This paper argues that Edward B. Lewis served as a type of independent academic radiation LNT-cancer risk assessment-stalking horse for the BEAR Genetics Panel, a task for which he had no expertise or experience (e.g., radiation, leukemia, epidemiology and statistical modelling). His efforts produced an insufficiently documented, strongly biased, and high-profile paper in Science (May 17, 1957), whose principal conclusions had not been proven, he asserted privately, in writing. This inconclusive perspective was well camouflaged in the published paper by means of sophisticated wordsmithing. At the time his academic department head George Beadle came to chair the BEAR Genetics Panel in the summer of 1956, the Beadle-inspired-Lewis LNT activity acquired an urgency when a study of 70,000 offspring from survivors of the A-bombs failed to show genetic damage after a decade of careful study, undercutting Panel recommendations. With Beadle’s guidance, the Lewis effort redirected the Panel’s focus from the atomic bomb genetic damage study, which had acrimoniously disrupted Panel relationships and priorities, to more immediate disciplinary/professional opportunities with concerns about fallout, leukemia risks and a new cancer causation role for mutation. The serious limitations of the Lewis paper affected neither its publication in Science nor its receiving an editorial endorsement, possibly due to influence by powerful Panel members, such as Bentley Glass, one of only six senior editors for Science. The Science publication restored, even though improperly, the scientific and moral initiatives of the Panel and led directly to multiple high level LNT recommendations for cancer risk assessment based on the Precautionary Principle, which Lewis asserted, and which remains in place today in essentially all countries. The present paper explores how such a scientific long-shot and quasi-stalking horse, who was unsupported by BEAR Panel members during the withering criticism prompted by his Science article, nevertheless endured in the pursuit of his LNT goal, becoming strikingly successful in achieving a global cancer risk assessment revolution which remains in place.

1. Introduction

Calabrese (2021) recently published an historical assessment of the adoption of the linear non-threshold (LNT) dose-response model for radiation-induced leukemia. Leukemia is historically important since it was the first cancer type assessed in detail within the radiation-LNT context; the process was later generalized to chemical carcinogens and other tumor types (Calabrese, 2009, 2011, 2013, 2015, 2019). Edward B. Lewis, a young professor in the area of Drosophila genetics at the California Institute of Technology (CalTech), played a significant role in this cancer risk assessment story because his 1957a Science paper transformed the process of cancer risk assessment, eventually leading to the adoption of LNT, which was framed within the context of the Precautionary Principle.

An unappreciated aspect of the Lewis-cancer risk assessment story is that Lewis was professionally unsuited for this role. He lacked professional education and training in radiation (physics, biology and dosimetry), leukemia, epidemiology, cancer risk assessment and statistical modelling. He developed his paper without any collaborators who might have complemented his educational/work experience limitations. Given the significance of the issues that Lewis confronted, his lack of professional standing in crucial areas and a seriously flawed manuscript, it is puzzling how he could achieve publication in Science with an accompanying supportive editorial and endure the unrefuted criticism that challenged his study’s foundations. In spite of all this, he remarkably achieved widespread international regulatory agency success.

In the world of politics, the stalking horse concept is seen when a junior politician acts to promote the interests of a senior politician, who remains unseen in case the actions would damage him or her but nevertheless wants to provoke a debate or challenge to an opponent. In
the world of LNT science and its own version of politics, a recent historical analysis (Calabrese, 2021) of the seminal Lewis (1957a) paper suggests that he may have served the role of a stalking horse for leaders of the U.S. NAS Biological Effects of Atomic Radiation (BEAR) Genetics Panel to promote their LNT agenda. This novel and provocative suggestion will be assessed in this paper.

