



RESEARCH ARTICLE

# The Genesis of the Linear No-Threshold Hypothesis and the Delayed Protection of Reproductive Health, 1900–1960s

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## ABSTRACT

**Objectives:** This paper examines how the Linear No-Threshold hypothesis emerged in radiation research and why its adoption did not immediately translate into specific radiological protection guidelines for pregnant women and women of reproductive capacity. It analyses the tension between early scientific warnings about reproductive harm and the continued medical and institutional use of ionizing radiation.

**Methods:** The study is based on a historical reconstruction of medical and scientific debates on the reproductive risks of ionizing radiation from around 1900 to the 1960s. It draws on animal experiments, clinical practices, wartime and postwar research, and the positions of key institutions and scientists, including Hermann J. Muller, Alice Stewart, the Atomic Bomb Casualty Commission, and the International Commission on Radiological Protection.

**Results:** Despite early evidence of reproductive harm from animal studies, radiation was widely used in human medicine, including in potentially pregnant women, and even for pregnancy diagnosis. Nazi Germany exploited the sterilizing effects of radiation, and after World War II, the Atomic Bomb Casualty Commission reported increased risks of microcephaly in children born near atomic blast sites. Although Muller and Stewart strongly warned against radiation exposure to reproductive organs and supported a no-threshold interpretation of risk, conflicting analyses of epidemiological data – particularly at low doses – generated uncertainty. These disagreements delayed regulatory consensus within the International Commission on Radiological Protection.

**Conclusion:** The delay in issuing specific radiological protection recommendations for pregnant women until 1965 cannot be explained by ignorance of risk. Rather, it resulted from unresolved scientific disputes, institutional caution, and the difficulty of translating genetic theory and uncertain epidemiological evidence into binding regulatory standards. This case study thus highlights the intricate entanglement of scientific knowledge, political interests, and institutional authority in the making of regulatory standards.

**Keywords:** Linear No-Threshold (LNT) hypothesis, history of radiation research, radiation biology, International Commission on Radiological Protection (ICRP), Hermann J. Muller

## Introduction

In the 1920s and 1930s, geneticist Hermann J. Muller argued that any exposure to ionizing radiation could induce heritable mutations, with risk increasing proportionally to dose. His experiments on fruit flies (*Drosophila*) led him to argue that there was no safe threshold for radiation exposure. Muller later received the Nobel Prize in Physiology or Medicine (1946) for this research, which helped cement the idea in radiation biology. Based on his research, the Linear No-Threshold (LNT) model was formulated in the mid-1940s. Muller explicitly argued in his 1946 Nobel Prize lecture that radiation risk increases linearly with dose and that no safe threshold exists. The model was later institutionalized when it was adopted by the U.S. National Academy of Sciences in 1956 and by the International Commission on Radiological Protection (ICRP) in 1959.<sup>1</sup>

Despite its regulatory influence, the LNT hypothesis remains controversial to this day. While the model is well supported at moderate to high doses, at low doses (below ~100 mSv), the data becomes noisy, and epidemiological studies often cannot reliably detect an increased risk. Therefore, critics argue that the LNT has not been proven at low doses.<sup>2–5</sup> As a geneticist, Muller focused on heritable mutations rather than carcinogenesis. This begs the question of whether the model can be extended to cancer risk, which involves biological and conceptual extrapolations that were not self-evident.

Historians of science have argued that radiation risk models were shaped by Cold War governance, secrecy, and the need to manage public fear.<sup>6–9</sup> Scientific uncertainty was often resolved by policy necessity rather than by decisive biological proof. Creager does not argue that the LNT hypothesis is wrong per se, but that its authority came from institutional and political contexts.

