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Review

How self-interest and deception led to the adoption of the linear non-threshold dose response (LNT) model for cancer risk assessment

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ABSTRACT

This paper clarifies scientific contributions and deceptive/self-serving decisions of William L. Russell and Liane Russell that led to the adoption of the linear non-threshold (LNT) model for cancer risk assessment by the US EPA. By deliberately failing to report an extremely large cluster of mutations in the control group of their first experiment, and thereby greatly suppressing its mutation rate, the Russells incorrectly claimed that the male mouse was 15-fold more susceptible to ionizing-radiation-induced gene mutations as compared with fruit flies. This self-serving error not only propelled their research program into one of great prominence, but it also promoted the LNT-based doubling dose (DD) concept in radiation genetics/cancer risk assessment, by the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel (1956). The DD concept became a central element in their recommendation that regulatory agencies switch from a threshold to an LNT model. This error occurred because of a decision by W. Russell not to report that a large cluster of control group mutations found in an experiment for which preliminary results were reported in 1951. This failure to report that cluster and similar clusters continued throughout the careers of the Russells, resulting in massive overestimation of low dose radiation risks supporting the LNT. The Russell database and the repeated claim that those data show that there is no threshold dose rate for mutation in irradiated mouse stem-cell spermatogonia, have provided mechanistic validation supporting the epidemiological LNT hypothesis for radiation-induced leukemias and cancers. This reanalysis supports the threshold model for both males and females, thereby rebutting epidemiological extrapolations from the NAS and EPA claiming support for the LNT hypothesis for cancer risk assessment. The implications of the Russell errors/deceptions, how/why they occurred, and their impact upon society are enormous and need to be addressed by scientific/regulatory agencies, affecting regulatory and litigation activities.

1. Introduction

The role of the research of William and Liane Russell in radiation genetics and its application to genetics and cancer research has been substantial, spanning more than six decades, from 1947 to 2009. During this period, they revolutionized the field of radiation genetics from one that was dominated by the use of the *Drosophila* model as led by Hermann J. Muller to the use of the mouse model. The introduction of a model with a highly novel genetic mutation approach that would require massive numbers of mice was a controversial and risky proposition that needed to prove its scientific value and financial investment. It was such a massive effort that their approach could only be applied at a very unique federal government laboratory, Oak Ridge National Laboratory (ORNL), creating a one-of-a-kind facility for deeply focused mouse genetics research with application to radiation biology and risk assessment. The research of the Russells would seriously challenge the dominance of the *Drosophila* model for risk assessment, claiming the mouse to be some 15-fold more sensitive than the fruit fly (Alexander, 1954; Russell, 1956), as well as being the first research to demonstrate the occurrence of repair of genetic damage by dose rate studies (Russell et al., 1958). Those experiments provided novel mechanistic insights that would become of profound value to the broader epidemiological community, which was highly dependent upon such research that could test its dose response hypotheses at a level of detail and confirmation that population studies could not hope to achieve.

Many national and international advisory committees and regulatory

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agencies worldwide came to rely upon the findings of the Russells, especially with respect to hereditary and cancer risk assessment. In fact, the reach of the Russell research is a long one, impacting major risk assessment recommendations starting with the US NAS BEAR I Genetics Panel in 1956 for the adoption of LNT and its reaffirmation in 1972 by the Biological Effects of Ionizing Radiation (BEIR) I Committee and in subsequent editions of the BEIR Committees to the present time. Thus, the major and risky investment in 1947 by ORNL's Alexander Hollaender in W. Russell's specific-locus test (SLT) proposal for studying induction of mutations in mice has been seen as a major scientific success story, impacting how the world's regulatory agencies address the issue of radiation and chemical cancer risk assessment. The current paper, however, challenges this story in fundamental ways. It shows that the Russells profoundly influenced the US and world regulatory agencies through a series of incorrect conclusions, due to fundamental distortions of the scientific record, that have resulted in grossly incorrect risk assessment judgments and exposure standards and a massive waste of public resources at multiple levels of society that continues in a multiplicative metastatic-like fashion to the present time. The consequences of these actions are extensive and therefore beyond the scope of the present paper.

This is a story of science, mistakes that were made, mistakes that were hidden, unbridled self-interest, poor administrative oversight at ORNL, failure of the peer review process, and failures of repeated NAS BEIR Committees and EPA and other leading governmental agencies and advisory groups to probe deeply into the hidden Russell story. As a result, it has become hard to separate the world class research contributions that the Russells legitimately made from their self-serving hidden agenda/errors that corrupted scientific understandings, as well as regulatory risk assessment principles and practices. This paper tells this story with the goal of showing that the Russells' actions led to the adoption of undetected major errors in cancer risk assessment that came to direct NAS BEIR Committee recommendations, EPA decisions/activities and those of most other countries. This story must start with some background about W. Russell's approach for studying the induction of gene mutations in mice, which he first proposed in 1947, after which he and his wife, Liane, were hired by the Biology Division of ORNL.

2. The specific-locus test (SLT) in mice: a procedure whereby recessive mutations are easily and accurately recognized by observation of distinct phenotypes in the first generation

The SLT in mice, which was developed by William and Liane Russell, measures the frequencies of mutations to recessive alleles at seven different genes (Russell, 1951). Mice that are homozygous for the wildtype alleles at all seven genes to be tested are exposed to mutagens. (In each case, the wild-type allele is dominant to any recessive allele at the same gene [locus].) These mice, often referred to as being H males or females,[1] have agouti-colored fur with black eyes and normal-sized outer ears, and they are mated with animals from a tester stock (T-stock) that is homozygous for well characterized recessive mutations at these same seven genes, which make them have white fur with pink eyes and short outer ears. Progeny of each litter can be accurately classified for any of these effects by rapid observation by the time they reach 17 days of age. If none of the progeny received a recessive mutation at one of these genes from the wildtype parent, all of them have normal (wildtype) fur color, black eyes, and outer ears of normal size. However, if one (or more) received a mutation at one of the seven genes, its markedly different appearance reveals the gene at which the mutation occurred. The different coat color shows, by its appearance, which one of six coat color genes is likely to have mutated. Similarly, the presence of short outer ears reveals a mutation at the seventh gene that is tested. When mutation is being studied in germ cells of males, H males are mated with T-stock females, and when mutation is being studied in germ cells of females, H females are mated with T-stock males. In both instances, experimental and control mutation frequencies are calculated by dividing the total number of mutant offspring by the total number of offspring observed. Mutation frequencies were often divided by seven so that they could be expressed as an average per locus for the seven loci. Induced mutation frequencies were calculated by subtracting the control (spontaneous) mutation rate from the experimental one. While there was a strong desire to know how much mutational damage might occur from induction of dominant mutations in first-generation (F_1) offspring, there was no reliable method for collecting such information at that time. It was thought that recessive mutations would be easier to study, and W. Russell's SLT was unique among methods used to study mutagenesis in mice because recessive mutations could be detected already in the first generation.

Because of the ability to detect the presence of mutations at specific genes by quick observation, and because of the extensive federal support of the Russells' program at ORNL from 1947 to 2009, massive amounts of data were collected in experiments that explored different physical and biological variables. As a result, the SLT results at ORNL have provided most of what is known about the induction of gene mutations (and of small gene deficiencies involving them) by radiations and chemicals in mammals. In 1970 it was estimated that 5 million mice had been used during the first 22 years of W. Russell's experiments (Congress of the United States, 1970). The stocks required for the SLT were shared with a laboratory at Harwell, England, where additional findings were made regarding radiation effects. Later the same stocks from ORNL were shared with a laboratory in Neuherberg, West Germany, by which time most attention using the SLT had shifted to chemical mutagenesis. A summary of the impact of the research in the Mouse House was given by L. Russell (Russell, 2013).

W. Russell had major participation with committees involved in estimating the health effects of exposure to ionizing radiations, including BEAR and BEIR Committees and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).[2] While mice were also raised in the Mouse House for use in other types of research and to support other techniques for studying induction of mutations, the overwhelming majority were raised to support the SLT research. As described in L. Russell's (2013) "brief history", discoveries important to basic genetics and developmental biology, and not just to mutagenesis, also resulted from this program.

