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Muller letter reveals scientific scandal that discredits evidence used to support LNT

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ABSTRACT

A newly discovered letter written by Hermann J. Muller in August 1948, reveals that he claimed to have evidence that multiple papers by Frederick Hanson and Florence Heys, including those that supported the linear non-threshold (LNT) dose response model for hereditary and cancer risk assessment, were fraudulent and thus untrustworthy. Muller failed to bring this issue, which he referred to as a major scientific scandal, to the attention of the scientific community, remaining silent for the remainder of his career. Since Muller was a recipient of substantial funding by the Rockefeller Foundation (RF) and Hanson was a senior RF program director, instrumental in the process that awarded funding for Muller and other geneticists, it suggested that Muller may have been conflicted in his recognized obligation to the scientific community to expose possible scientific misconduct, and his desire to ensure both continuing funding from the RF and his advocacy for the adoption of the LNT model of radiation risk assessment. In this conflicted situation, Muller seems to have opted for self-interest, failing to bring his concerns/challenges about the publications of his RF funding colleague Hanson to public forum via acceptable venues that typically permit full exposition of disputes. Muller's decision to act in this manner permitted the papers that he deemed as untrustworthy to be widely, and continuously cited (to the present), and in this way, affect worldwide acceptance of the LNT model by the scientific community and regulatory agencies in ways that may negatively impact radiation science, subsequent LNT interpretation, and the public health.

1. Introduction

On August 27, 1948, Hermann J Muller [1], Nobel Prize recipient for Biology and Medicine in 1946, wrote a confidential letter to Everett R. Dempster, a professor of radiation genetics at the University of California Berkeley (Muller, 1948-see Appendix 1). In this letter Muller made a series of rather shocking accusations; Muller stated that the Drosophila radiation genetics papers of two researchers [viz. - Frederick B. Hanson (Ph.D.) and Florence M. Heys (Ph.D.)] then at Washington University, Saint Louis, Missouri, USA, "... at least from 1930 onwards constitute one of the great scandals of science, although all unbeknown to the scientific public". The papers of Hanson and Heys were significant as they were among the first wave of publications inspired by Muller's prior claims that he had induced gene mutations via X-rays in the fruit fly (and in so doing, was first to assert this scientific milestone). Muller's findings would lead to the establishment of the fields of radiation genetics, mutation research, and would profoundly influence the fields of hereditary cancer risk assessment.

The Hanson and Heys papers addressed a broad spectrum of topics in this nascent area of radiation genetics research, but had particular focus upon clarifying the nature of the dose response parameters of ionizing radiation, with key emphasis upon the low dose zone for its potential applications to human risk assessment [2–6]. While Hanson and Heys's publications on radiation induced mutation spanned the timeframe from 1928 to 1933, it is not clear when Muller's concerns about the trustworthiness of their findings began to emerge, although he expressed his views in 1933 or 1934 in a confrontation with Heys [1].

The present paper discusses how Muller addressed the issue of possible scientific misconduct by Hanson and Heys and its scientific and ethical implications, inclusive of its potential impact on cancer risk assessment. Herein, we shall also evaluate the conduct of Muller in this process, with respect to research and publication ethics, and his responsibilities to the research and regulatory communities when confronted with apparently falsified and/or fabricated research that was used to inform and direct regulatory agencies' priorities and public health decisions.

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Review Article





2. Beginnings of the Muller-Hanson relationship

In the fall of 1927 Hanson took sabbatical leave to work with Muller at the University of Texas. Hanson, a geneticist using rodent models, attempted to (rather quickly) learn research methods being used in radiation genetics studies of the fruit fly Drosophila, and, in this pursuit, was given an acutely pressing project by Muller. Muller had just returned from the 5th International Genetics Congress in Berlin, which Hanson also attended and presented a paper. At that conference, Muller presented what would become his Nobel Prize research. However, Muller was subsequently strongly criticized in private conversations by his best friend Edgar Altenburg [7], who told Muller that he needed to prove that the X-ray induced transgenerational phenotypic changes he observed were indeed the result of gene mutations, and not simply the effect of "punching holes in chromosomes" with very high radiation doses and dose-rates. Muller knew that Altenburg's questions needed to be addressed, and thus he assigned Hanson the task of evaluating whether ionizing radiation could induce reverse mutations, even though Hanson had no research experience at that time with fruit fly genetics.¹ Muller assumed that the occurrence of apparent reverse mutations would provide evidence - and therefore, reliable proof - that the gene was intact and that the X-ray treatment had induced "point mutations", thereby countering Altenburg's suggestions of merely acute structural effects. Muller's assumption was explored in depth over the next two decades, which ultimately led to the lack of support for his hypothesis [8,9].

