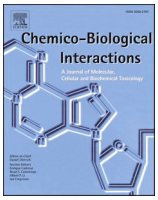
Chemico-Biological Interactions 359 (2022) 109917

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint



Research paper

Key historical study findings questioned in debate over threshold versus linear non-threshold for cancer risk assessment

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ARTICLE INFO

Keywords:
Mutation
Dose response
Linear dose response
LNT
Ionizing radiation
Hermann J. Muller

ABSTRACT

This paper demonstrates that the dissertation research of Ray-Chaudhuri (1939, 1944) that was used by Hermann Muller to support his radiation induced gene mutation hypothesis and linear non-threshold (LNT) dose response model during his Nobel Prize Lecture is "uninterpretable" with respect to these issues. The research failed to include essential research design information, resulting in reporting flaws that have never been previously identified. These observations are historically important because this dissertation was used to blunt powerful criticism of Muller's gene mutation research and strongly promoted his advocacy of the LNT model in radiation risk assessment.

1. Introduction

In 2011, I reported that Hermann J. Muller deliberately deceived his Nobel Prize Lecture audience when he claimed the that the long-used threshold dose model lacked scientific credibility [1,2]. My argument was based on the fact that Muller was knowledgeable of the results of the largest and strongest radiation-induced gene mutation study (i.e. Drosophila) to date (i.e. the Caspari study), with it showing clear evidence of a threshold response. This was supported by correspondence between Muller and Curt Stern [3,4]. While ignoring the Caspari findings during his Nobel Prize Lecture, Muller highlighted the dissertation research of Ray-Chaudhuri [5,6] at the University of Edinburgh to support this argument. The Nobel Prize Lecture statement is as follows: Muller [7] stated that the findings of Ray-Chaudhuri "leave, we believe, no escape from the conclusion that there is no threshold dose …. ". While I have published several papers that were critical of numerous aspects of the Ray-Chaudhuri dissertation research [8,9], the present paper provides evidence that the Ray-Chaudhuri study is "uninterpretable" with respect to the critical issue of dose response threshold and directly challenges Muller's Nobel Prize Lecture assertion on the matter.

2. Concerns with the ray-chaudhuri dissertation

It is important to place the significance of the Ray-Chaudhuri dissertation in historical context. It played a key role in restoring the credibility of Muller's claim that he produced gene mutations in his 1927 report in *Science* [10], following a decade on the defensive in which evidence had precipitously mounted that he had made an error in interpretation of his findings, confusing an observation with a mechanism [11–13]. The growing consensus was that Muller had induced modest to massive gene deletions in chromosomes that recombined, resulting in phenotypic changes in the next generation. Radiation induced phenotypic transgenerational changes were not considered an important finding but gene mutations were, thus the dispute over the Muller interpretation was of considerable significance. In addition, in 1930 Muller [14] proclaimed the dose response concept, The Proportionality Rule, the predecessor of the LNT dose response, with ionizing radiation inducing gene mutation down to a single ionization [14]. Since Muller's positions on the gene mutation and linearity at low doses were losing support during the 1930s [4], he sought a novel approach to revitalize both hypotheses via a single dissertation that would test the concept of whether radiation induced gene mutation could be best predicted by total dose or dose rate. Thus, the Ray-Chaudhuri dissertation would take on that challenge and the outcome would be important to Muller's career and critical to the field of dose response and radiation risk assessment.