However, less attention has been paid to how the emergence of the LNT hypothesis intersected with concerns about reproductive health and why specific protections for pregnant women were introduced comparatively late. This paper returns to the original sources of the LNT model and asks a) what its proponents – especially Muller and Alice Stewart – could reasonably claim on the basis of available experimental evidence. It also examines b) what Cold War regulatory bodies understood when they began setting radiation protection standards, particularly through the International Commission on Radiological Protection (ICRP). Although the ICRP was responsible for defining safe uses of radiation, it did not issue specific recommendations for pregnant women and women of reproductive capacity until 1965. By situating scientific debates within their institutional and political contexts, the paper argues that the delay was not primarily due to a lack of evidence, but to contested interpretations of that evidence. The history of reproductive radiation protection underscores the regulatory authority of international bodies in defining acceptable risk, while making visible the gendered assumptions that shaped exposure limits and protection models.

## Early animal studies

Studies of the increased radiosensitivity of developmental processes can be traced back to pioneering experiments on vertebrates and invertebrates conducted between 1903 and 1907. French biologist Georges Bohn (1903) was among the first to apply gamma rays from radium to amphibian larvae and sea urchin eggs.<sup>10–11</sup> German surgeon Georg Perthes (1904) observed growth inhibition in irradiated *Ascaris megalcephala*, a roundworm found in horses.<sup>12</sup> In the same year, Breslau anatomist Alfred Schaper conducted similar experiments with frogs and newts.<sup>13</sup> American surgeon Philip K. Gilman and Johns Hopkins radiographer Frederick H. Baetjer (1904), along with Polish anatomist Jan Tur (1906), irradiated chicken eggs.<sup>14–15</sup>

Across all cases, the outcomes were consistent: growth inhibition, malformations, and eventual death. These experiments revealed a pronounced vulnerability of cell nuclei and a general deceleration of developmental processes, especially in the central nervous system. They stand among the earliest documented observations of the teratogenic effects of radiation on developing embryos. In 1906, French physicist and medical doctor Jean Alban Bergonié, together with histologist Louis Tribondeau, was the first to propose that the radiosensitivity of tissues is directly proportional to their proliferative activity and inversely proportional to their degree of differentiation.<sup>16</sup> While this “law,” published in a communication to the French Academy of Sciences, remains a foundational concept in radiobiology, it is essential to acknowledge that it is only an approximation, and there is evidence today that numerous counterexamples contradict it.<sup>17</sup>

Building on early experiments with invertebrates and birds, researchers soon turned their attention to mammalian embryos. As early as 1903, Heinrich Albers-Schönberg conducted experiments on rabbit and guinea pig testicles, observing significant changes in their function following radiation exposure.<sup>18</sup> Since 1905, numerous studies have specifically explored the effects of radiation on pregnant mammals. New York physician Sinclair Tousey (1905) irradiated pregnant cats;<sup>19</sup> in Vienna, endocrinologists Otfried Otto Fellner and Friedrich Neumann (1907) conducted experiments on pregnant rabbits;<sup>20</sup> and Berlin doctor Karl Lengfellner (1906) focused on guinea pigs.<sup>21</sup> In 1907, Heidelberg ophthalmologists Eugen von Hippel and Hermann Ernst Pagenstecher observed radiation-induced malformations, further confirming the heightened vulnerability of embryonic development in mammals.<sup>22</sup> In 1907, Hannover physician Karl Försterling reported growth inhibition in several mammalian species, including a goat.<sup>23</sup> He presented his findings at the Third Roentgen Congress that same year, immediately sparking discussion. One participant later recalled how a foreign guest, struggling with the German language, anxiously asked the other doctors “in tormented words” whether similar malformations had been observed in children.<sup>24</sup> Indeed, this early animal research laid the groundwork for medical applications of radiation on human reproduction.

## Early human experiments

In 1899, long before radiation therapy became standard medical practice, Swedish doctors Tor Stenbeck and Tage Sjörgen were already experimenting with X-rays to treat skin cancer.<sup>25</sup> One of their most striking cases involved a woman with a carcinoma on her nose. Stenbeck administered an astonishing 150 roentgen sessions over nearly a year, a slow, painstaking process by any standard. Yet the results were extraordinary. The tumor disappeared, and when doctors followed up nearly three decades later, the cancer had not returned. It was an early glimpse of the power and promise of radiation in medicine.<sup>26</sup>

While Swedish doctors were achieving early breakthroughs with X-ray therapy, similar experiments were unfolding elsewhere.

