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The Selby-Russell Dispute Regarding the Nonreporting of Critical Data in the Mega-Mouse Experiments of Drs William and Liane Russell That Spanned Many Decades: What Happened, Current Status, and Some Ramifications

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Abstract

The Russells began their studies of the hereditary effects of radiation in the late 1940s, and their experiments contributed much to what is known about the induction of gene mutations in mice. I had a close association with them for about 26 years, and they relied on me considerably for database management and statistical support. In 1994, I was shocked to discover that, in experiments on males, they had failed to report numerous spontaneous mutations that arose during the perigametic interval and were detected as clusters of mutations. I realized that their nondisclosure of this information meant that the decades-long application of their data to estimate hereditary risks of radiation to humans using the doubling-dose approach had resulted in a several-fold overestimation of risk. I accordingly reported the situation to funding agencies. The resulting complicated situation is referred to here as the Selby-Russell Dispute. Highlights of the resulting investigation, as well as what occurred afterward, are described, and reasons will be provided to show why, in my opinion, the hereditary risk from radiation in humans was likely overestimated by at least 10-fold because the Russells decided not to report critical information from their massive experiments.

Keywords

ionizing radiation, Russells, masked mosaic, spontaneous mutation, doubling dose, first cleavage gonadal mosaic

Introduction

This commentary is based on my after-dinner speech presented on April 16, 2019, at the meeting of the International Dose-Response Society at the University of Massachusetts in Amherst, Massachusetts. It is not surprising that William (Bill) Lawson Russell and Liane (Lee) Brauch Russell are sometimes referred to as the most famous scientific couple in the history of Oak Ridge National Laboratory (ORNL), which is located in Oak Ridge, Tennessee. They are 2 of very few scientists from ORNL who have received the United States Department of Energy's (DOE's) most prestigious award, the Fermi Award, and they were both elected to membership in the United States National Academy of Sciences. Bill was a key member of committees that estimated the hereditary risk of radiation for most of his long career. Figure 1 shows Lee and Bill in around 1950 as they appear in a painted mural found in the main cafeteria of ORNL.

Bill was 11 years older than Lee. They met when she was a summer student at The Jackson Laboratory in Maine. I had a close association with them from 1966 through 1972 and from 1975 through 1995. I was Bill's only PhD student. Because of their age difference and the mandatory retirement age, Lee was my boss during most of my career. Bill and I had research interests that overlapped greatly, but Lee was much more interested in determining what changes had occurred in specific-locus mutations at the chromosomal or DNA level. Bill and I

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Figure 1. Lee and Bill Russell in around 1950.

often talked about issues related to our mutagenesis research as well as other common interests. Our interactions were almost always pleasant. For about 25 years, he was one of the best friends that I ever had, and I thought the world of him.

My relationship with Lee was warm for about the first decade. She was extremely hard working. Unlike Bill, she worked long hours in mouse rooms, usually along with one of her technicians. When doing so, she was often closely examining mice with mottled fur. My research efforts were often frustrated by insufficient technical help over long periods or by being pulled off of experiments in progress because either Bill or Lee wanted me to do some other experiment. In my opinion, favoritism to certain employees was a significant problem for me and others. It resulted, to an important extent, from Lee's extensive involvement in the Tennessee Citizens for Wilderness Planning (TCWP) organization. She edited the newsletter for decades. While Lee was terribly busy with scientific work, she was sometimes also extremely busy with TCWP work. If you were active in TCWP, you were likely to be a much better friend of Lee. At one point, she nudged me along by gifting me with an annual membership, which I felt obligated to renew for many years, although I only attended one meeting. During the little time that I had to myself outside the work at the laboratory, I gave much higher priority to my wife and 2 daughters and to my church than I did to environmental activism.

At times, I certainly benefitted greatly from my friendship with both of the Russells. I did several large experiments using the same technique for studying the induction of recessive mutations that the Russells used, which I will describe below. However, most of my career was focused on studying the induction by ionizing radiation of dominant mutations that cause skeletal malformations, cataracts in the lens, or stunted growth. I belonged to the last generation of students who depended on proficiency with slide rules to get through college. I fortunately learned how to program computers and, as a result, came to play a major role in statistical support and database management for the Russells. Had I not played those roles, the Selby-Russell Dispute would never have occurred. Bill died in 2013 at the age of 92. Lee died on July 20, 2019.

The Mega-Mouse Experiments, the Dispute, and Some of the Ramifications

Soon after Lee and Bill married in 1947, they came to ORNL to conduct an experiment to determine whether X-rays could induce gene mutations in spermatogonia. They set up a specific-locus experiment in which recessive mutations at 7 genes could be identified easily in first-generation progeny. Mutations were detected by a major change in the fur color for 6 of the genes or by the presence of a much smaller outer ear for the seventh. Because the mothers in these experiments were homozygous recessive for known recessive mutations at these 7 genes, they were white with pink eyes and had short ears. The males had only normal genes at those 7 loci and thus had agouti-colored fur with black eyes and normal outer ears. Offspring in each litter were examined when about 3 weeks of age. If none of them received a recessive mutation from their father, they all had fur color, eye color, and ears of normal size just

like he did. However, if one received a mutation at 1 of the 7 genes, its strikingly different appearance revealed the gene at which the mutation had occurred. When the combined frequency of mutations of the 7 types was compared between experimental and control groups, a statistically significant increase in the frequency in the experimental group showed that the radiation treatment had induced mutations.

In the Russells' first specific-locus experiment, male mice were exposed to a dose of 600 roentgens (R) of 250 kvp X-rays at a dose rate of approximately 90 R/minute, and all offspring were conceived after the long sterile period, thus ensuring that any induced mutations occurred in stem cell spermatogonia. The first preliminary results were published in 1951, at which time "53-54" specific-locus mutations had been found among 48 007 offspring in the experimental group in comparison to 2 among 37 868 offspring in the concurrent control.[1] Although that experiment was completed within a few years, its final results were not published until 1959, at which time the mutation frequencies were said to be 111/119 326 and 6/106 408, in the experimental and control groups, respectively.[2] Those results were of great interest to committees that made early attempts to estimate hereditary risks of radiation in humans. The actual results were, however, substantially different, with there being 90 additional mutations in the control group for a spontaneous mutation frequency of 96/106 408, with the mutation frequency in the experimental group being the same as it was reported to be in 1959. Although the event that caused this change occurred in 1951, I did not discover it until 1995. While the Russells subsequently admitted that the event that caused this difference did occur, they have never reported the revised control mutation frequency. The complicated situation that followed after I discovered the unreported event and similar events, and pointed out their significance, is what is referred to as the Selby-Russell Dispute.

