The History of the Linear No-Threshold Model and Recommendations for a Path Forward

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Abstract—**The intent of this paper and the accompanying video series is to inform the scientific community about the historical foundations that underpin the linear no-threshold (LNT) model's use for cancer risk assessment. There is a clear distinction here: this effort is about the history of how LNT came to be the regulatory paradigm and model for cancer risk assessment that it is today and not a discussion of the pros and cons of the LNT model. The overarching goal of this effort is to reframe the conversation around low-dose response models in light of this history and to determine how this history influences the scientific understanding of low-dose radiation responses. The timing of this series is intentional, as the International Commission on Radiological Protection (ICRP) has embarked on a mission to review the entire system of radiation protection. This effort necessarily requires rigorous scientific debate that must be based in fact. The history of the LNT model is paramount to this discussion, and it warrants consideration. Unfortunately, rather than engendering respectful debate, the topic of cancer risks associated with low dose radiation exposures has forged two disparate and sometimes contentious camps: (1) low doses, no matter how low, present some form of health risk and (2) an alternative model better represents the actual risks. The video series, conceived by John Cardarelli II, current President of the Health Physics Society (HPS), features Edward Calabrese, professor of toxicology in the School of Public Health and Health Sciences at the University of Massachusetts at Amherst, being interviewed by HPS Past-President Barbara Hamrick, CHP, JD, with support from Daniel Sowers, the Chair of the HPS Public Information Committee, and HPS Executive Director Brett Burk. Emily Caffrey, the Chief Editor of our Ask-the-Experts website (https://hps.org/publicinformation/ate/), was invited to watch the completed series as an independent peer reviewer. Further, an email address, factcheck@hps.org, was created to allow for peer-review by the scientific community to facilitate ongoing discussion and allow for corrections to the record as necessary. It is the sincere hope of this team that this work inspires new discussions about the system of radiological protection. We encourage everyone in this field to watch all 22 episodes to be informed about the underpinnings of current regulatory policy in the US.**
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INTRODUCTION

THE INTENT OF this forum article and the accompanying video series is to inform the scientific community about the historical foundations that underpin the linear no-threshold (LNT) model's use for cancer risk assessment (available at http://hps.org/hpspublications/historylnt/index.html). The timing of this series is intentional, as the International Commission on Radiological Protection (ICRP) has embarked on a mission to review the entire system of radiation protection (Clement et al. 2021). The Health Physics Society (HPS) provided comments to ICRP in 2021. This effort necessarily requires rigorous scientific debate that must be based in fact. The history of the LNT model is paramount to this discussion, and it warrants consideration. Unfortunately, rather than engendering respectful debate, the topic of cancer risks associated with low-dose radiation exposures has forged two disparate and sometimes contentious camps: (1) low doses, no matter how low, present some form of health risk and (2) an alternative model better represents the actual risks. HPS position statements have supported the latter position for more than 20 y. These are summarized in 2020 and 2021 letters from HPS Past-President Eric Goldin, CHP, to the International Radiation Protection Association (IRPA) in response to their request for associate member input into the ICRP review efforts.

Following Comte's mantra "To understand a science, it is necessary to know its history," a team was developed to understand and communicate how these differing views came to fruition. The end result was a video series, conceived by John Cardarelli II, CHP, Certified Industrial Hygienist, Professional Engineer. The series features Edward Calabrese, a professor of toxicology in the School of Public Health and Health Sciences at the University of Massachusetts at Amherst, being interviewed by HPS Past-President, Barbara Hamrick, CHP, JD, with support from the Chair of the HPS Public Information Committee Daniel Sowers, CHP, and HPS Executive Director Brett Burk. Emily Caffrey, CHP, the Chief Editor of the HPS Ask-the-Experts website, was invited to serve as an independent peer-reviewer of the video series.

Edward Calabrese has spent the better part of a 50-y career researching and reconstructing the history of the LNT model, including going so far as to purchase copious personal letters between Nobel Prize laureate Hermann J. Muller, his best friend Edgar Altenburg, all the members who served on the first National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) genetics panel, and numerous others relevant to the historical LNT story. Calabrese has published over 1,000 papers in peer reviewed journals and 12 substantial toxicology/risk assessment textbooks. He is co-editor of over 24 books and continues to serve on numerous major national/international committees, including a series of National Academy of Sciences (NAS) committees, since the early 1980s. Edward Calabrese is a traditionally trained toxicology professor who is not afraid to challenge the status quo. His efforts have resulted in an impressive set of honors, including the Marie Curie Prize and an honorary doctorate from McMaster University. While there are many other accomplished scientists and historical scholars who have addressed the history of the dose response in some manner, Calabrese is unique in his depth, range, the striking nature of his discoveries and assertions, clarity of analysis, and willingness to provide documentation for each episode as required by HPS in the months following the interview.

