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Review article

Ethical failings: The problematic history of cancer risk assessment

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ABSTRACT

This paper demonstrates that unethical conduct by the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel led to their recommendation of the Linear Non-Threshold (LNT) Model for radiation risk assessment and its subsequent adoption by the US and the world community. The analysis, which is based largely on preserved communications of the US NAS Genetics Panel members, reveals that Panel members and their administrative leadership at the NAS displayed an integrated series of unethical actions designed to ensure, (1) the acceptance of the LNT and (2) funding to radiation geneticist panel members and professional colleagues. These findings are significant because major public policies in open democracies, such as cancer risk assessment and other issues impacted by public fears of radiation or chemical exposures, require ethical foundations. Recognition of these ethical failures of the BEAR I Genetics Panel should require a high level administrative, legislative and scientific reassessment of the scientific foundations of cancer risk assessment, with the likely result necessitating revision of current policies and practices. The BEAR I Genetics Panel, 1956 *Science* journal publication should immediately be retracted because it contains deliberate misrepresentations of the scientific record that were designed to manipulate scientific and public opinion on radiation risk assessment in a dishonest manner.

1. Introduction

The radiation genetics community (e.g., US NAS BEAR I Genetics Panel), with the strong leadership of Nobel Laureate Hermann J. Muller, played a pivotal role not only in the contemporary understanding of genetic mutation but also in the establishment of principles for cancer risk assessment. This is seen in the policies and practices of cancer risk assessment in the US as directed by the Environmental Protection Agency (EPA) and other agencies and governments throughout the world. These organizations largely obtained their beliefs from a salient report that was produced by a Muller-led NAS BEAR I Genetics Panel in June 1956, and immediately became a prominent story in the *New York Times* (Leviero, 1956), *Washington Post* (Haseltine, 1956) and numerous other media organizations. The report was notable because it recommended a fundamental change in how radiation risk assessment is conducted (BEAR I, 1956). In essence, the panel rejected the three-decade practice of using the threshold model that assumed safe exposures could be attained if kept below a quantitatively determined threshold dose. Instead, the Panel recommended adoption of a linear non-threshold (LNT) model that declared that any dose of radiation-no matter how small-was unsafe in terms of genetic risks. Within two years of that publication (December 1958) LNT was applied to cancer risk assessment for radiation by the US National Committee for Radiation Protection and Measurement (see Calabrese, 2019a). This same linear dose response view would later be adopted by EPA for ionizing radiation and chemical carcinogens based upon the NAS Genetic Panels' recommendations (Albert, 1994; Calabrese, 2019a). Thus, the NAS BEAR Genetics Panels and EPA started a real risk assessment revolution.

While the LNT recommendation was the end result of seven months of Genetics Panel activities, it was clearly the brain-child of Muller, starting in 1930 when he created the phrase "The Proportionality Rule"—according to which the dose response for radiation-induced mutation was linear all the way to zero exposure (Calabrese, 2013a). After some 26 years of frustrating advocacy failures as part of multiple national/international advisory committees (Calabrese, 2009), all the necessary success-related elements converged, thereby resulting in the recommendation by the Genetics Panel that the US apply Muller's proposal of linearity to radiation risk assessment (BEAR I, 1956; Calabrese, 2019a). The US and other countries have not looked back since, even though the scientific foundation and adoption of LNT has long been at the center of considerable controversy. Such controversies have mostly been due to (a) its potential for very high costs of implementation, that is, the need for very strict industrial and community standards (b) its influence on toxic tort litigation in which it increases the likelihood of

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massive plaintiff settlements for alleged harms and (c) challenges to remove valued existing technologies and compounds from the marketplace due to pressure from LNT-based cancer concerns. More recently, LNT has also been blamed for being too strict and "causing harm" in the sense that low doses of many harmful agents paradoxically may induce hormetic-mediated beneficial effects, actually reducing toxic hazards and cancer risks of these agents (Calabrese, 2008; Cook and Calabrese, 2006).

While much has been written about the actions of the BEAR Panels that set the stage for the switch to adoption of LNT (Calabrese, 2011a,b, 2012, 2013a,b, 2014, 2015a,b, 2016, 2017a,b,c, 2018a,b, 2019a,b,c, 2020), the issue of Panel ethics is now being raised. Ethical concerns with respect to LNT started on December 12, 1946, when Muller (1946) stepped onto the podium in Stockholm to deliver his famously influential Nobel Prize Lecture that proclaimed the demise of the threshold model.[1] Although these concerns extend to the present time, they centered primarily on the radiation geneticists (i.e., BEAR and Biological Effects of Ionizing Radiation (BEIR) Genetics Panels) who guided the country and world in determining how to assess the genetic and cancer risks from exposures to ionizing radiation. The final living member of that original group of geneticists, James Crow, died at the age of 95 in 2012, some 45 years following the death of Muller in 1967. This elite group of radiation geneticists, which was originally organized by the NAS in November 1955 for meetings at Princeton University, was believed to be a "Dream Team" based on their heighted acclaim bestowed by the *New York Times and Washington Post* in their June 13, 1956, front-page stories. However, the image of this "Dream Team" was tarnished by a series of revelations that accused this group of adopting the skewed philosophy of "an end justifies the means".[2] That is, these revelations documented that the BEAR I Genetics Panel would do whatever it took to make the adoption of LNT a reality, even if they had to deceive the world. For in the end, the members of this Panel believed that it knew more and understood better than anyone else the hazards of radiation and the dangers from exposure. Therein lies the problem and the ethical dilemma that has emerged because this small group of radiation geneticists seized this opportunity, as the distinguished BEAR I Genetics Panel of the highly prestigious US NAS, and acted in the way that brought ideologically-motivated and self-serving decisions that would impact human life for over six decades, being left unchallenged.

This paper explores many decisions and actions of this Genetics Panel whose role was to serve as governmental advisors in a democracy. In some ways, the actions of the scientists of this Panel mirrored that of those involved in making and employing the atomic bomb. For instance, was the decision to drop the bomb a responsibility of the nuclear physicists of the Manhattan Project who made the atomic bomb or the President of the US. As is well known, Truman and not the physicists made that decision. In the case of cancer risk assessment however, it turns out that the geneticists, rather than the elected government officials, would mislead the US and world governments, enabling their favored, but flawed, theory to be adopted and used to enact global polices. In many ways, the radiation geneticists and their world of mutations, transposable elements and evolutionary theory were as mysterious and technical to the nonscientist leaders as were nuclear physicists and their world of fissionable radionuclides, subatomic particles, and quantum theory. However, when it came time to face the terrible decision, the leader of the Manhattan Project and nuclear physicists, Robert Oppenheimer, did not try to usurp that power from the President, as some in his community hoped. However, this was not the case of the 1950s Genetics "Dream Team." With a certain aplomb and an amazing array of lies and sophisticated deceptions, the "Dream Team" leveraged their media savvy and revered reputations to obviate standard practices and achieve its desired LNT outcome, unwittingly creating a perfect toxicological storm. With a lack of circumspection and interrogation, leaders across the world readily and all too willingly adopted and implemented the LNT plan with little, if any, verification and fact-checking.

2. A new lens into the ethically challenged BEAR I genetics panel

Bringing that story into sharper focus is a recent publication (Calabrese, 2020) showing that the US NAS BEAR I Genetics Panel refused to evaluate a ten-year study by the US NAS and Japan Atomic Bomb Casualty Commission (ABCC). This study was called the Neel-Schull (1956) Report on the effects of the atomic bomb blasts on offspring of the atomic bomb-exposed parents born after May 1, 1946. The Neel-Schull study had over 70,000 subjects exposed across a broad range of radiation doses. In sharp contrast to the US BEAR I Genetics Panel, a similar contemporary British Genetics Committee enthusiastically welcomed the opportunity to evaluate the findings of this human study. A detailed review of the final British report [Medical Research Council (MRC), 1956] reveals that the Neel-Schull Report (1956) significantly impacted the conclusions/recommendations of the British report in that it reduced the public health concerns resulting from low dose exposures. For example, the British report stated: **"We consider, therefore, that an individual would, without feeling undue concern about developing any of the delayed effects, accept a total dose of 200 r in his life-time, in addition to radiation from the natural background, provided that his dose is distributed over tens of years …"**

[1] Signs of Muller's questionable ethics can be seen nearly two decades earlier. For example, when Muller published his major paper in the journal *Science* in July 1927 on radiation-induced gene mutation, it contained no data. He merely discussed the results of only the first of three experiments that led to his Nobel Prize. Muller knew he was in a race to be "first" and he worked out an arrangement with the editor of *Science* James Mckeen Cattell, a former longtime Columbia University professor who was a colleague with Muller's advisor during Muller's time there. This was critical since Lewis J. Stadler was only several months behind Muller in showing his own version of radiation-induced gene mutations. Further, after Muller finally presented his data three months later in Berlin, he then published his findings in a conference proceedings manuscript that was not peer-reviewed. This paper contained no methods and materials, no discussion of the findings and no references. Thus, Muller manipulated the peer review process in the journal *Science*, did not submit his research to peer review and unfairly treated rivals, such as Stadler, who played by the rules. One reason for avoiding peer review is that Muller knew that some peer reviewers could hold up acceptance over the possibility that he had not induced gene mutation but only created massive gene deletions with the extremely high doses of radiation used (i.e. some 95,000,000-fold greater than background). This criticism was discussed soon after the *Science* publication. In the end, his series of ethically-challenged actions would be rewarded as they would ensure that he was "first" and this would be critical in his later winning of the Nobel Prize (Calabrese, 2018a).

