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Review Article

The National Academy of Sciences Biological Effects of Atomic Radiation (BEAR) Genetics Panel recommended no second-generation genetic damage study of the offspring of the atomic bombings in Japan

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ABSTRACT

This paper provides the basis for the recommendation of the BEAR Genetics Panel for the US NAS not to support an assessment of genetic damage of the second generation of offspring of parents exposed to the atomic bomb explosions in Japan in 1945. This recommendation was largely based on a report by James V. Neel and William Schull, directors of the first-generation ongoing study. Neel was also a member of the Panel. As expected, the first-generation study continued. The current paper was based on an assessment of a series of unpublished letters and the Neel-Schull report obtained within the Neel and James Crow preserved papers.

1. Introduction

One of the major scientific developments in the aftermath of the dropping of the atomic bombs on Hiroshima and Nagasaki was the creation of a long-term study of the effects of such bombings on the offspring of those exposed. James Neel, a physician and Ph.D. in genetics and a professor at the University of Michigan, was placed in charge of that study. He was joined by William Schull, Ph.D., an epidemiologist from the University of Texas. They worked within the framework of the Atomic Bomb Casualty Commission (ABCC) to oversee and conduct this study. Neel directed this study until his death in 2000, at which time the study was still in progress. In addition to being director of this study, Neel was invited to become a member of the BEAR I Genetics Panel scheduled for its first meeting in November 1955. The timing of the start of Panel activities coincided with the finalization of the findings after ten years of assessment. Since the report was nearly finalized when he was invited, Neel decided to send an advanced copy to Hermann Muller and to share a copy of the report with the President of the NAS, Detlev Bronk, in connection with the start of the BEAR I Genetics Panel meetings. This was viewed as nearly perfect timing since Neel fully expected the Panel to take on the role of evaluating the findings of this ten-year study, a report that would be unique in the medical sciences and epidemiological evaluation [1–9].

While Neel did not report on the findings of his study at that first meeting, he did make it known that the study was now available for review and that he had given a copy to the President of the NAS, Dr. Detlev Bronk. It was noted that the report, which would not be finalized and published until 1956 [5], showed that the 10-year study of approximately 75,000 children of parents exposed to the atomic bomb explosions showed no significant genetic damage. To the shock of Neel, during the opening session of the BEAR I Genetics Panel, Hermann J. Muller was dismissive of the new report, calling the negative findings "illusionary" [6]. The comment of Muller was neither challenged nor debated at that opening meeting of the BEAR I Genetics Panel. The basis of the Muller judgment was unfortunately not explored, and the data of this massive ABCC study of Neel were not even discussed by the BEAR I Genetics Panel. Calabrese [2] has reported on the emerging conflict between Muller and Neel concerning this major study, Muller's dismissive attitudes, and their subsequent public and private debates. During its deliberations, the BEAR I Genetics Panel seemed to take the easiest path forward, given the intense time pressures and thus putting its principal reliance upon radiation mutation studies with *Drosophila* that had dominated the scientific literature up to that point as well on emerging mutational data with mice [5].

Approximately six years later (1962), interest was generated within the US NAS concerning whether the study of Neel/Schull for the ABCC should be expanded now to include second generation offspring since surviving children would be entering into their reproductive phase soon.

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These perspectives led to a series of letter exchanges between R. Keith Cannon, who was Chairman of the Division of Medical Sciences for the NAS, and James Crow, who was now the Chairman of the BEAR I Genetics Panel, on how this issue should be approached. These letters are preserved in the James F. Crow papers at the University of Wisconsin, Madison.

It is now well known that a second-generation study of genetic effects was not undertaken. However, the basis of this decision not to proceed with one has remained obscure and is not formally documented in the open literature. Consequently, it was decided to attempt to acquire the correspondence between Crow, Neel, Cannon and other relevant individuals and to piece together the decision-making process, with a particular focus on its scientific basis. This effort has been largely successful due to the preservation of the James Neel and James Crow papers that retained what appears to be nearly a complete documentation of this process.

2. Documentation of communication

As a result of this situation, on June 11, 1962, the US NAS, Division of Medical Sciences sought the guidance of the BEAR I Genetics Panel on the **"feasibility and potentialities of a study of the second generation of offspring of exposed parents in Hiroshima and Nagasaki"** [10].

On June 28, 1962, Crow [11] wrote back to Cannon stating: **"Although we have had some informal discussion and correspondence among the members of the Genetics Subcommittee the of the BEAR complex, we have not really got down to business. I have been authorized to appoint a committee to look into the problem of the possible continuance of the genetic study into the second generation.**

As the enclosed letter will show you, I have asked Sturtevant, Stern and Neel to serve in this capacity. Dr. Stern and Dr. Neel have already tentatively agreed, but the matter has not been raised previously with Dr. Sturtevant. I shall let you know when I hear from this group; my expectation is that they will all be willing to serve."

The invitation letter of Crow [12] to Stern, Sturtevant and Neel on June 28, 1962, stated: **"Some time ago I discussed with the BEAR Committee the need for an evaluation of the genetics aspects of the study of the Atomic Bomb Casualty Commission. The committee has authorized me to appoint a committee to look into the problem.**

I should like to ask the three of you to serve in this capacity. I hope Jim Neel will serve as chairman, at least for the initial task of getting the group into communication.

