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Review article

The Muller-Neel dispute and the fate of cancer risk assessment

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ABSTRACT

The National Academy of Sciences (NAS) Atomic Bomb Casualty Commission (ABCC) human genetic study (i.e., The Neel and Schull, 1956a report) showed an absence of genetic damage in offspring of atomic bomb survivors in support of a threshold model, but was not considered for evaluation by the NAS Biological Effects of Atomic Radiation (BEAR) I Genetics Panel. The study therefore could not impact the Panel's decision to recommend the linear non-threshold (LNT) dose-response model for risk assessment.[1] Summaries and transcripts of the Panel meetings failed to reveal an evaluation of this study, despite its human relevance and ready availability, relying instead on data from Drosophila and mice. This paper explores correspondence among and between BEAR Genetics Panel members, including James Néel, the study director, and other contemporaries to assess why the Panel failed to use these data and how the decision to recommend the LNT model affected future cancer risk assessment policies and practices. This failure of the Genetics Panel was due to: (1) a strongly unified belief in the LNT model among panel members and their refusal to acknowledge that a low dose of radiation could exhibit a threshold, a conclusion that the Néel/Schull atomicbomb study could support, and (2) an excessive degree of self-interest among panel members who experimented with animal models, such as Hermann J. Muller, and feared that human genetic studies would expose the limitations of extrapolating from animal (especially Drosophila) to human responses and would strongly shift research investments/academic grants from animal to human studies. Thus, the failure to consider the Néel/Schull atomic bomb study served both the purposes of preserving the LNT policy goal and ensuring the continued dominance of Muller and his similarly research-oriented colleagues.

1. Introduction

Cancer risk assessment was built upon the assumptions that "Carcinogens are Mutagens" (Ames, 1973), that radiation-induced mutations follow a linear dose response down to a single ionization (BEAR, 1956), and that chemical carcinogens, which also act via mutagenic processes, should be assessed in the same way as radiation for the explicit purpose of cancer risk assessment (Albert, 1994; Calabrese, 2009, 2013, 2018a). Because of the linearity recommendation of the US NAS BEAR I Genetics Panel (1956), its reaffirmation by the Biological Effects of Ionizing Radiation (BEIR) I Genetics Committee (1972), and its adoption by the US EPA as policy (1975), which itself was based on BEIR (1972), the LNT cancer risk-assessment paradigm became established and "finalized" over the twenty year period from 1956 to 1975 (Calabrese, 2015, 2018b, 2019). The present paper documents, for the first time, the reasons why extensive negative findings demonstrating no genetic damage in children born after May 1, 1946 to atomic-bomb survivors were never utilized by the 1956 BEAR I Genetics Panel in its evaluation and recommendation of an appropriate dose-response model for risk assessment. The analysis herein determines that the Genetics Panel elected not to assess the ABCC genetic study of Néel and Schull, showing no radiation-induced genetic effects. This refusal eliminated a strong challenge to the LNT dose-response model that the Gentics Panel had already planned to recommend and it preserved the continued dominant role of non-human experimental models, such as Drosophila and mice, in the assessment of radiation-induced genetic damage. Thus, the Panel's refusal to consider the ABCC genetic study meant that substantial grant monies would continue to flow to animal geneticists (like the Panel members themselves) instead of being diverted to epidemiologists conducting human studies. This paper further documents that the extensive human data of the ABCC study were also ignored by BEAR II in 1960. Later, however, the Neel-Schull study was evaluated by the BEIR (1972) Genetics Committee but rejected in favor of methodologically similar transgenerational studies conducted in experimental animals that were claimed (a claim now refuted) to provide significant mutational support for LNT.

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[1] The BEAR I Genetics Panel (1956) directed their risk assessment to genetic risk. In 1960 BEAR II Genetics Panel added cancer risk, also adopting an LNT model.

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1.1. Background information: lack of genetic damage in children of survivors conceived after the atomic-bomb blasts

In many ways, the belief in and adoption of LNT was fueled by the dropping of the atomic bombs on Hiroshima and Nagasaki in August 1945, which not only heightened the significance of Hermann J. Muller's mutational discovery but also probably affected his being awarded the Nobel Prize a year later. This award granted Muller a highly visible platform to promote the LNT concept that he had vigorously supported for many years (Calabrese, 2019). Soon after the bomb blasts and the end of the war, joint scientific efforts by Japan and the US were initiated to study the survivors of the bombings and their future children. James Néel, a PhD in genetics (University of Rochester-with Curt Stern as advisor, 1939) and MD (University of Rochester, 1944), and a future member of the BEAR I/BEIR I Genetics Panels, became the first director of the ABCC study (whose name was changed to the Radiation Effects Research Foundation [RERF] in 1975), initiating a comprehensive and prolonged study on birth outcomes of the children of survivors (Neel et al., 1953; Neel and Schull, 1956a, 1956b; Neel, 1998; Schull, 2010; Schull and Neel, 1959, 1981; Grant et al., 2015).

These genetic epidemiological studies would involve the collection of data on vast numbers of subjects for multiple endpoints over time, including, but not limited to, congenital defects, viability at birth, birth weight, sex ratio, survival of children during the neonatal period, physical/anthropomorphic parameters, malignancies, structural rearrangements of chromosomes, aneuploidy, and point mutations, which included specific nucleotide changes, small deletions, insertions and rearrangements (Neel and Lewis, 1990; Schull, 2010; Grant et al., 2015).

The sample size was substantial with an original size of ~70,000 newborn children covering the time from 1948 to 1954 (i.e., ~5000–7000 children born/year in both Hiroshima and Nagasaki). The starting date was subsequently pushed back to May 1, 1946, further increasing sample size. The researchers periodically revised risk estimates as radiation doses were reconstructed in 1957, 1965, 1986, and in the 2000s (Schull, 2010). In general, the many dose reconstructions revealed that gamma-ray dose estimates at Nagasaki remained constant over the decades, while the estimated neutron exposures markedly dropped. A similar pattern was also the case for Hiroshima. However, regardless of the dose reconstructions (i.e., based on survivor interviews, shielding estimates of every individual, revised estimates of total bomb yields, statistical modeling assumptions, and other factors), the genetic findings remained such that none of the progressively updated studies yielded statistically significant results in the exposed children as compared to controls over the next six decades (Neel et al., 1953; Neel and Schull, 1956a; Neel and Lewis, 1990; Neel, 1998; Grant et al., 2015).

Of relevance to the present paper is that one of the major revised scientific updates of the ABCC genetic study was finalized toward the end of 1955, with publication scheduled by the NAS for early in 1956, fortuitously overlapping with the activities of the BEAR I Genetics Panel, which convened from November 1955 to June 1956 (Neel and Schull, 1956a, 1956b; Schull and Neel, 1959).

The ABCC genetic studies would reveal similar patterns of responses over time, with some endpoints being followed for prolonged—but limited—periods, such as anthropomorphic parameters that were age dependent. Other parameters continued to be followed across many decades, while others, such as the sex ratio, were followed for two decades then dropped (Schull et al., 1966). Regardless of the research strategies, the changes in technological developments, or the spectrum of endpoints measured, the results failed to show exposure related effects. At times there even were slight-to-modest decreases compared to the unexposed controls for multiple endpoints, such as for frequencies of malignancies in the first generation of offspring (i.e., reduction by 14%), decreases in structural rearrangements of chromosomes (i.e., reduction by 31%), decreases in aneuploidy (i.e., reduction by 23%), and decreases in point mutations for electrophoretic mobility of proteins (i.e., reduction by 29.4% with over one-million locus tests) in the radiation-exposed groups versus controls (Awa et al., 1968; Neel and Lewis, 1990; Satoh and Neel, 1988). Furthermore, the parents of the control children were slightly younger, with more years of education and higher occupational status than the exposed parents, thereby biasing toward the possibility of observing adverse effects, which would have favored an LNT conclusion (Neel and Lewis, 1990).