[2] While the *New York Times* and the *Washington Post* created the "Dream Team" image for the BEAR I Genetics Panel with the help of the NAS and Rockefeller Foundation (RF), in reality the Panel was far from a "Dream Team". The Panel members, in general, had little experience in conducting low-dose dose response experiments. At the time of BEAR I only Demerec and Russell had extensive experimental dose response experience. Of these two, Demerec was far more experienced. Yet, his experience with *Drosophila* was about 25 years earlier. Muller, Kaufmann and Hollaender had limited relevant low dose research experience. The remaining 11 members of the Panel had very weak/limited to no dose response experience. Furthermore, the majority of the geneticist panel members had never published an article on radiation-induced mutations prior to their selection on the Panel.

The principal reason why the US BEAR I Genetics Panel chose not to consider the Neel-Schull (1956) study was the Panel members' long-standing ideological support of LNT. Muller and others on the Panel refused to give standing to the Neel-Schull (1956) study because it did not support the linearity assumption or belief that low-dose radiation induced genetic damage, a conclusion which was at odds with the Panel's deeply seated beliefs (Calabrese, 2020). A second reason for refusing to assess the Neel-Schull (1956) study is that Muller and others on the Genetics Panel feared that research money would be redirected toward human studies and away from their research efforts with animal models (Calabrese, 2020). Thus, the decision of the Panel not to evaluate the atomic bomb study of Neel and Schull (1956) achieved two intertwining purposes: (1) it assured acceptance of LNT and (2) promoted self-serving interests related to research funding (Calabrese, 2020).

3. Ethical issues faced by Muller and stern prior to the BEAR I genetics panel

3.1. Deception # 1: Muller's Nobel Prize Lecture

In his Nobel Prize Lecture, Muller (1946) said that there was no scientific foundation for the threshold dose-response model and that radiation risks thus needed to be based on the LNT model. Muller made this statement even though he had recently seen evidence of a threshold response for gene mutation in what was the most significant experiment up to that time on the topic. That experiment was a large-scale chronic lifetime low dose rate radiation Drosophila study from the University of Rochester (Caspari and Stern, 1948), a study on which Muller was a deeply involved and paid consultant. What makes his high profile statement that there was no scientific foundation for the threshold dose response model even more astounding is that Muller recommended in writing that Curt Stern, the study director, replicate this research because it strongly challenged the LNT hypothesis and was competently done (Calabrese, 2011a; b, 2012). Replication was no trivial task, however, because it necessitated obtaining more funding and conducting additional experiments that would require about two years to complete. His recommendation reveals how seriously the troublesome Caspari threshold data were viewed by Muller. Yet, Muller was telling the audience of the Nobel Prize Lecture audience one thing in public (i.e., the threshold approach was effectively dead) while offering contradictory statements in private letters to Stern that were written within a few weeks on either side of the Nobel Lecture. Muller would go on to use the Nobel Prize as a platform to broadly promote his LNT views while either neglecting to share the contradictory findings of the Caspari study or deliberately distorting Caspari's findings (as will be shown later). For example, within four months of his Nobel Prize Lecture, Muller spoke at the New York Academy of Medicine, affirming his Nobel Prize Lecture message, stating that there was **"absolutely no threshold dose"** for mutation and that induced mutations were proportional to the total dose (Muller, 1948) knowing full well that the Caspari/Stern data demonstrated otherwise.

3.2. Deception # 2: total dose vs. dose rate–the Ray-Chaudhuri study

In the 15 years before receiving his Nobel Prize, Muller was involved in a serious scientific dispute with Lewis J. Stadler, who was a University of Missouri plant-radiation geneticist whose very high standing was comparable to that of Muller (Stadler, 1954). Stadler concluded that Muller was wrong in the interpretation of his mutation data. Stadler asserted that Muller did not induce gene mutations in his 1927 major discovery, but rather caused modest to massive gene deletions along with large-scale chromosome damage (Calabrese, 2017a). Thus, Stadler believed that Muller's "major" discovery was actually quite trivial, and that Muller had incorrectly interpreted his data. Over time these two titans in the world of radiation genetics challenged each other repeatedly with new experimental findings, much like a prolonged high stakes scientific chess match. This long-running scientific display of genetic talent has been addressed in considerable depth, with the conclusion that over time the position of Stadler became the more convincing and dominant one, which left the frustrated Muller scientifically compromised[3] (Calabrese, 2017a). In fact, modern nucleotide technology definitely proved that Stadler was correct, even including loyal and accomplished former Muller students (James Crow, Seymour Abrahamson, Edward Novitski, and William Lee) siding with Stadler (Crow and Abrahamson, 1997; Novitski, 2005; Byrne and Lee, 1989; Calabrese, 2017a,b).

Muller was astute enough to recognize that this prolonged research debate with Stadler was not going to end well. Being a highly talented researcher, Muller sought to adopt a new research strategy that could give him a win on his two big issues: gene mutation and LNT. He combined these two goals into one project, which became a dissertation on the concept of total dose versus dose rate at the University of Edinburgh with a Ph.D. student Ray-Chaudhuri in the 1938–1939 timeframe. Muller strongly supported the radiation mantra that genetic risk was explained by total dose rather than dose rate. All exposures were assumed to be mutagenic and cumulative regardless of the dose rate, according to the total-dose hypothesis. Ray-Chaudhuri tested this hypothesis and reported that his findings supported Muller's total dose hypothesis using the fruit fly model of Muller (Ray-Chaudhuri, 1944; Calabrese, 2011b, 2015a). This development was significant because it allowed Muller to partially escape the unrelenting critical focus of Stadler and to report data supporting his two themes with a different research method.

So important to Muller was this development that he prominently cited it in his Nobel Prize Lecture and explicitly used it to discredit the threshold model. In the Nobel Lecture Muller indicated that the Ray-Chaudhuri data **"leave, we believe, no escape from the conclusion that there is no threshold dose"**. Given the setting of a Nobel Prize Lecture this was a remarkably outrageous and risky statement.

The Muller-highlighted Ray-Chaudhuri (1939, 1944) study had important limitations such that one had to question the quality of Muller's mentorship and value of the data. Based on preserved correspondence Ray-Chaudhuri (1938) was mostly on his own during the conduct of his dissertation.[4] Muller was not present for the conduct of preliminary experiments designed to clarify some research methods and for at least the first four of the eight experiments for the sex-linked recessive and translocation endpoints. Muller provided preliminary, but apparently insufficient, instructions on how to prepare complex

[3] In 1956, Muller (1956a) was compelled to acknowledge that collective research with *Drosophila* now indicated that a very large proportion of what he originally called "point mutations" were seen as gross genetic deficiencies/deletions and other structural changes, essentially confirming the long-standing position of Stadler. Muller (1956a) went so far as to write that **"there is no doubt that in X-rayed *Drosophila* also, at least when the irradiation is applied to condensed chromosome stages, such as those of spermatozoa, deficiencies as well as other demonstrable structural changes arise with much higher frequency, relative to changes that appear to involve but one gene …"** This statement illustrates the eroding of Muller's position concerning the similarity of X-ray-induced vs spontaneous mutations and his statement that a high proportion of the gene changes were point mutations. Muller was in near full surrender to the Stadler position. However, by this time Muller had his Nobel Prize, but was essentially being forced to admit that he really did not **"produce gene mutations"** as proclaimed by the Nobel Prize award statement. By 1956, it was clear that he had very little remaining wiggle room. Stadler had won the dispute.