The team arrived in Amherst in October 2021 for 14 h of taping, with no questions provided in advance and a very demanding schedule to follow. No member of the team had ever met Edward Calabrese before the interview meeting. It was an important two full days, with Calabrese engaging in the many hours of taping without referring to notes. He has not been financially compensated for activities associated with the documentation, including preparation, interviews, and considerable after-interview hours providing documentation and other related issues by HPS. The result of that interview with Edward Calabrese is a 10-h, 22-episode series titled, “The Historical Foundation of the Linear No-Threshold Model.” The series was intended to be about three to five short videos describing how and why the LNT model serves as the fundamental model for cancer risk assessment. The project expanded after learning a history that many in the radiation protection profession may have never been taught regarding surprising, powerful, and disturbing details that included several Nobel Prize laureates, the influence of money, scientific integrity issues, ethical and moral dilemmas, and scientific misconduct.

The distilled message of Edward Calabrese is that the scientific community made a fundamental mistake on the nature of the dose response curve—a mistake built on scientific errors, profound bias, professional self-interest, and scientific misconduct. This mistake led our scientific community and regulatory agencies to incorporate an LNT model, making it the default cancer risk assessment model. It is a shocking and highly-referenced expose that should be considered by the ICRP in their review of the entire radiation protection system and should prompt the scientific, regulatory, and legislative communities to investigate whether this history warrants changes to policies that rely on the LNT model. We encourage everyone in this field to watch all 22 episodes and draw their own conclusions.

A BRIEF SUMMARY OF THE HISTORY OF THE LNT MODEL

The history of the LNT model has been greatly influenced by the long reach of Hermann J. Muller, the 1946 Nobel Prize recipient, and his many prestigious colleagues in the field of radiation genetics (Episodes 2 and 3). Prominent scientists suggested that he may have confused an observation of a transgenerational phenotype change with a gene mutation mechanism (Episodes 4 and 5) using very high doses and dose-rates of x rays (e.g., at least 810 R within 12 min). The concept of genetic repair mechanisms was unknown in the 1930s, despite the understanding of evolutionary biology. Muller’s findings were published in *Science* without accompanying data and thus avoided the peer review process (Episode 4). Muller nonetheless received great acclaim and created a false narrative that he produced gene mutation. It took some 30 y before Muller was forced to publicly admit that he was wrong but only after he had received the Nobel Prize some 10 y before (Muller 1956).

This confusion and the conclusions drawn in its wake had a profound impact on the assumed nature of radiation dose response, which eventually led to the LNT-single hit model lacking the capacity for repair (Episode 6). This caused radiation geneticists to believe all genetic damage was cumulative, irreparable, and irreversible. This flawed perspective transformed the field of radiation protection and created a vehicle for an ideology that has influenced governmental policies, educational messages, research agendas, technologies, social programs, individual lifestyle decision-making, and, of course, cancer risk assessment. Personal letters among the NAS BEAR genetics panelists and transcripts of their meetings showed that some members of the radiation genetics community had a vested interest in maintaining this ideology so that they would continue to receive research funding. This same self-serving game plan was seen in multiple key scientific pressure points where Muller was present, always protecting his gene mutation error and the LNT concept. Most visible was when Muller misled the Nobel Prize audience in his December 1946 acceptance lecture by stating there is “*…no escape from the conclusion that there is no threshold dose….*” (Muller 1946). He based this on the flawed and, once again, non-peer reviewed research of one of his Ph.D. students while ignoring a key threshold finding of a then-recently completed study by Ernst Caspari, which Curt Stern shared with Muller on 6 November 1946. Muller responded to Stern on 12 November 1946, one month before his Nobel lecture, stating that he could not find fault with the Caspari study within his role as a paid consultant to the research (Episode 8).

There is further evidence of flaws in the system as the three studies conducted by Delta Uphoff and Curt Stern during the Manhattan Project were used to "…save the [single] hit theory" (Episode 9). Stern used Uphoff's three studies along with two other previously published studies (i.e., Spencer and Caspari) to conclude an LNT response in a short "meta-analysis" paper in *Science*. In it, Stern promised to publish "a more detailed account of the work" by Uphoff but failed to do this. In fact, the two chronic dose-rate studies by Uphoff that attempted to discredit Caspari's chronic study (threshold finding) were never published and have not been found for 70 y. The remaining third experiment of Uphoff was an acute study and was never published in the peer-reviewed literature but exists only as an interim document submitted to the funding agency. Nonetheless, Stern's one-page paper that summarized the five Manhattan Project studies advocating an LNT response model became one of the most cited and important papers that led the US government to accept the LNT model for cancer risk assessment (Uphoff and Stern 1949).

