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The linear No-Threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations

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ABSTRACT

The linear no-threshold (LNT) single-hit (SH) dose response model for cancer risk assessment is comprehensively assessed with respect to its historical foundations. This paper also examines how mistakes, ideological biases, and scientific misconduct by key scientists affected the acceptance, validity, and applications of the LNT model for cancer risk assessment. In addition, the analysis demonstrates that the LNT single-hit model was inappropriately adopted for governmental risk assessment, regulatory policy, practices, and for risk communication.

1. Introduction

This paper provides a detailed historical assessment of the origin and progressive development of the linear no-threshold dose response (LNT single-hit model). The time period of this historical assessment starts in 1927 after Muller reported inducing transgenerational phenotypic changes (i.e., heritable mutations) in *Drosophila* via the use of very high doses of X-rays[1] to the present time, with the recent discovery of critical errors made by the U.S. NAS (National Academy of Sciences) BEIR (Biological Effects of Ionizing Radiation) I Genetics Subcommittee (1972) [105] leading to the acceptance of LNT and perpetuating these errors via the subsequent BEIR committees now through BEIR VII. The paper not only details the peer-reviewed literature but also makes extensive use of the personal papers of numerous leading individuals that helped to determine the acceptance of LNT by the scientific and regulatory communities as well as the general public. Despite its standard toxicological analysis framework, this paper also has elements of a scientific detective story with its many unexpected historical twists and turns. This analysis is also different than the traditional scientific review as it documents a disturbing effort by some leaders of the radiation genetics community of the 1940s-1960s to force the acceptance of the LNT model, at almost any cost. Also discussed is the well-documented evidence of deceptions, obfuscations, and deliberate scientific misconduct, all of which significantly affected the broader scientific and medical communities, and regulatory agencies of the U.S., such as EPA, and worldwide. This, in turn, affected cancer risk assessment policies, practices, and recommendations, and had a major impact on environmental regulation, the public health and medical practices throughout the world.

2. LNT and biological evolution

The linear no-threshold dose response (LNT) in biology was first proposed in 1928, making it now 90 years old [118]. This idea emerged from a stellar duo of physical chemists from the University of California at Berkeley. The leader was Professor Gilbert N. Lewis, a world famous scientist, who would be nominated for the Nobel Prize some 42 times. However, on this occasion, Lewis would step out of his field and enter the more uncertain, murky and speculative domain of biology, postulating a possible mechanism for biological evolution.[2] Finding the principal mechanism for evolution was perhaps the most fundamental question challenging the biological community in the aftermath of Darwin's Origin of the Species and Mendel's discoveries concerning heredity. The situation created a profound intellectual challenge and great competition within the biological sciences. The search centered on the belief that the answer to the evolution question would be directly

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[1] In December of 1927 at the AAAS meeting in Nashville Muller [85] discussed the possibility that he may not have induced gene mutation but massive large scale heritable chromosomal deletions and aberrations.

[2] This 1928 paper [118] on the mechanism of evolution was preceded by Lewis's 1925 Silliman Lecture at Yale University in which he addressed the broad question of evolution, exploring possible mechanisms. Lewis was therefore predisposed to applying his knowledge of the chemical and physical sciences to the study of evolution.

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Abbreviations

AAAS	American Association for the Advancement of Science
AEC	Atomic Energy Commission
APS	American Philosophical Society
BEAR	Biological Effects of Atomic Radiation
BEIR	Biological Effects of Ionizing Radiation
CAG	Carcinogen Assessment Group
EPA	Environmental Protection Agency
ERDA	Energy Research and Development Administration
FDA	Food and Drug Administration
ICRP	International Commission on Radiological Protection
JCAE	Joint Commission on Atomic Energy
LNT	Linear No-Threshold
NAS	National Academy of Sciences
NCRPM	National Council of Radiological Protection and Measurement
NEPA	National Environmental Protection Act
NRC	National Regulatory Commission
PNAS	Proceedings of the National Academy of Sciences
RF	Rockefeller Foundation
SH	Single-Hit

linked to how gene mutations were induced and passed on to subsequent generations.[3]

As early as 1910, Thomas H. Morgan had oriented his *Drosophila* laboratory at Columbia University to the study of genes via the pursuit of heritable mutations. However, despite conducting a vast number of experiments designed to 'artificially' induce genomic mutations by a host of noxious chemicals and physical agents, all attempts seemed to fail. A century later this seems hard to believe, since Morgan's group threw nearly everything it could at the fruit fly genome including high doses of ionizing radiation, all without apparent success. This cascading series of experimental failures, while not discouraging future experimental attempts to induce mutation, led to the belief that the genome must be very stable, nearly immutable. Nonetheless, the answer to the "mechanism of evolution" question required finding a means to mutate the genetic material. What was needed was a novel approach. A solution to this challenge was eventually developed by Hermann J. Muller, at the University of Texas at Austin, and former graduate student of Morgan. Muller modified the experimental fruit fly model, making mutations more readily and unequivocally detected.[4] Muller discovered that very high doses of X-rays administered to the male parental generation induced numerous phenotypic changes in subsequent generations, entitling his paper the 'artificial transmutation of the gene'. Muller was very strategic in the framing of the title since mutation of the gene was believed to be the mechanism for evolutionary change. Moreover, while others had previously reported success with the induction of chromosomal aberrations ([53,77–79] [5]), Muller would clearly emphasize that it was the transmutation of the gene that was the fundamental feature of evolutionary change.

The actual data to support Muller's assertions were reserved for a presentation at the 5th International Genetics Congress in Berlin during September (11th-18th) of 1927 [87]. Muller, who inexplicably failed to cite the prior publication of Gager and Blakeslee [53], quickly became an international figure with much public attention. However, the paper containing the data for the major findings was relegated to an obscure conference proceedings [87]. A review of the Muller proceedings paper reveals it lacked an adequate presentation of research methods, cited no references, was sloppy in the presentation of data, and with three experiments, each with study design limitations. An assessment of this publication strongly suggests that this Nobel Prize research was not peer-reviewed [27].[6] Nonetheless, the findings were reproducible, broadly accepted as novel and highly important, principally because of the enhanced capacity to induce what were believed to be gene mutations [168]. In this rush for discovery primacy, Muller [86] acted by publishing his key paper in *Science* (July 22, 1927) three months prior to the Congress, without showing any data. How this occurred was never explained by Muller or the journal nor did the Congress Proceedings [87] paper receive criticism, possibly because others confirmed its basic findings and/or never read it, being content to read the more highly cited, but data-deficient *Science* publication [86]. On April 24, 1928, Muller would make a follow up presentation of his mutation findings, publishing a substantial discussion of the data in the Proceedings of the U.S. National Academy of Sciences (PNAS) on September 15,1928[7] [88].

Inspired by the findings of Muller, Gilbert Lewis and his colleague Alex Olson soon published a follow-up paper in Nature [118], proposing that the mechanism of evolution was genomic mutation induced by cosmic and terrestrial radiation following a linear dose response (they used the term proportional rather than linear). The linear relationship was significant since it would explain observed changes in all species, ranging from least to most susceptible to mutation. The Olson and Gilbert [118] explanation was based on the findings of Goodspeed and Olson [55] [8] on radiation-induced mutation in the primrose plant at a dose some 500,000 fold greater than background.

The LNT model (using the term 'proportional' for linear) was thus first applied to the concept of biological evolution, not cancer/genetic risk assessment. Initially the hypothesis of Olson and Lewis [118] was supported by research of Hanson and Heys [61] from Muller's laboratory and Washington University, who stated that "natural radiation may be responsible for the mutations which are the grist of the natural selection mill with the resulting evolution of new forms." This remarkable conclusion was derived from an investigation of fruit fly mutations in an abandoned uranium mine. Other support for the Olson and Lewis hypothesis was provided by Refs. [46,47,72].

Due to the prominence of the theory of evolution and the reputations of Lewis and Muller, this hypothesis of Olson and Lewis quickly drew considerable attention. However, in the end it failed to gain traction within the genetics and evolutionary biology communities

[3] As early as 1916, Muller would state in a lecture that "the central problem of biological evolution is the nature of mutation …" [39].

[4] Muller's flies had a mutant X chromosome with a crossover suppresser. This was a large inverted segment that blocked the crossing over phenomenon. These flies also had a recessive lethal mutation along with a dominant bar-eye mutation. This permitted the heterozygous females to be visually identified, thereby essentially eliminating an error in phenotype identification.

[5] Gager and Blakeslee [53] would report the occurrence of radium-induce mutation in the Jipson Weed in January, 1927, this being the first report of an exogenous agent inducing gene mutation. This discovery of Gager and Blakeslee [53] has been sustained over nearly a century. However, the findings of Muller [86] simply overwhelmed the field with his far greater capacity to produce mutations. Gager and Blakeslee would occasionally remind the field of their priority while giving credit to Muller for his findings. See Ref. [28] for a discussion of the Gager/Blakeslee and Muller interactions.

[6] A July 8, 1946 letter of Muller to Edgar Altenburg [92] revealed that the paper he read at the 1927 Genetics Congress was published in the proceedings without any change from the presentation text, thus strongly supporting the belief that the key Nobel Prize winning paper was not peer-reviewed [181,182].

[7] Muller [88] cited his Congress Proceedings paper in his PNAS September 15, 1928 paper with the correct page numbers, but with the incorrect year of 1927 rather than 1928. In fact, Muller's PNAS citation was not listed in the basic Web of Science search. This citation was detected in a "cited reference search" of the Web of Science. The 1927 publication date was again used by Muller in a paper by Muller and Mott-Smith [100]. It appears that Muller may have used the 1927 date rather than the actual publication date (1928) to enhance his claim to primacy for the discovery of gene mutation.

[8] The Goodspeed and Olson [55] paper was used since it provided data rather than the "discussional" paper in *Science* by Muller [86].

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since cosmic and terrestrial radiation were only able to account for about 1/1300 of the background mutation rate in the control group fruit flies to what would become the Muller Nobel Prize research using linear modeling [100]. The hypothesis of Olson and Lewis [118] would not be revived, with attention eventually being redirected toward endogenous metabolism with its vast generation of reactive oxygen species (ROS) as a likely mechanistic engine of evolution [43,73].

The reason for the striking failure of the normally highly astute Lewis to discern the problem may have been related to the fact that Muller failed to show any data in his epoch-making *Science* paper, while the proceedings of the 5th International Genetics Congress was published too late and not generally available. As noted above, Olson and Lewis [118] had to rely on the limited findings of Goodspeed and Olson [55]. Thus, it is likely that Lewis was forced to be too speculative in his quest to be the first to offer a plausible mechanism for evolution. A chronology of the history of the LNT is provided in Appendix 1.

3. LNT and the proportionality rule

Even though Muller rejected the hypothesis that background radiation-induced mutation acting via a LNT dose response was the mechanistic engine of evolution, he nevertheless would soon accept the validity of the LNT theory and its later linkage with the single-hit mechanism for ionizing radiation-induced mutation and eventually for cancer as well. While it is not yet possible to pinpoint the timing of the adoption of his belief in LNT, it was probably directly linked to the results of two investigations under his direction. It appears that Muller accepted the validity of the LNT for mutation from findings reported in several published studies [57,59–61,115] [89]. Muller had made the assumption that the dose response was linear down to a single ionization event though the **lowest** cumulative dose from these investigations was extraordinarily high, i.e., approximately 285 rads (r), administered at a high dose rate. In contemporary terms, this was roughly the equivalent of receiving 1000 modern chest X-rays in 3.5 min or about five chest X-rays/second. In fact, the lowest dose using the C1B *Drosophila* model in Muller's Nobel Prize research was nearly 6 fold greater than this dose.

While the above papers were commonly cited by Muller as supporting the LNT perspective during this period of concept consolidation, he failed to properly balance and integrate other contemporaneous publications from similar credible studies that did not support the LNT perspective [125,155,175]. Table 1 provides a listing of contemporary radiation-induced mutation studies that supported the LNT/proportionality relationship and those that contradicted it. All of the studies supporting the LNT were conducted at very high doses/dose-rates, hundreds of thousands times greater than background. While Muller remained silent with respect to the challenging studies, he would eventually need to address the issue of cumulative dose, dose-rate, and the nature of the dose response in the low dose zone via improved and more insightful experimental protocols.

The period from about 1927 to 1932 represents the first stage in the historical assessment of the LNT model. While Muller provided the experimental vehicle, Olson and Gilbert [118] created the conceptual framework (i.e., linear dose response) and application (i.e., evolution mechanism), even if those were ultimately rejected. Oliver [115] and Hanson and Heys [59–61] provided evidence to support the occurrence of LNT, even though at extremely high doses/dose-rates. In fact, as this period would come to a close, Muller would transform these developments into no less than a quasi-biological law called the Proportionality Rule, the term Muller used for the LNT concept. The 'proportionality' term was apparently borrowed by Muller from the Olson and Lewis [118] paper, transformed into a 'Rule', which quickly gained standing within the radiation genetics community, but not much further. Table 2 provides a series of citations and a quote within each, showing how the radiation genetics community used the concept of proportional dose response to describe the linear dose response for ionizing radiation and mutation. As described with the quote from Hanson [58] the mutation incidence was directly proportional to dosage and that 'Muller named this the proportionality rule'.

The seminal work of Muller [86] reported for the first time that an external agent, ionizing radiation, could induce gene mutations (i.e., 'artificial transformation of the gene') in the fruit fly genome as inferred from phenotypic changes observed in the next generation. While this was the principal focus for Muller and about which most observers focused, he also directed attention to the concept of dose response, since his Nobel Prize study designs [87] were inadequate to assess the dose-response relationship issue.