[4] In a September 23, 1947 letter of reference for Ray-Chaudhuri to the vice Chancellor of Delhi University, Muller (1947) independently confirmed his little involvement in the research by stating that **"Although under my supervision, the work was carried out with very little immediate guidance on my part … …"** While this letter was meant to support the application of Ray Chaudhuri, the general absence of Muller most likely had a significant detrimental effect on the research.

genetic crosses with *Drosophila* before the experimentation began. In general, the correspondence reveals that Ray-Chaudhuri could not figure out how to accomplish such necessary crossings, at least during the initial stages of the dissertation research. In his June 8, 1938 letter to Muller he stated that **"I am very sorry to say that I got mixed up in the beginning … I don't know how far I will succeed."** Ray-Chaudhuri then states that now he understood why Muller was uncertain if he could actually figure out how to prepare the *Drosophila* stocks for the experiments given the complexity, knowledge and experience needed. It was not clear how this limitation would affect the study but it likely led to introducing novel multiple sub-strain-like genetic variants into the experimentation and further variability as discussed in the following section.

In the sex-linked endpoint experiment, Ray-Chaudhuri (1944) employed three radiation doses (i.e. 400, 1300, and 2000 r). These included three different dose rates which yielded the different total doses. The number of cultures tested and lethals for each of the eight experiments for the control and the two lower dose rate groups were provided in Table III of the Ray-Chaudhuri (1944) paper. In contrast, only summary data were provided for the third radiation treatment group, that with the highest dose rate (i.e. 29.0 r/hour, yielding 1300 r after 45 h). Without this highest dose rate experiment-treatment group specific information available in detailed form, it is not possible to determine which of the eight specific experiments included this radiation treatment group throughout its entire temporal testing period. This is relevant for study interpretation as it affects whether this exposure group had a concurrent control group that matched each specific experimental time period. Furthermore, it is not possible to determine what specific strain of *Drosophila* was used for this specific radiation treatment or whether more than one strain was used during the experimental process, since, in a very strange twist, two strains (i.e. a second being introduced midway during the major experiment) were used in the sex-linked lethal endpoint study (see comment below # 7). Likewise, no information was provided on sample size, number of lethals, and diet information on the females for this specific radiation treatment. Failure to provide this information represents a serious confounding limitation. There was no explanation offered why these data were omitted.

Ray-Chaudhuri further prevented a reasonable understanding of his research with his 1939 abstract publication. The abstract gave the total dose of radiation for the shorter duration (i.e. 45 h exposure) treatment group as 2000 r, not the 1300 r value as reported in the journal publication (Ray-Chaudhuri, 1944). This inexplicable change in total dose reduces the per cent of lethals per unit of radiation by about one third between the values presented in the abstract and that of the published manuscript five years later even though they reported on the same study. No explanation was given for this striking discrepancy. Furthermore, based on the limited information provided in the abstract it appears that this treatment group may have been studied over the eight experiments. If this is the case then this radiation treatment group would be affected by the inter-experiment dietary changes, the loss of the control group in experiment # 4 and use of more than one *Drosophila* strain (see itemized comments below).

From an ethical perspective, this same June 8th letter of Ray-Chaudhuri (1938) informed Muller that the initial translocation experimentation failed to produce translocations at low dose; that is, a radiation dose that was over 24,000-fold greater than background. These data, which would contradict the LNT hypothesis, were excluded from his published study (Ray-Chaudhuri, 1944). However, the 1938 letter of Ray-Chaudhuri indicates that Muller was informed of this decision and did not object.

Ray-Chaudhuri published the findings on only the three final experiments on the translocation endpoint. There were no significant increases in translocations with both the lowest dose rate that was administered for 720 h and with the highest dose rate (i.e. about 60 times greater than the low dose rate) that was administered for the shortest period (i.e. 9 h). In both cases there was one translocation with error estimations that seemed to overlap the control group values. This is inferred since the paper showed that the low confidence interval translocation response estimates for both treatment groups encompassed a 0.00% response. However, this paper again inexplicitly failed to include the control group data and its confidence intervals, precluding precise direct comparisons. These data not only suggest the possibility of a threshold but they also failed to support the total dose hypothesis.

In a subsequent publication on this research in which Muller (1939) now indicated that this study was **"carried out by himself (written in the third person) and Dr. S.P. Ray Chaudhuri"**, he neglected any mention of study limitations nor did he acknowledge the decision to exclude data from experiments that showed no treatment related genetic damage; likewise, he also failed to mention that the results supported the opposing hypothesis and a possible threshold. While the above general statements are troubling, these were not the only issues of concern with the now "Muller and Ray-Chaudhuri study". Limitations of this dissertation research include that the study:

1) was of only modest size for both the sex-linked lethal and translocation endpoints and lacked the reporting and documentation of multiple essential methodological details;
2) failed to include key information regarding the occurrence of lethal clusters, the occurrence of female sterility, sex ratios, and the age of the males;
3) failed to provide information on whether mold suppression chemicals were used in the study, which agent(s) were used and the doses and whether controls were treated similarly as treated groups.
4) displayed persistent problems with temperature control including excursions of 2–3 C for the treated flies. Control flies were maintained within a different temperature system that also had control irregularities, making the control and treatment groups different in this regard (Ray-Chaudhuri, 1938). Since no experiment-day-specific data were presented on temperature variation it is not possible to assess the impact of this factor further.
5) lacked a control group with one (i.e. experiment # 4- Ray--Chaudhuri, 1944-Table III) of the sex-linked experiments; this was due to a significant failure of the temperature control system that resulted in a large drop in temperature;
6) acknowledged changing methods of rearing flies between experiments, making it difficult or impossible to directly compare responses between affected experiments or to combine the data across all experiments, which, however, is what Ray-Chaudhuri did. For example, he changed the food for the females which significantly altered the time of sperm retention, and thereby creating issues with differential radiation exposure to sperm and a sperm aging effect variable, which is an important methodological consideration. This methodological change was not reported in the published study.
7) had multiple sub-strain-like genetic variant groups comprising the total number of flies in the control and each treatment group in both sex-linked lethal and translocation experiments. However, the proportion of these different genetic variant fly groupings markedly differed across the respective control and radiation treatments. They made-up different proportions of flies in each experimental group. For example, the most common specific genetic variant fly group in experiment # 1 comprised 36.5% of the controls, 45.8% of the low radiation dose and 33.3% of the high dose radiation group. Similar types of differential distributions were reported for the other different genetic variant fly groups for the control and treatment groups. All sex-linked lethals and translocations were summed across the different genetic variant fly groups to produce the total number affected for each group. When the abstract and paper were published the genetic variant proportional differences by treatment group information

was not included. However, the disproportional representation/use of genetic variant fly groups across control and treatment groups introduced a new variable into the study that could not be controlled. Information on genetic variant fly group use and their susceptibility for any parameter (e.g. sex-linked lethality) was not presented, even though this information was clearly collected and documented based on the Ray-Chaudhuri (1938) correspondence with Muller. This flawed process would continue throughout the experiments for both endpoints.

8) adopted the use of a new genetic strain for use in the sex-linked lethal endpoint study without explanation midway through the study, with data being combined across all experiments. This new strain displayed a control group mutation incidence of about 20% of the strain it replaced. No information on potential sub-groups for the new genetic strain was provided nor to what extent their distribution varied across the control and treatment groups;
9) showed a dose selection process for both endpoint experiments to be also problematic. The low dose group is estimated to provide an exposure 24,000-fold greater than background, making these studies of little relevance for low dose extrapolation, the real goal of the experiment;
10) displayed statistical analyses that were also problematic; the mathematician JBS Haldane (1939), a committee member, wrote that **"unfortunately the author has used a faulty statistical method"** that led to **"serious mathematical error."**
11) was also criticized by Caspari (1947a) in a letter to Stern, stating that Ray-Chaudhuri inappropriately used the same control for sperm that were aged and non-aged, further questioning the reliability of the results;
12) was further challenged by Caspari (1947b) who noted that **"his errors are so large"** (background variability) making the results hard to interpret, along with having poor application to other research, such as Caspari's when lower radiation doses/dose rates were studied.