3. The cluster problem

In 1995 Paul Selby disclosed to the US Department of Energy (DOE) that the Russells had observed numerous large clusters of gene mutations in experiments on males in the SLT, starting with their first experiment and continuing throughout their decades-long studies. The circumstances that led to this disclosure and the DOE mandated investigation that followed have been described in considerable detail elsewhere (Selby, 2020). The occurrence, magnitude and significance of these clusters of gene mutations in experiments on males was not reported by the Russells in the scientific literature and remained unknown or hidden from their peers until they were forced to reveal some of this information in 1996 (Russell and Russell, 1996). The question is why the Russells did not share these surprising, but substantial and challenging, findings within the published literature nor with colleagues at ORNL or other potential collaborators who were working with the SLT. To make the matter more complex, L. Russell was interested in understanding the

[1] The letter H stands for hybrid, and these mice are F_1 hybrids produced by crossing males of the C3H or C3Hf inbred strain with females of the 101 inbred strain.

[2] Both L. Russell and Paul Selby served along with W. Russell and others on the BEIR III Committee; Selby succeeded W. Russell on the Delegation of the USA to UNSCEAR and continued in that role for 21 years.

underlying biological mechanism that led to the large clusters of gene mutations (Russell, 1964). In her write up, she decoupled her proposed biological mechanism from the finding of large clusters of gene mutations by not disclosing any evidence that such clusters had been found in W. Russell's SLT experiments.[3] The answer as to why she decided not to reveal that any of her hypothesized clusters of whole-body mutations had been found in those same experiments of W. Russell is unknown, of course, because she failed to address the matter.[4] One may raise the issue that the unexpected occurrence of large clusters of gene mutations had the distinct potential to seriously undermine the utility of the SLT as a risk assessment tool/model right at the start of their careers at ORNL. It should be kept in mind that when those studies began it was thought that it might take many years, and perhaps a decade, to obtain meaningful results. However, by not revealing the cluster, W. Russell could already in 1951 claim that "Comparison with similar data from *Drosophila* shows a higher induced mutation rate in the mouse." Soon he would often claim that the induced mutation rate in mouse spermatogonia was 15-fold higher than in the fruit fly (Russell, 1956).

Thus, from 1951 until 1995, nearly a half century, the Russells successfully disguised the occurrence of such clusters of gene mutations in their SLT experiments on male mice. However, this issue became a cause of concern to Selby in November 1994 when he realized that a large unreported cluster in an experimental group from 1955 almost certainly represented the same type of cluster that L. Russell had predicted in her 1964 paper. He realized this when he saw the data on that cluster while computerizing the W. Russell SLT data from many of his radiation experiments on males at the request of the Russells (Selby, 2020). This troubling discovery, along with his awareness of (a) another unreported cluster of gene mutations in a control group of a chemical mutagenesis experiment on male mice by W. Russell in 1986 and (b) the two papers written by L. Russell (1964, 1979) on the mechanism causing large clusters, led Selby to report these research anomalies to DOE authorities. He was encouraged by DOE to search for more evidence of unreported clusters of gene mutations in the Russell SLT database. This subsequent investigation by Selby yielded highly important findings going back to the 1951 study in which a single male in the concurrent control produced a cluster of 90 offspring with the same mutation among the total of 402 progeny that he sired during his entire life, and it revealed that the cluster problem was much worse than Selby had imagined when he first alerted the DOE. These revelations led to a major hearing under the direction of the DOE. The external Expert Panel of the DOE determined that the Russells had made a serious error in excluding the clusters of gene mutations and needed to correct their historical findings (Russell and Russell, 1996, 1997). This also implied that all of the Russell ORNL-based findings and their applications to the field of risk assessment should also be re-examined and appropriately addressed. The panel also asked Selby to publish his own corrections of the results from the Russells' failure to include the gene mutation cluster data (Selby, 1998a, 1998b). The Selby-Russell dispute has been discussed in detail by Selby (2020). The net result of the DOE Expert Panel investigative process is that the Russells acknowledged an error of 120 %[5] in estimates from their data of the spontaneous mutation rate per generation, while Selby (1998a, 1998b) argued that the Russell correction, as major as it was, was still a significant underestimation of their error. Prior to assessing the risk assessment implications of the Russells' actions for cancer risk assessment and related issues, a brief summary of the mechanism proposed by L. Russell will be provided.

4. Gene mutation clusters: two types/two mechanisms

4.1. Clusters of gene mutations produced by masked mosaics

The occurrence of more than one mutant of the same type among the total offspring produced throughout the lifetime of an H parent in an SLT experiment is referred to as a cluster, and that total number of offspring produced is referred to as the sibship size. It is important to realize that each such cluster includes all instances of the same mutation being found among all offspring in a sibship, which often means that many of the numerous litters sired by one male, for example, include no occurrences or only one occurrence of the same mutation that is present in all mice in the cluster. There is no way to tell from the appearance of the H parent that it will produce a cluster. Fig. 1 shows how the offspring from successive matings of an H male reveal the presence of a cluster, and the example shown is a "large cluster" with approximately the same fraction of the offspring included in the cluster as was found in that first cluster by W. Russell in 1951. The example shown is a mutation at the *pink-eyed dilution* locus.[6]

One of the main biological variables of interest concerns the particular reproductive cell (or germ cell) stage that is being tested. Some of those stages (stem-cell spermatogonia and primary oocytes) last for long periods of time (years in male mice and many months in female mice), which greatly increases their importance for hereditary risk estimation.

L. Russell's hypothesis (Russell, 1964, 1979) states that a spontaneous mutation that will eventually result in a cluster of whole-body mutants begins as a mutation in a single strand of a chromosome during the "perigametic interval" (this interval, which was first named as such in the Russells' 1996 paper, was defined by them as being "subsequent to the last premeiotic mitosis and before the first postmeiotic one of a parental genome"). **That is, the mutation that is present in every offspring of such a cluster of whole-body mutations found in an SLT**

[3] L. Russell's proposed mechanism was based almost exclusively on the rare offspring found in the SLT that had patches of light fur or mottling for which she had collected much data from breeding tests. According to her hypothesis, the mice with patches or mottling, which were offspring scored in the SLT, had a new spontaneous mutation already present when they were at the two-cell stage of development. According to her hypothesis, if the same event occurred one generation earlier, the affected mouse, while having a wildtype phenotype, would produce clusters of whole-body mutations when used as the H parent in the SLT. She did mention three mice that produced large clusters of whole-body mutations to support her hypothesis, but she gave no indication that those clusters were found in W. Russell's SLT experiments (Russell, 1964).

[4] Indeed, in 1963 W. Russell (Russell, 1963) reported the extreme complication caused by finding such a large cluster in his female control. He made no mention of finding similar large clusters in his previous SLT experiments on males (including one in the control group of his very first experiment), even though those clusters would have similarly complicated data interpretation. Also, in her 1964 paper presenting her hypothesis, L. Russell did not mention the large cluster in W. Russell's female control that obviously supported her hypothesis.

[5] That is, they stated that previous estimates based on their data of the spontaneous mutation rate per generation, which is needed, for example, to apply the DD method of hereditary risk estimation, should be multiplied by 2.2 to obtain the correct value. This statement is an admission that they had made an error of 120 % when estimating that mutation rate (i.e., {{2.2–1.0} × 100 %}). Accordingly, if all other parts of the risk calculation remained the same, their failure to report the clusters led to overestimation of hereditary risk by 120 %.

[6] The normal procedure (with only rare exceptions) was to count only those mutants that lived until weaning age (at least 17 days). While mutants at 6 of the loci (all except those at the *short-ear* locus) can be identified earlier, it was realized that a small fraction of newborn baby mice die (or are lost for other reasons) prior to weaning, and it was assumed that this loss was similar between experimental and control groups. Thus, the mutation frequencies were based on the offspring present at the time of weaning, at which time all mice were counted and classified as to their sex and the presence of any abnormalities, with the results being recorded on a Weaning Tally Sheet.

