

Commentary

Key Studies Used to Support Cancer Risk Assessment Questioned

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This paper reassessed studies conducted under the leadership of *Drosophila* geneticist Curt Stern which played a pivotal role in the acceptance of the linear dose-response model by the U.S. National Academy of Sciences Biological Effects of Atomic Radiation (BEAR) I Committee and the subsequent generalization of their recommendations on the linearity dose-response paradigm for ionizing radiation and chemically induced cancer. The analysis finds serious concerns and flaws in important aspects of these experiments, their assessment, and interpretation. Of particular concern was the failure of Stern's group to provide the necessary and promised experimental

documentation to support the findings of three critical summarized experiments published as a brief technical note in *Science*. While this analysis questions the validity of the reported findings and their interpretations, it raises an even more serious concern about the process by which leaders in the radiation genetics community accepted such findings without requiring the necessary documentation and then used this information to support the acceptance of the linear dose-response in public policy matters as affected by risk assessment practices that have continued to the present. *Environ. Mol. Mutagen.* 00:000–000, 2011. © 2011 Wiley-Liss, Inc.

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INTRODUCTION

The most important publication in the history of risk assessment was the 1956 report of the U.S. National Academy of Sciences (NAS), called the BEAR I report [U.S. National Academy of Sciences, 1956]. It achieved this distinction since it directly led to a dose-response revolution, convincing governments worldwide to replace the threshold dose-response model for assessing the risks of ionizing radiation on germ cells with the linear dose-response model. The key conclusions of the BEAR I report that changed the dose–response default status from threshold to linear at low dose are embodied in the following two quotes on page 17 of that document:

“Any radiation dose, however small, can induce some mutations. There is no minimum amount of radiation dose which might be exceeded before any harmful mutations occur.”

“...if we increase the radiation that reaches the reproductive glands by *X* percent, the number of mutations caused by radiation will also be increased by *X* percent.”

These dose-response conclusions proved not to be restricted to a narrow biological question; they were generalized to radiation-induced cancer one year later by the National Committee on Radiation Protection (NCRP) (and soon thereafter most international advisory organizations)

and then generalized again for all genotoxic chemical carcinogens by the U.S. NAS Safe Drinking Water Committee [National Academy of Sciences, 1977; Calabrese, 2009]. The key societal element in the linearity transformation was that the presumed safety of a threshold dose-response model was replaced with an “acceptable risk” concept of a linear dose-response model. With linearity as the guide for cancer risk assessment, no exposure to a

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carcinogen would be without risk, no matter how low or seemingly inconsequential. The present paper re-examines key publications directed by the eminent geneticist Curt Stern, upon which the linearity decision was, in large measure, based. The present analysis will demonstrate the presence of serious scientific and evaluation flaws in these papers along with a failure of the investigators to provide critical methodological and complementary research findings to validate their conclusions. This paper will also demonstrate that these flawed and unsupported findings were broadly accepted by key leaders in the genetics community and played an important role in the acceptance of linearity at low dose by the BEAR I Committee for radiation induced germ cell mutation and its generalization to cancer risk assessment for radiation and chemical carcinogens for use by federal and state regulatory agencies in the context of legislative requirements.

THE BEAR I COMMITTEE

The key issue for the BEAR I committee as it was created in April 1955 was making a scientifically based decision on whether radiation-induced germ cell mutation followed a threshold or linear dose-response model. As the BEAR I Committee began its deliberations, data from two biological models (i.e., fruit fly and mouse models) would have its primary interest. Considerable mutational data also existed on plants, some of which was directly related to the nature of the dose response. However, plant data were not given the same high priority as the animal findings in committee deliberations.

GERM CELL MUTATION: DROSOPHILA AND MICE

The fruit fly has long been a staple of mutational research, starting in 1910 when Morgan reported on naturally occurring mutations and the later application of this concept by Muller, who in 1927, showed that high doses of ionizing radiation induced germ cell mutations [Muller, 1927]. Research on the effects of ionizing radiation on the mouse genome, especially in the low dose zone, occurred later. For example, the U.S. federal government, under the Manhattan Engineering District (MED), initiated large scale studies during World War II, starting in 1943 under Donald Charles at the University of Rochester. What came out of this massive effort was disappointing as Charles published only a single 3.5 page note (lacking study methods) [Charles, 1950]. Former members of his group published a similarly brief review of the overall work in 1961, six years after Charles died of leukemia [Charles et al., 1961]. This substantial investment on mouse germ cell mutation research, involving more than 250,000 mice, had no noticeable impact on the BEAR I Committee. Starting much later was mouse research under Russell at Oakridge National Laboratories. While Russell

generated data in the early 1950s, the dosages were high, in part due to model insensitivity, causing frustration about whether new and more sensitive models were needed to provide insight on the nature of the dose response in the low dose zone for radiation-induced germ cell mutation [Jolly, 2003]. According to Rader [2004], Russell's mouse studies by themselves were "literally unusable for determining acceptable risk" at the BEAR I meetings.

The focus of the scientific debate at this critical time over whether ionizing radiation induced germ cell mutations in a threshold or linear manner would be contested with fruit fly data obtained largely following treatment of mature sperm [Ofstedal, 1964]. With its three decade head start *Drosophila* research had the most data and numerous geneticists studying ionizing radiation induced mutations. Thus, there was considerable insight into the nature of the animal model, its advantages and limits, how studies were designed, what they might yield, how they could be analyzed, and their relevance to humans. Based upon research with this *Drosophila* mature sperm model system, the genetics community would conclude and promote the belief that genetic damage caused by exposure to ionizing radiation was linear, cumulative, and deleterious. This perspective was confirmed, consolidated, and significantly extended in a series of highly influential studies under the direction of Curt Stern.

