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From Muller to mechanism: How LNT became the default model for cancer risk assessment☆

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ABSTRACT

This paper summarizes the historical and scientific foundations of the Linear No-Threshold (LNT) cancer risk assessment model. The story of cancer risk assessment is an extraordinary one as it was based on an initial incorrect gene mutation interpretation of Muller, the application of this incorrect assumption in the derivation of the LNT single-hit model, and a series of actions by leading radiation geneticists during the 1946–1956 period, including a National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel (Anonymous, 1956), to sustain the LNT belief via a series of deliberate obfuscations, deceptions and misrepresentations that provided the basis of modern cancer risk assessment policy and practices. The reaffirming of the LNT model by a subsequent and highly influential NAS Biological Effects of Ionizing Radiation (BEIR) I Committee (NAS/NRC, 1972) using mouse data has now been found to be inappropriate based on the discovery of a significant documented error in the historical control group that led to incorrect estimations of risk in the low dose zone. Correction of this error by the original scientists and the application of the adjusted/corrected data back to the BEIR I (NAS/NRC, 1972) report indicates that the data would have supported a threshold rather than the LNT model. Thus, cancer risk assessment has a poorly appreciated, complex and seriously flawed history that has undermined policies and practices of regulatory agencies in the U.S. and worldwide to the present time.

1. Introduction

While a role of the environment in affecting the occurrence of cancer has long been known (e.g., the occurrence of testicular cancer in chimney sweeps) (Pott, 1775), transitioning this recognition of concern into an experimental science proved to be difficult as seen in the series of failures to induce skin cancer in animal models during the early years of the 20th century. Finally, after many failed attempts, in 1918 Japanese researchers made the experimental breakthrough by the repeated administration of coal tars to the ears of rabbits to produce papillomas and carcinomas (Yamagiwa and Ichikawa, 1918). This seminal finding paved the way for experimental research to assess possible environmental causes of cancer.

In a similar manner, researchers early in the 20th century began to explore whether it was possible to induce mutations in plants and animals (Campos, 2015). While it took nearly three decades, Muller (1927a) reported that X-rays induced gene mutations in fruit flies, narrowly beating three independent teams of botanists who likewise reported inducing transgenerational phenotypic changes with X-rays/radium.[1] Muller's findings, like that of the Japanese cancer researchers, quickly transformed the field. For his discovery, Muller received the Nobel Prize in 1946. The current paper clarifies the historical foundations of the LNT single-hit dose-response model, its unique dependence upon the gene mutation interpretation of Muller in 1927, and how this interpretation became accepted by the scientific community and regulatory agencies. Most importantly, it will be shown that: (1) Muller's claim that the X-ray-induced transgenerational phenotypic changes were due to gene mutations was an interpretation lacking convincing evidence; (2) the induced transgenerational phenotypic changes

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[1] In January 1927, in the *Proceedings of the National Academy of Sciences* (Communicated January 14, 1927), Gager and Blakeslee (1927) were the first to report cases of gene mutations. Thus, Muller's July 1927 publication was the second to report the gene mutation phenomenon. Muller gained acclaim because he produced many mutations quickly. However, Gager and Blakeslee repeatedly reminded the field of their primacy. In his effort to secure scientific honors, Muller (1927a, 1928a) failed to cite the earlier work of Gager and Blakeslee (1927).

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were due to chromosomal deletions and aberrations, not Muller's proposed gene "point mutations"; (3) these developments undermine the historical and scientific foundations of the LNT single-hit model since it was built upon Muller's gene mutation interpretation (see Calabrese, 2017a for a significantly expanded analysis of this issue); (4) Muller and other leading U.S. radiation geneticists would collude in a series of articles to promote acceptance of the LNT, making deliberate deceptions and misrepresentations of the scientific record; (5) the deceptive practices would infiltrate and culminate in the actions of the U.S. NAS BEAR I Genetics Panel that recommended adoption of the LNT model by regulatory and public health agencies in 1956 (Anonymous, 1956) (See Calabrese, 2015a, b, c); (6) the mouse data used to provide the experimental basis for the subsequent reaffirmation of the LNT for cancer risk assessment was similarly problematic, that is, the BEIR I NAS/NRC (1972) Committee used a flawed historical control group that significantly overestimated risk in the low dose zone, yielding a linear dose response (see Calabrese 2017b, c); (7) use of a corrected historical control value yields a threshold rather than the linear dose response and; (8) this new assessment indicates that the LNT has been flawed from the start, yet national and international regulations have continued to be based upon it (Calabrese, 2015a, 2017d).

2. Muller and mutation

Hermann J. Muller, a radiation geneticist at the University of Texas/Austin, truly burst upon the national and international scene following his presentation at the 5th International Genetics Congress in Berlin during September 1927. His highly anticipated presentation convincingly demonstrated to an eager and massive grouping of geneticists from around the world that X-rays could induce transgenerational phenotypic changes in *Drosophila* perhaps providing a mechanism for evolution. Muller claimed that these changes were the result of induced gene mutation, tiny genomic changes, with Muller coining the term "point mutation". Muller not only claimed to be the first to ever artificially induce gene mutation, he produced copious numbers of them. Muller's presentation drew especially great anticipation since his article in the journal *Science,* published about three months earlier, only discussed some of the new findings, inexplicably failing to show any data. Thus, Muller, with a flair for the dramatic, disproved the doubters and set himself on a path that 19 years later would result in another trip to Europe, Stockholm, to receive the Nobel Prize in Biology and Medicine.

Muller's stunning results soon inspired: (1) numerous laboratories to redirect their research to the assessment of ionizing radiation induced mutations (Campos, 2015); (2) the creation of the Genetics Society of America (GSA) (1931) a few years later, bringing zoologists and botanists who were researching genetics under one integrated professional society; (3) the concept of a Proportionality Rule that describes the linear dose response for the ionizing radiation induced mutation response (Muller, 1930a); (4) the interdisciplinary collaboration of leading physicists and radiation geneticists to create the first mechanism-based cancer risk assessment model (LNT single-hit model) using target theory (Timofeeff-Ressovsky et al., 1935) and (5) the discovery of chemically induced mutations by Charlotte Auerbach in the 1940s (Auerbach and Robson, 1946). The reach of Muller was long and influential, inspiring the focus of Carson (1962) in her seminal book *Silent Spring,* that is normally given credit for starting the environmental revolution of the late 1960s and 1970s and continuing to the present. Muller wrote a powerfully supportive review of *Silent Spring* in the New York Herald Tribune published on the Sunday prior to the book's publication four days later (Muller, 1962). Thus, the X-ray induced "gene" mutation findings of Muller and his leadership over the next 40 years would profoundly affect the environmental movement and the fields of genetic toxicology, cancer risk assessment and numerous medical, radiation and public health practices.

There is therefore little question that Muller had a major influence on the scientific community and the general public, originating from the belief that he had actually demonstrated that X-rays produce gene mutations in the fruit fly. While the above summary highlights some of the societal impact of Muller, there are important parallel concerns with Muller's scientific legacy. In brief, Muller (1927a) made the critical assumption that the numerous X-ray induced transgenerational/heritable phenotypic changes that he reported were the result of induced gene mutations. Muller knew that transgenerational/heritable phenotypic changes via X-ray-induced chromosomal aberrations was not a significant finding (Muller, 1928b). This had been reported previously and would not affect an understanding of basic biological themes such as evolution and its potential mechanism. This was why Muller (1927a) entitled his groundbreaking July 22, 1927 article in *Science* "The Artificial Transmutation of the Gene".