The explanation for the additional 90 mutants in the concurrent control is as follows. Males in these experiments were normally mated with 1 female at a time, and females were replaced when they stopped producing offspring. Most males sired approximately 100 offspring. In the concurrent control of their first experiment, 6 males had 1 mutant among their progeny, but 1 male produced 90 offspring with the same mutation among his 402 offspring. The finding of more than 1 mouse with the same mutation among the progeny of 1 wild-type parent is called a cluster. The Russells bred that one male with many more females when trying to determine the cause of that unusual event. We now know, thanks to Lee, that most spontaneous mutations result from a single-strand mutation that occurs after the last premeiotic mitosis and before the first postmeiotic one of the parental genome—that being an interval for which Lee[3] coined the term "perigametic interval." Such a mutation is present before the primordial gonad forms, and the parent looks completely normal and is thus described as a masked mosaic. When such a parent is used in a specific-locus experiment, anywhere from none to about 50% of its progeny express the phenotype for the spontaneous mutation. In my papers,[4,5] I refer to such clusters as first cleavage gonadal mosaic (FCGM) clusters to distinguish them from the rare clusters that have always been reported that result when a treatment causes so much killing of stem cell spermatogonia that the testes are repopulated from few cells.

The Russells were undoubtedly appalled at having such an extreme complexity occur in their high-profile first experiment, and they did not report that cluster. They did, however, preserve the original data. By not reporting that cluster, they did not have to spoil what otherwise looked like an obvious difference between experimental and control groups that yielded an easily calculated induced mutation frequency. Also, they could claim that the specific-locus test was a simple straightforward technique for demonstrating induction of mutations in mice that could be applied to examine many variables of interest, and they could conclude that the mouse was 15 times more sensitive to the induction of mutations by X-rays than the fruit fly. In my opinion, the sanitized version of their results facilitated expansion of their program into perhaps the largest biological research program ever funded by the government at one institution. They probably hoped that such a cluster would never occur again. Soon their research program occupied all 3 floors of a huge building that was commonly called the Mouse House. It contained 66 separate rooms that contained mice, the total population of which probably often exceeded 250 000.

Over the next decade, the Russells' specific-locus experiments provided valuable data on the influence of total dose, dose rate, types of radiation, differences between different stages of reproductive cells in both sexes, and dose fractionation. Bill's discovery of the dose-rate effect opened up the whole new field of DNA repair. The Russells certainly thought that their specific-locus data should be applied in hereditary risk estimation, and they were well aware that the only way in which their data could be used to estimate hereditary risk in humans was by the doubling dose (DD) method, in which the DD is calculated by dividing the spontaneous mutation frequency per generation by the induced mutation rate per R, thus yielding the DD, which is the number of R needed to induce as many mutations as occur spontaneously. Although the calculation of the DD is straightforward, questionable steps are required when using it to derive an estimate of the extent of hereditary damage in the first generation in humans following radiation exposure. Discussion of those uncertainties is not needed for my story. Individuals or committees that applied the DD method would have assumed that the mutation frequency in the male controls reported by the Russells was the spontaneous mutation frequency per generation in males. Instead, it was an approximation of the spontaneous mutation frequency in male germ cells outside the perigametic interval.

The Dispute primarily involves the failure of the Russells to report, in anything resembling a timely fashion, the clusters of spontaneous mutations in the male. It is extraordinarily puzzling, after knowing how they handled the cluster in their first experiment, that in 1963 they did report the finding of a cluster of the same type in the control for experiments on female mice. More about that later.

Bill was particularly interested in the data on the induction of dominant mutations that cause abnormalities in the mouse skeleton that I demonstrated were induced by acute irradiation of male mice in my postdoctoral research in West Germany.[6] As a result, and at his urging after I returned to the United States and was hired by ORNL, I applied those data by proposing an alternative method for estimating hereditary risk to humans in the first generation following radiation exposure. I called it the direct method. Bill liked my approach so much that he presented it as an alternative to the DD method at the next meeting of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). At that time, the approximately 10 geneticists at that meeting met for several days with their consultant—who at the time was K. Sankaranarayanan (known as Sankar). They knew that, near the end of the 2-week meeting, Sankar would give a short presentation on the Genetic Subgroup's decisions to the parent committee. Bill received strong support for adopting the direct method from the geneticists on the Subgroup who worked with mice; however, some other members wanted to use only the DD method. Near the end of the first week, a vote was taken, and it was decided to include the direct method in the next report. Thinking that their work was done, all mouse geneticists except Bill returned home after the first week. Those opposed to using the direct method took advantage of their absence and reopened the discussion during the next week. Another vote was taken, and it was decided not to use the direct method. Bill was furious about how this had been handled. When Bill returned to Oak Ridge and told me what had happened, he and I agreed that the problem was that many of the Subgroup's members had used the assumptions of the DD method for so long that they had grown too comfortable with them. We prepared a list of the assumptions used in each method, and Bill used that list to challenge the Subgroup's decision. The end result was that the 1977 UNSCEAR[7] report included first-generation estimates of hereditary risk made by both the direct and the DD methods.

By the mid-1960s, the Russells had entered extensive amounts of their data on males into ORNL's mainframe computer. The effort was likely made to ensure that the results would not be lost from such important experiments if there would be a calamity such as a fire. Two copies of each data set, to be stored at separate locations, were printed out for each experiment before the data were removed from the computer. The data entry cards were stored. When I began computerizing my skeletal records in the early 1980s, Bill asked me to accomplish the same objective for the specific-locus experiments, which I did as a major undertaking with the help of 2 information technology experts. By this time, ORNL housed the world's largest configuration of a Digital Equipment Corporation Programmable Data Processor-10 (PDP-10) computer. All of those previously computerized records were reentered into that computer—this time to stay. In spite of the size of that mainframe computer, the data were too voluminous to be added with all results for a single experiment in a single computer file. There had to be 4 separate linked files for each experiment: one each for details on female parents, on male parents, on all litters, and on the mutations found. Soon data from new specific-locus experiments were being added to the PDP-10 computer promptly after their collection.

In the early 1980s, I discovered that my methods for studying induction of dominant mutations causing skeletal malformations also worked well on the strains of mice used in specific-locus experiments, and I began doing experiments in which we examined skeletons of mice from some of Bill's experiments on the supermutagen ethylnitrosourea. Because it was extremely rare to see Bill in a mouse room, one day in 1986, I was surprised to see Bill squatted down toward the back of the room where mice for one of those experiments were raised. The head technician, Pat Hunsicker, was showing him something in a mouse pen on one of the lower racks, and I wondered what could possibly be of so much interest. It turned out that one pen in the male control group contained a cluster of black juvenile mice. I then realized that a FCGM cluster had occurred in the male control at ORNL similar to the one that had caused so much consternation and complication in the female control ever since 1963.