THE STERN STUDIES

The center of dose-response study was the laboratory of Curt Stern, a professor of genetics at the University of Rochester since 1939 before moving to the University of California at Berkeley in August 1947. The Stern studies were of considerable importance because they were part of a major funded activity of the MED/Atomic Energy Commission (AEC), were directed by a leader in the genetics community, were assessing responses at the lowest doses of ionizing radiation yet tested and offered the best opportunity to clarify the nature of the dose response for germ cell mutation. They would be key studies for not only the scientific community but governmental advisory and regulatory organizations in the U.S. and worldwide for occupational, medical, and environmental risk assessment and for broader atomic policy considerations.

There were three general research projects to assess the nature of the dose response for ionizing radiation under the direction of Stern, each lead by a different person. The first project was lead by Warren P. Spencer, a professor on leave from the College of Wooster, with nearly 20 years research experience with *Drosophila*. The second project was directed by a senior entomological behavioral geneticist researcher, Ernst Caspari. The third project was not originally planned but created after unexpected findings from the Caspari study which challenged a linearity dose-response interpretation. The third project was given

to a recent graduate of Russell Sage College, Delta E. Uphoff, a new master's student at the University of Rochester. The data collection of the three projects ran sequentially: Spencer's from December 1944 to June 1945, Caspari's from October 1945 to August 1946, while Uphoff's initial experiment, a partial replication of the Caspari experiment, ran from September 1946 to April 1947. During the summer of 1947, Uphoff [Uphoff and Stern, 1947] conducted another experiment at the University of Rochester, a "chronic" (i.e., 21 day) exposure to gamma rays. The final Uphoff experiment was performed at the University of California at Berkeley in the first half of 1948. Muller was an official consultant to the series of projects, providing the Muller-5 strain flies which were not susceptible to crossing-over genetic alternations. He also guided the group on breeding practices, data interpretation, and manuscript refinement.

SUPPORT FOR A THRESHOLD DOSE RESPONSE: THE CASPARI AND STERN STUDY

Caspari and Stern wrote a manuscript describing their investigations for the AEC [Caspari and Stern, 1947]. This manuscript was classified by the U.S. government until August 12, 1947, after which it was submitted in November 1947 to the journal *Genetics*, where Stern was the editor and published [Caspari and Stern, 1948]. While these two manuscripts of Caspari and Stern [1947-1948] are nearly identical, with no differences in the data tables, there are some important changes. In the Caspari and Stern [1947] paper, Hermann J. Muller is not included in the Acknowledgments but he is included in the Acknowledgments of Caspari and Stern [1948]. The most significant change between the two manuscript versions is that a key sentence in the Conclusion of the 1947-AEC [Caspari and Stern, 1947] version was dropped in the 1948 version [Caspari and Stern, 1948]. The sentence is as follows: "*From the practical viewpoint, the results presented open up the possibility that a tolerance dose for radiation may be found, as far as the production of mutation is concerned*" (page 15). This change suggested support for a threshold dose response and will be discussed later. The Spencer research was published [Spencer and Stern, 1948] in *Genetics* following its declassification (i.e., March 5, 1947).

Spencer's research under the direction of Stern assessed the effects of X-rays on sex-linked recessive lethality in *Drosophila* males from short term (2–40 min) exposures (i.e., 10–96 r/hr). The cumulative doses ranged from a high of 4,000 r to the lowest then yet tested of 25 r. The study indicated a dose-response relationship that supported a linearity interpretation.

Caspari's research under the direction of Stern assessed the effects of gamma rays (i.e., radium needle) on *Drosophila* sex-linked recessive lethality. In contrast to the Spencer

and Stern [1948] study, females were mated and exposed to radiation (2.5 r/day) for 21 days with sperm stored in the female's spermatheca. Cumulative doses were similar between the studies, both ~50 r. The females were fed a diet that suppressed egg laying during the 21 day irradiation exposure and then placed on a diet and altered environmental conditions to facilitate egg laying and development. The Caspari and Stern study using the aged sperm showed no statistically significant treatment effect, findings supporting a threshold rather than linear model. This finding created a significant problem for Stern and Muller, both strong advocates of a linear at low dose risk assessment model.

SUPPORT FOR THE THRESHOLD MODEL IS A "PROBLEM"

The findings of Caspari and Stern [1948] were of considerable interest since they provided support for the threshold dose-response model at the lowest dose rate of ionizing radiation yet tested. A draft manuscript was shared with Muller in early November 1946. Muller immediately recognized their significance, challenging the linear perspective; within a week he suggested that this experiment be replicated even though he noted that he had no reason to dispute the work of Caspari [American Philosophical Society, 1946]. Despite his knowledge of these novel findings, the credibility of the investigators and his own role as a consultant to Stern's research, one month later, on December 12, 1946, Muller would deliver his Nobel Prize Lecture, unequivocally affirming the validity of the linear dose-response model and claiming still further that there was no excuse any longer to accept a threshold perspective [Muller, 1946]. During this same time period, Caspari also sent a copy of his findings to the Milisav Demerec, the influential head of genetics at the Cold Spring Harbor. According to Caspari, Demerec was not pleased that his data challenged a linearity perspective, even suggesting ways to circumvent this problem and to "save the hit theory" [American Philosophical Society, 1947a].

So strong were mounting concerns over the challenge to linearity that even Stern suggested to Caspari that his data must be in error, due to spuriously high control group values [American Philosophical Society, 1947b]. High control group responses would likely preclude the detection of the radiation induced mutation effect at such low dose rates. However, a search of the published literature by Caspari indicated that his mutation frequency was in agreement with the observations of others, including very experienced *Drosophila* geneticists. Stern was finally forced to withdraw his control group mutation frequency criticism after Muller provided him with a large body of control group data for aging *Drosophila* sperm, confirming the observations of Caspari.