In particular, the ABCC needs advice as to the feasibility and potentialities of a study of the second generation children of exposed parents of Hiroshima and Nagasaki. Dr. Cannon, Chairman of the Division of Medical Sciences of the National Academy, writes that a review of various aspects of the program is planned prior to discussions with the Director of ABCC, Dr. Sterling, in November.

I hope that you will be able to prepare a report or recommendation on this subject in time for consideration at the November conferences. I see no reason why such a report needs to be extensive or detailed."

On July 3, 1962, Cannon [13] wrote to Crow stating: **I am delighted to receive your letter telling me that the Genetics Subcommittee of BEAR was being stimulated to review the question of genetic studies of the second generation of survivors of the bombings in Japan."**

On that same day Neel [14] wrote, as follows, to Stern and Sturtevant giving his opinion on the matter. **"In my opinion, the probability of demonstrating a genetic effect amongst the F_2, in the face of the results of the study on the F_1, is very, very low indeed. This is not only for genetic reasons but also because of the expected dissemination have the children of exposed individuals throughout much of Japan, with the attendant administrative problems which this would raise for any study. If, however, a majority of our committee should feel that studies on the F_2 were indicated, you may be assured that Schull and I will cooperate in every possible way."**

This perspective of Neel was supported by the Nobel Laureate, Joshua Lederberg [15]. Lederberg stated that **"My reaction is much like that of Neel. I felt that when the study was first proposed right after the war that the job had to be done and done as well and thoroughly as possible (which I think it has been)—largely for political and ethical reasons. I also thought that the likelihood of important results was very small …."**

In December 1962, Neel and Schull [16] issued a four-page assessment of possible genetic studies on the F_2 of the radiation survivors of Hiroshima and Nagasaki along with two tables and a figure. This review provided a quantitative evaluation of the value of a study being able to detect genetic damage. This assessment considered the number of births in both cities, their temporal trends, their capacity to track individuals for evaluation, the likelihood of death before the age of 20 and other factors. This document would provide the driving decision-making basis for the Subcommittee.

The Neel and Schull analysis [16] first assessed the number of possible subjects. They estimated there would be about 11,000 births from parents from Hiroshima and Nagasaki. They then scaled this figure up to 15,000 for the two cities combined, as they wrote, to be generous, for a possible study. Next, they assumed that of this 15,000-population sample, there would be a 10% cumulative death rate from birth to the age of reproduction. The Japan Life Table figures for that period indicated 11.6% mortality for males and 10.7% mortality for females. Thus, Neel and Schull were continuing to be generous. In current times, the approximate death rates have decreased profoundly to about 0.5%. Neel and Schull also assumed that there would be 2.5 offspring for each marriage for each F_1, assuming that no F_1 survivors would have a child with another F_1 survivor. The 2.5 estimate was appropriate for that time period but would be reduced significantly in contemporary Japan. Integrating these values yielded a sample population estimate of 33,750. Neel and Schull noted that their estimates did not include the occurrence of marriages of F_1 x F_1. Next, Neel and Schull calculated a sample loss of 20% through migration. This exercise would then result in a sample size of 27,000 that would need to be followed for 40 years. Neel and Schull [16] wrote on page 2 of their report that **"the probability of observing any genetically determined differences between this group and a suitable control group cannot in our opinion be estimated in a meaningful way."** Later in that same paragraph they offered the key generalization: Most geneticists would agree that the magnitude of any induced genetic effect would certainly be greater in the F_1 than in the F_2 as here defined."

Based on their evaluation, Neel and Schull [16] stated: "**In summary, it seems unlikely that if the completed studies on the F_1 failed to reveal any clear cut genetic effects or parental exposure to radiation, the problem will be further advanced by studies of the F_2."**

In a February 14, 1963 letter [17] to Crow, Neel indicated that he had sent this December 1962, Memorandum [16] to Stern and Sturtevant. In response to a December 13, 1962, letter from Neel [18], a December 21, 1962, letter of Stern to Neel [19] concluded by stating: **"Therefore, I do not think it advisable to pursue studies of F_2."** Sturtevant was also sent the same letter from Neel [18] as received by Stern. However, Sturtevant apparently misplaced it and eventually "on excavating his desk" found the unanswered letter. His conclusions in a February 10, 1963, letter to Neel [20] were fully consistent with that of Stern. Based on the Neel and Schull report [16], the BEAR subcommittee of Neel, Stern and Sturtevant provided a guidance statement quoted below [17]. Note that Crow waited until August 26, 1963 [21] to inform Cannon of the Neel committee recommendation. On October 2, 1963, Crow [22] provided a follow-up letter to Cannon indicating that he was still waiting to hear from all the Committee members, but that what he

had heard was supportive of the Neel subcommittee recommendations. Cannon acknowledged the Crow letter on October 9th [23]. It was not until May 5, 1964 that Crow wrote back to Cannon [24] stating that "I have submitted this recommendation [see quote immediately below] to the entire committee and have heard no contrary suggestions, so this may be regarded as the advice of the Genetics Subcommittee."