Breeding Record of H male # 377 in the control group of SLT experiment ABC

Litter #	Male Parent	Female Parent	Birthdate	Male Offspring	Female Offspring
1	# 377	#468	August 10, 1964		
2	# 377	#468	September 1, 1964		
3	# 377	#468	September 22, 1964		
4	# 377	#468	October 15, 1964		
5	# 377	#765	November 10, 1964		
6	# 377	#899	December 5, 1964		
7	# 377	#765	December 9, 1965		
8	# 377	#765	January 10, 1965		
9	# 377	#899	February 2, 1965		

Fig. 1. This figure illustrates what one "large" cluster of gene mutations would look like in a hypothetical specific-locus experiment on male mice. The results are shown for H male # 377 in the control group. He was initially mated with T-stock female # 468. They produced four litters containing 10 males and nine females. By the second litter it was obvious that the same mutation had been found three times, and among the four litters there was one cluster of four mutants, all being at the *pink-eyed dilution* (*p*) locus. Because there was a desire to have a better idea of the percentage of offspring in the entire sibship that carried the same mutation, male # 377 was then paired with two additional females, and by late February of 1965, when all of the litters shown above had been weaned and carefully recorded on Weaning Tally Sheets, a cluster of 12 mutants had been recorded among the total of 44 offspring. The sibship size at this time was accordingly 44, and there were 33 "independent events". That is, every one of the 32 wild-type offspring represented a single stem-cell spermatogonium that had been evaluated for the presence of a mutation, and the 12 mutant offspring all represented the same single spontaneous mutational event arising by the mechanism proposed by L. Russell. Thus, there were 33 independent events. Although not shown above, male # 377 was then mated with numerous other T-stock females, and after all of his offspring were evaluated for mutations his total sibship size was 234 (i.e., all offspring sired by H male # 377), with 69 of them being *pink-eyed dilution* mutants. Those 69 represented 29 % of the progeny, which agrees closely with L. Russell's hypothesis that, on average, 25 % (between 0 and 50 %) of the progeny of a masked mosaic will result from a single cluster. According to the procedure of the Russells when finding such a cluster between 1951 and 1995, they would have kept this fascinating occurrence a secret.

experiment on males was already present in their H father when he was a zygote.[7] At the two-cell stage, this embryo has a mutation at one of the seven genes tested in the SLT. These cells divide rapidly to produce a population of cells in which half are heterozygous for the spontaneous mutation. About four days after conception, three cells are randomly selected from this population to form the inner cell mass (ICM). There are four possible combinations of cells in the ICMs regarding heterozygosity, with the extremes being none mutant and all mutant. These cells then divide rapidly. About four days later, five cells are randomly selected from the population to form the gonad primordium. There are six possible combinations of cells in the gonad primordium, with the extremes again being none mutant and all mutant. Depending on the outcome of the selections, the adult gonad ranges from being 0 to 100 % heterozygous for the 'new' spontaneous mutation. That H mouse is phenotypically wildtype. While L. Russell (1979) suggested that three cells and five cells are selected to form the ICM and gonad primordium, respectively, she emphasized that these numbers are not known with precision, and she suggested ranges of uncertainty. **The Russells in their 1996 paper characterized H parents that had such a "hidden" recessive gene mutation as "masked mosaics".** L. Russell hypothesized that the resultant distribution of the percentage of offspring of a masked mosaic H parent having the same mutation (and thus being in the cluster) would have a mean of approximately 25 %, with a broad distribution ranging from 0 to 50 %.

[7] As noted in L. Russell's (1964) paper, there is a possibility that such mutations can occur during the first-cleavage; the important point is that by the time the embryo consists of two cells, one of those cells is heterozygous for the new mutation. Thus, that male, which otherwise would be homozygous for the dominant wildtype gene at each locus, is actually a heterozygote for the new mutation at one of those loci, but **importantly** he is heterozygous in only one of his two cells then present.

4.2. "Putative" treatment-induced (TI) clusters of gene mutations

This other type of cluster can easily be confused with some of the spontaneous clusters occurring by the mechanism proposed by L. Russell. These other clusters, called treatment-induced (TI) clusters, result when a radiation/chemical treatment kills such a high proportion of stem-cell spermatogonia that the testes are rebuilt from so few stem-cell spermatogonia that, when the male mouse eventually becomes fertile again, two (or very rarely a few more) of the offspring trace back to the very same spermatogonium in which a specific-locus mutation was induced.[8] How the Russells addressed the occurrence of putative TI clusters is briefly summarized below, including their occurrence, when the experiments were conducted, how they impacted study findings and how they were handled differently from clusters arising from masked mosaics.

Occurrence of TI Clusters: The Russells (Russell and Russell, 1959) reported the finding of six TI clusters of two mutations each in their 600 R X-ray experiment (90 R/min) and one TI cluster of three mutations in their 1000 R X-ray experiment (90 R/min), and they stipulated that they included all of those mutations in their mutation frequencies.[9] The only other time (before 1996) when any TI clusters were mentioned in radiation experiments of the Russells was when it was reported (Russell et al., 1979a) that two clusters of two mutations each were found in an experiment on males treated with tritiated water. Five TI clusters of two were reported by Selby in 1972 that were found in his Ph.D. dissertation experiments[10] done under the direction of W. Russell, and those were handled in calculations in exactly the same way as the Russells had specified in 1959. Because only nine TI clusters had ever been mentioned in W. Russell's radiation experiments before the Russells' *Proceedings of the National Academy of Sciences* (PNAS) paper in 1996, it was surprising to read in that paper the following statement: "Of 26,167 sibships from irradiated males, 44 contained small specific-locus clusters. Among these 44 (found in 20 experiments that involved treatments producing spermatogonial killing, as indicated by temporary sterile periods), there were 41 clusters of two, two clusters of three, and one cluster of five mutants." The experiments in which the 44 "putative" TI clusters were found were not identified in the 1996 paper, and the crucial information regarding fertility data and sibship size that is needed to judge the strength of the evidence supporting the diagnosis of being TI was not presented. Although a much later paper (Russell and Hunsicker, 2012) identifies the experiments for a few of those TI clusters and mentions again the seven TI clusters reported in 1959, there is no information presently in the literature to reveal the experiments from which the remaining 32 clusters came that the Russells assumed to be TI clusters in 1996.

Perspective on both types of clusters: The DOE Panel insisted that the Russells publish data on the clusters of mutations produced by masked mosaics. Selby had not pointed out any problem to DOE regarding TI clusters because he had no idea that the Russells had not reported the great majority of them. Perhaps because the Russells realized that some of the clusters produced by masked mosaics for which the cluster size fell toward the lower end of the distribution from 0 to 50 % might easily be confused with TI clusters, they never revealed the presence of those many additional "putative" TI clusters. However, by doing so in 1996 they were revealing an additional major complication that they had hidden. They preferred to conclude that all 44 of those clusters were "putative" TI clusters and not clusters produced by masked mosaics.

With the exception of the experiment involving Cumming (Russell et al., 1979a), all mention of such TI clusters in their radiation experiments ceased after the mention of seven of them in the paper in 1959 until the 1996 PNAS paper published at the insistence of the Expert Panel (Russell and Russell, 1996). Also, there is the puzzle that W. Russell did publish details on one masked mosaic in 1963 (Russell, 1963) that being in the female control, without any mention of finding numerous clusters of that type in experiments on males.[11] That cluster in the female control greatly complicated his analyses of data in females.

5. The Russells' correction factor (CF) for the spontaneous mutation rate per generation

Based on the recommendations of the DOE external Expert Panel, the Russells (1996) provided a correction factor (CF) for masked mosaic mutations. By providing this CF, they were admitting that their previously reported spontaneous mutation rate per generation was only 45 % (i.e., $1 \div 2.2$) of what it should have been, which means that hereditary risk was overestimated by a factor of 2.2-fold (or 120 %).

The Russells' calculation of the CF of 2.2 was made as follows:

A = the recessive mutation rate per locus based on "singleton[12] whole-body mutants" per locus in SLT experiments on male mice = 6.64×10^{-6}.

B = the recessive mutation rate per locus based on "singleton whole-body mutants" per locus in SLT experiments on female mice = 1.60×10^{-6}.

[8] In most SLT experiments on males, the males are not paired-up (mated) with T-females until at least seven weeks after the mutagenic treatment to ensure that all mutation data relate to events in stem-cell spermatogonia. In a few experiments, however, matings began immediately after treatment so as to determine mutation rates in the various post-spermatogonial stages. Mature sperm are much more resistant to the killing effects of radiation and some chemical treatments. Thus, in experiments involving large doses of a mutagen, males are often initially fertile, followed by a sterile period, and they only become fertile again after the population of stem-cell spermatogonia recovers sufficiently.

[9] They also determined how many "independent events" had been found. For example, if there were 80 mutations found in a sibship that included two TI clusters of two, there would only be 78 independent events. W. Russell included all mutations when calculating mutation rates and probably in one-tailed statistical tests to determine if the increase over the historical control was statistically significant; however, he used the number of independent events when calculating confidence limits along with adjusting the number of offspring scored to, in the same example, [(78/80) × total sample size]; thus confidence limits would be based on 78 mutants divided by a slightly smaller sample size (Russell, 1972).