In the years that followed, I urged Bill numerous times to publish his finding of that one cluster. He would usually say that he intended to publish it, but he never got around to it. On at least 2 occasions, I stressed to Lee the importance of updating the ORNL historical control in males to include the more recent data including that cluster. I also made sure that Lee and Bill knew that one such cluster containing 2 mutants had been reported by Searle[8] in the male control at the Harwell Laboratory in England and that 2 such clusters in the male control had been reported by Ehling's[9] group in Neuherberg, Germany. The existence of those 3 clusters made it seem even more important to acknowledge that such a cluster had now been found in the male control at ORNL. When Lee finally updated the ORNL historical control in males in 1992, she refused to even mention that cluster.[10] My concerns about not reporting the cluster at that time were 2-fold. I knew about the complications in analysis resulting from the cluster in the female, and it seemed that everyone studying mutagenesis should know that the same problem had now occurred in the male. Also, in the early 1980s, I had suggested a multiple-decision procedure for classifying specific-locus experiments on chemicals that was dependent on 2 comparisons with the male control data.[11] That method had been applied by a Gene-Tox committee in 1981 to all past experiments,[12] and Lee was using it for new experiments. I had written a computer program for the procedure, and Lee would give me the experimental data from a new experiment so that I could supply her with the statistical results that she reported in her paper. In view of the finding of the unreported cluster in the male control, I thought that my multiple-decision procedure no longer made sense, especially because Lee's committee, on which I had served, had stressed the importance of using updated historical control data. Lee obviously did not appreciate my stressing the need to include the cluster. Because she was my boss and completely controlled my level of technical support, I was between a rock and a hard place. I never would have considered it possible at that time

that the cluster that had been found in 1986 was simply the tip of the iceberg of similar problems. It is perhaps because my energy was so focused on my own experiments at that time in an attempt to improve the direct method of hereditary risk estimation that the obvious effect of such clusters on the calculation of the DD did not occur to me. It is fortunate that it did not because, if it had, and I had made an even bigger issue of that cluster, I would probably have been fired.

In early 1994, we were notified that the PDP-10 computer would be shut down on December 10 of that year, and all data had to be migrated to other computers before that date. The Macintosh computers that we then used could easily accommodate those massive data, and it became my responsibility to migrate the data from the PDP-10 to my Macintosh computer and combine the 4 files for each experiment into a single file. This was a huge and complex task, and it could not have occurred at a worse time. Early on in the effort, I was given 2 people to assist me on the project for short periods, but I had to supervise the entire effort closely and do most of the work myself. I had also learned in the spring of 1994 that the funding for my experiments was being severely trimmed and that my entire project would likely be terminated in the fall of 1995. I then lost all of my technical help toward the end of 1994. By working incredibly long hours, I still managed to do everything necessary so that, should my funding be restored, my large series of experiments on dominant mutations would still be done well. A major crisis occurred after Bill came to my laboratory on September 1 and pressured me to do everything necessary to complete the transfer quickly. He stated that those files were their legacy, and it became obvious that my health and my experiments meant nothing to Lee and him in comparison to those files. On the following day, I had by far my most unpleasant interactions ever with both Lee and Bill—one at a time. After that, they left me alone so that I could do the work, and I somehow managed to finish the transfer on December 9—one day before the deadline.

One late night as I was working on the data transfer—probably in November—I ran across data on a huge cluster of mutations in an experimental group from an experiment done in 1955. As I looked at it, I had an epiphany and the relationship between such clusters, occurring in either the experimental or control groups, and the calculation of the DD and risk estimation became apparent. In the mid-1980s, I had written a computer program that simulated specific-locus experiments, and I immediately began to apply an improved version of that program to try to understand more about the implications of the unreported clusters. I soon became convinced that failure to report those clusters had led to a substantial overestimation of hereditary risk. A very scary period of my life then began. I was terribly busy with my own experiments until Easter of 1995, after which I read or reread all relevant papers to see whether the Russells had ever reported any details on clusters of this type in mutation experiments on males. They had not; however, I was intrigued to find what appeared to be 2 clusters of the same type mentioned in papers by Lee.[13,14] She had described them in a way that did not reveal that they were first found in specific-locus experiments. Her wording suggested that they were irrelevant to mutation frequencies. She even gave a name to one of them, calling it the "Cr" cluster.[14]

I decided that I must make sure that the DOE, which provided primary funding for the Russells' research, knew about the unreported clusters and their importance. On June 8, 1995, I mailed a detailed letter describing my findings to David Smith, the top official in the DOE funding chain. At that time, I only knew about 4 such clusters, and for 2 of them I had only vague knowledge gleaned from Lee's papers. The earliest such cluster that I described in my letter was the one mentioned earlier from an experimental group in 1955, and then there was the one in the male control that had troubled me since 1986. In my long and detailed letter, I also documented numerous specific complaints about management issues that I hoped would convince DOE to continue support for my research. In a telephone conversation, Marvin Frazier, who was Smith's "top lieutenant," urged me to try to discover if there were any additional serious problems in the Russells' reporting of their results, while I still had access to their data. As a result, I went to the Mouse House late in the evening on July 17 with the hope of finding the origin of the 2 clusters of spontaneous mutations mentioned in Lee's papers. I had no idea where to start. Purely by luck, the very first file drawer that I opened contained a thin folder labeled "Clusters." Among the sheets of paper in it, I noticed a messy page, filled with handwritten details, on which I spotted the phrase "Cr cluster:" Next to that phrase was the code for the K experiment in which it had been found, and I immediately recognized that as being the computer code of the Russells' first experiment. By having that clue, within just a few minutes, I found the folders containing detailed records on the "Cr-c[a] cluster" from the K experiment. There, before me, were the complete records on that first cluster that I described early in this paper. This experience would be similar to being told that you must find a needle in a large haystack and then finding that needle in the very first handful of hay that you picked up. Handwritten notes indicated that a detailed summary had been given to Bill on September 29, 1953, and a xerox copy was given to Lee on May 20, 1977.

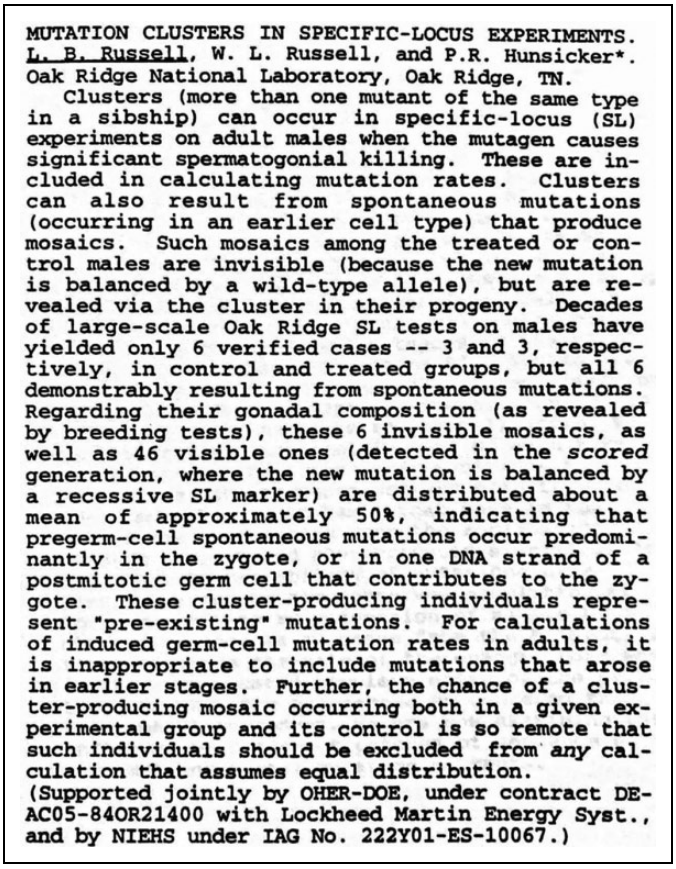
The few hours that I spent doing detective work that night revealed several more shocking details, which I described to Smith and Frazier in an e-mail on July 20. Smith called me to let me know there would have to be an investigation and that someone from ORNL would contact me about what to do next. On July 22, I mailed materials describing this shocking situation to Mike Shelby and Jack Bishop, the top officials in the funding chain at the National Institute of Environmental Health Sciences, which funded the specific-locus experiments on chemical mutagens, which had been the primary application of the specific-locus test by the Russells almost all of the long time that I had known them. On one of the next few days, I made an additional visit to the Mouse House in the middle of the night during which I discovered more troubling details and made photocopies. I hoped to make more such searches because I had only scratched the surface of the material that needed to be examined. However, my access to the data ended

before I could look again. I think it was on the afternoon of July 26 when I received a call telling me to report to the office of David Reichle, an associate director of ORNL. He had been sent the materials. He told me that an investigation would be made and that I must meet with Barbara Ashdown, the Director of Ethics, early the next morning. Now that ORNL knew that I had reported what the Russells had done, I made no further attempts to examine their data files.