Upon his return to Washington University following the University of Texas sabbatical, Hanson initiated a series of fruit fly experiments on a wide variety of topics, with the collaboration of a doctoral student, Florence M. Heys, who was working on rodent reproductive physiology. However, despite their findings supporting the LNT model, as noted above, Hanson and Heys reported additional findings that conflicted with Muller's of how various physiological factors, such as starvation and anesthetic gases, affected the occurrence of ionizing radiationinduced gene mutation [10,11]. In fact, Hanson and Heys's findings about the effects of anesthetic gas were of considerable interest, given that anesthetic treatments were routinely employed during the Drosophila studies. Hanson and Heys's findings suggested that the use of anesthetic gases could enhance gene mutation, and hence be a potential confounding variable in fruit fly radiation studies, affecting how these findings may influence interpretations of assessing the risks of low dose ionizing radiation. One could see how Muller would have considerable interest and concern with the implications of such findings.

3. Muller accuses Heys of scientific misconduct

Muller had not criticized Hanson and Heys's research until their findings gave the impression of being potentially unfavorable toward his studies of the effects of starvation and anesthetic gas, in which he showed that these factors had no impact on the capacity of ionizing radiation to induce gene mutations (see Hanson and Heys [11] for discussion; Muller [12]). Without providing a clear explanation, Muller

wrote a letter to Dempster in which he claimed to have noted troubling irregularities in Hanson and Heys's findings, based on genetic methods and statistical applications that Muller regarded as indications of scientific misconduct. Muller further suggested that such irregularities could be noted in the Hanson and Heys research as early as 1930 - and possibly prior. In this way, the irregularities cast doubt on all the Hanson and Heys's radiation studies. In his discourse, Muller concluded that these acts of scientific misconduct were conducted by Heys, but not Hanson.

The reason for excluding Hanson from blame appears to be related to Muller's belief that Hanson was quite removed for the actual research, analysis, and drafting of papers. Muller believed that Hanson was dependent upon what was provided to him by Heys. Even though Hanson was first author on the papers, Muller concluded that Hanson, having authority over Heys, placed his own name on each paper as first author, yet knew very little of the specific research methods used by Heys. It is probable that this information was provided to Muller by Hanson and/or Heys - and possibly others - although this is not explicitly known. Based on his belief, Muller then singled out Heys as the so-called "culprit" in this commission of falsification/fabrication scientific misconduct, effectively absolving Hanson of culpability.

4. Muller, a "silent" whistleblower, identifies a scientific scandal

Muller informed Dempster that evidence of scientific misconduct would be clear to anyone who could understand and apply statistics. However, Muller never expressed his criticisms in a public forum, providing only several general critiques in his private letter [1] without any formal documentation of which of Hanson and Heys's papers were problematic, what aspects of particular papers were evidence of misconduct, and who was responsible for such improbity. This is highly irregular; in any formal accusation of scientific misconduct, specific evidentiary documentation needs to be provided, which Muller failed to do.

It seems that following his confrontation with Heys, Muller [1] decided to undertake a *quasi*-replication of some of the Hanson and Heys's research. In an unusual display of self-proclaimed "scholarly heroics" and setting himself as *de facto* judge, Muller then stated that not only was Hanson not at fault in this falsification and/or fabrication, but that Muller took it upon himself to "save" Hanson's reputation by redirecting his own research (and students' time and efforts) to repeat some of Hanson and Heys's findings, and then write a manuscript based on that research. According to Muller, the studies were performed "correctly" this time, since he was directing their design, methods, and conduct.

Despite this attempt to "save" Hanson's reputation, it is not readily apparent how replicating several previous studies, or conducting a modified version of the original studies, would provide a basis for "clearing" Hanson of allegations of scientific misconduct, while at the same time attributing fault to Heys. The fact that a series of subsequent experiments may obtain different findings than previous (Hanson and Heys's) studies could have a number of possible causes and explanations. Thus, from the start, the idea that Muller was going to "save" Hanson's reputation from charges of scientific misconduct appears to be a questionable proposition, at best, and a seemingly performative, and self-serving endeavor. In that light, a more likely reason for Muller's follow-up study may have been to reaffirm his own earlier findings, which differed from those of Hanson and Heys.

