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Review Article

Muller mistakes: The linear no-threshold (LNT) dose response and US EPA's cancer risk assessment policies and practices

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ABSTRACT

This paper identifies the occurrence of six major conceptual scientific errors of Hermann Muller and describes how these errors led to the creation of the linear no-threshold (LNT) dose response historically used worldwide for cancer risk assessments for chemical carcinogens and ionizing radiation. The paper demonstrates the significant role that Muller played in the environmental movement, affecting risk assessment policies and practices that are in force even now a half century following his death. This paper lends support to contemporary research that shows significant limitations of the LNT model for cancer risk assessment.

1. Introduction

Hermann J. Muller is widely considered to be one of the leading scientists of the 20th century, having been awarded the Nobel Prize in 1946 for producing what he claimed were gene mutations. Muller further claimed that such gene mutations could be produced by very low dose radiation exposure. While Muller's scientific impact with this discovery was indeed profound, his scientific and societal influence has been far deeper, going beyond the areas of basic and radiation genetics. He was one of the principal architects of the environmental revolution, inspiring the likes of Rachael Carson with her profoundly influential book, *Silent Spring*, and providing what have become many of the scientific foundations for hereditary and cancer risk assessment for ionizing radiation and chemical carcinogens in the United States and worldwide. Muller's reputation and impact, as substantial as they were during his life, have continued to grow over the half century since his death in 1967, with numerous testimonials in prominent journals [1–4], annual awards in his honor, and other tributes to his scientific contributions.

In contrast to these deserved testimonials, my (EJC) research into the life and scientific contributions of Muller has led me to see other personal qualities and a different dimension to his scientific legacy. These views on Muller are largely derived from two decades of research on the historical foundations of cancer risk assessment and its dependence upon the linear no-threshold (LNT) dose response model and its putative underlying mechanisms. This has involved detailed assessments of the vast majority of Muller's publications, copious preserved historical correspondence, recorded discussions/presentations, copies of grant proposals, and related documents, books and dissertations related to his life and professional activities.

2. Muller's cumulative errors

Despite the widespread appreciation and acceptance of Muller's scientific contributions, Muller holds the troubling distinction of making fundamental mistakes on at least six major radiation genetics concepts of the 20th century. These mistakes occurred and were perpetuated mostly because of his capacity to exhibit an unrelenting and uncompromising personality, the synergistic and reinforcing nature of these mistakes, his potential for profound self-interest and an overly dominating political/ideological agenda for which, to him, the ends justified the means [5–7]. Fig. 1 highlights these six major scientific mistakes that profoundly affected the field of radiation genetics, chemical and radiation risk assessment, and many critical regulatory actions by agencies like the US Environmental Protection Agency (EPA). Each of these major

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scientific errors are summarized herein in such a manner as to frame their collective impact on the major issue of worldwide cancer risk assessment policies and practices, all of which trace their origin and cumulative and continuing actions to the six Muller mistakes. In fact, as major a figure as Muller was in the domain of experimental science in the early to mid-decades of the 20th century, we suggest that Muller's major impact on science and society is seen in the cascading impact that his major scientific errors have had on cancer risk assessment, environmental standard setting, and on the adoption of nuclear energy. In fact, the impact of Muller on risks from low doses of radiation has directly led, for example, to increases in chemical and radiation air pollution from the alternative of burning fossil fuels (from a marked reduction in nuclear energy production) and elevated levels of carbon dioxide and its often claimed potential impact on climate change, as well as to increasing fears of using more precise medical diagnostic procedures and therapeutic treatments related to radiation.

3. MISTAKE # 1: Major misunderstanding of evolution: Muller's Mistake proved disastrous for risk assessment and society

Muller's evolution error had its foundation as a graduate student when he learned that mutations observed by external observation of *Drosophila* were quite rare. It was widely commented upon in the 1920s by *Drosophila* geneticists that only about 400 such mutations had been seen in about 20–25 million fruit flies–that being only about one for every 50,000 flies observed [8,9]. Based on these copious shared observations, Muller came to the conclusion that the genome was extremely stable. He wrote:

> **"… In the course of this work, animals and plants have been drugged, poisoned, intoxicated, etherized, illuminated, kept in darkness, half smothered, painted inside and out, whorled round and round, shaken violently, vaccinated, mutilated, educated and treated with everything except affection, from generation to generation. But their genes seem to remain oblivious, and they could not be distracted into making an obvious mistake …. …"** [8].