Ashdown and I met. She was quickly convinced that the Russells' raw data had to be secured so that there was no chance that they could be altered. I told her that I could no longer trust what the Russells had reported and that the data needed to be examined by a group of independent scientists. In my view, the experiments were well planned and well executed, and it appeared that the Russells had preserved data that revealed the complications that they had chosen not to publish. Ashdown soon had all of the tally sheets from individual experiments and related records, up through approximately 1990, locked up in an available empty room. The ORNL agreed to copy all the records and retain the originals before giving copies to the Russells. Until the Russells received the copies, they or their technicians would be permitted to look at those records, with an agreed upon person being present.

Ashdown said that until the investigation occurred, I had to notify her of anyone that I told about the situation. I assumed that the Russells had to play by the same rules. The Ethics Investigation Committee was to consist of 4 scientists, one recommended by each of the following: DOE, the Biology Division, the Russells, and me. The person I recommended initially accepted and then, because of some unforeseen complication, could not serve. I had to quickly come up with a replacement and chose Christian Streffer from Germany, with whom I had served on UNSCEAR.

It became necessary to get me out of the Mouse House quickly. At first, I expected to lose my job at ORNL, but then I was transferred on August 1, 1995, to the Health Sciences Research Division, where I had to learn how to do work related to Superfund sites. For several months, I was allowed to return to the Mouse House during the evening. An agreed-upon person would let me into my locked laboratory so that I could prepare skeletons for work that I still hoped to complete. I also had to quickly box up all of my research papers and many other materials and put them into a caged area in a huge storage building at the main ORNL site. Over 4000 skeletons, in individual glass bottles, from my interrupted experiment were stored in a large closet at my new work site. I was told that I would be sent a property removal form that would permit me to move the stereomicroscope with which I examined skeletons from my locked laboratory to my new Division. I needed it to examine a group of skeletons of particular interest. For weeks, I had been expecting to find that form in my mailbox in the Mouse House, but it was never there. One evening, when checking my mailbox, which was just outside the office of the Section's secretary in the Mouse House, I noticed a huge stack of mail on her desk. Luckily the door to her office was not locked. I looked through that stack to see if my removal pass



MUTATION CLUSTERS IN SPECIFIC-LOCUS EXPERIMENTS.
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Clusters (more than one mutant of the same type in a sibship) can occur in specific-locus (SL) experiments on adult males when the mutagen causes significant spermatogonial killing. These are included in calculating mutation rates. Clusters can also result from spontaneous mutations (occurring in an earlier cell type) that produce mosaics. Such mosaics among the treated or control males are invisible (because the new mutation is balanced by a wild-type allele), but are revealed via the cluster in their progeny. Decades of large-scale Oak Ridge SL tests on males have yielded only 6 verified cases -- 3 and 3, respectively, in control and treated groups, but all 6 demonstrably resulting from spontaneous mutations. Regarding their gonadal composition (as revealed by breeding tests), these 6 invisible mosaics, as well as 46 visible ones (detected in the *scored* generation, where the new mutation is balanced by a recessive SL marker) are distributed about a mean of approximately 50%, indicating that pregerm-cell spontaneous mutations occur predominantly in the zygote, or in one DNA strand of a postmitotic germ cell that contributes to the zygote. These cluster-producing individuals represent "pre-existing" mutations. For calculations of induced germ-cell mutation rates in adults, it is inappropriate to include mutations that arose in earlier stages. Further, the chance of a cluster-producing mosaic occurring both in a given experimental group and its control is so remote that such individuals should be excluded from *any* calculation that assumes equal distribution.

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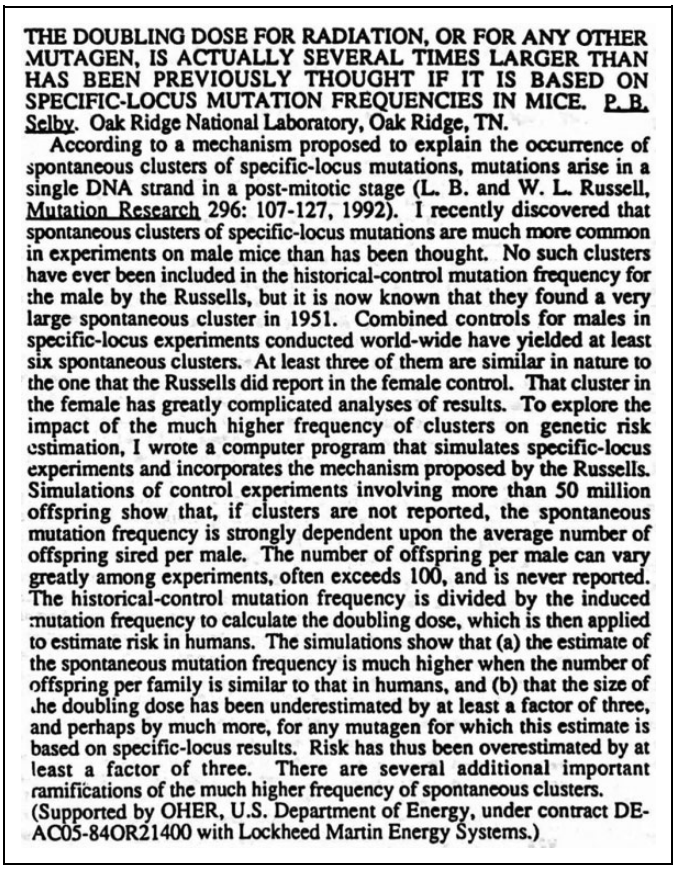
Figure 2. The abstract[15] of the Russells for the Environmental Mutagen Society meeting in 1996.

was there. It was! However, a more interesting discovery was that Lee had left, on the top of that stack, instructions for her secretary to submit an attached abstract for the meeting of the Environmental Mutagen Society (EMS) Society to be held the following March in Vancouver, British Columbia. The Russells' abstract is shown in Figure 2, and it was published.[15] The Russells were obviously trying to get out in front of the story by putting out their spin at a meeting before the Ethics Investigation Committee met the following summer. The most interesting parts of the abstract are as follows: "Decades of large-scale Oak Ridge SL tests on males have yielded only 6 verified cases—3 and 3, respectively, in control and treated groups, but all 6 demonstrably resulting from spontaneous mutations." And then later: "These cluster-producing individuals represent "pre-existing" mutations. For calculations of induced germ-cell mutation rates in adults, it is inappropriate to include mutations that arose in earlier stages." It is noteworthy that the Russells' abstract made no mention of the DD method of hereditary risk estimation.