The resultant manuscript written by Muller, which presented his new experimental results revealed differences from the findings published by Hanson and Heys [10,11]. Muller suggested that these new findings refuted the earlier papers of Hanson and Heys, and that such new results fortified Muller's view that Hanson and Heys's work was not trustworthy. Muller provided this manuscript to Hanson, who then sent it to *American Naturalist* for publication, where it was accepted and published

¹ The lack of adequate training in the area of *Drosophila* radiation genetics would become problematic for Hanson and Heys and affect all of their research in this area. As Muller stated in his letter to Dempster, "A close reading on the description of the genetic methods usedas well as a perusal of the smoothness of the curves in all the papers, will be enough to prove this to anyone who has any knowledge of genetics or feeling for statistics." The Hanson [22] paper specifically refers to problems with their genetic experimente by Hanson and Heys created fundamental problems with their research and this was linked with concerns with how the data were presented. It is possible that the fabrication and/or falsification accusations of Muller were the result of a combination of both lack of professional capacity and ethical violations.

with only Hanson listed as author. In highly disparaging comments in his August 1948 letter to Dempster, Muller [1] then stated that "Hanson never had anything to do with it [the manuscript he wrote] except to sign it and send it to the publisher, just as he had done with other papers allegedly written by Hansen and Heys."

It was apparently Muller's position that Hanson therefore could not have been the guilty party in prior misconduct because he did not do the research, was far removed from it, and simply signed his name on to what manuscripts were provided to him (including those of the accusedas-culpable Heys). For Muller, this afforded "clear" substantiation that Hanson was innocent of scientific fraud! But, as matter of fact, Muller's explanation – and its undergirding rationale - even if plausible or true, do not provide a professionally safe landing for Hanson, but rather, only identified different ethical failings than those that Muller alleged of Heys. Somewhat tongue-in-cheek, one could posit that with friends like Muller, Hanson didn't need any enemies, as Muller "protected" Hanson from an accusation that may be difficult to prove, and in his attempt to "heroically" do so, in reality exposed and revealed that Hanson was guilty of readily demonstrable scientific misconduct as regards publication authorship.

5. Questions that Muller's letter to Dempster failed to address

In the main, there are several key issues that Muller did not address; these include:

- 1. Why would Muller send the manuscript to Hanson absent expectation (or obligation) of professional collaboration, such as requesting comments/criticisms or possibly an invitation for co-authorship? Given Hanson's and Muller's respective longstanding academic careers, and their assumed understanding of the ethical rules, responsibilities and protocols of academic research and publication, it is unlikely that Hanson would receive a manuscript from his former sabbatical mentor and then list only his own name as author, without explicit invitation and approval by Muller;
- 2. Why would Muller have permitted Hanson to submit such a manuscript for publication without listing his name and his student researchers' name(s) as co-authors (or at least to fully and explicitly acknowledge their respective contribution)?
- 3. Why didn't Muller write a letter to the journal immediately following this paper's publication that asserted some level of his collaboration (and co-authorship) and/or clarified Hanson's actual role in this research?
- 4. Why did Muller keep this situation quiet for 15 years, waiting three years following the death of Hanson, to only then write this confidential letter to Dempster?
- 5. Why did Muller send this letter to Dempster and (it seems) no one else? This letter (of Muller to Dempster; as presented in Appendix 1) perhaps affords some hint: Might it be that Muller, in writing that he was "sorry to have to tell you", suggests that Dempster and Hanson had a positive professional association/relationship, of which Muller was aware?
- 6. Why did Muller remain silent on this falsification and/or fabrication issue for such a long time, yet still continue to consider it a major breach of scientific ethics, without ever exposing such misconduct, and in fact, actually subsequently participating in such improbitious conduct himself?
- 7. Muller sent his critical letter to Dempster in August 1948. Caspari and Stern [13] published their key Manhattan Project X-ray-induced mutation paper in January 1948 in the journal, *Genetics*. Muller was a paid consultant to the Stern-led Manhattan Project study, and was sent a draft copy of that manuscript in November 1946 to review. On January 14, 1947, Muller provided a detailed assessment of that manuscript to Curt Stern [14]. In that report, Muller positively cited the research of Hanson and Heys that supported the LNT model in/for interpretation of findings. However, in his 1948 letter to

Dempster, Muller [1] strongly stated that the papers of Hanson and Heys could be not be trusted, as they were suspected of fabrication and/or falsification, a view that Muller claimed to have held since 1933. Caspari and Stern's final published paper continued to cite Hanson and Heys's research [3,5], as initially presented in the draft that was reviewed by Muller.

