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Review Article

LNTgate: How LNT benefited from editorial actions

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ABSTRACT

This paper illustrates how the acceptance of the linear non-threshold (LNT) dose response model was unethically advocated and advanced both by key scientists within the radiation genetics community, and by editorial practices in *Science*, a leading international scientific journal. Four key papers became the cornerstones in the acceptance of the LNT model. In the publication process of these papers, editorial decisions to circumvent peer review occurred in at least two cases. As well, the summarized data of one paper were never shared with the scientific community and remain missing to date. Publication of a paper in *Science* on which a senior editor of the journal was a co-author is alleged to have intentionally falsified the research record (BEAR Genetics Panel). These findings raise the question of whether foundational papers for major contemporary regulatory policy (i.e., LNT/cancer risk assessment) that lack scientific legitimacy, as identified herein, should be retracted. These findings also should serve as the basis for considerable ethical concern, as well as a prompt for ongoing ethical diligence and rigor in the conduct and publication of scientific research.

1. Introduction

Over the past decade, a series of papers has clarified, to a significant extent, the historical foundations of the LNT-dose response model used in cancer risk assessment [1–9]. These detailed reviews have revealed numerous occasions of bias, error, intentional research misconduct, and self-interest by leaders of the radiation genetics community of the 1940s–1960s era. Their actions created a revolution in dose response and regulatory policy that resulted in the replacement of the threshold dose response model with the LNT model for cancer risk assessment. These radiation geneticists shared a common professional perspective, if not ideology, as espoused by the 1946 Nobel Prize recipient Hermann J. Muller. Their work has had considerable influence upon individuals, such as Rachael Carson, to institutions including the Federal Radiation Council (FRC) during the 1960s, the United States Environmental Protection Agency (US EPA), and the regulatory agencies of many countries, which has persisted to date. Their stated goal to achieve broad scientific – and public – acceptance of the LNT dose response model has entailed nearly a century of dedicated effort, beginning soon after Muller published his groundbreaking paper in July 1927 [10]. In that publication, Muller claimed to have induced gene mutations in fruit flies through the application of ionizing radiation, though further scrutiny has demonstrated that he did not do so.

Historical assessment has generally focused on several key players and their activities. However, equally important has been the central role of the journal *Science* in enabling scientific advocacy-like activities that led to the acceptance of LNT. Herein, we address four highly influential papers that were reflective of biased publishing, which were pivotal to advancing the LNT model, and which were used inappropriately in practice, policy, and public health decisions.

2. Case # 1: Muller's publication in *Science* ostensively describing groundbreaking radiation-induced gene mutation, without accompanying data, to gain primacy in the race for the Nobel Prize. This paper would provide the scientific foundation that led to the LNT dose response concept

In the early-mid 1920s, Muller and others were in competition to be the first to induce gene mutation, with intent on elucidating a putative mechanism of evolution. While a number of papers had shown ionizing radiation-induced transgenerational phenotypes due to chromosome alterations, these studies were not deemed significant, given that the mechanism of evolution was assumed to involve what Muller would call "point mutations", viz.- small changes within the gene.

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In this effort to be first, Muller [10] would initially report apparent ionizing radiation-induced gene mutations in November 1926, based on the first of three experiments that would become the basis of his being awarded the Nobel Prize. During that period, Gager and Blakeslee [11] first reported in the *Proceedings of the National Academy of Sciences* the results of their studies demonstrating ionizing radiation-induced gene mutation in *Datura.* Six months later, Muller [10] published a paper in *Science* entitled: "Artificial Transmutation of the Gene", which provided no data, but instead claimed to be a discussion of results of his (Muller's) findings of induced gene mutations. This paper failed to cite Gager and Blakeslee [11], thus giving no acknowledgment of their observations.

This sequence of events prompts the question of how Muller's paper was published in *Science,* sans data. It is now widely accepted that Muller rushed to publish this paper to establish primacy for both this topic and his position in the field [10]. This was exactly what Muller intended and was certainly instrumental in his being awarded the Nobel Prize, 19 years later (1946), for his research on induced gene mutation.