Muller's Nobel Prize research initially involved experimentation with a homogenous strain of *Drosophila* females with heterozygous males. In this first experiment he exposed the flies to four 'doses' which were Dose x Duration of X-ray exposures [i.e., 12 (i.e., 810 r total dose over the 12 min), 24, 36, and 48 min]. The two highest doses/durations were quite toxic, inducing sterility in 70–80% of the males. At the lowest dose/duration tested Muller induced a single apparent mutant offspring with a phenotypic change. The phenotypic change rate would increase notably for the 24 min treatment (i.e., 1620 r) over the response of the 12 min exposed group. Choosing not to replicate this four dose/duration treatment study, which suggested the possibility of a threshold at the 12 min duration, Muller switched to his new C1B fruit fly strain, which was a model that gave unambiguous sex-linked mortality results. However, instead of testing over the original four doses, Muller opted to use only the 24 and 48 min duration periods, thereby seemingly attempting to prevent a possible no effect dose at the low end while still maintaining a dose that retained a high risk of toxicity/sterility. This follow up two dose experiment yielded a limited dose response that also was not linear with Muller reporting the increase as a square root function ($\sqrt{2}$) rather than a doubling (2-fold increase) for a linear response.

Follow up research by Oliver [115] using the C1B strain model would be critical in establishing Muller's belief in LNT. In this four dose study the lowest dose tested was sufficiently effective in that it increased mutant lethals by nearly six fold over control values, making a linear dose response. However, when a legitimate challenge to an LNT mutation interpretation was published, as in the case of Stadler [155], it was ignored. For example, Stadler [155] assessed mutagenicity involving 13 radiation doses in barley with the three lowest doses showing no enhanced mutation over the control, reflecting the possibility of a threshold dose response and a challenge to the LNT concept. Despite its enhanced power and greater dose response relevance, such findings were apparently ignored even though Stadler [155], raised the possibility of there being a threshold in his discussion by stating that 'the 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 … '.

Stadler would more seriously challenge Muller for the rest of his life (dying of cancer in 1954) over the key assumption that Muller had actually established what he claimed: induced the artificial transmutation of the gene (i.e., mutation) [96,101,127,158,159].[9] While Muller continued to assert that the X-rays induced precise 'point' mutations in single genes (e.g., what today would be called base pair mutations) Stadler [156–158] hypothesized that Muller's mutations were not precise but often, and perhaps totally, manifestations of massive deletions and various genic rearrangements that could involve multiple genes [26]. In contrast to Stadler's description, Patterson and Muller [127] referred to these transgenerational phenotypic alterations as due to 'progressive' mutations/changes, which they argued were the essential foundations of evolutionary change. If Stadler's views were to be persuasive then the

[9] Even after his death, Stadler would challenge the Muller interpretation as his last Ph.D. student Gerry Nuffer [113], who acknowledged the help of Stadler, would publish detailed findings in maize showing no evidence that X-ray-induced transgenerational phenotypic changes were due to gene mutation. He identified a variety of other chromosomal/gene interactions (e.g., position effects) that might account for the findings, thereby challenging the generality of the Muller findings to plant genetics. The challenge of the Stadler/Nuffer findings were broadly applied by others although the authors were astutely careful in their wording.

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significance of Muller's findings would be profoundly diminished, with the results representing a more modest extension of earlier X-ray induced chromosomal (i.e., non-gene) aberration research. While these two titans (i.e., Muller and Stadler) of radiation genetics were unrelenting in their debates (since the stakes were so high) Muller [90] would temporarily prevail (as 'validated' by his Nobel Prize in 1946), possibly due to the power of his personality, and that he outlived Stadler[10] who struggled with cancer over the last eight years of his life. However, once molecular techniques had advanced following the deaths of Muller and Stadler, the data would clearly reveal that Stadler's views were largely vindicated [50,52,111,112,114,123,139,165–167,170]. In contrast, at the high doses used by Muller [86,87] the damage to the mature fruit fly spermatozoa genome would be dominated by massive deletions and other large genetic lesions [117], making the progressive point mutation hypothesis untenable. Reflecting the view that Stadler's interpretations were not only correct but also vindicated can be seen in the judgments of two of Muller's closest radiation geneticist colleagues, Crow and Abrahamson [41]. Nonetheless, the early and widespread acceptance of Muller's far more poorly supported interpretation of the nature of the X-ray-induced genetic damage at high doses would lead directly to the creation of the clearly flawed LNT Single-Hit model.

4. Linking LNT with single-hit

By the end of 1932, Muller had developed what seemed to be a firm belief in LNT for X-ray induced gene mutation. However, this belief was without an underlying mechanism or an experimental study in which the protocol would be able to test the legitimacy of the LNT model. These ostensible weaknesses (e.g., very high doses, lack of mechanisms, weak cytogenetic analysis) of the data supporting LNT would be partially rectified by the end of the decade, even if the studies themselves providing the 'rectification' had important limitations. In the case of mechanisms, Muller received a huge boost when he linked up with Timofeeff-Ressovsky, the outstanding Russian radiation geneticist, working in Berlin from 1932 to 1934 and several other international leaders in the physics community such as Neils Bohr, Max Delbruck and Kevin Zimmer. Muller and Timofeeff-Ressovsky would provide some of the key mutational data while the physicists contributed the mechanism, based on X-ray exposure and target theory. While target theory was first developed for use in predicting how chlorine disinfection might kill bacteria (see Refs. [22,36]), it was soon adopted by physicists ([42,130,178]) to explain X-ray-induced mutagenicity. The physicists demonstrated that the more hits needed to produce a gene mutational effect, the more threshold-like the dose responses would appear ([10,180]). In contrast, as the number of hits approaches one, the more linear the dose response would appear (Fig. 1). Thus, the conclusion was judged to be clear. The X-ray induced linear dose response for genomic mutations in the male fruit fly mature spermatozoa was best accounted for with a single hit model using target theory. As a result of this radiation biologist-physicist collaboration, the LNT-Single Hit (SH) model was created.[11] The result of this collaboration was published in 1935 by Timofeeff-Ressovsky and colleagues. Unfortunately, this potentially groundbreaking paper was published in a new journal that was cancelled after only one year, profoundly reducing its potential impact on the

Table 1
Dose response mutagenicity data at the time of linearity concept consolidation (Circa 1928–1934) (Source: [13]).

Reference		#Doses		
Supportive of Linearity				
Oliver [115]	*Drosophila*	5 doses	X-ray	Lowest dose 275 r
Hanson and Heys [62]	*Drosophila*	2 doses	Radium	Lowest dose 6315 r
Hanson and Heys [63]	*Drosophila*	13 doses	X-ray	Lowest dose 445 r
Timofeeff-Ressovsky [169]	*Drosophila*	5 doses	X-ray	Lowest dose 1400 r
Not Supportive of Linearity				
Muller [86,87] (Exp 1)	*Drosophila*	4 doses	X-ray	
Muller [86,87] (Exp 2)	*Drosophila*	2 doses	X-ray	
Weinstein [175]	*Drosophila*	2 doses	X-ray	
Hanson [57]	*Drosophila*	2 doses	X-ray	
Hanson and Heys [60]	*Drosophila*	2 doses	X-ray	
Stadler [133]	Barley	15 doses	X-ray	
Serebrovsky and Dubinin [146]	*Drosophila*	3 doses	X-ray	

[10] In order to preserve the uniqueness and significance of the artificial transmutation of the gene concept/findings, Muller would publish an 82 page paper in 1930 with his University of Texas colleague J.T Patterson. The focus of the paper centered on whether the X-ray-induced transgenerational phenotypic changes were due to losses (deletions) and rearrangements of portions of chromosomes or rather the so-called "progressive" point-like, genetic changes that he believed drove evolution. This article, in many ways, reflected the pattern of Muller's professional life. He marshaled as much evidence as possible, presented it in excruciating detail and never compromised on an essential point knowing in advance that he had to defend the artificial transmutation of the gene concept [26]. What then was the basis of his belief that he had induced intra-genic (i.e., "real") mutations. The cited reasons for this belief/conclusion included: (1) the general randomness and specificity of induced phenotypic changes (called mutations); (2) identical phenotypes were independently affected; (3) that phenotypic changes were dose dependent; (4) that numerous toxic chemicals were not effective in producing such changes and (5) (similar to 4) "most important of all, probably, is the fact that a direct and simple proportionality has been shown to exist between the frequency of the induced mutations and the amount (energy) of the radiation absorbed." Patterson and Muller [127] cited Hanson and Heys [60] and Oliver [115] to support this conclusion. Patterson and Muller [127] then stated that "there is no indication in the results of any lower critical intensity, or threshold value, beneath which there is no (or a relatively lesser) effect." In the body of the paper Patterson and Muller [127] would also emphasize that X-rays could on occasion induce reversible changes such as white eyes to red and the reverse, supporting a view that relatively modest phenotypic changes could be induced that reflected normal "spontaneous mutations". The problem with the Muller argument was that it was based on logic, inference and parsed arguments. Missing from his views was actual proof concerning the nature of the radiation-induced genetic lesions over the tested dose range. Thus, from 1930 to the mid-1950s the Stadler and Muller perspectives would collide, awaiting advances in methods that would permit determination of the nature and size of genetic lesions. Of importance was that Painter [130–132] provided novel cytogenetic staining techniques for *Drosophila* chromosomes based on the earlier work of McClintock [80–82] for corn. These techniques would clearly show that the X-ray treatments used by Muller produced a very high level of chromosomal aberrations, weakening his point mutation argument. The reverse mutation explanation offered by Muller was also refuted in multiple studies (e.g., [70,71,174]. Additional methodological advances would emerge with the development of the Southern blot [153] and PCR a decade later [102]) which further supported the Stadler position.

[11] The mutational effect was viewed as being caused by one or a few discrete, basic biophysical effects, which were conceived to be "hits" on a "target". The genetic mutation was assumed to be a "pure physical event" with no physiological or biological involvement [173]. From a range of ideas as to what constituted a hit, it was possible to then derive statistical models of dose-responses. If only a single hit on a single target was needed to induce the effect, with the percentage rate of the effect graphed on a logarithmic scale, the dose response would appear then as a straight line. The various mathematical model predictions were then compared to actual data in the dose-response studies. The visual confirmation of the emerging theory with actual mutagenic dose response data made the LNT single-hit model believable and readily accepted. This process led Timofeeff-Ressovsky et al. [169] to assert that gene mutation was a "one-hit" process, caused by a single ionization from a quantum of radiation on a sensitive region of the genome. They even went so far as to estimate the physical features of a sensitive region, it being about the size of a large organic molecule [10].

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Table 2
Documentation of the introduction of the proportionality rule concept into the mutation literature, 1929–1960 (Source: [17]).

References	Quotes
Hanson and Heys [60]	"It is only to be expected that the number of mutations be directly *proportional* to the number of rays to which the organisms are exposed." Page 207
Muller [89]	"Since then Hanson, using radium, and Oliver in our laboratories using X-rays, have both found that the frequency of mutations produced is exactly *proportional* to the energy of the dosage absorbed ... There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work." Page 236
Oliver [115]	"That is there is a direct *proportionality* between the percent of lethals and the length of time of treatment may be seen more readily by a comparison of the t1 values calculated from the results for each of the given doses." Page 45
Stadler [155]	"Mutation frequency increased approximately in direct *proportion* to dosage." Page 13
Hanson and Heys [63]	"Taking the amount of ionization in air as a measure, the mutation rate seems to vary approximately in direct *proportion* to the intensity." Page 142
Oliver [116]	"By inference it can be added that the cosmic and the terrestrial radiations of higher energy content also are capable of producing mutations in *proportion* to their power of ionization." Page 480
Oliver [116]	"The relation of *proportionality* to the dosage applies not merely to the lethals in general, but, more specifically, to the lethal gene mutations." Page 485
Oliver [116]	"... [gene mutations and gene rearrangements] ... all probably occur in direct *proportion* to the dosage, no matter how small a dose is used." Page 486
Patterson [126]	"In general their results [i.e. [59,115]] justify the conclusion that the rate is directly *proportional* to the dosage employed." Page 133
Hanson and Heys [62]	"Further evidence of the *proportionality rule* from a study of the effects of equivalent doses differently applied." Page 335
Hanson and Heys [62]	"Experiments planned with a view to determining within what limits the *proportionality rule* holds show again a strict correspondence existing between the amount of radium administered and the consequent biological effect, the induced mutation frequency obtained varying directly with the dosage." Page 343
Hanson [58]	"The rate seems to be directly *proportional* to the dosage. Muller has named this the '*proportionality rule.*' For example, when all other factors are kept constant, doubling the time of exposure also doubles the number of lethal mutations." Page 486
Oliver [117]	"The frequency of induced mutations is directly *proportional* to the intensity of the treatment." Page 391
Delbruck [44]	"The *proportionality rule* gave the basis for the single-hit interpretation ..." Page 359
Stern [161]	"The *proportionality rule* has been proven to hold over a wide range. Figure 155 shows that, for Drosophila, the relation is essentially linear over the range from 25 r to several thousand r. It has further been shown that the frequency of induced mutations is independent of the time over which the radiation is applied." Page 433
Stern [162]	"It has been established for a variety of experimental organisms that the number of mutations induced by radiation is proportional to the dose. This *proportionality* has been proven to hold over a wide range of dosages." Page 491

scientific community. The obscurity of the Journal and the fact that it only lasted one year, prevented the paper from citation in leading indexes, creating what would have been a virtual academic death sentence had these authors not been so prestigious and professionally connected. Nonetheless, Muller's Proportionality Rule now had a potential mechanism that could account for its findings and a new name: Linear-No-Threshold (LNT) single hit model.