The "final" version of the Caspari and Stern manuscript [1948], as noted above, removed the sentence in the Conclusions which had suggested a tolerance or

TABLE I. Differences Between Spencer/Stern (1948) and Caspari/Stern (1948)

| Spencer/Stern | Caspari/Stern |
|--|---|
| Exposure: X-rays | Exposure: gamma rays (radium needle) |
| Animal Model: males exposed prior to mating | Animal Model: females exposed after mating |
| Exposure Duration: acute exposure (minutes) | Exposure Duration: chronic exposure (21 days) |
| Dose Rate: ~15,000-fold greater than Caspari | Dose Rate: ~1/15,000 of Spencer |
| Plastic vials to hold flies | Glass vials to hold flies |
| Temperature: 24°C | Temperature: 18°C |
| Diet: cornmeal molasses | Diet: honey yeast agar |
| Age (males): ≤7 days, most 2–4-days old | Age (males): ≥5 days |
| Controls poorly matched with treatment exposure period. | Controls closely matched with treatment exposure period. |
| Temperature Control: poor, highly variable based on external conditions. | Temperature Control: good |
| 50-r treatment group: 2 groups with different dose rates and exposure periods all combined. | A single 50-r treatment group; all treated similarly. |
| Mold Control: used Moldex throughout study. | Possibly less Moldex used in the 21 day radiation exposure period due to the lower temperature (18°C vs. 25°C). |
| Not corrected for lethal clusters. If so, the treatment group (50 r) used would have had its mutation rate decrease by –8% versus 4% for controls. | Corrected for lethal clusters. No differences between control and treatment. |
| Control radiation exposure not given. | Control radiation exposure reported as 0.6 r. |
| 50-r treatment group had 20,400 less flies than the Caspari experiment. | The study was designed to minimize the possibility of lethal clusters. |
| The study was not designed to affect the occurrence of lethal clusters. | F ₀ Breeding Protocol Differed: 50 females/100 males; females ≤16-hours old. |
| F ₀ Breeding Protocol Differed: 40 females/40 males; females – 2-days old | Radiation Exposure Condition Differed: 50 females/capsule; food in capsule. |
| Radiation Exposure Condition Differed: 20 males/capsule; no food in capsule | Lethal Designation Protocol Differed: Used 2 female heterozygotes in F ₂ to identify lethality. |
| Lethal Designation Protocol Differed: Used 6 heterozygote females in F ₂ generation to identify lethality. | A single wild-type male offspring lead to a designation of a semi-lethal. |
| A single wild-type male offspring lead to a designation of a viable culture. | |

threshold for the production of ionizing radiation induced sex-linked recessive lethal mutations. In addition, the entire discussion strangely, but strategically, centered on why there was no radiation treatment effect in the Caspari and Stern study [1948], whereas there was no questioning the Spencer and Stern findings [1948] even though both studies used the same cumulative dose. While this is a legitimate area of inquiry, the authors knew from the start that these two studies were fundamentally different and not directly comparable. Despite the use of profoundly different research methodologies between the two studies, Caspari and Stern [1948] concluded by asserting that before their findings could be accepted it would be necessary to exclude all factors that differed between the Spencer and Stern [1948] and Caspari and Stern [1948] studies that could have lead to the lack of a treatment effect in the Caspari and Stern paper [1948]. This was an extraordinary statement. To notify the scientific community not to accept the findings of your research unless and until future research would convincingly demonstrate that none of the methodological differences between the two studies could account for the observation was highly unusual. It should be noted that more than six decades later most of the methodological differences remain unexplained. The extensive experimental differences between these studies are documented in Table I.

DIFFERENCES BETWEEN THE SPENCER AND CASPARI STUDIES

Spencer and Stern exposed male fruit flies to x-rays, with the entire dose administered over a few minutes, with the flies held in plastic vials and reared at 24°C. In contrast, the Caspari and Stern study exposed females with stored/aging sperm to the same cumulative dose over 21 days in stored glass vials at 18°C at a dose rate about 1/6,000 to 1/15,000 of the Spencer and Stern treated flies. The control data in the Spencer and Stern study [1948] were poorly matched for their 50-r treatment group (i.e., the key treatment group comparison with the Caspari and Stern study [1948]). In fact, Spencer and Stern [1948] had two 50-r treatment subgroups. The control mutation rate was averaged over 70 weeks of observation while the 50-r treatment subgroup 1 was only tested over 11 weeks, about 15.7% of the control group's experimental duration. The 50-r subgroup 2 was exposed over 45 weeks (i.e., 61% of the control group experimental duration). The two 50-r subgroups were administered the x-rays with a dose rate that inexplicably differed by about 1.7–2.5-fold. The mutation data from both 50-r subgroups were then combined into one 50-r treatment group for all group effects without providing any information about the responses of the two subgroups. Considerable data from Caspari and

Stern [1948] and Uphoff and Stern [1947] had demonstrated large monthly variation in control group mutation rates. Such a lack of matching of control and low treatment groups as well as the lack of matching by the two 50-r subgroups themselves calls into question the validity of the Spencer and Stern [1948] study for the low dose groups. These critical methodological limitations were never discussed by Spencer and Stern [1948] nor in any of the subsequent papers that have assessed the dose-response findings of Spencer and Stern [1948]. Despite a lack of an explicit discussion of how such methodological weaknesses affected their interpretations, Spencer and Stern [1948] nevertheless noted that “*at low dosages in the range of 25 r and 50 r . . . the control mutations may equal or exceed in number those produced by the radiation [by normal variation]. It is therefore important to collect a large body of control data and to collect these data in so far as possible at the same time and with the same environmental and genetic conditions as the radiation data to reduce errors from control fluctuation to a minimum.*” The comparison of the control and 50-r treatment group data by Spencer and Stern [1948] did not satisfy their own methodological criteria. In contrast to the Spencer and Stern study [1948], the control and treatment group data collections were properly matched in the Caspari and Stern study [1948]. Consistent with the above-quoted perspective of Spencer and Stern [1948], in the Caspari and Stern study [1948], the control group displayed higher mutation rates than the 52.5-r treatment group during three of the eight treatment months, indicating that natural background variation for this mutational endpoint can be larger than a possible treatment effect at low dose.