Based on review of Muller's Nobel Prize laboratory notebook it appears that he only discussed the results of his first experiment in the *Science* paper. Like Gager and Blakeslee, Lewis J. Stadler was also in competition to be first to show inducible gene mutation. Stadler initially presented his radiation-induced gene mutation data at an American Association for the Advancement of Science (AAAS) conference in Nashville, TN in December (1927), soon thereafter publishing a data-based report in *Science* [12]. Thus, it appears that Stadler's work was preceded approximately three months by Muller's. Stadler, and the Gager and Blakeslee team followed standard protocol at the time, submitting their data-based research manuscripts for characteristic peer review. However, Muller not only failed to provide data in his *Science* paper, he additionally sought to defer (or perhaps intentionally avoid) peer review by later publishing his data in an unreviewed conference proceedings, with the text of that paper representing a verbatim transcript of Muller's reading at the conference (Muller [13] - letter to Altenberg, July 8). Of further concern is that his conference proceedings paper lacked a methods section, did not provide a discussion, and failed to cite any references. These Conference Proceedings were published in an obscure publication, with poor distribution. As a result, nearly all the researchers citing Muller's research did so by referring to 1927 *Science* paper, which lacked any data.

To be sure, hindsight is often the clearest; in retrospect the publication in *Science* enabled Muller to establish primacy in the field of induced gene mutation, despite the fact that his data were not presented, and when subsequently made available, those data – and the methods used to obtain them - were not subject to peer review. It is also important to note that Muller ran out of time in conducting his third experiment due to his attendance at a forthcoming conference in Berlin, and hence did not include a control group.

Failure to undergo peer review would prove to be important, since Muller's key interpretation of gene mutation would be challenged. He had confused an observation (i.e., transgenerational phenotype change) with a mechanism (i.e., gene mutation). Had his manuscript undergone legitimate peer review, Muller likely would have been forced to temper his claims about gene mutation, greatly affecting the significance and impact of the paper. In the end, Muller's claim to have induced gene mutation, which won him the Nobel Prize, was not sustained, having lost much credibility based on Stadler's work [14–17] that directly refuted Muller's subsequent reverse gene mutation hypothesis. In fact, by 1956 Muller would agree with Stadler's argument [3,18].

Further discrediting of Muller's interpretation of gene mutation occurred long after his death, when measurements of nucleotides confirmed that Muller mostly induced gene deletions, and not gene mutations [5]. Yet, it cannot be overlooked that the apparent laxity in review and lack of publication stringency promoted unverified claims, giving Muller the considerable gravitas that was contributory to his being awarded the Nobel Prize. This is an obvious example of how editorial decisions led to distorting the search for truth, rewarded professional self-interest, and at least tacitly allowed manipulative behavior and unfairness to professional competitors in the field (who were far more rigorous and propitious in their presentation of research methods and findings). Such ineptitude in the scientific publication process further enabled Muller to create the first LNT initiative in 1930 (i.e., the Proportionality Rule concept for radiation induced gene mutation).

3. Case # 2: *Science* published summary data by Curt Stern from the Manhattan Project that were not peer reviewed; key data of this paper have never been reported elsewhere, and have been missing for 70 years. Yet, these "missing" findings were the basis for the US National Academy of Sciences BEAR I Genetics Panel recommending the LNT model and its subsequent widespread acceptance. This paper also provided the "mechanistic" foundation for the seminal Lewis paper (see case # 4)

A second instance of editorial irresponsibility was similar to the Muller episode, and occurred some 20 years later. Muller was working as a paid consultant to Curt Stern, and Delta Uphoff was also involved in this case (see Calabrese [5,19,20]. Once again, findings by Uphoff and Stern [21] that were not peer reviewed were published in *Science. as* a one-page note summarizing five experiments that Stern directed during the Manhattan Project. Two papers had been previously published in the journal *Genetics* where Stern was the editor [22,23], while the remaining three experiments were conducted by Uphoff, a first semester Master's student, who was working for Stern.

The Uphoff experiments were essential to advancing the LNT concept in that they served to; (1) discredit the paper of Caspari and Stern [23], which had shown evidence of a threshold for mutation during a chronic "low" dose mutational study; and, (2) support a linearity model of ionizing radiation-induced gene mutation. The Caspari study had created a serious problem for Muller, Stern, and their radiation geneticist colleagues since it did not support a linear dose response for mutation but indicated a threshold interpretation. Even though it was clearly among the best studies on that topic, Stern initially rejected the findings, claiming that control values were aberrantly high, which led to an incorrect conclusion that the data showed a threshold response for gene mutation. Caspari countered this criticism by citing multiple studies by respected geneticists that supported the appropriateness of the control group used, which resulted in Stern withdrawing his objection [1,2,20].