5. Dose-rate and LNT

While the professional disputes between Muller and Stadler over transgenerational phenotypic changes and mutations were significant, acceptance of Muller's gene mutation view was essential for the development of the LNT single-hit dose-response model. It is now known that the lowest doses employed by Muller in his Nobel Prize research induced massive deletions throughout the genome with many probably approaching and exceeding 100 kb (kilobase) size along with other major genetic alterations [50].[12] The physical deletion of large chunks of DNA, damaging dozens to multiple hundreds of thousands of nucleotides, affecting numerous genes in large numbers of cells, as well as inducing substantial inflammatory responses within and between cells, is not compatible with the basic features of the LNT-SH model as described by Timofeef-Ressovsky et al. [169]. Despite the fact that modern advances [69,139] refuted the single-hit interpretation by Timofeef-Ressovsky et al. [169], these critical insights have only recently been used to reassess the validity and historical foundations of the LNT single-hit model [24–26].

The scientific basis for the LNT single-hit theory as developed by Refs. [86,169] and others was improperly framed, based upon incorrect assumptions, lacking essential understanding of induced genetic damage and its biological significance. Thus, from a theoretical basis, the LNT single-hit theory-model represented a type of biological reach that was excessively ambitious, lacking credible genotoxic information required for the development of a mechanistic model for risk assessment/regulatory purposes. Yet, despite such serious limitations, the LNT findings would be integrated with the one-hit mechanism; it was easily understood from a conceptual perspective and would be later readily (if uncritically) adopted by governmental regulatory agencies.

While the LNT single-hit model was a key step forward, its credibility remained limited, having only a descriptive high dose experimental basis requiring substantial extrapolation from high to low dose and a mechanism that was expressed with mathematical simplicity through experimental validation at low doses. Despite such multiple challenges coupled with the lingering and documented doubts of Stadler and others, Muller would eventually develop a way to attack the model-validation question experimentally.

This new experimental approach was based on the assumption that X-ray induced mutations were cumulative and irreversible. Under such a set of conditions, it was predicted that the total/cumulative mutation damage would be the same regardless of whether the dose of radiation was given acutely or spread over a prolonged period of time. It is not clear where Muller first got this idea but the concept was similar to the Bunsen-Roscoe Law (1862) and Haber's Law [12,84,176,177] both of which described a type of Concentration X Time = Constant relationship. Several references relating to application of the Bunsen-Roscoe Law were available to Muller and his graduate student Ray-Chaudhuri in the years leading up to the research and may have influenced them [68,143,160]. The Bunsen-Roscoe Law has been referred to as the 'Reciprocity Law', discovered by the famous chemist Robert Bunsen and his colleague H. Roscoe in 1862. This 'law' indicates that the amount of product of a photochemical reaction is the result of the total amount of radiation energy hitting the photochemical system, in effect, an intensity x time formulation. The strengths and limitations of Haber's Law had been broadly assessed but usually within the framework of inhalation toxicity, not radiation genetics, or dose-genomic mutation incidence. When Muller became the advisor of Ray-Chaudhuri at the University of Edinburgh in the late 1930s, this new experimental dose-time framework became his dissertation area, working with mature

[12] If Painter's cytogenetic staining of *Drosophila* had been available a decade earlier so that the extensive X-ray induced damage to chromosomes of Muller's fruit flies in 1927 were better appreciated, it may have averted the development of the LNT Single-Hit theory. However, by the time Painter had published his findings, the Timofeeff-Ressovsky et al. LNT Single-Hit model concept was well on the way to being finalized.

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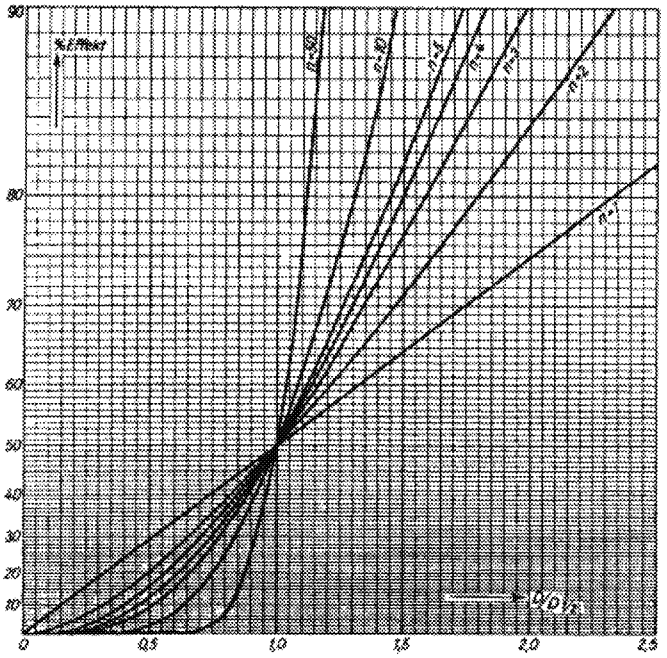

Fig. 1. Model dose-response curves, calculated theoretically for various number of "hits," n on a single "target" assumed necessary to produce the effects (From [180]).

male fruit fly spermatozoa. Ray-Chaudhuri would cite the Bunsen-Roscoe Law as the theoretical framework for his research on the dose-intensity x time relationship [131,132]. The most likely reason for citing the Bunsen-Roscoe Law rather than Haber's Law was that several papers had been reported on the effects of X-rays on biological end-points based on the Bunsen-Roscoe Law, whereas Haber's Law had yet to be applied in such a manner.

Using the Muller fruit fly model [132], Ray-Chaudhuri obtained data that provided support for the LNT hypothesis for radiation-induced mutagenicity based on the mature male spermatozoa, all with a quantitative model that appeared theoretically sound. An important problem remained however, since the research of Ray-Chaudhuri had critical limitations. In general, these problems included inadequate control groups, acknowledged major statistical errors by this Ph.D. Committee [56], and issues with experimental quality control features, some of which were recognized by Caspari in correspondence with Stern (American Philosophical Society [3,4]). In specific terms, the Ray-Chaudhuri study was of modest size and lacked the reporting and documentation of multiple essential methodological parameters. The paper also did not include data on lethal clusters, the occurrence of female sterility and fertility, sex ratios, as well as the age of the males, and other factors. He also made a decision to change to a different fruit fly strain midway through the set of experiments, a decision without any explanation. Of significance was that the new strain displayed a control group mutation incidence of approximately one third of the strain it replaced. Yet, Ray-Chaudhuri simply combined the data of the different strains claiming there were no strain differences. None of these limitations were noted by Professors Haldane or Muller in their written assessment of Ray-Chaudhuri's dissertation (Ray-Chaudhuri material – Muller File, Lilly Library, Indiana University). Furthermore, in letter exchanges between Ray-Chaudhuri and Muller, it was clear that Muller was not present for most, if any, of his experiments due to travel, failing to offer crucial, timely and hands on guidance (Muller to Ray-Chaudhuri, Muller File, Lilly Library). Nonetheless, all these weaknesses were carefully submerged, as Muller was seemingly intent on using the Ray-Chaudhuri study to promote the LNT in the face of much skepticism. In fact, Muller [90] would use the Ray-Chaudhuri data to promote the LNT model in his Nobel Prize Lecture.

Muller would frame the dose-rate study of Ray-Chaudhuri as a possible game changer. However, this would not be the case if the experimental limitations could not be overcome. In fact, the soon to be initiated Manhattan Project mutation studies would provide such an opportunity. Muller once again found himself involved, this time as a paid consultant with Professor Curt Stern at the University of Rochester. The research was to evaluate the effects of X-rays/gamma rays on fruit flies, with the intent of assessing the nature of the dose response and dose-time response for transgenerational genomic mutations. That is, Stern was going to assess whether linearity at low doses occurred, making use of Muller's dose-rate methodology, and the Muller-5 strain of fruit fly. This study would be a far stronger one than Ray-Chaudhuri's with respect to technical capacity, study design, sample size, statistical power, quality control, professional supervision, and at a dose rate approximately 1/6 of the Ray-Chaudhuri studies.

6. The Manhattan Project: testing the LNT hypothesis

One component of the Manhattan Project assessed whether the dose-response for mutagenicity induced by ionizing radiation was linear via a total dose/dose-rate experimental protocol using the fruit fly. Those associated with the study expected the X-ray-induced mutations to be independent of dose-rate, and explained by the total dose received based on the Ray-Chaudhuri [131,132] findings. However, a significant problem occurred when Ernst Caspari, who was conducting the chronic exposure part of the research, reported to Stern in August 1946. His findings not only did not support the total dose hypothesis, but also displayed a threshold, showing a tolerance dose [14]. These findings were potentially important since they challenged those of Ray-Chaudhuri [131,132], which in turn had been used as key foundational support for the LNT. As noted above, the Caspari study had much going for it. In fact, the integration of the Spencer/Caspari experiments combined to yield a dose-rate study that was designed to 'settle' the dose-rate question that the Ray-Chaudhuri report initiated.

Upon learning of the Caspari chronic experimental data, which supported a threshold and/or tolerance dose, Stern refused to accept the findings as valid, claiming that the problem was not with the dose-rate and linearity hypotheses but with Caspari's control group. This involved Stern's claim that because mutations in this control group were aberrantly high it would lead to the absence of a treatment effect, and show a false threshold dose response [5].[13]

What eventually evolved in response to the Caspari/Stern dispute would be both surprising and historically significant. Caspari refuted the claims of Stern by showing that his control group was consistent with the published literature, forcing Stern to withdraw the criticism [5]. However, Stern (and perhaps with Caspari's consent) wrote in their discussion of the manuscript that the strikingly new threshold supportive findings should not be accepted until it could be determined why these results seemed to conflict with the acute data of the Spencer experiment [154]. A problem with this position was that the Spencer and Caspari studies used significantly different methods and it was not practically possible to resolve their divergent results (see Table 3 for differences). Stern seemed, however, very comfortable accepting the methodologically inferior Spencer report [154] rather than the threshold-supporting findings of Caspari.

Stern asked Muller to review the now drafted Caspari manuscript just prior to his Nobel Prize trip/lecture. Muller acknowledged its receipt and commented on it in a letter to Stern (November 12, 1946 - [91]) stating that these findings (1) challenged the current LNT dose-response paradigm, (2) needed to be replicated, and (3) that Caspari was a competent researcher and he would not dispute his research findings. Despite such a written statement just prior to his Nobel Prize,

[13] See Calabrese [14] for a detailed, point-by-point discussion of this dispute.

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Muller would go on to claim in his Nobel Prize lecture that there was no scientific evidence to support even the possibility of a threshold dose response. The only option he insisted that was possible was the linear dose response. He believed there is 'no escape from the conclusion that there is no threshold dose' (Nobel Prize lecture, HJ Muller, December 12, 1946). The above described sequence of events suggests that scientific certainty about this key issue had devolved into a belief system.

The Caspari and Stern draft manuscript sent to Muller on November 6, 1946 contained the following sentence in the conclusion: 'From the practical viewpoint, the results presented open up the possibility that a tolerance dose for radiation may be found, as far as the production of mutation is concerned'. This statement of Caspari and Stern ([31]- page 15) which was sent to the AEC archives and to Muller, made it clear that Caspari and Stern believed that a threshold for ionizing radiation induced mutation was 'possible'. In fact, the only changes in the entire paper after Muller's review was the elimination of this sentence in the summary and the addition of Muller's name in the acknowledgement section. These insights into Muller's dynamic intervention with the Caspari and Stern manuscript reflects that both Stern and Caspari believed that a threshold interpretation best applied to their mutation data. Yet, Muller would inexplicably override this possibility, while recommending replication of the study in private communications with Stern [Muller Letters to Stern - November 12, 1946 [91] and Jan 14, 1947 [93]]. The conflict that Muller had with the Caspari data became obvious. How he dealt with it became problematic.

We see that Muller not only had a strong belief in the LNT but a profound bias as reflected in his misleading and deceptive comments at his Nobel Prize lecture. Muller would go on to repeat the original criticisms of the Caspari work [94,95],[14] relating to the control group while Muller's own research produced copious data indicating that the Caspari control group data was fully consistent with his own data and the published literature [19].

The situation became more complicated when Stern tried to replicate the Caspari findings from the fall of 1946–1948, now working with a new graduate student, Delta Uphoff. The first major experiment by Uphoff was problematic, as it appeared that the control was aberrantly low, about 40% below normal. Having just gone through the Caspari control group dispute, Stern needed to get the control group issue settled. He then entered into a series of letter exchanges with Muller on the topic, focusing on the Caspari and Uphoff data. Since Muller was extensively researching control group spontaneous mutation variability with the same model (in his continuing dispute with Stadler over gene mutation), he was in an ideal situation to inform Stern. In these letter exchanges Muller was highly supportive of the Caspari data.[15]

As a result of this evaluation, the Uphoff data were viewed as 'uninterpretable' as Uphoff and Stern [171] wrote in a then classified full-length manuscript for the Atomic Energy Commission (AEC). Further complicating the matter, these authors (Stern and Uphoff) blamed the problem on 'investigator bias' (i.e., 'may reflect a personal bias of the experimenter') in the discussion of the paper without explaining what this meant and who was to blame for the bias, as well as whether such bias affected other ongoing experiments and staff, and how Caspari's study would be interpreted. The second of the replication experiments of Uphoff would also yield a similarly aberrant low control group, thereby making two major experiments uninterpretable. The final Uphoff experiment was also problematic, not because of the control group, but because the low dose radiation treatment induced mutations that exceeded predictions of the LNT model by several fold [14].