> **"The subcommittee charged to examine the potentialities and feasibility of studies on the second generation of children of exposed parents of at Hiroshima and Nagasaki, has, on the basis of general genetic consideration thus the facts contained in the Neel-Schull memorandum submitted on December 6, 1962, to the Advisory Committee of the ABCC, reached the following conclusion: It is highly improbable, in view of the results of the studies of the children of irradiated survivors of Hiroshima and Nagasaki, that studies of the grandchildren of these same persons could be expected to result in statistically significant evidence for the genetic effects of the atomic bombs."**

Crow [25] (no date on this memo) then subsequently informed the entire BEAR Genetics Panel of the above conclusion of the Subcommittee, sharing the identical quote given immediately above. The Panel included members such as George Beadle, Bentley Glass, William Russell, Alexander Hollaender and Sewall Wright, as well as Hermann J. Muller, with none of these geneticists challenging the opinion of Neel and Schull. This latter point is very notable as this partial listing of the BEAR I Genetics Panel, along with Crow, was believed to represent the elite of radiation geneticists in the US at that time. Since the F_1 vs F_2 perspective was so dominant as an accepted perspective, it is curious that Cannon was even interested in exploring a second-generation study and challenged Crow to address the issue. Nonetheless, the comment of Neel and Schull [16] started with the word, "Most" geneticists, meaning that they believed there might be some differences of opinion on this matter. However, they did not cite any paper offering a different opinion. Further, as noted above, there was no dissent on the matter among the geneticists of the BEAR I Genetics Panel, a group with a history of high-level disagreements and debate on scientific issues.

A further consideration of this matter is that F_1 offspring would not themselves be exposed to any biologically important dose of radiation. While some F_1 offspring would marry F_1 offspring, those were not considered (Neel and Schull were "neglecting" them), and any induced mutations causing effects transmitted from the F_1 would be in a total sample in which half the DNA came from a parent whose parent was not irradiated. Thus, if Neel could not demonstrate an effect in the F_1, it would seem unrealistic to expect to find one in the second generation. Thus, it is very unlikely that the BEAR I Panel would have felt it even worth discussing whether the study should be extended beyond generation one. Also, if there even were any F_1 offspring with serious radiation-induced effects, they might not have been able to have children anyway.

Back at that time there were few data available on the incidence of diseases (including congenital anomalies) having an important hereditary component among live-born humans. Now, however, it is estimated that, in humans, the incidence of genetic or partially genetic diseases having serious health consequences before the age of 25 years is 5.32% [26]. Almost all of that 5.32% is the result of mutations that have been present in the population for many generations. The Genetics Panel had previously discussed and addressed the issue of genetic equilibrium, with it likely taking hundreds of generations for many recessive mutations with slight deleterious effects to be selected out of the population. A relevant finding reported by Selby and Selby [27,28], in their experiments on mice on induction by radiation of dominant mutations that cause skeletal malformations, is relevant to this situation. They found that such mutations commonly have incomplete penetrance and variable expressivity. Thus, for example, such a mutation might persist for many generations and only cause a health issue in a few of many individuals carrying it. Mouse mutations of this type have been used to estimate hereditary risks from radiation in humans for congenital malformations and other genetic disorders [26].

Thus, a major reason why the possibility of demonstrating an effect of induced mutations in Japan would have been extremely small, in comparison to demonstrating one in a mouse study, is that in humans there would be considerable "noise" from mutations already in the population. As a result, it would be almost impossible to detect a "signal" caused by radiation-induced mutations. The "noise" consists almost entirely of mutations that preexist in the human population combined with a relatively small number of spontaneous mutations occurring in the parents that were exposed to the nuclear blast. In contrast, in most mutation experiments on mice, because hybrids between two inbred strains are used, there would be markedly reduced heterozygosity of the mouse parents, relative to that existing for parents exposed in Japan.

That level of "noise" in the human population is much higher than in laboratory mice because it includes the accumulation of spontaneous mutations that have occurred during previous generations, some of which persist in the population for a hundred generations or longer. In contrast, mice tested for induction of mutations almost always have a much lower level of "noise" as the result of their stocks being inbred (resulting from brother x sister genetic matings for at least 20 generations), thereby greatly reducing the frequency of spontaneous mutations present from much earlier generations and thus raising the relative frequency of (and the ease of detecting) any radiation-induced mutations.

3. Conclusion

The underlying reasons for the decision of the US NAS not to study the second generation of offspring from parents exposed to the atomic bomb explosions in Japan in 1945 is provided. This has never been provided in the journal literature but is found within original letters of the participants including the leadership of the US NAS and the BEAR Genetics Committee. The entire sequence of events is now documented and should be a valuable reference for historians of science and others interested in this significant historical decision.

CRediT authorship contribution statement

Edward J. Calabrese: Conceptualization, Writing – original draft. **Paul B. Selby:** Conceptualization, Writing – original draft.

Use of generative AI and AI-assisted technologies

No AI software was used in the preparation of this manuscript.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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