Yet, gene mutation is and was required for evolution. Rather than correctly concluding that the interpretation should be that the genome was surprisingly resistant to external damage and/or that undiscovered repair mechanisms could repair almost all damage, Muller came to believe that such gene mutations, whatever the cause(s), could not be effectively repaired or else there would be no sufficient driving force or mechanism to make evolution possible. Mutations were needed to create biological novelty that would be subjected to the pressures of natural selection. While this hypothesis seemed convincing to Muller, he failed to consider other possibilities. For example, Muller could have created a series of testable hypotheses that were consistent with the observations of very rare visual mutations in the fruit fly. For example, similar observations could have occurred had there been a very high rate of induced mutations, but with most of them being efficiently repaired. The fact that Muller would exclude the possibility of gene mutation repair would have highly significant implications for the cancer risk assessment process. This perspective is strongly reflected nearly 30 years later in comments by Tracey Sonneborn during the National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Panel meeting on February 5, 1956:

> **"…. ordinary consideration of life inescapably involves exposure to irradiation and other mutagenic agents, quite apart from the additional exposure due to the atomic age, medical uses of irradiation and other man-controlled superimposed mutagenic agents."** With this background exposure framework, Sonneborn [10] argued that **"…. inescapable mutation provides an ample means for evolutionary advance and for genetic adaptation to changing conditions of life. It also involves mainly genetic damage under present conditions. Additional mutations only add further damage without materially increasing the capacity to adapt and evolve. Given inescapable mutations, genetic**