With World War II over, the Atomic Energy Commission (AEC) needed to have reliable data to guide it on the assessment of the health effects of low doses of radiation. The AEC had invested in mammalian and insect (i.e., fruit fly) studies at the University of Rochester. In the case of the mammalian studies as lead by Professor Donald Charles, no effective guidance was forthcoming. This was believed to be due, at least in part, to the well-known and highly frustrating reluctance of Charles to release/publish his findings unless fully confident with the experimental results. Even after the use of over 400,000 mice, little of value was shared with the scientific community by that group. This included a brief, three-page summary in 1950 [34], some five years after the war ended. By 1954 with no follow-up publication, Charles had resigned from the University and a year later he committed suicide [6]. A summary paper was eventually published in 1961 that was far too late [35], as these efforts had been surpassed by the striking research findings on dose-rate using the mouse model by William L. Russell as discussed below.

For differing reasons, Stern was also being challenged to produce results. In his case, the problem was that each large experiment had a significant concern or flaw as discussed above. Refusing to accept the idea that his research would not achieve the stated goals, Stern decided to rehabilitate the uninterpretable (and experimenter biased) data of Uphoff and to re-marginalize the findings of Caspari, without sharing the detailed 'inside' story validating the Caspari control group as described earlier. This resulted in Uphoff and Stern [172] publishing a one page technical note in *Science* summarizing all five major experiments (i.e., Spencer, Caspari and three by Uphoff), integrating them to claim support for the LNT. They promised the *Science* readership a subsequent highly detailed paper with all the necessary methods, materials, and data. However, they failed to fulfill this pledge. Nevertheless, lacking supporting data the *Science* paper became highly influential, propelling the acceptance of LNT, even though there is no evidence that Stern's radiation geneticist colleagues ever requested the detailed follow-up paper.

6.1. Facilitating the acceptance of LNT: role of Rockefeller Foundation and the National Academy of sciences – the BEAR I Genetics Panel

During the early 1950's aboveground testing of nuclear weapons led to increased worldwide exposure to various radionuclides prompting public health concerns. This would lead to the Rockefeller Foundation (RF) funding the U.S. NAS to undertake a detailed assessment of multiple areas of concern (i.e., oceanography and fisheries, meteorology, waste disposal and dispersal, agriculture, pathology, and genetics). The President of the Rockefeller Institute for Medical Research (later renamed Rockefeller University) as well as the President of the National Academy of Sciences (NAS) at that time was Detlev Bronk. In reality, therefore, Bronk was responsible for funding some of his activities as President of the NAS. In this dual role, Bronk selected Warren Weaver, a mathematician, and the long-term scientific director of the RF, to chair the NAS Biological Effects of Atomic Radiation (BEAR) Genetics Panel. Furthermore, Weaver knew most, if not all, of the BEAR I Genetics Panel members, and had long funded some of them such as Sonneborn and Muller, contemporaneously, during the time of the Genetics Panel proceedings. As reported by Wynchank [179], prior to the creation of the Genetics Panel, the RF had funded close to four million dollars to the University of Indiana for research in the area of radiation genetics alone.

At the start of the BEAR I Genetics Panel Weaver showed his power

[14] In footnote 1 on page 10 of [94] Muller stated that "Uphoff and Stern have published a report of further work, with doses as low as 50 r, given an intensity as low as 0.00165 r per minute. The results obtained are entirely in conformity with the one-hit principle. A consideration of these results, together with the early work, leads to the conclusion that the deviation first referred to (the Caspari and Stern [32] findings) was caused by a value for spontaneous mutation rate that happened to be unusually high." Muller [95] would continue his discredited criticism of the Caspari and Stern [32] paper, repeating the "unusually high control frequency" (page 476) conclusion as a basis to reject its challenge to linearity. These statements of Muller complemented the deceptions of Stern, thereby further enhancing the acceptance of LNT while also preventing his deceptive remarks at the Nobel Prize lecture from being discovered.

[15] See Appendix A, Calabrese [16] for a set of the Muller-Stern exchanges.

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over funding support by stating that 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' ([104]; BEAR I Genetics Panel Transcripts February 5, page 35). This is a significant statement as it had the intention of encouraging Panel members to align their recommendations with what the RF believed was important if they wanted to continue to receive Foundation funding. Weaver would further contextualize his funding remarks with the statement: 'There may be some very practical results – and here is the dangerous remark – don't misunderstand me, we are all just conspirators here together'. Weaver's comments are unambiguous, linking project outcomes to RF funding interests and the needs of the radiation geneticists of the Panel.[16]

At the time of the convening of the BEAR I Genetics Panel, the threshold model guided U.S. government policy for assessing risks for both non-carcinogens and carcinogens. Members of the radiation geneticist community, as lead by Muller, had long challenged this view hoping to change it to a proportionality/LNT model. However, on multiple occasions on national and international advisory committees, radiation geneticists had failed to be sufficiently persuasive, never having the votes to replace the threshold with the LNT model. This was principally due to the fact that these Advisory Committees were dominated by persons trained in medicine rather than radiation genetics. This situation would change by design of the RF, via Bronk and Weaver. They made sure that there would be a distinct Genetics Panel that would be separate from a Medical (i.e., pathology) Panel and the RF would uniquely highlight and distribute its findings via multiple, highly visible and influential venues. This is really all it would take to affect a change in national policy for the next six decades.

I was interested in reading the meeting transcripts of the BEAR I Genetics Panel, seeing a substantial debate between proponents of the threshold and LNT models. While I knew that LNT had won the dispute, I wanted to see how these experts debated, which arguments dominated, and which geneticists were most persuasive. My expectations were far too high. As it turned out there was no debate. What happened early on in Panel activities was that Tracey Sonneborn, Muller's colleague at the University of Indiana, read into the record the equivalent of the Radiation Geneticist Mantra, indicating a belief that all radiation-induced mutational damage was cumulative, irreversible, and lacking repair. This combination of factors led to their belief that the dose response for radiation induced mutations was linear down to a single ionization. Radiation genetic risk assessment was best explained based upon the total dose; dose-rate, regardless of how low, would only result in cumulative damage. Sonneborn was not challenged on any point. This was a curious situation since most of the members of the Panel were often opinionated, at times had disputes with each other, and sometimes these interpersonal disputes were rather inflammatory. For example, Muller resigned from the editorial board of Advances in Genetics in a dispute with Demerec, the Editor-in-Chief, over publication of a manuscript by Ref. [33]. Demerec accused Muller of attempting to impose his version of scientific censorship [45]. Yet, despite their apparent personal rift, they were in full agreement on LNT.

Since the BEAR I Genetics Panel was in agreement that the dose-response was linear for radiation-induced mutagenicity it soon found itself with little to do. To fill this void, Weaver challenged the geneticists on the Panel to independently provide their detailed written estimates (including methodology) concerning the number of genetic defects the American public would experience assuming the gonads received a specific dose of ionizing radiation. This genetic damage was to be estimated for the next ten generations. Since the Panel was comprised of a broad range of geneticists (e.g., bacterial, paramecium, fruit fly, mammalian, clinical, population-based, etc.) each was encouraged to use their own education, training, and research methods to derive their independent answers. It was felt that if the estimates of harm from such divergent, but complementary perspectives closely converged, it would enhance confidence in policy recommendations.

Following their meeting on February 6, 1956, the Panel members were expected to complete their analyses over the next month. Of the 12 geneticists on the Panel (i.e., there were 13 to start but one resigned due to academic obligations), nine took up the challenge and provided detailed separate reports within the next month. The other three Panelists declined to submit comments, principally because they believed there was too much uncertainty such that any estimates would not be reliable. In the case of the human geneticist, James Neel, at the University of Michigan and expert on the effects of the atomic bomb on Japanese survivors, he was particularly animated in asserting his position based on written correspondence with Weaver. Neel believed that the uncertainty would be so substantial that it would be unethical to even provide them. More specifically, Neel wrote to Weaver the following on April 17, 1956:

> "The geneticist has social responsibilities, but he also has the responsibilities as a scientist. One is that in an area as critical as this one is, he must beware of letting his conjectures get too far in advance of his facts. It is to me an exceedingly tenable position, having stated the general genetic argument, to say flatly that we know so little about the quantitative aspects (see Ref. [20])."

The letter once again reflected the opinion of Neel that providing population-based estimates of genetic damage was an indefensible exercise and that he would oppose doing such that 'he would go down with flags flying and guns booming to the last' [108].

When the nine separate assessments were received, they were given to Jim Crow to collate, organize, and summarize so that the Panel could more easily assess the submitted reports (his specific function was 'to go through all the damage estimates, compare them, and display assumptions, methods, input, and results in some sort of chart or graphic form'. [20]; page 4). Upon his initial review of the received estimates, Crow sent a letter to Weaver on March 7, 1956 [37] stating the following:

> "Upon looking at the estimates I realized two things. One is that nobody seems to have very much confidence in them. The second point is that those who arrived at comparable estimates usually did it by comparable procedure so that they are not very independent."

Less than one week later Crow again wrote to Weaver [March 12, 1956 [38]]. 'The groups differ widely in their confidence in the best estimate, as indicated by their grossly discrepant minimum and maximum estimates.' In a follow up March 29, 1956 letter to Weaver [39], Crow wrote, 'The limits presented on our estimates of genetic damage are so wide that the reader will, I believe, not have any confidence in them at all.' That is, even though the expert radiation geneticists were told to assume that the dose response would be linear (thus already restricting group variability), the estimates nonetheless profoundly varied. The degree of disagreement was so substantial that Crow asserted that if these values were shared with the scientific community and the general public that it was likely that the Panel's scientific and policy recommendations would have little credibility. This was the key

[16] Obtaining grants to support research was important to some NAS BEAR Genetics Panel members. Personal Correspondence of some of the BEAR Genetics Panel members reveals they were motivated, at least in part, by self-interest, to overstate public health risks to promote their scientific and personal/professional agenda [18]. The fact that distinguished radiation geneticists of the BEAR Genetics Panel may have been willing to exaggerate risks (i.e., be dishonest - in their words: "stretch a point") to enhance their chances to obtain funding, is a critical finding as this type of self-interest has been usually only applied to scientists funded by private interests. What the comments reveal is that academic researchers who are dependent on government/foundation grants may be similarly susceptible. In the present case, these findings may be profoundly significant as the switch to the LNT model had major public policy implications.

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Table 3
Differences between Spencer/Stern and Caspari/Stern [32,154] (Source: [14]).

	Spencer/Stern	Caspari/Stern
Exposure	X-rays	Gamma rays (radium needle)
Animal Model	Males exposed prior to mating	Females exposed after mating
Exposure Duration	Acute exposure (minutes)	Chronic exposure (21 days)
Dose Rate	~15,000-fold greater than Caspari	~1/15,000 of Spencer
Vials	Plastic vials to hold flies	Glass vials to hold flies
Temperature	24 °C	18 °C
Diet	Cornmeal molasses	Honey yeast agar
Age (males)	≤7 days, most 2–4 days old	≥5 days
Controls	Controls poorly matched with treatment exposure period	Controls closely matched with treatment exposure period
Temperature Control	Poor, highly variable based on external conditions	Good
50-r Treatment Group	2 groups with different dose rates and exposure period all combined	A single 50-r treatment group all treated similarly
Mold Control	Used Moldex throughout study	Possibly less Moldex used in the 21 day radiation exposure period due to the lower temperature (18 °C vs. 25 °C)
Lethal Clusters	Not corrected for lethal clusters. If so, the treatment group (50 r) used would have had its mutation rate decrease by −8% versus 4% for controls.	Corrected for lethal clusters. No differences between control and treatment
Control/Background Radiation	Background exposure not given	Background exposure reported as 0.6 r
Sample Size Comparison	50-r treatment group had 20,400 less flies than the Caspari experiment	
Study Design	The study was not designed to affect the occurrence of lethal clusters	The study was designed to minimize the possibility of lethal clusters
F_0 Breeding Protocol Differed	40 females/40 males; females – 2 days old	50 females/100 males; females ≤16-h old
Radiation Exposure Condition Differed	20 males/capsule; no food in capsule	50 females/capsule; food in capsule
Lethal Designation Protocol Differed	Used 6 heterozygote females in F_2 generation to identify lethality	Used 2 female heterozygotes in F_2 to identify lethality
Viability criteria	A single wild-type male offspring lead to a designation of viable culture.	A single wild-type male offspring lead to a designation of a semi-lethal.

factor for Crow and the entire Panel. The assessment by Crow of the profound disagreement in the estimates amongst the participating nine geneticists would now be seen against the backdrop and context of the Sonneborn statement:

> … "the thing of most value in all this calculation would be to show how one can use different methods to make estimates, and see to what extent methods, if possible, variations in approach, lead to different answers. So that if they converge, or tend to converge, then we might have more willingness to put them forth." (BEAR I Genetics Panel Transcript, page 257)."

The problem of a lack of genetic damage estimate convergence by the panelists came to a head. There was really no way to proceed with confident recommendations. Further, these 'discrepant' estimates would have been even more discrepant had the views of the three non-participating geneticists, such as Neel, somehow been integrated into overall analysis. So what was the next step forward?

