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Review article

LNT and cancer risk assessment: Its flawed foundations part 1: Radiation and leukemia: Where LNT began

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ABSTRACT

This paper evaluates the scientific basis for the adoption of the linear non-threshold (LNT) dose response model for radiation-induced leukemia. This LNT risk assessment application for leukemia is significant because it: (1) was generalized for all tumor types induced by ionizing radiation and chemical carcinogens at relatively high doses and; (2) it was based on the mechanistic assumption of low dose linearity for somatic cell mutations as determined from responses in mature spermatozoa of fruit flies. A serious problem with the latter assumption is that those spermatozoa lack DNA repair. The acceptance of the LNT dose response model for cancer risk assessment was based on the convergence of recommendations of the BEAR I Genetics Panel (1956a) for reproductive cell gene mutations and those of Lewis (1957a) for somatic cell mutation and its capacity to explain apparent and/or predicted linear dose responses of ionizing radiation-induced leukemia in multiple and diverse epidemiological investigations. Use of that model and related dose response beliefs achieved rapid, widespread and enduring acceptance in the scientific and regulatory communities. They provide the key historical foundation for the sustained LNT-based policy for cancer risk assessment to the present. While previous papers in this series have challenged key scientific assessments and ethical foundations of the BEAR I Genetics Panel, the present paper provides evidence that Lewis: 1) incorrectly interpreted the fundamental scientific studies used to support the LNT conclusion even though such studies show consistent hormetic-J-shaped dose response relationships for leukemia in Hiroshima and Nagasaki survivors; and, 2) demonstrated widespread bias in support of an LNT conclusion and related policies, which kept him from making an objective and fair assessment. The LNT recommendation appears to have been uncritically accepted and integrated into scientific and regulatory practice in large part because it inappropriately appealed to existing authority and it garnered the support of those who were willing to risk greatly exaggerating the public's fears of environmentally-induced disease, such as enhanced risk of leukemia, with the goal of stopping the atmospheric testing of atomic bombs. Adoption of the LNT recommendation demonstrated extensive penetration of ideological influence affecting governmental, scientific and regulatory evaluation at the highest levels in the United States. This paper demonstrates that the scientific foundations for cancer risk assessment were inappropriately and inaccurately assessed, unethically adopted and require significant historical, scientific and regulatory remediation.

1. Introduction

Much has been written about the historical significance of the 1956a NAS BEAR I Genetics Panel report that recommended a switch from a threshold basis to a LNT dose response model regarding radiation risk assessment for gene mutation of reproductive cells. This recommendation provided the foundation for generalizing the linearity of radiation-induced gene mutation to somatic cells for cancer risk assessment (NCRPM, 1960; Calabrese, 2019a,b). Generally overlooked in such historical analyses has been the significant impact of Edward B. Lewis, professor of Biology at the California Institute of Technology (Cal Tech). Lewis was significant in multiple ways, stemming from an article he published on May 17, 1957a in *Science*. That article claimed that ionizing radiation-induced leukemia in a linear dose response fashion based on four complementary areas of converging clinical and epidemiological evidence, highlighted by the leukemia incidence in survivors

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of the atomic bomb explosions in Japan.

The impact of his paper became evident immediately since it was accompanied by a highly favorable and national priority-oriented editorial endorsement. In his 1957 editorial entitled "Loaded Dice," Graham DuShane[1] wrote that **"E.B. Lewis shows that there is a direct linear relation between the dose of radiation and the occurrence of leukemia … Thanks to Lewis, it is now possible to calculate-within narrow limits-how many deaths from leukemia will result in a population from any increase in fallout or other sources of radiation".** One week later the Lewis paper became the subject of discussion/debate in the prestigious nationwide Sunday morning program, *Meet The Press* (Lipshitz, 2007). Soon thereafter, on June 3, 1957, Lewis (1957b) testified before Congress emphasizing his belief in LNT and concerns with its public health implications. One week later, on June 10th, *Life Magazine* published a major story based on the Lewis paper, entitled "A Searching Inquiry in Nuclear Perils."[2] Later that year he received an appointment to the prestigious National Committee for Radiation Protection and Measurements (NCRPM). The culmination of this appointment was the first recommendation by a leading national advisory group to apply LNT for cancer risk assessment, overturning the long-standing dominance of the threshold model (NCRPM, 1960; Calabrese, 2019b).

During the period of research and manuscript development (1955–1957), Lewis communicated with Linus Pauling, the 1954 Nobel Prize Laureate in Chemistry, on cancer risk assessment for radiation, supporting Pauling's recommendation to end atmospheric testing of nuclear weapons, a position that led to Pauling receiving his second Nobel Prize, the Peace Prize in 1962. Thus, for a brief period, the unassuming Ed Lewis transformed himself and the field of cancer risk assessment while powerfully impacting world politics. While Pauling received the Nobel Peace Prize for his leadership to end atmospheric testing, nuclear fallout and to secure a Test Ban Treaty, his arguments depended to an important extent on the research of Lewis, which makes one wonder why the Prize was not shared.

The present paper evaluates how this lab-based *Drosophila* geneticist with no experience in radiation (i.e., chemistry, biology and dosimetry), epidemiology, cancer research, leukemia or risk analysis became motivated from his narrowly focused laboratory microcosm such that he could successfully challenge scientific beliefs and regulatory policies concerning ionizing radiation-induced cancer, especially leukemia, at low doses. Wrapped up in this story is the mythology of Edward Lewis as a non-biased professorial seeker of truth and protector of public health. This belief in the character of Lewis was important at that critical time, as it gave credence to his science and authenticity to his perspectives. This myth is examined through the lens of those who knew Lewis well and via his writings, testimonies and correspondence in an effort to gain insight into his character and how it may have affected his leadership on the LNT-cancer issue. Within that context, this evaluation explores the impact of influential leaders of the radiation genetics field such as Curt Stern and Hermann J. Muller on scientific and policy decisions affecting the Lewis (1957a) publication. The paper also assesses the implications of Lewis taking on new fields without collaboration, and whether he did this correctly. In the end, this analysis considers whether Lewis should be viewed as fair-minded and competent, biased and scientifically flawed, or somewhere in between. That assessment is important for determining whether his approach for assessing cancer risk assessment was appropriate. This question is not just an academic exercise since Lewis' reach has been long, extending nearly seven decades, ensuring that the US and the world would adopt and retain linearity for cancer risk assessment.

2. Edward B. Lewis[3] and His influence on cancer risk assessment

Edward B. Lewis became interested in science and fruit flies while in high school and took these interests to the University of Minnesota (Lipshitz, 2004; Lewis, 2004). While there, he had the good fortune of having his fruit fly interest converge with that of Professor Clarence Oliver, who received his Ph.D. from the University of Texas under the direction of Hermann Muller (Nobel Prize, 1946). Oliver's Ph.D. research was very significant to Muller, and eventually Lewis, as Oliver demonstrated a linear dose response for X-ray induced genetic damage (Calabrese, 2009, 2013a,b). These findings became the scientific basis for Muller's belief in the linear dose response for radiation-induced mutation and provided the framework for Muller creating, in 1930, the phrase "The Proportionality Rule" for what would become the linear dose response (Calabrese, 2019a,b). Lewis took his Oliver-based research inspiration to Cal Tech where he undertook a Ph.D. in fruit fly genetics under Alfred Sturtevant, who had been a fellow graduate student with Muller at Columbia University, with both working under the direction of Thomas Hunt Morgan (Nobel Prize, 1936). Morgan left Columbia University for none other than Cal Tech. In this close-knit world of fruit fly genetics, Morgan would retire from Cal Tech in 1942, which was the year when Lewis received his Ph.D. Thus, even from the start of his academic career Ed Lewis was never very far from the LNT concept.

[1] Graham DuShane, the editor-In-chief of *Science*, was an expert on the embryology of amphibians, not radiation, cancer, dose response or risk assessment. Yet, he felt confident enough on the complex issues of the Lewis (1957a) paper to write a definitive editorial that provided Lewis and his article all the credibility needed to be taken seriously at the highest levels of science and policy. Given his lack of background and experience in these areas, it raises the question of whether DuShane had the idea for the editorial and whether he wrote it. Of potential significance is that one of the only six editors of *Science* at the time of Lewis' (1957a) paper was Bentley Glass, Ph.D. in genetics from the University of Texas with Muller as his advisor, member of the radiation geneticist establishment and the BEAR I Genetics Panel, a committed LNTer and a very connected scientist. Given the limited number of *Science* editors at that time, it is likely that the review of the Lewis manuscript (if there was one) was influenced by Glass. Further, Glass may have had a role in conceptualizing, writing or fine-tuning the DuShane editorial. While this perspective is speculative these questions are open to further study and clarification. Several months after the Lewis (1957a) paper, Glass published a follow up paper in *Science* entitled "Genetic Hazards of Nuclear Radiation" reinforcing the Lewis linearity conclusions. In this paper Glass (1957) stated "Recent studies by E. B. Lewis on the origin of leukemia … …suggest that … radiation-induced mutations, seem to increase linearly with the dose of ionizing radiation and without sign of a threshold". He then further stated that such cancers "may result from the induction of mutations by radiation and their accumulation in somatic cells". Thus, there is little doubt that Lewis and Glass were in full agreement on the key issues of the Lewis paper and that Glass was strategically placed to influence the acceptance of LNT and to promote that agenda within the broader scientific community.

[2] In his dissertation on the "fallout debate" Christopher Jolly (2003) (page 486) noted that "Despite the disapproval of many in the medical community, Lewis' paper became the basis for many scientists' public pronouncements about somatic mutation effects of low-level radiation. Along with the 1956b BEAR Pathology report, the paper (Lewis, 1957a) was one of the more important documents in the fallout debate. In addition to serving as a lightning rod for the public controversy, Lewis' paper also helped to shape the direction of planned research on radiation effects …. .".

[3] Lewis was awarded the Nobel Prize in Biology and Medicine in 1995 for research on basic genetic mechanisms in *Drosophila*.

As Lewis was being drafted into the US military to become a meteorologist for the duration of World War II, he was promised a faculty position by the president of Cal Tech upon his return. After the war and a subsequent post-doctoral experience (1947–1948) in the UK, he returned to Cal Tech to begin his professorial career. Lewis was soon promoted from assistant to associate professor in 1949 and then to full professor in 1956. While Lewis was not inclined to scientific and public policy activism, he found himself working within such a culture at Cal Tech from the early-mid 1950s into the 1960s, some of which resonated with his scientific interests (Caron, 2003). At the center of this activism were Linus Pauling, Chair of Chemistry and Chemical Engineering, and two highly regarded geneticists, Alfred Sturtevant and George Beadle (1958-Nobel Prize in Biology and Medicine), both future members of the BEAR I Genetics Panel. They both knew Lewis well. Not only was Lewis a member of the same academic department, he also had a unique relationship with each. Sturtevant was Lewis' Ph.D. advisor who helped him secure his academic position (Lewis, 2004; Caron, 2003, 2004). After Beadle was recruited from Stanford University to Cal Tech to replace the retiring Morgan, Beadle hired the future wife of Lewis, a Stanford graduate who had worked with Beadle, to manage the Cal Tech Drosophila Stock Center. During her work at Cal Tech, she and Lewis met. Thus, Lewis had unique relationships with his former advisor as well as a mentor/supervisor of his wife. In fact, Lewis would be gently introduced into political activism and the nuclear weapons-related genetic research of Beadle in 1953 via a project to assess the genetic effects of various nuclear wastes from nuclear explosions. In his 1954 paper on that research, Lewis reported a linear dose response with fast neutrons on gene mutation, claiming it **"served as the best available prediction curve for the unknown dosages received at the nuclear detonation sites"**.

2.1. Activating Lewis: part 1 - the Sturtevant challenge

At about the same time Lewis was publishing his research on the genetic effects of nuclear waste material, Sturtevant delivered a high-profile Presidential Address on the genetic effects of high energy radiation to the Pacific Division of the AAAS on June 22, 1954 with his remarks being published in *Science* on September 10, 1954 (Sturtevant, 1954). Sturtevant stayed with this theme in a subsequent article entitled "The Genetic Effects of High Energy Irradiation on Human Populations" in the Cal Tech *Engineering and Science* magazine in January 1955. Sturtevant's presentation was quite significant, something that might legitimately be seen as the first shot in the LNT cancer dispute, a now 70-year-old conflict.

In this presentation Sturtevant (1954) stated that he was "disturbed" by fallacious comments of Chairman Lewis Strauss of the Atomic Energy Commission (AEC), which were highlighted in an official press release from the White House. The statement indicated that radioactive fallout from the recent hydrogen bomb test called Bravo on March 1, 1954, on the Bikini Atoll in the South Pacific was not a public health concern. Any airborne radioactive contamination reaching the US would be **"far below the levels which could be harmful in any way to humans …"** (Strauss, 1954). Sturtevant (1954) concluded that **"Every geneticist familiar with the facts knows that any level whatever is certain to be at least genetically harmful to human beings …"** Not only would Sturtevant use his interpretation of the available data as an argument, but he also assumed a position of moral superiority when he stated that **"I regret that an official in a position of such responsibility should have stated that there is no biological hazard from low doses of high-energy radiation."** Sturtevant (1954) was specific in his arguments by stating the radiation geneticist mantra at that time: the frequency of mutations is directly proportional to dose, there is no threshold, the effects are cumulative and there is no repair. His comments were bold and contradicted the contemporaneous US government position. In contrast, Strauss asserted that thresholds exist for mutations and that the fallout levels were comfortably below such thresholds. With more hydrogen bombs being planned for testing this would become a politically charged issue, with radiation geneticists taking center stage.[4]

2.2. Activating Lewis: part 2 - the George Beadle memo

While there was considerable response to the Sturtevant address and publication, the next step in the activation of Edward Lewis occurred when Beadle sent a memo (July 8, 1955) to his department faculty entitled "Possible Direct Effects on Man of Low Level Exposures to Ionizing Radiation" (Caron, 2003). In that memo Beadle cited research that radiologists died from leukemia ten-fold more frequently than other physicians (March, 1944, 1947, 1950). These findings troubled Beadle, motivating him to dispute the long-standing belief that the permissible or tolerance dose concept of the AEC was safe. Beadle was very much aware of the atomic bomb study data, having served on oversight committees for this research, which gave him special insight and access. He also had his own speculative thoughts on these matters, such that even very low background radiation levels were contributing to leukemia risks, thoughts that would later silently infiltrate the Lewis *Science* paper. Beadle was hoping to inspire his faculty to take up his challenge to figure out how low doses of ionizing radiation may affect human health … all within the ongoing social and political drama regarding atmospheric testing of nuclear weapons and growing fallout levels. The real target of the Beadle memo was the US AEC because the AEC radiation exposure standard suggested an increase in leukemia by 5 fold or more for those on the receiving end of the so-called "permissible dose" from radioactive fallout who were those living downstream from the Nevada nuclear testing site (Caron, 2003, page 21). The only one who took the Beadle challenge was Ed Lewis. Lewis would use the Beadle connection to obtain then unpublished data on leukemia from ongoing studies in Japan. As for other findings and how to integrate all of the information, Lewis was on his own (Caron, 2003, page 18).