The Spencer and Stern study [1948] also used a fruit fly diet that was intentionally different than that used by Caspari and Stern [1948]. The Caspari and Stern diet [1948] was honey yeast agar while that of Spencer and Stern [1948] was cornmeal molasses agar. The reason for the change to honey yeast agar was to suppress egg laying during the 21-day radiation treatment. In addition to egg-laying suppression this diet also affected other parameters with differences in the percent of sterile females (31.0 ± 1.7 honey yeast agar vs. 42.2 ± 2.7 cornmeal molasses) and the average number of F1 females per culture (12.1 ± 0.42 honey yeast agar vs. 19.27 ± 1.27 cornmeal molasses). Furthermore, in the 11 weeks of collecting data on the 50-r treatment subgroup the x-ray machine was checked only once, yet at most other times in the study it was checked on a weekly basis. Since the authors mention the occurrence of errors in dosimetry, it is not possible to detect the degree of error over the 11-week exposure period for one of their 50-r treatment subgroups.

Other differences between the two studies should also be noted. The studies used opposing strategies for sperm selection. Caspari and Stern [1948] selected males that

were ≥ 5 -days old whereas Spencer and Stern [1948] selected for males that were ≤ 7 -days old. The younger male selection would tend to yield sperm with higher mutation rates. Spencer and Stern [1948] noted that there was inadequate temperature control at different seasons of the year. The experimental test cultures used for the detection of lethals were held on open shelves in a laboratory cabinet. The authors noted that there were wide fluctuations in room temperatures at different times of the year (December–June). These temperature differences were said to have affected a number of processes, including, for example, the time for emergence of the flies in the culture. The temperature differences also clearly had important mutation implications as certain mutants can behave as semilethals at one temperature and as lethals at another temperature. According to these authors, failure to control temperature may adversely affect the accuracy of the mutation scoring. They noted that if the cultures had been reared at a constant temperature a larger group of semilethal and delayed emergence mutants with visible effects could have been included in the totals, increasing mutation totals by 10% or more. In contrast to this concern in the Spencer and Stern study [1948], temperature control was tightly maintained in the Caspari and Stern experiment [1948].

Another difference between these two experiments was that lethal clusters were identified and removed in the statistical analysis of the Caspari and Stern experiment [1948] as shown in [Uphoff and Stern, 1947, 1949], whereas this was not done in the Spencer and Stern study [1948] or even in the later reporting of its data [see Uphoff and Stern, 1949]. While adjusting for the lethal clusters had no effect on the outcome of the Caspari and Stern study [1948], it would have had an impact to reduce the treatment response in the Spencer and Stern study [1948] by several percent. However, the authors never indicated how such an adjustment would have affected hypothesis testing or its impact dose-response modeling. It should be noted that Caspari did raise the question of why his data were being adjusted for the occurrence of lethal clusters by Uphoff but those of Spencer were not in a letter to Stern [American Philosophical Society, 1949]. Stern never addressed the pointed question of why Spencer’s research was treated differently only that it was a needed adjustment for his work. Finally, it is also possible that the two experiments used different amounts of mold suppressant (Moldex) since Spencer and Stern [1948] conducted their experiment at 24°C , whereas the Caspari and Stern [1948] study was performed at 18°C during the 21 days of irradiation.

Given the large number of differences in experimental protocol between the two studies as well as missing, mismatched, and recombined data in the Spencer and Stern [1948] paper, there is little justification to speculate on why the results in one study were different than the other,

while holding acceptance of the Caspari and Stern [1948] study in abeyance. Yet the discussion of Caspari and Stern [1948] created in effect a type of scientific “Strawman” yielding impossible to resolve questions before dose-response findings supporting a threshold could be considered “valid.” In retrospect, the discussion was misdirected and inappropriate. However, with Stern as the editor of *Genetics*, this manuscript, with its obfuscated discussion, was fast tracked into publication, all with the encouragement of Muller [American Philosophical Society, 1947c]. It also had the benefit (whether by design or accident) of “buying time” for Uphoff and Stern to complete a replication of the Caspari and Stern study and providing a diversion for Muller’s Nobel Prize Lecture comments concerning the impossibility of a threshold response when he knew that data existed that could refute his statements.

UPHOFF’S REPLICATION OF THE CASPARI AND STERN STUDY

The findings of the Uphoff experiment that was designed to replicate the study of Caspari and Stern [1947] were included along with the summary data of two other experiments in a brief note in *Science* [Uphoff and Stern, 1949]. However, an insight into the thinking that motivated this research as well as how the authors viewed the data is seen in their 1947 publication for the AEC files [Uphoff and Stern, 1947]. Following the Caspari and Stern study [1947], Uphoff and Stern [1947] replicated that work as closely as possible except that the exposure to the gamma rays was over 24 hr rather than the 21 days of the Caspari and Stern [1947] study. In their data evaluation, Uphoff and Stern [1947] adjusted the control and treatment group responses of Caspari and Stern [1947] for lethal clusters. This resulted in a modestly decreased control group mutation rate from 0.2738 to 0.2489 and similarly so for the radiation treatment group mutation rate (i.e., 0.3118–0.2848). Such changes did not affect the statistical analysis/conclusions of the Caspari study but were performed to make the two studies as comparable as possible. In contrast to the Caspari and Stern experiment [1947, 1948], a significant treatment effect was reported by Uphoff and Stern [1947].