After reading the Russells' abstract, and knowing that it was just a few days before the deadline for abstract submission, I quickly prepared and submitted the abstract shown in Figure 3 for the same meeting. My abstract was accepted, and I was appointed the chairman of the session at which Lee's talk and mine would be given. The most relevant parts of my abstract,



THE DOUBLING DOSE FOR RADIATION, OR FOR ANY OTHER MUTAGEN, IS ACTUALLY SEVERAL TIMES LARGER THAN HAS BEEN PREVIOUSLY THOUGHT IF IT IS BASED ON SPECIFIC-LOCUS MUTATION FREQUENCIES IN MICE. P. B. Selby. Oak Ridge National Laboratory, Oak Ridge, TN.

According to a mechanism proposed to explain the occurrence of spontaneous clusters of specific-locus mutations, mutations arise in a single DNA strand in a post-mitotic stage (L. B. and W. L. Russell, Mutation Research 296: 107-127, 1992). I recently discovered that spontaneous clusters of specific-locus mutations are much more common in experiments on male mice than has been thought. No such clusters have ever been included in the historical-control mutation frequency for the male by the Russells, but it is now known that they found a very large spontaneous cluster in 1951. Combined controls for males in specific-locus experiments conducted world-wide have yielded at least six spontaneous clusters. At least three of them are similar in nature to the one that the Russells did report in the female control. That cluster in the female has greatly complicated analyses of results. To explore the impact of the much higher frequency of clusters on genetic risk estimation, I wrote a computer program that simulates specific-locus experiments and incorporates the mechanism proposed by the Russells. Simulations of control experiments involving more than 50 million offspring show that, if clusters are not reported, the spontaneous mutation frequency is strongly dependent upon the average number of offspring sired per male. The number of offspring per male can vary greatly among experiments, often exceeds 100, and is never reported. The historical-control mutation frequency is divided by the induced mutation frequency to calculate the doubling dose, which is then applied to estimate risk in humans. The simulations show that (a) the estimate of the spontaneous mutation frequency is much higher when the number of offspring per family is similar to that in humans, and (b) that the size of the doubling dose has been underestimated by at least a factor of three, and perhaps by much more, for any mutagen for which this estimate is based on specific-locus results. Risk has thus been overestimated by at least a factor of three. There are several additional important ramifications of the much higher frequency of spontaneous clusters.

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Figure 3. The abstract[16] of Selby for the Environmental Mutagen Society meeting in 1996.

which was published,[16] are as follows: "To explore the impact of the much higher frequency of clusters on genetic risk estimation, I wrote a computer program that simulates specific-locus experiments and incorporates the mechanism proposed by the Russells." And then later: "The simulations show that (a) the estimate of the spontaneous mutation frequency is much higher when the number of offspring per family is similar to that in humans, and (b) that the size of the doubling dose has been underestimated by at least a factor of three, and perhaps by much more, for any mutagen for which the estimate is based on specific-locus results. Risk has thus been overestimated by at least a factor of three."

When Ashdown visited me several weeks later to update me on plans for the investigation, I told her about the abstracts. She appeared shocked and upset. Lee and I gave our talks at the EMS meeting. Immediately after the session, Ronny Woodruff came up and introduced himself. He said that he was familiar with the existence of this type of cluster in fruit flies, with which he worked, and he had written to Lee to find out if the same types of clusters occurred in mice. She had never responded. He now understood why. Woodruff and I spent several hours discussing the situation and had interesting collaborations afterward.

On January 30, 1996, Ashdown gave me the Russells' combined 38-page responses[17,18] to my charges. They had submitted these documents to the Ethics Investigation Committee. Lee's response[17] provided very sketchy details about 8 clusters including the 4 that I had reported to the DOE. I submitted a response to their rebuttal to the Ethics Investigation Committee. The Russells had picked Dean Parker to be their representative on that committee. He submitted a list of questions for the Russells and me to answer before the investigation, and I gladly complied. I requested that a court reporter be present to record everything that was said during the Ethics Investigation Committee's sessions with me and the Russells and that was done. I also requested that I be permitted to observe the session(s) with the Russells and that they be permitted to observe the session(s) with me, thereby permitting the members to benefit from our knowledge of the situation in case those members needed some clarification in getting to the heart of the matter. This request was denied.

The investigation occurred at a hotel in Oak Ridge from July 21-24, 1996. By that time, 9 FCGM clusters were under consideration, and I felt certain that there were more, perhaps many more. Besides Parker and Streffer, the Ethics Investigation Committee consisted of the chairman, Mortimer Mendelsohn, who was selected by DOE, and Arthur Weissbach, nominated by the Biology Division. The most memorable happenings were as follows. Early in the session, Weissbach stated that he considered what the Russells had done to be no worse than his not publishing everything in his laboratory notebook. Amazing! When there was a lull in the questioning, I said that I had been told by Marvin Frazier after reporting the matter to DOE that, while I still had access to data, I should try to determine whether there were additional unreported complications. As I opened a file folder that contained photocopies of records showing additional complications, Mendelsohn stated that the Committee had enough to deal with in discussing what I initially reported, and they would not consider additional information. At that moment I realized that the Committee was not searching for the truth; it was simply trying to defuse a situation that was embarrassing for ORNL and DOE. In the debriefing session with me on the final day, at which the Committee described its preliminary conclusions, Mendelsohn told me that the Committee would have had to make a much bigger deal out of what the Russells had done if things had been the other way around and the Russells' actions had led to the underestimation of the hereditary risk to humans from radiation exposure. However, because the Russells' actions had led to the overestimation of hereditary risk, I should be satisfied with what the Committee considered to be the best resolution of the matter. There would be no reevaluation of the Russells' data by independent scientists; however, the Russells would be required to publish basic information on all of the clusters that were now known about. I was encouraged to publish my analysis.

The Russells promptly published the basic details in the Proceedings of the National Academy of Sciences of the United States of America (PNAS) on all of the clusters that I originally reported to DOE and on the 4 others mentioned above as well their view of the matter.[3] Rapid publication by them in PNAS was facilitated by their both being members of the National

Academy of Sciences. Several decisions made by DOE, ORNL, or both substantially delayed the publication of my 2 papers. One delay had an amusing outcome. At the debriefing, I said that I felt that I needed permission from Lee to include certain details about the clusters in my papers, and I asked how I should communicate my request to her. Ashdown said that I was not permitted to contact Lee directly. I could write a memo to Lee and give it to her to pass on to Lee. I gave Ashdown my memo on July 26. Ashdown did not give Lee that memo until I had complained sufficiently about the delay. Indeed, there was a 7-month delay before Lee got the memo and a further delay before Lee responded to me. In my memo, I requested additional details on the 9 clusters that I knew about. This was 1 more than the 8 that the Russells had reported in their supposedly thorough PNAS paper. They quickly published a correction[19] that updated their conclusions to include that ninth FCGM cluster, which was at the *a* locus and occurred in 1957. In Lee's response[20] to that memo from me that Ashdown took 7 months to deliver, I learned that that ninth FCGM cluster admitted to by the Russells and the FCGM cluster found in 1955 (which was the one that I noticed when I first realized the seriousness of the problem) both came from the same huge experiment on males treated with 300 R of ~90 R/minute X-rays. To my mind, it is almost as shocking that the Russells failed to report the finding of 2 FCGM clusters within a single experiment in the mid-1950s as that they failed to report that huge FCGM cluster in their first experiment.