3. Point mutations vs gene deletions

Within three months of his presenting these findings at the Genetics Congress[2] in Berlin (September, 1927) (Muller, 1928a), Muller (1927b) would publically express concerns that some might think that all he had done was to shoot large holes (i.e., deletions) throughout the genome with the high doses of X-rays used, noting that such concerns/questions were initiated by his longtime friend, close colleague, collaborator and confidante, Edgar Altenburg, a professor of genetics at Rice University. Within this anticipatory defensive context, at the December 1927 AAAS meeting at Nashville, Tennessee and in an April 1928 presentation to the U.S. National Academy of Sciences (NAS) Muller (1928b) tried to discount the possibility that his reported transgenerational phenotypic changes were due principally to heritable chromosome changes, suggesting as proof observations of reverse mutations (e.g., X-ray-induced reversible changes in eye color – red to white). Patterson and Muller (1930) would subsequently publish a massive 82-page paper supporting his argument. This was proof enough for Muller that X-rays induced small mutations in genes rather than vast and large deletions as suggested by Altenburg. Muller used apparent reverse mutation findings to preempt potential challenges to his gene mutation interpretation. Muller argued further that the assumed point mutations closely mimicked the type of gene mutation changes underlying the mechanism of evolution as might be seen with spontaneous gene mutations, spending much of the next

[2] The proceedings of this Congress contains Muller's paper, which included the data used for the basis of the Nobel Prize in 1946. The Congress proceedings paper of Muller had substantial limitations, being somewhat sloppily written, having three experiments, each with important weaknesses. It also lacked a methods section and provided no references, including no acknowledgement of the report by Gager and Blakeslee (1927) that preceded his *Science* paper (Muller 1927a) for the reporting of ionizing radiation induced gene mutation by six months. The general substandard quality of the manuscript made me wonder whether the Nobel Prize paper of Muller from the Congress proceedings had ever been peer-reviewed. A July 8, 1946 letter from Muller to Altenburg (Muller 1946a) revealed that the manuscript that he read at the Congress was exactly the same as published in the subsequent proceedings. Thus, it is virtually certain that the Nobel Prize research of Muller was not peer-reviewed (Calabrese, 2018). However, Muller had been acculturated into the need for and process of peer-review by Thomas Hunt Morgan, his Ph.D. advisor at Columbia University. Morgan helped to create the *Journal of Experimental Zoology* in 1903, which had a modern peer-review process from the start. In fact, Muller would publish several articles in this journal by 1920 (Harrison, 1945). Thus, Muller was part of a culture of peer-review as a necessity and expectation. Yet, he avoided it for the seminal findings for which he would be honored with the Nobel Prize.

Table 1
Stadler's challenge to Muller. quotes from Stadler (1932, 1954).

Stadler (1932). **Proc 6th Intern Cong Genet 1:274–294**
"To state that an induced variation is a gene mutation is not to explain it but merely to label it."
Page 274-275
"We do not demonstrate that a chemical change has occurred; we simply infer, since no mechanical explanation can be found, that the variation must be due to this invisible mechanism."
Page 275
"We may define mutation as a transmissible change in the gene. But we identify mutation by experimental tests, and these tests are not such as to establish conclusively, in specific instances, that a change within the gene has occurred."
Page 275
"In effect, any Mendelizing variation which cannot be shown to be due to a change involving more than one gene is a mutation."
Page 275
"… the occurrence of reversion is not proof that the original mutation could not have been due even to a deficiency."
Page 292
Stadler (1954). **Science 120(3125):811–819**
"But there was no test to identify mutations due to a change within the gene; it was simply inferred that the mutants that could not be identified as the result of specific mechanical causes were, in fact, due to gene mutation in the ideal sense (11)."
Page 813

40 years in this quest for a mechanism for evolution.

While these findings would temporarily satisfy the questioning and doubtful Altenburg and others, supporting the X-ray-induced point mutation interpretation, this concern would not go away but actually grew principally due to the persistent questioning and new research insights of the plant radiation geneticist Stadler (1932, 1954), Muller's most staunch, yet objective, respected, competitor and critic (Calabrese, 2017e).

4. Stadler challenges gene mutation interpretation

4.1. Cytogenetic advances

At the time of his groundbreaking mutation publication, Muller's (1927a) research suffered from an acknowledged limited cytogenetic evaluative capacity which prevented fine structure chromosome resolution ("… Drosophila cytology is elusive in its finer details" – page 721, Muller, 1928b), and thereby a reduced capacity to detect chromosomal deletions. Markedly improved chromosome cytogenetic resolution capacity was developed by the Cornell plant cytogeneticist, Barbara McClintock, in the prophase stage of meiosis with maize (McClintock, 1929). Two years later she would apply this novel technique to Stadler's X-ray treated corn in the summer of 1931. It revealed that what was once believed to be X-ray induced "gene" mutagens were sizeable chromosomal deletions. While these findings would force Stadler to re-evaluate and challenge his previously published X-ray induced "gene" mutational findings in barley (Stadler, 1928), they would make him raise the question of whether Muller's gene mutation interpretation with fruit flies was also incorrect. While Stadler would cautiously share his new doubts with the research community in several 1931 publications (Stadler, 1931a,b) and in private correspondence with leaders in plant genetics research like Karl Sax (Stadler, 1931c), Stadler (1932) would finally challenge the Muller gene mutation interpretation in a very public manner during his Plenary Address at the Sixth International Genetics Congress at Cornell University in the presence of Muller (Table 1).

From this opening round of public debate, Muller and Stadler would challenge each other over whether Muller had induced true gene mutations in his highly publicized high dose X-ray experiments. This research-generated debate would continue until the death of Stadler in 1954 (Stadler, 1954), involving numerous radiation geneticists trying to resolve this fundamental question (Calabrese, 2017a ; Lefevre, 1950; Voss and Falk, 1973). Copies of Stadler's research grants and interim reports to the U.S. NRC that describe his progressive series of multi-year research plans, research methods and experimental developments reveal a focused, high quality and productive research activity with numerous publications that challenged Muller's gene mutation interpretation (State Historical Society of Missouri, Stadler Papers). An extensive review of Muller's gene mutation hypothesis along with supportive and non-supportive literature findings is provided in the dissertation of Lefevre (1949), Stadler's Ph.D. student. In this instance Stadler would show his flair for excitement and self-confidence by directing his student (with the assistance of *Drosophila* specialists and with some formal assistance of Muller) to challenge Muller's gene mutation interpretation with Muller's own biological model. In this extensive study, Lefevre (1949, 1950) found no support for Muller's gene mutation interpretation based on reverse mutations.

To the outside viewer it suggested two outstanding scientists locked in a scientific dispute, with Muller compelled to protect his reputation, future, and legacy. These longstanding competitive research activities of Stadler and Muller were much like a high-level chess match in which all moves (e.g., research publications, professional society presentations) contributed important information. By the late 1930s and/or early 1940s Stadler and others had methodically shown that Muller lacked the needed proof for his gene mutation assertions (Calabrese 2017a). The subsequent development of improved cytogenetic staining for *Drosophila* chromosomes by Painter (1934) would reveal that the use of the very high X-ray doses and dose rates similar to Muller's key findings, like that of Stadler's research with barley and corn, produced copious chromosome aberrations including a high proportion of deletions, along with few, if any, possible gene (i.e., "point") mutations.

Muller's use of the reverse mutation concept was also found unconvincing as multiple papers showed several mechanisms (e.g., position effect) by which reverse transgenerational phenotypic traits could occur without any change in the gene[3] (Bedford and Dewey, 2002; Lefevre, 1950). Thus, every move that Muller made was seemingly countered by the research of Stadler or spin-off ideas his research had inspired. Furthermore, Stadler's and related publications would yield insights that were incrementally more definite, insightful and over time, more convincing than Muller's, much like forcing Muller into a corner.

[3] See the discussion from Lefevre (1949) dissertation for a detailed assessment of reverse mutation and position effect as related to Muller's gene mutation interpretation.

4.2. McClintock's new X-Ray induced mutation mechanisms

Complementing the Stadler gene mutation criticism were new mechanistic findings of Barbara McClintock's study with her breakfusion-bridge-cycle model of X-ray induced genetic damage (Comfort, 1997, 2001) which then led to strikingly new and transformative transposable element induced mutational insights. Her novel mutable gene concept was particularly attractive to Muller's University of Indiana Colleague and future Nobel Laureate Salvadore Luria (McClintock, 1948; Muller, 1948) as well as Muller's closest colleague and friend, Edgar Altenburg. In the case of Altenburg, he would devote much effort to understand the scientific foundations of McClintock's findings and its role in spontaneous and exogenously induced mutations. The McClintock discovery had very broad biological and biomedical implications. However, it would also take Altenburg back to his 1927 suggestion that Muller had been blasting large holes in *Drosophila* chromosomes by high dose X-ray treatments. Extensive and detailed correspondence between Altenburg and McClintock in the early 1950s reveal the significance that Altenburg placed on her findings and how it stripped much significance from Muller's gene mutation model.