[10] In the SLT experiments on males that were part of Selby's (1972) dissertation research, male mice were irradiated with 300 R of X-rays (at a similar dose rate to what Russell had used for adults) when at the following ages: newborn (within 9 h after birth) or at 2, 4, 6, 8, 10, 14, 21, 28 or 35 days of age. Three clusters of two mutations each were found in the males irradiated when newborn, and two clusters of two mutations each were found in the males irradiated on day 21. All five clusters were considered to be TI clusters. By the time Selby finished those experiments in 1972, almost all of the radiation SLT experiments at ORNL had been completed, which means that the Russells were aware of most of the "putative" TI clusters that they never mentioned in publications until 1996. (See later in the same paragraph of the text for details.) There is now much reason to wonder if the two clusters of two mutations each found for day 21 by Selby were really TI clusters. It seems much more likely that they were spontaneous mutations that perhaps arose by some different mechanism that produces small clusters instead of the large clusters explained by Liane Russell's hypothesis. Knowing this and other information beyond the scope of this paper, there is good reason to wonder if many of the Russells' 44 mutations considered to be "putative" TI clusters might similarly have been clusters of spontaneous mutations.

[11] At the time in late 1994 when Selby realized that this was a serious problem, the Russells had never published that there was even one masked mosaic mouse in SLT experiments on males or that there was any complication regarding clusters in SLT experiments on males. Selby had no idea how many H males had been used in radiation experiments or what the sibship sizes were in many experiments. The only method that he could think of to address his concerns was computer simulation (Selby, 1998a, 1998b).

[12] In their 1996 paper (Russell and Russell, 1996) they wrote: "Singly occurring whole-body mutants will be referred to as singletons."

C = **contribution from gonadal mosaicism expressed per locus**[13] = 9.6×10^{-6}.

$$\text{Per} - \text{generation CF} = \frac{A + B + C}{A + B} = 2.17 = \text{rounds to } 2.2.$$

This CF is designated $CF_{G\ (R)}$ to show that it applies to the spontaneous mutation rate per generation (represented by G) and that it was the Russells' preferred method for use in deriving a CF of the two methods that they proposed. When it is applied, the spontaneous mutation rate per generation is 1.78×10^{-5} mutation per locus (i.e., $2.17 \times [A + B]$, which is the same as $[A + B + C]$).

The Russells also described how the **contribution from gonadal mosaicism expressed per locus** could be derived from the total number of masked mosaics identified among the 37,735 H males tested in their experiments, and their calculated value was 11.4×10^{-5} (the calculation as shown in their Table 5 was: "6/37,735 × 1/7 × 1/2"). By adapting their proposed method into our equation for calculating the CF above, the variables A and B remain the same, and the variables D, E, F and G are defined as follows:

D = total number of masked mosaics identified in all experiments using H males = 6*

*6 is the number of masked mosaics recognized in the Russells' Table 6 of their 1996 PNAS paper that was applied in their Table 5. We will start with that number.

E = total number of H males = 37,735. (This is an essential number for the calculation of CFs that was first made available in the Russells' 1996 PNAS paper.)

F = total number of loci at which clusters of whole-body mutants produced by masked mosaics have been found = 7

G = contribution from gonadal mosaicism of H males and females = $\frac{D}{(E \times F \times 2)}$

$$\text{Per} - \text{generation CF} = \frac{A + B + G}{A + B} = 2.378 = \text{rounds to } 2.4$$

This CF is designated $CF_{G\ (6\ MM)}$ with the subscript indicating that it is based on the frequency of masked mosaics of six among 37,735 H males. When it is applied, the spontaneous mutation rate per generation is 1.98×10^{-5} mutation per locus.

Because the Russells based their CF only on visible mosaics, an increase in the acknowledged number of masked mosaics would have no effect on their CF of 2.2 for the spontaneous mutation rate per generation. Our method, however, makes it straightforward to adjust for an increase in the number of acknowledged masked mosaics by simply changing the value of D. In 1997 the Russells (Russell and Russell, 1997) acknowledged a mistake in their 1996 paper and reported one additional masked mosaic male. The addition of that one masked mosaic male increases the CF to 2.6, which is designated $CF_{G\ (7\ MM)}$, and it will be used in the present paper as the minimal estimate of the CF_G. When it is applied, the spontaneous mutation rate per generation becomes 2.14 $\times 10^{-5}$ mutation per locus. It is important to realize that, because there are strong reasons to think that seven might be a considerable underestimate of the actual number of masked mosaics that existed among the 37,735 H males on which the Russells based their reevaluation, a much more likely CF_G would be substantially larger than our minimal estimate.[14]

6. Is there a threshold dose rate in male mice?

It now becomes important to evaluate the validity of W. Russell's frequent statement that there is no threshold dose rate for mutations in the stem-cell spermatogonia of male mice in view of the more realistic estimates presented above of the spontaneous mutation rate per generation. His conclusion that there is no threshold dose rate in males clearly had major, if not decisive, impact on the development of, and continuing support for, the LNT hypothesis (Calabrese, 2016a, 2016b).

According to the 1956 "Report to the Public" of the BEAR I Genetics Panel (NAS/NRC, 1956), each person receives 4.3 roentgens (R) of background radiation over a 30-year period. This estimate of background radiation, which refers to a mean estimate, is used here because it was employed by the BEAR I Genetics Panel that made crucial decisions regarding genetic risks of radiation. A dose of 4.3 R in 30 years is equivalent to a dose rate of 2.73×10^{-7} R/min.

Russell and Kelly (1982) published a statistical analysis of all experiments at ORNL and Harwell that tested effects of X-rays or gamma rays on mouse stem-cell spermatogonia. Their analysis included W. Russell's final two chronic experiments, including the one at the lowest dose rate of 0.0007 R/min (i.e., 2000–3000-fold greater than background). The equation for the line that fit all male data for what were considered chronic exposures (from 0.8 R/min to 0.0007 R/min) was $Y = 8.10 \times 10^{-6} + (7.32 \times 10^{-8})D$ with Y equal to the specific-locus mutation rate per locus and D being the dose in R. In their analysis, a mathematical model was used in which straight lines were fitted simultaneously to the acute and chronic data using the method of maximum likelihood. The lines were forced through the same Y intercept but not through the control point based on the reported mutation rate in the male control. Solving this equation for 4.3 R (i.e., background radiation) yields an experimental mutation rate of 8.41×10^{-6} mutations/locus (i.e., $Y = \{8.10 \times 10^{-6} + [(7.32 \times 10^{-8}) \times 4.3]\} = (8.10 \times 10^{-6} + 3.15 \times 10^{-7}) = 8.41 \times 10^{-6}$ mutations/locus).

[13] The figure of 9.6×10^{-6} is taken directly from Table 5 of the Russells' 1996 PNAS paper. It is based on their estimated frequency with which "visible specific-locus mosaics" were found in 1,842,410 offspring (experimental and control combined) from SLT experiments, which was 4.8×10^{-5}, and by making the assumption that mosaics could only be detected at five of the seven loci. $[(4.8 \times 10^{-5}) \div 5] = 9.6 \times 10^{-6}$. Mosaics were mice with mottling or patches of light fur. Uncertainties and assumptions associated with this estimate were discussed in their paper, but they argued that because it was the better of their two suggested estimates, they would only use it to derive their CF.

[14] It is important to understand the basis for the ½ in the Russells' equation of (6/37,735 × 1/7 × 1/2) for the contribution from gonadal mosaicism expressed per locus when based on masked mosaics, as it was explained on page 13076 of their 1996 PNAS paper. H males are produced by mating males of the C3H inbred strain with females of the 101 inbred strain. The spontaneous mutation that produces a masked mosaic could have come from either the C3H strain male or the 101 strain female, and because only one of those two specific genes from its parents ends up in each of the H males' offspring, the Russells included the ½ ("divided by 2") in their calculation. **They also assumed equal likelihood of occurrence of masked mosaics in the two sexes and strains.** The Russells provided 95 % confidence limits (shown in parentheses) for their estimates of the spontaneous mutation frequencies per locus resulting from visible mosaics and masked mosaics (all expressed $\times 10^{-5}$), with these being 9.6 (7.7, 11.7) and 11.4 (4.9 and 24.3), respectively. In their paper pointing out the existence of the seventh acknowledged masked mosaic male (Russell and Russell, 1997), they recalculated their estimate of the spontaneous mutation rate per locus resulting from masked mosaics (as based on masked mosaics) and its 95 % confidence limits (all expressed $\times 10^{-5}$) to 13.3 (6.2 and 26.1).