In the United States, Chicago physician Émil Herman Grubbé, a medical student working with Crookes tubes, learned of Röntgen's 1895 discovery. He later claimed to have immediately treated several cancer patients with the new technology.<sup>27–28</sup> Due to radiation damage, Grubbé lost his left hand, nose, upper lip, and most of the right side of his face.<sup>29</sup> He had undergone more than 90 surgeries. Another pioneer, William James Morton, who is largely forgotten, began using X-rays to treat cancer as early as 1902.<sup>30</sup> Morton authored one of the earliest textbooks on the medical use of X-rays, helping to introduce the new technology to American physicians.<sup>31–33</sup> Surgeon Robert Abbé achieved the first successful treatment of a bleeding cervical carcinoma with radium in 1903, using a sample personally provided by Marie Curie.<sup>34</sup> Despite these efforts in North America, it was in Europe, particularly Germany and France, that the first organized radiological communities emerged, laying the groundwork for the field's formal development.

At the Women's Clinic at the University of Freiburg, under the leadership of Bernhard Krönig, Carl Joseph Gauß introduced radiation therapy. Gauß later became director of the University Women's Clinic in Würzburg and co-founded the journal *Strahlentherapie*. He is also credited as the first physician to systematically experiment with temporary sterilization, beginning in 1910<sup>35</sup>—a method he would later promote prominently during the National Socialist regime.<sup>36–37</sup>

Elsewhere in Germany, other leading gynecologists were advancing the use of radiation treatment. In Heidelberg, Carl Menge<sup>38</sup> and Heinrich Eymer emerged as key figures, with Eymer publishing an influential atlas in 1913 featuring 75 roentgenograms.<sup>39</sup> In Berlin, notable practitioners included Ernst Bumm,<sup>40</sup> Kurt Warnekros,<sup>41</sup> and Manfred Fraenkel;<sup>42</sup> in Munich, Albert Döderlein;<sup>43</sup> and in Erlangen, Ludwig Seitz<sup>44</sup> and Hermann Wintz.<sup>44</sup> Together, these physicians helped establish Germany as a center for early gynecological radiotherapy.

## Experiments on pregnant women

With human radiation experiments becoming increasingly popular, attention turned towards the unborn in the womb. One striking example is Lars Edling, head radiologist at Lund University Hospital in Sweden. In

1924, he published an article in the *Journal of the Radiological Society of North America*, in which he strongly endorsed the use of X-rays for diagnosing pregnancy.<sup>45</sup> Edling reported personally conducting approximately 270 such examinations, presenting them as evidence of the method's clinical value while ignoring its potential long-term consequences.

In 1930, Berlin physician Kurt Kirschmann published a textbook for roentgen technicians in which gendered expectations were embedded not only in the content but also in the grammar.<sup>46</sup> The doctor (*Arzt*) was assumed to be male, while the assistant (*Assistentin*) was unmistakably female. In his foreword, Kirschmann noted, somewhat condescendingly, that most of the young ladies (*Damen*) found it easy to follow even the scientific background material, including tables, curves, and the like. Yet, notably absent from the textbook was any discussion of reproductive health risks—no mention of potential dangers to pregnant technicians or to fertility. Whether this omission stemmed from ignorance, oversight, or a deliberate choice to avoid discouraging women from entering the profession remains unclear.

