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Dose response and risk assessment: Evolutionary foundations☆

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ABSTRACT

The present paper indicates that the origin of the LNT concept for ionizing radiation was based on insufficient understanding of evolution, which precluded the possibility of repair of gene mutation. The denial of such repair processes had important implications, leading to a belief in a linear dose response and thus in Hermann J Muller's proclamation of a Proportionality Rule for ionizing radiation. The paper documents how the lack of repair concept dominated the radiation geneticist community to the 1960s leading to the establishment of the linear no threshold dose response (LNT) model for radiation and chemical reproductive and cancer risk assessment. Research from the late 1950s onward would establish the occurrence, generality, and efficacy of genetic and cellular repair processes. While the assumption of a lack of gene mutation repair was wrong, Muller was correct that dose-response concepts need to be founded on mechanistic understandings of evolution. Such mechanisms require the integration of constitutive and inducible adaptive and repair mechanisms that operate in the low-dose zone. This perspective reflects the comment of Dobzhansky (1973) that "nothing makes sense in biology except in light of evolution." While this is a powerful scientific dictum, it assumes a correct understanding of evolution, something that the origins of the LNT dose response lacked. Such modern mechanistic repair developments reveal that the historical foundations of LNT were flawed from the start. Nonetheless, they have been carried forward to the present time, principally by environmental health regulatory agencies that decoupled risk assessment policy from a sound evolutionary foundation.

1. Introduction

In 1930 Hermann J. Muller proposed a "Proportionality Rule" to describe the capacity of ionizing radiation to induce gene mutation. A biological "rule" has historically represented a general concept with broad applications. During the latter part of the 19th century, as experimental science was becoming established, it was not uncommon for investigators to dignify a major discovery with strong supportive evidence with the term "law" or "rule"[1]. The Proportionality Rule represented a general belief about the nature of the dose response in the low-dose zone for the effects of ionizing radiation on gene mutation. Muller (1930) claimed that all ionizing radiation-induced gene mutation damage was cumulative, not reparable and irreversible, leading to a linear dose response that embodies the Proportionality Rule.

2. Analysis

The Proportionality Rule of Muller was preceded by the 1928 paper of Olson and Lewis using the proportionality dose-response concept for a gene mutation mechanism of evolution based on Muller's (1927) showing that X-rays induced gene mutations in reproductive cells of *Drosophila*. Even though the dose rates used by Muller were massive (i.e., approximately 100-million times the background) (Calabrese, 2019), Olson and Lewis (1928) assumed that gene mutations would be produced in a proportional manner down to and below background radiation levels affecting all organisms. Olson and Lewis (1928) viewed their explanation for a mechanism of evolution as reasonable since ionizing radiation was then the only known mutagen, while during the previous 15 years no one had succeeded in inducing mutations in attempts made using numerous chemical and physical stressor agents.

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[1] A relevant example for the present paper would be the 1906 Law of Bergone and Tribondeau that the radio-sensitivity of a tissue is proportional to its proliferative activity and inversely proportional to its degree of differentiation. This law guided radiation oncologists for the following half century (Ducoff, 2002).

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Muller (1929) described the numerous failures to induce gene mutation during the years preceding his 1927 discovery as follows: efforts to induce gene mutation "have been by no means lacking, on the part of numerous investigators, to find the cause, or a cause, of visible mutations, by trying all sorts of maltreatments for the attempt to produce such changes. 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, whirled 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 ….". In Muller's (1929) paper, it was reported that only about 400 visible mutations had ever been observed in a total of about 20 million fruit flies. These observations led Muller to a belief in the apparent remarkable stability of the fruit fly genome while still being inquisitive about the cause and biological meaning of the very low production rate of visible mutations.

In the quest to understand the driving force of evolution and how gene mutations occurred, Muller (1929) opined that a cause of evolution was background radiation from cosmic rays, terrestrial earth, and related environmental sources, adopting the position of Olson and Lewis (1928). He further stated that even though the fruit fly mutations that he had observed were indeed "very scattered and very infrequent … …the total number of mutations so produced per year must be very considerable," leading him to conclude that they "have found at least one of the natural causes of mutations, and hence of evolution."[2] Thus, in the quest to understand the cause(s) of evolution, Muller (1929) proclaimed that background radiation was at least part of the explanation.