Even though the findings were consistently not statistically significant, Schull and Neel (1959) would indicate that it was not an absolute negative but one that was dependent on sample size, statistical power, and level of detection. Despite these remaining uncertainties, they emphasized that each progressive negative study with larger sample sizes would reduce that uncertainty and serve to better refine potential upper-bound risks, always assuming a linear response. Thus, Goldstein and Stawkowski (2015) would characterize Néel as one who kept his belief in LNT while still only reporting increasing evidence of thresholds for genetic risks, greatly frustrating his colleagues in the radiation-genetics community, such as Muller and Crow. The problem was not with Néel's "thresholds" *per se*, as he still held open the possibility/probability that adverse effects may occur at lower doses, or with a larger sample size, or when more sensitive endpoints could be introduced into the protocol. Problems for Néel arose since these negative findings would show that the predictions of human adverse effects based on LNT-based experimental models (i.e., on the fruit fly or mouse using the LNT model, such as predictions made by the BEAR I Genetics Panel) would appear to be strikingly incompatible with the human genetic data from the ABCC study. Néel simply kept publishing results showing non-statistically significant genetic risks that were far less than his geneticist colleagues in the radiation field had estimated (Schull and Neel, 1959, 1981; Schull et al., 1966). This would raise embarrassing questions concerning the reliability of these LNT animal models in predicting quantitative human responses.

Cancer endpoints in epidemiological investigations of the atomic-bomb survivors in the Lifespan Study (LSS) have been insensitive to possible risks below 100 mSv (Ricci and Tharmalingam, 2019). Given these statistical limitations on detections at low doses, cancer risk predictions by the US Environmental Protection Agency (EPA) adopted the assumption that genetic damage (i.e., the mechanism for cancer) was linear and its detection was below the sensitivity of the data collected by epidemiological studies with endpoints of multi-stage cancer. This provided a biologically based foundation for low-dose extrapolations (Albert, 1994). The LNT-related decision adopted by the EPA in 1975 was based on the recommendation of the BEIR I Genetics Committee (1972). EPA specifically acknowledged the Russell findings in the male mouse (Calabrese, 2017a,b). It is striking, however, that the EPA based its linear foundation for cancer risk assessment on this mouse investigation while, at the same time, ignoring Néel's nearly 30-year-long ABCC genetic study on humans. Furthermore, the lack of statistically significant findings in the ABCC study involved radiation exposures that not only exceeded human background levels by several orders of magnitude but also was delivered at an extraordinarily high dose rate, further enhancing risk. In retrospect, these negative epidemiological results are not surprising because even though double-strand breaks can be induced in human stem cells (in vitro) by 0.3–0.5 Gy in 30 min, none of that damage remains after 24 h due to repair processes. Furthermore, at lower doses (0.05 and 0.1 Gy), no damage occurred at any time point (Schroder et al., 2019). These negative human findings are consistent with the now revised mouse mutagenicity estimates of the Russell data (Russell and Russell, 1996; Selby, 1998a,b; Calabrese, 2017a/b). The following section addresses the BEAR I Genetics Panel and their scientific leadership and policy role in future developments.

1.2. BEAR I genetics panel

It is important to note that the atomic-bomb genetic data were available to the national advisory committees as soon as they were convened, beginning with the US NAS BEAR I Genetics Panel in November 1955, continuing into the 1960s, and then with the BEIR Genetics Committees and the US EPA from 1970 forward. Despite the availability of these findings, the meeting summaries and transcripts of the NAS BEAR I Genetics Panel (1955–1956) meetings indicate that no evaluation of this major study was conducted, even though its study director, James Néel, was a participating member of the Genetics Panel. Furthermore, the succeeding Bear II Genetics Panel of 1960, which contained almost the same personnel (including James Néel and the 1958 Nobel Prize recipient, George Beadle, as the new chair), also failed to consider/evaluate the ABCC human genetic study.

1.3. BEAR genetcs panel - first meeting

The invitation for Néel to participate in what would later be called the NAS BEAR I Genetics Panel was vague in describing a specific course of action. In his October 8, 1955 letter to Néel, NAS President Detlev Bronk (1955) wrote: "… I have decided that it will be desirable to have a series of conferences on some of the more significant aspects of this particular problem (i.e. he is referring to atomic radiation). The genetic effects of atomic radiation are among the most important of these considerations". In the next paragraph, Bronk writes: "I am writing to ask you to serve as a member of a panel of leading geneticists and a few other specialists in related fields to meet for three days to discuss the subject, to formulate significant issues for further study, to state conclusions that can be drawn from existing information and to recommend needed research." Thus, the invitation indicated only that a three-day meeting would be held, with no reference to a long-term commitment. In actuality, the three-day meeting transformed into a long-term BEAR I Genetics Panel lasting about eight years. However, the more immediate goal was to produce a report by June 1956, with a first draft by April.

During opening remarks of the November 20, 1955 meeting of the Genetics Panel, NAS President Bronk circulated amongst the Panel members ten NAS reports on radiation, including an earlier version (date not identified) of Néel's ABCC atomic-bomb offspring-survivor study. Following remarks by Bronk, Chairman Warren Weaver asked about the availability of the currently updated and expanded ABCC offspring-survivor study. Shields Warren, a Panel member and chair of the ABCC, indicated that Néel's next major report "will be ready in the near future" … "it is just now nearing readiness for a final report." (BEAR, 1955). Later in the meeting, James Crow would state that "We need to know more about man himself, about the effects of radiation." This comment was reinforced by Tracy Sonneborn who stated "I agree with Crow that we need intensive effort to acquire information in regard to man. No amount of extrapolation is as relevant as the direct information on man himself." However, Muller soon put a halt to this discussion focusing on human data with his statement that: "We should beware of reliance on illusionary conclusions from human data, such as the Hiroshima-Nagasaki data, especially when they seem to be negative." After that point in the Panel meeting the issue of Néel's Hiroshima-Nagasaki study and his apparent "illusionary conclusions" were never mentioned. It was as if Néel's study had received the equivalent of a scientific "Scarlet Letter" from the intellectual leader of the group, the Nobelist Hermann J. Muller. At that key moment in the meeting Néel fell silent and let the Muller criticism stand. Later that same day, Néel made a very tepid rejoinder stating that "the proper study of mankind is man" but with no specific application and to no avail. Thus, the issue of the availability, use, and importance of Néel's Hiroshima-Nagasaki study was never again raised, including in the meeting summary and the Panel's goal statement by Weaver. It is important to note that in November of 1955 (date unknown), Neel (1956a) (Néel letter to Muller, October 18, 1956a, 1956b, 1956c, 1956d, 1956e, 1956f) indicated that he had sent Muller a mimeographed copy of the Neel-Schull (1956a) monograph on the ABCC genetic atomic-bomb study. While Néel may have been under the impression that Muller (Muller (1956a) had read this monograph, Muller would indicate in a letter to Néel (October 24, 1956), nearly a year later, that he had never read this major study because he was too busy. Thus, Muller's dismissive comments about Néel's report at the opening session were purely speculative and judgmental as Muller never read the report and had no idea about its contents.

2. Neel informs Weaver and Muller of findings

Following these developments, Néel wrote to Warren Weaver (with a cc to Muller only) on January 23, 1956 (Neel, 1956b), more or less re-introducing himself by stating that **"As you** may know, for some time now I have been deeply involved in studies on the potential genetic effects of the atomic bombs in Hiroshima and Nagasaki. Dr. W.J. Schull and I have been working for the past two years on the report on this experience, and expect to get the final manuscript off to press by April 1, 1956.

The last chapter of that manuscript deals with the permissible inference to be drawn from the Japanese experience. In that chapter, we have strongly suggested that the state of our knowledge regarding the population genetics of man (or any other animals, for that matter) is so poor that speculation concerning the long range effects of radiation on the genetics of human populations is, to say the least, extremely risky." He then goes on to say that "our own manuscript was already in circulation at the time of the meeting …. " With this statement, intellectual/scientific differences were established and clarified. While Weaver wanted specific, quantitative risk-assessment guidance, Néel indicated that the human data from his ABCC experience, and even animal model data, would not support this. In contrast, Muller indicated that any estimates to be provided by the Panel would ignore Néel's study.