This brief overview of the Ray-Chaudhuri dissertation indicates that it is, at best, a possible learning scaffold for future research. These findings "acclaimed" in Muller's Nobel Prize Lecture failed to provide data upon which reliable conclusions could be based. In fact, there is such a bewildering array of problems with the conduct, decision-making, lack of clarity and failure to report relevant information of this study. Those problems prevent reliable reconstruction and resolution of critical uncertainties that compromise its scientific value. As in the case with the Spencer study, Muller appeared unwilling to provide an objective appraisal to document critical scientific limitations of the Ray-Chaudhuri dissertation research. This analysis also raises new ethical issues concerning both Muller and Ray-Chaudhuri regarding the exclusion of negative data and the misrepresentation or obfuscation of the research record.

While these numerous limitations of the Ray-Chaudhuri study were carefully kept out of sight by Muller, he soon saw his next opportunity for scientific "redemption" in the Manhattan Project. The *Drosophila* genetics studies of the Manhattan Project, under the direction of Curt Stern, closely followed the guidance of Muller, and they would provide a major re-evaluation of the total dose versus dose rate study that Ray-Chaudhuri's dissertation had, in effect, piloted. However, this time the resources were at hand to do it in a big way, under the oversight of Stern, with senior Ph.D. researchers (i.e., Warren Spencer and Ernst Caspari) and with Muller's guidance. Muller would no longer have to rely on the efforts of a poorly supervised graduate student who had marginal resources, and Muller would also provide the strain of *Drosophila* that he wanted tested.

In retrospect, the Ray-Chaudhuri study was too limited and flawed to stand on its own or to provide support for Muller's combined hypothesis package of gene mutation and LNT. Nonetheless, while waiting for the data from the Manhattan Project to emerge, Muller strongly promoted the Ray-Chaudhuri findings and their implications for his gene mutation findings and the LNT hypothesis, while successfully camouflaging the experiment's many limitations. To therefore make his threshold denial statement at the Nobel Prize Lecture, Muller would need to ignore the threshold supporting data of Caspari while at the same time embracing the flawed pilot study of Ray-Chaudhuri and hope that no one would notice.

Despite these deceptions, the real problem for Muller and other ideological LNTers was the emerging, and possible game changing data of Caspari. Those data had the potential to discredit the Ray-Chaudhuri claims, as well as to make Muller's seminal gene mutation achievement fall under the smothering criticism from Stadler's research. The situation made Caspari's research centrally important since it supported a threshold response in a low dose rate life time study. It became a cause for great concern in the fall of 1946 and the object of a series of coordinated attempts to discredit it (Calabrese, 2011b). In an odd twist on this situation, Caspari initially defended his control group mutation rate (which supported a threshold model) against the challenges of Stern. However, he was then "recruited" by Stern to join the process of marginalizing his own work, possibly fearful that if he didn't go along with such deceptions he would no longer have the prospect of the support of Stern and Muller for future jobs and research funding. This was a likely survival tactic by Caspari that was necessary given Muller's reputation for defending his interests at nearly any cost. The ethical questions raised are significant. This career saving strategy for Caspari seems to have worked out well for him, in that he began his academic career at Wesleyan University and, going full circle, ending back at the University of Rochester.

4. The Manhattan project deceptions

"What can be Done to Save the Hit Model?" These are the words written by Millislav Demerec[5] to Ernst Caspari (see Caspari, 1947a for this quote) after he had read a draft of Caspari's Manhattan Project manuscript that showed strong evidence of a threshold response for gene mutation in the largest study done to date on the topic. This study was designed to be a centerpiece in the US government's Manhattan Project for the assessment of genetic effects of ionizing radiation. However, the field of radiation genetics was dominated by those committed to promoting the acceptance of the LNT single-hit model in society and regulation. These comments of Demerec were then shared with Curt Stern by Caspari (1947a). Below are examples of how Stern in his role of principal investigator of the Manhattan Project genetic damage studies responded to the sentiment of the letter from Demerec.

4.1. Deception # 1: Curt Stern actions - editorial manipulations

The threshold study findings of Caspari were initially rejected by Curt Stern, based on his assertion that the control group mutation rate was aberrantly high. Follow up literature research by Caspari revealed this challenge to be incorrect, with Stern then reversing his position (Calabrese, 2011b). In fact, one of the multiple references that Caspari cited to support the validity of his control group was by Bertwind Kaufmann, a future member of the BEAR I Genetics Panel (Kaufmann, 1947). Nonetheless, Caspari and Stern (1948) still would not support the use of their novel threshold findings. In their paper, they downplayed

[5] Demerec was a significant player in the radiation genetics community. He was the Head of the Genetics Department at the Carnegie Institute. He had an extensive publication record concerning *Drosophila*, covering two decades with greater than 50 peer-reviewed papers. He likewise had a strong publication record concerning bacterial mutations. He was originally educated at Cornell for his Ph.D. as a maize geneticist with the renowned Emerson, who led the most prestigious group in the US academic domain. In fact, Demerec had far more and broader experience than Muller.

the reliability of the findings, arguing that the results should not be accepted until it could be shown why they differed from an earlier (i.e., conducted one year earlier) acute study using the same fruit fly model that supported linearity (Spencer and Stern, 1948). They did this even though the Caspari study was extremely well done without any identified methodological flaws. In their paper, Caspari and Stern (1948) neglected to point out that the Spencer and Stern (1948) study had substantial methodological limitations including the lack of X-ray instrumentation calibration, poor temperature control, dose rates that differed by up to 10 fold between different dose treatments, failure to match control and treatment groups over the same exposure time period, and the combination of treatment groups with the same cumulative doses but with different dose rates (Calabrese, 2011b). In fact, none of these weaknesses were noted in a detailed letter by Muller assessing the Spencer and Stern study (Calabrese, 2011b).

Of further ethical concern is the existence of evidence indicating that the peer review process was avoided in the publication of this paper (Spencer and Stern, 1948) in *Genetics*, a journal in which one of the authors (Stern) was editor-in-chief. These limitations were not difficult to detect and likely would have been highlighted if an appropriate peer review process had been used. The actions of Stern to avoid peer review of the paper and his failure to acknowledge its limitations were not only blatantly improper but implicitly led to promotion and acceptance of LNT. Likewise, the decision of Stern to hold data from the Caspari experiment in scientific "limbo", while not placing similar "restrictions" on the compromised Spencer and Stern (1948) paper (limitations that were not present in the Caspari study) further aided and abetted the acceptance of LNT. These actions support the view that an "LNT ideology" existed and that Stern used editorial powers and other tactics to advance this ideology while, at the same time, concealing his actions (and their broader implications) from the readership. The manipulation of the research record by Stern with regard to these Manhattan Project-funded studies closely resembles the duplicitous behavior of Muller on multiple occasions, as noted earlier in this article.

4.2. Deception # 2: Curt Stern actions - scientific community manipulations

During this period, Stern communicated on multiple occasions with Muller about the control groups from the Caspari (see Caspari and Stern, 1948) and Uphoff (see Uphoff and Stern, 1949) studies, with Muller strongly supporting and favoring the reliability of Caspari's experimental findings (see Calabrese, 2013b for a detailed reporting of their written communications). These communications led Stern to reject the replication studies by his new graduate student Delta Uphoff, since they displayed aberrantly low control-group values (Calabrese, 2011b). In a formal paper to the US Atomic Energy Commission (AEC) which was initially classified as secret, Uphoff and Stern (1947) stated that their findings were **"uninterpretable"** as well as compromised due to **"investigator bias"**. Yet, less than six months later, and with no explanation being provided, the Uphoff control group data came to be considered valid and thus no longer **"uninterpretable"** and biased. Apparently, these data had become essential and were now needed to support the LNT hypothesis and the originally supported threshold study of Caspari was now rejected once again by Stern. In spite of their reinterpretation, data from these two studies plus the Spencer and Stern (1948) paper were combined to produce an abbreviated one-page, data-less summary that was then published by Stern in the journal *Science* (Uphoff and Stern, 1949). This paper essentially claimed that the Manhattan Project had established linearity of response in the low-dose range for ionizing radiation. At the end of the paper, Stern pledged to publish both the missing section on methods and materials and the supportive data in a follow-up paper, but that never happened (Uphoff and Stern, 1949). Stern also failed to share with the scientific community that the previously rejected Uphoff data was reported by themselves to be decidedly uninterpretable and strongly tainted with investigator bias even though it was now the central data in support of LNT.