2.3. Lewis: the "Fallout Memo" and radiation-induced leukemia

2.3.1. Fallout Memo - draft 1

Within four months of receiving the Beadle memo, Lewis had developed a draft called the "Fallout Memo" dated November 28, 1955. In a note that same day to Pauling, Lewis revealed that he was circulating this draft amongst Cal Tech colleagues for critical feedback. Despite seeking faculty perspectives on this memo, Lewis already had concluded that the best way to address the fallout issue was to use Japanese survivor studies on leukemia; however, he needed reliable exposure estimates, which he was hoping to obtain from the AEC via the intervention of Beadle. Lewis expressed little hope that animal model studies would be useful, arguing that risk estimates and policies need to

[4] After reading the Sturtevant (1954) article in *Science* Muller wrote a letter of support, assuring him that, "As you must surely know, I thoroughly agree with every part of it." (Muller to Sturtevant, September 22, 1954). Curt Stern responded in a similar manner to Sturtevant's article in Cal Tech's *Engineering and Science magazine*. He wrote Sturtevant that "I thought it was excellent. I wish I had written it!" (Stern letter to Sturtevant, Feb 8, 1955).

be based on human data.[5]

Early on, Lewis may not have realized the extent to which he would become drawn into the politically charged debate on the effects of radiation on leukemia and its impact on health, government and military activities. In the interview with Caron (2003), Lewis reflected upon his decision to enter this new area of "political" science:

"I think I was prompted by a lunch conversation at the Athenaeum in which I became aware that some faculty, possibly physicists, I am not sure, were unaware of the possibility that ionizing radiation, even at low levels, could induce cancer" (Caron, 2003) page 26.

The underlying scientific inspiration or justification for Lewis' focus on cancer was based on earlier speculations of Hermann J. Muller that some cancers would occur following the induction of mutations in somatic cells. Nearly two decades earlier than the Lewis draft and ten years after his reporting of X-ray induce mutation in *Drosophila*, Muller wrote **"it is but a logical step to conclude that carcinomas, and leukemias arising after irradiation represent mutations induced by the latter"** (Jolly, 2003, page 68; Carlson, 1981, page 245). While Muller, therefore, had made the link to cancer, he was so heavily involved with genetic risk assessment and transgenerational effects that cancer was rarely given attention. Nonetheless, that 1937 statement by Muller at an interdisciplinary conference in Paris caught Lewis' attention and gave him an opening even though there was a paucity of data to support the assertion (Caron, 2003; Lewis, 1998). The fact that Muller was a Nobel Prize recipient with considerable prominence may also have drawn Lewis to the question. In an autobiographical accounting, Lewis stated that:

"When the US began testing atomic weapons in Nevada, I became intrigued with the possibility that the induction of cancers by ionizing radiation might be linearly related to the dose just as mutations in the germ line of *Drosophila* had been shown by H.J. Muller, as already mentioned. I was surprised to find that it was generally assumed that there would be a threshold below which there would be no induction of cancer" (Caron, 2003, page 30).

The US government initiated above ground nuclear testing in Nevada on January 27, 1951. By the time that Lewis submitted his paper to *Science,* dozens of above ground tests had been conducted in Nevada, thereby creating considerable controversy with the eventual number approaching 100 before they ended.

Despite Lewis' eventual promotion of the linear (LNT) dose response in the *Science* paper, he appeared reluctant at this stage to fully adopt the linearity position for cancer (e.g., somatic cell mutation) as seen in the statement that he wrote in this first draft of the 1955 Fallout Memo:

"It is unlikely that the somatic effects will show the simple linear relationship to dosage that the genetic effect shows and that direct effects will be as independent of the time over which the dosage is administered as the genetic effects are. Nevertheless, for discussion purposes it may be useful to inquire what the rate of leukemia per r unit per given population would be if the relationship to dosage is linear and if all forms are considered radiation-induced." (Lewis, 1955, page 4).

The comments of Lewis were limited in that he did not address why he thought it "unlikely" somatic cells would show the "simple linear relationship" as he believed reproductive cells did based on the Manhattan Project fruit fly studies of Stern (Spencer and Stern, 1948; Uphoff and Stern, 1949). At that time there was no knowledge that somatic cells possessed genetic damage (*e.g.*, DNA) repair while mature spermatozoa lacked this capacity.

2.3.2. *Fallout Memo - draft #2*

Over the next year Lewis would expand this limited first draft into something far more substantial. On November 30, 1956, Lewis sent a copy of the new draft to Pauling. This was about five months after the highly acclaimed publication of the BEAR I Genetics Panel (1956a) report (June 12, 1956).[6] Lewis' second draft on the risks from fallout provides an important glimpse into the development of his eventual 1957 paper, which would be framed within a linearity hypothesis and provide quantitative estimates of leukemia induced per radiation dose. This draft included a detailed evaluation of Japanese atomic bomb survivor leukemia risk. Very limited consideration (i.e., one paragraph) was given to X-ray-induced leukemia in ankylosing spondylitis (AS) patients. Over the next approximately four months, Lewis would considerably expand the AS evaluation while adding comparable sections on children with an enlarged thymus who developed leukemia after X-ray treatment and leukemia deaths in radiologists. The apparent plan was to quantify the radiation-induced leukemia risks from these four exposure groups (i.e., atomic bomb survivors, AS patients, thyroid patients and radiologists) to determine if they were quantitatively consistent. If there was agreement with the quantitative risk estimation of radiation-induced leukemia, then he might have a persuasive story.

[5] That the *Drosophila* geneticist Lewis abandoned the use of animal models in the assessment of leukemia risk from ionizing radiation very early in the evaluation process in favor of epidemiological findings was a curious development as the laboratory/animal model area provides complementary insights of essential value in risk assessments. In his first draft of the Fallout Memo he indicated that he performed a survey of the animal model literature for radiation-induced leukemia and acknowledged that leukemia could be induced in mice. While it is not known what literature he reviewed (see paragraph below), there were at least three significant published studies in prominent journals in 1954 on the effects of atomic bombs on rodents and the induction of leukemia (Furth and Upton, 1954; Furth et al., 1954; Upton et al., 1954). Nonetheless, he was dismissive of their value for the fallout assessment. While Lewis did not explain the basis for this opinion, the data indicated a threshold for leukemia induction at a very high dose, undercutting a linear dose response hypothesis. This research was being conducted at Oak Ridge National Laboratory by Jacob Furth and Arthur Upton, two highly accomplished animal model cancer researchers. There is no evidence that Lewis communicated with these researchers on these ongoing studies.In his November 30, 1956 draft paper that was sent to the NAS BEAR Genetics Panel Lewis cited the 1954 paper of Furth and Upton entitled "Leukemogenesis by Ionizing Radiation", one of the above three cited animal study papers. This paper was not cited in the final version of the Lewis (1957a) paper that was published about five months later in *Science*. No reason has been found to explain the decision to drop this reference. This paper provides data showing very high thresholds for radiation-induced lymphoma after a nuclear detonation. It also shows a very high threshold for X-ray induced myeloid leukemia for males. The data also suggest the possibility of a hormetic response for thermal neutrons with contaminating gamma rays for males for myeloid leukemia. In the case of thymic lymphoma similar low dose-hormetic-like effects were seen for male and female mice. These findings were in apparent conflict with the linear interpretation that Lewis offered in the *Science* paper.Furth was the first to demonstrate that ionizing radiation could induce leukemia in a mouse model in 1929 (Weinhouse and Furth, 1993). Furth was one of the most prominent researchers in the area of mouse leukemia and their predictive relevance to humans. In 1959 Furth provided testimony to the Joint Congressional Hearings on radiation and fallout where Lewis also testified. At that time Furth was a professor at the Harvard Medical School and President of the American Association for Research on Cancer (1957–1958). In his testimony he characterized the position of Lewis, which was that there was no threshold for inducing cancers as "pure speculation not backed by data." (Furth testimony was submitted/attached with the testimony of Shields Warren (1959).

[6] On this same day (November 30, 1956) Lewis sent this draft manuscript to the NAS BEAR Genetics Panel, now being chaired by his academic department chair, George Beadle. In the transmission letter to the Panel Lewis indicated that Beadle encouraged him to send the draft. The Lewis draft paper had an impact as seen in the follow up letter by Muller (December 5, 1956) to all Panel members which asserted that "If Lewis is anywhere near right" this would mean that the number of leukemiacases caused directly by the fallout over the next a half century would be 80,000. Muller would go on to say "That would seem to me to be a fairly heavy price to pay for the tests … …"

A significant problem with Lewis' approach is now apparent. In the draft earlier sent to Pauling, Lewis already provided a detailed leukemia risk estimate for Japanese survivors and the stated goal of hoping that there turned out to be dose-risk convergence with the other leukemia conditions. Because risk assessment has a number of subjective modifiable assumptions, changing any assumption can lead to profoundly different risk estimates. Whether consciously or not, one could choose assumptions and keep modifying assumptions until a convergence of risk estimates occurred, reflecting a possible self-fulfilling expectation, that is, getting the answer you wanted and thinking you were correct. In his detailed November 30, 1956, draft and the 1957 *Science* paper, it appears that Lewis failed to make *a priori* methodological provisions to avoid this pitfall.

The Lewis analysis also failed to consider another factor with transforming implications for the validity of his quantitative estimates of leukemia risk for Japanese survivors and for risk comparisons with other groups/conditions. Investigative peer-reviewed publications by Sutou (2017, 2020) on "Black rain" saturated with radioactive fallout (from radionuclide mixtures) in the days after the atomic explosion in Hiroshima indicated that external and internal exposure to radiation was much higher than previously thought in the "low dose" areas (i.e., areas more distant from the bomb hypocenter). This led Sutou to conclude that the estimated cancer risks per dose, including leukemia in the areas more distant from the hypocenter, would have been significantly decreased. That is, the lower cancer risks at greater distance from the hypocenter were associated with higher doses than previously suspected, indicating that the radiation exposure was less potent than estimated. Equally importantly, Sutou's findings revealed that a large part of the radiation dose is missing in all studies using atomic bomb survivor data, meaning that all such studies involved large systematic errors related to assigned doses. These findings weaken a principal conclusion of the Lewis paper regarding convergence of leukemia risks at similar doses from the different groups studied. The Sutou analysis was based on a 1957 paper (which he had translated into English and reprinted) that provided a contemporary analysis relevant to the Lewis research. There is no indication that Lewis was aware of it. Nonetheless, the issue of re-entry (i.e., within three months of the explosion) and risk was not unknown to contemporary researchers. This was reported in an English language paper by Watanabe (1961) showing increased leukemia risk with re-entry, thereby supporting the Sutou argument.[7]

Pauling used the leukemia risk estimates within Lewis' second draft in some of his anti-nuclear presentations and discussions with the media. For example, Pauling used the estimates to claim that 10,000 people would die of leukemia if the British exploded another hydrogen bomb (Divine, 1978, p123). The sharing of preliminary estimations of leukemia risk without peer review with a very politically active person such as Pauling was never recognized to be a mistake by Lewis. Yet, the sharing of the draft of this second Fallout Memo with Pauling provides important insight into the intentions of Lewis, making one seriously question or perhaps even dismiss a belief in his disinterested objectivity and lack of political agenda.

As Lewis developed the second draft, he made the commitment to endorse the linear dose response, a position not espoused in the first draft of his Memorandum. This change in perspective was related to his assessment of the Japanese bombings and, to a more limited extent, his assessment of X-ray treated ankylosing spondylitis (AS) patients. However, these studies needed to be linked to a mutation mechanism showing a linear dose response. He made the latter connection with the research of Curt Stern on fruit fly reproductive cells at the University of Rochester during the Manhattan Project.

"There is insufficient evidence on hand to evaluate the shape of the curve relating dose to incidence of leukemia, especially in the low dose region. The data on leukemia among Japanese survivors and the data on leukemia among patients irradiated for ankylosing spondylitis are compatible with a linear dose curve but they by no means prove the point …. .Since mutation in the germ cells shows a linear relationship to dose measured in r units for doses as low as 25 r, somatic mutation rate and dose are probably linearly related" (Lewis, 1956, Second Fallout Memo, page 6).