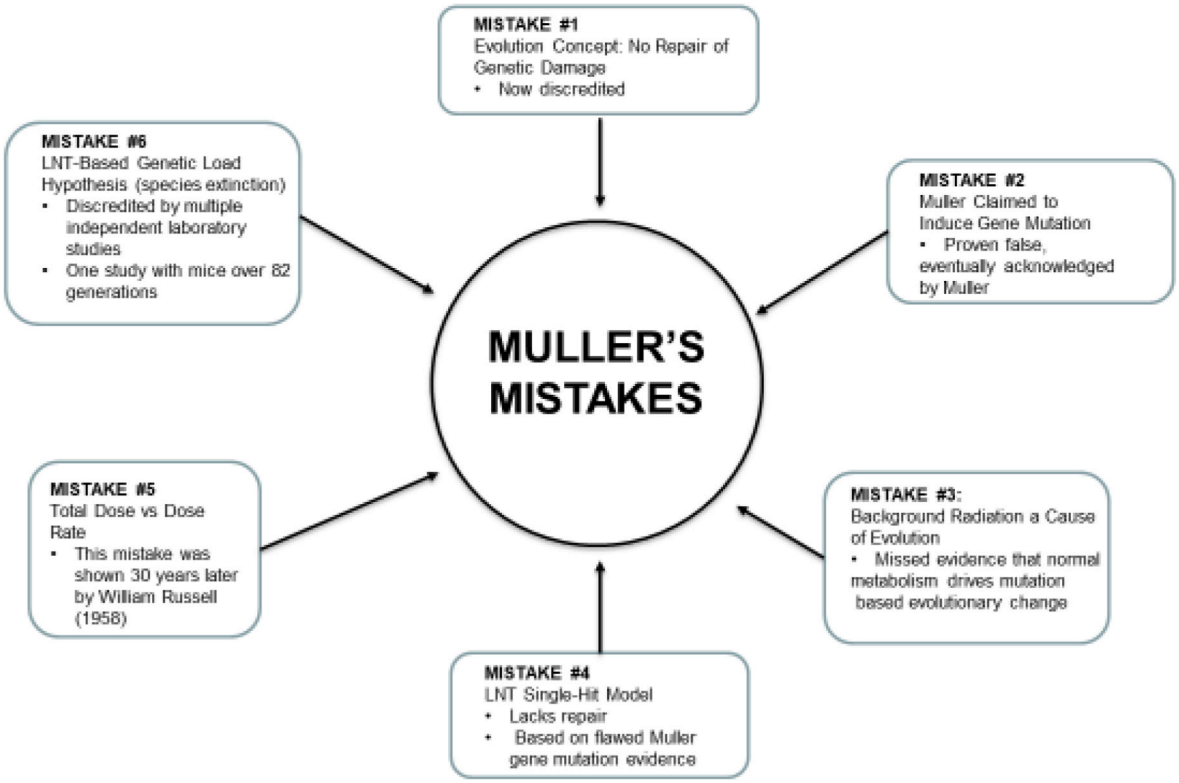

Fig. 1. Muller's mistakes that led to current, misguided cancer risk assessment policies/practices.

adaptation and evolution depend principally upon selection, not upon more numerous mutations" [9].

In fact, this was the most fundamental of the cache of Muller errors, affecting a vast range of decisions and actions of Muller and by the many subsequent individuals and organizations that he influenced up to the present time. In all the highly complimentary biographies and testimonies written about Muller, this fundamental error has never been mentioned and, worse, never corrected.

4. MISTAKE # 2: Muller failed to induce gene mutation and did not deserve the Nobel Prize

Muller [11] reported that he induced transgenerational phenotypic changes in fruit flies that he claimed were due to the "artificial transmutation of the gene", which he called "point mutations". However, from his initial claim of inducing gene mutation with X-rays, Muller was challenged to prove that he had not confused an observation with a mechanism [12]. Muller used a massively high radiation dose rate that was about 100 million times greater than background radiation [13]. The exposure was so great that high proportions of the normally rather insensitive fruit flies died or were sterilized. Muller chose the use of such high doses since James W. Mavor (1883–1963) used massive doses of X-rays that sterilized about 90% of the flies in order to induce only about a two-fold increase in crossing over frequency [14,15]. Thus, Muller never intended to use low doses in his breakthrough experiments; he followed the very high dose experimental approach of Mavor. However, Muller was unable to provide mechanistic proof of gene mutation, despite a massive attempt to address the issue of X-ray induced reverse mutation [16,17]. Rather, experimental mutation evidence was accumulated over the next two decades that discredited his gene mutation conclusion [18]. In fact, some ten years after receiving his Nobel Prize, Muller [19] would finally acknowledge in writing that he had mostly induced major chromosome damage, including modest to massive gene deletions, rather than true mutations.

"… there is no doubt that in X-rayed Drosophila also, at least when the irradiation is applied to condensed chromosome states, such as those of spermatozoa, deficiencies as well as other demonstrable structural changes that appear in much higher frequencies relative to changes that appear to involve but one gene …." [19].

Later investigations using nucleotide measurement techniques further confirmed that he had failed to induce the point mutations that he claimed [13,20,21]. Yet, Muller maintained the visibility and prestige associated with having induced gene mutation for a prolonged period of time, which was long enough to win the Nobel Prize. However, he would eventually lose the argument, even with his former highly supportive and accomplished students [22].

The implications of this second mistake would then set the stage for subsequent mistakes that depended on his belief that he had induced gene mutations.

5. MISTAKE # 3: Background radiation: cause of evolution

Muller was highly motivated to find a means to induce gene mutation since he was in a race to discover the underlying cause of evolution. Muller had spent much of the 15 years prior to his 1927 report in *Science* [11] trying unsuccessfully to induce mutations with massive doses of many types of toxic chemicals and physical stressors. However, once he had induced his version of "gene" mutation with X-rays (i.e., 100,000,000-fold greater dose rate than background), Muller then made the assumption and assertion (though he could not show it) that ionizing radiation acted in a linear manner all the way down to a single ionization [23], assuring that background radiation would then be considered a cause of evolution [8]. Muller would have no idea that the driving force for background mutation is oxidative stress from metabolic processes [24–26]. A Muller-inspired perspective on this matter was well-summarized by his former graduate student and a contemporary leading radiation geneticist, Bentley Glass [27], who stated that:

"for longer-lived animals, a greater [mutation] fraction may well be caused by the background, since the over-all mutation rate in different species holds fairly constant (within about one order of magnitude) although the exposure to background radiation increases enormously with length of life. If the low-level radiation of the background in fact causes a proportionate increase of mutation, then in a species that lives a thousand times as long as *Drosophila* and whose gonads are equally exposed, all spontaneous mutation would be caused by the background." (emphasis added).

