Environmental Research 155 (2017) 276–278

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Obituary notice: LNT dead at 89 years, a life in the spotlight

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ARTICLE INFO

Keywords:
LNT
Dose response
Risk assessment
Cancer
Hormesis
Environmental regulations

ABSTRACT

Considerable recent findings have revealed that the linear dose response for cancer risk assessment has not only outlived its utility in predicting risk but is based on a flawed scientific foundation. The present article characterizes this demise of a key concept of environmental risk assessment, in the framework of a figurative obituary of a long-lived concept that has poorly served society. This obituary is intended to illustrate an integrated mix of poignant and improper historical judgments that led to both the acceptance and ultimately the demise of this once intellectually facile and nearly universally accepted concept.

1. Introduction

The linear dose-response relationship for carcinogen risk assessment, otherwise known as the linear-no-threshold (nicknamed LNT) model died on January 10, 2017 due to an academic version of multiple system failure. This involved a poor theoretical basis, an incapacity for validation and a rejection by hundreds of studies, along with a striking ineptness for accurate predictions in the low dose zone (Calabrese, 2009, 2011a). Speeding its demise was a recently discovered series of epic scandals involving some of the best and brightest from the worlds of academia and government. Its final demise came with two recent publications in the journal *Environmental Research* (Calabrese, 2017a; Calabrese, 2017b) showing that LNT exhibited several serious academic mutations, which allowed it to be misapplied and to grow unchecked, a process that would ultimately lead to self-destruction. LNT was finally put to rest in a grave outside Washington, DC. The ceremony was surprisingly well attended by numerous inconsolable consultants and governmental regulators who made their economic livelihoods based on the tenets and applications of LNT in cancer risk assessment. The service was presided over by a former head of the US EPA, who had a difficult time keeping her composure, having lost a long time, but fundamentally misunderstood ideology, which harmed nearly everything it touched because of its blind acceptance and unproven character.

1.1. LNT: its life, significance and demise

LNT was always the star of the show, starting with its highly auspicious birth—an event that was heralded by some leaders of science as the key element in explaining life itself as well as the origins of man on earth. In 1928 LNT was born by the creativity of two physical chemists from no less than the University of California at Berkeley. One of these chemists, Professor Gilbert Lewis, an academic jack-of-all-trades and master of all, himself having been nominated for the Nobel Prize some 42 times, only to be repeatedly overlooked due to human jealousy born of rivalry. Despite his own death on a Saturday afternoon in March 1946 due to an apparent accidental release of cyanide during an experiment, Professor Lewis remains well known to all high school and college chemistry students for his famous Lewis acids and bases concepts. However, Lewis and his colleague Axel Olson decided to leave the comfort of their physical chemistry laboratory and proffer an explanation for a truly big question - how did we get here? Their answer to the evolutionary conundrum, they believed, was to be found in the recently published work of the radiation geneticist Hermann Muller, a professor at the University of Texas at Austin. Muller and many rivals long believed that unlocking the mechanism of evolution was the biggest question in biology and that whoever got there first would take home the Nobel Prize. Muller worked on this question for over 15 years, and then finally closed in on it late in 1926, a scant few months ahead of the competition. As he neared the research finish line in the spring of 1927, Muller used his contacts at the journal *Science* (Muller, 1927) to publish the first report of an exogenous agent, in this case X-rays, capable of producing mutations.

Lewis and Olsen did not hesitate to use Muller's discovery to declare that they had now figured out the mechanism of evolution. The engine of evolution, by their account, resulted from mutations occurring from continuous exposure to low levels of background radiation emanating from the cosmos and terrestrial earth. Their explanation, however, needed and therefore assumed a linear dose-response profile for radiation to insure that mutations could actually occur at background levels. Lewis and Olsen offered this explanation even though Muller's research at the time never revealed the true nature of the dose

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http://dx.doi.org/10.1016/j.envres.2017.02.031
Received 26 January 2017; Received in revised form 21 February 2017; Accepted 24 February 2017

response for X-ray-induced mutations at low doses. Their explanation, based on an assumed extrapolation of Muller's dose response curve, was published in a 1928 article in the prestigious journal *Nature* (Olson and Lewis, 1928). Thus, the LNT was born, not in the service of and application for environmental risk assessment, but out of an unproven assumption to answer the most vexing question in life.