However, Stern did not abandon efforts to prevent acceptance of Caspari's findings. The report was sent to other noted geneticists, such as Bertwind Kauffman and Milislav Demerec, for review. An exasperated Demerec could find no problems with the research, concluding his comments with the query about what could be done "to save the hit model" (Caspari [24] - Letter to Stern, September 25). Stern would write to another colleague, Edward Novitski (Stern [25] - Letter to Novitski, March 19), referring to the situation as the "Caspari problem". Muller would render his opinions, but despite this intentionally conjoined effort, could not find a way to discredit the study. In his critique of the Caspari study Muller (Muller [26]- Letter to Stern, January 14) would write that he "had so little to say" that was critical, and offered nothing substantial.

In the absence of revealing any ostensible problems with the Caspari findings, Stern wrote a discussion of the paper [23], with the apparent agreement of Caspari, in which he stated that readers should not use or apply the findings until it was determined why these did not support the linear dose response as reported in the acute dose experiment of Spencer and Stern [22]. In retrospect, the argument can be seen as rather comical, given that Stern knew that the Spencer and Caspari studies methodologically differed in more than 25 ways, and yet he claimed that it was practically impossible to ascertain why these two studies had differing results, recommending that the threshold finding not be acted upon until the differences between the two studies were resolved.

Evidently, this was the best retort he could muster prior to Uphoff's replication of the Caspari study [21].

There are three Uphoff experiments very briefly summarized in the *Science* paper [21]. It is a one-page technical summary with only the final mutation rates provided, with no information on research methods, supportive or contrary findings, and/or limitations. The authors recognized and acknowledged that there were limitations, and promised a detailed follow up paper containing all the critical missing information. However, that was never done. None of Uphoff's experimental findings were ever subjected to peer review or published in greater detail.

The first experiment was characterized in a preliminary report to the funding agency [(i.e., Atomic Energy Commission (AEC)] [27]. In that report, the authors claimed that the control group mutation response was aberrantly low, making the findings "uninterpretable". In an unusual and unexpected statement, they suggested the possibility that this may have been affected by investigator bias, without explaining what was meant and/or inferred by this. It was generally well known within the closely-knit radiation genetics community that Stern did not want the Caspari data to be accepted as valid. It is likely that the possible "investigator bias" was rooted in their desire to establish the LNT model, and that the Caspari data, being the proverbial "fly in the ointment", had to be discredited and dismissed. Ultimately, it remains unclear whether the aberrant findings were due to bias, lack of experience, lack of guidance, or random effects. All that is known is that the control group data seemed aberrantly low and also differed widely from Muller's massive unpublished control group data which he had shared with Stern and in the view of Uphoff and Stern [27], were not credible. Muller's findings also supported the reliability of the Caspari control, consistent with the published literature [1,2]. There is no evidence that the second and third Uphoff experiments were ever written as reports. It is known, however, that the remaining two experiments exhibited concerns, one with another aberrant control group value, while the other experiment exhibited a marked mutagenic effect, exceeding a linear prediction by about three-fold, calling into question the findings of each of the Uphoff studies. When Uphoff and Stern wrote their one page technical summary paper for *Science* they failed to share the fact that less than a year previously, they deemed the Uphoff data to be "uninterpretable". Contrary to their earlier view, they used these very same "uninterpretable" data as basis for foundational support for the LNT model. This information was obscure (and perhaps intentionally obscured). These inconsistencies remained opaque until an assessment of this situation was published more than 60 years later [19]. The data for experiments two and three were never made public, and have not been found. All that exists is the one-page, overview paper published in *Science* [21].[1]

Stern's colleagues in the radiation genetics community were similarly supportive of the LNT model, and never called for the detailed paper that was promised. As problematic as the Muller situation was in 1927, the issue(s) of Uphoff and Stern's work is more concerning, since the data from the final two Uphoff experiments are missing. Furthermore, the data of the first experiment were considered uninterpretable, have never been subjected to peer review, and can not be reconstructed for proper evaluation. The role of editorial stewardship in this episode is also significant in that there was no attempt to hold Stern accountable for producing peer-review of his findings.

4. Case # 3: the NAS BEAR I Genetics Panel: *Science* published a report that misrepresented the research record, obscured data from the public. Bentley Glass, a member of the BEAR Genetics Panel, was one of only six senior editors at *science* at this time

Did the BEAR I Genetics Panel commit scientific misconduct by falsification of the research record? Was the decision to mislead, or deceive the scientific community deliberate, given the Genetics Panel's apprehension of sharing the uncertainties in, and lack of agreement about the findings of their work, and the effect(s) and implications of such ambiguities upon methods of projecting genetic damage, and the role and value of their work for federal policy recommendations? These possibilities were recognized and discussed by Panel members (for overview, see Calabrese [1,2,5]), which led to their decisions to: (1) suppress disagreements, (2) alter the research record, and (3) in these ways, not to reliably share findings with the scientific community. Bentley Glass, a member of the BEAR I Genetics Panel and one of only six senior editors at *Science,* would have had to at least be complicit in this scientific misconduct, in his position as a steering figure at *Science*.