In 1938, an official newspaper of the National Socialist German Workers' Party (NSDAP) described the profession of the roentgen technician as particularly well-suited to women, claiming that “she has the capacity for exact detail work and can easily subordinate herself.”<sup>47</sup> The article downplayed the health risks, stating that such dangers had now been minimized. Beneath the surface of this endorsement, however, lay a deeper reality: Germany was facing a shortage of roentgen technicians, a gap partly caused by growing awareness of the profession's health hazards, particularly for women.<sup>48–50</sup> The advertisement had two main goals: to attract more women to the job and to convince both them and the public that it was a safe work environment. It also reflected the Nazi regime's view of women as obedient and suited for support roles, while avoiding any mention of the serious health risks—especially to fertility—that still came with the work.<sup>51–52</sup>

## After World War II

In 1946, just a year after the end of World War II and the atomic bombings of Hiroshima and Nagasaki, Hermann Joseph Muller received the Nobel Prize in Medicine for his groundbreaking research on radiation-induced genetic mutations. Back in 1927, Muller had exposed fruit flies (*Drosophila melanogaster*) to X-rays in his Texas laboratory, demonstrating that radiation could cause heritable genetic damage. What made his work revolutionary was his ability to precisely measure mutation frequency, establishing a direct correlation between radiation dose and genetic harm. In the immediate aftermath of the war, when the devastating power of radiation had become globally evident, Muller's findings gained new urgency. In his Nobel lecture, he famously warned that there is “no escape from the conclusion that there is no threshold dose,” a statement that cast serious doubt on the safety of any level of radiation exposure.<sup>53</sup> Muller's position underscored the unpredictable and irreversible nature of genetic damage, particularly in the context of reproductive health and future generations.

To systematically study the health effects of the bombings, the U.S. government established the Atomic Bomb Casualty Commission (ABCC) in 1947. It became a central institution in postwar radiation research, tasked with examining both the immediate and long-term consequences of ionizing radiation on the human body, including its impact on unborn children.<sup>54</sup> In 1954, James N. Yamazaki, Stanley W. Wright, and Phyllis M. Wright of the ABCC examined a total of 98 mothers who had been pregnant at the time of the Hiroshima and Nagasaki bombings.<sup>55–56</sup> Among their children, one striking commonality emerged: reduced head circumference (microcephaly) and significant intellectual disabilities, particularly in those exposed closer to the blast.<sup>55–56</sup> The severity and frequency of these abnormalities correlated directly with radiation dose, with the most severe effects observed in pregnancies during the first two trimesters, when brain development is especially vulnerable. The findings from Japan provided powerful confirmation of earlier experimental research, dramatically heightening the relevance of Muller's discovery that radiation causes genetic mutations.

The ABCC's findings laid the groundwork for the establishment of international radiation protection standards, most notably through the International Commission on Radiological Protection (ICRP). However, in its early years, the ICRP did not extend special protections to pregnant women or women of reproductive age. As late as 1958, ICRP's main commission member Karl Ziegler Morgan expressed his frustration with the existing priorities, stating: "I personally feel that it is a bit ridiculous to permit three times as much exposure to the eyes as to the gonads and the rest of the body."<sup>57</sup> Ironically, despite this comment, Morgan and his colleagues continued to place greater regulatory emphasis on ocular safety than on reproductive health. That many members likely shared this view is reflected in the slow pace of change: the ICRP did not issue specific recommendations to protect pregnant women and women of reproductive capacity until 1965. This is nearly two decades after the atomic bombings and well after the dangers of fetal radiation exposure had been scientifically documented.

### The contribution of Alice Stewart

Before the ICRP moved to protect pregnant women, another set of studies forced the issue back into the spotlight. In 1956, a brief communication in *The Lancet* caused a sensation: "Malignant Disease in Childhood and Diagnostic Irradiation in Utero" by Alice Stewart and her team.<sup>58–60</sup> Between 1952 and 1955, 1,416 children in Britain had died from leukemia and other malignant diseases. Stewart's research team analyzed about a third of these cases, contacting mothers through detailed questionnaires to investigate any history of radiation exposure during pregnancy. The results were startling.