2. LEWIS: as a stalking horse of the BEAR Genetics Panel

Lewis became motivated to assess the leukemia and radiation issue after a July 1955, memo from George Beadle (Caron, 2003), his academic department chair, encouraging the biology department faculty to assess the effects of low level exposures to ionizing radiation within the emerging radiation fallout controversy. Lewis took the challenge and by November 1955, he developed his first Fallout Memo. Yet, this first draft memo was far from impressive, reflecting what was not much more than a cursory interest. It was a four-page memo entitled “Memorandum of Fallout” that had two sections: (1) “Genetic Effects of Fallout” (three pages) and (2) “Direct Effects of Irradiation” (slightly more than one page). The numbers of references cited were limited to four for section 1 and three for section 2 (Lewis, 1955). Despite this limited development, the references centered on atomic bomb and leukemia studies, which would prove to be the principal focus of subsequent efforts. One year later Lewis (1956a) expanded the effort into a second Fallout Memo, a document that was far more developed with the goal of assessing leukemia risk from ionizing radiation via the use of the LNT model. This Fallout Memo represented a draft of what would become his Science publication, which he titled “Leukemia and Ionizing Radiation”. That draft paper was almost exclusively centered on the survivors of the Japan atomic events, with a very modest recognition of leukemia in X-ray treated patients with ankylosing spondylitis (AS).

During the time period of the Lewis involvement with the Fallout Memo, the NAS created the BEAR Panels, including the Genetics Panel that included George Beadle and Alfred Sturtevant from Edward B. Lewis’ department. The Panel had their first meeting in late November 1955, and published its landmark report recommending the adoption of LNT for genetic risk assessment on June 12, 1956 (BEAR, 1956).

Despite the LNT recommendation of the Panel and its substantial publicity, all was not well within the ranks of the NAS BEAR Genetics Panel. During the early to mid 1950s the radiation genetics community was seeking to extend its prominence. Supporting such professional posturing involved making claims that radiation-induced mutation was a significant public health and medical concern and that there was no safe level of exposure. This initiative was being led by the 1946 Nobel Laureate Hermann J. Muller in multiple venues. However, concerns were raised within the radiation genetics field in 1953 when a preliminary report indicated that the offspring of survivors of the atomic bombs were not showing evidence of hereditary damage (Neel et al., 1953). This trend would continue through the next reporting period, which was towards the end of 1955. In fact, the ten-year study of over 70,000 offspring of the survivors of the bombings at Hiroshima and Nagasaki continued to show no hereditary damage (Neel and Schull, 1956). These findings so disturbed the LNT-committed NAS BEAR Genetics Panel that they denied scientific standing to the Neel and Schull (1956) research (i.e., refused to assess the study), even though it was a major international study under the auspices of the NAS, was led by one of the Panel members (James V. Neel) and was essential to the charge of the Panel (Calabrese, 2020a,b).

With the blatant shunning of the NAS human genetics damage study, the Panel chose to rely, instead, on fruit fly data for human risk assessment because it supported the LNT model [see Calabrese (2020b) for a detailed critique the Panel’s LNT position]. Despite this action by the Panel to ignore the negative findings of Neel and Schull (1956) and to advocate for an LNT acceptance, the Panel-driven LNT-ideological momentum had taken a scientifically meaningful hit because of the results of Neel and Schull, which made low dose radiation appear far less scary than had been presented in the media, at times based on viewpoints expressed by radiation genetics leaders on the BEAR Genetics Panel. Of course, such hereditary damage might occur in subsequent generations of atomic bomb survivor offspring, but that would be difficult to study and was beyond the realm of contemporary debate.

Despite the rejection of his report by the NAS BEAR Genetics Panel, Neel shared it with a parallel British Genetics Panel. That Panel endorsed Neel’s findings and incorporated his study’s insights into its public health recommendations (Calabrese, 2020b). The mutation risk assessment message was therefore quite different between the two Panels, with the Neel and Schull (1956) study being a principal factor. Adding more controversy to this issue was the public challenging of Muller by Neel at an international Congress in early August 1956, followed by a WHO meeting with the Neel-Muller conflict coloring the two-week period, with neither one giving any ground. This dispute had become personally contentious, with other geneticists choosing sides, which was becoming disruptive to the radiation genetics community, spilling over to the activities of the BEAR Genetics Panel (Calabrese, 2020b).