The Proportionality Rule was problematic since it reflected an incomplete understanding of evolution, with damage being not reparable. This accounts for the assumption that damage accumulates over time, resulting in a linear response. It is curious why Muller would have intuitively thought that genetic damage could not be reparable, since nature displays a vast array of efficient repair processes such as wound healing, repair of broken bones, and other conditions. Why would gene mutations be different? What was the scientific evidence? A series of classroom written examinations that Muller administered to students at the University of Texas at Austin during the years leading up to his 1927 paper, found in his Nobel Prize research data notebook, reveal a commitment to the natural selection theory of evolution. However, **no exam question** related to induced genetic damage and its repair**, suggesting that Muller's view of evolution did not embody the repair concept.**

For Muller, evolution was explained within a neo-Darwinian framework of diverse-random mutations, with the vast majority being deleterious and eliminated, but with natural selection of the very low proportion that result in enhanced survival. In 1930, Muller and Altenburg, in fact, wrote that " …. evolution must have proceeded through gene mutations, that is, through the very rare gene mutations which happened not to be detrimental, and which therefore could withstand the test of natural selection." The perspective that Muller expressed was that the genome was very stable, nearly immutable in a relative sense, but weakly susceptible to background radiation-induced random mutation, a view that was adopted by Dobzhansky (1937) in his book Genetics and the Origin of the Species.

The view of Muller in 1930 was still the dominant perspective 26 years later when the US NAS convened the BEAR I Genetics Panel to estimate the effects of ionizing radiation on genetic endpoints. At the Panel meeting on February 5, 1956, Tracy Sonneborn (1956) stated that " …. 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 (1956) 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 [3]. **Additional mutations only add further damage without materially increasing the capacity to adapt and evolve. Given inescapable mutations, genetic adaption and evolution depend principally upon selection, not upon more numerous mutations"** (emphasis added). These perspectives that are incorporated in the writings of Dobzhansky and Sonneborn can be traced back to the highly influential paper of Timofeeff-Ressovsky et al. (1935) that formulated the linear one-hit model. This target theory-based mechanistic model for ionizing radiation-induced genetic damage demanded that there could be no repair of gene mutational targets (Ducoff, 2002). This perspective was promoted by the 1933 physics Nobel Prize recipient Erwin Schrodinger (1944) in his booklet "What Is Life" and the radiation physicist Douglas Lea (1947) in his book "Actions of Radiations on Living Cells" furthering its widespread adoption. This framework provided the foundational support for Muller's Proportionality Rule and the linearity-derived belief system of radiation genetics that guided the BEAR I Genetics Panel (1956) in their risk assessment deliberations [4].

This non-repair/mutation/natural selection view of evolution had many scientific implications, including the nature of the dose response in the low-dose zone for radiation-induced mutation. This would also be the case later for chemical-induced mutations. For Muller the focus was on induced mutations and the natural selection process. Beneficial genes would win the game of evolutionary selection. It was never about repair, its upregulation, and other adaptive responses.

The evidence to support Muller's Proportionality Rule at the time of its proposal was quite limited. The works of three groups were cited, two from Muller's laboratory (i.e., Hanson and Oliver) and one of Stadler at the University of Missouri, who was working with plants. In his 1929 paper, Muller also cited the research of Little and Bagg (1923) with mice, which showed limited evidence of radium-induced mutation at least in part due to the "very small dose of X-rays used ….". In the same paper, Muller (1929) also noted the unpublished findings of MacDowell et al. who "found no evidence of the production of mutations". Muller would go on to state "a stronger treatment ….might well be necessary before the effects could be clearly demonstrated". The research of Hanson and Heys (1929) displayed a linear dose response with

[2] In 1930 Muller and Mott-Smith analyzed the hypothesis of Olson and Lewis (1928) in considerable detail based upon the experimental data that Muller (1927) generated in his groundbreaking paper in which he claimed to have induced gene mutation via the administration of very high dose rates/doses of X-rays to fruit flies. Using a linear dose-response model, they estimated that the amount of gene mutations that background radiation contributed to their control group fruit flies was only 1/1300 of the total observed. This estimation led Muller and Mott-Smith (1930) to dismiss background radiation as having an important impact on evolution. In 1956 the UK expert committee on ionizing radiation reported that the estimate of Muller and Mott-Smith (1930) for background radiation damage had been further reduced to 1/10,000 of the total genetic damage observed, further reducing the role of background radiation in evolution (MRC, 1956-page 44).

[3] These comments of Sonneborn suggest no appreciation of the Muller and Mott-Smith (1930) paper that dismissed background radiation as an exposure having material impact on the process of evolution. There is no indication of what the "other mutagenic agents" are that serve to drive the evolution process. The perspective of Sonneborn (1956) concerning a lack of gene mutation repair was supported by a parallel expert UK committee (MRC, 1956, page 30) which stated: "Thus, in contrast to most other types of biological response to radiation, damage to the genetic material cannot be repaired and the effect from repeated exposures is cumulative."