Intriguing though it was, the explanation of Lewis and Olson would fail to gain traction, eventually being discredited by Muller himself. Background radiation was so low or weak that it could only explain about 1/1300th the mutation rate in Muller's control group (Muller and Mott-Smith, 1930; Muller, 1930), making the LNT too inept for a plausible explanation. In a strange way, Lewis' mistake was compounded by the failure of Muller to present any data in the *Science* paper, forcing the overzealous Lewis to speculate.

Although Lewis and Olson receded from the messy world of evolutionary biology and their failed attempt to explain the mechanism of evolution was soon forgotten, the LNT model that they had fictionalized was not. In fact, Muller himself adopted it as his own model and he would soon become known as THE stepfather of LNT. A scant two years later Muller would reenergize the LNT concept, rename it, and then transform it into no less than a new universal biological law, calling it the Proportionality Rule (Muller, 1930). The Proportionality Rule, or LNT, was destined to become a central dogma of the radiation geneticist community.

Just as evolution needed a mechanism so did the Proportionality Rule; soon it would get one. The mechanism would emerge from a series of creative forays between big-time physicists and radiation biologists who met in Copenhagen during summers early in the 1930s—the likes of which involved Neils Bohr, Muller, and others with similar high standing. In a type of role reversal the physicists offered a mechanism that linked their concept of radiation target theory to several sets of new data from Muller's laboratory showing a linear dose response for radiation-induced germ cell mutation. The physicists proposed a single gene-single hit model that could reliably predict Muller's linear dose-response observations. The greater the number of gene hits beyond one, the more progressively the dose response resembled a threshold model. This enhanced version of LNT, now called the "single-hit" LNT model surfaced in 1935 in a newly created journal in the German language (Timofeeff-Ressovsky et al., 1935). However, because the journal never saw a second year of publication, the "single-hit" LNT model was never cited in leading scientific indices and spread among colleagues only by word-of-mouth and reprints.

To recount, an article in a prestigious journal literally fictionalized an unproven LNT into existence (born) in order to rationalize an evolutionary hypothesis that would soon be fully discredited by Muller, who surprisingly would then soon adopt the fictionalized LNT as his own after a theoretical physics' article in a short-lived and unknown journal was used to rationalize it back into existence (reborn). Thus, LNT not only was born and died, but, on the belief of one man and the mere musings of physical theory, also was reborn and even given a theoretical and intellectual foundation for the future—all without experimental proof of its existence. In fact, under such circumstances, it would be hard to imagine how the "single hit" version of LNT could have possibly failed. After all, it was surrounded, supported and collectively created by past, present and future Nobel Prize winners in physics and biology. But there was no getting around it, key experiments in support of LNT remained absent and the mutterings of support by prominent scientists would eventually ring hollow, and Muller knew it. Thus, Muller proposed an idea for a seminal experiment to calm the doubters and give LNT standing within the scientific world.

Muller knew that it was probably impossible to prove or validate the LNT in experimental systems. The dose of radiation would be so low that even theoretically small effects would be practically impossible to measure. LNT was, more than anything else, a belief rather than a science. That is, LNT really could not be directly tested. As an alternative, Muller proposed a dose-rate experiment to see if X-ray-induced mutations would be cumulative and irreversible. If this were the case, then the dose response should be linear even down to a single ionization. So, in the late 1930s Muller directed a project that, in effect, tried to determine whether the same number of mutations would occur when a dose was given all at once or spread over a number of smaller doses. If the amount of damage were the same in each case, LNT would be supported. In this key experiment Muller's scientific intuition proved correct and his belief in the Proportionality Rule or LNT—call it what you will—was sustained, at least for a while. At the time, however, this was an important moment for LNT, "proving" that it was not only real (Muller, 1951) but was also in the process of gaining many new converts from the field of radiation genetics.