Although the Panel was evidently biased in its constituents' views concerning dose response [2], it cannot – and should not – be assumed that there was intent to commit scientific misconduct. Rather, a combination of unexpected contingencies appears to have enabled such occurrence. During the early stages of the BEAR I Genetics Panel, Tracy Sonneborn wrote radiation geneticist doctrine that supported the belief and adoption of LNT, and was encouraged to read this into the official record by Chairman Weaver during a formal session of the Panel. Based on the transcripts of that session, Sonneborne's comments were adopted by the Panel, without challenge. Sonneborne indicated that any and all exposures to ionizing radiation, regardless of how minimal, induced gene mutation, and that this damage was cumulative, irreparable and irreversible. This position fostered the acceptance of the LNT dose response model [5]. Thus, while the threshold model had been dominant for about 50 years, it was directly challenged by radiation geneticists who supported LNT.

This was an important moment in the Panel's activities as it solidifies their decision that LNT should be the model recommended for adoption in public health policy. The Panel budget had sufficient funds to support a series of meetings, and Weaver challenged each of the twelve constituent geneticists on the Panel to estimate the occurrence of adverse genetic events in children whose parents' gonads were exposed to a specific dose of ionizing radiation, with risk estimates for up to ten generational effects. Each geneticist was asked to independently determine risk estimates once they returned home from the meeting, and all were instructed to write up detailed assessments, and return these estimates to James Crow before the next meeting (in about three weeks). The 12 geneticists had broad expertise with bacteria, paramecia, mice, human subjects and other models. Sonneborne suggested that this diversity in foci would prove to be a strength, if it showed convergence in estimates of genetic damage. Weaver ensured that all the geneticists acknowledged prior to their assessment that the dose response was linear in the low concentration zone [1,5].

Of the 12 geneticists invited to develop these estimates, three declined, based upon their opinion that realistic speculation of this sort was impossible to make with any confidence. The other nine geneticists provided detailed written evaluations to Crow within the agreed time period (NB: all nine dated reports have been obtained by the authors). What Crow saw troubled him, as there was considerable disagreement among the damage estimates submitted, with differences on the magnitude factor of many thousands. Crow informed Weaver of this in writing, suggesting that this exercise was, in fact, problematic in its outcome. An example of the uncertainly in damage estimates is seen in the values derived by Bentley Glass, which ranged from a low confidence value of 100,000 to the massive value of 200,000,000. Crow did not want the public to see how uncertain the experts were, as well as how much they differed amongst themselves [20]. The highly divergent estimates would certainly refute the LNT model, and in so doing essentially undermine the very reason why the Panel was established in the first place: to provide professional consensus toward informing and directing major policy recommendations. But a consensus clearly was lacking. Even though the participating Panel members firmly asserted their belief in LNT, most were unsure about how to formulate more precise damage estimates.

[1] At the time of the Uphoff and Stern paper [21], Bentley Glass was the *Science* journal editor for genetics (Glass [28] – Letter to Stern, March 11).

The challenge was what to do next. Although Crow was one of the youngest members of the Panel, and only authorized to collect/organize the expert opinions, he eliminated the lowest three determinations (i.e., those involving bacteria and human estimates), reduced the number from 9 to 6, and reduced the uncertainty by over 80% - from approximately 4000-fold–750-fold (mean values). Yet there was still far too much uncertainty to appease Weaver, and others. Ultimately, the uncertainty factor (based upon the six Panel member determinations used) was further reduced to 100 [1,5], although there is no record of how this was done.

We find it especially troublesome that the Panel published their findings in the journal *Science* and explicitly stated that 12 geneticists were requested to provide estimates of the risk, therefore only six provided estimates [1,5]. This was demonstrably incorrect (viz. -since nine agreed and provided detailed genetic damage estimates), and led to falsification of the research record.

It can be presumed that such lack of verity was purposefully intended to obfuscate the unacceptably large uncertainty estimates of the nine geneticists who actually responded. Also notable was that the paper also failed to indicate that three geneticists declined the invitation, for cause, as noted above. While Crow may be responsible for instigating this scientific misconduct, clearly all involved were complicit. Making matters worse was that Glass, as senior editor, did not insulate *Science* from involvement and, as a result, *Science* would publish the allegedly false information in support of the LNT model, thereby contributing to this recommendation becoming perhaps the most significant error in the history of risk assessment.