4.3. Deception # 3: more Muller involvement in the deceptions

During the years immediately following completion of the genetic studies supported by the Manhattan Project, Muller (1950a,b, 1954) published several key papers that repeatedly mischaracterized the Caspari study control group findings (see Caspari and Stern, 1948) as being aberrantly high while supporting the control group values of Uphoff (see Uphoff and Stern, 1947, 1949), thereby contradicting his multiple private letters with Stern and multiple papers that supported the Caspari data (see Caspari and Stern, 1948) in the genetics literature (Calabrese, 2015a, 2019c). Several examples of his deceptions are described below.

Uphoff and Stern (1947) wrote in their "Discussion" section: **"In his extensive studies on the effect of aging on the mutation rate in sperm, HJ Muller's values are much closer to the control rate observed by Caspari and Stern than to that found in the present work."** (i.e., the Uphoff data). A letter from Curt Stern to Ernst Caspari (Stern, 1947) stated: **"The radiation data continues to be puzzling. Delta's difference between control and experimental group appear to be due mainly to a much lower control group than yours. However, Muller informs me that the data given an aged control to be close to yours. Thus, my first idea that your results could be "explained away" by assuming your control value happened to be unusually high seems unlikely. Rather does Delta's control appear too low"**. It is significant that Muller (1954) continued to contradict himself (see pg. 474) nearly a decade later, repeating the deception of the **"unusually high control frequency"** for Caspari so that he could support the LNT model.[6]

A further example of Muller's deceptions is instructive. In 1950 (footnote 1, page 10) Muller (1950a) stated **"Uphoff and Stern have published a report of further work, with doses as low as 50 r, given an intensity as low as 0.165 r per minute. The results obtained are entirely in conformity with the one-hit principle. A consideration of these results, together with the early work, lead to the conclusion that the deviation first referred (the Caspari and Stern 1948 findings) was caused by a value for spontaneous mutation rate that happened to be unusually high."** Muller's dishonesty is demonstrated by the fact that he failed to inform the reader that Uphoff's experimental data displayed aberrantly low control group responses based on Muller's own laboratory data with several hundred thousand fruit flies. He also neglected to state that he had communicated his criticisms of the Uphoff findings to Stern in writing as well as his support for Caspari's control data. Furthermore, multiple studies by Muller and his student Helen L.

[6] See the Appendix in Calabrese (2013b) for a detailed accounting and documentation of the letter exchanges between Stern and Muller on the issue of the Caspari and Uphoff control groups. An analysis of these written communications provides no support for the later published statements of Muller that the Caspari control group was unusually high. Likewise, the Muller letters contradict the revisionist notion that the Uphoff control values were in the normal range. These letter exchanges supported the written statement of Uphoff and Stern (1947) to the US AEC that the Uphoff data were "uninterpretatable" due to the very low control group values, to which investigator bias was thought to have contributed. No criticism of the Caspari controls were offered to the US AEC in a formal report (Caspari and Stern, 1947) nor in the subsequent journal publication (Caspari and Stern, 1948). This series of private letter exchanges between Muller and Stern over the Caspari and Uphoff control groups contradicts the Uphoff and Stern (1949) paper and the later Muller (1950a,b, 1954) journal assertions that criticized the Caspari controls, giving acceptable status to those of Uphoff. Lacking in this circumstance was that none of this letter exchange documentation and the serious questions it raised was provided by Stern in his *Science* publication (Uphoff and Stern, 1949) in order to enhance the capacity of the scientific community to better assess the Uphoff and Caspari control group data. This information only came to be viewed by the scientific community in 2013 (Calabrese, 2013b).

Byers at the University of Indiana also supported the mutation frequency of Caspari's control group (Byers, 1954; Byers and Muller, 1952). This meant that Muller's support for Caspari's control group data extended from his research at Amherst College between 1940 and 1945 and into his career at Indiana, over an entire decade. Thus, Muller directly contradicts his career research findings, his letters to Stern specifically addressing the question, the supportive literature that Caspari reported to Stern, and official research reports to the US Atomic Energy Commission (AEC). Yet, the devastating and erroneous criticisms leveled against Caspari's research by Muller, the hyper-combative and Nobel Laureate, were never contradicted publicly, as far as we know. However, the available data are extensive, consistent and supportive of a conclusion that Muller was dishonest and repeatedly lied, which—because he was not challenged about this—protected his reputation and the LNT mantra. These findings strongly suggest that there was complicity by Stern, Uphoff and Caspari, all of them entangled within a fear of professional retribution.

The multiple misrepresentations of the above-cited literature by Muller, Stern and others would eventually contaminate the scientific literature as they sought to develop and control their LNT narrative by using such false information. Their success is illustrated by the following comment by the prominent radiation geneticist Ralph Singleton (1954). **"Caspari and Stern (1948) studying chronic gamma radiation found no increase over controls for doses of 2.5 r/day for 21 days. However, it was later documented by Uphoff and Stern (1949) that the controls used by Caspari and Stern had an abnormally high sex linked lethal frequency and that actually there was an effect of the chronic gamma radiation of 2.5 r/day**". We therefore see that Singleton adopted the scientific misinformation/falsehoods of Stern and Muller**.** Nearly identical statements were also published by other radiation geneticists such as Lefevre (1950), Higgins (1951) and the very well-known Karl Sax (1950) in the journal *Science.*

Such comments by radiation geneticists such as Singleton and Sax would have made it clear to Muller and Stern that they had now successfully answered the question of Demerec: What Can We Do To Save The Hit Model? They had achieved the goal of neutralizing the Caspari study and, in effect, saving the LNT model so that it could soon be handed to the BEAR I Genetics Panel, which would then recommend it to the world.

5. The NAS BEAR I Genetics Panel: ethical issues

5.1. The ethics of stacking the deck

The NAS BEAR I Genetics Panel was selected by individuals who were responsible for funding most of the academic geneticists on the BEAR I Genetics Panel. Detlev Bronk, President of the NAS, was also the President of the Rockefeller Institute for Medical Research Sciences (soon to become Rockefeller University) and a member of the Rockefeller Foundation (RF) Board of Directors. The long-time director of research at the RF, Warren Weaver, who helped to select geneticists for the Panel, was chosen by Bronk to be the Panel Chair, even though not a geneticist himself. Because Weaver directed the funding of many leading academic geneticists, including Panel members, he knew their research, personalities and views on the LNT hypothesis. So uniformly consistent was their thinking on dose response that all Panel members endorsed a statement by Panelist Tracy Sonneborn early on (i.e. Sunday morning, February 5, 1956, on the first day of the two day meeting in Chicago) in the activities of the Genetics Panel that articulated the LNT mantra: radiation induced genetic damage was cumulative, irreparable, irreversible and linear in its dose response (Calabrese, 2015a). These views of Sonneborn were strikingly similar to those expressed by Sturtevant (1954), another Panel member, nearly two years before at the Pacific Division of AAAS (Pullman, Washington, June 22, 1954).

A strategic decision of Bronk was to create a Genetics Panel that would be separate from and free of a strong threshold bias that had been a characteristic of most medical panels. At that time, geneticists operated as part of a medically-dominated panel, but as a group they represented only a small minority of committee memberships and were thus typically out-voted on key dose-response issues (Whittemore, 1986; Jolly, 2003). However, due to the administrative leadership of Bronk, the decision to create a separate hand-picked Genetics Panel, ensured that this group of geneticists would finally control their own destiny and receive national publicity of their own on key low dose genetic risk concerns.

As a result, the Panel, composed of hand-picked geneticists, decided on the nature of the dose response in the low-dose zone without any debate or even discussion, all members quickly and officially "rubber-stamped" the geneticist's LNT mantra of Sonneborn. In fact, the decision to go linear was really made prior to the selection of the Panel, hence the speediness of the decision. Bronk simply needed to choose a compliant, yet fiercely ideological, group of geneticists to carry out his mandate, while allowing them to think that they were calling the shots. It was a brilliantly conceived stratagem with plausible deniability. This interpretation may sound extreme but it is supported by Panelist James Crow (1995). In his historical reflection Crow noted of the BEAR I Genetics Panel that **"the debate over the nature of the dose response for ionizing radiation and mutation had been decided before the convening of the BEAR Committee in November 1955"**. The committee was stacked and the outcome preordained.