Altenburg would repeatedly encourage Muller to study and assimilate the findings of McClintock (Altenburg, 1952a,b,c, 1953a). Altenburg would provide Muller with a 25-page manuscript on McClintock's transpositional element concept and its relationship to X-ray-induced mutations (Altenburg, 1953a,b). However, Muller (1953) claimed he was too busy to read the manuscript while also being dismissive, claiming that no one could understand the "jumping gene" (i.e., transposable element) concept (Altenburg, 1953a; Muller, 1953), a common technique to distract attention from a perceived competitor while protecting one's legacy. However, Muller was not successful in drawing Altenburg back into his sphere of dominance, but rather, Altenburg (1957) would devote an entire chapter to McClintock's mutable gene (transposable element) concept in the second edition of his Genetics textbook. Altenburg, an excellent writer, made the challenging writings of McClintock readily understandable for geneticists and interested biologists. In this chapter, he claimed that a substantial proportion of high dose X-ray-induced mutations are due to chromosome deletions/rearrangements rather than Muller's "point mutations" and that such genetic damage was likely mediated by transposable elements (Table 2). The profound intellectual transformation of Altenburg to the McClintock model was a significant sign that the era of Muller was waning. During this same period Russell et al. (1958) would publish his highly influential dose rate challenge to Muller. With multiple scientific challenges facing him, Muller would transform his laboratory into one that would try to extend the findings of Russell into *Drosophila* rather than exploring the dramatic and more complex new ideas of McClintock. Within a month of the Russell et al. (1958) publication Muller was exploring dose rate. In the six years of redirected and intense research on this topic Muller's laboratory was plagued with a series of apparent false starts and a generally ambivalent finish. Thus, the final years of Muller's laboratory productivity were weak, perhaps a function of aging and health deterioration (Calabrese, 2017b).

Of further importance, as suggested above, was the discovery by McClintock (1950, 1951, 1953) that transposable chromosomal elements affected the occurrence of both spontaneous and exogenously induced mutations, including mutations induced by ionizing radiation and chemical mutagens such as mustard gas as used by Auerbach with *Drosophila*. Subsequent findings indicate that the early X-ray-induced transgenerational phenotypic findings of Muller (1927a) and Timofeeff-Ressovsky et al. (1935) were likely the result of X-ray activation of McClintock's transposition element process which induced massive chromosomal damage, such as small to massive deletions and other types of chromosomal aberrations (Ratner et al., 2001). These collective developments served to strongly reinforce the fundamental criticisms by Stadler of Muller's gene mutation interpretation, while supporting the McClintock transpositional element mediated mutation model.

5. LNT single-hit model, dose rate and the Manhattan Project

While Muller was in serious dispute with Stadler throughout the 1930s for his gene mutation interpretation, there was nonetheless a worldwide mesmerizing euphoria of Muller's mutation discovery (see Campos, 2015), one element of which resulted in a unique interdisciplinary collaboration between leading physicists and radiation geneticists as led by Delbruck and Timofeeff-Ressovsky, respectively. From the mid-1930s their research provided the LNT model with a hypothetical mechanistic basis via the use of target theory (Timofeeff-Ressovsky et al., 1935). This concept was then transformed into a biostatistical model (i.e., LNT Single-Hit model) which revealed that the shape of the dose response in the low dose zone was largely a function of the assumed number of target hits required to produce a gene mutation (Zimmer, 1941). The fewer the hits needed to produce gene mutations the closer the linear dose response for gene mutation was approached.

Since his X-ray induced gene mutation interpretation had experienced serious scientific challenges and setbacks through the 1930s, Muller needed another approach to redirect the mutation debate to restore support for his gene mutation interpretation and low dose linearity model and their integrative linkage. Muller's idea was an intriguing one that served, at least in part, both purposes, with a new application of a "dose x time = constant" experiment as seen in the Bunsen-Roscoe Law or with Haber's Law. Over the decade of the 1930s using his Proportionality Rule Muller had asserted that X-ray induced mutation damage was progressively cumulative and could not be repaired. As a result of these characteristics the damage should be predicted by the total dose, not by dose rate. If the total dose hypothesis were true, then the dose response for mutation should be linear at low dose, all the way down to a single ionization. Muller would test this idea in a

Table 2
Quote from Altenburg E. (1957). Genetics. Holt, Rhinehart and Winston, New York, NY.

Are all mutations due to chromosomal rearrangements?

… The possibility, therefore, arises that mutations might often be due to invisibly small deletions, rather than to an actual change in a gene–a change that we refer to as a "point" mutation. We cannot be sure, for example, that the yellow body-color mutant in Drosophila has a "yellow" gene in place of a "gray" (the normal allele of yellow). For all we know, the body color of the mutant might be yellow because the normal allele has been deleted. In fact, yellow mutants of independent origin differ somewhat in the intensity of their yellow pigmentation and, in the case of certain "extreme" yellow, it is very likely that the mutation is due to a very small deletion. In general, there is no way of telling from the outward appearance of a mutant what sort of genetic change caused the mutation. Inversions and duplications are also known to have mutant effects–inversion because of a "position" effect, and duplications either for the same reason or because of the genic unbalance they cause.

Now deletions, inversions, and duplications are all the results of chromosome breakage and rearrangement. Therefore, in the present state of our knowledge, all mutations might conceivable be due to such rearrangement and not to any actual alteration in the gene itself."

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dissertation by Ray-Chaudhuri at the University of Edinburgh using X-rays and mature spermatozoa of *Drosophila.* The findings of this dissertation matched up very well with Muller's predictions supporting the total dose/LNT hypothesis. These results provided support at a critical stage to Muller's gene mutation theory. In fact, during Muller's (1946b) Nobel Prize lecture, he cited the research of Ray-Chaudhuri (1939, 1944).

The problem with this newly adopted dose-rate vs total dose strategy to defend the gene mutation interpretation was that the study of Ray-Chaudhuri had a series of important design and execution limitations, requiring corrections, improvements and replication (Calabrese, 2011, 2017a). In fact, there were so many limitations (e.g., limited sample size, quality control issues, changing animal models during the experiment, lacked documentation of essential methods, major statistical errors, failure to collect critical information), it suggested that the normally critical Muller might have lowered his academic standards in order to provide support to his sagging gene mutation interpretation.

The Ray-Chaudhuri dissertation in some ways served as a pilot study for the far more substantial efforts lead by Curt Stern, University of Rochester, during the Manhattan Project starting in 1943. Stern would initially direct an acute study by Warren Spencer, a highly regarded *Drosophila* specialist who was on leave from his faculty position at the College of Wooster (Ohio, USA). While the Spencer part of the study went as planned, a significant problem for Muller, a paid consultant on this project, occurred when the data from the low dose chronic genetic toxicity study, led by Ernst Caspari, revealed a significant dose-rate effect and a threshold for mutagenicity, contradicting the Ray-Chaudhuri (1939, 1944) conclusions. These findings by themselves had the potential to land a severe blow to the LNT single-hit theory. These findings were just preceded by 15 years of research lead by Stadler that successfully weakened the plausibility of Muller's gene mutation interpretation and now along with new mechanistic insights of McClintock on X-ray-induced mutations. This situation became sufficiently threatening to the policy goals of key leaders of the radiation genetics community such as Muller and Stern who strongly advocated the adoption of the LNT single-hit model. What happened next to the field of radiation genetics could not have been predicted.

The above set of events, which collectively placed the LNT single-hit model at risk, set the stage for what is referred to as "LNTgate" (Calabrese, 2015c, 2016, 2017d), a series of obfuscations, deceptions, and misrepresentations of the scientific record all designed to ensure that the LNT single-hit theory would replace the threshold model for cancer risk assessment. This sequence of events has been reported in detail over the past seven years via a series of progressively informed historical discoveries (Calabrese 2011, 2013, 2015a,b,d, 2016, 2017b,c,e).

The LNTgate actions were mediated via the leadership of Curt Stern and Hermann J. Muller during the second half of 1946, continuing for more than a decade. These efforts lead to the actions of the NAS BEAR I Genetics Panel to sustain and integrate these successful manipulations into the scientific record and government regulatory policies. These ideologically directed activities would be guided by the academic "offspring" of Muller and Stern, such as Jim Crow, Bentley Glass, and other esteemed leaders of the radiation genetics community. The process became fully successful when the next generation uncritically accepted as scientific fact, the mistakes, deceptions, and misrepresentations handed down by the icons of the field. This is, in fact, the domain where key features of the fields of regulatory policy and cancer risk assessment are today.

6. Saving the hit model

The LNTgate process had an unexpected spontaneous origin. It began when Ernst Caspari informed Stern, his supervisor, that his dose-rate findings contradicted those of Ray-Chaudhuri (total dose). As noted above, the observation of a threshold response for mutation was not only not expected but, as it turned out, actually "not permitted", resulting in Stern refusing to accept the Caspari findings (Calabrese, 2011). Giving the appearance of objectivity, Stern blamed Caspari's threshold "discovery" on the use of a faulty control group that he insisted was aberrantly high. Stern did not provide any evidence to support this critical judgment. However, Stern was aware of earlier publications with control group responses for this model that supported the Caspari interpretation based on prior correspondence (Stern, 1938), but he either forgot this or refused to share it. Regardless, the Caspari year-long study had reached an impasse with the Stern judgement, a major crisis.