What could account for these two studies yielding a different finding besides the obvious differences in exposure rate? First, the mutation rates of the radiation treatment groups between the two experiments were similar (Caspari, 0.2848; and Uphoff, 0.2542), being within 11–12% of each other. The principal difference between the two studies was the control mutation rates (Caspari and Stern, 0.2438; Uphoff and Stern, 0.1682). The Uphoff and Stern [1947] control was nearly 40% lower than the Caspari and Stern control [1947].

Uphoff and Stern [1947] addressed these differences by first refloating the proposition that the controls of Caspari and Stern [1947] displayed an abnormally/spuriously high mutation rate. However, as discussed above, this was not supported in several studies [Rajewsky and Timofeeff-Ressovsky, 1939; Ray-Chaudhuri, 1944; Kaufmann, 1947] showing that as sperm age they develop more sex-linked recessive lethal mutations, with similar mutation rates as were observed by Caspari and Stern [1947]. Furthermore, since Muller sent Stern substantial data which supported the findings of Caspari and Stern [1947], the Uphoff and Stern criticism [1947] of Caspari and Stern [1948] was withdrawn. The data indicated that it wasn’t that Caspari and Stern [1947] had an unusually high control group mutation rate but rather that Uphoff and Stern’s control [1947] was unusually, perhaps aberrantly, low. Statistical testing revealed that it was significantly different from the Caspari and Stern findings [1948]. In their conclusion, Uphoff and Stern [1947] stated that “*in view of the former results on chronic irradiation (i.e., the Caspari and Stern experiment [1947], as well as the fact that the control rate of the present report is unexpectedly low, a final interpretation of the results cannot be offered.*” Of further interest in the report was the statement of potential observer bias (i.e., presumably Delta E. Uphoff and not Curt Stern). On page 3 (bottom), it is stated that “*the earliest control value is particularly low, and the question may be raised whether at this initial stage of the project it may reflect a personal bias of the experimenter.*” In the final analysis there was no clear answer whether there was bias to see a lower control to detect a treatment effect, lack of research experience or simply chance variation. However, in an ironic twist, it should be noted that in 1928 Muller reported his own failure to establish a control mutation rate for the same lethal recessive sex-linked trait, attributing it to “inexperienced persons” in his laboratory [Muller, 1928].

THE SCIENCE JOURNAL PUBLICATION: STERN’S META-ANALYSIS

The findings of Uphoff’s three experiments were published as slightly more than a one-page technical note in *Science* [Uphoff and Stern, 1949]. The authors promised to provide a detailed follow-up paper with the study methods, analysis procedures, and other data. However, no follow-up paper was ever published despite Stern’s continued leadership in the field. In contrast to Uphoff’s initial experiment, the first of Uphoff’s two remaining experiments attempted to closely replicate the earlier Caspari study, now using aged sperm within a so-called chronic exposure of 21 days. The treated flies showed a 0.2834 mutation rate which was similar to the other 52.5-r exposures, whether the exposure was acute or

chronic. However, the control group mutation rate was again problematic, being inexplicably low at 0.1765. No manuscript has been found that was submitted to the AEC on experiment two during the fall of 1947 as was done with the acute experiment of Uphoff. The third and final Uphoff experiment followed the Caspari design except that the dose was about double (100 r vs. 52.5 r) that used by Caspari. This experiment displayed a control mutation rate of 0.2352, a value similar to the original Caspari and Stern mutation rate [1947]. It also reported a significant treatment effect consistent with a linear interpretation. Before we address the issue of Uphoff's aberrant controls, let us consider the third experiment.

Uphoff and Stern [1949] made a key assumption in the assessment of their 100-r follow-up experiment. They decided that its results could be most reliably compared against the observed mutation rate per r based on the Spencer and Stern study [1948]. These authors reported that such a mutation rate per r was about 0.002%. If this mutation rate were applied to the 100-r experiment of Uphoff and Stern [1949], the control mutation rate of 0.2352 would increase by about 0.20% to 0.4352, a value close to the observed 0.4658, a finding consistent with a linear model. This interpretation played a pivotal role in the conclusions offered in the Uphoff and Stern paper [1949].

The critical flaw in this interpretation of Uphoff and Stern [1949] was due to the numerous experimental differences between it and the Spencer and Stern study [1947] that could affect mutation rates. The best choice for a standardized comparison for the Uphoff and Stern [1949] 100-r experiment would have been the Caspari and Stern paper [1948] since it was not only essentially identical to that of the 100-r experiment of the Uphoff and Stern study [1949] it also had considerably greater statistical power.

While supporting most strongly a threshold interpretation, the data of Caspari and Stern [1948] was not inconsistent with a linear model. That is, there was a nonstatistically significant increase in the mutation rate of about 11.5% (based on the seven months of direct matching of control and treatment groups). If the 11.5% increase was assumed to reflect a linear dose-response relationship (although not detectable as a significant treatment effect in hypothesis testing) and applied to the 100-r study, a mutation rate of 0.3100 would have been predicted based on its control value of 0.2352. These estimates are far below the 0.4352 mutation rate of Uphoff and Stern [1949]. In fact, the rate of increase of Uphoff and Stern is 2.66-fold greater than that predicted for a linear response using the Caspari and Stern study [1948], an increase that would be highly unlikely at this dosage [Edington, 1956]. Such an aberrant response could have reflected a third case of an "unexpected" response by Uphoff. Two earlier experiments resulted in "unexpectedly" aberrant control

group values, enough so that both Uphoff and Stern [1947] even discounted their attempt to challenge the Caspari experiment. These data also need to be viewed within a framework that their documentation was never published. Thus, there has never been a bonafide basis for relying on it.