Néel seems not to have known Weaver well before the NAS meeting even though Weaver had been funding many leading US geneticists for several decades (Wynchank, 2011). For example, in the years prior to the creation of the BEAR I Genetics Panel, the Rockefeller Foundation had funded nearly four million dollars to the University of Indiana for research in the area of radiation genetics alone. Since Néel received funding from the NAS for the ABCC study, he had not been highly dependent on the Rockefeller Foundation, as were the other academic geneticists on the BEAR I Genetics Panel. Néel also revealed that he had selectively made the manuscript on his new study available informally at the time of the November meeting. Nevertheless, there was no evidence of the report ever being discussed at the November meeting. Néel's letter of January 23, 1956, was important because it formalized his attempt to apprise Weaver of his ABCC report and also had great relevance to the Genetics Panel. There is, however, no evidence that Weaver acted on this communication. Finally, that Néel only copied Muller on this letter to Chairman Weaver can be seen as a type of passive-aggressive response by Néel to Muller's highly critical comment concerning the "illusionary conclusions of human genetic data" at the November meeting. This was an indication of Néel's sensitivity to Muller's devastatingly critical comment about his Hiroshima/Nagasaki study and an implied suggestion that his human study was important for the Panel, representing a challenge to Muller's comment.

2.1. BEAR I genetics panel - second meeting

The second meeting of the Genetics Panel occurred on February 5 and 6, 1956. The most significant development during that two-day meeting was the adoption of a set of consensus principles that emphasized a belief in the linear non-threshold (LNT) dose response for radiation-induced mutations. The principles had been drafted a few days earlier by Sonneborn and were read to the entire Panel (Cal-

abrese, 2015) at the meeting. At the end of the meeting on February 6th, Weaver challenged the geneticists to estimate the number of adverse population-based transgenerational effects that would occur in the US population over the next ten generations should the parents of the current generation be exposed to 10 rad of ionizing radiation (e.g., Weaver's cumulative estimate from 30 years of parental reproductive radiation exposure) and assuming an LNT dose response (Calabrese, 2015). The imposition of the LNT assumption may have been given to help ensure an outcome of damage estimates that would display a strong convergence amongst the panelists, eliminating a major source of potential variation. Each geneticist was to develop their own independent damage estimate, sending via the mail a detailed report to Dr. James Crow prior to their next meeting on March 1.

This proposal greatly concerned Néel. In his letter to Weaver of February 14, 1956c, Néel stated: "You will recall that I stated at the recent meeting my conviction that our knowledge was far too fragmentary to permit a meaningful quantitative treatment of this problem …. .My reasons for this stand are spelled out in some detail in Chapter XV of the monograph which Dr. Schull and I are now preparing on the Japanese study. Although there are dangers in presenting this one chapter apart from the entire monograph, nevertheless I have decided to send a copy of this chapter to every member on the Committee as soon as possible, probably within the next two weeks. While I do not expect to make many converts, this will perhaps make the reasons for my stand somewhat clearer." On February 21, 1956d, Néel sent a memo to the Genetics Panel, attaching Chapter XV. He stated that "you will recall that at the recent meeting in Chicago I expressed certain reservations concerning our ability to develop worthwhile predictions concerning the genetic effects of irradiation. The paper supplies at least part of the details on which that position is based."

Together, the transcripts and detailed summary written by Bentley Glass (1956) provide a more insightful reconstruction of the Panel meeting held on February 5/6, 1956. The Glass write-up matches closely in content and time with the transcripts, but not fully. For example, Glass noted that during the meeting Néel said he would have chapter XV of his study mimeographed and sent to all the members of the Panel. However, according to the transcripts, Néel never made such a statement in the meeting. Néel may have mentioned this to Glass during a break or after the session had ended. As noted above, Néel would later write to Weaver on February 14, 1956, about sending the chapter to the entire Panel. However, this had been part of his plan while the meeting was in progress. Néel's letter also suggested that he had talked about it informally, to some extent, with other Panel members. In fact, on February 8, 1956, two days after concluding the Chicago meeting of the Genetics Panel, Néel sent Gioacchino Failla, a non-geneticist Panel member, a copy of his chapter XV (Neel, 1956e).

The 241-page study monograph by Neel and Schull (1956a) contained highly detailed research chapters on each endpoint, described each trait/endpoint in detail, and contained sections on research designs, statistical methods, and results and discussion/perspectives. No statistically significant findings were reported for any of the endpoints. Even though the study of Neel and Schull (1956a) was a major development, the NAS leadership had not made it available to the Panel, and Néel, for unknown reasons, only made Chapter XV available two months later in the second half of February 1956. Yet, Néel's actions, as seen in his February 21st letter to the Genetics Panel, shared only one of the fifteen chapters. His memo expressed little, if any, urgency, and only a desire to be better understood (Neel, 1956d). Furthermore, the Panel members had prepared and/or sent in their specific estimates of genetic damage before or about the time of receiving Néel's chapter. Although Néel could have used the next Panel meeting to explain the negative findings of the atomic-bomb study and his contrary position, this never happened. During the follow-up one-day meeting on March 1, 1956, in New York City, six geneticists, including Néel, did not attend, thereby precluding discussion of his ABCC findings and its potential for substantially impacting the Weaver assignment (Néel, Feb. 27, 1956f; Weaver, March 2, 1956 memo). In fact, a review of each of the submitted assignments (i.e., 9 of the 12 geneticists each submitted an independent written estimate) reveals that none cited the material provided by Néel (Calabrese, 2015, 2019).

The genetic findings in the ABCC study provide insight as to why Néel objected to estimating genetic defects that may occur in ten generations of children of adults in the US population who were theoretically exposed to 10 rad. Although this request was made to all geneticists of the Panel during the BEAR I Genetic Panel meetings, Néel (along with two others) declined to provide an estimate, claiming that it was impossible to do with scientific reliability (Calabrese, 2015, 2019).

Instead of considering the human data from survivor children of the atomic bomb, the Genetics Panel relied on fruit-fly data from Curt Stern at the University of Rochester (Spencer and Stern, 1948; Caspari and Stern, 1948; Uphoff and Stern, 1949) and emerging male-mouse data from William Russell, who was also a BEAR I Genetics Panel member. Russell's data were discovered several decades later to contain a significant error in the control-group value, affecting its application as discussed below (See Calabrese, 2011 for a detailed evaluation of the Stern studies that show his findings failed to support a linear dose response).

With his failures both to act more forcefully earlier in the Genetics Panel process and to attend the March 1, 1956 meeting, Néel lost his opportunity to affect the direction of the project. Nonetheless, he privately wrote to Weaver about how upset he was with the direction of the Panel. Néel also stated that some of the tactics adopted by James Crow reflected a deliberate attempt to improperly skew the data, thereby playing down the enormous uncertainty and presenting a false picture in order to gain acceptance by the scientific and regulatory communities (Néel, March 8, 1956g; April 17, 1956h). Despite these privately expressed opinions, it is apparent that Néel never again raised the subject of incorporating human studies, and he simply offered mildly supportive written statements on subsequent drafts and the final report of the Genetics Panel.

The substance of Néel's concerns was reflected in the vast range of damage estimates provided by the nine geneticists, even though each geneticist had been instructed to assume an LNT model. The geneticists were asked to provide a best estimate, with lower and upper bounds. The lower-to-upper values ranged considerably, with the most extreme showing a 2000-fold range in the case of George Beadle (Calabrese, 2015). Using Weaver's 10 rad (0.1 Gy) value, the mouse and Drosophila geneticists estimated a most likely average increase in genetic damage that would result in an additional absolute increase beyond background for 2–10% of the offspring. In the case of the atomic-bomb survivors, the approximate exposure for the highest two-exposure classes was estimated to be about 100–150 rad (1.0–1.5 Gy) over a short period of time, a cumulative value about 10–15 fold higher than the 10 rad, 30-year cumulative assigned Weaver value (Neel and Schull, 1956a). Based on the LNT model as developed by the BEAR I Genetics Panel, the adverse responses in the exposed populations in Japan would have been predicted to be linear and proportionally greater than that predicted using the Weaver value. Since the Néel human genetics study found no increase above controls for any endpoint and exposure level, including for exposures 10–15 fold greater than the Weaver value, it was clear that the actual negative findings of Néel even with their statistical limitations, were in direct contradiction of the theoretical positive predictions of the BEAR I Genetics Panel. Thus, one can understand the basis of Néel's frustration with the conclusions and direction of the Panel.