5. Case # 4: In 1957, *Science* published a profoundly influential paper by Edward B. Lewis that asserted that ionizing radiation induced leukemia in a linear dose response pattern. The paper achieved significant status consequential to receiving a positive editorial by *Science's* editor-in-chief, who as matter of fact, did not possess experience in, or expertise about the topic. The Lewis paper has been shown to be the product of bias and has been scientifically discredited. Inarguably, the prestige of the journal contributed to this paper becoming iconic, and being one of the most influential in fortifying the acceptance of the LNT model

Edward B. Lewis, a fruit fly geneticist, with no experience in epidemiology, cancer, radiation chemistry/dosimetry, quantitative risk assessment and other related disciplines, nevertheless had his work on radiation-induced cancer epidemiology published in *Science*, with notable editorial endorsement. How this happened may be due, at least in part, to the efforts of Bentley Glass. Glass was a Ph.D. student of Hermann Muller, and NAS BEAR I Genetics Panelist, who was a senior editor of *Science* and ideologically committed to the LNT model. Glass had been given an advanced draft of the Lewis paper in late November 1956 [8,9]. The Lewis [29] study has recently been assessed, with overwhelming evidence showing that Lewis was overtly biased in his method(s) and analysis [7,8]. In retrospect, the quality of the peer review undertaken in this instance by *Science* must be questioned (or, perhaps, inquiry to whether there was peer review at all). Within a week of this paper's publication, the chair of the AEC was questioned in depth about its findings on a Sunday television program called "Meet the Press". Lewis was invited to testify to Congress a week after the television broadcast, and *Life* magazine did a major story on the topic. Thus, the Lewis paper exerted influence that effectively turned the scientific community – and public health establishment at large - from the longstanding use of the threshold dose response model to LNT.

6. Discussion

Herein, we recount four key and fundamentally flawed instances in which a leading scientific journal demonstrably and negatively affected the course of cancer risk assessment. The opportunistically ambitious Muller arranged publication in *Science* well in advance of completing his second, and so-called definitive experiment. Muller's research was never peer reviewed. Hence, Muller [30] was given robust opportunity to proclaim his Proportionality Rule - the earlier term for the LNT model. When the scientific community finally recognized the inaccuracies in Muller's scientific assertions about gene mutation [14,15] (see Lefevre [16,17] for earlier literature), Muller persuaded Curt Stern to attempt replication of the findings of a flawed doctoral dissertation research conducted at the University of Edinburgh [31]. When these studies did not go as planned, Muller and Stern endeavored to discredit the work of Caspari (i.e., from the studies of Uphoff) that Muller and Stern used to make their case to discredit the threshold model, and once again published non-peer reviewed data in the journal *Science.* Those original data have remained missing for 70 years.

Yet, the radiation genetics community appeared unconcerned, at least as they leveraged the adoption of the LNT model (a lack of concern apparently shared by Bentley Glass, as a senior editor at *Science* at the time). Even when 85 years old, Glass [32] continued to uphold misrepresentations of the research record, and to justified his evidently duplicitous actions. Glass repeatedly claimed that there were no significant differences in genetic damage risk estimates as determined by the geneticists on the Panel, although he also stated that while there were initial differences in reported estimates, Chairman Weaver sent the participating panelists back to "work out the damage estimates independently". The following day, Glass asserted, that the panelists returned and their estimates showed considerable agreement, absent the prior major uncertainties. That statement of Glass has been fully discredited [1,5,32,33].

We ponder how far Glass – and others involved – would have gone to advance the LNT model, and their respective professional standings and reputations. Obviously, we demonstrate, the entire BEAR Genetics Panel had gone so far as to commit scientific misconduct, and for such irresponsible, and patently unethical activity to be both overlooked, and knowingly advocated, through the publication decisions of one of the leading international scientific journals. We present these facts to both challenge an ideologically accepted LNT cancer risk assessment policy and as an object lesson. Indeed, Thomas Kuhn [34,35] argued vehemently that science must be regarded as a human enterprise, and not merely as some endeavor that is invulnerable to individuals' professional and personal ambition, bias, and competitiveness. Simply put, science is subject to each and all of the character traits of the scientist – and society [36,37]. Recognition of that reality dictates that doctrinal self-criticism, self-monitoring, and self-correction must apply to science and public health regulatory policies as a collective of professionals who remain dedicated to the ethical probity of its practice. Absent this fundamental, and arguably higher goal, science becomes unworthy of public trust.

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EJC developed idea, research and wrote the manuscript. JG revised, reviewed and edited manuscript.

Competing interest

The authors declare no conflict of interests.

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.

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