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REVIEW

Muller's Nobel Prize Lecture: When Ideology Prevailed Over Science

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This paper extends and confirms the report of Calabrese (Calabrese, E. J. (2011b). Muller's Nobel Lecture on dose-response for ionizing radiation: Ideology or science? *Arch. Toxicol.* 85, 1495–1498) that Hermann J. Muller knowingly made deceptive comments in his 1946 Nobel Prize Lecture (Muller, H. J. (1946). Nobel Prize Lecture. Stockholm, Sweden. Available at <http://www.nobelprize.org/>. Accessed December 12) concerning the dose-response. Supporting a linearity perspective, Muller stated there is “no escape from the conclusion that there is no threshold” while knowing the results of a recent study by Ernst Caspari and Curt Stern contradicted these comments. Recently uncovered private correspondence between Muller and Stern reveals Muller's scientific assessment of the Caspari and Stern manuscript in a letter from Muller to Stern 5 weeks (14 January 1947) after his Nobel Prize Lecture of 12 December 1946. Muller indicated that the manuscript was of acceptable scientific quality; he indicated the manuscript should be published, but the findings needed replication because it significantly challenged the linearity hypothesis. These findings complement the previous letter (12 November 1946 letter from Muller to Stern), which revealed that Muller received the Caspari and Stern manuscript, recognized it as significant, and recommended its replication 5 weeks before his Nobel Prize Lecture. Muller therefore supported this position immediately before and after his Nobel Prize Lecture. Muller's opinions on the Caspari and Stern manuscript therefore had not changed during the time leading up to his Lecture, supporting the premise that his Lecture comments were deceptive. These findings are of historical and practical significance because Muller's comments were a notable contributory factor, changing how risks would be assessed for carcinogens (i.e., changing from a threshold to a linear model) throughout the 20th century to the present.

Key Words: linearity; threshold; risk assessment; ionizing radiation; mutation; carcinogen.

INTRODUCTION

In his Nobel Prize Lecture, Hermann J. Muller strongly supported the conclusion that the effects of ionizing radiation

on germ cells would follow a linear dose-response relationship. This conclusion was in marked contrast to the accepted dose-response paradigm of the 1930s and 1940s that the dose-response for ionizing radiation would follow a threshold dose-response (Calabrese, 2009; Kathren, 1996). In fact, it was not surprising that Muller would have supported the linearity dose-response argument as he had long advocated that perspective even though there was insufficient evidence to decide the matter in a scientific sense (Jolly, 2003). What made the Nobel Prize Lecture far more notable than his reaffirmation of linearity were his comments that there was in fact “no escape from the conclusion that there is no threshold” for ionizing radiation-induced germ cell mutation (Calabrese, 2011b). This was a strikingly absolute statement for which one would have expected Muller to provide new findings to affirm this conclusion. However, Muller (1946) simply referred to a series of older studies that were consistent with linearity, all of which had study design and/or methodological limitations, preventing a firm conclusion.

THE PROBLEM

There was a problem with the absolutism of his statement. Muller had been a consultant to the University of Rochester on a study funded by the Manhattan Project under the direction of Professor Curt Stern, also a well-known radiation geneticist. As a result of his involvement with this project, Muller was sent a manuscript by Stern of a study conducted by Ernst Caspari on 6 November 1946, 5 weeks before his Nobel Prize Lecture (Calabrese, 2011b). The findings supported a threshold dose-response for ionizing radiation on male fruit fly germ cells. These findings were not expected as the dominant dose-response paradigm among the radiation geneticist community was linearity at low dose. This study was important because it dealt with a lifetime (i.e., chronic) exposure at the lowest dose rate yet evaluated. A similar study by Warren Spencer under the direction of Stern, supporting a linearity perspective, had been conducted the previous year with the same cumulative