Showing some degree of independence, Caspari would not accept Stern's judgement that his control group displayed aberrantly high values. He dove into the literature and found a series of papers, which explicitly addressed the control group question, with all supporting his position (Calabrese, 2011). When Caspari assembled these findings, Stern withdrew the control group criticism. During this period, Caspari informed M. Demerec, head of the Genetics Department for the Carnegie Institute, of his mutation threshold dose-response findings and the problems it was creating. This prompted the influential Demerec to write Caspari asking "what can be done to save the hit model" (Caspari, 1947). This statement seemed to express what Stern and Caspari might well have been thinking. With the control group issue no longer a viable means to discredit the Caspari findings, the "save the hit model" strategy of Stern became publishing the manuscript, but framing the discussion to prevent the data from being accepted/used, while still showing competence of the research team, thereby securing the LNT/Ray-Chaudhuri framework. This seemed like the best possible outcome for Stern and Caspari.

The strategy adopted was to assert that the Caspari data could not be accepted or used until it could be determined why he obtained a threshold in the chronic study, while Warren Spencer obtained an apparent linear dose response a year earlier in an acute study with the same fruit fly model while working under Stern. This created a false standard, as the two studies had more than 25 methodological differences; there would be no possible practical means to determine why the studies differed (Calabrese, 2011). The only way that this highly nuanced perspective (i.e., the recommendation not to use the Caspari findings until it resolved the differences with the Spencer study) could have been published was if Stern was the journal (i.e., *Genetics*) editor and there was no peer-review, and this was most likely just what happened (Calabrese, 2011)! In fact, even though Stern proposed this unrealistic situation, no one, of course, ever explicitly accepted this challenge over the next 70 years, including himself, Caspari or Muller. It was a tactical move in the broader strategy to "save the hit model". So Caspari and Stern prepared this manuscript with this obfuscation and sent it to Muller for review on November 6, 1946 with Muller answering on November 12, 1946 (Calabrese, 2011). Muller indicated that he was upset that Caspari found a threshold since this could be a serious problem for LNT acceptance and Stern needed to replicate the study (not to explain why the Caspari study differed from the Spencer study as emphasized in the discussion as this was impossible to do). Thus, Muller was fully informed that the strongest study (i.e., chronic exposure to ionizing radiation) to date (i.e., Caspari experiment) showed a threshold for mutation one month prior to the Nobel Prize lecture of December 12, 1946 (Muller, 1946b). The linearity supporting acute exposure experiment of Spencer had a series of methodological limitations (e.g. inadequate temperature control, inexplicably combining different dose-rate groups with the same total dose, inadequate X-ray machine

calibration) that affected the reliability of the low dose study results (Calabrese, 2011). Yet Stern, Muller and others never identified such limitations, even in Muller's detailed review of this research (Muller, 1946c). These criticisms of the Spencer study (Spencer and Stern, 1948), were first reported more than six decades later (Calabrese, 2011).

In his crucial moment of making scientific history, Muller (1946d) deceived the world with his statement that there is no possibility for a threshold response ("no escape from the conclusion that there is no threshold") to ionizing radiation induced mutation and that risks needed to be assessed via the LNT single-hit model (Nobel Prize lecture, Dec 12, Muller, 1946b). Muller made this statement having seen the Caspari study and not offering any technical or other criticism (Muller, 1946e). Thus, a type of collusion began to take shape between Stern, Caspari, and Muller to do as Demerec urged. In a follow up letter to Stern (Muller, 1947) Muller supported publishing of the Caspari paper since there were enough caveats (i.e., obfuscations) and restrictions to make the paper non-threatening to the LNT acceptance.

In 1949 Stern manipulated or colluded with the leadership of *Science* to ensure LNT would be strongly promoted (Uphoff and Stern, 1949). This was similar to how Muller (1927a) was treated two decades earlier showing no data on his Nobel Prize experiments nor seven years later (1956) in the journal's dealings with the fraudulent NAS BEAR I Genetics Panel publication (Anonymous, 1956). Here is how it happened. While the Stern research team hoped that the follow-up replication studies would put an end to the Caspari study-created crisis, it simply created a new one. The first replication experiment (i.e., led by a new master's student Delta Uphoff) was unacceptable to Stern, this time because the control group was aberrantly low. The control group's values were so outside the norm that Stern had to check with Muller who strongly affirmed (in writing) that the Caspari control group values were appropriate while rejecting Uphoff's (see Calabrese, 2015a,b for the letter correspondence documentation). The troubled Stern would go so far as to blame her for having been biased [i.e., "may reflect a personal bias of the experimenter" (Uphoff and Stern, 1947)], with this leading to the low control group values (Calabrese, 2015b). This phrase was stated in the Discussion of the manuscript that was sent to the Atomic Energy Commission (AEC) (and which was immediately classified). This amazing statement should have raised a plethora of questions by the scientific community for Stern and Uphoff but it was hidden from view. For example, how did the alleged bias start? How long did it continue? How might it have affected other experiments, other team members and others, the data analysis and manuscript write up? A follow-up experiment by Uphoff also suffered the same fate with an aberrant control group value. This situation was turning into a professional disaster. So the question was not just what could be done to save the hit model but also the reputations of Stern, Caspari, and Uphoff and other members of the Manhattan Project at the University of Rochester. Stern would again show his creativity (or deviousness). Since essentially no one had read the classified material discounting the results and blaming Uphoff and her alleged biases leading to the uninterpretable findings, Stern used his contacts with the journal *Science* to publish a one page technical note of the experiments of Spencer, Caspari, and Uphoff. In this limited technical note, Stern showed no transparency, neglecting to inform the reader that he had found the low control studies of Uphoff unacceptable less than a year before and now he concluded these findings were fully acceptable. No criticisms of the Spencer study were mentioned despite its obvious significant limitations (Calabrese, 2011). Stern also reintroduced criticism of the Caspari study without evidence. In this mini-meta analysis, Stern restored the LNT model, literally "saving the hit model". In the final paragraph, Uphoff and Stern (1949) promised the *Science* readers to provide a comprehensive paper with methods, materials, missing data and other relevant information. Yet, they never did.

Muller and Stern actually promoted the discredited findings of Uphoff while marginalizing the Caspari paper. More specifically, at the time Stern asked Muller to help resolve the Caspari-Uphoff control group issue, Muller had been studying spontaneous mutations in the fruit fly in his ongoing disputes with Stadler concerning whether he induced gene mutation (Calabrese, 2017a). Thus, Muller was sitting on a treasure trove of control group spontaneous mutation data. As noted earlier, in multiple letters to Stern, Muller unequivocally sided with the Caspari findings while rejecting those of Uphoff (Calabrese, 2015a, b). With this as prologue we now fast forward a few years and find Muller (1950, 1954a) rejecting the Caspari study based on this control group being abnormally high, contradicting the literature, his own data/publications and his multiple letters to Stern, while never providing proof for his statements. The evidence reveals Muller dishonestly strove to discredit the Caspari study, and preserve LNT, while protecting himself from being accused of lying during his Nobel Prize Lecture. The 1950 paper of Muller was just preceded and perhaps inspired by an article by MIT's Robley P. Evans in *Science* (Evans, 1949) criticizing the LNT model, using the threshold findings of Caspari (Caspari and Stern, 1948). After Muller read the Evans article, he wrote to Stern criticizing the paper of Evans, blaming the criticism of LNT on the findings of Caspari (Muller, 1949). Muller urged Stern to contact Evans and discredit the Caspari work. No evidence has yet been found that Stern communicated with Evans on this matter.[4] However, shortly after that letter exchange with Stern, Muller published his false criticisms of Caspari's control group. Furthermore, on August 10, 1949 Altenburg (1949) wrote Muller about the Caspari threshold findings, acknowledged the reliability of the findings yet in search of a mechanistic explanation. Apparently, Muller had thought that Stern and his efforts had fully neutralized the threshold findings of Caspari, but this was not apparently the case.