Before the Ray-Chaudhuri dissertation is considered here, it is necessary to jump forward to the Manhattan Project for critical experimental perspectives. During the Manhattan Project research was conducted under the direction of professor Curt Stern, a highly regarded

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https://doi.org/10.1016/j.cbi.2022.109917
Received 21 February 2022; Received in revised form 18 March 2022; Accepted 23 March 2022
Available online 1 April 2022

Drosophila geneticist. This research was intended to assess the capacity of ionizing radiation to induce mutations in Drosophila. Muller, a professor at Amherst College at that time, was hired as a paid consultant to the project. Given Muller's high stature and experience, he influenced Stern to replicate the Ray-Chaudhuri study but in a far more substantial manner than done in the dissertation. The research goal was to determine whether total cumulative dose or dose rate was the best predictor of radiation induced mutation risk. Muller supported the total dose hypothesis which assumed that all radiation induced gene mutations were cumulative, non-reparable and irreversible, leading to a linear dose response, down to a single ionization. This hypothesis was assessed in separate experiments by Ernst Caspari and Delta Uphoff, under the direction of Stern. In their experiments the control and treated fruit flies were placed into identical but different incubators in the same room and operated by the same condenser. Since the radiation treatment emits gamma rays, a lead shield was placed between the two incubators to greatly reduce exposure of the radiation to the control group. Measurement of the efficiency of the lead shielding to reduce the gamma ray exposure indicated it was 99% effective [15,16]. The radiation exposure therefore is estimated to have resulted in the control group being exposed to about 0.6 r over the course of the three week experiment. The radiation was delivered to the control at a rate that exceeded background by about 100-fold. The Caspari and Uphoff experiments therefore lacked a non-exposed control group. While the issue of the Caspari and Uphoff control groups and their exposure to radiation will be addressed in a separate communication, the Ray-Chaudhuri experimentation was unique because its dosing was 40 fold higher (i.e., 50 vs 2000 r) than these other two studies. A close reading of the Ray-Chaudhuri [5,6] published paper and dissertation reveals no mention of control and treatment group incubator placement/location (s). It is not known if the control or treatment group incubators were in the same room or not, nor was mention made of lead shielding. Since there was no evidence of increases in mutation incidence in the control group, this strongly suggests that the control group was not close to or in the same room as the treatment group or protected from exposure in some way. This creates two possible options. One is that the Ray-Chaudhuri research mimicked that of Caspari and Uphoff and were conducted in close proximity in the same room, with lead shielding used. This is the option favored by the author since Muller had experience directing student research with radiation and fruit flies using lead shielding [17] and was influential in the design and conduct of the Manhattan Project studies of Caspari and Uphoff. If this were the case it may be estimated that the cumulative dose to the control group would have been about 24 r, a very high dose, resulting in an apparent threshold-type/no effect response. The other option is that the two groups were placed sufficiently far apart in one room or were placed in other rooms at sufficient distance, with no significant additional exposure. No information permits resolution of this uncertainty. What this means is that the Ray-Chaudhuri study failed to properly describe in the dissertation methods section the details about the location of the control and treatment group incubators with respect to each other. The committee members, including Muller as chair, failed to provide proper oversight on this matter.

The decision of Muller to use the Ray-Chaudhuri study to challenge the validity of the threshold model in his Nobel Prize Lecture was improper since the dissertation, as written, did not provide the capacity to support that conclusion. In the end, Muller used the Nobel Prize Lecture to support an ideological rather than a scientific perspective. Of further interest is that it was this dissertation that rescued Muller from the unrelenting criticism of Stadler and others concerning Muller's use of "reverse mutation" to defend his gene mutation hypothesis. It is unfortunate that the specific methodology was not provided because the answer would have had the potential to clarify the nature of the dose response in the low dose zone, assuming other aspects of the research were acceptable. However, Muller used the Ray-Chaudhuri research to restore and promote his research standing and then to use it to advocate for LNT at the Nobel Lecture and many other venues. In fact, in 1956 at the start of the NAS BEAR I Genetic Panel meetings, Muller would continue to cite the significance of the Ray-Chaudhuri study for low dose extrapolation, supporting a linear model (Muller letter to Weaver, January 21, 1956 [18]) and never be challenged by the scientific community.

Funding

EJC acknowledges longtime support from the US Air Force (AFOSR FA9550-19-1-0413) and ExxonMobil Foundation (S18200000000256). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

Author contributions

EJC developed the concept, investigation, original draft, writing, editing, funding acquisition and resource, analysis, methodology and was responsible for project administration.

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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