The final report[21] of the Ethics Investigation Committee, dated October 23, 1996, was given to me in December by Steven Stow, who had become the Director of Ethics. Ashdown was present when I was given the report, and curiously she refused to accept a copy with the statement that she was afraid someone might see it on her desk. After a few requests, Stow gave me a copy of the court reporter's transcript of the sessions with me. He never permitted me to see copies of the transcripts of the meeting(s) with the Russells or with anyone else; he said that I could not see the transcript(s) of the meeting(s) with the Russells because they had said such awful things about me. I already knew that the Russells felt (1) that my lack of loyalty to them was a major character flaw, (2) that, because I would have been nothing scientifically without them, my criticisms of them should not be taken seriously, and (3) that there would have been no problem if I had simply brought up the issue with them directly. The 2 summary paragraphs of the final report, designated A and B, regarding the "allegation that W. L. and L. B. Russell purposely covered up experimental data on mutant clusters in their mouse specific-locus mutation research" are of particular interest. Paragraph B will be discussed later, but Paragraph A reads as follows:

> A. We find no evidence of a deliberate cover-up on the part of the Russells. Early in their research they reported spontaneous clusters from time to time, and in 1964, L. B. Russell published a seminal scientific interpretation of the mechanism of mosaicism and mutant clusters. The Russells and others in the same field came to a common understanding that spontaneous clusters should be eliminated from data involving the estimation of induced specific-locus mutations. Given these circumstances, we find it reasonable that their later research and writings de-emphasized this phenomenon, although it would have been better had they reported the clusters more consistently. Also, we note that over the years the Russells' experimental records have been open and available to other investigators.[21]

I was somewhat startled by the third sentence dealing with the "common understanding." Does this mean that some highly secret agreement was made between the Russells and a few other leading geneticists in the early 1950s that nothing should be reported about FCGM clusters? I doubt it.

By 1963, the Russells had deliberately chosen not to reveal the existence of at least 4 clusters occurring in males. Yet, in that year, Bill reported[22] finding the same type of cluster in the female control. I find that to be amazing. Here is what Bill wrote when he reported that cluster: "A reliable figure for the spontaneous mutation rate in females is not yet available. We have obtained only two mutations in our control population and one of these was observed as a sizable cluster. Estimation of the mutation rate is complicated by our not yet knowing whether to treat the cluster as a freak event or, at the other extreme, as something to be expected in a high proportion of the spontaneous mutations in females."

If a secret agreement really existed, it is mind boggling that Bill would write that. Also, if such a "common understanding" really existed, it seems that Lee and Bill would surely have mentioned it when they made their long responses[17,18] to the Ethics Investigation Committee during the previous December. In 1992, the Russells[23] reported their final data on the mutation frequency in the female control as being 2/166 826 and in addition 1 cluster of 6 mutants in a sibship of 59.

After moving to the Health Sciences Research Division, I was told to submit a proposal to the DOE to complete the large series of experiments that I had initiated in 1989. Soon after the DOE rejected my proposal, I received a pink slip. As I was almost done packing things up in my office, after regular working hours, on what—I thought—was to be my last day working at ORNL, I had an unexpected visit by my section head and my immediate supervisor in which they told me that they would find out the next day before noon whether a plan would work to keep me employed by ORNL, if I was interested. With my 2 daughters at a private college at the time, I was certainly interested. The last-minute plan worked, and I accepted a position in Robert Ross's group, which primarily reviewed toxicology studies for the US Environmental Protection Agency. I had to take courses and pass tests to become board certified in general toxicology. I continued to work in that group until I could retire with a full pension from ORNL in November 2000. I continue to do similar work, part-time, as a consultant with the Summitec Corporation in Knoxville, Tennessee. Just before that fateful day that I had expected to be my last working day at ORNL, Keith Eckerman, who worked down the hall from me during my last few years at ORNL, had kindly tipped me off that all of

the unclaimed research materials stored in the building where I had stored almost all of my research materials were scheduled to be destroyed in a few days if not removed by the owners. No official at ORNL had felt any obligation to inform me of this. (It is possible that no members in my management chain at that time, except near its very top, knew that I had been told to store my materials in that building.) Thank goodness, Eckerman somehow learned about the plan. On the same morning when I was waiting to see if the effort to save my job would work, I moved all of those materials to a storage compartment off-site that I still rent. Thus, I came within a few days of losing almost all of the records from my entire research career. Incidentally, I had been required by ORNL management to have Eckerman be one of my internal reviewers before I could get my 2 papers[4,5] on FCGM clusters cleared for release from ORNL. He bravely gave my papers a favorable review. Had he not done so, I doubt that they would ever have been published.

The UNSCEAR published its most recent annex[24] on the hereditary effects of ionizing radiation in 2001. I disagreed with many things in that report, which kept the DD at 1 Gy in spite of providing a reasonable summary of the Russells' and my publications regarding the Dispute. Sankar, the consultant for that annex, was insistent that his viewpoint be presented if the report that he prepared, with input from the committee, was to be used. I will make no attempt to explain that long story here. It was suggested that I publish a critique of the annex, but I was unable to get the critique accepted for publication by any of the 4 journals to which I submitted it. My coauthors on that critique were Ronny Woodruff and James Thompson, Jr. That unpublished manuscript is probably one of the most important ones that I ever tried to publish. I no longer have any contact with UNSCEAR. In my opinion, that annex[24] substantially overestimates the hereditary risk to humans from radiation.

Before stopping all work on mutagenesis, I published 3 of the many papers that I had initially expected to publish on my interrupted Assessment of Dominant Damage experiments.[25-27] One of those papers[26] reports our finding of a cluster of 6 mutant offspring from a masked-mosaic father that produced 26 offspring. That is the first such cluster identified for a dominant skeletal mutation, and it shows that the topic of this paper is also relevant to dominant mutations of a type that have obvious relevance to serious handicaps in humans.