7. LNT and the NAS BEAR Genetics panel

The next stage of the LNT story would take place with the NAS BEAR I Genetics Panel which first convened in early November, 1955 at Princeton University. As Muller had learned from many earlier frustrations, success within Advisory Committees is highly dependent upon who is selected. In the case of the BEAR I Genetics Panel, the answer was clear from the start, as the Panelist Tracy M. Sonneborn, a Muller colleague at the University of Indiana, read their radiation geneticist mantra into the recorded proceedings with no debate or dispute. All firmly believed that mutational damage was cumulative and irreversible with the dose response being linear down to a single ionization. Multiple notable radiation geneticists at that time were not advocates of the Muller perspective but they were either directed to other NAS BEAR I panels such as was the case of Ralph Singleton (agriculture panel) or not selected as was the case of McClintock. In retrospect, the deck was stacked along with an administrative leadership that would keep the panel focused on the big picture goals of the Rockefeller Foundation (RF) that both funded and directed the Panel while in

[4] The papers of Evans have been preserved at MIT. However, they have yet to be organized for scholarly use and it is unknown when they will be available. Of interest would be whether Stern ever sent Evans the letter Muller suggested. A check of the Stern files at APS revealed no record of a letter of Stern to Evans.

the administrative structure of the NAS.[5]

Despite the endorsement of the LNT single-hit model by leading research geneticists and physicists it was widely recognized that the fundamental data to support the LNT single-hit model was inappropriate. The model was dependent on point mutations, not large deletions, gene rearrangements, and other gross aberrations. In his final and masterful paper, published posthumously in *Science,* Stadler (1954) would illustrate how Muller's mutational data could not provide a credible biological basis for the LNT single-hit model. Despite the prominence of the journal *Science,* the stature of Stadler and the timeliness of the article, this criticism of the LNT single-hit model was never discussed by the NAS BEAR I Genetics Panel. In fact, not once in the transcribed pages of the Panel meetings were Stadler or McClintock's research on gene mutation ever mentioned.

At the second meeting of the Panel (in Chicago), Warren Weaver, Chair of the Genetics Panel and Director of Research for RF, tried to entice members of the Panel with RF funding if the Panel Report would support RF initiatives (e.g., LNT). Weaver indicated he would "try to get a very substantial amount of free support for genetics if at the end of this thing we have a case for it. I am not talking about a few thousand dollars, gentlemen, I am talking about a substantial amount of flexible and free support to geneticists" (Anonymous, 1956 - BEAR I Genetics Panel Transcript, February 5, 1956, page 35).[6] Weaver would further state that "There may be some very practical results — and here is the dangerous remark — don't misunderstand me, we are all just conspirators here together". The Weaver remarks obviously link the Panel deliverables to RF funding for geneticists, including those sitting in the room. Further discussions of the Panel during the February 5/6, 1956 meeting would reveal that to be successful in the eyes of Weaver, the Panel would need to present strong agreement/consensus for the estimation of genetic risks to the U.S. population assuming a linear dose response. However, an unanticipated problem came about 4–5 weeks later (March 1956) when the Panel members displayed multiple profound disagreements: they argued about whether it was possible to even estimate population risks, how to derive the estimations, how any derived estimates of damage related to true (real) risks, and what the risks actually were. With this confusion, the highly divergent results of the independent risk estimates that were carried out over 10 generations were seen as an unusable scientific "mess", such that Panel member, Jim Crow, would claim that no one would believe the policy recommendations of the Panelists since they could not agree amongst themselves. In a March 29, 1956 Letter to Warren Weaver, Crow (1956) stated that:

> "The limits presented on our estimates of genetic damage are so wide that the readers will, I believe, not have any confidence in them at all."

Lacking authority to do so, Crow, who was to organize the technical reports for Panel discussion, decided to arbitrarily drop the three lowest estimates of risk; by so doing he markedly reduced the variation, giving the false impression of more expert Panelist agreement than was the case. Even after dropping the three, there remained considerable uncertainty, being still too large to show to the scientific community and general public. One might have thought that the Panelists whose estimates were dropped would have strongly fought to have them retained. There is some evidence of significant disputes between Demerec and Muller on this matter based on a letter from Muller to Beadle in August 1956 (Muller, 1956) indicating that Muller did not want to be part of writing a scientific justification for their LNT recommendation. He indicated that he was already too frustrated with his debates with Demerec over the value of *Drosophila* versus bacteria in their risk estimations and did not want to air the so-called dirty laundry in public. He had thought that they had agreed to disagree. However, the available record does not reflect the details of this matter, as it likely occurred in the March 1956 meeting once Crow received the detailed write-ups for which there was no meeting transcript. Muller also noted his unresolved debates with the human geneticists of the Panel further confirming his unwillingness to seek a consensus report justifying their scientific recommendations. This lack of blatant open dispute/rebellion suggests that the group consensus was to present a united front that Weaver had earlier pointed out was necessary, perhaps using this funding carrot to achieve agreement. However, panelist James Neel, who refused to provide an estimate, strongly disputed the legitimacy of the proposed genetic damage estimation activity (Neel 1956 a, b). He argued that any consensus agreement was an illusion based on a self-fulfilling decision to reduce variability by forcing the use of similar models with similar process assumptions. Even with Crow stacking the deck, the risk estimates were still too variable, leading Weaver and Crow to encourage/coerce the Panel not to show their range of estimates to the outside world since it would destroy their credibility. The Panel would keep it private. There was no "minority" report nor leaking to the media. The "control" of the group was evident as those such as Demerec and Neel would not publically challenge the group view despite fundamental differences.

8. The NAS BEAR I Committee Genetics panel *science* publication story

The BEAR I Genetics Panel published a major article in *Science* (Anonymous, 1956) on their findings and recommendations. This paper had three significant misrepresentations of the Panel's research record. The first involved the Panel stating that the 12 geneticists of the Panel were invited to provide estimates of genetic risks for the entire U.S. population exposed to a certain dose of ionizing radiation, but only six accepted the challenge and provided the write up. Yet, nine of the 12 actually did, with Crow dropping three estimates as noted earlier.[7] In fact, I had obtained the nine detailed assessments. Second, the *Science* paper indicated that the minimum and maximum estimates of genetic damage range was ±10 or 100 fold. However, the actual average minimum-maximum damage range was about 750 fold. Third, the Genetics Panel *Science* paper neglected to report that three Panelists refused to participate, principally because they believed that such estimates could not be reliably done.

A written record exists that documents that the NAS BEAR I Committee Genetics Panel voted not to share their data with the scientific community and others (Calabrese, 2015a). After the Panel's publication in *Science* it was specifically challenged by

[5] Dr. Detlev Bronk was President of the Rockefeller Institute for Medical Research (later named Rockefeller University) and President of the National Academy of Sciences (NAS) during this time, confusing the roles of the Rockefeller Foundation and the NAS in this BEAR I Genetics Panel process.

[6] The concept of self-interest science (i.e., exaggerating fears of radiation to enhance research funding) of some members of the BEAR I Genetics Panel was documented via uncovered correspondence (Calabrese, 2014).

[7] It is interesting to note that the three estimates that Crow dropped (i.e., Demerec, Wright, and Kauffmann) were the areas with which Muller (1956) acknowledged serious issues in his letter to Beadle. Since Muller and Crow had a very close professional and personal relationship, it is tempting to speculate that Muller may have influenced Crow to drop the three estimates. This perspective is attractive since it is doubtful that Crow, one of the youngest members of the Panel, would have acted so precipitously without significant senior backup support. This would have been especially the case if he were doing Muller's bidding. Further documentation will be need to evaluate this hypothesis.

several leading U.S. academic researchers to share the scientific basis for the report and again the Panel formally voted not to do this as well (Calabrese, 2015a). Of significance is that the Panel had never even written such a scientific basis for their LNT recommendation. This should be seen as failed leadership by the NAS President Detlev Bronk and Chairman Weaver, a sign of scientific arrogance, or a type of defense posture. The Panel vote during August, 1956 not to provide a scientific basis for this major recommendation to adopt the LNT single-hit model for risk assessment was then passed on to NAS president Bronk, who accepted their decision. The NAS administration was therefore fully complicit in this process (Calabrese, 2015a).

The NAS BEAR I Committee Genetics Panel therefore falsified the research record, creating a significant cover up. Providing a detailed write up of their process would have revealed the deliberate misrepresentations of the research record. It would also have revealed a highly embarrassing fundamental lack of competence by such prestigious leading geneticists who simply could not properly address this risk estimation problem, as highlighted by Crow's amateurish and incorrect response (Calabrese, 2015a, b). It would also have taken considerable effort to complete such a report, something that should have been done during the activity of the Panel.

The goal of the NAS BEAR I Genetics Panel was to recommend adoption of the LNT in the U.S. and worldwide. Within about two years the LNT recommendation was adopted by national and international advisory committees, eventually becoming worldwide policy for cancer risk assessment. Thus, the most significant policy recommendation for cancer risk assessment lacked a written scientific basis. Most striking is that the Panel, including Muller, and the president of the NAS made this decision. It is ironic that the U.S. National Committee for Radiation Protection and Management (NCRPM) adopted LNT for cancer risk assessment in December 1958, based on the documentation-lacking NAS BEAR I Genetics Panel report days prior to the publication of Russell et al. (1958) demonstrating the existence of dose rate for ionizing radiation in the mouse model. Apparently, the status of the Genetics Panel and the NAS was so high that no documentation was needed for governments worldwide to adopt their transformative recommendations. As recently noted by Calabrese (2017a), **s**even of the members of the highly prestigious NAS BEAR I Committee Genetics Panel had no research experience with the effects of ionizing radiation on mutations. In fact, Crow, who had never published on the topic, made the decision on which estimates to retain. It is also ironic that Demerec and Neel, who were amongst the most appropriately experienced, did not contribute to the radiation risk estimates. Thus, the vision that the country was being guided by the most prestigious and experienced grouping of geneticists on the matter of radiation induced genetic damage was yet another myth to enhance acceptance of the LNT.