dose but the radiation was administered over only a few minutes rather than 21 consecutive days of the Caspari study (Caspari and Stern, 1948; Spencer and Stern, 1948). Thus, the dose rate of Caspari's chronic study was only about 1/15,000 of the acute study of Spencer. The Caspari study had a number of improvements over the Spencer study, such as far better temperature control, more careful matching of treatment and control groups to environmental conditions, better documentation of exposure, adjustment for lethal clusters, and more uniform exposures in the key 50 r cumulative exposure comparison group. There were also about 25 potentially important methodological differences, which precluded a direct comparison between the studies. Although the dose rate was still high in the Caspari study relative to normal background for humans, it was the most relevant study for a low-dose rate chronic study to date by far (Calabrese, 2011a). Despite his unique knowledge of the research methods, Stern's study team, and the experimental findings, Muller would use his Nobel Prize Lecture to proclaim his no escape assertion, knowing full well that the Caspari study did not support linearity. This lack of support for linearity of the Caspari study led to Muller's statement (i.e., 12 November 1946 letter back to Stern) that although he had no reason to dispute the study, it needed to be replicated due to its direct challenge of the linearity paradigm (APS, 1946). Based on this set of circumstances, one might wonder why Muller publicly stated, on the most significant scientific stage in the world, that "there is no escape from the conclusion that there is no threshold" while privately advising Stern that the Caspari study, which contradicted his linearity belief, needed to be replicated and to be done so as soon as possible. He also knew quite well that such a replication was not trivial but would require a substantial effort by multiple individuals over about a year. Muller's two statements are thus clearly in conflict with each other.

MULLER'S OPINIONS

So what did Muller think upon further reflection? Did he take back the replication suggestion? After a detailed review did he discredit or significantly challenge the Caspari study findings? No, as discussed below, he not only reasserted the need for the replication but also emphasized that there was very little about the Caspari study that he could offer suggestions on. In fact, Muller (14 January 1947) (APS, 1947) noted that "... I have so little to suggest in regard to the manuscript." Thus, the study of Caspari successfully passed Muller's critical assessment.

In his 14 January 1947 letter to Stern, Muller also reaffirmed the need for replication by stating: "Unfortunately, therefore, a repetition seems to be imperative" when referring to the Caspari study. The remainder of that sentence concludes, "Although I do not see why that should hinder one from publishing the present paper, with the cautions which it

contains." This was a very odd final phrase because he had just indicated in the letter how well the study was conducted. What did Muller mean with the phrase "cautions which it contains?" What were the cautions to which Muller refers? The so-called cautions refer to the following statement in the conclusion: "Before accepting the dependence on the time factor of radiation effects on mutation rate at low doses, it will be necessary to exclude all the factors discussed above which may have depressed the mutation rate in our experiments." The discussion reviewed some five factors (i.e., methodological differences): there were still another 20 methodological differences between the acute exposure study of Spencer and Stern (1948) and the chronic exposure study of Caspari and Stern (1948) that could have affected their different outcomes. It would never be possible to resolve these differences ... theoretically or experimentally. In fact, it has now been over 60 years and no study has ever made an attempt to do so. The discussion of Stern and Caspari, along with the comment of Muller (i.e., "cautions it contains" quote), would normally be hard to understand as it is contrary to the normal actions of investigators who publish their research. It also is especially difficult to understand, given the high quality of the research methods and the execution of the study itself. The authors truncated the discussion around why two studies with profound and numerous methodological differences might yield different findings. Furthermore, they argued that their findings should not be accepted until such differences in response were in fact resolved. At the same time, these investigators, especially Stern, made no similar demand for acceptance of findings in the Spencer paper, which was published within the same issue of the journal, *Genetics*. In fact, the most relevant contemporary discussion of the Caspari and Stern manuscript is seen in the Muller letter to Stern (14 January 1947) in which he tries to explain how a threshold dose-response might have occurred and why he may disagree with such an interpretation. Yet these arguments were strangely lacking in the actual paper. This highly unusual, but consistent, set of facts and actions supports the conclusion that the discussion of the Caspari and Stern paper was an attempt to misdirect an assessment of the significance of the findings and place its results into a framework so that other scientists would not cite it or rely upon it, thereby marginalizing the paper.