5.2. The decision not to evaluate the ABCC - Neel-Schull (1956) study

Members of the Genetics Panel were well aware of the ongoing genetic studies on the children of survivors of the atomic bomb blasts. Some Genetics Panel members, such as Muller and Beadle, were part of advisory committees for these activities. In journal articles, Muller (1950a) would describe his concern that such studies would have scientific limits, likely missing outcomes of recessive mutations that might only be detected in later generations. These statements by Muller found resonance in comments by other Panel members, such as James Crow (1957), who stated this position during a review of the Neel-Schull (1956) study monograph. It is interesting to note that progressive multi-generational research revealed that even very high dosing with X-rays for 75 consecutive generations failed to show any reproductive and genetic damage in mice (Spalding et al., 1975). However, the concern here is not about the actual findings, as important as they are, but with the decision not to even consider the atomic bomb study as directed by James Néel, a Ph.D. in radiation genetics, a physician, a University of Michigan Medical School Professor, and even a Genetics Panel member. The decision of the Genetics Panel not to evaluate this study, given the mission of the BEAR I Genetics Panel, is difficult to fathom and must have been devastating to Néel. This is especially so because the Neel-Schull study concurrently received considerable praise and use by the British Genetics Committee (MRC, 1956) and, furthermore, its findings have been sustained to the present time (Calabrese, 2020). As a substitute, the Genetics Panel based its recommendations heavily on the fruit fly model, relying principally upon only one publication, the one-page summary paper by Uphoff and Stern (1949). The Panel's curious decision to exclude the atomic bomb study seemingly went unnoticed by the non-Panel world until the omission was recently reported (Calabrese, 2020). Why it had never been previously revealed is uncertain, but it was facilitated by Néel's lifetime silence on this omission. Likewise, major agencies such as the US EPA failed to explore the historical foundations of their LNT policy.

Ironically, after the Weaver-lead Panel excluded for evaluation the Neel-Schull (1956) study of humans exposed to atomic bomb radiation, Weaver then challenged each geneticist to estimate the number of human birth defects in the US population that would occur over multiple generations after a single exposure of the first generation to a high gonadal dose of radiation. These estimations of risk were to be completed in 2–3 weeks, assume linearity, and be based on each

scientist's own animal model (i.e., bacteria, paramecia, fruit fly, mouse, etc.) (Calabrese, 2015a). In fact, Néel had done precisely such a study for one generation (albeit in Japan, not the US) and had offered it to the Panel. Yet, the Panel would completely ignore a real, massive, highly overseen, multi-year, international human study under the auspices of the US NAS to create a series of individual, rapid, speculative, interspecies extrapolations of radiation risk from bacteria to man. The results of this exercise yielded genetic damage estimates over a vast range, showing considerable uncertainty and disagreement amongst the geneticists. Given this situation, one would be hard pressed to use such uncertain speculations as the basis for recommendations for any scientific or societal purpose, yet this was done and was broadly promoted.

5.3. The BEAR I Genetics Panel misrepresents the research record in its Science publication

The challenging exercise that Weaver gave to the geneticists of the BEAR I Genetics Panel, as discussed above, created enormous problems. The generally ill-equipped geneticists provided their detailed estimates as requested, all within a few weeks of the assignment of Feb. 6th and before the next meeting, March 1. Three (i.e. James Néel, Tracy Sonneborn, Clarence C. Little) of the 12 members thought that the assignment could not be reliably done and refused to provide estimates, leaving nine. Those nine reports were sent to James Crow to organize and collate for later distribution to the Panel. However, when Crow read the reports, he became concerned because the estimates of transgenerational damages were enormously variable (i.e. 4000 fold) (Calabrese, 2015b), with no semblance of agreement (Calabrese, 2015a; b, 2016). Crow wrote to Weaver expressing his grave concerns for how could any policy recommendations be taken seriously from this Panel if the members themselves could not agree. Crow felt the Panel was doomed to failure. It never should have conducted such an exercise, because it was highly biased and all were forced to assume an LNT model. On his own, Crow unilaterally dropped the three most extreme estimates, involving bacteria and humans, which left only estimates based on fruit fly and mouse data. As bizarre and improper as this obviously was, none of the Panel members protested to stop the dissemination of this estimate, probably seeing the omissions as the only way forward to support the LNT. Néel did state that Crow's actions were simply self-fulfilling and biologically meaningless, reinforcing his initial decision not to provide estimates (Calabrese, 2015a, 2016, 2019a). Nonetheless, the range of variation was now reduced to about 750 fold, which was still considered too great to offer credibility. So, the decision was to simply declare that the range of uncertainty was only 100 fold, a number they believed to show credible, but limited/acceptable uncertainty, and appear reasonable, despite its dishonesty. When the BEAR I Genetics Panel published its paper in *Science* stating that all 12 geneticists were invited to provide detailed estimates of genetic damage, but only six provided them, nothing was written about the actions of Crow. Thus, the Genetics Panel apparently was willing to misrepresent the research record in the journal *Science,* and not one of the Panel members is known to have ever publicly challenged these improper actions, which were only exposed recently (Calabrese, 2015a).

5.4. Néel does not inform the US BEAR I Genetics Panel

The fact that Néel did not inform Weaver, or the BEAR I Genetics Panel members, that he had shared his unpublished report with the British Genetics Committee does not appear to be an oversight. It seems to have been deliberate. However, Néel was "requested" by the NAS (i.e., the Division of Medical Sciences of the National Research Council) to provide a copy to the British (Letter from James Néel to Harold Himsworth, November 7, 1955). Néel gave the British his report a few weeks before the BEAR I Genetics Panel met for the first time. Néel received criticisms/comments from the British Panel (Letters from Harold Himsworth to James Néel, March 8 and 21, 1956a,b), and none of this material was shared with the US BEAR I Genetics Panel. However, after Néel learned that Weaver and Bronk would meet with the head of the British Genetics Committee in the US in the first week of April 1956, he informed Weaver about his actions and that he had received feedback from the British committee (James Néel letter to Warren Weaver, March 16, 1956). Nonetheless, Néel still chose to not share this information with the BEAR I Genetics Panel itself, nor was he apparently asked by Weaver to do so. Although Néel never challenged Genetics Panel members in committee meetings, he did so several months after the report was released at a major European conference and at a WHO workshop where he finally had the courage to challenge Muller. This event was captured by a *New York Times* writer (Hillaby, 1956), who covered the Conference and noted that Néel exposed key weaknesses in the extrapolation of human responses from animal models, especially from insect models, such as *Drosophila*. Néel emphasized the need to base exposure standards on human data, something that BEAR I refused to consider (Calabrese, 2020). During both the European conference and the WHO meeting, Muller displayed his typically relentless combative qualities by attempting to intimidate Néel and others, regardless of the personal and social consequences.

During this confrontation period with Néel (see Calabrese, 2020 for a discussion of their interactions), Muller (1956b) published a paper in the WHO proceedings that supported the LNT and cited research by William L. Russell and much earlier research by Lewis J. Stadler (See Muller and Dunn, 1928). In the case of Russell, Muller provided no specific citations. All of Russell's published papers at that time were obtained and reviewed. None provided support for the Muller statement. Furthermore, in the case of Stadler, the reference cited by Muller proved not to be a published paper but a conference presentation. The only information available in the Muller citation was the title of the Stadler talk, its date, duration (15 min) and the building/room location for the talk. Thus, neither the Russell and Stadler citations were appropriate nor did they support his LNT argument. Two years after his 1928 presentation, Stadler (1930) provided dose response data for mutation (i.e., 15 dose study) that clearly made a strong case for a threshold response, as seen by the Stadler (1930) quote: "**The absence of mutation in the cultures given the three lowest doses might suggest the possibility of a threshold intensity below which mutation did not occur … …"** (page 13). It seems likely that Muller in 1956 failed to cite this paper by Stadler (1930) on radiation induced mutation and dose response because it did not support his perspective.

The inaccurate and misleading references provided by Muller were professionally inadequate at best, and possibly dishonest, but they were not questioned by the WHO. It is interesting to wonder why Muller would have made two such rather bizarre "mistakes" in the same direction on the LNT issue. Perhaps these "mistakes" did not occur at random but were deliberate, reflecting his support for an LNT conclusion. Of relevance is that Muller had made similar "mistakes" with the control-group data of Stern-Caspari-Uphoff as well as other technical issues, in each case erring in favor of an LNT conclusion. Again, Muller would face no apparent consequences for these deliberate misrepresentations of the research record (see Calabrese, 2015a for a discussion). James Crow (1995), a close colleague of Muller, has pointed out that it was well known that Muller would attempt to win arguments by exaggeration and overstatement. Crow found this dishonest feature of Muller's character exasperating because it backfired, as he was often caught in such circumstances. Muller repeatedly mislead, misrepresented and made deliberately false statements in an effort to promote his LNT goal, not limited to the examples presented here.