Before the problem was known regarding large clusters produced by masked mosaics, induced mutation rates were calculated by subtracting the control mutation rate from the experimental mutation rate. That procedure seemed logical because it was assumed that spontaneous and induced mutations all occurred as independent events, and if these mutations were only being evaluated at seven genes, those events would occur in an amazingly small fraction of the vast numbers of reproductive cells that exist in an animal before it produces its offspring. With those assumptions, it would be irrelevant to consider sibship size when collecting data to determine mutation rates. Accordingly, if a large experiment would be done, for example, such as the first SLT of W. Russell in which more than a 100,000 offspring were examined for mutants from male mice exposed to a large dose of X-rays and from the concurrent control, the experiment could be done without any concern about sibship size, and it would be a simple matter to determine the induced mutation rate. Simply subtract the control rate from the experimental one. As the number of experiments increased, each with its own concurrent control, the control groups were combined to produce the historical control. In 1962 Russell (Russell, 1962) published his historical control rate of 28 mutations in 531,000 offspring, and that estimate of the control rate seemed so precise and massive–was referred to as reliable–that there ceased to be any need to collect more concurrent control data in most experiments. Indeed, a revised historical control mutation rate was not published for the Russells' radiation experiments on males until 1996.[15]

Biology, however, turned out to be much more complex than the simple assumptions noted above upon which this idea of reliability was built. Now that it is known that, on average, one quarter of the offspring of masked mosaics carry the same mutation, it matters a great deal whether such a masked mosaic male has 1, 30, 100 or 500 offspring. Masked mosaic animals are rare—not because masked mosaicism is a rare event in general—but rather because it is an extremely rare event when a mutational assay only looks at seven genes. Thus, among the vast numbers of H males and females used in the Russells' SLT experiments to produce several million scored offspring, there have likely been only perhaps from 20 to 40 masked mosaics that were parents in the totality of their experiments. Because of the large sample sizes required in SLT experiments, the cost of doing the experiments per mouse observed for mutations decreases considerably when experiments are designed to have larger sibship sizes. Also, as the average number of offspring per litter (i.e., sibship size) increases, the chance of detecting clusters of mutations involving more than 5 % or so of the offspring in a sibship increases.

When mutations occur very rarely and sometimes in large clusters, decisions about sibship size take on immense importance for both experimental design and data analysis **because those spontaneous mutations are no longer occurring as independent events**. For our purposes here, we merely note that if mean sibship size would be about 70 and the total number of offspring scored for specific-locus mutations in a control group would be 100,000 (conditions that approximate those in W. Russell's first control group), and if the frequency of masked mosaics is 7/37,735, there would be only a 27 % chance that even one masked mosaic male would be among the H males fathering the offspring. However, if mean sibship size were instead 20, there would be a good chance (97 %) of finding one cluster, and it would likely include from 2 to 10 mutants. Numerous examples will be provided in a more technical paper (Selby and Calabrese in preparation) to better illustrate the impact of sibship size and other variables now that it is known that masked mosaicism cannot simply be ignored. It should be kept in mind that the overriding reason for conducting experiments in mice was to provide information relevant to hereditary risk in humans, which have small sibships—in many modern cultures averaging less than two. As a result, the way in which sibship size is handled when evaluating SLT data has taken on great importance. It is now obvious that calculation of induced mutation rates for radiation experiments by subtracting the historical control mutation rate from the experimental mutation rate greatly magnifies estimates of the risks to people from mutations induced by radiation exposure.[16]

In her "Response by L.B. Russell to Charges of Scientific Cover-Up" (Russell, 1995) that she submitted to the DOE external Expert Panel over half a year before that Panel had its hearing with the Russells, Selby and others in Oak Ridge, L. Russell clearly demonstrated that she, at least by late 1995, understood our argument that clusters produced by masked mosaics would occur vastly more often when sibship size is small. She wrote as follows:

> "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."

Based on her definition of what a sibship is, and her statement above, it is clear that L. Russell understood the serious complications in estimating and applying the spontaneous mutation rate per generation that arose because of their experimental design and the way in which they had reported their SLT data. There is no evidence that before 1996 she ever considered adjusting estimates of experimental and control mutation rates to make them apply to small sibships, as described briefly in this paper and extensively in our more detailed technical paper (Selby and Calabrese in preparation). The relevant sibship question is when did L. Russell as well as W. Russell come to appreciate the implications of sibship size and its risk assessment implications. It is now known that she was very confident in her 1995 answer, and we know that this is not a trivial question. Since the major studies with large sibships had been finalized long before by the Russells, it is not unlikely that this question was considered and decided upon by L. and W. Russell. What is known is that before 1996 they never published a paper addressing this topic in an attempt to "correct" the record. This strongly suggests that L. Russell knew about the problem and its experimental and risk assessment implications and that the Russells remained silent on this important issue. Because remaining silent would have sustained/preserved their scientific reputations, their doing so may be considered self-serving and consistent with their other deceptive practices.

To summarize regarding the significance of sibship size to the Russells' SLT data, the CF (if based on a reasonable estimate of the frequency of masked mosaic males) fully adjusts the background mutation rate to a sibship size of one. As explained in Appendix 1, that background rate applies to all sibship sizes under the conditions that all mutants are counted and that there are vast amounts of data for all sibship sizes. Because the CF must always be applied to derive an estimate of the background mutation rate that is meaningful, the only unbiased way to calculate a meaningful adjusted induced mutation rate is to apply the

[15] The historical control for the Russells' radiation experiments on males was not updated until 1996 (Russell and Russell, 1996), when it was revised by adding 16 mutations in 409,437 offspring, thereby bringing the mutation rate for the Russells' radiation historical control to 44 mutations in 940,937 offspring. In the same paper they added two additional mutations found in 99,817 offspring from controls that were concurrent with their chemical mutagenesis experiments to estimate that the historical control mutation rate for their combined radiation and chemical experiments in males is 46 mutations in 1,040,754 offspring.

[16] This ramification takes on additional importance because the DD, which is an essential part of the risk calculation in the DD method of hereditary risk estimation, is derived by dividing the spontaneous mutation rate per generation by the induced mutation rate per R. SLT data were the most important data for this calculation in many national and international reports.

appropriate adjustment to the experimental rate before the background rate is subtracted from it. That adjustment is defined and calculated in Appendix 1 and is termed the $P_{MM\ \#/L}$, with # indicating how many masked mosaic males were found in 37,735H males and L indicating that it is the rate per locus for the seven genes tested in the SLT. $P_{MM\ 7/L}$ was calculated to be 6.63×10^{-6} and is thus appropriate for comparisons to the background mutation rate calculated using the $CF_{G\ (7\ MM)}$ of 2.6. Each experimental rate thus contains (1) $P_{MM\ 7/L}$ (i.e., the spontaneous mutations resulting from masked mosaics), (2) singleton spontaneous mutations and (3) radiation-induced mutations.

While the sibship size issue is of considerable theoretical importance, it does not affect the interpretation of the Russell findings below because the conditions used in our assessment satisfy the requirement that the CF adjustment applies to all sibship sizes, as demonstrated in Appendix 1.

Before continuing with our analysis, it should be mentioned that, although the TI clusters relate to a more common problem (since there were 44 such events among the 37,735H males) than the one caused by masked mosaics, that complication likely biases experimental mutation rates only slightly higher. That complication will be dealt with in a later paper because it appears to be relatively minor in the present analysis. Readers should, however, be aware of the problem. One caveat, however, is that if several of the 44 TI clusters were actually spontaneous mutations produced by masked mosaics, the values of CF_G would increase significantly. The Russells in their 1996 PNAS paper admitted that some of the "putative" TI clusters might actually be clusters produced by masked mosaics.