Néel's attempts to interest the BEAR I Genetics Panel in assessing his recently completed ABCC genetics study were shunned by his colleagues. However, Néel elected not to take no for an answer. He had another option, or so he hoped. For Néel sought a second bite at the apple so to speak, and perhaps a bit of both professional redemption and revenge. An opportunity existed because the British Medical Research Council (MRC) had created a panel that paralleled the efforts of

the BEAR I Genetics Panel in subject matter, but with the British starting some five months earlier. The British and the US efforts would eventually become coordinated, trying to ensure a high level of agreement, along with their "independent" reports being published on the same day (June 12, 1956). Without informing Weaver, Néel sought a more receptive audience with the British Panel and got it. This relationship would become known to Weaver by a letter to him from Néel dated March 16, 1956i, revealing that Néel had been in communication with the British effort and had shared his major ABCC report with them. Néel wrote that "the British counterpart of your committee has spent a great deal of time going over a first draft of our report on the Japanese experience. We have had an extensive exchange of correspondence, and they are quite familiar with the many, many reservations which I hold when it comes to the matter of calculating genetic damage from a given dose of irradiation at the present time. In point of fact, I find my thinking much closer to that of my British colleagues than to my American colleagues on many of the points involved." He went on to write that he would be meeting on April 4, 1956, in New York City with Sir Harold Himsworth, the chairman of the British genetics committee, to discuss his findings (note that a day later Himsworth would meet with Weaver and Bronk). Thus, given their willingness to evaluate in depth the Néel findings and to have their chair meet with Néel, it is not surprising that the British panel's report displayed a "reluctance to concede that all radiation was harmful genetically" as noted by Hamblin (2007). Despite the pressure to display a high level of international agreement on critical issues of genetic risk, Charlette Auerbach (1956) wrote that "There is nothing in the British report corresponding to the categorical American statement: "Any radiation is genetically undesirable", or "From the genetic point of view, they (the radiations) are all bad". Likewise, in their remembrance of Himsworth, Black and Gray (1995) stated that the Himsworth-guided British report on radiation genetics "suggested levels at which an individual not feel 'undue concern about developing any of the delayed effects'". Letting the report (MRC, 1956) speak for itself, on page 62, item 255 it states; "We consider, therefore, that an individual would, without feeling undue concern about developing any of the delayed effects, accept a total dose of 200 r in his life-time, in addition to radiation from the natural background, provided that his dose is distributed over tens of years …. "

This conclusion in the British report was preceded by a substantial acknowledgment of the efforts of Néel and Schull, including the sharing of their report of the ABCC study with the British Panel. Thus, although Néel's research was ignored by the US NAS BEAR I Genetics Panel, it was appreciably acknowledged, assessed in depth, incorporated into the British report, and provided the scientific foundation for the striking quotation given above. This relationship with the British panel and its scientific staff (including Tobey C. Carter) would come in handy later that year when Néel and Muller would confront each other over public scientific differences expressed at a WHO Workshop in August 1956 (See next section). The bottom line is that the Néel and Schull (1956a, 1956b) report had the potential to significantly affect the risk-assessment outcome in the United States, if it had been considered.

3. The Muller-Neel dispute and controversy

Even though Néel did not discuss the lack of adverse findings of his ABCC study during the BEAR I Genetics Panel meetings in 1955 and 1956, this changed in six weeks when he dramatically and publicly challenged Muller during a nearly two-week period in Copenhagen. The interaction began with Néel's presentation on the opening day of the First International Congress of Human Genetics (a major WHO meeting held in Copenhagen, August 1–6, 1956) (Neel and Schull, 1956b) and spilled over into a meeting of the WHO Study Group on the Effects of Radiation on Human Heredity (August 7–11, 1956) that immediately followed at the same venue. The battle lines were drawn early when Néel and his colleague William J. Schull delivered their findings from the ABCC human genetic study at the WHO Congress, which not only showed no evidence of adverse effects after nearly a decade of investigation but also contradicted the predictions of Muller and other radiation geneticists on the BEAR I Genetics Panel. In his presentation, Néel challenged the validity of extrapolating mutational data from fruit flies and mice to humans. For Néel and Schull, the most reliable way to estimate the human response to high levels of ionizing radiation would come from epidemiological studies, the type of studies they were doing. This declaration was a shot across the scientific bow of Muller that was captured by a *New York Times* writer, John Hillaby. The August 2, 1956 *Times* headline "Geneticist Finds No Atomic Harm" memorialized Néel's principal conclusion (Hillaby, 1956).[2]

Using the data of his ABCC study, Neal reported no statistically significant responses to exposures of ≥100 rad for one or both parents (Neel and Schull, 1956a, 1956b). Néel provided the upper 90% confidence limits of detection for numerous endpoints. Thus, in the ABCC study Neal and Schull were unable to discern a significant treatment effect even at very high exposures. Their report incorporated exposure shielding into the analysis, which, with increased sample size, made this report a significant advance over the previous publication (Neel et al., 1953).

The *New York Times* story revealed that Néel also undercut Muller and his colleagues who experimented with Drosophila by questioning the relevance of their animal models for human risk assessment. At the end of day one, the *New York Times* writer described the formation of two camps of radiation geneticists, the so-called "Mullerians" (i.e., the followers of Muller) and the "Anti-Mullerians" (i.e., those including Néel and Schull). In a very public international setting, Néel had transformed, in a matter of ten months, from the quiet and submissive person seen on November 20, 1955, to a far more self-confident and assertive individual. The scientific thrust of Néel's presentation was drawn directly from the material that the BEAR I Genetics Panel chose to ignore several months earlier. John Hillaby noted that several conference delegates challenged Muller, "arguing that direct parallels between radiation damage on mice and insects were not valid. They said the "Mullerians" failed to take into account the fact that mutant (unorthodox) genes act differently when produced by two or more doses of radiation. If true, this means that all estimates of genetic damage based on the assumption that all mutants were detrimental (whether produced by one dose or more) were overestimates." Hillaby continued by noting that "the anti-Mullerian viewpoint was advanced by Dr. J.V. Néel and Dr. W.J. Schull of the Hereditary Clinic at the University of Michigan, Ann Arbor …. .They concluded that there was no increase in still births, sexes of infants, birth weight or gross malformation in the children examined. They said categorically that, although there might be genetic damage as yet undetected, there was no statistical evidence of it from the cases they examined."

As the next meeting began, Muller would become further inflamed as Néel opened his presentation with the statement: "In view of the known species differences both in the genetic structure of populations and in the apparent genetic responses to irradiation, when considering the genetic impact of increased exposure to ionizing radiation we should prefer not to attempt to extrapolate from other species to man, but rather to base our thinking entirely on human data." Muller was upset with Néel, in large part, because he never suspected that the passive Néel would not only assert the validity of the ABCC genetic study but also challenge the predictive utility of his own research. Muller felt blindsided and did not like it. Néel would explain later in a letter to Muller (Neel, 1956a) that he could not have blindsided him because he had previously sent him the entire Neel and Schull (1956a) monograph in November of 1955, upon which his (Néel's) presenta-

[2] This New York Times headline stands in striking contrast with the first paragraph of the New York Times article on the BEAR I Genetics Panel on June 13, 1956 (Leviero, 1956). He wrote: "a Committee of outstanding scientists reported today that atomic radiation, no matter how small the dose, harms not only the person receiving it, but also his descendants."

tion was based, and that he assumed Muller would have read the monograph. Such an assumption by Néel seems reasonable considering the importance of the monograph and its direct bearing on Muller's own research predictions. This situation contributed to the theatrics orchestrated by Muller at the WHO Workshop as detailed in a letter of Muller to Beadle on August 27, 1956 (Muller, 1956b).