[4] The Proportionality Rule and supportive no repair mechanism theory may well have been deeply influenced by Muller who was a visiting scholar with Timofeeff-Ressovsky as well as an active participant himself in the radiation geneticist-physicist contingent discussions during this period when the 1935 paper was formulated.

progressive degrees of lead shielding but did not include dosing information, compromising its value. In the case of Oliver (1930), a linear dose response was reported for several genetic damage endpoints, including possible gene mutations, with the lowest dose rate used being about 30 million fold greater than background radiation dose rate, greatly limiting its capacity to estimate near background effects. With respect to the plant research, Stadler (1930) assessed mutagenicity involving 13 radiation doses in barley, with the three lowest doses showing no occurrence of mutations, reflecting the possibility of a threshold dose response. Despite its enhanced power and greater dose response relevance, such findings were not appreciated or misinterpreted in Muller's work, even though Stadler (1930) explicitly raised the possibility of there being a threshold in his discussion by stating that "absence of mutation in the cultures given the three lowest doses might suggest the possibility of a threshold intensity below which mutations do not occur … … …". With such limited data to support the Proportionality Rule claim in the presence of some contradictory evidence, the proposal of a dose response "Rule" for ionizing radiation-induced mutation seems scientifically inappropriate.

Despite the lack of supportive and dose-rate-relevant data (i.e., Oliver, 1930), another major concern with the Proportionality Rule perspective is that one of the key assumptions was wrong, leading to a false conclusion. While it was not known at the time of its proposal, the rate at which endogenous base damage in DNA occurs is far from rare in many cells, occurring millions of times per cell per day, with most (i.e. > 99.9999%) being repaired (Pollycove and Feinendegen, 2003). This repair may be the reason why there were so few visual mutations reported. It was also not recognized at the time of that publication (Muller, 1929) that background radiation accounted for such an apparently low proportion of the control group mutations (Muller and Mott-Smith, 1930-see footnote #2).

As noted above, the proposal of the dose response Proportionality Rule was based on the assumption of a stable genome, which was exposed to background radiation all within the biological mandate of evolution. Other types of biological processes could be considered, which might result in similar very low apparent mutation rates as observed in the fruit flies. For example, it could have been hypothesized that this same set of observations could have occurred if the genome was very susceptible to induced gene mutation but that it also had the capacity to repair that damage. The net result could have appeared similar to Muller's "stable genome", but the dose response implications would have been dramatically different. In this latter case one could readily derive data-based threshold or hormetic models or a combination of both as has been widely published in the current literature. Thus, instead of proposing a Proportionality Rule, the possibility of several testable dose-response hypotheses could be considered, which is exactly what today's science would dictate. However, a poorly-supported linearity belief, in which gene mutations would not be repaired but subjected solely to natural selection, was transformed into a dose-response Rule with far-reaching implications extending to the present day.

Muller offered his speculations on the role of dose on both mutation and survival. He opined that all ionizing radiation exposures produced mutations in a dose-proportional manner, that the vast majority of them are harmful, and that beneficial mutations are selected for that enhance survival. There was no opinion on whether some beneficial mutations could facilitate the repair of the mutational damage that is induced by ionizing radiation. If this were the case, then what would be the implications for the dose-response relationship? It indicates that the dose-response relationship should be assessed via a dose-time response since repair would occur at a time after the initial damage.

When low doses of ionizing radiation induce damage in DNA, what tends to occur? In general, cells have damage "detection" systems. If the induced damage is minor and falls within routine ongoing cellular damage frequency dynamics, it is repaired by constitutive processes with the dose response likely showing a threshold. However, if the damage exceeds routine background daily dynamic variation, the detection systems that sense the excess damage cause the upregulation/induction of repair processes (Sykes and Day, 2007). Considerable evidence shows that upregulation is quantitatively linked to the degree of damage, thereby facilitating full repair within a time window. The detection system typically slightly overestimates the degree of harm, generating a modestly excessive repair response much like a biological safety factor that ensures that the repair will be completed within an efficient time period (Calabrese, 2008). The net result of this process is that all induced damage is typically repaired as well as some normally present background damage. In fact, this process results in a temporary decrease in the net damage for a period of time (i.e. the so-called hormetic benefit). At low doses, there is a paradoxical decrease in damage due to the original damage-inducing event. However, if the original exposure is excessive, the repair process may become overwhelmed, resulting in both unrepaired damage and the occurrence of concomitant inflammatory processes that may enhance a damage spiral. Thus, what occurs at lower doses cannot be accurately predicted by exposures/responses at higher doses. In Muller's early scientific era of 1910–1930, these biphasic dose responses for both radiation and chemicals were being actively reported, including those with a dose-time-response perspective (Calabrese and Baldwin, 2000a-e). These were reported for a broad range of endpoints, typically in microbiological, insect, and plant experimental models where a large number of doses could be well studied.