So what did Muller think with 20:20 hindsight, that is, after the Nobel Lecture was past and he had returned to the University of Indiana? His 14 January 1947 letter reveals the following insights:

Muller writes to Stern saying: "There is hardly any room left for a reconciliation of the present results with those being obtained by you with those previously obtained by Ray-Chaudhuri, short of some sort of systematic error that has somehow been overlooked." However, in his letter, Muller neglected to point out key limitations of the Ray-Chaudhuri experiment (Calabrese, 2011b; Ray-Chaudhuri, 1944) such as poor temperature control, changing the strain of fruit fly

midway through the study, and yet still combining data of the two strains to gain statistical power without providing any justification. There was also insufficient detailing of research methods, inadequate data on quality control parameters, as well as a failure to provide information on age selection criteria for males, sex ratios of offspring, and rates of sterility and fecundity as well as data on lethal clusters, all of which are important in this type of study. The Ray-Chaudhuri study also employed a dose rate that was significantly greater than that employed by Caspari. If Muller were really thinking that some type of systematic error or other experimental factor might have been overlooked, the Ray-Chaudhuri study gave more than ample reason for concern. In essentially all respects, the Caspari study was superior to the Ray-Chaudhuri study and more relevant to the low-dose chronic exposure issue. Yet, Muller based much of his threshold dose-response rejection quote in the Nobel Prize Lecture on the significance of the Ray-Chaudhuri data, so there would be no criticism of the Ray-Chaudhuri paper by Muller, even though well deserving, only an affirmation that Caspari's experiment be replicated.

Muller again states: "One could, for instance, say that a given number of ions in a sperm cell is required in order to raise some physico-chemical condition above a certain threshold, while above it they can [cause a mutation]. That is of course an explanation to fit the result, but one which seems highly improbable."

Muller states: "Neither am I happy with Caspari's surmise that we are dealing with events having too low a frequency to be subject to statistical rules. It seems to me that this is demonstrably not the case either. What the "joker" is then I cannot guess but it seems to me that there probably is one."

We see, therefore, that Muller struggled with the data of Caspari, especially given his strong advocacy of a linearity perspective. Is there a threshold? He does not think so . . . calling it highly improbable . . . Is there insufficient statistical power to resolve the issue as Caspari seems to suggest? Muller is not inclined to support this explanation either. Unable to resolve the issue scientifically, Muller then more or less throws his proverbial hands into the air and states (actually restates) that the replication is needed.

Back to the Nobel Prize Lecture Comments of Muller: Why did Muller claim that there was "no escape from the conclusion that there is no threshold"? In the end, Muller knew that the only way to scientifically resolve the issue was via a new study. He supported this position before Stockholm and after Stockholm, even though he was not too happy with it. The bracketing of Muller's opinions to include the time of his Nobel Prize Lecture is important because an argument could be raised that Muller's opinions on the Caspari study may have changed from the time of his 12 November 1946 letter to Stern until the Nobel Prize Lecture, thus giving him plausible deniability. The 14 January 1947 letter refutes that argument and possibility. Muller's comments at Stockholm did not reflect his current understandings, the limitations of the

linearity hypothesis, and the important need to resolve outstanding scientific questions; his statements during the Nobel Prize Lecture on the nature of the dose-response were therefore misleading and deceptive as he gave a very clear and striking message to all who heard or read his remarks; he indicated that the question had been answered and the answer was linearity. He may well have believed that linearity would prevail, but he also knew that there was this major study by Caspari that had just been completed that suddenly placed a roadblock on the march toward linearity. So rather than allowing the Caspari study to be a roadblock to linearity, Stern and Muller used the discussion of the Caspari and Stern paper to impose their roadblock to the acceptance and application of the Caspari findings and to blunt criticism of Muller's Nobel Prize Lecture and its impact on his reputation. In fact, if the Caspari and Stern (1948) paper had not been marginalized by its own intentional "self-destructive" discussion, Muller's deceptive Nobel Prize Lecture comments would have exposed him to serious and damaging criticism.

CONCLUSION

The 14 January 1947 letter confirms that Muller's Nobel Lecture comments were deceptive. For Muller, there is no escape, as he deliberately used the Nobel Prize Lecture to gain support for his ideology.

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