9. LNT, William Russell and the dose rate challenge

Within 2.5 years of the June, 1956 NAS BEAR I Genetics Panel *Science* publication, another *Science* publication would challenge one of the basic tenets of the BEAR I, Genetics Panel's recommendations. The paper was by William L. Russell of the Oakridge National Laboratory, also a member of the NAS BEAR I Genetics Panel. During June and July of 1958 Russell's group (Calabrese, 2017a, b) made a major discovery, that dose-rate, not total dose, was the key predictor of ionizing radiation induced mutation for mouse spermatogonia and oocytes. The Oak Ridge group kept this breakthrough discovery quiet, not presenting the findings at the International Genetics Congress in Burlington, VT in the middle of August. Russell did share the findings with a New York Times reporter during the Conference who wrote an article (Schmeck, 1958). The breakthrough paper was published on December 19, 1958 and with it was a timed release front page story by a Pulitzer Prize journalist (i.e., Nate Finney) for the Buffalo Evening News who specialized in atomic energy (note that the NY Times was then on strike) (Finney, 1958; Russell et al., 1958).

The Russell research revealed that damage from ionizing radiation was not cumulative, but reversible and had the potential to yield a threshold, suggesting the existence of DNA repair, a possibility that Altenburg shared with Muller soon after publication of the paper (Altenburg, 1958). In effect, Russell had discredited the mantra of the radiation geneticist community, creating a major problem. His strategy would be to promote the acceptance of his research while, at the same time, creating an impression of adhering to the radiation geneticist mantra. Russell did not want to be ostracized and marginalized from his field by his ideological radiation geneticist peers. Russell had seen the dominating and uncompromising personality of Muller in action many times while a member of the Genetics Panel (Crow, 1995) and with James Neel, whose paper Muller tried to prevent from being presented at an international genetics conference during the summer of 1956. In fact, Russell's supervisor, Alexander Hollaender, negotiated a follow up "reconciliation" meeting between Neel and Muller (January 1957) at Oakridge, essentially in the presence of Russell (Neel, 1956a, b; Neel, 1957a, b; Novitski, 1956) (Table 3). Thus, Russell knew only too well how hostile Muller could get if one deviated from the radiation genetics ideology. Russell would walk this dose-response tight rope until after the death of Muller in April 1967, after which Russell would unleash a profound set of criticisms of the radiation genetics mantra and the LNT concept (Russell, 1969, 1973).

Despite these findings, their massive expansion by Russell and their powerful challenge to the LNT single-hit recommendation of BEAR I, it would take some 14 years before a new powerful NAS Committee, now called the BEIR I Committee with the Genetics Subcommittee being chaired by Muller's protégé Jim Crow to reconsider the LNT recommendations of BEAR I. During this process the BEIR I Genetics Subcommittee re-examined the BEAR I report and made two clear initial determinations (Calabrese 2017a,b). The first was that the risk assessment recommendation of BEAR I (Anonymous, 1956) needed to be based on a mammalian model rather than on a fruit fly. The second factor was their acknowledgement that the BEAR I Genetics Panel (Anonymous, 1956) made a mistake in denying dose-rate. The recognition that dose-rate rather than the total dose best predicted mutation damage, meant that the radiation geneticist belief of cumulative and irreversible damage with each dose would be replaced. This finding also meant that linearity may be at risk of being replaced by the threshold dose response, reversing the 1956 position of the BEAR I Genetics Panel. However, despite these new challenges to the LNT model, the Genetics Subcommittee still had a strong disciple of Muller in charge with Crow[8] and would find some rationale to keep the linear dose response model as the default if possible.

Even though the findings of Russell revealed a true threshold for oocytes, the same could not be said for spermatogonia, where the dose-rate related damage, which was mediated by DNA repair, was only able to reduce total mutations induced acutely by 70% and not the 100% needed to achieve a threshold (Figure 1). The BEIR I Genetics Subcommittee therefore concluded that even though it was now known that an ionizing radiation threshold existed for mouse

[8] Toward the end of his career, Crow would acknowledge that Muller and he were amongst the strongest advocates of LNT and that they were too extreme in their views and actions (Crow, 1995).

Table 3
Quote from Neel (1959) letter to Beadle, September 14, 1959.

"There is no mind in science today for whose brilliance I have greater respect than that of Dr. Muller. In the first upsurge of concern concerning the effects of the increasing exposure of the human species to the radiation which followed World War II, it was Muller who had thought most about the problem, and Muller whose point of view dominated the picture. When Jack Schull and I pulled together our monograph on the findings in Japan, we felt obligated to try to fit these findings into the context of present knowledge. The outgrowth of that attempt, our Chapter 15, was a number of questions concerning Muller's argument. We couldn't prove that he was wrong, but we didn't feel he could prove that he was right. In other words, we felt that there were a number of unvalidated assumptions behind a good many of his points. One aspect of this evaluation of ours was a little critique of the significance of mutation rate studies. This critique I delivered at the WHO Study Group on the Effect of Radiation on Human Heredity which met in Denmark in the summer of 1956. I regarded it as part of the normal scientific interchange, but Dr. Muller apparently regarded it as an attack upon his life's work. There developed a rather strained relationship which persists until the present day, I am afraid, and keeps coming back to me in small ways which I consider beneath the dignity of a great man. Be that as it may, Alex Hollander was Chairman of that meeting in Denmark. Muller apparently insisted to Hollander that my statements were unacceptable and should be modified, to the point where Hollander arranged a meeting between Muller and myself at Oak Ridge, in an effort to reconcile the differences of opinion. At this point a number of the British participants in the WHO Study Group got wind of what was afoot, through no efforts of my own, and got their own backs up. It so happened that they agreed with my point of view and in effect transmitted the message that if any pressure were brought upon me, they would withdraw their own papers."

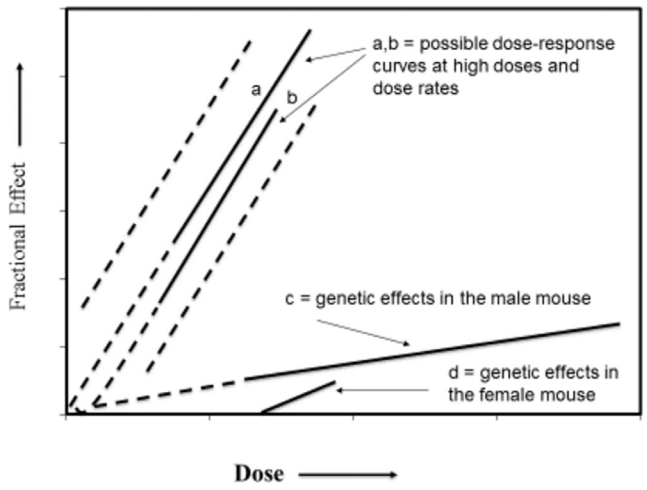

Figure 1. BEIR dose rate graph 1972. Hypothetical dose-response curves for leukemia and genetic effects (Source: NAS/NRC 1972 – page 98). Solid line = observed. Dashed extension of solid lines = unobserved. Line "a" and "b"; possible dose-response curves at high doses and dose rates. Parallel dashed lines = rough limits of error for lines a and b. Lines c and d represent genetic damage in the male and female mice, respectively.

oocytes, the LNT would be based on responses of the mouse spermatogonia. While this logic was convincing to the Genetics Subcommittee one would have to wonder why this didn't require further evaluation. Could there be an evolutionary explanation for why oocytes might show a threshold while spermatogonia didn't? Do oocytes have a more efficient DNA repair system than spermatogonia? Are responses of reproductive cells directly applicable to somatic cells?

These above noted questions were not explored or debated by the BEIR I Genetics Subcommitee. The point here is that the Genetics Subcommittee failed to broadly consider the question and were directed by the Crow leadership to obtain the desired outcome. Thus, Crow and his Genetics Subcommittee retained the LNT based on the non-threshold mutation data of the mouse spermatogonia. These views were accepted by a non-inquisitive U.S. EPA in 1975 and reaffirmed in 1977 all with reference back to the Russell research (Calabrese, 2017c).