Tony Searle was a well-known geneticist who worked at the Harwell Laboratory. That laboratory in England and the laboratory in West Germany where I did my postdoctoral research were the only other laboratories in the world that did extensive specific-locus experiments using the mouse strains obtained from the Russells. I served with Searle on UNSCEAR for approximately 6 of the 21 yearly meetings that I attended. He undoubtedly provided the most valuable input to UNSCEAR from the Harwell Laboratory during the many years when Bill and I served on UNSCEAR. In September 1998, I sent Searle the report of the Ethics Investigation Committee. The following excerpts from his letter to me of October 5, 1998, are relevant here. He wrote: "Many thanks for your letter of Sept 15, with its low-down on *l'affaire Russell* and with a lot of documents in the case. Although I finally fully retired in May last year and haven't worked actively in radiation genetics since before 1986 (apart from publishing a few oddments), I still found them of great interest, though I don't feel I can make any very useful comments, apart from expressing no surprise at all that you weren't impressed with the investigating committee's report. The idea that there was a "common understanding" with Bill on the treatment of spontaneous clusters makes me smile wryly too. I think you should be congratulated on dragging the facts about specific locus clusters "kicking and screaming" into the scientific literature." And then later: "In my opinion, what's needed now is a book about the whole sensational saga. Perhaps it could be called "The megamouse experiments" and, if well written, it could become as popular as "The Double Helix". When you think of the colossal amount expended on these mammoth experiments, it seems only right to me that the public should be told something about what went on behind the dry contents of scientific papers."

At various times in the past 20 years, I have toyed with the idea of writing a book to describe the research done by the Russells and myself—including our backgrounds, why we did the experiments that we did, the most important results that were reported, how those results were used, how the Dispute came about, and what happened afterward. My goal is to present the information so that it can be understood by people lacking scientific training, but with footnotes and appendices to make it more useful to scientists who want to know more.

My first contact with Edward Calabrese was when he called me in April 2016. I have learned much from him about how committees made decisions in the early days of hereditary risk estimation. I had my own reasons for questioning the validity of application of the linear no-threshold (LNT) dose–response model to radiation and certain chemicals. However, before talking with Calabrese, I never considered the implications of the Dispute beyond the area of hereditary risk estimation. I think that Calabrese is correct in suggesting that the LNT model would probably never have been adopted if the Russells had reported their actual findings.[28] It is a huge problem that the LNT hypothesis became engrained in the mind-set of many scientists and bureaucrats and is commonly applied in policy. Now that I realize the vastly broader ramifications of the complicated and unpleasant situation that I uncovered, I have made substantial progress in writing the aforementioned book.

Since the meeting of the Ethics Investigation Committee, 3 papers about clusters have been published by 1 or both of the Russells, if the short correction is included.[3,19,29] The complex analysis reported in their first PNAS paper[3] is their detailed response. The only important disagreement between the Russells and me is related to the extent of underestimation of the spontaneous mutation frequency per generation. The Russells[3] claim that it should be 2.2 times higher than it was, but I say that it should be at least 6.9 times higher. Figure 4 shows how these 2 estimates of the extent of the underestimation were made. The same total mutation frequency for singleton mutations is used for both estimates. The Russells' estimate is based

The Four Components of the Total Spontaneous Mutation Frequency Per Generation	The Russells*	Selby
1. FCGM Clusters from Fathers	3.36×10^{-5}	17.1×10^{-5}
2. FCGM Clusters from Mothers	3.36×10^{-5}	17.1×10^{-5}
3. Other Mutations from Fathers	4.65×10^{-5}	4.65×10^{-5}
4. Other Mutations from Mothers	1.12×10^{-5}	1.12×10^{-5}
A = Total of Four Parts:	12.49×10^{-5}	39.97×10^{-5}
B = Total for Singleton Mutations (*i.e.*, Components 3 + 4)	5.77×10^{-5}	5.77×10^{-5}
Extent of Underestimation (A÷B)	**2.2 times**	**6.9 times**

*In the Russells' PNAS paper[3], all mutation frequencies are expressed per locus, which mean that they are one-seventh as high as those shown here. The mutation rate for "Other Mutations from Mothers" is taken from Table 1 of reference 23 and includes the sum of the female control and the group called "Ineffective", which refers to data from treated females under conditions in which no induction of mutations was demonstrated. The mutation frequency for that group was 4 mutations in 325,214 offspring.

Figure 4. The Russell and Selby Methods of Calculating the Extent of the Underestimation of the Spontaneus Mutation Frequency Per Generation.

entirely on experimental data, while my estimate is based on computer simulations that incorporated Lee's hypothesis on the origin of FCGM clusters. My estimate of a 6.9-fold underestimation is based on the assumption that the probability that one of the first 2 blastomeres of an embryo is heterozygous for a new spontaneous mutation at 1 of the 7 loci (ie, the "potential FCGM probability") is 1/1500. The derivation of that probability is explained elsewhere[4] along with an illustration of Lee's model. The experimental basis for that probability was provided by Ehling's[30] data from Neuherberg, where the finding of 2 clusters in the male control was reported in the total sample of 248 413 offspring. Our paper[4] suggested that the true "potential FCGM probability" is probably higher than 1/1500, and it seemed to me that 1/1050 would have been a better choice. If I had assumed that probability, my estimate of the extent of the underestimation would be much higher than 6.9 times the singleton frequency.

The Ethics Investigation Committee clearly understood the crucial significance of my argument about the need to consider the effect of small sibship size when considering clusters. The second of 2 summary paragraphs of the Committee's final report reads as follows:

> B. On the other hand, we welcome and applaud P. B. Selby's recent scientific emphasis on clusters and their effects on estimating mutational risk. We believe he will stimulate greater attention being paid to clustering, particularly in the context of comparisons between subjects with large sibships (such as the experimental mouse) and subjects with small sibships (such as the human). A good example of renewed attention is the work already well underway on the frequency of clustering by the Russells.[21]

When Lee[17] wrote her "Response by L. B. Russell to Charges of Scientific Cover-Up" to the Ethics Investigation Committee in late 1995, she appears to have clearly accepted my finding that conducting experiments on small sibships would lead to a much higher frequency of spontaneous clusters, when she wrote:

> It should be noted that if each H male were allowed to have only 1-2 offspring rather than ~100, one would have 50-100 times more males to obtain the same number of offspring, and there would then be an appreciably higher probability that mosaics would be found on both sides of the comparison. Obviously, it would be prohibitive from a practical and expense point of view, to conduct a mutagenesis experiment of this type.[17]

The Russells' "work already well underway" as described by the Committee was obviously their detailed PNAS paper.[3] That paper obscured the critical issue by instead using the following complex sentence[3] (boldface type for emphasis is mine):

Singleton whole-body spontaneous **mutants** could trace to mutations in the cell lineage ancestral to parental germ cells (see above), or **might have one of two other origins**: (*i*) as *m*/*m**///m/+ mosaics in which, by chance, only the *m*/*m** blastomeres contributed to the embryo, or (*ii*) **as offspring of a** +/*m**///+/+ ***masked*** 50:50 **mosaic that produced too small a sibship to reveal a cluster**.

Reading only the words in boldface type reveals that this statement is really no more than a translation that admits to the same problem. In my opinion, the same 2 sentences could accurately and more clearly be translated as follows: It is neither reasonable nor practical to think that experimental data could be used to provide a meaningful estimate of the spontaneous specific-locus mutation frequency per generation.

Yet, the Russells' solution to the problem was to present massive amounts of experimental data—involving almost 3 million progeny—to which 2 alternative complex analyses were applied. Both of their methods involve much subjectivity and ample opportunity for misclassification. In stark contrast, my approach was to build Lee's elegant hypothesis for the origin of such clusters into my computer program for simulating specific-locus experiments. My simulations involved 57.4 million progeny, and the output from my program indicated whether or not every mutant was derived from a masked mosaic regardless of sibship size. By using their experimental approach, the Russells completely failed to address the concern of the Ethics Investigation Committee regarding small sibships.