3. The Lewis *science* paper - 1957

A key factor affecting the judgment of Lewis to support a linear dose response interpretation was the ionizing radiation-mutation studies of the Manhattan Project; his "25 r" comment in the quote above refers to the Spencer and Stern (1948) publication, a study on which Muller was a highly involved consultant. Lewis then made his leap of scientific faith based on the reputation of Stern and the perceived quality of the Spencer and Stern (1948) report. He then applied it to his set of human leukemia studies, concluding that **"Although the numbers are small there is no obvious indication of a threshold dose for the induction of leukemia."** (Lewis, 1956, Second Draft p 5). The impact of the Stern-lead and Muller-influenced Manhattan Project studies is also evident with his citation of Uphoff and Stern (1949) in the highlighted quote below within the Lewis (1957) *Science* paper:

"**A linear relationship between the incidence–of leukemia and dose of radiation, which is suggested by the available data for man, may have its explanation in a somatic mutation hypothesis (41). Gene mutation has long been known to show a linear relationship with respect to dose of ionizing radiation from studies with *Drosophila.* This linearity has been extended by Spencer and Stern (43) to doses of 50 and 25 R. Gene mutation is also known to be directly proportional to the accumulated dose of radiation, even when the radiation is chronically administered at a relatively low dose rate, as in the studies of Uphoff and Stern (44)."**

Based upon his May 17, 1957a, paper in *Science* and the inflated endorsement by the *Science* editor-in-chief, Lewis was invited to testify before the Joint Congressional Committee on Atomic Energy (JCAC) on June 3, 1957b, only two weeks after publication of his paper. Lewis' concluding statement at the Congressional Hearings was a definitive one as far as policy was concerned:

"The point here, however, it seems to me—that is, my personal opinion-that the only prudent course is to assume that a straight-line relationship holds here as well as elsewhere in the higher dose region" (Lewis, 1957b, page 959).

Complementing the presentation from Lewis and the public statements of Pauling, James Crow (1957), a prestigious radiation geneticist from the University of Wisconsin and BEAR I Genetics Panel member, would testify at these same Congressional Hearings that the American public could expect over the next few years an additional 8000 infants with gross defects, 20,000 still births, and 40,000 embryonic deaths with even more such effects in subsequent generations from the continued atmospheric testing.

3.1. Lewis and linearity: criticisms accumulate

As expected, the Lewis paper generated a series of responses both supportive and critical, with the most critical coming from high profile

[7] The US NAS BEAR Pathology Committee (1956c) (see page 40) dismissed the occurrence of exposure from fallout in Hiroshima. In their January 22, 1956 meeting Panel member Jacob Furth asked: "Were they not all exposed to fallout, for example?" Eugene P. Cronkite answered: "There was no fallout at Hiroshima." Chairman Warren Shields further responded: "No. It was an air burst high enough so accurate measurements were made quite early, which rules out any significant fallout." Cronkite finished this discussion as follows: "I think it can be categorically stated that at Hiroshima there was no fallout … …" This conclusion was shown to be erroneous by Sutou (2017, 2020), who concluded that the exposures to ionizing radiation were underestimated by 50% to several fold, significantly affecting the reliability of what were thought to be low dose risk estimations by the NAS BEAR Pathology Committee (1956b) and others, such as Lewis (1957a).

scientists such as Austin Brues (radiobiology), Richard Doll (epidemiology), Alynn Kimball (biostatistics), and Richard Mole (general radiation health effects, especially leukemia) (Lipshitz, 2007). As Mole (1958) would state, the case put forth by Lewis, despite having serious limitations, quickly gained traction, due to the endorsement of the *Science* editor and the actions of Pauling. This prompted the development of well-formulated opposing arguments from complimentary perspectives to counter the Lewis momentum. The Mole comment is telling: **"… … these detailed criticisms of Lewis's analysis would hardly have been worthwhile if his conclusions had not gained a wide currency as a quantitatively accurate assessment."**

Each of the four areas assessed by Lewis had weaknesses exposed. For example, Brues (1958) ridiculed Lewis' "low" dose methodological approach to estimate leukemia risks in radiologists, noting that this group had recently been estimated to have received about 2000 r over many years (Braestrup, 1957), a value of essentially no relevance to low dose risk assessment. This criticism was reinforced by Mole (1958) who suggested that Lewis' exposure values for the risk assessment may have underestimated exposure by a very substantial 50-fold. Court-Brown and Doll (1958a), leading epidemiologists, went one step further by rolling out a new analysis on British radiologists showing that leukemia in this group displayed no enhanced risk. Of even greater public health significance, Court-Brown and Doll (1958b) and Court-Brown et al. (1960) also published a prospective study showing that the incidence of leukemia in nearly 40,000 children whose mothers received diagnostic X-rays during pregnancy was not significantly increased. In general, the exposures covered a range up to 5 rads, making the Lewis predictions even less tenable.[8] Mole (1958) and Kimball (1958) further challenged the analysis of the Japanese survivor data. They revealed massive dose uncertainty and an invalid representation of findings that exaggerated risks and led to a linear response when it was not justified. Each of the four areas developed by Lewis felt the brunt of strong rebuttals from talented opposition.

In the area of AS, it appeared that Lewis had extended his analysis and its applications too far. In fact, one could even raise the issue of his being disingenuous beyond that of challenging his competence. More specifically, the study on AS and radiation-induced leukemia was a major effort funded by the British Medical Research Council. In the preface of the final published report (Court-Brown and Doll, 1957), the Council stated that **"the present investigation was undertaken in the hope of obtaining an indication of the effects of small doses of radiation on human beings. From the nature of the case this could not be obtained directly, for few of the patients had received less than a mean dose of 250 r to the bone marrow; but it was hoped that a sufficiently precise relationship between the high doses of radiation studied and the corresponding increased incidence of leukemia could be derived to allow extrapolation to be made with reasonable confidence to lower levels of dosage. Unfortunately, this hope was not fully realized, for it is possible to derive more than one type of dose response relationship for the data,"** The authors of the report stated to the Council in the preface of the report **"that until much more work has been done it will not be possible to decide between the alternative hypotheses."** However, Lewis failed to share this information with the reader while using the study to promote his goals. Because Lewis benefitted from having the image of the disinterested scientist seeking truth, it should have been incumbent upon him to share perceived uncertainties and to display principled leadership and intellectual openness when offering his perspectives within his article and to the US Congress. He clearly failed to do so.

[8] In her biography of Alice Stewart, Greene (2020) noted that the studies of Court-Brown and Doll on AS patients as well as their report on leukemia on A-Bomb survivors "came to conclusions that corroborated the findings of the A-Bomb studies—cancer risk could be extrapolated from high to low dose and there was effectively no risk at low dose." (page 88).

Table 1
Atomic bomb induced leukemia risk estimates.

Distance from Hypocenter (meters) (Radiation Dose)	Population #/Sample Size	Cases/ Deaths	Leukemia Risk Per 100,000 People; Annual (A) or Undefined Period	Relative Risk
Folley et al., 1952-**Hiroshima and Nagasaki**				
0–999	1400	4 Combined	285.7	24.0
1000–1499	10,596	13 Combined	137.7	11.6
1500–1999	19,002	7 Combined	36.8	3.1
>2000	67,267	8 Combined	11.9	1.0
Lange et al., 1954-**Hiroshima and Nagasaki**				
0–999	2463	18 Cases	730.8	116.2
1000–1499	17,668	33 Cases	186.8	29.7
1500–2499	56,960	14 Cases	24.65	3.9
>2500	159,085	3 Cases	6.29	1.0
Lewis, 1957a- **Hiroshima and Nagasaki**				
0–999	1870	18 Cases	962.5	57.9
1000–1499	13,730	41 Cases	298.6	17.9
1500–1999	23,060	10 Cases	43.4	2.6
>2000	156,400	26 Cases	16.6	1.0

The same pattern of not disclosing relevant information to his readers is also evident regarding the children with an enlarged thymus who were medically irradiated. The key study used by Lewis (1957a) to estimate X-ray induced leukemia was that of Simpson et al. (1955). What Lewis failed to share with the readership was the perspective of these authors. In their Discussion they stated: "**While the data presented establish the high incidence of cancer following thymic irradiation, they allow no definite conclusions to be drawn as to the relationship to the radiation exposures. This is particularly true of leukemia, which was apparently not associated with any one form of [radiation] treatment or with high radiation doses. It is possible that the children covered by this study are especially prone to develop leukemia. Efforts are being made to obtain an adequate control series to investigate this possibility."** In the conclusion of their paper, Simpson et al. (1955) were quite definitive. With respect to radiation-induced leukemia with these patients **"No such relationship could be demonstrated in the case of leukemia."** Thus, while Lewis could decide that he wanted to use a data set to test a hypothesis (i.e. LNT), it seems reasonable to think that he should at least have let his readers know that the scientists who presented those data did not support the conclusion that he had reached.

3.2. *The Japanese-Atomic bomb leukemia data: the linearity debate*

Despite the criticisms regarding the AS, thymus patients and radiologist assessments, the prime focus of Lewis' initial analysis was fallout and leukemia risks, based on studies of the atomic bomb Casualty Commission (ABCC) in the early 1950s. Over time the atomic bomb-leukemia research area would become the principal driver in the LNT-cancer story, with the other lines of research receding in significance. In his *Science* paper, Lewis (1957a) cited Folley et al. (1952), Lange et al. (1954) and Moloney and Kastenbaum (1955) and unpublished sources of leukemia data that most likely were shared via the intercession of Beadle with the AEC. Upon these papers and unpublished data, the LNT-leukemia argument of Lewis (1957a) would rest.

In the cases of Folley et al. (1952), Lange et al. (1954), and Moloney and Kastenbaum (1955), the leukemia data were reported up to 1953. The unpublished data brought the cases up to September 1955. The

leukemia incidence is high when subjects were close to the hypocenter of the blast but decreases in an approximately linear fashion with distance from the hypocenter (Lewis, 1957a) (Table 1).[9] This linear perspective framed the thinking of Lewis, permitting him to estimate leukemia risk to background and below exposures, a perspective captured in the editorial of DuShane (1957).

After the decade of the 1950s there has been continuing evaluation of leukemia incidence in the atomic bomb survivors extending the duration from 1950 to 2001 (Ishimaru et al., 1978; Beebe et al., 1978; Shimizu et al., 1990; Hsu et al., 2013) using differing dose reconstruction methods. The linearity conclusions expressed by Lewis (1957a) for the Japanese leukemia findings have been extended by these studies and incorporated into risk assessment and policy worldwide.

4. The Cuttler-Welsh – 2015 hormesis challenge to linearity

In 2015 Cuttler and Welsh (2015) [10] retrospectively challenged the leukemia linearity interpretation of the Lewis (1957a) paper. They claimed that the dose response was hormetic based on Wald (1958) (Table 2, Fig. 1) from the same atomic bomb survivor data set used by Lewis (1957a).[11] The Wald (1958) manuscript was submitted for publication about seven months after the Lewis (1957a) paper was also published in *Science*. The Wald (1958) data were incorporated unchanged into a major UNSCEAR (1958) report on ionizing radiation. The Lewis (1957a) and Wald (1958) papers were therefore closely contemporary using the same source material. Lewis (1957a) used data from Hiroshima and Nagasaki up to September 1955 while Wald (1958) used data only from Hiroshima but to December 1957. In contrast to the more flamboyant nature of the Lewis publication, the tone of Wald (1958) was reserved with no J-shaped dose response conclusion, simply recommending more research in the low dose zone. The reason for the discrepancy between the Lewis (1957a) and Wald (1958) studies was due to the manipulation of the control group data starting at 2000 m from the hypocenter by Lewis (1957a) whereas the control group started at 3000 m in Wald (1958). Cuttler and Welsh (2015) argued that Lewis (1957a) missed the hormetic dip with his failure to follow the response out to lower doses. Cuttler and Welsh (2015) concluded that the Lewis method was methodologically flawed based on the use of an LNT assumption. Following the Cuttler and Welsh (2015) paper, Cuttler (2018) re-examined this situation restating his hormetic interpretation. Since neither of these two challenging papers (Cuttler and Welsh, 2015; Cuttler, 2018) generated notable citation interest either with support or rebuttal, it suggested the need to ascertain which perspective may be supported by the published literature: Lewis versus Cuttler and Welsh.

While the Cuttler and Welsh (2015) paper argued for a hormetic-like decrease in risk based on the Wald (1958) study (Table 2 and Fig. 1), it did not consider other studies also from the 1950s. A peer-reviewer of the Cuttler (2018) paper suggested the need to assess the hormetic hypothesis over several decades after the 1950s, a fact that was reported by Cuttler (2018) in his revised paper. The following section addresses these issues.

4.1. Historical atomic bomb survivor leukemia reassessment

The number of leukemia cases from Hiroshima was considerably greater than in Nagasaki, being approximately two to three-fold greater, depending on the study. In addition, there was debate over factors such as neutron exposure which was greater in Hiroshima (1.7–1 ratio) with the two cities being difficult to directly compare. This led to the Nagasaki data having small numbers of cases in the 1950s, resulting in the Hiroshima leukemia data often being the only one presented in various key publications.[12] Given these and other technical considerations the focus was directed to Hiroshima. Table 2 provides a summary of the six studies which provides J-shaped findings on leukemia for Hiroshima (Fig. 1). One additional study provides the summated findings for the 1950s decade combining the leukemia data for both cities, presenting data on males and females separately (Jablon et al., 1964) (Table 2 and Fig. 1).