Despite these experimental inconsistencies, Uphoff and Stern [1949] concluded that "*it appears*" that irradiation at low dosage induces mutations in fruit fly sperm. One sentence later they reached the general conclusion that there is "*no threshold below which irradiation fails to cause mutation.*" Given the importance of this conclusion the scientific bases were too limited and inadequate. Just how did Uphoff and Stern [1949] come to this conclusion.

To achieve this goal, Stern had to marginalize Caspari and Stern [1948] even further than attempted in its own constraining discussion while at the same time repackaging the discredited Uphoff and Stern [1947] paper. This latter point was important for two reasons. First, a revitalized Uphoff and Stern paper [1947] would discredit Caspari [Caspari and Stern, 1948]. Secondly, if Uphoff and Stern [1949] could convince their peers that the aberrantly low control group was normal variation, it would also provide support for the second experiment of Uphoff, again with an aberrantly low control group. Uphoff and Stern [1949] failed to disclose or cite their Uphoff and Stern [1947] AEC paper which concluded that these data were un-interpretable due to the aberrantly low control mutation rates. This 1947 AEC paper also had asserted the validity of the Caspari and Stern [1947] control group mutation rate. Their 1947 AEC paper [Caspari and Stern, 1947] was truncated in AEC archives with negligible or no circulation within the scientific community. In fact, their 1947 AEC paper has never been cited until now. Of importance is that the mutation rate with the aging sperm was estimated to rise by 0.05–0.08%/week [Uphoff and Stern, 1947]. Over three weeks this would yield an increase of 0.15–0.24% on top of a background of ~0.10%. This would lead to an estimated mutation rate of 0.25–0.34%, a value consistent with the Caspari data. These findings and the interpretation of their 1947 AEC paper were disregarded by Uphoff and Stern [1949]. They then used the *Science* paper to assess whether the Caspari and Stern [1948] paper failed to detect a treatment effect due to "errors of sampling," a nuanced version of spuriously high control values. Thus, the same "challenge the control group" strategy was used again, although it had been previously asked and addressed in detail about a year before with no new findings having emerged to challenge it. Next came the major change in their perspective. Uphoff and Stern [1949] now asserted that their controls were not aberrant but part of the norm. In this way, their uninterpretable data became interpretable. They were now able to minimize and even discredit further the findings

of Caspari and Stern [1948] while promoting the acceptance of their discredited experiment and enhancing the linearity interpretation.

The question was whether Stern would be able to pull off this scientific slight of hand without any debate or controversy. It is a bit like science's version of the famous "follow the pea game." In this case we are trying to follow the studies. In fact, he did pull it off. Subsequently published papers by leading researchers indicated that he was indeed successful in this strategy. For example, Higgins [1951] stated that low levels of radiation produced mutations in fruit fly sperm and that the apparent inconsistency of previous results (i.e., Caspari and Stern [1948]) were due to different experimental techniques and "errors in sampling" by Caspari and Stern [1948]. No evidence was produced to support this now accepted conclusion. The use of the term "errors in sampling" was lifted straight from Uphoff and Stern [1949]. It is not clear where the basis of the statement of errors in experimental techniques came from as there was no documentation to support it. Likewise, Singleton [1954] stated that Uphoff and Stern [1949] demonstrated that the controls of Caspari and Stern [1948] were spuriously high and that there actually was a treatment effect at 2.5 r/day. This statement of Singleton [1954] was of considerable value as he had been the leading opponent of the linearity perspective within the geneticist community. In effect, this statement by Singleton [1954] cleared any remaining path of resistance to the acceptance of Uphoff and Stern [1949] just prior to the convening of the BEAR I Committee. The data however clearly contradicted the conclusion of Caspari and Stern [1948]. In fact, it is odd that Caspari never responded with a letter to the editor to present the data that would have easily countered this view. Uphoff and Stern [1949] had now, in effect, rid themselves of the Caspari "problem," as Stern referred to the Caspari and Stern [1948] findings, in a letter to Edward Noviski [American Philosophical Society, 1948]. They made it "disappear" by wrapping it in a 1949 version of a meta-analysis of only their data, redefining what was the norm for control variation and never providing data to support this position.

The continued success of the Stern strategy may be seen in publications after the completion of the BEAR I Report. The future Nobelist EB Lewis in 1957 published a profoundly influential article in the journal *Science* arguing that ionizing radiation induced leukemia with a linear dose response. In this paper, Lewis [1957] used the findings of Stern and his colleagues to reinforce his position as follows:

Gene mutation has long been known to show a linear relationship with respect to dose of ionizing radiation from studies with *Drosophila*. This linearity has been

extended by Spencer and Stern [1948] to doses of 50 and 25 roentgens. Gene mutation is also known to be directly proportional to the accumulated dose of radiation, even when the radiation is chronically administered at a relatively low dose rate, as in the studies of Uphoff and Stern [1949].

A further comment was published by James V. Neal [1958], member of the BEAR I Committee. He also used the Stern findings to assert his belief in the linearity dose-response paradigm. He stated that "*In 1927, Muller for the first time clearly demonstrated the mutagenic effects of ionizing radiation. The first work on this subject was done with rather considerable doses of radiation, but, during the past decade, it has been demonstrated to the satisfaction of most geneticists that in the fruit fly, Drosophila, the mutagenic effects of radiation extend to doses as low as 25 to 50 r Spencer and Stern [1948]; Uphoff and Stern [1949]. Inevitably in work of this type the question of a 'threshold' arises. For technical reasons, it is rather difficult and extremely laborious to study the genetic effects of x-ray doses very much lower than 25 r in higher organisms, and no one has clearly demonstrated the mutagenic effects of doses below this level. On the other hand, in the face of all the evidence concerning the straight line relationship between dosage and mutation production, to me today the burden of proof is clearly on him who assumes that there is a threshold as regards the mutagenic property of x-rays.*"

Similar perspectives have been expressed by other leaders in the radiation research community. For example, writing in *JAMA*, Norwood [1958] noted that "*Spencer and Stern, using more than 50 million flies, showed that genetic damage was proportional to dosage in the important range of 25 to 50 r.*" It is also notable that none of these authors who highlighted the Spencer and Stern [1948] and Uphoff and Stern [1949] research ever acknowledged the findings of Caspari and Stern [1948] in accordance with the recommendations of the discussion of Caspari and Stern [1948] that their findings will not be accepted until differences between their findings and Spencer and Stern [1948] be resolved.