5.5. Self-interest funding support: how to use the NAS Genetics Panel

Following the WHO meeting in August of 1956, Muller wrote to George Beadle (Hermann Muller to George Beadle, August 27, 1956c) about the outcome of the WHO meeting during which there was intense debate about the issue of research directions (Calabrese, 2020). The

WHO committee developed a research compromise offering a balance between animal and human studies, a balance that Muller did not favor. In this letter, Muller wanted the BEAR I Genetics Panel under Beadle's leadership to reverse or push back against this research compromise position and to take a position that favored Muller's own research interest. As Muller wrote to Beadle on August 27, 1956c, **"I think that one of the functions of our own American committees ought to be to help restore the balance."** Being on multiple committees with overlapping missions, Muller was permitted to have multiple bites at the same apple.

While Muller's self-interest is transparent, it is of value to appreciate the scope of Muller's actions to influence the proposed WHO research agenda. In fact, Muller brought two documents that were developed within BEAR I Genetics meetings to read and share at the WHO Workshop. During this WHO meeting, Muller repeatedly disrupted the proceedings in an attempt to read these documents into the record, for which he was repeatedly not recognized and rebuked. He created considerable discord, especially by challenging the actions of the group leader, Allen Stevenson (Calabrese, 2020). Soon after the meeting Muller then used his influence to prevent publication of a workshop summary by Stevenson, fearing that it might favor the need for more human studies at the expense of his research area. He organized the actions of several animal model geneticists at the WHO workshop to write letters challenging the plan for Stevenson to write a summary. In this case, Muller was successful as Stevenson was worn down by the continuing dispute and simply abandoned the effort. Below are citations to the letter-based dispute between Muller-Stevenson as well as the final decision (Hermann Muller letter to Alan Stevenson, October 5, 1956d; Bruce Wallace letter to Alan Stevenson, October 11, 1956; Sterling Emerson letter to Hermann Muller October 11, 1956a; Sterling Emerson letter to Allan Stevenson, October 12, 1956b; P. Dorolle letter to Hermann Muller, October 16, 1956; Hermann Muller letter to P. Dorolle, October 24, 1956e; I.S. Eve letter to Hermann Muller, November 16, 1956).

In a letter of October 24, 1956, from Stevenson to Néel about the Muller interactions at the WHO meeting, Stevenson wrote: **"Everyone was helpful but I was amused at how rude old Muller was. I rather got the impression that he is a bit of a menace to progress in some ways as he is so authoritative and yet he has reached an age when he is like the patriot who says 'my country right or wrong'. In other words, he cannot face awkward facts if they upset the tidiness of some of his theories. … the weak logic of his load of mutation theories and correctness seems to me to be full of holes."** There is no evidence that Néel disputed this characterization of Muller by Stevenson.

It is important to appreciate that other members of the Genetics Panel acted in a similar fashion as seen in an exchange between Panelists Demerec and Dobzhansky in which they express a desire to gain power and influence by using the Panel to feather their academic/research nests (Calabrese, 2014). Demerec wrote to Beadle advocating the need to convince funding agencies/foundations to create a one hundred million dollar funding initiative for training geneticists, especially in light of public fears about genetic hazards. In a moment of candor, Demerec stated that he nevertheless has **"a hard time keeping a straight face when there is talk about genetic deaths and the tremendous dangers of irradiation. I know that a number of very prominent geneticists, and people whose opinions you value highly, agree with me"**. This prompted Dobzhansky to respond saying **"Let us be honest with ourselves–we are both interested in genetic research and for the sake of it, we are willing to stretch a point when necessary"** (see Calabrese, 2014 for full discussion). The key suggestion here is the willingness to exaggerate risk and to scare the general public and elected officials to ensure the flow of grant money. Thus, Muller was not the only one trying to steer funding in their direction, but he was a leader in this regard.

5.6. Other panel member dishonesty

During the Genetics Panel meetings in the winter of 1956, Weaver introduced the research of plant radiation geneticists, Arnold H. Sparrow and W. Ralph Singleton (page 110, Feb., 5/6, 1956 BEAR I Genetics Panel, transcripts). The assessment of the Sparrow and Singleton research was then handed off to Panel member Kaufmann (1956) who stated that these authors showed that 0.41 r/day induced a modestly elevated (i.e., less than twice the control-group value), but statistically significant, formation of micronuclei in an effort to show that plants also display a linear dose response. However, what Kaufmann neglected to state was that, in their 1953 paper, Sparrow and Singleton (1953) wrote that a threshold was observed at the lower dose of 0.084 r/day. Kaufmann (1956) showed a table from the paper with the 0.41 r/day data, but he stripped out the response of the lower dose. A quote from the Sparrow and Singleton paper provides insight: "**The data in table 2 show that 0.084 r per day caused no significant increase but that 0.41 r per day (or higher) did show a statistically significant effect (table 2).**" The misrepresentation of the research record is striking in that Kaufmann's transcribed words of that session are directly contradicted by the earlier publication. It is difficult to understand why Kaufmann filtered the data to fit an LNT narrative when anyone reading the actual paper would have seen what occurred. The actions of Kauffman suggest that the LNT paradigm was so demanding that any data not supporting it must be omitted.

6. Perspectives

Over the span of many years, unethical behavior has corrupted the actions of many scientists attempting to promote acceptance of the LNT. The initial precedents for such ethical breaches, however, were the unscrupulous actions of two very prominent scientists, Muller and Stern, against the Caspari study in the fall of 1946. Their actions were principally centered on discrediting this study in any way possible and began by having Stern reject the validity of Caspari's control data. However, that challenge failed after Caspari documented multiple supportive data from other publications. Stern then got serious and moved to phase 2 of his "kill" the study plan. This consisted of framing his paper's discussion to advise the readers of the journal not to use Caspari's threshold findings until the discrepancies between the Spencer and Caspari studies could be reconciled. This proved a ridiculous argument, however, because such an understanding could never be practically addressed given the large number of methodological differences between the two studies (Calabrese, 2011b). Stern undoubtedly understood that. It was his version of an editorial deflection, an ingenious way of making the Caspari study seem irrelevant without adversely affecting Caspari's reputation.

The next ethical concern relates to when Stern failed to establish any such restrictions on the acceptance of the Spencer study, which supported the LNT concept. Within this context, Stern never acknowledged the many methodological flaws of the Spencer study even though numerous important examples have been identified herein. Those examples were also inexplicably missed by Muller in his review.

Another ethical breach occurred when Muller informs the Nobel Prize Lecture audience that the threshold model should no longer have any standing in the assessment of radiation induced mutations. Muller's Nobel Prize proclamation denying the existence of a threshold ironically occurred after he had just read the most substantial study that had ever been done in support of the threshold theory, and for which he was a consultant. In his detailed evaluation of the Caspari study, it should be noted that Muller was unable to find any methodological flaws. Furthermore, Muller's explicit promotion of the Ray-Chaudhuri study during the Lecture was another expression of his capacity to exaggerate and misrepresent scientific reality to promote his agenda. Even worse in this case was that the cited paper excluded negative findings that contradicted the LNT hypothesis, further implicating Muller in matters of

possible unethical scientific activities via misrepresentation of the research record.

Muller's duplicity did not stop there. In his next effort, he tried to reverse his own research and written record concerning the Uphoff and Caspari control groups but was finally caught in a series of documented dishonesties in multiple journal publications (Calabrese, 2015a, 2019a). No geneticist challenged the Muller lies and deceptions, including those who knew the data, including Stern, Uphoff, Caspari and probably Edward Novitski, who had joined the research team.

Yet another grand indiscretion occurred when Stern acted to resurrect the uninterpretable data on the Uphoff control groups, which he had earlier discredited after receiving multiple written communications from Muller. Stern's written report discrediting the study proved quite damaging as it not only blamed the experimental failure on aberrant data stemming from investigator bias but he also sent the report to his granting agency, the US AEC. However, in the report he revealed neither the source of bias (himself, Uphoff or the entire team), nor its cause (origin), nor its current status (is it still ongoing?). If Stern was not accusing himself of bias, who then was the alleged source? Uphoff only recently joined the group and thus seemed an unlikely suspect. If it did not come directly from Stern or Uphoff, then perhaps it came from the pervading culture of the group? This is an extremely important issue because it questions the validity of the subsequent Uphoff and Stern (1949) paper that was so broadly influential. Stern promised to publish all the data at a later date as well as the methods and materials sections, which had also been omitted from this 1949 *Science* paper. Even though Stern never kept his promise, his efforts successfully influenced the beliefs of other scientists and convinced many of what was false and what was real, exactly the Muller plan.