A comprehensive set of papers published over the decade of the 1950s was obtained that considered similar information but with progressively expanded data due to newly reported leukemia cases. In general, data collected prior to 1950 was considered incomplete and less reliable. The set of 1950s papers used in this analysis is the composite set of historical papers cited by Heyssel et al. (1960), Watanabe et al. (1960) and Beebe et al. (1962) but with the addition of the BEAR I Pathology Panel Report (1956b) that also contained new data and the report of Jablon et al. (1964) for Hiroshima and Nagasaki for males and females for the entire decade of the 1950s. The Jablon et al. (1964) report was necessary since the above cited follow up papers only reported findings for Hiroshima. The report of Tomonaga (1962) was not included since it reprinted the data from Hiroshima from Watanabe et al. (1960) and overlapped with Jablon et al. (1964) with Nagasaki but without the separate gender presentation. The evaluation of the series of papers on the same but progressively larger data sets is instructive. Despite the same data source for leukemia cases and deaths there are critical differences in the presentation of data with respect to dose that created the opportunity for new analyses. These include differential distance categories from the hypocenter employed in the analyses. For example, some authors spaced cases/deaths via 500 or 1000 m intervals from the hypocenter or some mixed combination. Other authors used smaller or larger distance spacing approaches. There was also the introduction of various dose reconstructions, with the first such analysis published in 1957 based on new estimates of shielding and bomb yields and then periodically updated over time (i.e., 1965, 1986, 2002). Some authors combined all cases regardless of the severity of symptoms of radiation effects while other authors presented data on leukemia separately for those exhibiting acute toxicity symptoms and those not showing such symptoms. It was the broad range of analytical approaches that revealed the series of hormetic/J-shaped dose responses (Table 2, Figs. 1–3).

4.2. The new atomic bomb leukemia analysis: Non-linearity Predominates

An hormetic J-shaped dose response was first reflected in the Moloney and Kastenbaum (1955) study (Table 2 and Fig. 1). This J-shaped finding was noted by neither the authors (Moloney and Kastenbaum, 1955) nor by Lewis (1957a) despite his citing the paper. This

[9] All studies in Tables 1 and 2 provide cases of leukemia whereas two studies provided data on both cases and deaths due to leukemia. In these latter papers both cases and deaths were combined for Folley et al. (1952) since the numbers were small. However, these endpoints are presented separately for Watanabe (1961) since the number of cases and deaths are sufficiently robust (Table 2).

[10] The first suggestion of a hormetic dose response for the atomic bomb survivor data and leukemia was by Jaworowski (2010) who commented upon the UNSCEAR 1958 report data summary. He stated that "hormesis is clearly evident …. in a table showing leukemia incidence in the Hiroshima population, which was lower by 66.3% in survivors exposed to 20 mSv, compared to the unexposed group (page 165)". These observations were then further discussed by Cuttler (2014a,b).

[11] Wald (1958) noted that the numbers of cases changed in the time between the Lewis study and his report. More specifically, he stated that some of the cases from Lewis were dropped for different reasons while numerous new cases were added for his evaluation. He claimed that the cases from 1950 to 1956 were considered "fairly" accurate.

[12] The BEAR Pathology Committee (1956c) noted the differential focus on Hiroshima as compared to Nagasaki. Cronkite (page 39) stated: "I could not understand why all the emphasis was based on Hiroshima." Bugher reported: "Although the intent was for these two studies to be more or less concurrent and interconnecting, in fact they have gone on pretty much independently, with the tendency of the group at Hiroshima to neglect Nagasaki."

Table 2
Atomic bomb induced leukemia: Evidence of hormesis.

Distance from Hypocenter (meters) (Radiation Dose)	Population #/Sample Size	Cases/ Deaths	Severe/Non-Severe	Leukemia Risk Per 100,000 People; Annual (A) or Undefined Period	Leukemia Risk per 100,000 People severe/non-severe	Relative Risk
Moloney and Kastenbaum, 1955-Hiroshima						
0–999	1200	15 Cases	14/1	1250.0	1886/222	27.5
1000–1499	10,500	24 Cases	15/9	288.0	666.7/109	13.5
1500–1999	18,700	5 Cases	3/2	26.7	171.5/11.8	1.5
1500–2499	17,200	2 Cases	1/1	11.6	105.0/6.15	0.76
>2500	50,500	4 Cases	0/4	8.0	NA/8.06	1.0
NAS, Pathology Committee 1956a-Hiroshima						
0–999	1200	16 Cases	14/2		246.2/58.6	27.9
1000–1499	10,500	28 Cases	15/13		87.9/20.8	9.9
1500–1999	18,700	6 Cases	2/4		15.1/3.1	1.5
1500–2499	17,200	2 Cases	1/1		13.9/0.8	0.038
>2500	50,500	8 Cases	0/8		NA/2.1	1.0
Wald, 1958- Hiroshima						
0–999	1241	15 Cases		151.1 (A)		44.4
1000–1499	8810	33 Cases		46.8		13.8
1500–1999	20,113	8 Cases		5.0		1.5
>2000	32,692	3 Cases		1.1		0.32
>3000	32,963	9 Cases		3.4		1.0
Heyssel et al., 1960-Hiroshima						
0–999	237	3 Cases		1266.0		436.6
1000–1499	6163	18 Cases		292.1		100.7
1500–1699	3605	2 Cases		6.9		2.4
1700–1999	4817	0 Cases		0.0		0.0
2000–10,000	342,279	10 Cases		2.9		1.0
Watanabe et al., 1960-Hiroshima						
0–1000	1400	2/11		17.8/98.2 (A)		9.8/55.8
1001–1500	10,596	14/18		16.5/21.2		9.1/12.0
1501–2000	19,002	13/20		8.5/13.1		4.75/7.4
2001–5000	67,267	10/10		1.48/1.48		0.81/0.84
Non-exposure	187,447	34/38		1.81/1.76		1.0/1.0
Jablon et al., 1964-Hiroshima and Nagasaki (Female)						
0 –< 1400	N/A	N/A Deaths		42.0 (A)		8.0
1400–1999	N/A	N/A Deaths		2.0		0.4
2000–2499	N/A	N/A Deaths		3.0		0.6
>2500	N/A	N/A Deaths		5.0		1.0
Jablon et al., 1964-Hiroshima and Nagasaki (Male)						
0 –< 1400	N/A	N/A Deaths		73.0 (A)		12.2
1400–1999	N/A	N/A Deaths		8.0		1.25
2000–2499	N/A	N/A Deaths		3.0		0.50
>2500	N/A	N/A Deaths		6.0		1.0
Beebe et al. (1978) – Hiroshima						
<900-1099	2093	75 Cases		35.8*		18.2
1100–1199	1540	29 Cases		18.8		9.6
1200–1299	2129	24 Cases		11.3		5.4
1300–1399	2752	15 Cases		5.5		2.6
1400–1499	2844	15 Cases		5.3		2.5
1500–1699	6995	20 Cases		2.9		1.4
1700–1999	10,794	24 Cases		2.2		1.05
2000–2499	15,230	22 Cases		1.4		0.66
>2500	46,325	99 Cases		2.1		1.0
Beebe et al. (1978) – Nagasaki						
<900 -1,299	1,866	39 Cases		20.9*		11.0
1300–1399	1067	16 Cases		15.0		7.90
1400–1499	936	8 Cases		8.5		4.47
1500–1699	1551	6 Cases		3.9		2.05
1700–1999	2420	9 Cases		3.7		1.94
2000–2499	6043	8 Cases		1.3		0.68
>2500	76,270	145 Cases		1.9		1.0

*Ratio: 10^3 cases/1950 census population.

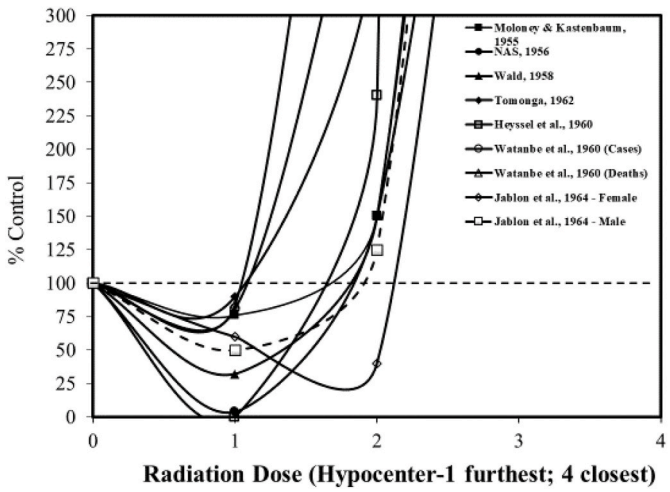

Fig. 1. Atomic bomb induced leukemia risk (1950–1959), Based on Column # 7, Relative Risk in Table 2.

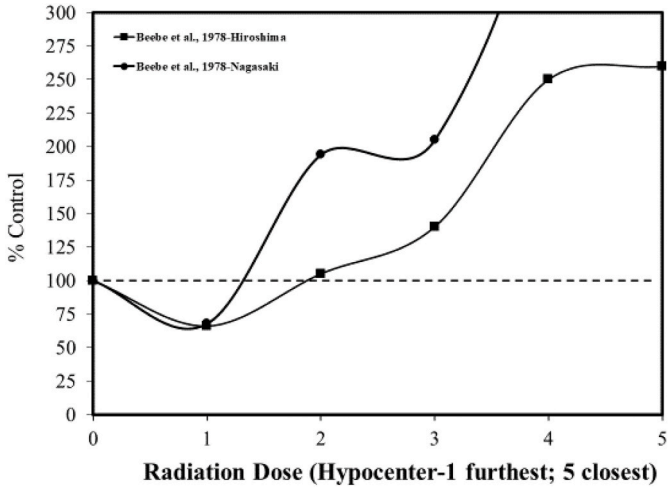

Fig. 2. Atomic bomb induced leukemia risk (1950–1974).

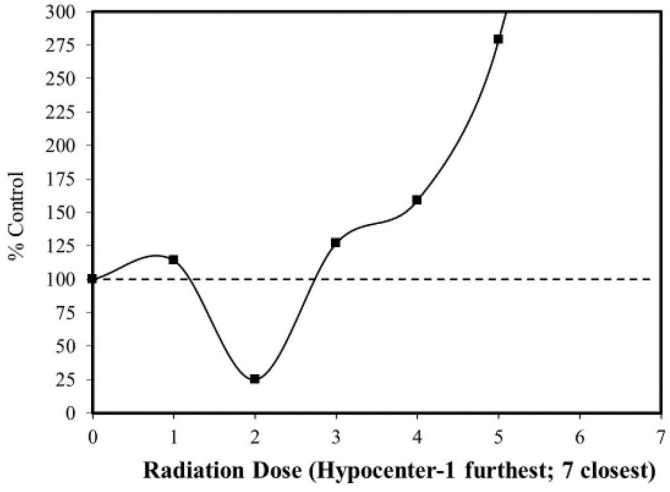

Fig. 3. Estimated relative risk for leukemia of Hiroshima atomic bomb survivors (1950–1985) – Shimizu et al. (1990).

hormetic biphasic effect only occurred for patients that did not show acute effects. Such a new dimension to the data analysis permitted Moloney and Kastenbaum (1955) to assess responses over a broader dose range. The leukemia cases were nearly the same as the findings given in the Lange et al. (1954) paper but now the authors separated their cases based on the presence or absence of external radiation-induced symptoms. The number of cases presented in the Moloney and Kastenbaum (1955) paper increased over time, subsequently being further summated by the US NAS BEAR Pathology Committee (1956b) (Table 2, Fig. 1). Consistent with the previous report of Moloney and Kastenbaum (1955) the dose response in the NAS BEAR Pathology Committee Table 2 was J-shaped, now with ten more cases than reported in the Moloney and Kastenbaum (1955) paper (i.e., 50 vs. 60 total cases). While Lewis (1957a) cited the BEAR Pathology Committee report (1956b) it did not cite this table or the data.

Other studies displayed hormetic dose responses without separately reporting on those with non-clinical radiation changes (Table 2, Fig. 1). In these studies, the distance from the hypocenter was extended further, permitting a broader range of doses to be assessed for the occurrence of cases and without grouping those cases, as was done in the Lewis (1957a) publication. This approach resulted in a multi-study response convergence presenting J-shaped responses (Table 2, Fig. 1) of this paper.

These findings reveal that the observations of Cuttler and Welsh (2015) based on Wald (1958) were not anomalous but commonly observed prior to and after the cited publication of Wald (1958), including the entire decade of the 1950s. These findings also displayed a common pattern with respect to exposure, external symptoms and occurrence of leukemia.

Since this pattern consistently demonstrated a threshold and even a J-shaped response how did Lewis come to conclude that the data supported a linear dose response? It is not obvious why Lewis presented an "expanded control" group with distance from the hypocenter being beyond 2000 M and why he did not discuss the severe vs no severe symptom patients as in the case with Moloney and Kastenbaum (1955) and the NAS BEAR Pathology Panel report (1956b). Lewis's writings and testimony are silent on these questions. Other researchers such as Moloney and his colleagues, who were members of the ABCC, as was Wald, reported the J-shaped findings in tables but in each case failed to discuss the possibility or occurrence of a J-shaped dose response. This was also the case for the NAS BEAR Pathology Committee (1956b).[13] The J-shaped dose response for radiation-induced leukemia for the decade of the 1950s for both cities was summarized by Jablon et al. (1964). However, despite being a consistent feature of the epidemiological findings, it was ignored or missed by all research groups publishing on this topic. Thus, Lewis was not alone in his linearity conclusions.

Evidence supporting the hormetic dose response for leukemia amongst the atomic bomb survivors has been consistently shown, extending from the 1950 observations, for an additional 25 years to

[13] The BEAR Pathology Panel (1956c) acknowledged the J-shaped leukemia findings on January 22, 1956 as seen in the comments of Cronkite (pages 44 and 45): " …. .if one takes the incidence of leukemia at all distances in which there was no symptoms to radiation, he gets a curve which is parallel to it but a lessor incidence." This comment is a clear acknowledgement of the J-shaped findings for cases that did not show external radiation damage. Cronkite then provided a key non-scientific response: "This is the part which is very disturbing …. There is something going on that I don't know." He then attributes these findings to the Kastenbaum ABCC reports which are cited in this paper as Moloney and Kastenbaum (1955) and the NAS BEAR Pathology Committee (1956b) table with updated cases as discussed in the text of the present paper. While the stage was set to consider the possibility of a J-shaped response the issue was not developed further, defaulting to the comfort zone of the linear dose response, brushing aside the J-shaped possibility as likely due to a "small number" of cases based on the comment of panelist John Bugher.

cover a 40 year potential latency period (Table 2, Figs. 2 and 3) (Beebe et al., 1978; Shimizu et al., 1990). The initial findings of Moloney and Kastenbaum (1955), the NAS BEAR Pathology Committee (1956b), Wald (1958), Watanabe et al. (1960), Heyssel et al. (1960) and Jablon et al. (1964) were not only extended and sustained as the total number increased over time, but also with differing dose reconstruction strategies in 1957, 1965, and 1986. The hormetic effects in both cities for the same distances from the hypocenter were consistent (Table 2, Figs. 1–3).