CONCLUSIONS

General

- (1). Curt Stern assumed that the linear dose-response model was accurate and critically important for public policy. Consequently, Stern directed his scientific efforts to ensure that experiments challenging a linear at low dose perspective would need a higher degree of scientific proof, being subjected to greater efforts at replication and more scrutiny than results that supported a linearity perspective.

- (2). This conclusion is supported by (a) the decision to only replicate the findings of Caspari and Stern [1948] and not the Spencer and Stern paper [1948] which supported the linearity perspective, (b) the assertion that the Caspari and Stern findings could not be accepted until it could be determined why they differed from that of Spencer and Stern; (c) the repeated attempts to challenge the findings of Caspari under the assumption that the control group data was spuriously high despite substantial data to the contrary; (d) attempts to enhance the credibility, mask the criticism and further the acceptance of the series of Uphoff experiments; and (e) failure to adjust the Spencer and Stern study [1948] for lethal clusters as was the case for the Caspari and Stern research [1948].
- (3). The actions displayed by Stern raise questions about whether and to what extent philosophical/ideological perspectives may have influenced his science. The present analysis suggests that he used his very elevated reputation, his associations with other leaders in the genetics field, his relationship with key journals such as *Science*, and the complexity of his research to mask his intentions and activities. He was successful in achieving his goal of ensuring acceptance of the linear model via these multiple manipulations and obfuscations as they reinforced similar biases within the genetics community.
- (4). The data from Spencer and Stern [1948] and Caspari and Stern [1948] were actually in close agreement on the nature of the dose response in the low dose zone, even though one more strongly supported linearity and the other a threshold interpretation. In both studies, it was clear that at the low doses tested they were close to the limits of detection of a treatment effect. In fact, Spencer and Stern [1948] noted that it was not uncommon for control mutation rates to exceed those seen at 25 and 50 r, due to background variation. In a similar fashion, in three of the eight months of the Caspari study, the controls displayed a higher mutation rate than the treatment group. These observations indicate that in this low dose area both studies found it difficult to distinguish treatments from controls. A treatment effect could become statistically significant when a control group yielded an uncharacteristically low value, something that could happen by chance. This possibly happened in the Uphoff replication of Caspari. The control response was about 40% lowered than expected, leading to the significant treatment effect. Although the control mutation rate was so low in the Uphoff replication experiment, Stern was initially committed to using it. However, the literature research of Caspari which disputed the Stern position and the surprising and copious data of Muller forced him to back down, even though only temporarily.
- (5). While the evidence is circumstantial, it appears that Stern was determined to suppress the acceptance of the Caspari study. The discussion of Caspari and Stern [1948] was, in retrospect, a professional oddity despite its scholarliness, yet this discussion was endorsed by Muller, another strong proponent of linearity. When viewed within the framework of promoting the acceptance of linearity at low dose, the decision was another example of Stern placing a road block in the path of acceptance of the Caspari data while trying to appear reasonable and objective.
- (6). Even the case of Spencer and Stern [1948], a study that most geneticists of that era could support, had serious methodological issues that challenge the validity of its low dose findings. Nonetheless, both the authors themselves and the genetics community failed to note weaknesses that are obvious in retrospect.
- (7). The Stern papers represent a case study for assessing scientific findings within a broader societal context. Stern was an accomplished scientist but his actions suggest strong ideological tendencies. While this historical reassessment has academic interest, the principal significance is that the actions of Stern manipulated the scientific appraisal and the quality of the scientific record on the issue of the dose-response default model, the results of which were to change the course of risk assessment throughout the world for the next 60 years.

Specific

- (1). The Caspari and Stern study [1948] supported a threshold dose response. The changing of its conclusion from its initial publication by the AEC [Caspari and Stern, 1947], and the misdirecting of its discussion appears to have been designed to prevent a fair-minded consideration of this possibility.
- (2). In Uphoff and Stern's attempt [1947] to replicate the Caspari and Stern study [1947, 1948], the control group was "unexpectedly" low, leading the authors to deem the study findings as uninterpretable. This rejection of the study data by Uphoff and Stern [1947] was never revealed in subsequent publications of Stern and colleagues. It was to a large extent hidden in the archives of the AEC.
- (3). The Uphoff and Stern technical note [1949] in *Science* included three experiments—two with aberrant control values and one with an aberrantly high treatment group response. The authors never explicitly addressed the aberrant responses and their earlier documentation (see Uphoff and Stern, 1947) which supported the aberrant control group interpretation. They simply reversed their position, without ever mentioning this action, incorporated the discredited data into their 1949 meta-analysis to support a linear-

ity interpretation [Uphoff and Stern, 1947]. Promised documentation to support these studies was never provided.