In this letter Muller first tells Beadle that "If you had heard Jim Néel's paper before the WHO meeting … you will see how radically he and I differ regarding not merely the significance of the Drosophila data for man but even reading what the Drosophila data show with respect to Drosophila itself". Muller then hit on the issue of priorities for research funding. He complained to Beadle that the statement on WHO research priorities "lays far too little emphasis on work with other organisms than man and it is up to us to remedy that defect." He then described the research priorities of WHO and various national funding organizations as "a fundamental and scandalous mistake" that needed to be challenged in every possible way. In the letter he went on to say that now that he has "got that off his chest" he wanted to return to the problems caused by Néel at the Copenhagen meetings. He stated that "It is important for our group to realize that there is a deep split in the WHO group, somewhat similar to our own group … There was one group lead by Néel, Carter, Penrose, the medical statistician Stevenson from Belfast, Tege Kemp and (at strategic points) Dr. Eve of WHO and Bruce Wallace … which tried to minimize the importance of the work which has been done and can still be done on other organisms than man in giving evidence regarding genetic damage in man. Néel had (by whose decision I do not know) been assigned the task of discussing how extrapolation is made from animal data to human conclusions and in my opinion he botched the matter up thoroughly, before an audience few of whom had the background necessary for a critical appraisal of his treatment." Muller then said how he kept objecting and challenging Néel, making "myself thoroughly disliked." Muller indicated that even though Alexander Holleander was the chair and on his side of the debate, he was an ineffective chair, being dominated by the official reporter (Stevenson) who seemed to act as if he were the chair rather than Hollaender. Muller then indicated that he had earlier obtained permission from Weaver to share with the WHO group key issues raised by the BEAR I Genetics Panel. Muller stated that "time and again" Hollaender would ask him to share the BEAR Panel information and each time Stevenson would block Muller's comments and prevent possible discussion. Muller wrote that this frustration continued for three days. Finally, however, he got Hollaender's support and made an abbreviated commentary, ignoring the interruptions of Stevenson.

Muller followed this late August letter with another to Beadle on October 1, 1956e, again expressing his frustration with Stevenson and his concerns on the direction of research funding. Muller stated that Stevenson would be writing a preface for both the WHO report and the discussion responses to each authored paper. He was very concerned that Stevenson had sent his preface and the discussion texts to the participants for comments. Muller indicated that **"This is a source of much concern to me since in my opinion both the preface and the discussions have been very heavily "slanted" so as to throw unjustifiable doubt on the conclusions of geneticists working with other organisms than man and I am uncertain whether or not to withdraw my name from the entire publication."**

To the outside reader, now 60 years later, this is a remarkable story of Muller's combative persistence over multiple days in challenging both Néel and Stevenson to the point of general annoyance. In many ways, Muller appeared to meet his match on "combative persistence" with the likes of Stevenson. Muller speculated to Beadle that Stevenson constantly objected and interrupted him because he (Muller) was trying to argue that major genetic concerns **"cannot be studied effectively in human material"**. In the end, it appears that Muller won an important partial victory when Hollaender finally reasserted himself as chair and appointed Muller and Néel to a subcommittee that would draft research recommendations. Muller referred to the document on research recommendations, which was approved by the broader committee, as a "compromise".

This contentious interaction with Néel came to a head in a battle over publishing the prestigious workshop proceedings. In this instance, Muller applied his influence and forced Néel to either conform to his views or risk not being published. Thus, in the fall of 1956, Néel and Muller would have a series of unproductive letter exchanges over Muller's concerns with Néel's workshop paper. This situation necessitated a brokered face-to-face meeting that Alexander Hollaender, the workshop chair and a BEAR I Genetics Panel member, would host. During this progressively hostile exchange of letters, Muller unveiled a series of warnings and threats aimed at Néel who was some 25 years younger and just eight years into his appointment at the University of Michigan. In addition to threatening to prevent publication of Néel's paper, Muller warned of Néel's damaged professional reputation, his embarrassment to the WHO, and his hurting the genetics field by redirecting research funding from scientists who work on non-human experimental models, like Muller himself, to scientists who conduct human epidemiological studies[3] (Muller Letter to Néel, December 7, 1956c). Not only did Muller pummel Néel with such criticisms, he also informed others of his criticisms and intention to prevent Néel's publication, as seen in his letter of November 21, 1956, to Dr. Eve of the WHO, with copies to Hollaender and three other leading geneticists plus Néel (Muller, 1956d).

Muller continued to threaten to block the publication[3] of the paper unless Néel and Schull would agree to "wholesale rewriting of the paper which Dr. Muller demanded before he will agree to publication of the papers submitted at the WHO meeting" (Néel letter of December 11, 1956j to Hollaender). In this same letter of December 11, 1956 to Hollaender, Néel wrote "Dr. Muller insinuates that my treatment is grossly lacking in accuracy at several points. I have checked over most of these points rather carefully, and am unable to find my errors … I have the greatest possible respect for Muller … I also believe there is room for other points of view than Muller's in this area, and fail to see how in this respect, it is any more inappropriate for me to present my point of view in a WHO publication, than for Muller to give his at Geneva". Néel asked that Hollaender arrange for his paper to be reviewed by an expert in non-human models, requesting William L. Russell. Whether Russell reviewed it is not known, but Edward Novitski, a highly regarded Drosophila expert, did. However, his letter of December 17, 1956 (Novitski, 1956), to Néel did not address any specific error but simply restated Muller's concern that Néel's paper would

[3] The following is an excerpt from the Muller letter: "As I have explained previously, I cannot indicate my own approval of the publication of the working paper as part of the WHO report if this attack upon the credibility of extrapolating from animals to man …. is to be included. Although you yourself would in the end be the one most injured by publishing so demonstrably erroneous a set of points as those in the paper as it stands in the Aug. 7 edition … …Inclusion of your article as it stands in the WHO publication without criticism would, because of the very high prestige and wide distribution of that publication, cast unjustified doubt in the minds of an enormous and influential audience on the value of the contribution which studies in the genetics of other organisms than man have made and can make, when taken in connection with the evidence from man to the specific problems of spontaneous and radiation–induced mutation rate and mutational load in man, a least as far as setting a valid minimal estimate is concerned. Such a bias would not only tend to hamper those who have the practical job of taking steps to reduce radiation exposures to a level that is reasonable in the light of the probable mutational damage but would also tend to result in less support being given to research in the genetics of other organisms that the situation justifies. It is moreover unfair to the sponsors of the WHO publication, and to the World Health Organization in general, to put it in the position of publishing a paper so pivotal in regard to the problems at issue and not contested elsewhere in this publication, that is soon afterwards to be shown to have been so erroneous in both its stated and its implied conclusions. It is for all these reasons that I will not be able to find it advisable to approve of the publication of the working papers along with the report if your pages 6 to 9, and more specifically 6 through the first paragraph of 8, are not to have their purpose modified considerably."

likely seriously undermine "support for basic genetic studies on other organisms."

Hollaender attempted the reconciliation of Muller and Néel during private meetings at Oak Ridge National Laboratory on January 6, 1957. However, correspondence between Néel and Stern reveals that the efforts of Hollaender were more frustrating than successful (Néel, December 11, 1956k; January 9, 1957a). In his letter to Stern on December 11, 1956k, Néel wrote that "There are at issue questions of philosophy and questions of fact. On the philosophical side, I agree wholeheartedly to the genetic problem raised by the increasing exposure of man to ionizing radiation … But I feel that on the quantitative side, Muller's treatment outruns the available facts … I find Dr. Muller highly emotional on these matters and very difficult to discuss things with dispassionately. I have the greatest possible respect for Dr. Muller, and would be willing to go to any reasonable extreme to placate him. On the other hand, I am unable to accept the principle that no doubt should be raised in so public a place as the WHO forum concerning the validity of our quantitative data." (That is, regarding Néel's lack of support for animal to human extrapolation and the lack of genetic damage in the offspring of the atomic bomb survivors).

Finally, in his follow-up letter to Stern on January 9, 1957, Néel (1957a) states that "I have now had my session with Muller … Now a human geneticist has turned around and pointed out some of the difficulties in working with Drosophila. This almost comes under the category of man bites dog. I am afraid that Dr. Muller will be very unhappy when he finally reads Chapter XV of our monograph."

A day after the Néel letter to Stern, Muller wrote to Novitski, and his letter not only confirmed Novitski's presence at the Neel-Muller meeting but showed that Novitski was very helpful to the Muller case. Muller also indicated how much he appreciated spending an evening with Novitski and his family. With respect to the Muller-Neel meeting, Muller stated that **"I also** appreciated very much the time you gave in attending our discussion and you having jumped in such a helpful way at the critical junctions … Unfortunately I found a letter from Dr. Eve of WHO awaiting me on my return, proposing that the papers be published as they are and that I simply supply an addendum to my paper, to be circulated later (i.e., Muller's rebuttal of Néel's comments). I am however holding out against this, even though they say they have no time to wait".