Despite the consistent observations of hormetic dose responses the research community has been equally consistent in their efforts to ignore and distort those findings. An integrated follow up evaluation on the atomic bomb survivors and leukemia cases was provided by Beebe et al. (1978) in Table 2 (page 195), 1950–1974. The data showed a hormetic J-shaped response for both Hiroshima and Nagasaki, supporting the findings of the 1950s until the late 1970s. The number of leukemia cases had markedly increased from the decade of the 1950s, approaching 600 cases for both cities. The data revealed the "optimal" distance from the hypocenter at the time of the bombing, for the decrease in leukemia incidence. For both cites it is in the 2000–2499 m range as compared to the "control" group at >2500 m. The decrease in leukemia cases is about 30% for both cities in this optimal distance zone, continuing the earlier trend.

While the above statement provides the data in a hormetic framework, Beebe et al. (1978) also showed a hormetic effect for the leukemia cases of Nagasaki but not for Hiroshima. More specifically, these researchers provided the population number of each distance/dose grouping and the number of cases. However, in the analysis of the Hiroshima data as shown in their Table 2 they combined both the control and the low dose group values prorating doses (i.e., 0.0 rad and 1.0 rad) based on the number of people in each group. Thus, the group exposed to 1 rad had its exposure reduced to 0.25 rad. Likewise, the group without exposure above background was now exposed to the same quantity, that is, 0.25 rad. The authors combined the total number of people from both groups, now resulting in 61,555. The "adjustment" or manipulation of the control group data had significant implications as it eliminated the hormetic decrease in leukemia cases and smoothed out the curve, creating support for the LNT model. No justification was provided to support this action. This control group manipulation was not performed with the Nagasaki population. In their discussion the authors expressed concern about non-linear dose responses and were dismissive of the J-shaped responses in the Nagasaki findings due to the smaller sample size as compared to the Hiroshima data.

Consistent with this biasing strategy is the report of Brill et al. (1962) which provided an integrative "synthesis" of the Hiroshima and Nagasaki leukemia case findings. They reported strong support the linear dose response. This was achieved (see their, page 599) by manipulating (i.e. combining) the control group cases such that it combined doses from 0 to 20 rad, once again ensuring an LNT conclusion. Pollycove (1998) reported a similar type of control group lumping schemes by Miller et al. (1989) with respect to X-ray induced breast cancer which obscured a striking hormetic dose response. In these examples, there appears to be a predisposition to force a linear interpretation even if it requires control group manipulation after the fact. Thus, when one follows the data, the findings for both cities continued to support the hormesis dose response conclusion of Cuttler and Welsh (2015) based on the Wald (1958) study.

4.3. Institutional scientific bias

The major issue discussed above centered on the selection of the control group. In the case of the ABCC data, two control groups were identified. One is comprised of those who moved into the bombed cities after the bombing, called "Not-in-City" (NIC). The second group were survivors who were in the city, but at considerable distance or protected by sufficient shielding such that exposure would be considered small. While both groups have limitations, the BEIR I (1972) Subcommittee on somatic effects/cancer opted in favor of the "low" exposure group, dropping the NIC control due to the more apparent differences with the survivor population. In practice the BEIR I Subcommittee favored combining individuals into the control group that had exposures less than 10 rads. This type of research practice has been commonly followed or with some similar variations over time. In two studies presented in BEIR I (1972) the low dose groupings were: 0–5 rad and 5–19 rad (Ishimura et al., 1971), and 1–9 rad and 10–49 rad (Jablon and Kato, 1970) (cited in BEIR, 1972). In a follow up study by Ishimaru et al. (1979) the grouping was changed to 1–49 rad.

As noted by Jaworowski (2010), the hormetic effects were reported in the Wald (1958) paper as observed at 2 rad. Similar hormesis findings were reported by Beebe et al. (1978) and Shimizu et al. (1990). These findings indicate that lumping of the no-low dose groups to create the control group masks possible hormetic dose responses. It should be noted that James Crow was on the BEIR I general oversight committee and the genetics subcommittee. In the case of Edward B. Lewis, he was also on the general oversight committee but also a member of the somatic cell/cancer Subcommittee, the one that made this recommendation. As noted above, Table 2 (page 195) of Beebe et al. (1978) combined data for Hiroshima in the low dose zone when there was no scientific justification based on sample size and this led to a biased conclusion, that is, ignoring data which clearly showed a hormetic response for leukemia.

While the occurrence of hormetic effects (decreases in risk at low doses) can be difficult to detect in epidemiological studies, evidence of hormesis in the atomic bomb survivor studies has been widely reported. The occurrence of hormesis and the underlying chemico-biological interactions which are quite complex, are known to vary by individual, age of exposure, gender, endpoint and other modifying factors. Therefore, the hormetic zone for different health endpoints may display different dose optima ranges. Radiation quality, dose rate, including dose-rate history for internal radionuclides, and other factors are likely also important. This has implications for health endpoint data in which the "control" subjects are aggregated into various extensive radiation exposure ranges as commonly reported in the atomic bomb survivor studies. Despite such actions hormetic effects have been reported as seen in Shimizu et al. (1990) who found a hormetic response for leukemia within a 6–9 rad range. A similar hormetic response for colon cancer had a broader optimal range from 1 to 19 rad. Hormetic effects of lung cancer for males and females had an optimal range of 5–20 rad. In the case of lymphoma and hematopoietic cancers the hormetic range was 1–9 rad (Beebe et al., 1978). Hormetic responses for non-cancer endpoints occurred over a higher dose range than the cancer endpoints (Jablon et al., 1964; Mine et al., 1990), findings consistent with Sutou (2018, 2020) for relative mortality which was a function of distance from the hypocenter, the optimal distance in the 2800–3000 m range. These findings were in close alignment with the leukemia data presented in this paper (Figs. 1–3). These findings indicate that control group aggregation strategies can significantly affect study outcomes, dose response modeling and risk assessment estimates.

5. Lewis and His endorsement of LNT for cancer risk assessment

1. **Biased Methodology**: The Lewis research methodology had potential for bias. As noted earlier, this stemmed from the goal to demonstrate that the leukemia risk estimates were consistent across the four radiation-induced leukemia conditions. In draft 2 he derived a risk estimate for leukemia from Japanese atomic bomb survivors and acknowledged the desire that leukemia risks for AS support and not contradict the Japanese findings. Each separate radiation-induced leukemia risk condition needed to be conducted in a "blind' manner using *a priori* entry and evaluative criteria to avoid biasing in the risk assessment evaluation. There is no evidence these precautions were taken.

2. **Fails to Consider Confounding Variables**: The Lewis report failed to consider possible contributions of cigarette smoking, benzene or other factors that may affect the occurrence of leukemia risk. Cigarettes smoke contains various leukemogens such as benzene, nitrosamines (Seyler et al., 2013) and multiple radionuclides (Iwaoka and Yonehara, 2012; Sakoda et al., 2012). A survey from of Japanese adults from 1951 to 1954 indicates that mean annual consumption of cigarettes for adults (without differentiation by gender) in Japan was nearly 1500 (Stocks, 1970). This would have also contributed to exposure via passive smoke to children and other family members. Whether, and to what extent, smoking may have differed in the various exposure groups was not considered in the Lewis (1957a) paper. While this is a weakness of the Lewis (1957a), it is necessary to point out, once again, that the limitations of Lewis were not his alone. In fact, the ABCC atomic bomb survivor studies failed to introduce the collecting of data on cigarette usage until 1965 and then for males only, and then in 1969 for females, more than two decades after the bombing (Furukawa et al., 2010), an oversight with considerable public health and risk assessment implications. Yet, cigarette smoking had been identified as a strong risk factor for lung cancer in epidemiological studies by Doll and Hill in 1950. The collection of data from females for smoking occurred some five years after the US required cigarette package hazard labeling for diseases such as cancer.

   Lewis likewise did not consider as late as 1954 that only 19.4% of Japanese households had refrigerators or iceboxes (Replogle et al., 1996). This would lead to consumption of meats and fish preserved with various salts and nitrites, leading to increased nitrosamine exposure, another risk factor for leukemia. Other studies have associated the marked increased relative risk for leukemia to birth order (Wakabayashi et al., 1994) and blood types (Tavasolian et al., 2014). These additional examples are raised not in support of causal explanations but to highlight the need for a more integrative assessment rather than to relate leukemia to a single factor within a complex human societal framework. It was this type of perspective that Lewis may have missed by virtue of not having epidemiological collaboration. However, as can be seen by the obvious failings in the design, type of data collected and interpretations of some ABCC studies, having epidemiological expertise would not have assured Lewis of significantly improved study quality and outcomes.
3. **The Contradictory NAS BEAR I Pathology Committee Data**: Lewis (1957a) cites the NAS BEAR Pathology Committee (1956b) report but ignores reported nonlinear J-shaped findings, due to hormesis (See Table 1, Fig. 1). Lewis had multiple chances to view J-shaped radiation leukemia findings but never addressed the issue.
4. **Lewis Ignores Negative Human Genetic Damage Data**: Lewis used the exposure estimates of Neel and Schull (1956) to guide aspects of exposure. He also stated that it was essential to base his risk assessment on human data. However, the Neel and Schull (1956) ten-year study of the population (i.e., over 70,000 offspring of atomic bomb survivors) that Lewis was studying did not show significant genetic effects. Instead of being guided by the Neel and Schull (1956) report in this crucial matter, he adopted the reports of Spencer and Stern (1948) and Uphoff and Stern (1949) using fruit flies.
5. **Lewis Uses Flawed Fruit Fly Data**: Lewis was influenced by the efforts of Stern and Muller to ensure the acceptance of the linear (LNT) dose response model. It has been well established that Stern and Muller manipulated the circumstances surrounding the evaluation of the genetic studies of the Manhattan Project to affect the acceptance of the linear dose response (Calabrese, 2019a, 2020). The Spencer and Stern study (1948) relied upon by Lewis (1957a) had important methodological limitations that affected the validity of its low dose responses (Calabrese, 2020). For example, the investigators combined more than one dose rate within single dose categories, invalidating dose comparisons. In addition, Stern and Muller conspired to discredit the threshold supporting study of Caspari (see Caspari and Stern, 1948) which was methodologically superior to the Spencer and Stern (1948) study. Finally, the Uphoff and Stern (1949) report was largely based on experimental studies by Uphoff that displayed abnormal control findings, forcing these authors to conclude that their findings were not interpretable. These conclusions were discovered by the present author in previously classified documents sent by Stern to the AEC (i.e., their sponsor) but not revealed when the data were published about one year later (See Calabrese, 2011 and 2020 for a detailed assessment). Without being aware of these geneticist misrepresentations of the research record Lewis accepted the judgments of the two key leaders in the field.
6. **Failure to consider alternative causation:** The Lewis (1957a) low-dose LNT–radiation-induced leukemia hypothesis failed to provide adequate consideration for alternative causality. However, during the period of his research (1955–1957) alternative causality possibilities were sufficiently scientifically mature for consideration. For example, in 1942 Cooke provided considerable evidence that acute infections may be an important contributing factor in the occurrence of childhood acute leukemia. Building upon a robust series of observations (Ward, 1917; Maynard, 1921; Sternberg, 1926; Warren, 1929; Dameshek, 1930; Love, 1936; Pierce, 1936), Cooke (1942) assessed the relationship of infectious diseases and childhood acute leukemia initially in 126 patients. She reported that of the 126 patents 56 (44%) had an antecedent infectious disease history, with the majority being respiratory. These findings lead Cooke (1942) to undertake a massive follow up investigation across 33 children's hospitals and pediatric services in the US and Canada involving nearly 50,000 children and more than 1500 leukemia cases. Detailed temporal analyses indicated that acute infections frequently preceded the onset of the acute leukemia as was the case in the earlier studies. These findings lead to the conclusion that acute infection may be an important etiologic factor in the occurrence of leukemia. Since the development of leukemia is relatively infrequent following infections to large numbers of children, Cooke (1942) proposed that it occurs only in those with a type of defective immunological predisposition that promotes the development of leukemia following infections.

   According to Kaplan (1954), about 50% of all cases of acute leukemia of childhood are associated with a history of severe, typically nonspecific infection that preceded the onset of leukemia. Kaplan (1954) indicated that there was little disagreement by experts in the field that infection is a frequent preceding acute clinical manifestation in acute childhood leukemia. At the time of the Lewis (1957a) paper there were two principal interpretations for these observations. Cooke (1942) and Brown (1951) were of the opinion that infection was a major etiological factor in the development of acute childhood leukemia and emphasized the similarity of the age distribution of miscellaneous pediatric infectious diseases and its similarity with acute leukemia. Furth et al. (1935) hypothesized that leukemia may already be presenting an occult form in such cases and that the infection represents only the first clinical manifestation. It was Kaplan's conclusion that these two differing views were readily reconcilable since **"there is no reason why infection cannot play a causal role in the induction of a neoplasm."** In his seminal review of the historical literature on leukemia causation, Greaves (2006) noted that during a significant portion of the past century experts in the field supported the view that prior infections were the most likely cause of leukemia.