This rather lengthy list of ethically challenged behaviors is so overwhelming and sustaining that their root causes are mystifying and difficult to explain. With respect to LNT, however, the ethical breaches seem to arise from a deeply fixed conviction, ideology, or dogma that is incapable of change regardless of countervailing evidence. When actually confronted with iconoclastic evidence, scientists like Muller, Stern and members of the BEAR I Genetics Panel, demonstrably bent their ethical standards rather than alter their belief in LNT. They would seemingly do whatever it took to ensure its adoption.

The actions of the BEAR I Genetics Panel were enveloped in a diverse and expansive cascade of unethical actions to ensure the acceptance of LNT. These actions included: 1) biased Panel creation by Brock and Weaver, 2) deliberate exclusion of the atomic bomb study; 3) linkage of the report from the BEAR I Genetics Panel to large-scale self-interested funding via the RF; 4) the predominant use of limited and questionable data on *Drosophila* as the principal basis of radiation risk assessment; 5) deliberate misrepresentations of the scientific record as published in the journal *Science;* 6) deliberately hiding and misrepresentation of the lack of agreement amongst panelists on the topic of human risk; and 7) a deliberate choice to reject the reasonable request of scientists for a report that would explain the scientific basis underpinning the panelists' decisions. These actions were at least partly motivated by self-interest and the allure of obtaining extra funding for their own special areas of research. That this "promise" of future funding depended on the adoption, support and continuance of LNT as public policy was lost on none of the panelists. Such transgressions-both committed and omitted—by this Panel proved enormously successful, as EPA simply adopted the Panel's recommendations with little reflection and promulgated them to an unquestioning and incurious media. Many countries followed with confidence the example set by the prestigious US EPA and blindly accepted LNT, codifying it into a sacrosanct public policy that has now endured globally for many decades.

7. Ethical considerations

Generally accepted ethical norms have long existed that have application to the behaviors and actions of members of the radiation community and the NAS Genetics Panels (UNDP, 2020; IPDET, 2018). These norms include the need for transparency to ensure credibility and to avoid the appearance of personal interests that can influence decisions and outcomes. Ethical problems may also arise when members of an evaluation body are known to have already demonstrated prejudices, biases or ideologies before the body convenes or, for that matter, fail to present findings fully and completely during the evaluation process itself. Furthermore, the conduct of ethical practices must be devoid of financial enticements or of any influences–subtle or overt—that would affect its objectivity and clarity. Denying or avoiding the need for fair and rigorous evaluation because of time constraints or pending heavy workloads is likely to lead to ethical concerns if condoned. Other ethical concerns involve the omission of pertinent information solely because it would disagree with or refute positions held by any member(s) of the evaluation body. Given these examples of common ethical concerns, the actions of the radiation genetics/NAS Genetics Panels will now be considered.

This historical assessment of LNT has revealed numerous serious ethical concerns, most of which revolved around the misconceived idea that the "ends justify the means". These so-called "good ends" represent a desire by the Genetics Panel to limit excessive exposures to X-rays in clinical settings, to protect workers in medical and industrial settings, and to impact international policies concerning atmospheric testing of nuclear weapons. While the ends may have been perceived as "good" goals, each application of the LNT concept would now need a critical evaluation.

A series of unethical historical concerns that were related to the scientific development, to the peer-reviewed evaluation, and to the public promulgation of the LNT concept have been clearly documented herein. An important part of this story, however, involved the administrative leaders at both the NAS and the RF who were shown to play a dominant, but unethical, role in establishing LNT into regulatory policy. Together, these leaders formed a new and separate panel, composed of biased geneticists, whose views on dose response were known and supportive of LNT, thereby creating a panel structure that virtually ensured the recommendation of LNT. In the end, the Genetics Panel's endorsement of the LNT was more a proclamation of belief rather than the result of careful, rigorous, scientific review and discussion of all available data. Every step along the Panel's path was so constructed. For example, Chairman Weaver noted that substantial and very flexible funding for geneticists would be available via the RF, if the appropriate report was forthcoming (February 5, 1956 BEAR I Genetics Panel, transcript-page 35). **("There may be some very practical results—and here is the dangerous remark … don't misunderstand me. We are just all conspirators here together …. . I am not talking about a few thousand dollars, gentlemen. I am talking about a substantial amount of flexible and free** support **of genetics")**. Given the need for research money among academics, Weaver's statement simply reinforced the LNT focus and held out the offer of rewards to compliant Panel members. Although these actions were principally orchestrated at the level of administrative leadership, at the level of a Panel member there was apparently no problem in altering the research record to enhance the acceptance of the policy recommendations (e.g., Crow's omission of three of the nine geneticist's estimates of genetic damage; reducing the real level of disagreement about reported damage by expert Panel members) and in publishing the altered research in a leading journal. The Panel had no problem either in deciding to deny a requested report to the scientific community that would document the basis for the Panel's LNT recommendation or in obtaining the approval and support of Brock in their decision to deny the said requested report (Calabrese, 2015a, 2019a). In all of the above cases, accepted ethical norms and standards had been clearly violated.

These violations of ethical norms did not start with the NAS Genetic Panels but much earlier, with Muller's deceptive remarks at his Nobel Prize Lecture, with the failure of Stern to share with the scientific community his manipulation of the assessment of the Uphoff data and

with Stern's broken promise and failure to publish the methods, materials and related data in a forthcoming detailed paper. In the 1950s, several papers by Muller (1950a,b, 1954) continued to misrepresent the findings of Caspari and Uphoff to the scientific community and to incorrectly support LNT. Muller (1956b) continued his LNT-supportive activity in other situations, such as his publication within the WHO workshop proceedings with its incorrect citations.

The streaming of unethical behaviors by the Genetics Panel is remarkable, all serving the goal that LNT become the default model for cancer risk assessment. What makes this story compellingly important and, to an extent, shocking, is that this powerful unethical influence has continued across decades via cultural accommodation to the present, as though it was based upon an ethical foundation, when the reverse is actually true. For example, in 1972 the BEIR I Genetics committee stated that the BEAR I Genetics Panel based its recommendations principally on *Drosophila* because there were no adequate human data available at that time. This statement is a deliberate misrepresentation of the facts. Amazingly, James Néel was on that BEIR committee and apparently failed to challenge this false statement. This observation then also speaks to ethical violations of professional intimation and its result, fear of speaking up. In the Calabrese (2020) paper, Muller was shown to use language that threatened and humiliated the younger Néel. In fact, even after the death of Muller, Neel (1994) never mentioned the failure of the NAS to evaluate his study.

In the end, these observations lead to the conclusion that the Genetics "Dream Team", comprised of prestigious and accomplished individuals, some of whom have awards and annual lectures named after them, as well as including two Nobel Prize winners, was fully engaged in a masterful enterprise of unethical behavior that seems unprecedented, given the significance of the endeavor and its enduring and universal impact. It has remained a long hidden secret that the people, especially highlighted by the actions of Hermann Muller, and the process were both corrupt. So, are these findings of unethical conduct just a lifting of the historical curtain to learn that some scientific heroes were seriously flawed? Or is there something more? What is that something more? The US and the world have accepted-without a fair-minded evaluation-the assumption that LNT is correct but have now learned that this belief was based on mistakes, misrepresentations of the research record, and a series of cover ups, all wrapped in the lure of substantial financial self-interest. Confronted with the truth now, do we act to correct our mistake or continue to perpetuate the LNT myth?

8. A course of action

The discovery and unravelling of the sequence of serious manipulations and dishonesties by some leaders of the radiation community, especially by Muller and the NAS BEAR I Genetics Panel, upon society has had a devastating impact on environmental health, the philosophy and policies of regulatory agencies, national economies, public health, medical treatments, and the legal system, to mention but a few. What can realistically be done about this abuse of society by trusted and revered scientific leaders? For critically important symbolism, the Editor of *Science* should retract the BEAR I Genetics Panel article in *Science* with its misrepresentations of the scientific record. That publication should no longer be permitted to stand un-retracted. Second, and far more importantly, the scientific community, appropriate governmental agencies, and the political leadership must awaken to the corrupted history of LNT and act decisively to undertake a fundamental reevaluation of the scientific foundations of cancer risk assessment and to examine their effects on current policies and practices.

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