While most active scientists take a fair amount of criticism in different venues, this was one that was administered with uncompromising harshness by a Nobel Prize recipient who had exceptional standing in the scientific community. According to Néel, his publication in the workshop proceedings required being rescued by a number of British radiation geneticists because Néel was no match for Muller, one-on-one. Néel wrote to Beadle (September 14, 1959) that "At this point a number of the British participants in the WHO Study Group got wind of what was afoot, through no effort of my own, and got their own backs up. It so happened that they agreed with my point of view and in effect transmitted the message that if any pressure were brought upon me, they would withdraw their own papers. This reconstruction by Néel was supported by a letter Néel received from Tobey G. Carter, one of the British participants in the WHO workshop. On February 19, 1957, Carter (1957) wrote to Néel stating that "It came to my ears that a certain person was attempting to gag you, to the extent of threatening certain action if W.H.O. allowed you to publish your Copenhagen paper in the form in which you wanted to publish it. I therefore told W.H.O that I considered this to be illegitimate pressure, and that if they condoned it I should withdraw both my paper and my signature from the report." (see Lindee, 2013 and Calabrese, 2017b, footnote 1 for a discussion). It is interesting to note that in Carter's letter to Néel of February 19, 1957, he referred to the ABCC monograph as Néel and Schull's "Magnum Opus from the National Academy of Sciences". This suggests that he attributed considerable scientific value to that report.

That the British geneticists would have come to the defense of Néel in his dispute with Muller may be readily seen in a statement that was read to the British Institute of Radiology annual Congress (November 25, 1954 and then published in the *British Journal of Radiology*, during the meeting time (February 1956) of the BEAR I Genetics Panel (Carter et al., 1956). Note that the lead author was Tobey Carter who later acted on Néel's behalf.

"A good deal is now known about the magnitude of the somatic hazard (from ionizing radiation), but almost nothing quantitative about the genetic hazard. This fact is widely recognized among geneticists, who would doubtless, if they were concerned solely with the scientific aspects of the problem, prefer to remain silent on the subject about which they are so ignorant. However, there has been an insistent demand for quantitative pronouncements, with the result that a number of calculations have been published in which attempts have been made to evaluate the genetic harm to man. Their value is doubtful, but they have demonstrated a surprising measure of agreement amongst geneticists in three respects: first, admission of ignorance: second, recognition that almost any answer can be obtained from the calculations, according to the assumptions made and the numerical values fed in; and third, pessimism. Most geneticists would agree that it is very undesirable that members of a human population should be exposed to more than 25 r until after the breeding age, though it is doubtful if any could give really sound reasons for this belief. From all this it becomes apparent there is an urgent need for more factual information and less theoretical speculation".

3.1. HOW did BEAR I geneticsts view the Neel and Schull study?

An important underlying, but unanswered, question is what the BEAR I Genetics Panel members actually thought of the ABCC genetic study of Neel and Schull (1956a). Because the panel members never assessed this paper as a committee one is left with limited insights. Perhaps, the most directly relevant and explicit insight may be found in a book review of the Neel and Schull (1956a) monograph by panel member James Crow in 1957. Crow praised the study for the "size of the program", "care and attention to detail in the planning of the study", and for creating and sustaining the "cooperation of the Japanese-physicians, midwives and mothers". However, Crow noted several concerns, most important of which was his belief that there was an "extremely small" likelihood of observing any adverse genetic effects. In his book review, Crow only mentioned one factor limiting the capacity to detect an adverse effect. This was the relatively low sample size in the uppermost exposed groups. Of the 71,280 pregnancies at the time of the study, 3681 pregnancies were in families with one or both parents in the highest two exposure categories. Crow did not mention that an Ad Hoc committee in 1947 (Chaired by George Beadle and with Hermann J. Muller as a member) suggested that because only a relatively small proportion of the mutations affected dominant genes that might be predicted to display effects in the first post-bomb generation, the chances of these adverse effects occurring were low. They stated that dominant mutations, even though less common than recessive mutations, would be expected to be clinically significant and affect important health related endpoints. It was this type of advisory comment that lead Néel and Schull to measure stillbirths, congenital malformations and other serious adverse outcomes (Ad Hoc, 1947; see page 332). In addition, Crow argued that the statistical analyses were "all on the side of extreme conservatism," taking precautions to not falsely conclude there was a significant treatment effect. Crow would have preferred that each individual received an estimated unique dose (even if in error) rather than be grouped into exposure classes (e.g., a dose range for a group). If so, the regression method could have been used to develop dose-response relationships with confidence limits. It is assumed that linear modeling would have been used. However, Crow acknowledged that Néel and Schull made this type of modeling possible by making their data (on IBM cards) available to other investigators, something that the BEAR Panel and other groups could have considered doing.

Given the above caveats, Crow accepted the factual conclusions of the report. That is, with roughly 95% confidence and with an estimated exposure of 100 rad, Néel and Schull could detect treatment effects that approached and exceeded twice the background/normal risk. These were the limits of detection given background variation and the sample size. Since the sample sizes were far greater at the lower doses, the capacity to detect potential adverse effects was also assessed, but, here too, no adverse effects were detected. Since the dose of 100 rad could approximate a dose that is nearly 1000 times the annual background for a human, it becomes obvious that there was no practical demonstrable risk.

The assessment of Crow does not provide a basis to reject the consideration of the Neel and Schull (1956a) findings. On the contrary, the Crow description would strongly suggest that these findings needed to be taken seriously as part of the information to be evaluated by the entire Panel. Further, it would suggest that the Panel needed to add expertise in the area of epidemiology, as it was limited in this area.

4. The BEIR I genetics committee

In contrast to the Muller-led Genetics Panels (1956, 1960), the BEIR I Genetics Committee (1972) (without Muller who died in 1967) focused discussion on the Neel and Schull (1956a) ABCC genetic findings and other follow-up reports (e.g., Schull and Neel, 1959; Neel, 1966). Sixteen years after the report of the BEAR I Genetics Panel and with more negative studies accumulating, the BEIR I Genetics Committee (1972) acknowledged that there had been no statistically significant effects on genetic endpoints in the ABCC studies.

4.1. BEIR I misleads the scientific community with regard to BEAR I ignoring human genetic studies

On page 42 (right column), the BEIR (1972) Genetics Committee stated that "The 1956 Genetics report mainly relied on data from Drosophila and the laboratory mouse, as there were almost no relevant human data." This statement inexplicably dismisses the comprehensive human epidemiological investigation by Neel and Schull (1956a) on the children of survivors of the atomic bomb blasts. Yet, it does so in a way that implies that the BEAR I Genetics Panel actually reviewed the ABCC data. This seems to be an outstanding deception for which there is no supportive data, only much data showing that there was no such review. Furthermore, with a 16-year period of historical hindsight and the availability of the multiple Néel and Schull publications, this statement by the BEIR I Committee (1972) is extremely misleading, if not patently false.

4.2. New findings since BEAR I

The BEIR I Genetics Committee emphasized that the existence of a DNA repair-mediated dose-rate effect was denied by the BEAR I Genetics Panel and, furthermore, that the spermatogonial period of high DNA repair dominated the temporal lifespan of germ cells in male humans and mice (BEIR, 1972, page 44, left column). The Committee also noted that no treatment-related findings were reported in 45 consecutive generations in male mice (26-days old when irradiated) with single exposures of 200 rad (i.e., 20 fold higher/generation than the single generation 10 rad criterion of Weaver) across all the generations (Spalding et al., 1969). The BEIR I Genetics Committee (1972) acknowledged that there was no radiation-induced treatment effect in the Spalding et al. (1969) study on viability, fertility, growth, or abnormalities (page 45, right column). This was a massively challenging study since one of the principal concerns of the radiation genetics community was that some induced mutations may not elicit harmful effects for multiple generations. In terms of a human population, the 45-generation study was approximately equivalent to 1500 years of human life.

The remarkable findings from the Spalding study were dismissed as insufficient, needing more generations, larger sample sizes, and more and/or different/more sensitive endpoints. Spalding's research faced the same types of concerns as might apply to Néel's epidemiological investigations. Proving a negative is not possible. In the end, there is no practical escape from the dilemma as similar arguments are commonly made in animal bioassays where about 100 million mice/rats would be needed to detect a 1 in 10,000 increase in tumor incidence with a background incidence of 10%. And yet, a risk of 1 in 10,000 is viewed as too high. These arguments are predicated on the acceptance of LNT.

