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Ed

The Mistaken Birth and Adoption of LNT: An Abridged Version

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Abstract

The historical foundations of cancer risk assessment were based on the discovery of X-ray-induced gene mutations by Hermann J. Muller, its transformation into the linear nonthreshold (LNT) single-hit theory, the recommendation of the model by the US National Academy of Sciences, Biological Effects of Atomic Radiation I, Genetics Panel in 1956, and subsequent widespread adoption by regulatory agencies worldwide. This article summarizes substantial recent historical revelations of this history, which profoundly challenge the standard and widely acceptable history of cancer risk assessment, showing multiple significant scientific errors and incorrect interpretations, mixed with deliberate misrepresentation of the scientific record by leading ideologically motivated radiation geneticists. These novel historical findings demonstrate that the scientific foundations of the LNT single-hit model were seriously flawed and should not have been adopted for cancer risk assessment.

Keywords

risk assessment, mutation, linearity, history of science, cancer, X-rays

In 1927, Herman Muller mistakenly asserted that he had used X-rays to induce “gene” mutations in *Drosophila*.¹ Although flawed and unverified, this interpretation was well received and widely accepted by the scientific community.² Both the 1930 “Proportionality Rule” of Muller and the 1935 “LNT Single-Hit dose–response model” of Timofeeff-Ressovsky and colleagues³ were offspring to Muller’s mistaken conception of X-ray-induced “gene” mutations.¹ Critics from the genetics community, such as Lewis J. Stadler, Barbara McClintock, and others, soon argued convincingly that Muller’s idea lacked scientific proof and could be alternatively explained by mechanisms involving gross chromosomal deletions and aberrations rather than mutations within specific genes.¹ Responding to such criticisms, Muller quickly conducted research—albeit experimentally limited—to support the accuracy of his conclusions on X-ray-induced “gene” mutations, specifically that mutational responses were cumulative (ie, that the total dose—and not dose rate—was important), irreversible, and linear with respect to dose.^{4,5} Soon though, more experimentally rigorous studies were performed under the oversight of the Manhattan Project and produced results that seriously challenged Muller’s concept of “total dose”.⁶ Sadly and shockingly, influential leaders of the US radiation and genetics communities, including Stern and Muller, chose to misrepresent and thereby marginalize the more carefully performed studies.⁶⁻⁸

The alarming saga continues. In 1956, the prestigious NAS Biological Effects of Atomic Radiation (BEAR) I Genetics Panel deliberately misrepresented its own research to promote the acceptance of the linear nonthreshold (LNT) model by regulatory agencies.^{7,8} Moreover, the same NAS BEAR I scientists along with other experts from the scientific/regulatory communities⁹ “eagerly and wrongly” assumed that if the dose–response for X-ray-induced mutations in mature spermatozoa was shown to be not only linear but also “independent” of dose rate, then this same dose–response relationship could be used in risk assessment to generalize across all cell types, all doses, and all dose rates.^{7,8} In only a few years, mature spermatozoa were shown to be the exception and not the rule. Unlike most cells, mature spermatozoa were found to lack the ability to repair mutations induced by either chemicals or

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radiation,^{10,11} proving that the assumption of the NAS BEAR I Genetics Panel and its affiliates was wrong. In late 1958, William L. Russell showed that X-ray-induced mutations in the spermatogonia and oocytes of mice could indeed be repaired and—in direct contradiction to Muller’s ideas of “total dose” and irreversibility—were dependent rather than independent of dose rates,^{10,11} at low levels of radiation.

Fourteen years later, the Biological Effects of Ionizing Radiation I (BEIR I),¹² Genetics Subcommittee acknowledged the “mistake” of the NAS BEAR I Genetics Panel on dose rate but nevertheless retained the LNT recommendation because the reduced mutation rate in spermatogonia, as shown by Russell, had not regressed back to control values as it had for oocytes. Nonetheless, the BEIR I Genetics Subcommittee grudgingly indicated that, due to its repair capacity, spermatogonia rather than mature spermatozoa were better models for generalizing mutational responses across somatic cells. Russell referred to failed DNA repair capacity as an “odd phenomenon, restricted to spermatozoa and occasioned by the peculiar nature of the specialized spermatozoan cell”.^{10,11} In 1995, Paul B. Selby (1998a, b)^{13,14} detected a significant error that had routinely occurred in the historical control groups of Russell’s mouse-specific locus test. This final mistake was subsequently acknowledged and corrected by Russell and Russell¹⁵ along with Selby.^{13,14} If this mistake had not occurred or had been corrected before the creation of BEIR I, then the mouse spermatogonia data that supported continuance of the LNT model would have adjusted control mutational values to historical norms, supporting either a threshold or hormetic model depending on whether the correction of Russell or Selby, respectively, was used.^{10,11}