In retrospect, it is important to note that Muller's January 1947 evaluative letter to Stern about the Caspari paper failed to raise the issue that he believed the Hanson and Heys papers should be discredited. Therefore, we question why Muller's comments to Stern would positively reflect on (the LNT model supported by) Hanson and Heys's papers, while he was concomitantly excoriating Heys for dishonesty, and Hanson for complicit lack of oversight responsibility on these matters.

8. Lastly, - and perhaps most importantly - we opine that these issues, taken both individually and in sum, raise question(s) about if, and to what extent, the findings presented in each and all of these papers affect consideration of previously believed, current, and future assumptions and constructs underlying radiation risk assessment.

6. Ethical issues

In his letter to Dempster, Muller claimed that Hanson and Heys's work contained elements of fraud. Muller stated that these fraudulent issues dated at least to 1930, and possibly earlier, thereby (1) implicating any and all publications of Heys, and (2) de-valuing the work of Hanson and Heys as untrustworthy. Despite this, in his Nobel Prize Lecture [15], less than two years before his letter to Dempster, and a year after Hanson's death, Muller praised Hanson's research (with Heys) in support of the LNT model of dose-response effects. Why would Muller feel the need to privately challenge the alleged falsified and/or fabricated data of Hanson and Heys in the 1933–1934 period and again in 1948, yet praise it in his Nobel Prize Lecture? Perhaps there is more to the story.

From 1930 to 1932, and from 1934 until his death in 1945, Hanson worked for the RF. Hanson became highly influential within that organization, as the associate director of the natural sciences division [16]. This division funded academic genetics research in the United States and elsewhere. Carlson [17], in his biography of Muller, states that the RF provided critical funding for Muller while he was at the University of Edinburgh, and then subsequently during his tenure at Amherst College and the University of Indiana. Carlson [17] stated that Hanson specifically intervened at the most critical time during Muller's interview process at Indiana, calling the chair of the Biology Department to advocate for his appointment. The decision to hire Muller would ensure that the University of Indiana would become a leading center of radiation genetics research, and a prime recipient of research funding from the RF. Soon thereafter Hansen died, yet his advocacy for Muller's research was sustained by the RF [18]. In this way, Muller benefited from the support of the RF, and Hanson's role and actions, as a very much-admired entity at the RF [16]).

The question should be posed as to why Muller remained publicly silent about the major scientific misconduct he suspected of Hanson. A likely explanation is that it was in Muller's professional interest not to publicly challenge the reputation of Hanson, directly or indirectly, as this could cause considerable professional embarrassment to the RF, and possibly cost Hanson his position. How this may have affected Muller's funding from the RF is unknown, but such a blatant challenge of Hanson's reputation and professional standing (and institutional position and role) would certainly have been risky for Muller.

Indubitably, Muller perceived – and elucidated - ethical concerns about the conduct of Hanson's work. Hanson published – and claimed authorship of - research performed by Muller, without having done any work on these studies himself. Muller was fully aware of that, and by itself, this issue raises ethical concerns for both Hanson and Muller. Further, if Muller actually believed that the work of Hanson and Heys was fraudulent, then he had (and we assert would have known that he had) the obligation to at least state, if not challenge, this via appropriate venues.

One could appreciate why Muller tried to frame his letter to Dempster as "saving Hanson's reputation". However, Muller was in fact seemingly protecting his own reputation, ensuring continued funding from the RF and promoting his view of - and advocacy for - the LNT model. One could also wonder why in August 1948, Muller felt the need to confidentially write to Dempster to disparage Heys's reputation, and praise himself for saving Hanson's scientific career, only to then strongly chastise Hanson for putting his name on many papers for which he apparently did not warrant co-authorship.

Carlson [17] states that Muller's initial concerns with Hanson and Heys's research were ultimately resolved (page 154). But Carlson's narrative fails to address Muller's 1948 letter, in which, although some 15 years after-the-fact, still belies the fact that those issues of Hanson and Heys's alleged misconduct still had not been resolved in his opinion. In Muller's view, Heys, then at Baylor University, had repeatedly committed scientific misconduct. The data supporting the LNT model were still incorrect and being widely cited, and Hanson was credited for research he did not actually conduct. This was the essence of what Muller communicated to Dempster. To date, no evidence has been found that Muller ever rescinded the views he expressed in 1948. The impact of Muller's failure to publicly confront the apparent scientific misconduct of Hanson and Heys has played a crucial role in the adoption of the LNT model by the radiation genetics community [18-21]. The facts presented herein provide additional important detriment(s) to the troubling scientific legacy of both Hermann Muller and the historical foundations of LNT, which are clearly and inextricably related [18,20,21].