The above series of findings that challenged the LNT recommendation were countered by arguments regarding; (1) experiments in the fruit fly suggesting that low doses of ionizing radiation may produce more genetic effects than acutely high doses (Mukai et al., 1972); (2) concerns about enhanced responses to radiation with chromosomal structural changes; and (3) radioactive carbon and phosphorus that may get incorporated into DNA. However, the report failed to note that in children of bomb survivors the occurrence of structural rearrangements of chromosomes and other genetic endpoints were approximately 1/3 lower than in controls and, as noted earlier, contrary to expectations from the linear hypothesis. The remaining two arguments were also seen as limited. For example, the trans-mutational responses were considered to be only of minor public health importance. However, the first argument of BEIR I to support the continued use of LNT was a theoretical one, but nonetheless its strongest. Even though BEIR I recognized no evidence was yet available for human genetic effects of radiation, even at very high doses, data from animal experiments suggested that such changes were a possibility. BEIR I therefore argued that mild genetic effects in the heterozygous state are more difficult to detect and are often an order of magnitude more common in occurrence than dominant and more harmful conditions that would likely be removed from the gene pool (Fremlin and Wilson, 1982). Finally, even though the BEIR I Genetics Committee acknowledged that the stronger arguments rested with those suggesting that estimates of risk were too high (page 46 left column), this acknowledgment did not alter the committeee's final decision to endorse the LNT.

Despite the consistent, persuasive, and progressive findings of no radiation-induced treatment effects, the committee asserted that there were insufficient data to deny the possibility of adverse genetic effects (i.e., the detection-limit and sample-size arguments). Based on such reasoning, the committee rejected the use of a threshold model. Despite this theoretical LNT-based rejection of the threshold model, the committee felt compelled to base a recommendation on experimental data. Therefore, the BEIR I Genetics Committee, with W.L. Russell as a member, selected Russell's male mouse data, rejecting his female mouse mutagenicity findings that had displayed an exposure threshold 27,000 times background (Calabrese, 2017a,b). Despite the extensive nature of the Russell findings, the study data displayed potentially significant limitations and uncertainties and there were numerous reasons to question whether the data, even as reported, were adequate to support the LNT hypothesis. For example, Neel and Lewis (1990) noted that studies from eight different complementary experimental approaches provided estimates of the so-called doubling dose for mice. These attempts, though providing highly variable findings, collectively yielded estimates of approximately three-fold greater doubling doses than the Russell data. In another analysis, T.H. Roderick (1983) of the Jackson Laboratory in Bar Harbor, Maine, estimated that the recessive lethal mutation rate per locus in post-spermatogonial cells of mice for ionizing radiation was only 0.35×10^{-8}/0.01 Gy, while Russell's 7-locus system, which assumed that 7 genetic loci represented the responses of many thousands of genes in the mouse, yielded a rate of 45.32×10^{-8}/0.01 Gy, a 129-fold greater risk estimate provided by Roderick's.

Néel suggested that Russell's assumption of 7 loci being representative of genome-wide responses was inaccurate and comparable to taking a survey of 30,000 people (the number of genes for a human) and reaching a conclusion by interviewing only seven people. In addition, as noted above, Russell later learned that he had overestimated his mu-

tation risk by 2.2-fold because data on his control group were in error (Russell and Russell, 1996). Still later, Selby (1998a, 1998b) recalculated Russell's overestimation of risk to be even greater at 5 to 7-fold. Essentially, even the more modest risk correction of Russell and Russell (1996) changed what was a "linear" response to a "threshold" response for the male mice and even a "hormetic" response for the females (Calabrese, 2017a,b).

In retrospect, refusal by the 1972 BEIR I Committee to use Néel's human data in favor of Russell's mouse findings might seem odd, especially when the human data by that time had represented an accumulation of 25 years of negative results with progressively larger sample sizes. Sixteen years earlier, the BEAR I Genetics Panel (1956) employed a similar type of strange—perhaps even convoluted—decision-making process when it proposed that Russell's mutation rate for male mice be applied to the total estimated number of genes in the fruit fly to derive a value that would, in turn, be used to estimate the total number of radiation-induced mutations in humans after a single gonadal dose and after 10 generations. One can see why Néel, as a member of the BEAR I Genetics Panel, adamantly refused to endorse such speculative estimations of human risk.

5. Discussion

The major conclusion of this assessment is that the NAS BEAR I Genetics Panel failed to evaluate the ABCC atomic bomb study despite its acute human relevance, its ready availability, and the unique convenience and accessibility of the principal investigator, James Néel, for questioning by the Genetics Panel. The failure of the Panel to consider human data is both puzzling and important because these findings could have provided opportunities to assess the predictive values of the Drosophila and mouse models and to promulgate policies on real-life human responses with dramatic effects on public health as well as on broad national and international economic and social programs.

After sidestepping the opportunity to evaluate human data, the Panel members were requested by Chairman Weaver to estimate transgenerational adverse genetic responses that would occur in humans based on an LNT dose-response model and their own non-human experimental models, including bacteria, fruit flies, paramecia, and mice. Results of this request were very upsetting to some Panel members because the LNT estimates revealed such a profound lack of agreement that they would surely preclude acceptance of the Panel's LNT recommendations by the government and public (See Calabrese, 2019, for a detailed summary of this activity and other references). Having rejected consideration of Néel's human study, failing to reach agreement on the LNT-based risk estimates, and not knowing what to do next, the Panel evolved toward a path of scientific deception that essentially entailed creating the illusion of unified agreement on their risk estimates in order to acquire general approval of the LNT model. The Panel proceeded to conduct a dishonest and statistically flawed process that yielded a variability value of 100-fold, a value sufficient to support an authoritative public pronouncement with face-credibility. That is, the Panel experts would be seen as differing moderately in their perspectives but converging markedly in their ultimate scientific assessments given all the variables considered (Calabrese, 2015, 2019).

The Panel's process started with a decision by Panelist James Crow, who was selected to collate the nine submitted estimates from 12 panel members, to eliminate the three most divergent estimates—those derived from bacteria and humans, leaving only estimates from Drosophila and mice. In fact, when the Panel reported its findings in the journal *Science* in June 1956, it inaccurately claimed that only six instead of nine geneticists offered estimates (BEAR, 1956; Calabrese, 2015). The report in *Science* also neglected to state that three of the 12 panelists refused to offer any estimates of genetic damage because they claimed it could not be scientifically justified/defended. The failure to mention this resistance is significant because it obscured or entirely hid additional Panel uncertainty. Crow's expunging of three estimates effectively reduced what was a massive variation down to 750-fold, but this value was still deemed as too great for public uncertainty. What to do next? It was simply to officially state that the variation actually was 100-fold. In what amounted to a high-stakes game of scientific deception, the Panel refused to share their information with the scientific community when requested to do so by some outside scientists, a decision approved by Detlev Bronk, president of the NAS. The Panel presented a unified, unchallenged, and yet dishonest front (Calabrese, 2015, 2019).

Despite both the confrontation between Néel and Muller concerning the presentation of Néel's data at the WHO Conference in August 1956, and the challenge of publishing his manuscript in the WHO Workshop Proceedings, these conflicts did not become public in the subsequent NAS BEAR II Genetics Panel, which was chaired by George Beadle. That panel also failed to evaluate the still-growing Néel study, which suggests that Muller continued to dominate the Panel and steered it in his preferred directions. In personal correspondence, Néel would quietly complain to Beadle about the abusive Muller, but to no avail. A letter from Néel of September 14, 1959, during the time of the BEAR II Genetics Panel, illustrates how Néel felt about the situation. While Néel complained about such actions in private correspondence to Beadle, he chose to remain silent to the public:

"When Jack Schull and I pulled together our monograph on the findings in Japan, we felt obligated to try to fit these findings into the context of present knowledge. The outgrowth of that attempt, our Chapter 15, was a number of questions concerning Muller's argument. We couldn't prove that he was wrong, but we didn't feel he could prove that he was right. In other words, we felt there were a number of unvalidated assumptions behind a good many of his points. One aspect of this evaluation of ours was a little critique of the significance of mutation rate studies. This critique I delivered at the WHO Study Group on the Effect of Radiation on Human Heredity which met in Denmark in the summer of 1956. I regard it as part of the normal scientific interchange, but Dr. Muller apparently regarded it as an attack upon his life's work. There developed a rather strained relationship which persists until the present day, I am afraid, and keeps coming back to me in small ways that I consider beneath the dignity of a great man."