   The idea of a promotional etiology for acute childhood

leukemia due to an abnormal or dysregulated immune response to infection after birth became a more refined hypothesis since the 1980s and continues to be a supported hypothesis today for leukemia causation (Greaves, 1988, 1993, 2006, 2018; Lightfoot and Roman, 2004; Richardson, 2011). This hypothesis has potential relevance to the survivors of the atomic bombs based on the work of Abrams (1981), who assessed the occurrence of infectious diseases following bombings in Hiroshima and Nagasaki. The question that may be raised is whether young children exposed to the aftermath of the atomic bomb destruction would have experienced enhanced infectious diseases (Cooke, 1942; Kaplan, 1954) with an accompanying abnormal immune response that contributed to leukemia occurrence. While I am not aware of documentation of infectious disease incidence in the survivors of the atomic bombs in the weeks and months following these bombings, this appears to be not an unreasonable likelihood. Based on research concerning the effects of an atomic bomb explosion on a community, a massive increase in life threatening infections would be an expectation. A computer simulation of the effects of a single nuclear explosion 9 miles south of New Orleans, estimated that 35% of "survivors" would die from infectious diseases in the first year after the attack in the absence of medical countermeasures (Abrams, 1981). Many other infected people would survive, including young children who would be at potentially increased leukemia risk based on the above discussion.

In such a scenario the exposed children would have experienced infectious diseases at a rate and level of medical seriousness exceeding the control population (i.e. those at considerable distance from the atomic bomb hypocenter). These findings suggest the possibility that some portion of the observed acute leukemia in children reported in Hiroshima and Nagasaki were likely be causally related to infectious diseases. In 1987 McKinney et al. reported that the latent period between viral infectious disease and the occurrence of the leukemia is highly variable, ranging from 2.5 to 14.5 years. These findings suggest that enhanced occurrence of infectious diseases during the first year after the atomic bomb event might have the potential to affect leukemia disease incidence for a prolonged period, through the 1950s.

While there are differing mechanistic hypotheses concerning how infectious diseases may affect the occurrence of leukemia, the point is that Lewis (1957a) did not consider this issue, which was a viable contributory hypothesis, at that time. This was the case in light of the contemporary reports by Brown (1951) as well as by Kaplan (1954), who was a major figure in the area of leukemia causation and treatment and a member of the BEAR Pathology Panel. The failure of Lewis to consider a leading contemporary hypothesis for childhood acute leukemia represents a serious failing. This is especially the case since a more advanced version of this hypothesis remains under serious scientific evaluation.

7. **Control Group Manipulation:** The Lewis paper manipulated the distance from hypocenter leading to an LNT result. The combining of a broad range of low dose groupings has long been a methodological approach to ensure deriving a linear dose response. This has been shown to occur widely not only in atomic bomb survivor studies but also in other radiation and cancer literature (Pollycove, 1998). Selective exclusion of relevant information, what ever the reason, is disingenuous and misleading.
8. **When is Behavior Disingenuous?** While Lewis had the option to use the data of the AS studies to support his LNT hypothesis, however, as pointed out earlier in the text, he needed to share prominently the opinions of the AS study sponsor (Medical Research Council) and the research team (Court-Brown and Doll) that this study could not demonstrate credible evidence for a linear dose response. This was also the case with enlarged thymus patient study (Simpson et al., 1955).
9. **Failure to identify key assumptions:** Lewis failed to acknowledge that he extrapolated results with mature spermatozoa to somatic cells to assert his LNT commitment. In the middle of December 1958 Russell et al. demonstrated that mature spermatozoa in mice lacked the capacity to repair genetic damage induced by ionizing radiation but the spermatogonia could do so. This challenged the capacity of the Spencer and Stern (1948) and Uphoff and Stern (1949) data to be directly relevant to somatic cells, undercutting a fundamental basis of Lewis' LNT assertion in Draft #2 and in the *Science* paper (Lewis, 1957a).
10. **Errors of Omission**: In the *Science* paper Lewis (1957a) failed to cite the massive research undertaken by the US government on the effects of atomic bomb radiation on mice. These studies involved up to 7000 animals in dose response experimentation. A key 1954 publication by Furth and Upton wrote that the threshold radiation dose for leukemia induced was greater than 424 rads which exceeds the human median lethal dose. This is a massively high dose in a susceptible model. While these data need to be evaluated within the context of study strengths and limits and extrapolative relevance, it is again bewildering that Lewis (1957a) failed to discuss or even cite these atomic bomb explosion study findings. While his intent cannot be known, it must be noted that these findings were not supportive of the LNT perspective his paper emphasized.
11. **Congressional Testimony 1959 Misrepresentations**: Lewis writes on page 7 of his 1959 Congressional testimony that **"These studies (12–14) that have been reported since 1957 have contributed results which are in substantial agreement with the conclusion dawn in testimony presented by the present witness at the 1957 Hearing.**" This statement references the Wald (1958) report (Reference #14) which Cuttler and Welsh (2015) used to support the hormesis hypothesis, contradicting the Lewis perspective. Reference #12 is the Court-Brown and Doll (1957) reference that was not able to differentiate amongst possible dose response models. This reference was also not supportive of his statement. The third reference (#13), Court-Brown and Doll (1958a), flatly contradicts the Lewis (1957a) *Science* paper and his 1959 testimony. The data in Table 2 of the Court-Brown and Doll (1958a) paper indicate that the odds ratios of leukemia of radiologists from pre- 1921 and post-1920 to the present were less than the control population (0.3 and 0.7, respectively), suggestive of a hormetic response. The three references that Lewis stated supported his linearity testimony not only fail to do this but two supported an opposing hypothesis (i.e., hormesis).

6. Discussion

6.1. Hormesis findings in perspective

Despite the significant issue of bias and its use by the BEAR Genetics Panel and Lewis to manipulate the scientific evidence, public opinion, and risk assessment policy, it is important to first address whether low doses of radiation exposure at Hiroshima and Nagasaki actually decreased leukemia incidence. Hormetic-J-shaped dose responses were consistently presented (Table 2 and Figs. 1–3) in multiple papers by different research groups covering a 40 year latency period for males and females in both cities, a type of replication. In these studies, the number of cases expanded from about 50 cases in the early 1950s to more than 10-fold that number over another three decades along with several changes in dose reconstruction methods. These observations provide support for the stability and reproducibility of the hormetic dose response in these two expanding data sets.

These findings challenge a seven decade belief and worldwide risk

assessment policy and practices that the LNT dose response reliably predicts responses in the low dose zone for radiation-induced leukemia for atomic bomb survivors. Yet, despite the public availability of these data and their significance in worldwide cancer risk assessment such findings were only gently hinted at by Jaworowski (2010) [14] and then suggested in a limited manner by Cuttler (2014a,b; 2018) and Cuttler and Welsh (2015) for Hiroshima based on the single Wald (1958) paper. Even though the findings that Cuttler and Welsh (2015) cited were also reported by the UNSCEAR (1958) they were ignored and essentially given no real standing in the scientific community.

An analysis of how these data were considered by the authors and their peer contemporaries is similarly important in that the hormetic-J-shaped dose response data are presented in tables yet never commented on within the framework of a J-shaped dose response. This gives the distinct impression that the findings could not be real but most likely background variability. Of interest is that the US NAS BEAR Pathology Committee (1956a) reported evidence of a J-shaped response in one of their tables (Appendix I-12). However, an accompanying figure on the next page of that report based on that table represented the data as a linear dose response. It was as if the data made no difference. This was especially significant since the table and figure represented at this time included the totality of the available data. These observations suggest that the members of that panel followed a particular dose response belief system rather than following the data. However, as strong as that "belief" system was at that time it was not a universal belief as there was some diversity of views on the matter. For example, a well-established UK radiation medical scientist (RH Mole) wrote on this general issue in 1959: **"It seems to me that those who have not already committed themselves to recommendations for practical action because of a belief that the linear hypothesis is true, and who are able, therefore to view the evidence more dispassionately, will find very little evidence, as distinct from theorizing, in** support of **a linear hypothesis and more than a very little against it. The ease with which the linear hypothesis makes it possible to calculate spuriously accurate estimates of damage to whole populations is a temptation to believe in the hypothesis and this, like most temptations, is perhaps better resisted. A proper appreciation of the meaning of organization in living things makes the linear hypothesis really very unlikely"** (Mole, 1959). Nonetheless, LNT became not only the cancer risk assessment paradigm but a societal belief as well.

Despite this history and controlling beliefs that have the capacity to filter and prejudge data as suggested above, the present paper was stimulated by the Cuttler (2014a, 2018) challenge. The consistent J-shaped findings for the radiation-leukemia data therefore prevent a presumptive dismissal of now substantial J-shaped findings for leukemia but raise the question as to whether the hormetic effect is real or an artifact of some unknown combination of variables.

In addressing this question, it is important to note that hormetic effects are typically modest, being in the 30–60% range, which is where most of the reported decreases in leukemia incidences reside. However, the atomic bomb survivor studies, like the vast majority of epidemiological literature, have important limitations, which are magnified when assessing low dose effects (Taubes, 1995). This present assessment identified a number of limitations of Lewis (1957a) and subsequent reports by the ABCC/RERF investigators. However, some of the same criticisms would be applicable to a hormetic interpretation of those epidemiological data as well. Despite the consistency of the hormetic findings over time, with expanding numbers of cases and between the two cities, considerable uncertainty remains.

Due to limitations inherent in epidemiological studies to detect low dose effects the hormetic dose response concept has been constructed from the ground up, that is, with an overriding emphasis on *in vitro* and *in vivo* experimental studies linked over the past two decades to mechanistic foundations (Calabrese and Blain, 2011; Calabrese, 2013a,b; Calabrese and Kozumbo, 2021). This substantial literature indicates that hormesis is reproducible and a very generalizable phenomenon, being independent of biological model, inducing agent and endpoint measured (Calabrese and Mattson, 2017). In head-to-head comparisons with the threshold and LNT models hormesis strongly predominated. Thus, the dismissive attitude and beliefs of the past lack support. A recent paper in the journal *Cell on the Hallmarks of Health* one of the key hallmarks identified and assessed in depth was hormesis (Lopez-Otin and Kroemer, 2021). Furthermore, there have been a large number of experimental studies demonstrating hormesis in lifetime cancer studies using radiation and with relevant mechanism findings (Sanders, 2010).

What are the implications of these findings for risk assessment? While the data are supportive of a hormetic interpretation, there is uncertainty that may never be resolved due, in part, to data that was not collected and with cases long deceased. Given such uncertainty and disputes of low dose risk assessment, Calabrese et al. (2016) proposed a novel approach for cancer risk assessment using model optimization that integrates essential features of each model (i.e., LNT, threshold and hormesis). This assessment shows that the nadir of the hormetic response closely converges with the dose obtained from standard risk assessment practices using animal model data and two uncertainty factors (i.e., animal to human and interindividual variation). This value is similar to the dose associated with a cancer risk of 1/10,000 using LNT modeling estimates. This model convergence compromise provides a scientifically sound yet practical risk assessment path forward.

6.2. Lewis and his impact in perspective

The paper of Lewis captured the attention of the scientific community and general public. As a highlighted and editorialized publication in *Science*, the Lewis (1957a) paper became prominent very quickly as did its author. However, the peer review process of Lewis' paper became highly suspect given the series of detailed critiques, mostly in other journals, concerning his research methods and scientific judgements. In addition, the present paper provides a series of complementary criticisms and multiple examples of bias affecting his principal conclusions (Fig. 4).

The timing of the Lewis (1957a) paper occurred just prior to Russell et al. (1958) showing that dose rate was key to mutation and dependent on a DNA repair process. Even though the Russell findings were not a criticism of the Lewis paper it created the framework for considerable subsequent scientific challenges. It is noteworthy that Lewis failed to cite this paper as a significant development in his 1959 Congressional testimony, another peculiar error of omission.

The present assessment raises important questions about bias and how it may have affected the Lewis (1957a) paper and his Congressional testimonies. The evidence presented herein indicates that Lewis was not a fair broker of the dose response-leukemia risk assessment question. His bias was pervasive, multilayered, always in the direction of ensuring support for an LNT interpretation. It involves errors of commission such as using biased methods to obtain supportive findings and errors of omission, such as not discussing unsupportive studies including the atomic bomb studies with mice or the AS study and how the British Medical Counsel as well as Court-Brown and Doll (1957) could not use it to support LNT (Fig. 4). Yet, such contrary views were hidden from the reader. These biased actions carried over to his Congressional testimony, highlighted by the series of incorrect and arguably dishonest statements, misleading national legislative leaders. Despite the obvious and multiple series examples of bias and possible dishonesties, for nearly seven decades Lewis has been enshrined with the myth of a fair-minded scientist.

[14] Jaworoski (2010), a longtime member of UNSCEAR, wrote that the evidence of hormesis in the Wald (1958) paper and reprinted in the UNSCEAR (1958) report, was not commented on. He noted that "the standard policy line of UNSCEAR and of international and national regulatory bodies over many decades has been to ignore any evidence of radiation hormesis and to promote LNT philosophy."