Fig. 2 superimposes information from our analysis onto the figure published in the Russell and Kelly (1982) paper. The dark line that extends across the figure shows the background mutation rate calculated using the CF of 2.6. The dashed lines show the experimental mutation rates adjusted for the same fraction of total H males that are masked mosaics (i.e., 7/37,735). The way in which slopes were calculated is explained briefly in the caption and more explicitly in Appendix 1. As will be explained in Appendix 2, our method for adjusting the rate of occurrence of spontaneous mutations per generation [i.e., the $CF_{G\ (7\ MM)}$] is exactly the same as our method for adjusting experimental mutation rates. Our method converts those rates to what they would be if such mutations occurred as independent events. Thus, just as for singleton spontaneous mutations or radiation-induced mutation rates (e.g., the slope in the Russell-Kelly equation), the mutation rate for spontaneous mutations resulting from masked mosaics can be multiplied by the planned sample size to estimate the number of mutants expected of that type. As demonstrated in the appendices, although the adjusted CF and experimental mutation rates were calculated for a sibship size of one, they apply to all sibship sizes.

Adjusted induced mutation rates were calculated (by subtracting the adjusted background rate from the adjusted experimental mutation rate) for doses of chronic gamma radiation of 4.3, 10, 25, 50 … 90, 95, 100 and 300 R. Those rates were negative (suggesting no induction of mutations) for all doses through 90 R. Thus, as shown by the intersection of the dark line and dashed line in Fig. 2 at ca. 90 R, when the adjusted rates are considered there appears to be a threshold at ca. 100 R in the male that contradicts the LNT interpretation of Russell (1972, 1973) and BEIR (NAS/NRC, 1972). It is important to emphasize that these findings appear to be in remarkably close qualitative and quantitative agreement with mega-analysis epidemiological findings that support a threshold dose response (Ricci and Tharmalingam, 2019), thereby providing laboratory-based support of a leading epidemiological hypothesis for a threshold dose response estimate for radiation-induced cancer risks.

The slight potential importance of any radiation-induced mutations at these smaller doses is shown by the comparative numbers of the three categories of mutations in the adjusted experimental mutation rate. At 4.3 R for CF 2.6, and assuming that each hypothetical SLT experiment had 60,000 scored offspring, the total number of mutants expected in the experimental group would be 6.32 (with values shown to two places beyond the decimal point). Of these, the numbers of mutants expected to be radiation-induced, spontaneous "singleton" mutations and spontaneous mutations produced by masked mosaics would be 0.13, 3.40 and 2.78, respectively. The first two of these three values were calculated directly from the Russell-Kelly equation for the slope for chronic irradiation, and the third term applies the $P_{MM\ 7/L.}$ (i.e., $[6.63 \times 10^{-6} \times 60{,}000$ offspring $\times$ 7 loci] = 2.78 mutants). These findings predict that even if one were to use the now unjustified assumption of an LNT relationship, this analysis demonstrates that the estimate of any radiation effect is remarkably small.

It seems likely that if W. Russell had shared his actual data with the

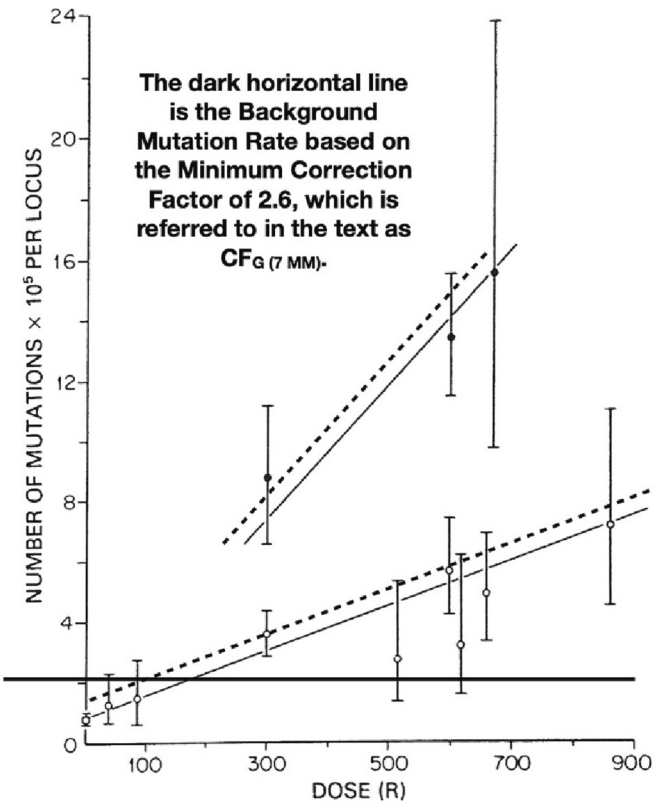

Fig. 2. With the exception of the dark line extending horizontally across the graph, the dashed lines, and the text inserted, this is the figure presented in the Russell and Kelly paper (1982) that shows their maximum likelihood plots, as described in the text, for specific-locus mutation rates in male mice irradiated with low-LET ionizing radiation delivered at acute (upper slope) and chronic (lower slope) dose rates. The long dark horizontal line shows the spontaneous mutation rate per generation of 2.14×10^{-5} mutation per locus that was calculated using the CF designated $CF_{G\ (7\ MM)}$ in the text. The slopes of the lower and upper solid lines are based on 12 experiments (involving a total of 593,911 offspring) and three experiments (involving 196,012 offspring), respectively. Data points for each dose were combined in the figure but kept separate in the computations. Error bars represent 90 % confidence intervals. The dashed lines show the adjusted slopes based on the presence of seven masked mosaics among 37,735H males. The equations defining the dashed lines have the same slopes as the solid lines, but the new Y-intercept of both dashed lines is the sum of the original Y-intercept and an estimate of the spontaneous mutation rate produced by masked mosaics in those experiments (see Appendix 1). Adjusted induced mutation rates were calculated by subtracting the background mutation rate based on the CF of 2.6 from the corresponding adjusted experimental mutation rates. The methods of calculating the adjusted background and adjusted experimental mutation rates convert those mutation rates to what they would be if such mutations occurred as independent events. Although our calculations assumed a sibship size of 1, they apply to all sibship sizes as demonstrated in Appendix 1. W. Russell did not extend the lines for the acute exposures to the ordinate because of the expectation that there would be repair at the high dose rates once the total dose had decreased to a certain (but unknown) dose.

BEIR I (NAS/NRC, 1972) Committee, rather than keeping the complication related to masked mosaics hidden, his findings would have been viewed as being strongly supportive of a threshold interpretation for both male and female mice. In fact, his adjusted data suggest the distinct possibility of a hormetic dose response in both sexes, with perhaps a stronger one in females. The implications of this data suppression by the Russells in retrospect were enormous because they improperly led to the LNT recommendation by the BEIR I (NAS/NRC, 1972) Committee and its later adoption by US EPA (1977), setting in place a major risk assessment policy for cancer risk assessment that affected all US health-related agencies and programs as well as in most countries and international advisory organizations (e.g. NATO countries, Safe Drinking Water Committee, International Commission on Radiological Protection (ICRP), United Nations Educational, Scientific and Cultural Organization (UNESCO), National Council on Radiation Protection (NCRP) and others). As noted, the data suppression was revealed in the discoveries nearly 25 years later by Paul Selby and in the decision of the DOE Expert Panel to force the Russells to finally attempt to correct the scientific record. Yet, despite the correction of the record, no follow up activity was undertaken by either NAS BEIR Committees, EPA, or other governmental/advisory groups and they never even acknowledged this major scientific concession of the Russells and its potential impact on risk assessment.

7. William Russell's views on threshold

In 1970 W. Russell made a presentation at the 14th International Congress of Radiation at Evian, France. In that presentation he stated that the original estimates of genetic risks of the BEAR I Genetic Panel (NAS/NRC, 1956) applied assumptions that radiation-induced gene mutation frequencies in *Drosophila* can be qualitatively and quantitatively extrapolated to humans. Based on these assumptions, there were a number of fundamental risk assessment beliefs (which Russell called "general principles of radiation genetics…applicable to mammals, including man") upon which genetic and cancer risk assessments were based. Russell (1973) indicated that these beliefs were that "(1) Gene mutation rate is directly proportional to radiation dose. (2) Gene mutation rate is independent of radiation dose rate. (3) Gene mutation rate is independent of dose fractionation. (4) There is no repair of gene mutational damage. (5) There is no threshold dose rate of radiation below which no genetic damage occurs. (6) There is no recovery from mutation with time after irradiation." He then stated that his research on the effects of ionizing radiation on mice within the SLT protocol involving several million mice led him to the conclusion that the above basic assumptions are not valid and that each of the six so-called general principles are not relevant to mouse spermatogonia and/or oocytes.

