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REVIEW ARTICLE

Muller's Nobel lecture on dose–response for ionizing radiation: ideology or science?

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Abstract In his Nobel Prize Lecture of December 12, 1946, Hermann J. Muller argued that the dose–response for radiation-induced germ cell mutations was linear and that there was "no escape from the conclusion that there is no threshold". However, assessment of correspondence between Muller and Curt Stern 1 month prior to his Nobel Prize Lecture reveals that Muller knew the results and implications of a recently completed study at the University of Rochester under the direction of Stern, which directly contradicted his Nobel Prize Lecture. This finding is of historical importance since Muller's Nobel Lecture gained considerable international attention and is a turning point in the acceptance of the linearity model in risk assessment for germ cell mutations and carcinogens.

Keywords Linearity · Threshold · Hermann J. Muller · Nobel Prize · Risk assessment · X-rays · Ionizing radiation

In 1927, Hermann J. Muller demonstrated that X-rays caused mutations in male fruit fly germ cells (Muller 1927). Nineteen years later, he would be awarded the Nobel Prize for this finding. Muller took his discovery seriously, trying to determine not just what it meant scientifically but for society as well. In fact, soon after his discovery, he expressed strong concerns about the indiscriminate use of X-rays, challenging the medical community to be aware of the benefits and dangers that X-rays may provide (Carlson 1981). As a direct offshoot of this concern, follow-up research in Muller's laboratory assessing the nature of the dose–response for radiation-induced germ cell mutations supported a linear interpretation thereby suggesting that there was no safe dose no matter how low or apparently inconsequential (Calabrese 2009, 2011). This was a theme that motivated the remainder of Muller's professional life. This motivation would be transformed into passion as the world entered its atomic phase with the dropping of the atomic bombs and the start of atmospheric testing of such weapons. In fact, with his Nobel Prize in hand and coupled with a commitment to educate societal leaders to the long-term dangers of atmospheric fallout for the human genome, Muller would be a force to contend with. In the end, it would be largely due to Muller's knowledge, leadership, message, perseverance, and passion that governments and society would change the way they viewed the risks of low doses of ionizing radiation (Carlson 1981). This leadership was evident in the 1956 recommendations of the US National Academy of Sciences (NAS) BEAR (Biological Effects of Atomic Radiation) I Committee, of which Muller was a member, that lead to governments changing how they evaluated the risks of germ cell mutation, regulating ionizing radiation as if there was no safe dose, using the linear dose–response model. Prior to the BEAR I Committee's recommendation, Muller and his geneticist colleagues were seen as bothersome governmental-medical critics; yet, with this public and transforming recommendation, they became in effect, now part of the system and its intellectual leadership. Within a year of the BEAR I report, the first efforts to regulate radiation-induced cancer risks were also placed within a linear context by the National Committee for Radiation Protection (NCRP). Within a few years, the linearity paradigm had transformed governmental

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regulatory agencies in many countries, including recommendations of the UN. Furthermore, some 20 years after geneticists took control of the ionizing radiation risk assessment issue, the next generation of geneticists and their chemical toxicologist peers, acting through the first NAS Safe Drinking Water Committee in 1977, followed the lead of the BEAR I Committee and applied linearity to cancer risk assessment for chemicals (National Academy of Sciences 1977). In retrospect, the transformation of a threshold guided risk assessment to one now centered on a linear dose–response started and reached completion with Muller (1890–1967), although he did not live long enough to see how most public health oriented and regulatory agencies worldwide dealing with radiation and chemical exposures had responded to his concerns and adopted his message (Bolt et al. 2009; Calabrese and Baldwin 2003; Hoffmann 2009).