Without having the authority or having been so instructed to do so, Crow decided to save the 'single-hit theory', like Muller and Stern did a decade earlier. Crow excluded several of the independently provided expert assessments. This action was taken despite the fact that each of the Panel members was considered a legitimate world-renowned geneticist with a unique area of specialization.[17] Crow made the decision to eliminate the contribution of Demerec based on bacterial estimates. This action was taken for the stated reason that Demerec's values differed the most from the other estimates due to the use of different methods and approaches. More specifically, Crow wrote to Weaver on March 12, 1956 [38] stating, 'I haven't included Dr. Demerec's estimate on the graph for it, too, is based on quite different assumptions that lead to a greatly different value than the others obtained.' The bottom line is that Demerec's estimate of genetic damage was far below the other eight expert estimates and added significantly to the lack of desired convergence that Sonneborn emphasized was necessary.

The diversity and complementarity of approaches for the genetic damage risk estimates had been deemed to be a key strength of this exercise. However, upon seeing the results, Crow now thought otherwise and eliminated the human population based estimates of Wright and Kaufmann, without justification. The Wright and Kaufmann estimates were the next to lowest estimates. Given that Crow repeatedly expressed concern about the substantial variability amongst damage estimates of the panelists it was not surprising that the three estimates that he eliminated were the lowest. By eliminating these three from the total, it markedly reduced the range of the 'discrepant' estimates.[18]

The actions of Crow to eliminate three expert estimates and the willingness of the Panel to follow his lead is striking. In many ways, this situation became perversely humorous, especially after reading the basis of Crow's personal 'expert' estimates. For example, consider the methodology of Crow, which, of course he accepted. Crow combined three methods to provide a 'best' estimate of genetic damage, including his version of upper and lower bounds. He first decided to use data from the fruit fly for a lower bound. He then decided that human risks from the Japanese bomb survivor data would comprise the upper bound. The 'best' estimate was the mouse data of Russell since it rested conveniently between the fruit fly and human data. While each of these biological models may be used to construct their own best estimate and upper and lower bounds of uncertainty, the integration of each of the models as described by Crow is strikingly inappropriate. The bizarre manner in which he did these was amateurish and revealed that Crow had little understanding of how to proceed. Yet, there is no record that this approach was criticized by any member of the Panel. Further, Crow had stated that his actions to eliminate the estimates of Demerec,

[17] There is a strong general impression/belief that the BEAR I Genetics Panel members were top experts on radiation genetics, based on experience/publication record. In fact, the majority of the geneticist panel members had never published an article on radiation induced mutations prior to their selection on the Panel. Several others had a limited (i.e., several papers) publication record in this area. The bottom line is that the "expert" Panel image was a myth created by the Rockefeller Foundation and U.S. NAS to enhance the acceptance of the policy recommendations of the final reports.

[18] The best estimates of genetic damage for these three eliminated geneticists was: Kaufmann – 195,000; Wright – 50,000; and Demerec – 5220. These collective estimates are approximately 70% lower than those of the remaining five geneticists (i.e., 275,000). George Beadle did not provide an estimate for generation #1 [19].

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Wright and Kauffman meant that the Genetics Panel estimates would only be based on the data from fruit fly and mice [109,110]. Yet, Crow ignored his own imposed 'rules' as he used human data for the upper bound, again without receiving any criticism. This simple vignette of Crow's methodology, its inappropriateness and his violation of his own exclusionary rules and with his actions never being challenged, may explain why the Panel voted not to share their methods and findings with the public and scientific community. Not only would these estimates have been rejected, but their highly acclaimed expert status would soon be challenged and perhaps ridiculed.

The actions of Crow were probably not criticized by other Panel members because significant uncertainties reigned, even by those submitting 'detailed' estimates. For example, in his letter to Weaver on February 20, 1956 [168]; Sturtevant stated

> "After going through these calculations I come out with a feeling that they are rather futile. At almost every step it has been necessary to make a guess, often with little to go on and with no real basis for setting limits within which the true value probably lies."

In effect, Sturtevant was agreeing with the above sentiment of Neel.

These insights of Sturtevant clearly contradict the subsequent more politically correct statement in the *Science* article of the Genetics Panel which asserted that – Each (i.e., expert geneticist on the Panel) thus said, in effect: 'I feel reasonably confident that the true value is greater than my minimum estimate and less than my maximum.' Based on the Sturtevant letter, the statement in *Science* is not true. Even if this statement in *Science* were accurate, it is extremely weak, given the very large range between upper and lower bounds for most estimates.

To make matters even more suspect, consider a further and insightful criticism from Jim Neel, Panel member. He states that the reason for converging of estimates following the elimination of the Demerec, Wright and Kauffman estimates was due to the strategy of Crow to select estimates that were not independent but that used essentially the same assumptions for gene number, mutation rates and other parameters [109,110]. In fact, Neel exposed the bias of Crow's decision to restrict estimates to *Drosophila* and mice, as this would yield the false impression of scientific agreement where there was little or none. Thus, according to Neel[107,108], Crow knowingly biased the assessment in order to create the impression of a high level of Panel expert convergence. This plan fell apart when the Panel had to construct uncertainty estimates (i.e. upper and lower bounds), and an effort to seek a group consensus failed. A similar consideration of Crow's own approach for upper and lower bounds illustrates the unreliability of their estimates.

The continuing duplicity of Crow is displayed in his March 29, 1956 letter to Weaver [39] in which he tells Weaver that 'I suggest one of two things: (a) omit the estimates entirely, or (b) give a single best estimate of the number of mutations, or a narrow range of estimates, based on direct extrapolation from mouse and Drosophila'. Crow then writes 'We then state that these are based on mouse data and let the reader add his own uncertainty factor.'

This letter of Crow illustrates two significant points. The first is that he wanted to opt for showing either no estimates or only a 'narrow range' assuming the convergence of estimates based on mouse and fruit fly data. This suggests that he was trying to ensure that the report would be censored to reflect only the conclusion that he favored.

Secondly, after informing Weaver that he recommended using only the mouse and fruit fly, he states that the reader should be told that the estimates are based only on the mouse. This amounts to flagrant dishonesty. Perhaps he did not want the public to know that predictions for people were based on a fruit fly. He also inexplicably suggested that the reader should construct their own uncertainty factor, using highly censored (i.e., inappropriate) data, lacking upper and lower bounds. This last suggestion reveals that Crow recognized that he and the panel were not able to provide competent expert guidance and that each 'guess' was as good as the next.

Having revealed the internal communications of Crow, Weaver and other Panel members on how they derived genetic risks, it becomes clear that the process employed was scientifically chaotic, inherently flawed, had significant elements of deception and dishonesty, as well as signs of widespread professional incompetence. Yet, while this was being hidden from the public, the process was fully enveloped by an appeal to authority (i.e., U.S. NAS and members who were world leaders and promoted as experts on the topic of radiation induced mutations).

The 100-fold range of uncertainty for the first generation U.S. population mutational responses reported in the *Science* article for the six remaining experts misrepresents data that had already been highly censored. The statement that the uncertainty range for the first generation was based on the six selected expert estimates, as reported in *Science* is not correct, as George Beadle, one of the remaining six, only provided an estimate over 10 generations, not for generation #1. Thus, the article could have stated the uncertainty range of 10–2000 fold for the tenth generation effect (745 mean value) (based on six estimates) and the mean of 756 (100–2857) for the first generation (based on five estimates). Since only five or six estimates were used, an entire listing was very feasible, thereby being fully transparent. However, Crow did not want to show the actual figures or how they were derived as he repeatedly emphasized in letters to Weaver.

The recommendation of the BEAR I Genetics Panel to switch to the LNT for genetic risk assessment was a major event, affecting policy, politics, public perceptions of risk, risk communication strategies, as well as providing scientific foundational support for the efforts of Rachel Carson, in her groundbreaking and highly influential book *Silent Spring* published in 1962.[19] As a result of the publicity generated by the Genetics Panel report the US Congress would hold Congressional Hearings in 1957 on the topic of radiation health risk assessment, with multiple Panel members testifying before Congress in support of the switch to the LNT [66]. The process of getting their message out would achieve a significant and very practical milestone in December 1958 when the US National Committee for Radiation Protection and Measurement (NCRPM) [106] generalized the recommendations of the BEAR I Genetics Panel to include somatic cells, and so by doing, applied the LNT model to the process of cancer risk assessment. Since members of the NCRPM also were members of other high-level advisory committees such as the International Commission on Radiological Protection (ICRP), the adoption of LNT by other advisory groups and regulatory agencies in other countries would follow. The inclusion of the same geneticists on multiple 'independent' Advisory Committees represented a strategy to advance specific policies, giving the LNT supporting committee members more opportunities to promote LNT.

7. The BEAR I Genetics Panel in perspective

While LNT became the accepted dose response model for cancer risk assessment as a result of the recommendations of the BEAR I Genetics Panel in 1956, it was readily susceptible to challenges, especially on the grounds that the data were based on fruit flies, not mammals. Making this situation even more potentially contentious was that the BEAR I Genetics Panel voted (i.e., written ballot) not to provide written documentation of the scientific foundations for their decision to recommend the LNT. The reliance upon the fruit fly was rooted in the failed efforts of Donald Charles at the University of Rochester with funding from the AEC during the Manhattan Project to provide findings within a reasonable time period with rodent models concerning ionizing radiation and mutation. Regardless of this striking failure, it was

[19] The historian Ralph [75] states: "not only did she [Carson] tap into this anxiety [about fallout] and direct it toward pesticides, she also used the public's understanding about the hazards of fallout to teach about the similar hazards of chemical poisons."

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generally recognized that the fruit fly model would be an interim one for risk assessment purposes. In fact, this was a principal motivation behind the massive investment on the extensive mouse specific locus test program at the Oak Ridge National Laboratory. Alexander Hollaender, who created and oversaw this initiative, understood that the public health debate would require data from mammalian models just as was provided in other areas of hazard and risk assessment, especially as seen with chemical and pharmaceutical products. With respect to the Genetics Panel not providing a scientific basis for the LNT recommendation, this decision [8,21,54] was passed up the administrative ladder, eventually to the President of the NAS, Dr. Bronk, who did not challenge their decision [9] thereby establishing an inexplicable precedent. The actual underlying explanation was, at least in part, about money, that is, grant money for geneticists. The Panel saw the situation as a type of zero-sum game. That is, if the Panel spent their limited time researching, writing, refining and attempting to obtain agreement on the scientific foundations of their recommendations, then there would be insufficient time to identify funding research priorities for the RF via the actions and leadership of Warren Weaver [9].

Lost in this debate over whether to provide a written scientific justification for the various policy recommendations, including LNT, were the written comments of Muller and his dispute with Demerec and how he could not accept Demerec's bacterial model and his critical judgements of Wright's human genetic damage assessment. Muller would note in a letter about this to the new BEAR Genetics Panel Chairman, George Beadle (see below), 'why should the Panel share its dirty laundry for the world to see?' He had already accepted this fact, stating that 'quarreling geneticists' could not resolve their scientific differences. Based on a copious record of personal correspondence over decades Muller and Crow had a close personal relationship. Consequently, previously undisclosed information as revealed in letters from Muller to Beadle might provide an historical insight as to why Crow excluded the data of Demerec and Wright when assembling the genetic damage estimates of the BEAR I Genetics Panel members as previously noted. The comments of Muller to Beadle permit one to speculate whether Crow's decision to drop Demerec and Wright were initiated by a communication between Muller to Crow. The coincidence seems too great to dismiss the possibility.

The attitude that Muller brought to the issue of providing a technical report to the scientific community that would provide the basis for the Genetics Panel's recommendation is enlightening. He stated to Beadle [97] (now the Chair of the Panel – having just replaced Weaver):

> "As for the preparation of a technical report ..., it seems to me that it would involve us in a lot of thankless work and disputatious rehash of points we have already considered, as well as airing our dirty linen before the public unnecessarily."

Muller then goes on to state:

> "After all, only geneticists would be competent to judge the validity of our technical report and geneticists do not need it...."

Of particular importance were his follow up comments:

> "So far as I can see, it would be a matter of quarrelling over what would be the most important points to put in and to what extent they were valid, things on which I thought we had agreed to disagree. Why, for instance, should I enter into a public dispute with Demerec on whether a bacterial generation[20] should be taken as corresponding just as closely to a human generation as a Drosophila generation does? This is only one little example of many ... ... Similarly, I think I would have to disagree with Wright concerning the frequency and importance of small detrimental mutations as contrasted with the conspicuous ones known as lethals and visibles."

This correspondence of Beadle and Muller may therefore provide pivotal insight into the dynamics of the Panel, their need for grant funding, why they failed in their responsibility to the country, and how Muller sought to blunt the influence of Demerec and Wright in the internal Panel disputes. It also revealed how Weaver and Crow were willing to disrespect one person's area of expertise, even after it was stated that it was their goal to integrate and assess the estimates of each expert from the diverse fields within genetics.

8. Dose-rate: Russell's challenge to LNT

While December 1958 would prove to be significant for the adoption of LNT for cancer risk assessment based on the actions of the NCRPM, it would also be ironically important for a potentially significant challenge to the scientific foundations of LNT. This challenge would become evident on December 19, 1958 when the journal *Science* published a significant paper by William L. Russell and colleagues [141] from the Oakridge National Laboratories demonstrating the effect of dose-rate for ionizing radiation-induced mutation in spermatogonia and oocytes in the mouse model. The findings of Russell were broadly significant enough to become a front-page story in the *Buffalo Evening News* as written by the Pulitzer Prize Winner Nate Finney [49], who had a long and serious interest in the societal and public health implications of atomic energy and nuclear weapons. The first public sensing of Russell's work was revealed four months earlier in an August 16, 1958 story in the *New York Times* [142]. However, at the time of the *Science* publication in December 1958 the *New York Times* was on strike, leaving the reporting field wide open for the *Buffalo Evening News* reporter [138].