More recent experimental results from Lee are fascinating in this regard. Around the time the Russells published their analysis in PNAS, Lee started an experiment in which males were exposed to bleomycin. When the results[31] were published in 2000 by Lee and others, it was noted that 2 clusters from males that were masked mosaics were identified among just 392 treated males. They concluded that the occurrence of those mutations was spontaneous in origin. Such a high probability of being a masked mosaic, which reduces to 1/196, suggests that the probability of 1/1500 that I used in my computer simulations may not have been nearly as high as it should have been. Also, our knowledge now that 2 FCGM clusters were found in a single experiment of the Russells in the mid-1950s further strengthens that view. I now think that the probability of 1/1050 suggested earlier in the Commentary as an alternative probability for use in my computer simulations would probably not be nearly high enough. Accordingly, the actual extent of the underestimation of the spontaneous mutation frequency per generation is probably a 10-fold increase or more. After learning about the bleomycin experiment, I immediately wondered how many mutants and total offspring were found for each of the 2 clusters and the loci at which the mutations occurred. Because I felt that I might be criticized if I contacted Lee directly to learn more, I called Mike Shelby, who was the last-named author on the paper. He had known about the investigation and was almost certainly the key person regarding funding for the experiment. Mike was concerned and told me that he would contact Lee. Soon afterward, I received a phone call from Hunsicker who assured me that Lee would provide me with the details as soon as she had time. Lee never did.

Table 1. Spontaneously Arising Clusters of Specific-Locus Mutations Currently Known to Have Occurred in Male Mice at Oak Ridge National Laboratory in Mutation Experiments Before 1996.[5,a]

Group in Which It Was Found	Number of Offspring in Cluster	Sibship Size in Which Cluster Was Found	Locus	Year When Found
Control	90	402	*c*	1951
Control[b]	166	297	*d*	?
Control	17	391	*a*	1986
Experimental	199	787	*d*	1955
Experimental	4	72	*p*	1959
Experimental[b]	311	608	*se*	? (1977 or before)
Experimental	83	228	*a*	?
Experimental	29	325	*a*	?
Experimental	2	25	*a*	1957

[a]Fathers of these clusters are referred to as masked mosaics, as explained in the text.

[b]The Russells classified these 2 events as resulting, instead, from males that were heterozygotes although they admitted in 3 places in their 6-page paper[3] that they could have been masked mosaics. Indeed, Lee's hypothesis, which was modeled in my computer simulations,[4,5] predicts that mutant clusters produced by masked mosaics would sometimes constitute half of the progeny in a sibship.

Table 1 shows all 9 of the FCGM clusters arising in irradiated or control males at ORNL that had been reported in the literature by 1996. Those data are extracted from Table 1 in my second paper[5] on FCGM clusters. (That table provides many additional details in its footnotes.[5]) The footnote to Table 1 in the present paper points out that, in their PNAS paper[3], the Russells do not include 2 of the 9 clusters as FCGM clusters while admitting 3 times that they might actually be FCGM clusters. Interestingly, the Russells reported that: "For the six masked mosaics, the mean of the individual germ-line proportions that are mutant is 34%; if the two clusters assumed to result from heterozygosity were in fact produced by mosaics that, by chance, had a cell proportion at the extreme end of the binomial distribution, the mean for the eight is 52%."[3]

Thus, the Russells found a better fit to Lee's model, which predicts a mean of 50%, when they considered the 2 clusters in question to be FCGM clusters. (They did not update their calculation when they added the ninth cluster in their correction in PNAS.[19]) No details have been made available on the 2 more recently reported clusters from the bleomycin experiment.[31] Notice the 4 question marks in the table for the years when clusters were found. In my memo to Lee that Ashdown held for 7 months before giving it to Lee, I specifically requested information on the year when each one of these clusters was found. Lee refused to provide that information. It appears that the Russells considered such information, as well as knowledge of the specific experiments in which such clusters occurred, to be proprietary. Because the Russells never took into consideration the problem related to small sibships, as the Ethics

Investigation Committee said they should, it is my opinion that the Committee was unwise to trust the Russells (instead of independent scientists) to do the mammoth task of reexamining the Russells' data. The Ethics Investigation Committee[21] noted that "The contested records of the Russells were copied and put under lock and key." In my opinion, it now seems even more obvious than it did in 1996 that the Russells' records preserved by ORNL should be carefully reevaluated by independent scientists and then be made part of the public domain. Those computerized data could also then be evaluated for numerous other types of potentially valuable information, which the Russells agreed with me (for many years before the Dispute began) should be done someday.

I often think back to an exchange that I had with Bill shortly before I got my PhD. One of my fellow graduate students told me that some scientists in the Biology Division made fun of Bill behind his back. They said that he made his experiments way too big, often yielding *P* values much less than .001. As a result, they said his experiments were far more expensive than necessary. This comment bothered me, and I asked Bill about it, of course being careful to phrase it in a milder way. Bill responded by saying, as best I can recall: "Paul, you and I have a special responsibility when conducting specific-locus experiments. Not only are the results of our experiments used to estimate the hereditary risk of radiation to people, but the experiments are so expensive that there is almost no chance that they will ever be repeated. Thus, we must make our experiments large enough to be certain that our conclusions are correct." I was completely satisfied by Bill's response. Now, looking back, his statement is deeply disturbing.

In my opinion, the Russells unjustifiably covered up an extremely significant repeating complication in their experiments. That action has had many harmful ramifications. It also seems reasonable to think that the Russells might not have had such successful careers if they had, in the 1950s instead of the 1990s, revealed this complication in the supposedly simple and straightforward specific-locus test that they, to a large extent, built their careers around. Some of their competitors were undoubtedly adversely affected by their success. It is a strange feeling to realize that had their careers been harmed by revealing the complication, I almost certainly never would have had such an exciting research career, and I never would have gone to Oak Ridge or met my wife there and have my 2 daughters and 6 grandchildren. It is also chilling to think about how the existence of the Russells' secret (which they could not even share with me as Bill's only PhD student) put my career in serious jeopardy for decades. My relationship with the Russells certainly did not play out in the way that I had hoped; however, I am thankful that I had the chance to do many exciting experiments and that I was able to bring to light a secret that the Russells managed to keep for almost half a century.

It should be noted that this commentary raises no new charges regarding the actions of the Russells beyond the issues considered by the Ethics Investigation Committee.[21] I will gladly share that Committee's report[21] with anyone who wants to see it. The related, and subsequent, finding related to bleomycin highlights the need to know much more about the complication considered by the Ethics Investigation Committee. This commentary represents my historical recounting of this episode, and the book that I am writing will provide much more detail. The Russells never denied the existence of any of the FCGM clusters that I revealed in their data. In my opinion, the discovery of numerous FCGM clusters is one of the most important discoveries by the Russells, and Lee's hypothesis to explain their occurrence may be the most important accomplishment of her remarkable career. It is unfortunate that almost all of the data showing the importance of this finding were only revealed to other scientists so late in the Russells' and my research careers.

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