While Muller received innumerable accolades for his achievements and leadership, recently unearthed correspondence between Muller and Stern (American Philosophical Society—H. J. Muller File 1946/1947a) challenge the veracity of Muller's strikingly unequivocal statement concerning the effects of ionizing radiation on germ cells in his Nobel Prize Lecture. His presentation was a galvanizing moment in the debate over the shape of the dose–response in the low-dose zone for ionizing radiation. During that memorable occasion, he stated that there could no longer be any doubt that the dose–response for ionizing radiation-induced germ cell mutation was linear. He then cited the work of several people (e.g., Oliver 1930; Hanson and Heys 1932; Timofeeff-Ressovsky et al. 1935) that linearity best described how radiation affected germ cells (i.e., fruit fly sperm). In this acknowledgment, he failed to qualify it by noting that the doses used were extraordinarily high, having no obvious relevance to the human condition. He also neglected to acknowledge other contemporary substantial findings that did not support a linear dose–response (e.g., Hanson and Heys 1929; Weinstein 1928; Stadler 1930; Serebrovsky and Dubinin 1930; Calabrese 2009). He then claimed that if that was not enough then there could be "no escape from the conclusion that there is no threshold" based on the research of his graduate student protégé, Ray-Chaudhuri. However, Muller did not mention that there were several concerns among his peers with these data, including confusion over the appropriateness of his control group, substantial variability [see Caspari–Stern Correspondence, November 7, 1947 (American Philosophical Society—E. Caspari File 1946/1947b)], inadequate reporting of research methods, small sample size, lack of data on quality control parameters, known problems with temperature control, lack of data on lethal clusters, sterility/fecundity, sex ratios, selection criteria for males, that he changed the fruit fly strain in the middle of the study and that the "very low dose" tested was still some many thousand fold greater than human background exposures to ionizing radiation. However, of greatest concern was Muller's failure to temper his Nobel Prize Lecture remarks in light of the fact that he had recently become aware of a large experiment conducted at the University of Rochester by Ernst Caspari and Curt Stern (American Philosophical Society—E. Caspari File 1946/1947b), which failed to support linearity. This study had heightened importance because it was testing the effects of ionizing radiation at the lowest dose rate then ever tested (2.5 r/day). These findings supported a threshold interpretation and challenged Muller's striking "no excuse" statement (American Philosophical Society—H. J. Muller File 1946/1947a). In fact, these experiments were conducted with a special strain of fruit flies that Muller had supplied to Stern. Muller was also a formal consultant to the project, given special clearance by the US government. The study was completed by August of 1946, a little more than 3 months prior to his Nobel Prize lecture. The following represents a series of letter exchanges between Stern and Muller concerning the Caspari and Stern manuscript (American Philosophical Society—H. J. Muller file 1946/1947a):

September 24, 1946: Stern to Muller: "Dr. Caspari's report on his work is now being typed and I wonder whether we could bother you with sending you a copy for your new comments."

September 27, 1946: Muller to Stern: "Also, I'd be glad to see Caspari's paper too."

November 6, 1946: Stern to Muller: "Caspari's manuscript has finally been typed and we would appreciate very much your critical reading of it."

November 12, 1946: Muller to Stern: "I have just arrived from an absence of over 2 weeks and find the Caspari manuscript here waiting for me. Unfortunately, it catches me again when I am in a tremendous pressure of work, trying to make up both the trip just passed and for another one to come in a few weeks. However, I see that it is very important and shall do all I can to go through it in a reasonable time, surely before I leave again early in December. I hope that Caspari can wait that long if necessary. In the meantime I wonder whether you are having any steps taken to have the question tested again, with variations in technique. It is of such paramount importance, and the results seem so diametrically opposed to those which you and the others have obtained, that I should think funds would be fourth coming for a test of the matter. It is not, of course, that I doubt Caspari's reliability at all, but only that I naturally share the same doubts which he himself expressed. Of course, I am only judging by the summary and a quick glance through the paper, and have not had the opportunity to read the details."

Thus, it is clear that Muller knew of the significant challenge to a linearity dose–response interpretation by the Caspari and Stern manuscript, and he knew this in the weeks just preceding his being awarded the Nobel Prize. Muller may have still believed that the linear dose–response model was the most appropriate. However, the data of Caspari and Stern would not have supported a statement that there was "no escape from the conclusion that there is no threshold." In fact, these data provided a possible basis for such an escape. While Muller knew of the findings and their importance to the dose–response debate, the US government had yet to declassify the report by the time of the Nobel ceremony so he could not have explicitly cited it. However, given his unique insight into the scientific foundations of threshold versus linearity dose–response model debates and the importance to place the matter on a strong scientific foundation, the most intellectually honest position at the Nobel Prize Lecture would have eliminated the "no escape" statement and emphasized the need for more research to determine the nature of the dose–response in the low-dose zone. However, Muller chose not to do this, confidently concluding his public remarks that the issue had been decided, yet we know now that he knew this was not the case.