Unfortunately, unforeseen problems soon emerged and the vindication of LNT proved to be short lived. Even though radiation geneticists had come to fully embrace LNT, it seems that Muller's dose-rate experiments had some important limitations such as his supervision of students and study design features. In addition, the Atomic Energy Commission was then seeking safety assurances for any personnel of the Manhattan Project who might be exposed to doses of radiation considerably lower than those used by Muller and his students in validating the LNT. In short, the U.S. Government needed to develop a safety program for radiation workers that would be both based on occupationally relevant doses and guided by the very best science. Thus, Muller needed to improve his approach to research on dose rates, this time with a greater degree of supervision, a stronger study design and a better quality control of laboratory procedures.

In concert with the Manhattan Project, a "dream team" of researchers from the fields of entomology and genetics was then organized at the University of Rochester to validate the LNT model at ever-lower doses of radiation. The research project was under the supervision of the outstanding geneticist Curt Stern who received assistance from Muller and other prominent scientists of the day. Anticipating straightforward confirmation of LNT, the team was more than surprised and disturbed when data emerged from high quality-controlled experiments that supported the well-entrenched threshold dose-response model instead of LNT. This sent the entire team into what could only be called "damage control". Deliberately violating scientific standards of unbiased objectivity, they sought unprincipled and frankly deceitful ways to preserve LNT and to discredit the findings. With a now well-known narrative, Stern and Muller connived to undermine the threshold model in deceptive ways, including Muller's comments at his Nobel Prize Lecture and repeatedly in the scientific literature, Stern's obfuscations, and staff members joining in with Stern either because of simply being afraid or refusing to speak up. They orchestrated a cover up that captured the field, eventually contaminating the US NAS BEAR Genetics Panel (1956), which committed scientific misconduct in an attempt to ensure that LNT would replace the threshold model for mutation and cancer risk assessment (Calabrese, 2011b, 2015). From the late 1950s until its recent demise, LNT would rule the risk assessment world. Even though it could not explain evolution, there was little else that was more significant in the environmental domain than LNT, with the possible exception of the new kid on the block by the name of climate change.

Despite their brilliance, however, Muller, Stern and colleagues would make two critical mistakes in judgment that would reveal the folly of their LNT recommendation. The first involved the use of the mature spermatozoa in mutation research. They incorrectly assumed that findings with the mature spermatozoa would apply to all cells—reproductive and somatic. However, before the decade of the 1950s ended, all signs suggested that this highly specialized reproductive cell was unlike all other cell types in that it lacked the capacity to repair genetic damage. By 1972, even members of Muller's own group of loyalists, such as Jim Crow the chair the US NAS BEIR Genetics Subcommittee, concluded that the US NAS Genetics Panel of 1956 got the key question of dose rate wrong and used the wrong cell type to

estimate cancer risks. The second major problem was revealed a quarter century later when a senior geneticist at Oak Ridge National Labs found an error in the historical mutation rate used by the US NAS BEIR Genetics Subcommittee for the derivation and support of LNT. Recent publications in *Environmental Research* (Calabrese, 2017a; Calabrese, 2017b) showed that if this error had been detected in 1972 by the NAS Genetics Subcommittee then LNT would not have been adopted/affirmed and the threshold model would have been far more likely to be recommended for assessing radiation risks.