Within the above dose-response context, studies showed that the initial occurrence of inhibitory or damage responses was followed by an adaptive (acclimation) response that results in a modest over compensation response. While these responses were widely reported for diverse endpoints, they closely paralleled genetic responses, especially in the areas of agriculture/insecticides, entomology, and microbiology. These genetic driver adaptive responses were reported for induced resistance in pest species following insecticide and certain medicinal treatments (Forgash, 1984; Voegtlin et al., 1924; Melander, 1914). It was not known at the time what the processes or mechanisms were, but it was believed to involve natural selection of either beneficial newly-mutated genes or of earlier mutations that had been segregating in the population. Adaptive responses due to natural selection of induced or present mutations yielded non-linear dose responses, contrary to the Proportionality Rule. However, these early "resistance" researchers were not oriented to dose-response evaluations. AJ Clark (1937), a leading British pharmacologist/toxicologist, reported that the dose response tended to follow a threshold dose response, with the threshold dependent on the inherent adaptive capacity of the individual.

By the late 1930s, Dobzhansky (1973) provided the first integrative explanation of the adaptive response to insecticide-induced resistance within an evolutionary framework based on natural selection. Further evaluation was provided by Luria and Delbruck (1943), who explicitly addressed the issue of survival adaptions within the context of differentiating between that of an induced novel beneficial mutation following the application of Poisson distribution of mutation frequencies or by preexisting adaptive genes. The development of the Proportionality Rule therefore reflects lack of appreciation of the broad occurrence of biphasic dose responses and their adaptive nature despite the available literature. Due to this truncated perspective, generation of a range of possible experimental hypotheses was not proposed.

The Proportionality Rule was therefore born out of a need to explain evolution. Since evolution was the cardinal belief, Muller (1930) concluded that LNT must be the fundamental dose response. While this is the foundational belief of LNT and its linkage to evolution, it was profoundly wrong, creating a flawed dose-response concept that lacked a dynamic constitutive and inducible repair component that is reflected in threshold and hormetic dose-response models, respectively. Thus, an observation was confused with a mechanism as was also done when claiming induced gene mutations even though the induced mutations were later shown to consist primarily of modest to massive gene deletions (Calabrese, 2019). The issue of repair and detoxification

processes is of utmost importance in dose-response evaluations, leading to recent efforts to develop novel dose metrics incorporating such processes (Wu et al., 2021).

In 1958, Russell et al. discredited the long-held LNT belief of Muller that there was no repair of radiation-induced mutations and that the total dose rather than dose-rate was the best predictor of genetic risk. In response to the Russell et al. (1958) findings, Muller switched his laboratory focus to try to detect flaws in the Russell findings using his fruit fly model (Krause, 1980). Muller knew that the Russell findings had the potential to discredit the Proportionality Rule/LNT. However, Muller could not find flaws with the Russell findings, providing confirming evidence that was cited in the BEAR, 1960 Genetics Panel report. However, despite his scientific confirmation of the Russell findings, Muller attempted to block the implementation of these findings in the risk-assessment process in a prolonged debate with Russell within ICRP committee activities in 1963 (Calabrese, 2017a,b). Following Muller's death in 1967, Russell made his public pronouncement disavowing the radiation geneticist mantra that there is no repair at an international conference in France in 1970 (Russell, 1973).

This historical analysis of the origin of the LNT concept has important implications. It clarifies how decisions on dose-response model selection should be made. For example, epidemiological data (and most experimental data) are too limited or variable to discern the nature of the dose response in the low-dose zone, typically not being able to differentiate amongst the models. In this case, regulatory agencies have defaulted to the LNT model, under the assumption to "err on the side of safety." This Precautionary Principle approach is shown in this paper to be based on non-evolutionary Proportionality Rule assumptions. It builds its "understanding" from the top down, that is, public health apprehensions, rather than from a possible bottom up perspective, which is an evolution-based mechanistic process. We propose that the environmental "default" assumption should no longer be based on a Precautionary Principle. Rather, it should be based on the scientific realism of an evolutionary model that rejects LNT, replacing it with a combined threshold/hormetic framework that is adaptive and repair-based. This approach would revolutionize risk assessment for carcinogens and hereditary effects and finally, after so many decades of non-evolutionary thinking, place environmental risk assessment within a fundamental evolutionary biology science framework.

3. Conclusion

The Proportionality Rule that Muller proposed was the precursor of the LNT single-hit model that became applied to cancer risk assessment by regulatory agencies in the 1970s to the present. This concept was the key framework for estimating risks in the low-dose zone for mutagens and carcinogens. While that time's newly-formulated Proportionality Rule lacked minimal scientific support, it was soon integrated within a target theory mechanism model that assumed no repair of mutational damage, ensuring a linear dose response. By failing to consider the possibility of constitutive and/or inducible gene mutation repair processes, options such as the threshold and hormetic models were ignored, resulting in a cancer-risk assessment process that precluded consideration of alternative testable hypotheses as demanded by the scientific process.

Author contributions

EJC, Conceptualization and Writing – original draft; DYS, Conceptualization, writing, review, editing; EA, Writing – review & editing.

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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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