One might suggest that after deeper reflection and study, Muller found the paper of Caspari flawed and should not be published. However, available evidence does not support this position. In a January 14, 1947 letter to Stern, Muller provided a detailed assessment of the manuscript, encouraging Stern to publish the manuscript. However, it is important to note that the entire discussion of the Caspari and Stern manuscript assessed why their findings differed from those of Spencer and Stern, which supported a linear dose–response within the context of an acute exposure to X-rays. The Caspari and Stern (1948) paper emphasized that their findings should not be accepted until it is possible to explain why the findings of the two studies differed. This position was bizarre since the two experimental approaches had nearly two dozen methodological differences (e.g., X-rays vs. gamma rays, adult males vs females, exposure duration 2 h vs. 21 days, dose rates differed by 15,000-fold, temperatures were different 18°C vs. 24°C, two entirely different diets) between them, making a direct comparison if not impossible, then extremely difficult (Calabrese 2011). Of interest was that Muller indicated that he found no harm in publishing the Caspari paper as the discussion greatly restricted the acceptance and application of the findings. The constraining discussion of the Caspari and Stern manuscript would protect Muller from criticism that he was in fact deceptive in his Nobel Prize Lecture. This discussion would also serve to protect the linearity dose–response model from a serious data-based challenge. The present assessment of Muller's Nobel Prize Lecture suggests that Muller was deceptive in his presentation, thus profoundly enhancing acceptance of the linear at low-dose modeling and risk assessment practices throughout the second half of the twentieth century to the present.

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Conflict of interest The author has no conflict of interest.

References

American Philosophical Society, Philadelphia (1946/1947a) Curt Stern Papers, Hermann J. Muller File, URL: http://amphilsoc.org

American Philosophical Society, Philadelphia (1946/1947b) Curt Stern Papers, Ernst Caspari File, URL: http://amphilsoc.org

Bolt HM, Marchan R, Hengstler JG (2009) Low-dose extrapolation in toxicology: an old controversy revisited. Arch Toxicol 83:197–198

Calabrese EJ (2009) The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. Arch Toxicol 83:203–225

Calabrese EJ (2011) Key studies used to support cancer risk assessment questioned. Environ Mol Mut 52 (in press)

Calabrese EJ, Baldwin LA (2003) Toxicology rethinks its central belief. Nature 421:691–692

Carlson EA (1981) Genes, radiation, and society: the life and work of H.J. Muller. Cornell University Press, Ithaca

Caspari E, Stern C (1947) The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in Drosophila melanogaster. MDDC-1200, US Atomic Energy Commission, pp 1–18. Found on the web at Hathi Trust Digital Library, http://www.hathitrust.org

Caspari E, Stern C (1948) The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in *Drosophila melaogaster*. Genetics 33:75–95

Hanson FB, Heys F (1929) An analysis of the effect of the different rays of radium in producing lethal mutations in *Drosophila*. Am Nat 63:201–213

Hanson FB, Heys F (1932) Radium and lethal mutations in *Drosophila* further evidence of the proportionality rule from a study of the effects of equivalent doses differently applied. Am Nat 66:335–345

Hoffmann GR (2009) A perspective on the scientific, philosophical, and policy dimensions of hormesis. Dose-Response 7:1–51

Muller HJ (1927) Artificial transmutation of the gene. Science 66:84–87

National Academy of Sciences (1977) Safe drinking Water Committee. National Academy of Sciences Press, Washington DC

Oliver CP (1930) The effect of varying the duration of X-ray treatment upon the frequency of mutation. Science 71:44–46

Serebrovsky AS, Dubinin NP (1930) X-ray experiments with *Drosophila*. J Hered 21:259–265

Stadler LJ (1930) Some genetic effects of X-rays in plants. J Hered 21:3–19

Timofeeff-Ressovsky NW, Zimmer KG, Delbruck M (1935) Nachrichten von der gesellschaft der wissenschaften zu Gottingen. Uber die nature der genmutation und der genstruktur Biologie Band I, Nr. 13

Weinstein A (1928) The production of mutations and rearrangements of genes by X-rays. Science LXVII:376–377