It was during this period of controversy when the second Lewis Fallout Memo/draft-Science journal manuscript was developed. If the radiation geneticists of the BEAR Genetics Panel were to win in the arena of public opinion and policy concerning the effects of low doses of ionizing radiation, their goals, strategies and tactics needed to change. In retrospect, Lewis entered this scientific drama just in the nick of time to become a hero to his radiation geneticist colleagues. Whether by accident, design or simply by the unfolding of complex human activities, Lewis confronted the “fallout” crisis and the risks of human leukemia, making use of human clinical and epidemiological studies, which were academic areas with which he lacked any educational background or on-the-job experience. Lewis made this seemingly arrogant and potentially risky professional decision based on dose-response mutation beliefs that he had adopted from key leaders in the field of radiation genetics, most notably Muller (Caron, 2003). He may also have sensed the potential power inherent in an academic position within an institution the likes of CalTech.

During this time Beadle had become the chair of the BEAR Genetics Panel and was in close, but separate, written communication with Muller and Neel over their tempestuous dispute relating to the human studies of Neel and their impact on the field (Calabrese, 2021). This controversy expanded in scope with the involvement of other geneticists and continued late into the fall of 1956. Beadle tried to suppress the controversy’s metastasizing destructive potential with an attempt to redirect his Panel toward critical future issues, including the role of mutation in cancer risk assessment. Following Beadle’s encouragement, on November 30, 1956 (with amended corrections sent on December 2, 1956) Lewis (1956b) sent his draft manuscript that strongly asserted a radiation-LNT relationship for leukemia to the BEAR Genetics Panel. While Lewis would get some technical assistance from Neel on newly released atomic bomb exposure information, the broader picture involved the policy implications of Lewis’ LNT leukemia risk estimates and the role of mutation. From a public policy perspective, the Neel and Schull (1956) study essentially pushed the issue of transgenerational genetic damage down the road at least a few decades. The BEAR Genetics Panel would use Lewis and his efforts to reinvent itself with a focus on radiation and cancer risks via mutational mechanisms.

While it is not clear how the BEAR Genetics Panel affected the Lewis manuscript, the draft underwent a series of important changes after the Panel review. For example, the following two sentences are from paragraph 13 (page 6) in the draft document: “There is insufficient evidence on hand to evaluate the shape of the curve relating to incidence of leukemia, especially in the low dose region. The data

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1 The Neel and Schull (1956) study undermined the assertions of Sturtevant (1954, 1955) and the beliefs of the community of radiation geneticists comprising the BEAR I Genetics Panel.
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.”

While this is the central conclusion, it was removed and then “repackaged” with new wordsmithing language into the Science paper to camouflage the meaning. So how did Lewis do this? This was achieved in the Science paper by reframing the conclusion: “A linear relationship between 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.” Lewis also neglected to share with the reader that the authors of the AS paper (Court-Brown and Doll, 1957) stated in the preface of their paper that due to the use of principally very high bone marrow doses “that until much more work has been done it will not be possible to decide between the alternative [dose-response] hypotheses.”

Paragraph 12 of the draft manuscript was removed from the published paper. That entire paragraph was focused on radiation-induced leukemia in animal model studies by Furth and Upton (1954). The question is raised as to why Lewis would remove reference to these studies when the radiation treatment induced both myeloid and lymphoid leukemia. Both types of leukemia were highly prevalent among the atomic bomb survivors (Lewis, 1957a) and therefore are relevant. However, Lewis only presented findings concerning results of the myeloid leukemia. After his brief several sentence summarization, he stated: “However, the statistical significance of these low dose results cannot be assessed since the total number of mice involved is not stated.” This gives the impression that the data from Furth and Upton (1954) were not presented in a manner that was useful. As noted above, the Furth and Upton (1954) paper evaluated the effects of radiation on both lymphoid and myeloid leukemia in mouse models. In the case of the lymphoid leukemia, the numbers of animals in each group surviving four months were provided with over 600 mice in the control group and over 800 mice in the low dose group along with five other higher dose treatment groups. In that experiment, the authors reported a threshold response for lymphoid leukemia at greater than 424 rads (r). In the case of this large lymphoid leukemia experiment, there would have been the opportunity for statistical analyses because the numbers of animals surviving were provided for each group. In the case of the myeloid leukemia experiments, Lewis was correct that the numbers of mice were not presented in their Figure 1. The authors highlighted the induction of myeloid leukemia at 128 r, but they did not discuss the effects at the lower doses tested (i.e., 16 and 32 r). While statistical analyses could not be conducted with the data as they were presented for myeloid leukemia, it is surprising that Lewis did not obtain a copy of the data set, especially given that he had acted in such a manner with Beadle in order to obtain unpublished human data on leukemia from atomic bomb survivors. In retrospect, one could easily suspect that Lewis excluded the animal studies because they did not support the LNT model. In fact, the lymphoid leukemia experiment displayed a clear threshold response with the value being quite high, in the range of a lethal median dose for humans, thereby refuting the LNT interpretation.