To summarize, the successful birth and adoption of LNT for cancer risk assessment was due to (1) the mistaken assumption by Muller that he had discovered X-ray-induced “gene” mutations, (2) the adoption of the “LNT single-hit model” that was based on Muller’s mistaken assumption, (3) the mistake by BEAR I of generalizing DNA repair-deficient mature spermatozoa as representative of all somatic cells, (4) the deceptions and misrepresentations of the scientific record by leaders of the radiation genetics community, including the NAS BEAR I Genetics Panel, and (5) the repeated mistakes made in assessing the control responses in Russell’s mouse-specific locus test. The EPA (1975, 1977)^{16,17} even extended and compounded these mistakes in 1975 and 1977 by further adopting LNT for chemical- (Albert et al., 1977)¹⁸ as well as radiation-induced cancer risk assessments, stating that its LNT decision (later proven to be wrong by both Russell and Russell in 1996 and then by Selby in 1998a, b)^{13,14} was based on the dose–rate findings of Russell as cited in BEIR I (1972). If any one (or more) of these mistakes had been avoided, then an invalid LNT, its birth, and its adoption by society would all have likely miscarried and been replaced by a more authentic dose–response alternative, such as a threshold or hormetic model.

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References

1. Calabrese EJ. Flaws in the LNT single-hit model for cancer risk: an historical assessment. *Environ Res.* 2017a;158:773-788.
2. Campos LA. Radium and the Secret of Life. Chicago & London: University of Chicago Press; 2015.
3. Timofeeff-Ressovsky NW, Zimmer KG, Delbruck M. Nachrichten von der gesellschaft der wissenschaften zu Gottingen. Über die nature der genmutation und der genstruktur Biologie. 1935; 1(13):190-245.
4. Ray-Chaudhuri SP. The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity. *Proceedings of the 7th International Congress on Genetics, Edinburgh 1939*; 246.
5. Ray-Chaudhuri SP. The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity. *Proc Royal Soc Edinburgh.* 1944;62:66-72.
6. Calabrese EJ. Key studies used to support cancer risk assessment questioned. *Environ Mol Mutagen.* 2011a;52(8):595-606.
7. Calabrese EJ. On the origins of the linear no-threshold (LNT) dogma by means of untruths, artful dodges and blind faith. *Environ Res.* 2015;142:432-442.
8. Calabrese EJ. LNTgate: how scientific misconduct by the US NAS led to governments adopting LNT for cancer risk assessment. *Environ Res.* 2016;148:535-546.
9. Anonymous. (Genetic Panel, W. Weaver, Chair). National Academy of Sciences (NAS), Biological Effects of Atomic Radiation (BEAR), Genetic Effects of Atomic Radiation. *Science* 1956;123: 1157-1164.
10. Calabrese EJ. The threshold vs LNT showdown. Dose rate findings exposed flaws in the LNT model. Part 1. The Russell-Muller debate. *Environ Res.* 2017b;154:435-451.
11. Calabrese EJ. The threshold vs LNT showdown. Dose rate findings exposed flaws in the LNT model. Part 2. How a mistake led BEIR I to adopt LNT. *Environ Res.* 2017c;154:452-458.
12. National Academy of Sciences (NAS)/National Research Council (NRC). *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR I)*. Washington, DC: National Academy; 1972.

13. Selby PB. Major impacts of gonadal mosaicism on hereditary risk estimation, origin of hereditary diseases, and evolution. *Genetica* 1998a;102/103(1-6):445-462.
14. Selby PB. Discovery of numerous clusters of spontaneous mutations in the specific-locus test in mice necessitates major increases in estimates of doubling doses. *Genetica*. 1998b;102/103(1-6):463-487.
15. Russell LB, Russell WL. Spontaneous mutations recovered as mosaics in the mouse specific-locus test. *Proc Natl Acad Sci U S A* 1996;93(23):13072-13077.
16. United States Environmental Protection Agency. ORP policy statement on the relationship between radiation dose and effect. *Fed Reg*. 1975;41(133):28409.
17. United States Environmental Protection Agency. Excerpts from radiological quality in the environment of the United States. Office of Radiation Programs EPA; 1977. 902/4-78-002.
18. Albert E, Train E, Anderson E. Rationale developed by the Environmental Protection Agency for the assessment of carcinogenic risks. *J Natl Cancer Inst*. 1977;58(3):1537-1541.

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