The findings of Russell were critical for modelling cancer risk assessment for ionizing radiation based on the Atomic Bomb Survivor data for cancer outcomes. However, these epidemiological findings have limited detectability at low doses (Taubes, 1995), and findings need to be extrapolated toward background exposure. In this key low dose extrapolation process the assumption of linearity was made by the BEIR I Genetics Subcommittee (NAS/NRC, 1972) with the findings of Russell serving as the biological dose-response "homing" device for the LNT model. In the late 1970s the U.S. EPA directly extended this linearity model based on ionizing radiation to chemical carcinogens (Albert et al., 1977). The EPA linear cancer risk assessment policy would be challenged in 2017 when Calabrese (2017b,c) reported that the Russell historical control had been found in error (Selby 1998a, b), and had been corrected for a massive error in 1996 by the Russells (Russell and Russell, 1996). Calabrese showed that if the corrected historical data had been used by the BEIR I (NAS/NRC, 1972) Genetics Subcommittee the male mouse would have shown a threshold while the female would show an hormetic response. These findings indicate that the basis for the LNT assumption was incorrectly formulated and that the adoption of LNT for risk assessment was incorrect.

10. Discussion

The present paper reveals that Muller did not discover what he claimed, that is, the "artificial transmutation of the gene" and this finding challenges the validity and application of the LNT single-hit model for cancer risk assessment (Calabrese, 2017a; Crow and Abrahamson, 1997). Muller was also incorrect on the issue of dose-rate (Russell et al., 1958) which had a significant impact on acceptance and promotion of the LNT single-hit theory (Calabrese, 2017b,c). Although complex, Muller's career was fundamentally centered on his quest to be the first to produce gene mutations, and then to defend this interpretation the rest of his life, against the findings of Stadler (1931a, b, 1932, 1954) and others and then over the remaining six years of his research career (1959–1964) on the issue of dose-rate (Calabrese, 2017a, b), while trying to avoid the alternative gene mutation model of McClintock (1950, 1951, 1953) and its advocacy by Altenburg (1957).

Current scientific understandings, therefore, reveal that Muller could not sustain the conclusion that his high dose X-ray induced artificial transmutations of the gene were "real" gene mutations. The strong preponderance of evidence in the 1930s suggested chromosome level heritable genetic changes based on advances in cytogenetic staining, findings that have been confirmed with nucleotide sequencing technologies (Calabrese, 2017a). Since Muller was incorrect with his gene mutation interpretations the LNT single-hit theory of Timofeeff-Ressovsky et al. (1935) lacked a scientific relationship with the data that was used as its foundation (as pointed out by Stadler, 1954). Despite being wrong on the fundamental biological issues, the Muller-led faction of the radiation genetics community was successful in achieving the adoption of LNT worldwide. This was largely due to its highly organized radiation geneticist network focus, profound exaggeration of risks, and collusions with the Rockefeller Foundation and the U.S. NAS (Calabrese, 2013, 2015a,b,d), and their massive LNT-promotion campaign immediately following BEAR I which affected

government, the scientific community, the media and the general public.

Since the deceptions (e.g., BEAR I) and significant errors (e.g., BEIR I) can be traced back to major scientific historical figures, Nobel Prize winners (i.e. Hermann Muller, George Beadle and Max Delbruck), prestigious U.S. NAS Committees (i.e. BEAR I and BEIR I) and at least one past NAS president (i.e. Detlev Bronk) (Calabrese, 2015a, b), it is important that the ideological history of cancer risk assessment in the U.S. be documented and become a part of the scientific and regulatory agency historical record to help ensure that vital public health policies and practices do not continue to be the offspring of a scientifically incorrect and dishonest past.

This historical assessment reveals a complicated dynamic amongst researchers, their colleagues, and rivals, all within a framework of politics, policies, social philosophies and personalities. Hermann Muller led the field, starting with redefining the concept of mutation and finding improved ways to assess it. Muller worked on these matters within a framework of wanting to be first, gaining recognition and its benefits and pushing this to extremes. One example of this obsession is seen when Muller claimed credit for an important discovery (i.e., first reported in *Drosophila* in which both genetic and cytological evidence of translocation were combined) that Curt Stern had made (Muller, 1929a, b; Muller and Painter, 1929; Stern 1926, Stern, 1929a, b). This resulted in getting the normally reserved Stern to confront Muller via correspondence. Muller was forced to publically apologize and correct the matter. However, symptomatic of this behavior and in this same general period, Muller would apparently manipulate an editor at *Science* to publish his discussion on X-ray induced mutation without providing any data, simply doing so as a means to ensure that he would be first - a tactic that was enormously rewarded.

Much of what Muller did over the next four decades was to preserve and defend the legacy of his breakthrough gene mutational findings/interpretation and the formulation of the Proportionality Rule (the LNT concept). In so doing, Muller would become the intellectual leader of the radiation genetics community, helping to ensure its importance and create new professional and funding opportunities. The principal challenge for Muller was the thoughtful reflections of Stadler and his capacity to create and test key hypotheses, the data from which would challenge Muller's interpretation of his "groundbreaking" findings. Stadler, who was unrelenting, objective and insightful, seemed to follow in the footsteps of Muller's Ph.D. advisor T.H. Morgan. These researchers, according to Muller (1946f), "abhorred what they termed "speculation", that they even distrusted the validity of the most essential lines of reasoning." Stadler and Morgan were leaders in that wave of skepticism whose participants "doubted the doubt 'til they doubted it out." (Muller, 1946f). In the end, Muller's interpretations were revealed via such follow up experimentation to be incorrect, that is, the very high doses he used produced heritable chromosomal, not gene, phenotype changes. More than 50 years later, with advances in nucleotide assessment methods, it would be shown that ionizing radiation could produce some gene mutations but at far lower doses (Asakawa et al., 2013; Colussi et al., 1998; Colussi and Lohman, 1997; De Serres, 1991; De Serres et al., 1967; Fossett et al., 1994; Furuno-Fukushi et al., 2003; Liu et al., 2003; Mognato et al., 2001; Nakamura et al., 2005; Nelson et al., 1994, 1995; Nohmi et al., 1999; Okudaira et al., 2010; Park et al., 1995; Russell and Hunsicker, 2012; Schwartz et al., 2000; Sudprasert et al., 2006; Thacker, 1986, 1992; Thacker et al., 1990; Toyokuni et al., 2009; Webber and De Serres, 1965; Yamada et al., 1996).

Muller loyalists, such as Charlotte Auerbach (1976) and others, would strain the limits of credibility by arguing that Muller was proven to be correct. These examples of revisionist history were based on an incorrect interpretation of his findings. Muller would excite the world with the claim he produced 40 gene mutations one weekend afternoon, more than the entire field had produced in a decade (Carlson, 1981). Yet, we now know that he was not producing gene mutations. In fact, Auerbach (1978) would eventually support Stadler noting that "Stadler tested many X-ray mutations of a particular gene in maize and found that all of them were deficiencies. Not long ago this conclusion was confirmed by experiments on a different gene in maze. Muller's evidence, gained from work with *Drosophila*, was less direct …" (Auerbach, 1978). While Auerbach (1978) gave the proverbial nod to Stadler's perspective, this was done even more emphatically by two very close colleagues and friends of Muller. Crow and Abrahamson (1997) acknowledged that Stadler's deletion interpretations had been convincingly supported with modern analytical methods and that Muller was simply too stubborn, holding on too long to a discredited position. However, old deeply held and self-serving beliefs such as Muller's original error of interpretation, would mesmerize the scientific community making it impossible to change, as it became an accepted myth leading to the creation of the LNT single-hit model for cancer risk assessment, affecting vast changes in public health risk assessment policies and risk communication strategies, while being susceptible to political and ideological manipulation.

The Muller story reveals a conflicted character, the discoverer of an apparent major breakthrough, something that he greatly desired. At the same time, Muller was tortured with the possibility that he was wrong, spoke too soon, that his mutations were really only holes that the X-rays had poked in the chromosomes. He knew only too well that if his mutations were really only poked holes there really wasn't much new or great with his "breakthrough" discovery. Thus, we have a life that sought to "hold on", while trying to prove that he actually had produced "real" mutations.

Eventually the scientific story of Muller's chromosomal rather than gene mutations would progressively emerge, even if it would take up to five decades after he received his Nobel Prize. The influence of Muller continues to be dominantly reflected in current regulatory policy, which was based on poorly formulated science, in need of corrective transformation by major agencies, such as the U.S. EPA, which however have been unable or unwilling to do.