- (4). Uphoff and Stern [1949] also incorrectly used the Spencer and Stern [1948] publication as the gold standard comparison for the Uphoff and Stern 100-r experiment to validate a linearity prediction. There was no justification for its use in this manner given the extensive protocol differences between the two studies.
- (5). Important new limitations have been identified in the Spencer and Stern paper [1948]. This study failed to properly match control exposure periods with those of the key low dose comparison group (e.g., 50 r). It employed two 50-r subgroups with differing matching periods with the control and with different dose rates. Yet these authors combined the data of the two subgroups to make a single 50-r treatment group without providing any data to justify this course of action. Detailed control mutation rate data of Caspari and Stern [1948] and Uphoff and Stern [1947] demonstrated wide monthly variability and strongly supported the need to closely match control and treatment exposure periods. The Spencer and Stern study [1948] also explicitly reported poor temperature control which they indicated adversely affected the accuracy of mutation rates. The scoring criteria of Spencer and Stern [1947] for lethality was to some extent admittedly subjective. Yet, the scoring was not single or double blinded. Since there was a strong belief in the linear model and its affirmation, the possibility of a bias may be raised. These findings raise important questions concerning the validity of conclusions concerning low dose responses in the Spencer and Stern [1947] paper, yet they were ignored in the meta-analysis of Uphoff and Stern [1949]. The limitations of the Spencer and Stern paper [1948] may also reflect the high likelihood that this manuscript was published without peer review. This 68-page, highly detailed manuscript, was formally received by *Genetics* on November 25, 1947, and published in January 1948(6) The conclusion of Uphoff and Stern [1949] that “*there is no threshold below which radiation fails to induce mutations*” was insufficiently supported and therefore not justified.

Lingering Questions

Stern’s (and Uphoff’s) broad and unequivocal conclusion [Uphoff and Stern 1949] was as surprising as it was unjustified, possibly due to the significance of the scientific and societal implications. Trying to make sense out of the Stern conclusion is disquieting and may lead to discussion which can be both speculative and judgmental. There are some questions to consider:

- Why did Uphoff and Stern [1949] transition from a very tentative statement that low doses of radiation “may” increase mutation rate but then offer such an unequivocal general conclusion supporting linearity regardless of how low the dose was?
- Why did Stern determine it was best to publish a one page technical note in *Science*, knowing the experimental details that lay beneath a brief conclusionary oriented summary?
- How did Stern go from dismissing the findings of Uphoff and Stern [1947] in the replication of Caspari and Stern [1948] to including it positively in his weight of evidence perspective of Uphoff and Stern [1949]?
- Why didn’t Uphoff and Stern [1949] inform the *Science* readership that the key data used in their analysis had been recently discredited by them after a detailed documentation of control group mutation incidence?
- Did Uphoff really agree with Stern on the key general conclusion? Or was she somehow forced to agree?
- Why didn’t Caspari challenge the de facto dismissal/ignoring of his findings?
- Why didn’t Stern raise any concern with the spuriously high treatment response in the 100-r Uphoff study?
- Why did Stern use the Spencer and Stern [1948] study as the gold standard for comparison with the Uphoff and Stern [1949] 100-r study, knowing the long list of experimental protocol differences between the two studies?
- Why did the “replication” study of Uphoff and Stern [1947] reduce the sample size by about 40% and expect to detect a treatment effect at low dose?
- Why didn’t Uphoff and Stern [1949] follow through with their stated commitment to provide the detailed paper documenting their methods, materials, and other relevant data?
- Was there ever a real commitment to publish the follow-up detailed paper or was this simply part of a broader plan of floating the conclusion in the world’s most visible scientific journal?
- Why did *Science* decide to publish a one page note and no methods, with only a promise by the authors that they would provide such information in a subsequent publication?
- Why did Stern apparently approve the highly unusual criticism of possible experimental bias by Uphoff possibly leading to the low control values [Uphoff and Stern, 1947]?
- Why didn’t Spencer and Stern [1948] display their weekly/monthly mutation rates for the controls and treatments as did Caspari and Stern [1948] and Uphoff and Stern [1949]?
- Did Stern misuse his role of journal editor in the publication of the Caspari and Stern [1948] paper?
- Why did the genetics community accept the undocumented findings and general conclusions without demanding that Stern follow through with his commitment to provide the detailed paper?

- Why didn't Caspari and Stern [1948] list even more potentially important differences between the studies that they would claim have to be "explained."
- Wouldn't the threshold model still be unacceptable to Stern if the Uphoff and Stern study [1947] had supported the Caspari and Stern study [1948]? This would not have answered why the Spencer and Stern [1948] and the Caspari and Stern [1948] studies differed.
- Why would Stern apparently not submit the Spencer and Stern and the Caspari and Stern manuscripts for peer-review?

Final Thoughts

The scientific community had a major stake in the assessment of studies published by Stern and colleagues concerning the nature of the dose response of ionizing radiation in the low dose zone yet remained strikingly silent over this matter. Despite the centrality of these findings and their broad acceptance by the scientific community, there were numerous concerns with the goals of the experiments, the capacity of the study designs to resolve key scientific questions, how the data were and were not reported, the scientific basis of conclusions, the publication of these papers, and finally how such findings should affect policy and risk assessment activities. The Stern Affair deserves a more detailed reassessment based on its central importance in the development of risk assessment policies and procedures and whether these may have been affected by deceptive actions by esteemed scientific leaders of the genetics community.

While this article questions several important scientific decisions by Curt Stern, such questioning is not intended to challenge his ethics, as he was highly regarded by his peers for his scientific and personal integrity [Bern et al., 1985]. Furthermore, there are also important limitations in the historical record that lead to informed but, nonetheless, speculative interpretations about the basis of some of Stern's actions. This is especially the case since it is not possible for Stern to explain his actions/decisions. Nonetheless, the important and challenging questions remain about the judgments of Stern, raising the broader question of whether this series of scientific decisions were the result of what happens when one's science becomes affected by transience concepts which in this case is what we now call the "precautionary principle." This issue raises a further serious and general concern as ideology-driven science represents a type of "intellectual" virus that can undercut the integrity of data-driven processes needed to guide critical societal decisions, and it can do so very effectively in a disguised and difficult to discern

manner, as appears to be the case with the history of low dose linearity.

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