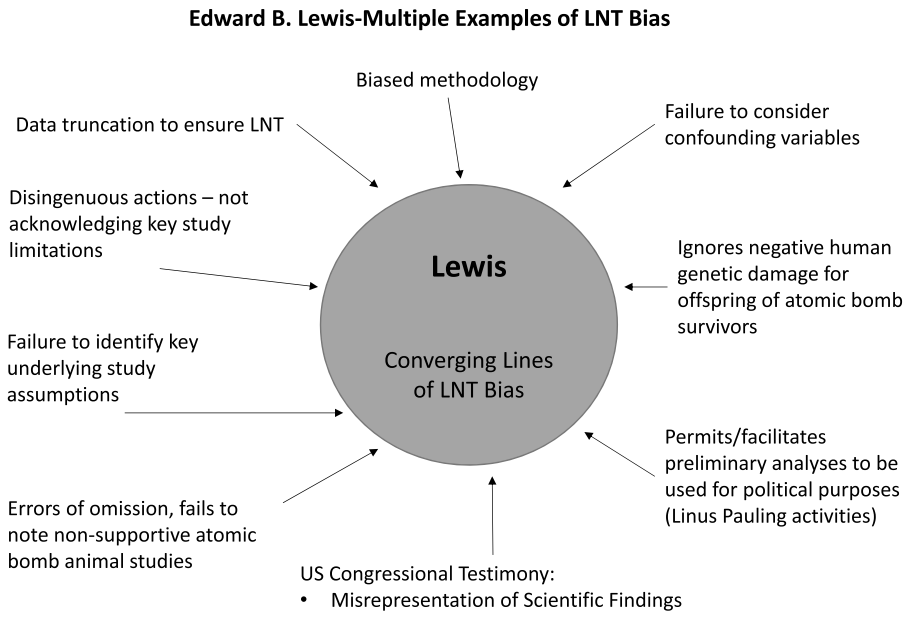

Fig. 4. Edward B. Lewis – Multiple examples of LNT bias.

The evidence overwhelmingly contradicts this view. Yet, this image was important to ensure the adoption of his LNT viewpoint. Even the technical criticisms of Lewis (1957a) by other contemporary scientists failed to address the bias concerns documented here.

The influence of BEAR I Geneticists is seen throughout the Lewis (1957a) *Science* publication. Who gave Lewis the idea? The inspiration started with Sturtevant and becomes refined and encouraged by Beadle. The cancer risk assessment calculations by Lewis were conducted in collaboration with another BEAR Genetics Panel member, James Crow. In the remembrance article about Lewis, Crow and Bender (2004) writes that the two (i.e., Lewis and Crow) **"had frequent discussions of statistical problems. We both made estimates of the consequences of a specified level of radiation, he for somatic and I for genetic. In each case, Linus Pauling took our numbers**[15] **and calculated the worldwide effects from radioactive fallout, present and future, making each of us a bit uncomfortable with the extrapolation."** The *Science* journal peer review and editorial were likely influenced by Bentley Glass (1957) who also acted to assure acceptance of the Lewis agenda with Glass' follow up paper in *Science*. In addition, Lewis also emphasized that the now compromised Spencer and Stern (1948) and Uphoff and Stern (1949) papers was the factor in making the final transition to accept and promote the LNT-cancer paradigm. Thus, the BEAR I Genetics Panel and the effects of Lewis' paper while distinct from one another, are essentially indistinguishable, part of a coherent general strategy that had many options. These options were further extended by the appointment of Lewis and Crow to the NCRPM leading to the first recommendation for LNT for cancer risk assessment by a major advisory organization. Unless one looks closely one doesn't see how the pieces seem to fit together.

In the end, the most troubling aspect of this story is that Lewis could not follow the data, being affected by culture and paradigm and their attendant controlling features. While he was surrounded by senior leadership in the persons of Sturtevant, Beadle and Crow, they proved poor role models in some important respects, being only too willing to misrepresent the research record once they had their chance with the BEAR I Genetics Panel (Calabrese, 2020).

Some of the biases displayed by Lewis (1957a) are also apparent in key papers of the ABCC and RERF. For example, this paper provides multiple examples of control group data manipulation whereby research teams transform a possible hormetic dose response into the favored LNT dose response. The examples of data manipulation in the assessment of epidemiological findings in the atomic bomb survivor studies area were not uncommon and take multiple shapes. For example, additional cases are seen in the Pinkston et al. (1981) study on head and neck cancer which combined results across 1–99 rads. Takeichi et al. (1976) combined findings from 1500–5000 m from the hypocenter, another manifestation of the same concept. However, there are examples when researchers from that same community did not manipulate the control group data as in the case of Shimizu et al. (1990) which continued to show the hormetic-J-shaped dose response using the then 1986 RERF revised dose reconstruction for 1950–1985. Despite these findings the LNT predisposition continued with the BEIR VII Committee (2006) as they estimated an excess of 170 leukemia cases from exposure of A-bomb survivors exposed to 100 mSv, yet the epidemiological data displayed a threshold at about 200 mSV and hormetic responses under that exposure.

In the end, the hormesis or threshold findings of Cuttler and Welsh (2015) are supported by the present research. However, the more important conclusion is that the scientific community, including worldwide regulatory agencies, such as the US EPA, uncritically followed the example set by the BEAR I Genetics Panel and the actions of Lewis (1957a), ignoring and often misrepresenting data affecting public health policies in a global way. This situation is not simply a failure of science but of ethics as well.

7. Conclusions

1. The epidemiological data on survivors of the atomic bombs displayed hormetic responses for leukemia in a highly consistent manner throughout the 1950s when the LNT-dose-response policy was being formulated and recommended.
2. The leukemia hormetic dose response findings have been consistently reported over a 40 year latency period in both Hiroshima and Nagasaki.
3. The adoption of LNT for cancer risk assessment was strongly influenced by Edward B. Lewis, based on his editorially endorsed

[15] Crow and Bender (2004) wrote that Pauling "took" their (i.e., Lewis and Crow) calculations. However, it would seem that he and Lewis "shared" their calculations with Pauling and let him use them without restriction. That is, Lewis and Crow were part of the Pauling process, permitting it to occur.

publication in *Science* in 1957a along with support of the radiation geneticist community lead by Hermann J. Muller and the US NAS BEAR I Genetics Panel.

4. This paper provides overwhelming evidence of bias by Lewis in favor of LNT, as has been shown with the NAS BEAR I Genetics Panel, precluding the capacity for objective and fair risk assessment of the cancer risk assessment issue.
5. The adoption of LNT was accomplished by manipulation of the media, legislators and the scientific community by ideologically-driven prominent scientists, such as Linus Pauling and Edward Lewis and the unethical practices of the NAS BEAR I Genetics Panel.
6. Jacob Furth, President of the American Association for Cancer Research, testified for Congress in 1959 on the Lewis petition to support LNT for radiation-induced leukemia. Furth informed the Congress that the position of Lewis was **"pure speculation not backed by data."** While Furth was correct in his appraisal the Lewis position is also refuted by the data itself.
7. The adoption of LNT by regulatory agencies such as EPA as influenced by the US NAS BEAR Panels and by scientists such as Lewis was in retrospect a profound error with major societal and scientific consequences and needs correction.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abrams, H.L., 1981. Medical problems of survivors of nuclear war. NEJM 305, 1226–1232.
Beebe, G.W., Ishida, M., Jablon, S., 1962. Studies of the mortality of A-bomb survivors. 1. Plan of study and mortality in the medical subsample (selection 1), 1950-1958. Radiat. Res. 16, 253–280.
Beebe, G.W., Kato, H., Land, C.E., 1978. Studies of the mortality of A-bomb survivors: 1. Mortality and radiation dose, 1950-1974. Radiat. Res. 75, 138–201.
Biological Effects of Atomic Radiation, 1956a. Report of the Panel on the Genetic Effects of Ionizing Radiation. US National Academy of Sciences, Washington, DC.
Biological Effects of Atomic Radiation, 1956b. Report of the Committee on Pathologic Effects of Atomic Radiation, vol. 453. US National Academy of Sciences, Washington, DC, pp. 1–12 appendix 1.
Biological Effects of Atomic Radiation, 1956c. Committee on pathologic effects of atomic radiation. Discussion Transcripts. US National Academy of Sciences, Washington, DC. January 22, 1956, page 40.
Biological Effects of Ionizing Radiation, 1972. US. National Academy of Sciences, Washington, DC.
Biological Effects of Ionizing Radiation, 2006. US National Academy of Sciences, Washington, DC.
Braestrup, C.B., 1957. Past and present radiation exposure to radiologists from the point of view of view of life expectancy. Am. J. Roentgenol. Radium Ther. Nucl. Med. 78, 988–992.
Brill, B., Tomanaga, M., Heyssel, R.M., 1962. Leukemia in man following exposure to ionizing radiation. A summary of the findings in Hiroshima and Nagasaki, and a comparison and other human experience. Ann. Intern. Med. 56, 590–609.
Brown, E.E., 1951. Infectious origins of acute leukemia. Arch. Pediatr. 68, 110–119.
Brues, A.M., 1958. Critique of the linear theory of carcinogenesis. Science 128, 693–699.
Calabrese, E.J., 2009. The road to linearity: why linearty at low doses became the basis for carcinogen risk assessment. Arch. Toxicol. 83, 203–225.
Calabrese, E.J., 2011. Key studies used to support cancer risk assessment questioned. Environ. Mol. Mutagen. 52, 593–606.
Calabrese, E.J., 2013a. Origin of the linearity no threshold (LNT) dose-response concept. Arch. Toxicol. 87, 1621–1633.
Calabrese, E.J., 2013b. Hormetic mechanisms. Crit. Rev. Toxicol. 43, 580–606.
Calabrese, E.J., 2019a. The linear no-threshold (LNT) dose-response model: a comprehensive assessment of its historical and scientific foundations. Chem-Biol. Inter. 301, 6–21.
Calabrese, E.J., 2019b. LNT: new historical perspectives. Chem-Biol. Inter. 308, 110–112.
Calabrese, E.J., 2020. Ethical failures: the problematic history of cancer risk assessment. Environ. Res. 193, 110582.
Calabrese, E.J., Blain, R., 2011. The hormetic database: the occurrence of hormetic dose responses in the toxicological literature. Regul. Toxicol. Pharmacol. 61, 73–81.
Calabrese, E.J., Kozumbo, W.J., 2021. The hormetic dose-response mechanism: Nrf2 activation. Pharmacol. Res. 167, 105526.
Calabrese, E.J., Mattson, M.P., 2017. How does hormesis impact biology, toxicology and medicine. NPJ Aging Mech 3. Article 13.
Calabrese, E.J., Shamoun, D.Y., Hanekamp, J.C., 2016. The integration of LNT and hormesis for cancer risk assessment optimizes public health protection. Health Phys. 110, 256–259.
Carlson, E., 1981. Genes, Radiation and Society. Cornell University Press, NY, p. 245.
Caron, J., 2003. Edward Lewis and Radioactive Fallout: the Impact of CALTECH Biologists on the Debate over Nuclear Weapons Testing in the 1950s and 60s. Undergraduate Senior Thesis. California Institute of Technology, Pasadena, California.
Caron, J., 2004. Biology and "the bomb". Eng. Sci. 2, 17–27.
Caspari, E., Stern, C., 1948. The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in Drosophila melanogaster. Genetics 33, 75–95.
Cooke, J.V., 1942. The incidence of acute leukemia in children. J. Am. Med. Assoc. 119, 547–550.
Court-Brown, W.M., Doll, R., 1957. Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. Medical Research Council Special Report Series No. 295. J. Radiol. Prot. 27, B15–B154. Reprinted in.
Court-Brown, W.M., Doll, R., 1958a. Expectation of life and mortality from cancer among British radiologists. Br. Med. J. 2, 181–187.
Court-Brown, W.M., Doll, R., 1958b. A prospective study of the leukemia mortality of children exposed to antenatal diagnostic radiography. A preliminary report. Proc. Roy. Soc. Med. 53, 761.
Court-Brown, W.M., Doll, R., Hill, B.A., 1960. Incidence of leukaemia after exposure to diagnostic radiation in utero. Br. Med. J. 2, 1539–1545.
Crow, J., 1957. Testimony to the Joint Congressional Committee on Atomic Energy (JCCAE). US Government Printing Office, Washington DC.
Crow, J.F., Bender, W., 2004. Edward B. Lewis, 1918-2004. Genetics 168, 1773–1783.
Cuttler, J.M., 2014a. Remedy for radiation fear-Discard the politicized science. Dose Response 12, 170–184.
Cuttler, J.M., 2014b. Leukemia incidence of 96,000 Hiroshima atomic bombs survivors in compelling evidence that the LNT model is wrong. Arch. Toxicol. 88, 847–848.
Cuttler, J.M., 2018. Evidence of a dose threshold for radiation-induced leukemia. Dose-Response 16 (4).
Cuttler, J.M., Welsh, J.S., 2015. Leukemia and ionizing radiation revisited. J. Leukemia 3, 1–2.
Dameshek, W., 1930. Acute monocytic (histiocytic) leukemia. Arch. Intern. Med. 46, 718.
Divine, R.A., 1978. Blowing on the Wind: the Nuclear Test Ban Debate-1954-1960. Oxford University Press, NY, p. 123.
Doll, R., Hill, A.B., 1950. Smoking and carcinoma of the lung. Br. Med. J. 4682, 739–748.
DuShane, G., 1957. Loaded dice. Science 125, 963.
Folley, J.H., Borges, W., Yamawaki, T., 1952. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. Am. J. Med. 3, 311–321.
Furth, J., 1959. Joint Congressional Committee on Atomic Energy (JCCAE). Government Printing Office, Washington, DC.
Furth, J., Upton, A.C., 1954. Leukemogenesis by ionizing irradiation. Acta Radiol. (CPH) 41 (Suppl. 116), 469–476.
Furth, J., Ferris, H.W., Reznikoff, P., 1935. Relation of leukemia of animals to leukemia of man. J. Am. Med. Assoc. 105, 1824–1830.
Furth, J., Upton, A.C., Christenberry, K.W., Benedict, W.H., Moshman, J., 1954. Some late effects in mice of ionizing radiation from experimental nuclear detonation. Radiology 63, 562–570.
Furukawa, K., Preston, D., Lonn, S., Funamoto, S., Yonehara, S., Matsuo, T., Egawa, H., Tokuoka, S., Ozasa, K., Kasagi, F., Kodama, K., Mabuchi, K., 2010. Radiation and smoking effects on lung cancer incidence among atomic-bomb survivors. Radiat. Res. 174, 1–21.
Glass, B., 1957. Genetics hazards of nuclear radiations. Science 126, 241–246.
Greaves, M.F., 1988. Speculations of the cause of childhood acute lymphobastic leukemia. Leukemia 2, 120–125.
Greaves, F., 1993. An infectious etiology for common acute lymphoblastic leukemia in childhood. Leukemia 7, 349–360.
Greaves, M., 2006. Infection, immune responses and the aetiology of childhood leukaemia. Nat. Rev. 6, 193–203.
Greaves, M., 2018. A causal mechanism for childhood acute lymphoblastic leukaemia. Nat. Rev. Canc. 18, 471–484.
Greene, G., 2020. The Woman Who Knew Too Much, second ed. The University of Michigan Press, Ann Arbor, p. 88.
Heyssel, R., Brill, B., Woodbury, L.A., Nishimura, E.T., Ghose, T., Hoshino, T., Yamasaki, M., 1960. Leukemia in Hiroshima atomic bomb survivors. J. Hematol. 15, 313–331.