The Russell findings were significant because over time they would unequivocally refute the LNT mantra of the radiation genetics community. These mammalian findings with spermatogonia and oocytes would indicate that radiation-induced mutation damage was not cumulative and could be reversible and the dose response therefore should not be assumed to be linear. The findings also suggested to Russell that DNA-repair must occur even though it had not yet been discovered.[21] In fact, Russell's (and Altenburg's) inferences were correct. The Russell data were seen as a possible game changer and would quickly affect research directions for the field. It was indeed ironic that within a week or two of the accepting of LNT by the NCRPM, its possible demise was being featured in the most prestigious scientific journal in the world.

Analyses of the Russell scientific writings and correspondence reveals that he tried hard not to explicitly and directly challenge the radiation geneticist community and the seemingly exquisite sensitivities of Muller. Russell was performing a type of balancing act, that is, he was trying to promote his findings while adhering to the radiation geneticist mantra and still supporting the LNT. As can be seen from the published literature and correspondence (Russell letters/memos to Muller [133–135], Muller letter to Russel [98], Russell would maintain this (and perhaps torturous) position until Muller's death in April 1967 when he would finally and unashamedly confront the radiation geneticist mantra on each of its fundamental tenets with the mammalian data he had accumulated over more than two decades on dose-rate

[20] It should be noted that Demerec had an extensive publication record with *Drosophila*, spanning two decades and more than 50 papers in the peer-reviewed literature. He also had a strong publication record with bacterial mutations. Thus, Demerec was uniquely qualified to see the relationship of bacterial susceptibility with that of *Drosophila*. In fact, he was far more experienced in this than Muller. Furthermore, Demerec was originally trained as a maize geneticist with Emerson at Cornell for his Ph.D. in the most prestigious group in the U.S. Demerec was perhaps the most broadly experienced geneticist in the country.

[21] Edgar Altenburg would write Muller about the novel Russell findings, likewise suggesting the existence of DNA repair (Altenburg to Muller, December 27 [2]).

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[137]. More immediate, however, was the fact that within a few months after the publication of the Russell findings, Muller had shifted over his lab to now incorporate dose-rate studies with *Drosophila* based on the research methodology of Russell [24,25]. This represented a significant shift as Muller's earlier research on dose-rate with Ray-Chaudhuri [131,132] involved only mature fruit fly spermatozoa. With the switch to the use of earlier stages of reproductive cells, Muller was reporting that he, too, now had observed the dose-rate phenomenon [119].

The findings of the Russell and Muller dose-rate research found their convergence in the report of the next BEAR Genetics Panel (i.e., BEAR II) chaired by George Beadle, Nobel Prize recipient (1958) in its 1960 publication ([103] – BEAR II). The incorporation of this information came late in the Panel process and probably would not have happened without a last minute intercession by Russell and his director at Oak Ridge, Alexander Hollaender, who requested/challenged George Beadle to ensure that the dose-rate information be included. Beadle agreed and instructed Russell and Hollaender to write that section of the report [64]. The re-written report was then sent to all members of the Panel, including Muller, with a summary of the preliminary fruit fly dose response data of Muller. However, unlike the BEAR I Genetics report, the BEAR II Genetics Panel Report (1960) was not widely distributed, had little to no acclaim and no ostensible impact on the field or public policy based upon citation, follow up debate, and other possible spin-off activities. Nonetheless, the BEAR II Genetics Panel acknowledged the existence of dose-rate in their 1960 report in both mice and fruit flies. However, while the Genetics Panel finally recognized the biological reality of dose-rate, they failed to confront the issue of the generalization of the 1958 NCRPM LNT recommendation to somatic cells. The new dose-rate findings were a potentially significant scientific problem that could discredit the major dose response policy recommendation to support LNT.

Within a few years, it would become clear that a possible explanation for why the dose-rate phenomenon might not have been observed in the earlier Ray-Chaudhuri study (1939, 1944) was because the mature spermatozoa lacked the capacity for DNA repair while this capacity was present in somatic cells and spermatogonia and oocytes. Thus, reliance on mature spermatozoa, which lack the capability of DNA repair, as the basis for cancer risk assessment using the LNT model was/is a fundamentally flawed approach. Yet, it was within this framework that LNT was created and 'matured' into broad acceptance within the scientific and regulatory worlds of the 1950s and 1960s as guided by Muller and the radiation genetics community.

The 1960s revealed that Russell's research would be extended so that it enabled a clear threshold response to be observed for mouse oocytes at a 'relatively' low dose-rate. The oocytes displayed a threshold for genetic damage at an exposure rate that was 27,000 times above normal exposure to radiation in the U.S. from background and other exposures [136].

The data of Russell created an important rift within the radiation genetics community. This was highlighted by an article of Harold Plough [129], a professor of biology at Amherst College, and former genetics graduate student with Muller at Columbia. Plough was also the person who helped to facilitate a position (i.e., Amherst College, 1940–1945) for Muller in the U.S. upon his return after an eight-year hiatus and with no other available offers. This rift was significant as Muller and another (future) Nobel Prize recipient Salvador Luria, excoriated Plough as seen in letter exchanges and in articles/letters-to-the-editors to the *Boston Globe* (Menzies, June 19, [83]); Luria, July 2, [74]; page 18) and *Washington Post* (Simons, June 19, [147]). During this dispute, Jim Crow wrote to Muller, telling him that Plough was totally out of step with the rest of the radiation genetics community and that no one believed that thresholds for radiation-induced mutation exist [40]. The letter of Crow was curious since it was written after the BEAR II Genetics Panel (1960) (of which he and Muller were members) acknowledged the findings on dose-rate for Russell and Muller and after reports of Russell which clearly showed that a threshold exists for the mouse oocyte for ionizing radiation induced mutation. The letter of Crow to Muller was never challenged or corrected by Muller, despite its obvious factual flaws.

During the same time interval, Muller would become engaged in a substantial debate over the role of dose-rate in human risk assessment especially within the context of his role on expert committees of the ICRP [23–25]. In these debates, he claimed that the dose-rate data were inadequate to apply to human risk assessment. Part of his rationale was that differences in dose-rate responses between insects and mammals had not been resolved and therefore the mammalian data of Russell should not be used in human risk assessment. Yet, he argued that there was an evolutionary basis for this apparent interspecies difference in which dose-rate would have been more strongly selected for in mammals than in insects [99]. The point here is that at every possible turn Muller would attempt to preserve LNT, even if it meant being deceptive and dishonest (e.g., his comments about Caspari's control group) or inconsistent, as in this case, or imposing of censorship as in the case of his dispute with Demerec [48] and in his attempt to prevent Neel from speaking at an international symposium on his Japanese atom bomb survivor data ([25]; footnote 1).

9. Russell challenges radiation genetics mantra

While Russell finally broke ranks with the radiation geneticist community, it was not until the 1969–1970 time period as revealed in several publications and conference presentations (Table 4) [136]. In his 1970 presentation at the 14th International Congress of Radiation Research at Evian, France, Russell [137] stated that the original estimates of genetic risk (which were made by the BEAR I Genetics Panel) [7] for radiation (and, as noted by Ref. [17]) and later for chemical carcinogens were based on the two major assumptions that: (1) radiation-induced gene mutation frequencies in the fruit fly have extrapolative relevance to humans and (2) results from radiation experiments on fruit fly spermatozoa illustrate general principles of radiation genetics and thus can be applied to humans (i.e., the mantra of the radiation geneticist). What followed from these two overreaching assumptions was a series of six specific and fundamental risk assessment tenets (i.e., "general principles") upon which genetic and, as noted by Calabrese [17], cancer risk assessments were based. According to Russell [137], his radiation geneticist colleagues believed that,

> 1) Gene mutation rate is directly proportional to radiation dose; 2) Gene mutation rate is independent of radiation dose rate; 3) Gene mutation rate is independent of dose fractionation; 4) There is no repair of gene mutational damage; 5) There is no threshold below which no genetic damage occurs; and 6) There is no recovery from mutation with time after irradiation.

Following two decades of conducting genetics research on mice at Oak Ridge National Laboratory, Russell had evaluated the effects of ionizing radiation on over a million mice (radiation-exposed and control groups combined) in the largest progressive/cumulative mammalian study ever conducted. From this extensive experience, Russell [137] concluded that, ' … the first assumption is probably not valid, that the second is definitely incorrect, and that none of the six 'general' principles applied to mouse spermatogonia and/or oocytes.' During his presentation, Russell offered scientific evidence supporting these conclusions. This presentation had the potential to be a major galvanizing event that led to substantial debate while offering the opportunity for a significant mid-course correction concerning the nature of the dose response in the low dose/dose-rate zone. However, it failed to do so.

During this period (i.e., 1970) Russell would accept membership on the first NAS BEIR Genetics Subcommittee (BEIR I) which was to be chaired by Jim Crow. The central issue of this Genetics Subcommittee would be how it would address the nature of the dose response in the low dose zone. In effect, this was to be the next battle in the threshold versus LNT confrontation. It was then about 15 years since the

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precedent-setting BEAR I Genetics Panel report of 1956. During that time, the environmental revolution had started in earnest following Carson's [30] book, *Silent Spring*, the passage of the National Environmental Protection Act (NEPA) following the massive Santa Barbara oil spill in January/February 1969, signed into law by the U.S. Congress in December 1969, and the creation of EPA in 1970. Likewise, the role of quantitative risk assessment using low dose modeling received a strong boost by the seminal publication of Mantel and Bryan [76] that introduced the concept of low dose modeling for cancer risk assessment. This publication originated from the herbicide (i.e., aminotriazole) Cranberry scare during Thanksgiving of 1959 in the U.S. during the Presidential campaign between John F. Kennedy and Richard M. Nixon [65].

Mantel and Bryan [76] proposed that an arbitrary acceptable risk for carcinogens be set at 1/100,000,000 (1×10^{-8}) over a lifetime using the probit model. Regardless of the model, the concept of acceptable risk rather than reliance on a true biological threshold had taken hold at the National Cancer Institute (NCI) for chemical carcinogens and at the NAS for ionizing radiation. The creation of the BEIR I Genetics Subcommittee in 1970 occurred at a strategic moment as it was at the time of EPA creation, yet, before the Agency had constructed guiding principles for carcinogen regulation in the mid-1970s. Thus, even though the NAS BEIR I Committee was created to offer guidance to the country on the health concerns associated with the expansion of the domestic use of ionizing radiation, its recommendations would be more broadly influential, serving as an ideal source of highly respected scientific/public health guidance for environmental cancer risk assessment.

10. BEIR I

Following the death of Muller on April 5, 1967, the BEIR I Genetics Subcommittee (1970–1972) addressed the question of cancer risk assessment anew. They did this by reviewing what the BEAR I Genetics Panel wrote some 15 years before and reflecting upon what had been learned in the interim years. While much was discussed, several key concepts and findings emerged. The most important conclusion of the BEIR I Genetics Subcommittee was that the BEAR I Genetics Panel of 1956 made a mistake on the key concept of dose-rate. This conclusion was based on the data of Russell from the mouse specific locus test, which subsequently had matured and expanded, now having more than a decade of widespread exposure and scrutiny within the scientific community. Being wrong on dose rate was not a simple or singular point. It meant that genetic damage was not cumulative, could be reversed, and was repairable. These findings exposed multiple flaws in radiation geneticists' central beliefs. In the period between the discoveries of Russell in 1958, to the creation of the BEIR I Committee in 1970 DNA repair had been discovered, as predicted by Russell. The basis for the recommendation of LNT had, therefore, been convincingly challenged on scientific grounds.

The BEIR I Genetics Subcommittee also raised another fundamental point that challenged the BEAR I Genetics Panel report. This concerned the fact that the LNT, as derived from fruit fly data via the research of Muller and Ray-Chaudhuri and the Stern-Manhattan Project studies, used mature spermatozoa that were now known to lack DNA repair. The use of a biological model lacking DNA repair to estimate risks in somatic cells possessing DNA repair is fundamentally inappropriate. Yet, that is precisely what the LNT-based cancer risk assessment paradigm had long been based on. BEIR I also knew that it had to transition to the so-called modern era-that is, adopting a rodent model with cells that possessed DNA repair. The real challenge was whether they could do this and still retain LNT. This was an especially significant challenge since the dominant intellectual and ideological paradigm amongst the geneticists was LNT, a perspective that had become rooted not only in the science, but also within their culture.

In contrast to the BEAR I Genetics Panel, the BEIR I Genetics Subcommittee provided a written basis for their recommendation of the adoption of the LNT. This recommendation was very much like a reaffirmation of the status quo, lacking the fairness of an independent competition between two ideas (i.e., LNT vs threshold). In the case of the threshold vs LNT debate the Genetics Subcommittee would not only play a significant role but so to would the findings from animal studies and epidemiology.

These two disciplines represent important components in the overall risk assessment process. However, neither of these complementary methodologies is capable of adequately addressing the LNT question. This can be best appreciated by the fact that the mega-mouse study of the U.S. FDA, which used over 24,000 mice could only confidently estimate risk down to the 10^{-2} (1/100) area and is therefore referred as the ED01 study [11]. The limitations of epidemiology are also widely known within the legal system in the U.S. only accepted as a causal judgement when the odds ratio is ≥ 2, that is, when the risk at least doubles [164]. This is far greater than values of $1/10^6$ (or even 1/10) that are implicit in present risk assessment practice.