The published manuscript of Lewis also misrepresented the paper he cited (Simpson et al., 1955) to support his LNT-leukemia estimates for patients with an enlarged thymus. What Lewis neglected to inform the reader was that the authors disavowed any causal relationship between the X-ray exposures and leukemia in these patients. The authors stated that there is “no definite conclusion to be drawn as to the relationship to the X-ray exposures. This is particularly true for leukemia, which was apparently not associated with any one form of [radiation] treatment or with high radiation doses.” Simpson et al. (1955) also were emphatic in their conclusion that no effect of radiation treatment “could be demonstrated in the case of leukemia.”

The series of Lewis’ misrepresentations of published articles is striking. It nonetheless is surprising that he failed to acknowledge the limitations that authors placed on their published findings. Furthermore, these perspectives of Lewis apparently were not affected by the Science peer review process.

At the time of the Science paper, Lewis was a relatively unknown scientist, but from a prestigious University with some notable faculty, including Linus Pauling. The BEAR Genetics Panel had a prestigious cast, with Muller, Sturtevant, Beadle, Crow, Glass, Wright and others. What happened over the next seven months was extraordinary as the members of that Panel observed the revised Lewis manuscript become published in Science, receive a glowing editorial (DuShane, 1957) and then gain the attention of the scientific, policy and political communities worldwide.

At the time of the Lewis publication, Beadle (1957a) would make two identical presentations (i.e. the same manuscript but different titles) based on the Lewis paper. Beadle used these two events to rise above partisan interests and seek to reconcile the vast scientific and policy divide between several Nobel Prize winners on radiation and leukemia risk. Beadle undertook this effort with AEC Commissioner Willard Libby (Nobel Prize in Chemistry for Carbon 14) who challenged the Lewis linearity perspective and two who supported it, namely Linus Pauling (Nobel Prize in Chemistry) and Albert Schweitzer (Nobel Peace Prize). The Beadle presentations were given on May 8, 1957, at CalTech and at the Sigma XI meeting at Stanford on May 24, 1957. Beadle, who would receive the Nobel Prize in 1958, used these opportunities to improve strained relationships with the AEC, a major funding agency, due to “fallout” damage from the Sturtevant presentation and publications. He also used it to reposition and promote the standing of radiation genetics in the scientific world and to protect and promote the career of Ed Lewis, perhaps along with serving Lewis a little taste of humility.

Beadle sought to achieve these goals by first asserting his belief in the radiation genetics mantra: that induced mutations were irreversible, non-reparable, and cumulative with the dose response being linear down to a single ionization. He therefore made it clear that he held firm to the party line, using a section subheading of his written presentation called “No Threshold”. Crafty academic statesman that he was, Beadle gave ground to the Libby side of the debate by acknowledging that even though high doses of radiation can induce cancer it was unknown by what mechanism the cancer occurred. Thus, there was scientific uncertainty. However, if it could be shown that the mechanism was via gene mutation then the dose response would surely be linear at low doses.”

