicts the LNT hypothesis. Instead of following the antinuclear NCRP policy based on taking precautions against fearful myths, the NRC should recognize the evidence of radiation's beneficial health effects for exposures that are below thresholds for detrimental effects (*11*).

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Regarding LNT: The Negative Consequences of Reliance on LNT/ALARA

TO THE NEWSLINE EDITOR: I was intrigued by the commentary from Siegel, Sacks, and Greenspan (*1*) regarding 3 petitions (*2*) requesting that the Nuclear Regulatory Commission (NRC) cease using the linear non-threshold (LNT) hypothesis as the basis for radiation safety regulations. These regulations accept the LNT hypothesis and its "as low as reasonably achievable" (ALARA) partner principle. Any challenge to the established NRC dogma merits a thorough and rigorous discussion. Unfortunately, the NRC relied on only a portion of relevant information that supported their position and failed to consider the complete set of data that offers a scientific basis for rejecting the LNT hypothesis. Arguments against the NRC's rejection have considerable merit and must not be ignored by regulators.

By its very nature LNT/ALARA focuses on radiation detriment and not the collective set of repair mechanisms that mitigate the effects of ionizing radiation, particularly at low doses. The NRC does not properly evaluate the well-known repair and mitigative mechanisms, including adaptive response, the human immune system, and DNA repair mechanisms. In addition, hormesis and radiation damage thresholds are not considered (*3*,*4*). Although these comments outline a limited number of concerns, the case against LNT/ALARA is strong (*1*,*2*). In addition, there are numerous negative consequences of perpetuating the reliance on LNT/ALARA including:

(1) LNT/ALARA creates an atmosphere that fosters and perpetuates radiophobia and inhibits research using low-dose radiation in the detection, prevention, and treatment of cancer and other diseases, including COVID-19. Unwarranted fears have effectively retarded research and could result in missed diagnoses in instances where imaging doses are too low to produce adequate tissue resolution (*5*).

(2) The continued development and utilization of nuclear power in the United States and Western Europe have been inhibited by LNT/ALARA exaggerations of the impacts of nuclear accidents. These mischaracterizations reinforce unjustified fears regarding the detrimental effects of radiation (*6*,*7*) and inadvertently promote the use of higher-polluting energy-generating sources.

(3) Increased regulation of radiation and radioactive materials and the associated costs to implement LNT/ALARA compliance further dampen the expansion and use of the beneficial uses of nuclear technology.

(4) Nuclear facilities, particularly in the commercial nuclear power reactors and fuel cycle areas, devote significantly more resources and attention to imagined safety efforts driven by LNT/ALARA than to real industrial safety hazards that have injured workers.

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processed from targets irradiated at Brookhaven, which produces ^{225}Ac using a high-energy proton beam. "We demonstrated that the accelerator route can generate about 60% of the current annual supply of ^{225}Ac in just 12 days," said Dmitri Medvedev, a scientist in the Brookhaven Collider Accelerator Department.

In 2020, FDA acknowledged receipt of a drug master file for the Tri-Lab accelerator-produced ^{225}Ac, outlining details about the facilities and processes used in manufacturing, processing, packaging, and storing the radioisotope to ensure that the product meets specifications. "The drug master file is one step forward toward this ultimately being used in an FDA-approved product," said Roy Copping, who leads the Tri-Lab production program from the ORNL side. Researchers at ORNL are currently looking at 2 ways to further increase output: processing batches more frequently and processing larger targets. As part of the Tri-Lab effort, a research and development team developed in-cell technology to manage gas created in the production process. The team began developing the technology in November 2020, spent several months testing it outside the hot cell, then implemented it in the hot cell in April 2021. The technology benefits production at ORNL and is extensible to future target processing at Brookhaven and Los Alamos. For more information about the Tri-Lab effort, see: https://www.isotopes.gov/sites/default/files/2021-01/Actinium225Brochure%20-%20FINAL%20for%20web_sm.pdf.

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Gene Therapies for Rare Diseases

On October 27 the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), 10 pharmaceutical companies, and 5 nonprofit organizations announced a partnership to accelerate development of gene therapies for individuals who suffer from rare diseases. Although ~7,000 rare diseases have been identified, only 2 heritable diseases currently have FDA-approved gene therapies. The new Bespoke Gene Therapy Consortium (BGTC), part of the NIH Accelerating Medicines Partnership program and project-managed by the Foundation for the National Institutes of Health, is intended to optimize and streamline the gene therapy development process.

"Most rare diseases are caused by a defect in a single gene that could potentially be targeted with a customized or 'bespoke' therapy that corrects or replaces the defective gene," said NIH Director Francis S. Collins, MD, PhD. "There are now significant opportunities to improve the complex development process for gene therapies that would accelerate scientific progress and, most importantly, provide benefit to patients by increasing the number of effective gene therapies."

Gene therapy development for rare diseases is time consuming and expensive. NIH cited numerous challenges, including limited access to tools and technologies, lack of standards across the field, and a "1-disease-at-a-time" approach to therapeutic development. A standardized therapeutic development model that includes a common gene delivery technology (a vector) could allow for a more efficient approach to specific gene therapies, saving time and cost.

A clinical component of BGTC-funded research will support between 4 and 6 clinical trials, each focused on a different rare disease, expected to be rare, single-gene diseases with no gene therapies or commercial programs in development but with substantial groundwork already in place to rapidly initiate preclinical and clinical studies. For these trials, the BGTC will aim to shorten the path from studies in animal models of disease to human clinical trials. The BGTC also will explore methods to streamline regulatory requirements and processes for FDA approval of safe and effective gene therapies, including developing standardized approaches to preclinical testing.

NIH and private partners will contribute ~$76 million over 5 years to support BGTC-funded projects. This includes about $39.5 million from the participating NIH institutes and centers, pending availability of funds. Additional information and a complete list of participating NIH entities, industry partners, and nonprofit groups is available at: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium.

National Institutes of Health

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(5) Following the Fukushima-Daiichi accident, more than 100,000 individuals were evacuated and forced to abandon their family farms, homes, and jobs. The physical and psychological harm caused by these LNT/ALARA–driven evacuations vastly outweigh the imagined hazard of low levels of ionizing radiation.

I offer the following rallying cry to those seeking to use reason and scientific evidence to overthrow the LNT/ALARA dogma (with apologies to Winston Churchill): We shall challenge the proponents of LNT/ALARA in scientific journals, at conferences, in the media, on the internet, in public forums, and in classrooms. We shall defend valid science, whatever the cost may be.

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