These dramatic conclusions of Russell, which were offered at about the same time the BEIR I Committee began meeting, should have had a profound effect on the conclusions of the BEIR I Committee that was created in 1970 and continued until 1972. During this same period, Spalding et al. (1969) at another US DOE research institute reported the results of studies in which males of an inbred mouse strain were exposed to 200 rads of whole-body radiation (50 rads/min) per generation for 45 consecutive generations in order to assess potential adverse effects, in an effort to address concerns of possibly false negative gene mutation findings found after exposures of only the first several generations. These researchers found no effects on numerous traits including viability, fertility, growth, numerous visible abnormalities and lifetime survival curves. This seemingly remarkable lack of radiation-induced effects was then expanded further and carried out to 82 generations with no demonstrable negative effects (Spalding et al., 1981).

An additional consideration at the time of the BEIR I Committee (NAS/NRC, 1972) is that they noted that background radiation was estimated to induce less than one mutation event per cell per day, whereas dose rates inducing cancerous effects in humans—as shown in epidemiological studies—induced cellular mutations at a rate that is greater than 2600-fold/cell/second. The background radiation dose rate was approximately one hundred million to one billon times lower than the higher dose rates that adversely affected humans (e.g., leading to cancer occurrence) (p. 88). These rather dramatic findings led the BEIR I Committee to reject the "scientific" belief in linearity at low dose; however, it continued to apply linearity based on a type of Precautionary Principle. **In fact, the BEIR I Committee (NAS/NRC, 1972) stated that the use of the LNT for risk assessment and management needed to be explained properly in order "to prevent [its] acceptance as scientific dogma." (page 97). Thus, the adoption of the LNT for radiation, when said to be based on the recommendations of the BEIR I Committee, was not based upon a scientific determination.**

Despite their acknowledging the limitations of the LNT model for cancer risk assessment, the deceptive science of the Russells was able to still reaffirm the important scientific standing for the LNT and, in the final analysis, it made all the difference. As seen on page 65, the BEIR I (NAS/NRC, 1972) Committee stated: "The finding of a dose-rate effect for mutation induction in mouse spermatogonia and oocytes raised anew the question of whether there might be a threshold dose or dose rate below which all mutational damage would be repaired. Exploration of a range of dose rates provides no evidence of a threshold dose rate for mutation induction in mouse spermatogonia…**Therefore, we shall make the prudent assumptions that there is no threshold dose rate in the male and that the dose response at low dose rates is linear."** (emphasis added). Thus, the decision to "go" linear rested with the mouse SLT data analyzed in the present paper and depended on Russell's suppression of the key data on the occurrence of large clusters of spontaneous mutations. Now, in the absence of Muller, William Russell had become the dominant scientific force supporting the LNT model.

The BEIR I Committee's error (with W. Russell being a member), caused by its not having full knowledge of the data being hidden by the Russells, led to serious errors by other advisory groups and regulatory agencies that were influenced by the BEIR I Committee's assessment. Of considerable importance, the 1975 U.S. EPA radiation risk assessment policy was derived directly from the BEIR I (NAS/NRC, 1972) report. In a 1977 extension (US EPA, 1977) of the 1975 policy statement, the US EPA explicitly addressed the issue of dose-rate: "EPA uses primarily the recommendations of the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR) as expressed in the November 1972 report to arrive at dose to health conversion factors."

Chemical mutagens and carcinogens were also tested using the SLT. For example, that method was used to test five suspected chemical mutagens (i.e. four methane sulfonates: methyl, ethyl, n-propyl and isopropyl; and Myleran). Russell (1972) reported that mutational responses of the spermatogonia from these chemicals were not statistically different from the control group. However, these agents were mutagenic in short-term mutagenicity assays. In a 1984 review following much more extensive testing of chemicals, Russell (1984) stated that all 11 environmental mutagens that had been studied up to that time showed no significant induction of SLT mutations in the mouse stem-cell spermatogonia. The total experimental data for the 11 mutagens was only 12 mutations in nearly 300,000 offspring, which represented a point estimate of the mutation rate less than that of Russell's SLT historical control. The generally negative results were interpreted by Russell to be best accounted for by the capacity of stem-cell spermatogonia to repair induced genetic damage. In fact, Russell urged "that committees involved in genetic risk estimation give more weight than they have in the past to the likelihood that negative findings in mouse stem cell spermatogonia and arrested oocytes may be a result of repair.", a suggestion that has been largely ignored. Even in the case of the ethylnitrosourea (ENU), which was shown to be a supermutagen in the SLT by Russell et al. (1979b), Russell (Russell et al., 1982) noted that most mutations were repaired as long as the dose was not excessive, overwhelming repair capacities (Calabrese, 2016a, 2016b). The above conclusions regarding the inability of the SLT to detect any hint of induction of mutations by many chemicals that clearly induce mutations in short

term tests are much more remarkable when it is realized that the historical control mutation rate to which those chemicals were compared is now known to have been much smaller than the revised spontaneous mutation rate per generation. Because the data with ENU and a few other chemicals show that the SLT is sometimes extremely effective for detecting induction of recessive mutations by chemicals in mammals, the above findings by the Russells provide much reason to wonder about the wisdom of relying on some of the short-term tests that are presently being used to try to determine if humans might be at risk.

This perspective on W. Russell reveals a highly conflicted person, one trying to share his science (e.g., dose-rate effects and numerous other important discoveries) while hiding the limitations of his model. In fact, more than any other contemporary radiation geneticist, he challenged the leaders in the field to acknowledge major limitations of the LNT model for mutation and cancer risk assessment. Moreover, Russell directly confronted Muller on this issue at an ICRP meeting in 1963, but to no avail (Calabrese, 2016a, 2016b). It seems clear that Russell waited for the death of Muller to make his profound challenge to the field as in the 1970 presentation at Evian, and he may possibly have been persuasive in getting the BEIR I Committee to acknowledge that LNT should not be accepted as "scientific dogma". However, at the same time, Russell was trying to keep his mouse SLT program funded in the face of many challenges such as the competition for support from those using models that were much less expensive and far more sensitive (e.g., Ames Assay and other tests). In the end, it appears that for Russell it was more important to keep his funding and research program alive and robust at the expense of not challenging the LNT concept and not sharing his complicated findings regarding clusters of mutations with the scientific community.

8. Russell's claim that mice are 15-fold more sensitive to induction of mutations than *Drosophila*: mistake or self-interest?

In Russell's first SLT experiment, male mice were given a dose of 600 R X-rays at a dose rate of approximately 90 R/min, and there was an unexposed control group. All progeny used to estimate the mutation rate in stem-cell spermatogonia were conceived after the prolonged sterile period. That is the experiment in which the large cluster was found early in 1951 in the control group that has been discussed in several places in the present paper. The initial findings, published in 1951 (Russell, 1951), showed "53–54" specific-locus mutations among 48,007 offspring in the radiation-exposed experimental group, while only two mutations were reported in the control group for which there were of 37,868 offspring. The final results were not published until 1959, with the mutation frequencies being reported as 111/119,326 and 6/106,408, in the experimental and control groups, respectively.

Those initial results from the massive first experiment undertaken by the Russells at ORNL were of considerable interest to national and international advisory committees when estimating hereditary risks of radiation in humans. However, the actual findings differed considerably from what Russell reported. As discussed earlier, there were 90 additional mutants found as one large cluster of the same mutation among the 402 offspring of one H male in the control group, for a control mutation rate of 96/106,408. The mutation rate in the experimental group remained unchanged from the 1959 values. Although the cluster responsible for this increase of 90 mutants was detected early in 1951, it was almost 45 years later when Selby first discovered it and the shocking fact that it had occurred and been found in 1951.

A mechanistic explanation for the 90 control group mutants was provided by Liane Russell's (1964) hypothesis to explain clusters of whole-body mutants sired by what are now termed masked mosaics. However, she did not indicate that any such clusters of whole-body mutants had been found in any SLT experiment. It is now obvious that by not reporting that cluster, W. Russell was able to claim that mice were about 15-fold more sensitive to the induction of mutations by X radiation than *Drosophila*. It seems unlikely that in early 1951 the Russells had any firm idea as to what had caused the large cluster that greatly complicated the interpretation of their first experiment. Indeed, because the cluster occurred so early in their first experiment, there were probably some months during which the mutation frequencies in the experimental and control groups were rather similar if all mutations in the cluster were counted. Not to mention that big cluster appears to have been a strategic decision of the Russells because, in the absence of that complication, their data had the clear potential to create much interest in their research and position it to likely replace the longstanding use of the *Drosophila* model for exploring a wide range of variables suspected of having importance when estimating hereditary risks to humans. Also, by ignoring the clusters, they could claim that the specific-locus test was a simple straightforward technique for determining mutation rates in mice under numerous experimental conditions.