It is curious that the Muller research was published under Hanson's name had problems of its own. For example, Muller, the actual author, failed to provide any information on the doses and/or dose rates (or any technical information) relevant to the radiation exposure process. This peculiarity was not detected by Hanson (the officially listed author), any of the reviewers (if there were any), or the editor of the journal. Furthermore, there have been no letters to the editor – or commentary/ opinion papers - challenging the Hanson paper's findings. This failure suggests that the paper through which Muller claimed to have "saved" Hanson's reputation could not be replicated as published, may have further damaged Hanson's reputation as a scientist and, in the end, lacks any real scientific value. Perhaps then, in retrospect, Muller was fortunate (and/or prescient) in not co-authoring this paper.

It is now more than 95 years since the trustworthiness of the joint publications of Hanson and Heys's has been strongly challenged by Muller [1]. It is likely that these papers will continue to be cited in support of the LNT, with no knowledge of Muller's accusations and judgments, other than those reported herein. With the principal individuals long dead, and no knowledge of whether the research files of Hanson and Heys on these matters exist, there is no basis to undertake a formal evidence-based evaluation of Muller's accusations. However, given Muller's technical knowledge and status, and the importance of the LNT issue, we believe that it would be important for the involved journals (viz., Science, and *American Naturalist*) to appropriately note the papers of Hanson and Heys, and link their papers to this expository essay. We opine that at very least, such action would better inform researchers on the matter, and in so doing, help them pass their own

ethical judgment, and decide whether or not (and how) to cite Hanson and Heys's papers and work.

7. Conclusion

We offer that a newly discovered 1948 letter of Hermann Muller claimed that all of the jointly authored publications of Frederick Hanson and Florence Heys dealing with ionizing radiation contained elements of falsification and/or fabrication, and therefore were not trustworthy. These papers included a set of five articles used to support the Proportionality Rule/LNT dose response model. Despite Muller's strong beliefs and assertions on this matter and their important public health and policy implications, Muller failed to make his allegations public, although he sustained this belief from about 1933 to 1948, and most likely the remainder of his professional life. We believe that the reason Muller remained silent on these matters is closely linked to the fact that Hanson was a significant member of the RF and oversaw funding support of Muller's research since the mid-1930s. Public challenges of Muller's principal source of funding would not have been in his self-interest, and would have been likely to affect his relationship with both Hanson and the RF. In conclusion, we assert that these findings, their implications, and speculations of probable cause raise new and serious questions about the validity - and value - of national and worldwide cancer risk assessment policies, and the ethical integrity, bases, and regard of research that has been used to influence and promote the public health.

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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.

Data availability

No data was used for the research described in the article.

APPENDIX A

Transcribed letter by Calabrese that was written by Hermann J. Muller: Cold Spring Harbor Laboratory – Carlson Papers (EAC-001-046-90.jpg; EAC-001-046-92.jpg) HJM to ER Dempster. Dated: Aug 27, 1948

"I am sorry to have to tell you, completely confidentially, that the papers of Hanson & Heys, at least from 1930 on, constitute one of the great scandals of science, although all unbeknown to the scientific public, Heys, who is the culprit, has never admitted this, although I confronted her with the evidence in 1933 or 34. A close reading of the description of the genetic methods used, as given in the later abstracts, as well as a perusal of the smoothness of the curves in all the papers, will be enough to prove this to anyone who has any knowledge of genetics or feeling for statistics. In the attempt to save Hanson's reputation, CA Offermann, while working with me in Russia, tested most of these questions out again, + got really reliable results. These were published by Hanson alone in 1934 (Am. Nat 69:211-222) without his even putting Offermann down as a joint author. You will see that the results are in complete disagreement with those claimed by Hanson + Heys in the preceding years. As troubles for this Offermann was never able to get a job in scientific

world when he returned to this country from Russia."
"The 'Hanson' paper of 1935, being reliable except as to the name of the author could be referred to. (The actual author of the paper was in fact

"The 'Hanson' paper of 1935, being reliable except as to the name of the author could be referred to. (The actual author of the paper was in fact myself, while it was Offermann who conducted the work, which I planned the main outlines of, + Hanson never had anything to do with it except to sign it and send it in to the publishers, just as he did with the papers allegedly written by Hanson + Heys.)

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