This lifespan argument would come to dominate the thinking of leading radiation geneticists who tried to translate the perceived genetic risks in fruit flies and make them quantitatively relevant to human risks and evolutionary change, and then to causally relate such actions to background radiation [28–34].

6. MISTAKE # 4: The creation of the LNT single-hit model

In 1935 Timofeeff-Ressovsky et al. [35] proposed the LNT single-hit model for ionizing radiation. This model would be based on Muller's concept of gene mutation and his assumptions of a linear dose response and no repair of genetic damage [9]. This model soon spread worldwide and would come to dominate regulatory agency policies and practices four decades later with the creation of the US EPA. Of particular significance is that in 1930 Muller created the concept of the Proportionality Rule for ionizing radiation that assumed that there is no safe dose of ionizing radiation for gene mutations based on experimental radiation doses many orders of magnitude higher than background [23]. The Proportionality Rule was the first term used by the radiation geneticist community for what would later be the LNT concept.

7. MISTAKE # 5: Total dose (piggy bank theory), not dose rate (repair model) predicts risk

Muller's "piggy bank" or total dose theory of radiation-induced genetic damage started with Mistake # 1 and was continued in various permutational manifestations, such as seen in the total dose versus dose rate controversy [21,36]. Muller had insisted so strongly that there was no repair that this idea was adopted and universally accepted by the radiation genetics community until the late 1950s when Russell et al. [37] reported repair of radiation-induced mutations in mouse spermatogonia and oocytes, finally demonstrating that dose rate rather than total dose was the most accurate way to estimate radiation-induced mutational risks, with clear implications for a threshold. The BEAR I Genetics Panel of 1956 adhered to the total dose hypothesis [10], recognizing the dose rate findings of Russell et al. [37] four years later [38]. Nonetheless, even 15 years after the discovery of dose-rate effects and with data demonstrating a threshold in the oocytes of the mouse at a dose rate 27,000-fold greater than background [39,40], the US NAS Biological Effects of Ionizing Radiation (BEIR) I Committee [41] could not break free from the multi-dimensional Mullerian impact (e.g., concept formation, former students/close colleagues on BEIR I) still adhering to the LNT framework. It is worth noting that the Genetics Panel was chaired by Muller's close friend, and confidant, James Crow, along with several other original BEAR I Genetics Panel members.

8. MISTAKE # 6: Genetic load and the risk of species extinction

Muller argued that species would become at risk of extinction via the accumulation of recessive gene mutations over multiple generations. This was the basic idea underlying his genetic load hypothesis [42].

Muller [43] provided the following explanation:

> **"If a total of 300 r units, though finally recovered from to all appearances, produces an average of something like one mutation in every 3 to 6 immature germ cells (as happens in flies), then if people in general were subject to this in very many repeated generations, it will readily be seen that such a large proportion of the population would eventually die genetic deaths as to result in the dwindling away and probably, at last, the extinction of the human race. Long before that, however, the effect would be catastrophic, for the survivors would be loaded with detrimental weaknesses. Nevertheless, these effects might take hundreds of years or millenia to mature, and by that time it would be too late."** ([43], page 466).

In the late 1950s two major mouse radiation genetics research groups in the US undertook on a large scale the task of testing this Muller hypothesis. Their intent was to massively expose the gonads of young adult male mice to X-rays for multiple generations to see if they could detect evidence of reproductive fitness and longevity declines, suggestive of potential species collapse [44–49]. In the instance in which this procedure was followed for some 82 generations, the exposure in each generation was massive, just below the onset of lethality, with 200 r delivered at 50 r/min to males that were, on average, 26 days old, with no apparent impact on reproductive fitness and longevity. Eighty two generations in mice, with the assumption of a generation of 30 years in human, would be equivalent to about 2500 years in people! The investigators concluded that Muller's LNT-based genetic load hypothesis was not supported [49].