The story of Muller's discovery of gene mutation also speaks to the broader issue of science being self-correcting. Due to the courage and focus of Stadler, Muller's interpretations were challenged and tested in the laboratory. This inspired others, including perhaps a desperate Muller, to seek the truth.[9] These challenges would be tested in the domains of cytogenetics, position effects, transpositional elements, reverse mutations, and eventually with the use of the Southern Blot, PCR and other DNA technologies. We now know that Stadler was correct when he said that it was critical for the scientific community not to confuse the observation of transgenerational phenotypic changes at high doses with its unknown mechanism(s). In the end, Muller was trying in 1927 to discover the mechanism of evolution, and he "knew" that it must be gene mutation. However, he convinced the world (at least for a while), and maybe himself, that he had done so with his high dose *Drosophila* experimentation. However, the scientific community can thank Stadler and his collaborator McClintock for creating the necessary doubt that would eventually lead to science displaying a self-correction for Muller's claim. An important follow up question is whether regulatory agency "science", like that of experimental science, can be self-correcting. Now many years after Muller's

[9] In private letters with Altenburg (Altenburg, 1953c; Muller, 1953; 1954b,c), Muller would acknowledge problems with his reverse mutation explanation, the significant role of position effect and the influence of the mutable genes of McClintock.

incorrect interpretations were revealed, society still lives with a risk assessment model based on a mistaken set of Muller's interpretations. In 1995 Crow would reflect upon the impact of his generation of radiation geneticists in estimating ionizing radiation induced risks. With his then 20-20 hindsight Crow stated that Muller's leadership and action "oversold the dangers, and should accept some blame for what now seems, to me at least, to be an irrational emphasis by the general public and some regulatory agencies on low-level radiation …. ."

In the aftermath of the BEIR I (1972) recommendation and the adoption of the LNT perspective for regulatory agency policy and practice came a spate of biostatistical models offering estimates of cancer risk in the low dose zone following the linearized perspective. The broad range of linearized models were highly speculative attempts to estimate risks at very low doses often using some feature of enhanced biological plausibility, such as the number of theoretical stages in cancer development, the role of interindividual variation, the incorporation of carcinogen bioactivation and DNA repair and other approaches (Cornfield, 1977; Crump et al., 1976; Hoel et al., 1975; Krewski and Brown, 1980; Rai and Van Ryzin, 1981). This type of modeling started, for the most part, in 1961, with the Mantel and Bryan paper, based on the carcinogen contamination Cranberry scare during the Kennedy-Nixon election of 1960 followed by a hiatus until the mid-1970s after the creation of EPA and OSHA when legislative and regulatory activities intensified. These models were constrained by linear assumptions as provided by the BEAR I Genetics Panel, the BEIR I Committee and the official adoption of LNT from BEIR I in 1975 by EPA [see recommendation to support the LNT single-hit model by a subcommittee of the U.S. Department of Health & Welfare (Hoel et al., 1975)]. In between these two NAS committees there were many advisory groups of a national and international nature that followed BEAR I (Calabrese, 2013, 2015a). The linear assumption of these models in the mid-1970s and later were based on the predecessor NAS committees, with BEIR I having the latest and most direct impact since it was based on mice rather than fruit fly model of BEAR I. Given the above historical reconstruction, the risk assessment modeling activities would have been considerably different had EPA determined that the default should be a threshold or hormetic model. The rapid dominance of linear cancer risk assessment modeling in the late 1970s would not have occurred without the recommendations of the two NAS committees. These modeling activities were derived from biostatisticians who tried to derive more biologically motivated linearized models, not being aware of the plotting, scheming, deceptions, misrepresentations and mistakes of the two NAS committees. In the end, the real leaders were Muller, his radiation geneticist followers and their institutional partners. The subsequent linearized modeling was simply the following of the linearity script as written by the NAS BEAR I Genetics Panel.

These convergent entities reached a type of critical mass during the NAS BEAR I Committee Genetics Panel, facilitating no less than a scientific, social, psychological and politically-based risk assessment revolution within the U.S. and essentially all other countries adopting the LNT model for cancer risk assessment.

11. Conclusions

1. Muller incorrectly assumed he induced gene mutations in 1927 when he demonstrated that X-rays induced transgenerational phenotypic changes in *Drosophila* (Calabrese, 2017a).
2. The Muller findings had a major impact on the scientific community. His non-peer-reviewed data (Calabrese, 2018) and incorrect interpretations were widely accepted (Campos, 2015).
3. This incorrect gene mutation mechanistic interpretation lead to the development of the "Proportionality Rule" for dose response in 1930 by Muller and the LNT single-hit dose response model in 1935 by Timofeeff-Ressovsky et al. (Calabrese, 2017a).
4. Muller's gene mutation interpretations were strongly challenged in the genetics community, especially by Lewis J. Stadler and Barbara McClintock, who showed that Muller's gene mutation interpretation lacked scientific proof and could be explained by other mechanisms (Calabrese, 2017a).
5. Limited research directed by Muller supported a conclusion that X-ray induced mutations were best explained by total dose, not dose rate and the genetic damage was cumulative, irreversible and the dose response was linear (Ray-Chaudhuri, 1939,1944)
6. Muller's total dose findings were strongly challenged in Manhattan Project research with far stronger studies (Calabrese, 2011a). These findings were improperly marginalized by leaders of the U.S. radiation genetics communities including Stern and Muller who misrepresented the data via deceptions, false statements and obfuscations (Calabrese, 2011a, 2015b, 2016).
7. The inappropriate awarding of the Nobel Prize in 1946 to Muller for producing "gene" mutations gave an enormous credibility to the LNT risk assessment model, facilitating its acceptance within the scientific, medical, regulatory and political communities. It is likely that the award had long lasting societal impact that facilitated worldwide acceptance of LNT.
8. It was incorrectly assumed by the scientific/regulatory communities and prestigious advisory groups (e.g. U.S. NAS BEAR I Committee, Genetics Panel) (Anonymous, 1956) in the late 1950s that the responses of mature spermatozoa to ionizing radiation induced "gene" mutation which were linear at high doses and independent of dose rate and such doses could be generalized to all cell types, doses and dose rates (Calabrese, 2015b, 2016).
9. These assumptions were incorrect because it was later (i.e. early 1960s) determined that mature spermatozoa lacked DNA repair, thereby preventing its capacity to repair radiation and chemically induced mutation as could occur in somatic cells (Calabrese, 2017b, c).
10. The NAS BEAR I Genetics Panel deliberately misrepresented their own research findings and hid their contradictory findings to promote the acceptance of the LNT model for regulatory agency risk assessment (Calabrese, 2015b, 2016).
11. William L. Russell at the Oak Ridge National Laboratory starting in late 1958 demonstrated that ionizing radiation induced mutations in mouse spermatogonia and oocytes were dependent upon dose-rate, not total dose as had been assumed, due to their capacity to repair DNA damage (Calabrese, 2017b, c).
12. The BEIR I (NAS NRC, 1972) Genetics subcommittee acknowledged the "mistake" of the NAS BEAR I Genetics Panel on dose-rate but still retained the LNT recommendation because the significant reduction in mutation rate in the spermatogonia as shown by Russell et al. had not regressed to control values as in oocytes. Nonetheless, the BEIR I Genetics Subcommittee suggested that findings from spermatogonia had greater capacity for generalization to somatic cells, due to repair capacities, as compared to mature spermatozoa. Russell referred to failed DNA repair capacity as an "odd phenomenon, restricted to spermatozoa and

occasioned by the peculiar nature of the specialized spermatozoan cell." (Calabrese, 2017b,c)

13. Selby (1998a,b) in 1995 detected a significant error in the Russell mouse specific locus test historical control group. This error was subsequently acknowledged and corrected by Russell and Russell (1996) along with Selby (1998a,b). If this error had not been made or had been corrected prior to the creation of BEIR I the mouse spermatogonia data that was used to support continuance of the LNT model would have supported a threshold or hormetic model based on the Russell and Selby corrections, respectively (Calabrese 2017b,c).
14. Summary: The LNT for cancer risk assessment originated due to (1) a critical mistake by Muller that he had discovered X-ray induced "gene" mutation, (2) the adoption of the LNT single-hit model was based on this assumption, (3) a mistake in generalizing the use of the DNA-repair deficient mature spermatozoa for somatic cells by BEAR I (4) deceptions and misrepresentations of the scientific record by leaders of the radiation genetics community, including the NAS BEAR I Genetics Panel and (5) failure to detect the error in the Russell Mouse Specific Locus Test control group, which would have precluded support for LNT. EPA then extended the error by adopting LNT for cancer risk assessment, stating in 1975 and 1977 that it was based on the now recognized erroneous dose rate findings of Russell as cited in BEIR I (1972).
15. It is ironic that the misrepresentation of the scientific record by this NAS BEAR I Genetics Panel to promote their ideological agenda stands in sharp contrast to the memorialized quote on the Einstein statute on the very grounds of the U.S. NAS in Washington, DC. It states: "The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true." As the historical record shows the NAS BEAR I Genetics Panel did not follow the guidance of Einstein.

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Conflict of interest

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