The study found a clear association between fetal exposure to diagnostic X-rays and elevated rates of childhood cancer, even in the absence of visible abnormalities like microcephaly. Stewart made it clear that she was not the first to raise the alarm, deliberately

citing earlier warnings by Douglas Murphy. But unlike Murphy, Stewart said what he had only implied: even a single diagnostic X-ray during pregnancy could cause irreversible harm and should be avoided at all costs.<sup>60</sup> Yet, Stewart's groundbreaking findings were largely dismissed. According to historian Gayle Greene, the medical establishment, most notably epidemiologist Richard Doll, had worked actively to discredit her research and curtail its influence. Instead of addressing her data directly, critics often resorted to personal attacks. Doll and his allies went so far as to question Stewart's mental fitness, implying she had become senile. What appeared on the surface as scientific disagreement was, in reality, a concerted effort to protect institutional authority and minimize the perceived risks of medical radiation exposure, especially during pregnancy.

However, in 1962, epidemiologist Brian MacMahon from Birmingham provided strong confirmation of the link between prenatal X-ray exposure and childhood leukemia. His study analyzed data from 734,243 children born in the northeastern United States between 1947 and 1954.<sup>61</sup> Unlike Alice Stewart's earlier work, which relied on maternal questionnaires, MacMahon used medical records to determine exposure, thereby eliminating the possibility of recall bias, a primary criticism of Stewart's methodology.<sup>61</sup> His findings reinforced the validity of her conclusions and helped shift the scientific consensus toward greater caution in prenatal radiological practices.

Yet, in 1970, a study by Seymour Jablon and Hiroo Kato on atomic bomb survivors, published in *The Lancet*, challenged the conclusions drawn by both Stewart and MacMahon.<sup>62</sup> Their findings suggested that low doses of radiation, such as those experienced by many survivors in utero, did not lead to an increased risk of childhood cancer, casting doubt on the broader applicability of the prenatal X-ray studies.

To this day, the debate remains unresolved. On one side stand those, such as Hermann Joseph Muller, Stewart, and MacMahon, who uphold the LNT hypothesis—that is, the assertion that any amount of ionizing radiation carries some risk, no matter how small. On the other side are figures such as Edward J. Calabrese, Richard Doll, Jablon, and Kato, who argue that very low doses appear to have no measurable harmful effects and advocate a threshold below which exposure may be considered safe.<sup>2,3</sup>

### Conclusion

The linear no-threshold (LNT) hypothesis was difficult for the medical community to accept.

From the early twentieth century onward, experimental evidence – most notably from Hermann J. Muller's work on *Drosophila* – suggested that ionizing radiation could induce heritable mutations without a clear threshold. Yet the medical community struggled to reconcile this possibility with the therapeutic promises of X-rays and radium. Radiology emerged as a modern, life-saving specialty at the very moment its biological dangers were becoming increasingly apparent. The idea that a technology capable of curing cancer might simultaneously

threaten fertility and future generations was conceptually and professionally destabilizing. X-rays had even been used to diagnose pregnancy, reflecting the early optimism surrounding radiological medicine. This confidence, however, eroded as physicians themselves began to suffer the effects of ionizing radiation, revealing its capacity for harm as well as cure.

Conflicting interpretations of data divided researchers such as Muller, Stewart, and MacMahon from Doll, Jablon, Kato, and, recently, Calabrese, particularly in their assessments of genetic damage and cancer risk. Despite the establishment of the ICRP and its role in setting safety radiation standards, the conflict remained unresolved. As this study has shown, it was not until 1965 that the ICRP issued specific recommendations for protecting pregnant women and women of reproductive capacity. This prolonged delay reflects not a sudden discovery of risk, but its gradual resolution (or political stabilization) of long-standing disputes. This process was

accompanied by numerous personal tragedies, including cases of sterility and children born with microcephaly and other hereditary disorders.

These debates show that medical consensus does not arise solely from experimental results but is shaped by institutional authority and competing methodological approaches. Ultimately, the delayed protection of pregnant women was not simply an epistemic failure. Political factors also influenced the outcome, including U.S. government support for the Atomic Bomb Casualty Commission's findings advanced by Jablon and Kato, as well as Doll's sustained campaign against Stewart's conclusions. This historical case, therefore, raises broader questions about the epistemic status of animal experimentation in assessing human risk. To this day, the LNT model remains controversial, and its development reflects a persistent entanglement of scientific uncertainty, institutional power, and political interest.

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