The BEIR I Genetics Subcommittee based their judgement in large part upon a belief in the mechanisms of radiation induced cancer, and this was due to an initial event that involved mutagenicity, a view now widely seen as insufficient, requiring multiple steps/stages [48].[22]

If it could be shown that the dose response for mutagenicity was linear at low doses, it was widely believed that the dose response for radiation-induced cancer would also be linear. This was precisely why the mantra of the radiation genetics community of cumulative, irreversible and linear was central to the risk assessment process and regulatory Agency policy. The challenge facing the BEIR I Genetics Subcommittee was that now the paradigm-changing data of Russell had taken center stage. Russell's data was not trivial but based on the findings of more than a million mice in the largest cumulative mammalian genetic toxicity program ever undertaken. It was an example of Big Science and was funded and located within the AEC, which later became the ERDA and later still the Department of Energy. As such, it was a program that involved a large number of professional staff over several decades. The government had made a massive investment in this area for the explicit purpose of having a solid scientific foundation for the risk assessment process for ionizing radiation.

Over the decades since the 1950s Russell and his team published numerous papers on their progressive studies, with accumulating sample size. The initial striking findings of the 1958 *Science* journal paper, which demonstrated the existence of dose rate effects in spermatogonia and oocytes were confirmed and strengthened with its massive cumulative size. The findings for the male indicated that by lowering the dose-rate the mutation damage incidence could be significantly reduced as compared to the same total dose given acutely. The research demonstrated that the mutation incidence could be reduced by about 70% in males. In a series of parallel experiments with females, they demonstrated that at 'low' dose-rates that the amount of genetic damage could be reduced by 100%, that is, the low dose-rate females became indistinguishable from the controls. The findings of Russell were of striking significance, especially for the females since they demonstrated the unequivocal existence of a threshold for genomic mutation as induced by ionizing radiation. The mechanisms by which these decreases in mutation rate occurred was explained by the presence of DNA repair. Why the male did not return to the control group value as did the female was not known at that time. While it would seem that answering the question of why the females achieved a

[22] The actions of the BEIR I Genetics Subcommittee were deeply rooted in the Somatic mutation theory (SMT), a view that has directed cancer risk assessment to the present. While not the focus of the present paper, the SMT has been challenged from multiple perspectives [134,151,152] over the past decade. How such developments may affect the federal cancer risk assessment criteria remains to be seen.

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threshold and the male did not was extremely important, it was never resolved by the BEIR Genetics Subcommittee. A possible technical reason why it could not be easily addressed was because the number of exposure days was limited by the duration of spermatogonial development. This placed a constraint on what dose/dose-rate could be delivered to a particular stage of cell development, essentially limiting research to resolve the male threshold issue.

When the BEIR I Genetics Subcommittee [105] evaluated the Russell data it acknowledged the existence of dose-rate and the threshold response of the female. It also noted that the male spermatozoa showed a decrease by 70% in mutation rate as compared to the acute exposure, but still not a threshold. Based on their report, there was no discussion of why, from an evolutionary perspective, the oocytes would display a threshold while the spermatogonia did not. For example, perhaps the spermatogonia were simply progressively lessening their DNA repair capacity that would eventually result in the DNA repair deficient mature spermatozoa. Alternatively, perhaps a threshold may have been detected had lower dose-rates been evaluated. Is there an evolutionary reason why such a gender-difference would exist? Would such a difference exist in somatic cells? Of course, these questions were all premised on the assumption that the Russell findings were correct, accurately presented and interpreted. The judgement of the BEIR I Genetics Subcommittee was that the LNT should be retained/adopted based upon the spermatogonia of the Russell data. They decided to construct a linear dose response from the lowest dose tested (i.e., dose associated with the ~70% decrease in mutations in males) to the origin. They also made the assumption that the spermatogonial cells would be a better representation of somatic cells than mature spermatozoa. Thus, the BEIR I Genetics Subcommittee transitioned from dependence on the mature spermatozoa of the fruit fly for the LNT recommendation to the Russell findings with mouse spermatogonia while still retaining the LNT.

The BEIR I Genetics Subcommittee report [105] proved to be highly influential as it would serve as the basis for how U.S. regulatory agencies would estimate risk for both ionizing radiation and chemical carcinogens. This was first reported in 1975 (and reaffirmed two years later in 1977) by the US EPA. The agency explicitly cited the Genetics Subcommittee report and the dose-rate findings of Russell as described in the following quote from Calabrese, 2017b [25]-see quote, page 456):

> "EPA uses primarily the recommendations of the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR) as expressed in the November 1972 report to arrive at dose to health conversion factors. Besides the concept of linearity expressed in the policy statement (i.e., EPA, 1975– EPA Policy Statement on Relationship between radiation dose and effect. 41 Federal Register, 28409), it is further assumed that health effects that have been observed at dose rates much greater than those represented in this report are indicative of radiation effects at lower dose rates. Any difference in biological recovery from precarcinogenic radiation damage due to low dose rates is neglected in the BEIR health estimates."

The U.S. EPA Carcinogen Assessment Group (CAG) under the direction of Roy Albert [1] would also explicitly cite the recommendations and rationale of the BEIR I Genetics Subcommittee (1972) [105] as providing the basis for the use of LNT for the assessment of risk for chemical carcinogens. The EPA accepted the LNT model of the AEC/BEAR I Genetics Panel. This model was adopted by EPA since it was easy to apply. From a toxicological perspective, the agency simply had to identify the lowest dose of carcinogen that induced a statistically significant response and then draw a straight line to the origin of the graph in order to estimate cancer incidence at any exposure level. The biological plausibility of the LNT model was based on the assumed linearity of mutation dose response as recommended by BEAR I and BEIR I, within the framework of target theory. Albert [1] indicated that ' … any difference between chemical carcinogens and ionizing radiation could be waived aside as they both cause genetic damage … '. Thus, in retrospect, the long term investment in the research by Russell on the mouse specific locus test, which started in 1949 at Oak Ridge National Laboratory, proved to be a highly successful endeavor as it now provided the scientific rationale for carcinogen risk assessment for all U.S. regulatory and public health agencies.

The Russell findings were so massive and credible that they served as the fundamental basis for understanding how ionizing radiation and genotoxic carcinogens would act at low doses/dose-rates. This became a type of toxicological 'homing device' that complemented the necessary (and significant) but insufficient whole animal and epidemiological data which lacked the power to confidently assess low dose/ambient exposure effects. In effect, the Russell findings became the gold standard, providing the intellectual rationale for linearizing carcinogen dose responses. Despite this reaffirmation of the LNT, it was insufficiently appreciated that this foundation, based on the Russell data, had its own significant inconsistencies. For example, the oocyte showed convincing evidence of a threshold even at doses about 27,000 fold greater than background. There was also no data to indicate that the male, even though not showing a threshold at doses comparably greater than background, might not show one at lower doses/dose-rates. Nonetheless, this was the basis of the LNT over the next half century. Over this period of time many thousands of new research papers were used by proponents and opponents of the LNT but the rationale for the LNT would remain the same. It would revert back to BEIR I, the Genetics Subcommittee and the Russell findings. Even multiple studies showing that cosmic/terrestrial ionizing radiation appears necessary for improving a wide range of health indices in multiple species [51,67,128] was not sufficient to make a change from LNT.

11. BEIR I error discovered and corrected

Nearly 25 years (in 1995) after the convening of the BEIR I Genetics Subcommittee, Paul B. Selby, a senior geneticist at Oak Ridge National Labs, and a former Ph.D. student of William L. Russell, uncovered significant irregularities in the construction of the historical control group used in all the major mouse specific locus test studies and risk assessment applications. The irregularities were of such potential magnitude as to warrant an external assessment by a committee of four leaders in the field. The external expert committee, plus the Russells' and Selby agreed that the control group required correction, with an adjustment upwards for mutational incidence. The Committee requested the Russells and Selby publish their adjustments in the scientific literature. The Russells adjusted the mutational rate upwards of 120% [140] while Selby argued that the control values were wrong by 5–7 fold [144]. While this dispute was contentious, the tone of these published articles was non-inflammatory making it difficult for the field to appreciate the seriousness of the debate and its widespread implications. Over time, publications accumulated which addressed many of the issues debated by the Russells and Selby [140,144,145]. The net result was that the arguments of Selby had grown in statue with broad acceptance by leading radiation geneticists [24,25].

Despite this ongoing process, it was only recently that the question was raised concerning how would the Russell and Selby adjustments have affected the judgements/conclusions of the BEIR I Genetics Subcommittee [23–25]. This was a relevant question, for if the Russells had provided accurate control group information, it would have been available for the BEIR I Genetics Subcommittee through their 1970–1972 meeting period. In a recent paper, it was shown that if the Russells' upward correction had been made at the time of the BEIR I, the data would have revealed that the male mutation incidence at the low dose-rate would have displayed a threshold (i.e. the 70% decrease in mutation would be 100% with the error correction) [24,25]. If this had been the case, then the argument used by the BEIR I Genetics Subcommittee for the adoption of the LNT would have been invalid.

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Furthermore, if the analysis of Selby had been available and used, it would have supported a possible hormetic dose response interpretation.

These new findings are significant, since they argue that the basis of the modern LNT as originated with recommendations of BEIR I, was based upon a mistake and are therefore invalid. While science is supposed to be self-correcting, it is clear that it has taken nearly half a century for this error to be recognized and a correction proposed. The reasons for such a prolonged failure to detect the control group error are likely many, but require speculation. Perhaps the most reasonable is that the mouse SLT was a unique bioassay, requiring massive resources. It could only be conducted in large governmental laboratories. There was only one such location in the U.S. This would become an issue because many technical questions and methodologies were unique to the specific locus test, limiting the number of people with adequate expertise to review and correct possible errors. It also exposed flaws in the peer-review process. Journal editors may have been at a loss as to whom to send the Russell manuscripts to. This leads to an appeal to authority and an unwillingness to challenge authorities such as Russell. In fact, the only challenge would originate internally, which is not a surprise, as very few would have known as much as Selby and to have been in a position to offer highly technical criticisms.

Such corrections, when applied to the risk assessment actions of BEIR I, indicate that those actions would also need to be adjusted. This adjustment would confront the issue of whether this central and dominating recommendation of BEIR I that lead to the reaffirmation of LNT should be changed. In retrospect, the data indicate that the NAS BEIR I Genetics Subcommittee used the Russell data to re-affirm the LNT model and did so not knowing that the historical control data used in the Russell publications was incorrect by from 2 to 7 fold. Given the prestige of the NAS, the complexity of the mouse SLT, and the high esteem of the Russells, the data and the recommendation were assumed to be accurate. This unprecedented situation created the perfect scientific storm: the entire carcinogen risk assessment process of the US and essentially all other countries with appropriate regulatory governmental structures was based on a significant undetected mistake that is still guiding cancer risk assessment today.

12. Discussion

The history of the LNT is shown to have originated as an attempt to discover a biological mechanism that could explain evolution. While this proposal of Olson and Lewis [118] failed to be convincing, their idea that the dose response for radiation-induced mutation should follow a dose-related direct proportional relationship (i.e., a linear dose-response) was persuasive, at least to the radiation geneticist community. This view was quickly adopted by Muller and supported by laboratory findings under his direction. Muller would soon become the dominant influence in formulating the proportional response concept, its generality and scientific implications (i.e., Proportionality Rule). Soon after these descriptive developments of the Proportionality Rule model, the next step was the development of a proposed mechanism. This was achieved in 1935 by Timofeeff-Ressovsky et al. [169] in their classic paper that has been rediscovered, translated, and given modern prominence [150]. This action added the concept of target theory by leading physicists to provide the mechanism. Complementing the mechanism, Zimmer [180], one of three authors of the key 1935 [169] paper, provided the mathematical formulation, which functionally showed that the LNT model was due to a single hit (Fig. 1). It was this sequence of actions, which were the fundamental scientific building blocks of the modern LNT-single-hit model. Muller would then secure the biological credibility of the LNT in subsequent studies with Ray-Chaudhuri [131,132]; which indicated no support for the dose-rate concept. Total dose was all that counted, regardless of whether ionizing radiation was given acutely or chronically. This perspective would translate into a linear dose response model with adverse effects being predicted down to a single ionization. While Muller strongly supported the LNT, it is important to note that highly credible data challenging the LNT judgement were generally ignored or marginalized, even though having scientific credibility (Table 1).

The radiation genetics community was intellectually led by Muller, even though there were many strong personalities within the group. Muller was unique amongst the other talented radiation geneticists, showing a very strong commitment, extremely attentive to detail, with a highly critical and combative demeanor. As a result of his leadership, the field adopted his view that radiation induces mutation in a linear fashion. This group of radiation geneticists wanted this view to guide medical treatments and health/exposure standards for the general public and workers.

The entire scenario just described was based on the incorrect interpretation by Muller of X-ray induced gene mutation in *Drosophila* at very high doses and how this error mesmerized the scientific community and government leaders even in the presence of credible and devastating criticism by Stadler and others. Thus, the LNT-SH model was based on a mistake and consequently led to the flawed cancer risk assessment recommendations of the NAS BEAR I (1956) [7] and BEIR I (1972) [105] expert panels. Muller was therefore able to mislead the field, regulatory agencies and even the Nobel Prize committee. In fact, despite having been shown to be incorrect on his interpretation that he induced gene mutation, his views still control the textbooks and governmental risk assessment policies worldwide, even in 2019, despite overwhelming modern data to the contrary.