Beadle then stated that “data recently published by Professor Lewis (Science, May 17, 1957a) are consistent with this (LNT) view but are not sufficient to prove its correctness.” Beadle further stated that even though linear estimates of leukemia cases from the fallout may “seem reasonable on theoretical grounds, there is no proof of the correctness of the assumptions on which they are made”. In the case of strontium-90, which was highlighted toward the end of the Lewis paper, Beadle indicated that “there is no direct experimental evidence that Sr-90 does in fact produce leukemia.” In a subsequent personal communication with Libby, Beadle (1957b) would privately reiterate that Lewis had not yet made his case. Lewis (1957b) would also acknowledge to Libby that even through it was clear that he had not proven his low dose linearity case, he still thought that the threshold hypothesis was “folly”, scientifically unsupportable and poor public health policy. Despite its limitations of proof, for Lewis LNT was the only path to follow. Thus, of the two professors from CalTech, Lewis was the more aggressive and defensive while Beadle proved to be the diplomat.

While Lewis was the recipient of massive publicity and acclaim in the aftermath of the Science publication, it would come at a price based on a number of critical commentaries and articles from high profile scientists, including members of the NAS BEAR Pathology Panel that responded to

2 Note that Beadle made this statement some 17 months prior to Russell et al. (1958) reporting that dose rate rather than total dose was the dominating influence affecting mutation and that this suggested a DNA repair function, which was likely to undermine the LNT concept.
his article in Science (Brues, 1958; Court-Brown and Doll, 1958; Kaplan, 1959; Kimball, 1958; Mole, 1958). However, the leaders of the radiation geneticist community, especially the NAS BEAR Genetics Panel, failed to come to his defense, either as individuals or as a Panel. For example, no letters to the editor were published by Muller, Stern, Crow, Beadle and others. In the case of panelist Neel (1958), there was no rescuing of Lewis from these criticisms but actually a recognition that such criticism exists and that these issues were unresolved, a view similar to that expressed by Beadle (1957a). In fact, a statement issued by (Beadle, 1963), then president of the University of Chicago, revealed that his position had not changed.

One therefore finds that Lewis essentially did the bidding for the BEAR Genetics Panel when he “rescued” their focus and highlighted their importance following the Panel’s perceived undermining by the Neel and Schull (1956) report. Lewis argued that ionizing radiation induced mutation was the mechanism for radiation-induced leukemia at low doses based on data from multiple human conditions, ranging from atomic bomb survivors to patients treated with X-rays and to the radiologists themselves. Yet, he could not prove it, nor convince even his close colleague and department Chair George Beadle. However, Lewis strongly believed it to be true, even at the very low doses that the general public experiences as background from cosmic rays, the earth, our bodies and foods.

While it may appear that Lewis was abandoned by his radiation geneticist colleagues, their lack of support most likely indicates that they were sufficiently mature to know that leukemia was not their expertise and that he was now on his own. Nonetheless, the absence of even a gesture of public support from his close colleagues had to be difficult to experience. In the end, he had charted his own destiny.

The fact that Lewis was apparently abandoned and the object of considerable high-level criticism did not mean that he failed in his goal to have LNT adopted, even if it could not be proven. Indeed, just the opposite occurred! As a member of the influential NCRPM, he forged an intellectual compromise with one of his formidable critics, Austin Brues, a leader on the BEAR Pathology Panel. Lewis and Brues encouraged the rest of the committee to follow their compromise and recommend LNT be adopted (NCRPM, 1960). In the end, Lewis was forced to admit that he did not have the science to support his LNT beliefs. However, he got Brues to adopt a “Precautionary Principle” policy, which, in effect, meant that LNT would be adopted based on fear and/or lack of knowledge. It really didn’t seem to make any difference to Lewis. He achieved what he wanted, eventually getting the US and essentially all other countries to follow his lead. So, while Lewis may have started out as merely a stalking horse for Beadle and the BEAR Genetics Panel, he proved to be much more than that.

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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.

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3 Once the study of Neel and Schull (1956) was no longer ignored, it had the expected impact on the significance of the BEAR Genetics Panel (1960). The Panel quickly lost momentum and impact. As expected the Genetics Panel rubber stamped the Lewis-lead National Committee for Radiation Protection and Management (NCRPM) Precautionary Principle based LNT model for cancer risk assessment in their 1960 report. Now, instead of being the leaders, they were a copycat Panel. That Panel became progressively less effective and visible, eventually ending in 1964, with Jim Crow the new chair, having taken over from Beadle.