Hsu, W.L., Preston, D.L., Soda, M., Sugiyama, H., Funamoto, S., Kodama, K., Kimura, A., Kamada, N., Dohy, H., Tomonaga, M., Iwanaga, M., Miyazaki, Y., Cullings, H.M., Suyama, A., Ozasa, K., Shore, R.E., Mabuchi, K., 2013. The incidence of leukemia, lymphoma, and multiple myeloma among atomic bomb survivors: 1950-2001. Radiat. Res. 179 (3), 1–45.
Ishimaru, T., Hoshino, T., Ichimaru, M., Okada, H., Tomiyasu, T., Tsuchimoto, T., Yamamoto, T., 1971. Leukemia in atomic bomb survivors, Hiroshima-Nagasaki. Radiat. Res. 45, 216–233, 1 October 1950—30 September 1966.
Ishimaru, T., Otake, M., Ichimaru, M., 1979. Dose-response relationship of neutrons and γ rays to leukemia incidence among atomic bomb survivors in Hiroshima and Nagasaki by type of leukemia, 1950-1971. Radiat. Res. 77, 377–394.
Iwaoka, K., Yonehara, H., 2012. Natural radioactive nuclides in cigarettes and dose estimation for smokers. J. Radioanal. Nucl. Chem. 293, 973–977.
Jablon, S., Kato, H., 1970. Childhood cancer in relation to prenatal exposure to atomic-bomb radiation. Lancet 2 (7681), 1000.
Jablon, S., Ishida, M., Beebe, G.W., 1964. Studies of the mortality of A-bomb survivors. 2. Mortality in selections I and II, 1950-1959. Radiat. Res. 21, 423–445.
Jaworowski, Z., 2010. Radiation hormesis-A remedy for fear. Hum. Exp. Toxicol. 29, 263–270.
Jolly, J.C., 2003. Thresholds of Uncertainty: Radiation and Responsibility in the Fallout Controversy. Dissertation, Oregon State University, Corvallis, OR.
Kaplan, H.S., 1954. On the etiology and pathogenesis of the Leukemias: a Review. Canc. Res. 14, 535–548.
Kimball, A.W., 1958. Evaluation of data relating human leukemia and ionizing radiation. J. Natl. Cancer Inst. 21, 383–391.
Lange, R.D., Moloney, W.C., Yamawaki, T., 1954. Leukemia in atomic bomb survivors. 1. General observations. Blood 9, 574.
Lewis, E.B., 1954. The theory and application of a new method of detecting chromosomal rearrangements in Drosopholia melanogaster. Am. Nat. 88, 225–239.
Lewis, E.B., 1955. Memorandum on Fallout. November 28th. L.C.a.C.F. Pauling. Pauling Archives, Pasadena, CA.
Lewis, E.B., 1956. Second Draft of Leukemia and Ionizing Radiation. November 30th. LC. a.F.F. Pauling Archives, Pasadena, CA.
Lewis, E.B., 1957a. Leukemia and ionizing radiation. Science 125, 965–972.
Lewis, E.B., 1957b. Testimony to the Joint Congressional Committee on Atomic Energy (JCCAE), vol. 3. June, Washington, DC, p. 959.
Lewis, E.B., 1959. Summary-Statement of EB Lewis. May 7, 1959. Congressional Testimony, Fallout Hearings. Pauling Archives, Oregon State University, Corvallis OR.
Lewis, E.B., 1998. Ionizing radiation, cancer induction, and radioactive fallout. Bull. Pol. Acad. Sci. Biol. Sci. 46 (3–4), 185–191.
Lewis, E.B., 2004. Edward B. Lewis: autobiography. In: Lipshitz, H.D. (Ed.), Genes, Development, and Cancer: the Life and Work of Edward B. Lewis. Springer Publishers, New York NY, pp. 497–502.
Lipshitz, H.D., 2004. From fruit flies to fallout: Ed Lewis and his science. J. Genet. 83, 201–218.
Lipshitz, H., 2007. Lewis and the somatic effects of ionizing radiation. In: Lipshitz, H.D. (Ed.), Genes, Development and Cancer. Springer Publishers, New York, NY, pp. 415–431.
Lightfoot, T.J., Roman, E., 2004. Causes of childhood leukaemia and lymphoma. Toxicol. Appl. Pharmacol. 199, 104–117.
Lopez-Otin, C., Kroemer, G., 2021. Hallmarks of health. Cell 184, 33–63.
Love, A.A., 1936. Manifestations of leukemia encountered in otolaryngologic and stomatologic practice. Arch. Otoloryng. 23, 173.
March, H.C., 1944. Leukemia in radiologists. Radiology 42, 275.
March, H.C., 1947. Leukemia in radiologists. J. Am. Med. Assoc. 135, 179.
March, H.C., 1950. Leukemia in radiologists in a 20 year period. Am. J. Med. Sci. 220, 282.
Maynard, C.W., 1921. Acute myelogenous leukemia. J. Am. Med. Assoc. 76, 238.
McKinney, P.A., Cartwright, R.A., Saiu, J.M.T., Mann, J.R., Stiller, C.A., Draper, G.J., Hartley, A.L., Hopton, P.A., Birch, J.M., Waterhouse, J.A.H., Johnston, H.E., 1987. The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. Arch. Dis. Child. 62, 279–287.
Miller, A.B., Howe, G.R., Sherman, G.J., Lindsay, J.P., Yaffe, M.J., Dinner, P.J., Risch, H. A., 1989. Mortality from breast cancer after irradiation during fluoroscopic examination in patients being treated form tuberculosis. N. Engl. J. Med. 321, 1285–1289.
Mine, M., Okumura, Y., Ichimura, M., Nakamura, T., Kondo, S., 1990. Apparently beneficial effect of low to intermediate doses of A-bomb radiation on human lifespan. Int. J. Radiat. Biol. 58, 1035–1043.
Mole, R.H., 1958. The dose-response relationship in radiation carcinogenesis. Br. Med. Bull. 14, 184–189.
Mole, R.H., 1959. Criteria for a threshold in radiation effects. Br. J. Radiol. 32, 283–284.
Moloney, W.C., Kastenbaum, M.A., 1955. Leukemogenic effects of ionizing radiation of atomic bomb survivors in Hiroshima City. Science 121, 308–309.
Muller, H.J., 1954. Letter to AH. Sturtevant. September 22, 1954. California Institute of Technology, Pasadena, CA. CalTech Archives, Sturtevant Paper, box 11, folder 1.
Muller, H.J., 1956. Muller Letter to BEAR Genetics Panel. American Philosophical Society (APS), Philadelphia, PA, Neel Papers. December 5.
NCRPM, 1960. Somatic radiation dose for the general population. Science 131, 482–486.
Neel, J.V., Schull, W.J., 1956. The effects of exposure to the Atomic Bombs on Pregnancy termination. In: Hiroshima and Nagaski, vol. 461. National Academies Press, Washington DC. https://doi.org/10.17226/9548.
Pierce, M., 1936. Childhood leukemia. J. Pediatr. 8, 66.
Pinkston, J.A., Wakabayashi, T., Yamamoto, T., Asano, M., Harada, Y., Kumagami, H., Takeuchi, M., 1981. Cancer of the head and neck in atomic bomb survivors-Hiroshima and Nagasaki, 1957-1976. Cancer 48, 2172–2178.
Pollycove, M., 1998. Nonlinearity of radiation health effects. Environ. Health Perspect. 106 (Suppl. 1), 363–368.
Replogle, M.L., Kasumi, W., Ishikawa, K.B., Yang, S.F., Juji, T., Miki, K., Kabat, G.C., Parsonnet, J., 1996. Increased risk of Helicobacter pylori associated with birth in wartime and post-war Japan. Int. J. Epid. 25, 210–214.
Richardson, R.B., 2011. Promotional etiology for common childhood acute lymphoblastic leukemia: the infective lymphoid recovery hypothesis. Leuk. Res. 35, 1425.
Russell, W.L., Russell, L.B., Kelly, E.M., 1958. Radiation dose rate and mutation frequency. Science 128 (3338), 1546–1550.
Sanders, C.L., 2010. Radiation Hormesis and the Linear-No-Threshold Assumption. Springer Verlag, Berlin, p. 214.
Sakoda, A., Filap, K., Kawabe, A., Kataoka, T., Hanamoto, K., Yanaoka, K., 2012. Radioactivity of 210Pb in Japanese cigarettes and radiation dose from smoking inhalation. Radiat. Protect. Dosim. 150, 109–113.
Seyler, T.H., Kim, J.G., Hodgaon, J.A., Cowan, E.A., Blount, B., Wang, L., 2013. Quantitation of urinary volatile nitrosamines from exposure to tobacco smoke. J. Anal. Toxicol. 37, 195–2002.
Shimizu, Y., Kato, H., Schull, W.J., 1990. Studies on the mortality of A-bomb survivors. 9. Mortality, 1950-1985: part 2, Cancer mortality based on the recently revised doses (DS86). Radiat. Res. 121, 141.
Simpson, C.L., Hempelmannm, L.H., Fuller, L.M., 1955. Neoplasia in children treated with X-rays in infancy for thymic enlargement. Radiology 64, 840–845.
Spencer, W.P., Stern, C., 1948. Experiments test the validity of the linear R-dose mutation frequency relation in Drosophila at low dosage. Genetics 33, 43–74.
Stern, C., 1955. Letter to AH. Sturtevant. CalTech archives. Sturtevant Paper, box 11, folder 2.
Sternberg, C., 1926. Akute leukamie. In: Henke and Lubarsch: Handbuch der speziellen pathologiscche anatomie und histologie, 1. Julius Springer, Berlin, p. 76.
Stocks, P., 1970. Cancer mortality in relation to national consumption of cigarettes, solid fuel tea and coffee. Br. J. Canc. 24, 215—225.
Strauss, L., 1954. The H-bomb world opinion: chairman strauss's statement on the pacific tests. Bull. At. Sci. 10 (5), 161.
Sturtevant, A.H., 1954. Social implications of the genetics of man. Science 120, 405–407.
Sturtevant, A.H., 1955. The genetic effects of high energy irradiation of human populations. Eng. Sci. 28, 9–12.
Sutou, S., 2017. Rediscovery of an old article reporting that the area around the epicenter in Hiroshima was heavily contaminated with residual radiation, indicating that exposure doses of A-bomb survivors were largely underestimated. J. Radiat. Res. 58, 745–754.
Sutou, S., 2018. Low-dose radiation from A-bombs elongated lifespan and reduced cancer mortality relative to un-irradiated individuals. Gene Environ. 40, 26.
Sutou, S., 2020. Black rain in Hiroshima: critique to the Life Span Study of A-bomb survivor, basis of the linear no-threshold model. Gene Environ. 42, 1–11.
Takeichi, N., Hirose, F., Yamamoto, H., 1976. Salivary gland tumors in atomic bomb survivors, Hiroshima, Japan. 1. Epidemiologic observations. Cancer 38 (6), 2462–2468.
Taubes, G., 1995. Epidemiology faces its limits. Science 269, 164.
Tavasolian, F., Abdollahi, E., Vakili, M., Amini, A., 2014. Relationship between ABO blood group and acute lymphoblastic leukemia. Iranian J. Ped. Hematol. Oncol. 14, 1–4.
Tomonaga, M., 1962. Leukaemia in Nagasaki atomic bomb survivors from 1945 through 1959. Bull. World Health J. 26, 619–631.
United Nations Scientific Committee on the Effects of Atomic Radiation, 1958. Report to the General Assembly (New York, NY, United Nations).
Uphoff, D., Stern, C., 1949. The genetic effects of low intensity irradiation. Science 109, 609–610.
Upton, A.C., Furth, J., Christenberry, K.W., 1954. Late effects of thermal neutron irradiation in mice. Canc. Res. 14, 682–690.
Wakabayashi, I., Sakamoto, K., Masui, H., Yoshimoto, S., Kanamaru, A., Kakishita, E., Hara, H., Shimo-Oka, M., Nagai, K., 1994. A case-control study on risk factors for leukemia in a district of Japan. Intern. Med. 33, 198–203.
Warren, S.L., 1929. Acute leukemia: a review of the literature and of 28 new cases. Am. J. Med. Sci. 178, 490.
Warren, S., 1959. Testimony to Joint Congressional Committee on Atomic Energy (JCCAC) (Washington DC).
Watanabe, S., Tosio, I., Matsubayasi, Y., 1960. Statistical observation on leukemias in Hiroshima during the past fourteen years (1946-1959). J. Radiat. Res. 1, 81–90.
Watanabe, S., 1961. On the incidence of leukemias in Hiroshima during the past fifteen years from1946 to 1960. J. Radiat. Res. 2, 131–140.
Wald, N., 1958. Leukemia in Hiroshima city atomic bomb survivors. Science 127, 699–700.
Ward, G., 1917. The infective theory of acute leukaemia. Brit. J. Child. Dis. 14, 10–20.
Weinhouse, S., Furth, J.J., 1993. Jacob Furth. National Academy of Sciences, Washington, DC, pp. 167–197.