Above-ground nuclear weapons testing and the radioactive fallout in the US and across the globe raised public concern. Shortly after the Castle Bravo nuclear test on Bikini Atoll in 1954, the Rockefeller Foundation wrote to President Eisenhower and offered to pay for a study to understand the possible dangers associated with radioactive fallout in the environment and humans. This presented an opportunity for the radiation genetics community to challenge the credibility of the radiation experts at the Atomic Energy Commission (AEC), who supported a threshold model, by suggesting the fallout would cause birth defects based on an LNT model (Episode 10). These challenges, along with President Eisenhower's approval and Rockefeller Foundation funding, led to the US NAS creating six panels to advise the country on the concerns of nuclear energy and weapons, including a most crucial and visible genetics panel. These suggestions became a striking characteristic of the US NAS BEAR 1 genetics panel led by a non-geneticist and Director of Research for the Rockefeller Foundation (Episode 11). Surprisingly, this panel chose not to review 10 y of human data on genetic damage from the Japanese atomic bomb survivors despite their desire to know more about effects on humans. That study, led by James Neel, himself a BEAR genetics panel member, found no genetic effects in the population. Muller commented that they "*... should beware of reliance on illusionary conclusions from human data, such as the Hiroshima-Nagasaki data, especially when they seem to be negative"* (BEAR 1955). So the BEAR Panel decided not to discuss the only human study conducted to date and instead based their LNT recommendation upon fruit fly research using Spencer's acute study and the unpublished and non-peer reviewed Uphoff and Stern studies (Spencer and Stern 1948; Uphoff and Stern 1949), ignoring the threshold-findings of Caspari. Today, there remain no observable genetic effects in humans resulting from the radiation exposure studies of atomic bomb survivors (REFR 2022).

During the genetics panel discussion, each of the 12 geneticist members was charged with independently estimating the number of birth defects resulting from a gonadal dose of 0.1 Gy (Episode 12). They thought that if their independent estimates converged, then it might strengthen their case for shifting from a threshold model to an LNT model. In fact, three of the 12 geneticists refused to take on this challenge, and another three members, who had the lowest estimates, had their results removed in an effort to reduce uncertainty. The reason for the removal was to enhance the credibility to the public of their recommendation and masked profound individual uncertainties and great differences in damage estimates between the geneticists. The concern was voiced among the panelists that the public would be reluctant to follow their recommendation if the uncertainties were so great. Removing the three lowest estimates reduced the difference between estimates from about 4,000-fold to about 750-fold. Their resultant paper makes no mention that six members either refused to participate in the exercise or had their estimates removed. Inexplicably, the *Science* publication asserted that six geneticists took up this challenge when in fact three others refused and another three had their estimates removed (BEAR 1956). This is a clear misrepresentation of the research record. Further, the panelists still felt that the uncertainty was too large, and they agreed to state that the uncertainty was about a 100-fold difference without providing a justification. That final decision was approved by the President of the NAS.

The genetics panel produced their report, and it was published in *Science* (BEAR 1956) along with a separate Report to the Public, which received world-wide attention by major news outlets (Episode 13). The impact of their conclusions, combined with a massive media campaign, resulted in political, structural, and administrative changes throughout the US government. The functions of protecting public health were eventually removed from the AEC by President Eisenhower and given to the newly created Federal Radiation Council (FRC) in 1959. The FRC became dominated by LNT-supporting BEAR 1 genetics panel members. Under their influence, the federal government switched from a long history of the use of the threshold model to the adoption of the LNT model. These responsibilities were eventually given to the US Environmental Protection Agency in 1970.

Neel's study on atomic bomb survivors was shared with a British committee addressing the same question as the NAS BEAR committee, but the British committee chose to include it in their deliberations and final report. Both the American and British reports were published at the same time in 1956, but they had differing views on the genetic effects associated with radiation exposure. The American report strongly supported an LNT model, whereas the British report was more reserved. James Neel later shared his views about the need to include human studies during a 1956 conference in Copenhagen, Demark, that also included a meeting of the World Health Organization. His human-study conclusions were a direct challenge to Muller's LNT theory and its reliance on fruit fly data to estimate human risks to radiation, so Muller attempted to prevent Neel's presentation from being included in the conference proceedings until a British contingent of scientists strongly objected, threatening to remove their reports if Neel's was excluded (Episode 15; Neel 1959).

Efforts to reduce tensions between Neel[2] and Muller (1946) failed after they met months later in Oak Ridge, TN. The work of the BEAR Committee continued, but its Chair, Warren Weaver, resigned. He initially told the committee that there would be a very substantial amount of free support for genetics research if at the end of this work a real case is made for LNT. He even stated *"…and here is the dangerous remark—don't misunderstand me. We are just all conspirators here togethe*r" (BEAR 1955). It appears that research funding was a motivating factor in determining the conclusions of the influential American report.