From my perspective, the initial two decades of LNT development occurred in a manner that was typical of novel concept challenges and acceptance within science and society. This process became problematic and controversial only after Ernst Caspari, in August 1946, presented his data to Stern. These data did not support the Muller-Ray Chaudhuri lack of dose-rate findings. When seen in the perspective established above, one can better appreciate why Stern rejected the contrary findings of Caspari and why Demerec [3] was so concerned that he implored Caspari with the statement, 'What can we do to save the hit theory.' Stern and Muller, key leaders of the radiation genetics community, were strikingly challenged by the new data. The Manhattan Project was far more advanced than the research of Ray-Chaudhuri with Caspari's study having improved quality control and study design features. Earlier papers (e.g. [15]), revealed a series of

Table 4
Summary of the effects of dose-rate on the induction of mutations by radiation in the mouse (Source: [136]; page 623)*.

Russell Quote:
"Using the genetic techniques available today and the data discussed above, it is of interest to estimate the frequency of mutations that would be expected if a population of mice received the maximum gonadal dose of radiation (5 rem over a 30 year period) allowable for the general population in addition to background radiation. This radiation dose of 5 rem would be received at a dose rate of approximately 3.3×10^{-7} r/minute (0.00000033r/min). This is a dose rate that is over 27,000 times smaller than the lowest dose-rate used in studies with female mice in which no induced genetic effect was observed even when a dose of 400r was used. Therefore, no significant effect would be expected from this low dose (5 rem) even if it were delivered at a considerable higher dose-rate. This dose-rate is also 3000 times smaller than the lowest rate used in experiments with male mice. The lack of a threshold dose-rate, however, when males are considered means that one would expect mutations to be induced at the seven specific loci, and these could be detected, but an extremely large and costly experiment would be necessary. For example, if one uses the mutation rate obtained in the low dose-rate experiments, 8×10^{-8} mutations/locus/gamete/r, one would expect 280 mutations/100 million gametes or progeny tested (8×10^{-8} mutations/locus/gamete/r) (7 loci/gamete) (5 rem). This, obviously, is an experiment which is not feasible to carry out from any standpoint."

*Even this assessment by Russell is now recognized to have significantly overstated the mutation risk due to an error in the historical control group. Correction of this error using the Russell adjustment reveals a threshold response. Correction of this error using the Selby adjustment suggests an hormetic response [24,25].

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irregularities in judgements and behavior by Stern and Muller, first occurring after Caspari presented his data to Stern. These include:

1. Stern directing the writing of the manuscript discussion that challenged the acceptance of the Caspari data.
2. Writing a discussion that placed greater credibility on the acute exposure Spencer experiment that had numerous limitations. The support for the Spencer data was due to its apparent demonstration of a linear dose response (i.e., supported the geneticist mantra) – not to its scientific quality.
3. Muller's disavowing the possibility of a threshold at his Nobel Prize lecture, even after he had seen the Caspari data supporting a threshold and had strongly recommended that funds be obtained to replicate it.
4. Both Stern and Muller promoting the validity of the Delta Uphoff experiments which had aberrantly low control group values, which Uphoff and Stern stated in writing made these data uninterpretable.
5. Uphoff and Stern publishing a note in *Science* that included the uninterpretable findings and not sharing with the readership why data, unacceptable less than a year before in the formal report to the AEC, were now acceptable.
6. The failure of Uphoff and Stern to fulfill their pledge to the *Science* readership that they would publish a follow up paper with detailed methods, materials and supportive data.
7. The false reporting by Muller [94,95] that Caspari had an aberrantly high control group value, while his own data and memos explicitly confirmed the findings of Caspari and discredited the control data of Uphoff.

These obfuscations and deceptions by Stern and Muller would not only enhance the acceptance of the Uphoff and Stern [172] paper but would also lead to marginalization of the Caspari findings [148,149]. The goal of the Stern and Muller actions was no less than that of Demerec, which was to save the LNT SH model and to promote its acceptance. The perspectives of Stern, Muller, and others in the radiation genetics community were also shared by the leadership of the Rockefeller Foundation who selected geneticists who were LNT advocates for the NAS BEAR Genetics Panel. This bias was also seen in the selection of Weaver to Chair the Panel and his inappropriate remarks that (1) raised the possibility of sizable and highly flexible grant money for geneticists if their report was 'appropriate', (2) the inappropriate actions of Crow to exclude three technical estimates of genetic damage by the contributing geneticists, (3) the false reporting in *Science* by the BEAR I Genetics Panel concerning the number of panel members who provided radiation risk estimations, (4) the misrepresentation of variability of the six (i.e., five) estimates of the Panel and (5) the actions of the President of the NAS to support a decision of the BEAR I Genetics Panel not to provide a written report explaining the scientific basis of their recommendations.

Led principally by Muller, the BEAR I Genetics Panel was successful in convincing essentially all major advisory groups and countries to adopt their LNT recommendation. This scientific saga would be renewed with the dose-rate findings of Russell in the mouse model. Even though the findings of Russell would essentially disprove the radiation genetics core concepts of cumulative, irreversible and linear responses, the BEIR I Genetics Subcommittee, some 15 years after BEAR I, could not break free from the hold on the field that Muller had imposed and passed on to his scientist protégées, such as Jim Crow, who chaired the BEIR I Genetics Subcommittee. Finally, due to the vigilance and courage of Paul B. Selby [144,145,], key mistakes by Russell were revealed, forcing a revision of the Russell dose-response findings in 2017 [24,25], leading to a highly credible challenge to the LNT model.

Not to be forgotten in the LNT story is Muller's Nobel Prize. The international prestige of the Nobel Prize, received by Muller in 1946, provided enormous and enduring support for Muller's career, the field of radiation genetics, and the LNT. The awarding of the Nobel Prize for the production of x-ray-induced gene mutations provided the necessary credibility for the transformation of a clearly flawed hypothesis into a major environmental and public health belief system and cancer risk assessment policy. The Nobel Prize Committee's decision transformed a progressively discredited hypothesis (in light of the research of Stadler, McClintock and others) into a biological 'truth' following health concerns generated by the dropping of the atomic bomb in 1945 in Japan. The widespread adoption of the LNT may be directly tied to a flawed decision by the Committee to award Muller the Nobel Prize. It is likely that without the 'boost' provided by the Nobel Prize for Muller the history and acceptance of LNT would have been significantly affected.

The history of the LNT is complex, strikingly revealing the intersections of science, personalities, politics, power, financial temptations, and most importantly, beliefs. While a substantial part of this story was pieced together from the peer-review literature, other findings and insights were revealed via the NAS meeting transcripts and numerous letters, memos, and preserved papers of members of the NAS Genetics Panels and others. In fact, unless strenuous efforts were made to obtain and explore these additional sources of information, the story of LNT would still remain obscured and a false representation would persist regarding what the historical record now reveals.

13. Conclusions

The LNT single-hit dose-response model for cancer risk assessment was conceived, formulated, and applied in a manner which is now known to have been scientifically invalid. Contributing to the embrace of the LNT model were a series of scientific errors and the unfounded assumption that one could accurately extrapolate potential risk from very high to very low doses of ionizing radiation. This occurred despite findings indicating that (1) the type of genetic damage/mutation spectra is highly dose dependent (i.e., mostly gene deletions at the high doses used by Muller and not gene mutations), precluding accurate and valid low dose extrapolation, (2) the use of mature *Drosophila* spermatozoa which are haploid and lacking of DNA repair to extrapolate to mammalian somatic cells which are diploid and possess efficient DNA repair, and (3) the rejection of dose-rate in risk assessment which is now an important concept in ionizing radiation risk assessment. Thus, the concept of LNT single-hit for cancer risk assessment is shown to have multiple flaws that reveal its lack of scientific validity. However, despite these flaws the radiation genetics community of the 1940s-1960s promoted and strongly advocated the adoption of the LNT single-hit model to replace the threshold model. As documented in this review, on numerous occasions leading members of the radiation genetics community abandoned their scientific role and instead became ideological advocates for the LNT single-hit model, displaying questionable judgements and behaviors that reflected efforts to obfuscate, deceive, and even misrepresent the scientific record. These actions clearly played a significant role in the successful adoption of the LNT by the scientific and regulatory communities, as well as in widespread public health policy. By the early 1970s numerous limitations of the BEAR I Genetics Panel cancer risk assessment approach were recognized by the BEIR I Genetics Subcommittee, by replacing the fruit fly with a mammalian model and using diploid cells with DNA repair showing clear dose-rate effects. Nevertheless, LNT was still retained since a threshold for mutagenicity was only found in oocytes, and not in spermatogonia. However, more recent re-evaluations of the scientific basis of the BEIR I Genetics Subcommittee show that the data upon which its judgement was based were in error, requiring a significant historical control group adjustment. These adjustments now unequivocally reveal that the responses of both male and females displayed threshold dose responses, indicating that the basis of cancer risk assessment as recommended by the NAS BEIR I Subcommittee and accepted by virtually all regulatory agencies, is demonstrateably incorrect. These new findings have profound implications for regulatory agency cancer risk assessment, cost-benefit analyses, numerous public health practices, technological

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developments, use of nuclear power, and risk communication messages to the general public for both radiation and chemicals.

Declaration of interest

Author declares no potential conflict of interest.

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Appendix 1. A 90-year LNT Chronology: From mutation to cancer risk assessment

Statement	Year
First report of induced mutation; Gager and Blakeslee	January 1927
Muller report on X-ray induced mutation in Science	July 1927
Muller (and Gager and Blakeslee) presented data on mutations at Genetics Congress	September 1927
Stadler-presentation of X-ray induced mutation in plants-AAAS Conference	December 1927
Muller and Gager and Blakeslee - 5th Genetics Congress proceedings	undetermined date but published before Sept. 15, 1928
Muller - presentation to National Academy of Sciences on X-ray induced mutations	April 24, 1928-pub. Sept. 15, 1928
Stadler - publication of mutation data in Science	August 24, 1928
Muller - publication of mutation data in PNAS; in this publication he cited the proceedings of the 5th international genetics congress with correct page numbers but with a 1927 publication date which was incorrect.	September 15, 1928
Alex Olson and Gilbert Lewis - proposed linear dose response for mutation to be mechanism of evolution; published in Nature	1928
Oliver (Muller student) dissertation showing linear dose response for radiation induced mutations	1930
Muller proposes Proportionality Rule	1930
Stadler challenges Muller on gene mutation interpretation for reported transgenerational phenotypic changes induced by ionizing radiation. Challenge based on novel cytogenetic advances of McClintock.	1931 and then at 1932 6th international Genetics Congress
Timofeeff-Ressovsky et al. propose single hit model and link to Muller's linear dose response mutational data	1935
McClintock demonstrates new mechanism for radiation-induced mutation	1935
Ray-Chaudhuri (Muller's student) dissertation supports total dose/linear theory	1939
Manhattan Project-genetic mutation study starts at U. Rochester with Curt Stern directing project	1943
McClintock develops the transposition gene theory – new mutation mechanism	1944
Ernst Caspari's data support threshold rather than linear dose response in Manhattan Project research with Curt Stern	fall 1946-Muller sent data (November 1946)
Muller receives Nobel Prize for 1927 findings – misleads Nobel audience in lecture on dose response	December 1946
Stern fails to adequately replicate Caspari study with Delta Uphoff	1946–1948
Stern published Warren Spencer and Caspari papers in Genetics	January 1948
Salvador Lauria (future Nobel prize recipient) tries to convince Muller to incorporate McClintock's transposon findings into mutation theory	1948
Stern and Uphoff publish mini-meta analysis of Manhattan Project mutation research in Science	1949
Robley Evans, MIT, supports threshold model, based, in part, on Caspari threshold evidence in a Science publication	1949
Muller tries to get Stern to challenge Robely Evans; fails on this and then writes articles misrepresenting the Caspari control group data	1950 and repeats this argument again in 1954
Edgar Altenburg tries to convince Muller to incorporate McClintock's tranposon model into gene mutation theory	1952
Stadler criticizes Muller gene mutation explanation and single hit model in Science	1954
National Academy of Sciences BEAR I Genetics Panel, 1955–1956 recommend switch to LNT, misrepresent findings in Science paper and later refuse to provide scientific justification for their recommendation	Summer 1956
NCRPM applies LNT model for cancer risk assessment	December 1958
William L. Russell (Oak Ridge National Labs) published first evidence of dose rate for mutations with ionizing radiation, suggesting the existence of DNA repair	December 1958
NAS BEAR II Genetics Panel, report acknowledges dose rate in mouse and Drosophila	1960
Russell and Muller have debates in international advisory committees over the role of dose rate in human risk assessment	1963–1965
Muller dies	April 1967
Russell publicly renounces radiation genetics dose response mantra	1969 and 1970 based on dose rate findings
NAS creates BEIR I (1970) which retains LNT while rejecting total dose; it switches to use of Russell mouse data from fruit fly reliance. Committee is unaware of significant error in Russell control group data	report in 1972
EPA adopts LNT based on the use of the Russell data (which is still in error)	1975 and reaffirms it in 1977
EPA adopts single-hit LNT model for radiation and chemical carcinogen risk assessment, incorporating an independence of background modeling feature	1979 – notice in Federal Register
EPA switches from single-hit to multi-stage model for cancer risk assessment	November 1980
EPA adopts additive to background assumption for cancer risk assessment, drops independent to background	1986 – EPA cancer guidelines
Paul B Selby reports error in Russell control group in 1995; error confirmed by the Russells and corrected in the scientific literature separately by Russells [140] and Selby [144,145]	1996 and 1998
Calabrese applies Russells' and Selby corrections to BEIR 1972 risk assessment and reports that a threshold or hormesis response would have been reported if the control group error had been detected and corrected at the time of BEIR I	2017

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.cbi.2018.11.020.

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Appendix A. Supplementary data

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