9. Discussion

Muller's strikingly proclaimed gene mutational findings and their widespread implications, together with his dominant demeaner, leadership qualities and profound commitment to ideological beliefs likely resulted in his having the most significant impact of anyone on hereditary and cancer risk assessment within the scientific and world communities. In general, it is widely thought that Muller's major impact began with his July 1927 publication in *Science* announcing that he had induced gene mutations via X-rays in *Drosophila*. This discovery, when coupled with public concern caused by the atomic bomb explosions in Japan in 1945, resulted in his being awarded the Nobel Prize in 1946. For the Nobel Prize Committee, awarding the Prize to Muller was as much a scientific statement as it was a political one, ushering in the nuclear age, with its enormous challenges and opportunities. However, the present paper shows that the original error that Muller made as a graduate student, that repair of gene mutations did not occur [9], unfortunately drove the process of hereditary and cancer risk assessment worldwide and created the societal climate in which there was crippling fear of low dose radiation. This now discredited assumption became the key driver in cancer risk assessment, as it permitted Muller [11] to make use of his alleged gene mutation induction discovery in 1927 and place it within a Proportionality Rule concept in 1930 [23]. That concept soon morphed into the highly flawed LNT single-hit model [35]. The transformational conceptual leadership of Muller simply captured an uncritical, but concerned, scientific community and later the newly created regulatory community, as led by the US EPA.

The US Congress unfortunately entrusted decisions on scientific matters to the US EPA, an agency that was also mesmerized by the Mullerian mystique, with it also falling victim to his numerous mistakes, scientific misconduct, data censoring and profound ideological biases. The multiple errors of Muller have come to infiltrate the assessment of many advisory groups, such as the US NAS. For example, the US NAS Safe Drinking Water Committee [50] provided a listing of eight Muller-based/assumptions to support the LNT model for cancer risk assessment (Table 1). None of these assumptions are now supportable, yet such "prestigious" publications continue to guide the actions of regulatory agencies and the scientific community. Of particular significance in the adoption of the LNT model was the assumption by Crump et al. that carcinogens (chemical/ionizing radiation) act in a manner that is additive to background. This assumption has been shown to have significant determining effects on the adoption of LNT [51]. However, Calabrese (2018) has shown that the additive to background assumption was not supported in a comprehensive assessment of 45 carcinogens (including ionizing radiation) across 13 species. These historical and contemporary Muller-based errors [52] have never been corrected because the scientific community and the US EPA have failed to make the necessary efforts to understand the flawed historical foundations of this field and have committed the error of an uncritical appeal to authority (e.g., recommendations of the US NAS BEAR I Genetics Panel [10], US NAS BEIR Committee [41]). Ironically, the efforts of Muller to create a fear-based regulatory risk assessment process has led to the widespread abandonment of nuclear power and its low exposures to the public and to its long-standing replacement with the massive use of fossil fuels, markedly enhancing exposures to

carcinogenic chemicals and radiation from burning such fuels, as well as contributing enormous amounts of carbon dioxide into the atmosphere, which some claim is important in causing manmade climate change.

It is time for the scientific and regulatory communities to confront the troubling and scandalous historical foundations of hereditary and cancer risk assessment and the unjustified and crippling errors made on risk assessment policies, regulations, and practices, energy choices, and their societal impacts.

Table 1
NAS SDWC (1977) low dose linearity guiding principles: No longer tenable [5, 50].

Only one or two changes in a cell could transform it and this could lead to cancer	Not tenable
Human population heterogeneity was a factor, and some people may be at greater risk. Such heterogeneity leads to the conclusion that here was no population-based threshold.	Impossible to practically study
A transformed cell will be irreversibly propagated.	Not tenable
If the mechanism involved mutation, there would be no threshold; in fact, if there were no information on mechanism and cancer occurred, mutation should be assumed.	Not tenable
It is necessary to assume that a single molecule or a few molecules can cause a mutation. Therefore, linearity at low dose can be assumed.	Not tenable
There is also the assumption that the exposure would be directly additive to background, if acting via the same mechanism. This would also support the linearity conclusion.	Not tenable
Available mutagenicity data with radiation indicated that it was linear at relatively "low" doses.	Not tenable
Since chemical carcinogens act like ionizing radiation, low dose linearity should also be assumed to be the case for such chemicals.	Not tenable

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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