Although the rapid rise and success of LNT was due to plotted actions in the 1950s of formidable supporters (i.e., from the radiation genetics community and from the US National Academy of Sciences and its silent partner the Rockefeller Foundation), LNT was not without its formidable opponents as well. During the 1930s and 1940s, most opposition to LNT came from a medical community that had long maintained a loyal relationship with the threshold dose-response model. The medical community was afraid that LNT might limit the use of X-rays and radium in the treatments of cancer and other diseases because of possible risks to workers and patients. The medical community was smart and powerful and it controlled the agenda and the playing field. Nevertheless, it was still out maneuvered by key leaders of the Rockefeller Foundation who had a “Manchurian Candidate” by the name of Dr. Detlev Bronk, a simultaneous president of both the Rockefeller University and the US National Academy of Sciences. In an unprecedented move, the Foundation urged Bronk to organize the BEAR Committee and gave him the money and power to bestow opportunity and influence upon the dogma-driven community of radiation geneticists. This move diminished the medical community's hold over LNT and, at the same time, empowered LNT supporters, setting the stage for a major scientific revolution. With the medical community now neutralized and with Bronk in the driver's seat at the National Academy of Sciences, LNT simply had an easy ride to the top.

While the fledgling nuclear industry tried to fight back, it was simply outclassed by LNT, which could now easily frighten the public and politicians with warnings of cancer and images of deformed babies. This would be the principal modus operandi of LNT. Over the next 50 years LNT took on the chemical industry and set its sights on their universe of potentially harmful agents. The battles were long, hard and nasty, but in the end LNT whipped big industry. Even a series of Republican presidents could overcome neither LNT nor the stealthy long-term bureaucrats who frustrated their every move.

So, if the medical, nuclear and chemical communities could not disable LNT then what was the insidious disease that led to its demise? In such cases one nearly always looks for something else to blame. However, the truth of the matter is usually much closer to home. All LNT had to do was look into a mirror and see its weaknesses, which were always camouflaged by its handlers at the NAS, the Rockefeller Foundation, the EPA and other organizations, who benefited from LNT's outrageous scare tactics. LNT really knew that the discovery of dose rate effects and DNA repair was going to be a serious problem. LNT and its supporters did their best to deflect the impact of this discovery in multiple ways but it could not be denied. There were also many other adaptive responses that helped to ensure survival in a threatening world. These adaptive mechanisms could be turned on by very tiny doses of a plethora of agents and stresses, protecting all things biological. These observations led to the view that LNT could not make accurate predictions in the low-dose zone and, in fact, was only a player at high doses where relevance to human environmental exposures was almost non-existent. Over the past several decades thousands of studies have revealed that LNT could not be counted on to do the job as its predictions were routinely off by orders of magnitude. In fact, LNT had become an embarrassment to most toxicologists and radiation health scientists. The final straw for LNT occurred when it was revealed that the NAS BEIR I Genetics Subcommittee confirmed its existence because of an error which the recent papers in *Environmental Research* (Calabrese, 2017a; Calabrese, 2017b) finally corrected. When the error was fixed, LNT once again looked into the mirror and saw nothing. It knew that its time was up.

2. Conclusion

As the once-dominant dose-response model, LNT had many lessons to teach. Professors George and Draper wrote some 30 years ago, "all models are wrong, but some are useful" (George and Draper, 1987). Time has shown that LNT was indeed dreadfully wrong and not even particularly useful. For example, it significantly increases the cost of environmental clean ups without protective advantage and has denied people opportunities to receive novel and highly effective, low-dose radiation medical treatments. LNT is much like Swiss cheese; it has far too many holes to be useful and should certainly not guide policy. Unfortunately, LNT became a dogma, a belief that could not be tested, and had highly prestigious and deceptive proponents to ensure its survival. It was also used to frighten citizens and to intimidate politicians. However, LNT's nearly century-long life of ups and downs could end on a positive note if it were to symbolize how science becomes eroded when an ideologically-driven hypothesis is blindly followed, never proven and incuriously defended as central dogma—never in doubt but often wrong. Skepticism, objectivity and hypothesis testing are at the heart of science, not the ideological defense of dogma. If LNT's life and death can teach society this lesson, then its near century-long life may at least partially compensate for the innumerable disservices it has already dealt society.

Acknowledgement

This research has been supported by awards from the US Air Force and ExxonMobil Foundation. The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

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