Yet, even with this rather sharp and troubling portrayal of Muller, Néel did not press Beadle for an assessment of the ABCC findings, suggesting that he knew it was fruitless.[4] Based on the performance of Muller at the WHO conference and its aftermath in the Neel-Muller confrontation, Néel may not have wanted this intense conflict to continue, especially given its apparent futility. Thus, while Néel would likely have been strongly embraced within the scientific culture of the leading British radiation geneticists, in the BEAR genetic culture he was respected but marginalized and controlled, a frustration that occasionally became evident.

Néel (1957b) would nonetheless attempt to push his agenda but in ways that were less directly confrontational. For example, on April 28, 1957, four months after the debate with Muller at Oak Ridge, Néel gave a presentation at the annual meeting of the US National Academy of Sciences on the role of human genetics. He stated that it had **"finally come of age, to the point where studies in man, not from looking to man for the qualities which have made Drosophila and Neurospora so useful to the geneticist, but, in part at least, from taking advantage of certain specific attributes of man and the populations in which he gathers, attributes not shared by other organisms."** This was a rather clever and oblique way of Néel reassert-

[4] On May 4, 1960 Beadle (NAS BEAR II documents) would hold a press conference on the release of the BEAR II (1960) Genetics Panel report. When asked the question: Dr. Beadle, do you think that there is any hazard from fallout at its present level as a genetic hazard? What is the genetic hazard at the present level? Beadle responded as follows: "The general opinion of geneticists is that there is no evidence of radiation that is without effect. There is no evidence of threshold." Beadle certainly had the opportunity to discuss to Neel and Schull (1956a) findings that had not detected adverse genetic effects in the offspring of atomic bomb survivors but did not do so.

ing himself and again telling his genetics colleagues that the best way to study man is to study human populations. Later in that presentation Néel would emphasize that there were very large differences in susceptibility to radiation-induced mutation between the two key predictive models, Drosophila and mice, making predictions of human responses from such models very uncertain. When extrapolating from animals to humans during the normal practice of government risk assessment, a precautionary assumption exists whereby humans are considered more sensitive than animals, typically by a factor of at least ten. However, at this meeting Néel asserted that his human genetics studies would "exclude this possibility" of greater susceptibility, thereby once again emphasizing the significance of human data and how they should drive the risk assessment process (Neel, 1957b). Such a public statement by Néel suggested his high level of frustration with the BEAR Genetics Panel on both excluding his data from evaluation and not allowing its decision to do so a matter of public debate. It was another example of Néel's passive aggressiveness. Although many might not perceive his real message, geneticists, like Muller, were very sensitive to what Néel was saying.

Muller had a similarly strong dispute with William Russell over the significance of Russell's discovery of dose rate and the implications for the mutation response and a possible threshold dose response (Calabrese, 2107a,b). As with Néel, Russell would try to placate the seemingly never-yielding Muller. However, after Muller's death, Russell made a 1970 Conference presentation that offered a profound challenge to the radiation genetics community on its mantra that all genetic damage was cumulative, without repair, resulting in a linear dose response (Russell, 1973). The Néel and Russell episodes with Muller over the challenge of new findings illustrate the dominance of Muller within the radiation genetics community. He was both greatly respected for his achievements and yet feared by others for his capacity to harm their professional standing. In the end, both Néel and Russell were dominated by Muller as was the BEAR Panel, thus ensuring the adoption of the LNT.

We are therefore faced with the strange history of how the world came to adopt an LNT-based cancer-risk assessment, which was created by the US NAS Genetics Panels/Committees. My analysis has led me to the conclusion that Muller and his geneticist colleagues in the radiation community were very strong, ideologue-like, LNT supporters who implemented an ends-justifies-the-means philosophy and would even commit scientific misconduct to ensure the adoption of LNT. Although considerable evidence supports this view, this paper argues that the issue goes deeper than the LNT ideology and the Panel's dishonesties; it is one that envelops the universal common denominators of money, power, and influence. The historical record indicates that Muller did not want Néel to succeed because he strongly believed that this would significantly redirect grant monies from his (i.e. Muller's) research area of Drosophila to that of human population genetics. This is strongly supported by multiple letters amongst the BEAR I Genetic Panel (i.e., Beadle, Crow, Demerec, Hollaender, and Muller) and other leading radiation geneticists, including the WHO expert committee that witnessed the Muller-WHO episode and incidental spin-off letters. Based on that perspective, the genetics Panel found themselves wrapped in a conflict of interest that led them to ignore Néel's findings, which precluded a significant role for human data in radiation risk assessment. The emerging picture is one of panel members who had clear goals and filtered everything through that lens to achieve and/or perpetuate their professional success, which, in the process, also ensured adoption of the LNT policy goal. In effect, the Genetics Panel achieved two major goals for the price of one. The strong-willed, outspoken, never-relenting and dominating Muller would ensure that the Panel kept its focus, masterfully mediating their professional, scientific and ideological interests.

The Neel-Muller conflict over the primacy of which data should be used in human risk assessment was addressed, in part, long before their conflict and far more fully afterwards, based on a review of the environmental and occupational health standards for chemicals and radiation (Calabrese, 1978). That is, non-mammalian models had never before been used in human risk assessment. In the more modern era, after the creation of EPA in 1970, ambient air quality standards were soon established for ozone, nitrogen oxides, sulfur oxides, carbon monoxide, and particulate matter, and they were based on epidemiological studies. This was also the case for lead, asbestos, methyl mercury and several other agents. US federal agencies have used both mammalian models and human studies in the derivation of exposure standards. Although major debates occurred regarding the critical study upon which a standard should be based, these agencies had not neglected to review the available and relevant data in the blatant way that the BEAR Genetics Panels did. The most reasonable interpretation of the reason it took more than sixty years for anyone to discover and document the failure of the BEAR I Genetics Panel to assess the comprehensive, timely and relevant study of Neel and Schull (1956a) is simply because a decision not to review such a relevant study at the time would seem so bizarre, incredible and unprofessional that one is hard pressed to believe that it actually did happened.

6. Conclusion

Human genetic data from over 25 years of the ABCC study (i.e., 1946–1972) demonstrated support for a threshold model for radiation-induced genetic damage in humans, but that information were both ignored and then rejected by the BEAR I and BEIR II Genetics Committees, respectively. The findings, now nearly 50 years later (Grant et al., 2015), have consistently continued to contradict a linear dose response, supporting a threshold response for a complex array of endpoints of genetic damage in humans. Furthermore, the decision to base the LNT recommendation on the male mouse data of Russell is now seen as flawed (Calabrese, 2017a,b), providing no support for the BEIR (1972) decision in favor of LNT.

The failure to assess the human genetic study of Neel and Schull (1956a) at this most crucial time in risk-assessment history represents a profound abrogation of responsibility by the NAS leadership and the BEAR Genetics Panels. This affirmative "failure of responsibility" appears to have been a goal of Muller as it would ensure the adoption of LNT and the continued professional dominance of Muller and his like-thinking and similar research-oriented colleagues. The adoption of LNT occurred during a "perfect storm" consisting of: heightened societal fear of nuclear confrontation; continuing nuclear fallout from atmospheric testing; ideologically based policy and scientific leadership of the Rockefeller Foundation and the US NAS; and a handpicked, highly LNT-biased Genetics Panel that was dominated by an even more-determined Hermann Muller to ensure adoption of the LNT. This history should represent a profound embarrassment to the US NAS, regulatory agencies worldwide, and especially the US EPA, and the risk-assessment community whose founding principles were so ideologically determined and accepted with little if any critical reflection.

Uncited references

Bronk, 1955, Carter, 1957, Neel, 1957a, Neel, 1959, Novitski, 1956, Weaver, 1956.

Declaration of competing interest

The author declares no conflicts of interest.

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