In 1956, George Beadle was named the new Chair of the genetics panel and came up with a new approach to bring the fractured committee members together. He challenged professors at his university (CalTech) to look into cancer effects instead of genetic effects (Episode 16). Leukemia, with its short latency period, was the ideal cancer to study. Edward Lewis, a fruit-fly geneticist at CalTech, took up this challenge. Under Beadle's guidance, Lewis had access to unpublished data on the atomic bomb survivors and extended the subjects of his study to include three other populations: radiologists, ankylosing spondylitis patients, and children treated with x rays to reduce an enlarged thymus gland. Lewis' paper (Lewis 1957) received support and praise by members of the genetics panel and was published in *Science,* concluding that there is a linear relationship between radiation exposure and leukemia. Lewis does not share the limitations of these three additional datasets, whose authors explicitly warned against using these data to address cancer risk at low doses. He provides no explanation for his exclusions. His paper received unprecedented endorsement by the Chief Editor of *Science*, and within a few weeks, he was testifying in front of Congress. His paper was discussed on *Meet the Press*, a national syndicated news program. Lewis's 1959 congressional testimony described these and additional studies as supporting his LNT theory when, in fact, they did not.

In 1958, Bill and Liane Russell from Oak Ridge National Laboratory conducted research on hundreds of thousands of mice and discovered a genetic repair capability (Episode 19) that had never been observed before. By 1960, a near-final draft of the second report from the BEAR genetics panel excluded this significant finding, causing several panel members, including Muller himself, to write in protest. Ultimately, the final report included this finding and officially acknowledged the existence of genetic repair.

Despite the acknowledgement of genetic repair, the newly formed NAS Biological Effects of Ionizing Radiation (BEIR) Committee in 1970 recommended the continued use of the LNT model for cancer risk assessment (Episode 20). This recommendation was based on the Russells' work with mice in which the male mice did not show a clear threshold response while the female mice did (Russell 1969). That said, there was a 70% decrease in the effects in male mice between an acute vs. chronic exposure to radiation. Despite these findings, the LNT model was recommended in the 1972 BEIR Committee report and adopted by the US EPA in 1975.

In 1995, a geneticist and former graduate student of Bill Russell, Paul Selby, found an error related to cancer clusters in the original Russell data that dated all the way back to 1951 (Episode 21). He reported this to the US Department of Energy, and an ethics investigation followed that ultimately caused the Russells to correct the record. The dispute continues between the amount of correction that should have been made, but it was clear that a correction was necessary. Had this error been known by the BEIR committee in 1972, it is possible that the radiation protection paradigm in use today might look very different (e.g., threshold model).

DISCUSSION AND A PROPOSED PATH FORWARD

As scientists, it is our hope and belief that science is a self-correcting field based on testable hypotheses. For the LNT model, this does not seem to be the case as the evidence that the science associated with low-dose radiation exposure and potential health effects was flawed and slipped through the cracks, never following this self-correcting rule of the scientific process. The end result is the use of the LNT model as the default null hypothesis, which is contrary to the traditional study design where the null hypothesis of "no effect associated with radiation exposures" is either accepted or

[2] Neel JV. Letter to GeorgeW. Beadle, American Philosophical Society. 14 September 1959. Neel File.

rejected. This represents a logical fallacy and places the burden of proof always on any alternate hypothesis.

This forum article, the video series, and the supporting documentation bring to light the convoluted history of LNT that is replete with scientific misconduct and a lack of peer-review. Knowledge based on sound science should guide us in making appropriate recommendations associated with radiation exposures. Our Society and other international organizations have stated that reliance on the LNT model foments fear, increases environmental cleanup costs, may affect decisions to obtain potential life-saving medical examinations due to an unreasonable fear of initiating cancer, and adversely impacts the commercial nuclear power industry by increasing costs from construction through decontamination and decommissioning of nuclear power plants. The team recommends a series of steps to advance the science of low-dose radiation response:

- Re-examine the current regulatory and cancer risk models by replacing the most fundamental assumption (that any increase in dose is an increase in risk) with a true null hypothesis (that there is no effect);
- Work toward an understanding of the low dose response using an integration of evolutionary biology principles and current epidemiological research findings;
- Re-evaluate the regulatory paradigm of "as low as reasonably achievable" (ALARA) to determine its merit on a scientific basis; and
- Harmonize radiation protection by considering all dose-response models and applying the LNT model only to the point where adverse health effects are observed (e.g., above 100 mSv or 50 mSv y^{-1}).

Moving forward, these points will help the radiation protection community strengthen future recommendations by relying on a stronger scientific foundation. It is the authors' hope that this video series will finally put the LNT model up against scientific scrutiny, albeit 70 y past due, and the national and international community will reassess regulations to provide for optimized public health protection based on an integration of evolutionary biology principles and current epidemiological research findings, rather than flawed, ideologic science.

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