In retrospect, the sanitized version of the results that Russell reported facilitated vast expansion of their program, along with the enhancement of their professional reputations and that of ORNL. The occurrence of clusters arising from masked mosaics in experiments on males would continue to occur throughout the long career of the Russells, and it was consistently hidden and kept distinct from their risk assessment research.

9. Discussion

Although the complication regarding masked mosaics has made the evaluation of SLT results much more difficult than any observers could have anticipated, it must be emphasized that without the Russells' SLT experiments that used large numbers of offspring sired by individual males and the massive amounts of data that they collected, the extreme importance of masked mosacism to the spontaneous occurrence of hereditary diseases in mammals might never have been discovered. No other techniques for studying induction of mutations in mammals approach the potential of SLT experiments for discovering the phenomenon, or at least for coming to some quantitative understanding of its ramifications.

The now revised assessment of some of the most important data collected in the SLT by the Russells indicates that background radiation is of no importance in contributing to the spontaneous mutation rate in reproductive cells of mice. Furthermore, it seems likely that the great majority of spontaneous mutations in the mouse model occur because of unknown events that happen in one strand of the DNA in the perigametic interval (i.e., probably within the zygote and certainly before the two-cell stage). Those events appear likely to be surprisingly frequent when extrapolation to the entire genome is considered. That is because the mutations occurring in that interval discussed in this paper were found in only seven genes out of the tens of thousands of genes in mammals. Furthermore, of the relatively few masked mosaics clearly identified (by the Russells and in Neuherberg and Harwell), at least one was found for every one of the seven genes tested in the SLT (Russell and Russell, 1996). Indeed, the highest proportion occurred at the *a* locus, which is one of the genes least likely—out of the seven genes tested in the SLT—to mutate to either a spontaneous or radiation-induced mutation. **There is thus no reason to think that L. Russell's hypothesis is restricted to just a small part of the genome.**

This paper demonstrates that two of the major findings of W. Russell, both of which supported the LNT dose response model, were due to a decision by Russell to neither count nor report large clusters of gene mutations. Those two, accordingly unjustified, conclusions were (1) that his male mouse model is 15-fold more sensitive than *Drosophila* for induction of radiation-induced transgenerational gene mutations and (2) that in males there is no threshold dose-rate for induction of gene mutations by ionizing radiation. This withholding of information on clusters produced by masked mosaics reflects a fundamental data suppression strategy, raising obvious questions about research transparency and integrity.

It is important to place these decisions of W. Russell into a broader

context. His research approach with the SLT required a massive financial commitment involving a huge facility, large personnel requirements, and other resources. The resource-intense requirements of W. Russell were viewed as very risky but worth the gamble if his approach worked. So, when his first major experiment yielded a cluster of 90 mutations in the control, and when that cluster was even known to be present before the preliminary results of the experiment were made public for the first time, these data must have been extremely troubling to Russell, and, quite importantly, may have had the potential to undermine continuation of his very resource-intensive funding strategy right from the start. Thus, it was in W. Russell's self-interest not to share this information with others (and especially key people, possibly including the likes of Hollaender, who had hired him and was the Director of the Biology Division) and not to address the big cluster problem. With the removal of the mutations in the large cluster from the reported data, the findings showed a very exciting and profoundly important, even if potentially false, result, that mice were about 15-fold more sensitive to the induction of mutations by radiation than the fruit fly model of Muller and many others. These striking observations of Russell were not lost on the leaders in the field of radiation genetics because they offered a clear vision of the future direction of the field, with Russell's work being a centerpiece in a mammalian-directed strategy for human risk assessment rather than having to depend upon an insect model using *Drosophila*. Russell was soon appointed a member of the BEAR I Genetics Panel with the likes of Hermann Muller, George Beadle, and Sewall Wright among other senior leaders in the field.

The hiding by the Russells of potentially confusing data that had obvious relevance to important reasons for supporting their research did not stop with the first major study but continued throughout their careers. W. Russell, during his first decade at ORNL, also made what he thought was a major discovery of induction by radiation of dominant mutations that shortened the lifespans of first-generation offspring (Russell, 1957). Although he published those results in 1957, by 1959 he had completed a large-scale follow-up cancer/lifespan study using a much larger radiation exposure that provided no support for the findings of his earlier small experiment. Again, he chose to not report the results of the follow-up study for 34 years, at which time he did so to help win a major litigation in the UK, this being an action that was only recently exposed (Calabrese and Selby, 2022). This provides another example of W. Russell failing to report major study findings that affected the LNT debate and the funding of his research program, under the leadership of Hollaender. At the present time it is unknown whether Hollaender was aware of the actions of the Russells on these data suppression issues.

The US EPA relied upon the massive studies of W. Russell to test epidemiologic predictions that low dose radiation exposures could act in either a linear or threshold manner. Now, after becoming aware of Russell's data on clusters, together with his massive amounts of published data and L. Russell's hypothesis to explain the mechanism causing the clusters produced by masked mosaics, it appears that the threshold model, likely with a surprisingly high threshold dose rate, is supported in both male and female mice. The Russells' hiding of essential data for almost half a century played into the hands of those who supported the LNT model, and those who believed in the LNT model accordingly benefitted from W. Russell's interpretation that there was no threshold dose-rate in males. The hiding of those data also contributed to the unjustified decision of the BEIR I Genetics Committee to support an LNT model that was subsequently adopted by the EPA and which continues to the present time. (W. Russell was a member of the BEIR I Genetics Committee.) (Calabrese, 2016a, 2016b, 2019). The present assessment challenges the reliability of the Russell analyses, the recommendation of the BEIR I Committee to support LNT, and the decision of EPA to adopt LNT as they did in 1975.

The present analyses show that the corrected data of Russell not only support a threshold for radiation-induced gene mutation in both sexes of mice but are also consistent with epidemiologic studies that show the beginnings of an increase in cancer risk at greater than 100 millisieverts (Ricci and Tharmalingam, 2019)—that is, they support a threshold for humans as well. Furthermore, the reanalysis of the corrected Russell data strongly supports the conclusion that any theoretical mutation and/or cancer risk due to background radiation would be far below estimated thresholds (Calabrese and Selby, 2023-submitted). Even though these findings are based on the historical data of Russell, those data represent the most substantial and reliable data on a mammalian model in the scientific literature and provide a statistically robust and mechanistic test for the low dose epidemiologic hypotheses.

10. Major specific conclusions

1. Cancer and hereditary risk assessment for chemicals and radiation depend to a large extent on William Russell's interpretation of his data as he chose to report them. His decision to hide some major complications in his data created a deliberate falsification of the research record leading to major overestimations of the hereditary and cancer risks of carcinogenic chemicals and radiation.
2. The corrected Russell data support a threshold dose response for ionizing radiation for mutation and cancer.
3. The corrected Russell data indicate that background radiation has no detectable impact on human mutation and cancer risk.
4. The corrected Russell data are consistent with human epidemiologic data showing an increase in cancer risk occurring at greater than 100 millisieverts, thereby supporting a threshold dose response.
5. These collective findings indicate that EPA and other regulatory agency policies and practices worldwide are based on flawed and corrupt scientific practices.
6. US federal agencies [i.e., EPA, DOE and/or National Institute for Environmental Health Sciences (NIEHS)] need to initiate a comprehensive reassessment of the entire Russell SLT database to determine the actual frequency of occurrence of masked mosaics and their impact on the SLT-affected risk assessment estimates. Such an assessment would have global risk assessment implications.

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Credit authorship contribution statement

EJ Calabrese and PB Selby both similarly contributed to concept development and writing of each draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

Appendix 1

The method that the Russells used in their 1996 paper (Russell and Russell, 1996) to estimate the spontaneous mutation rate per generation resulting from masked mosaics by using the number of acknowledged masked mosaics, when corrected for the additional masked mosaic that they acknowledged in their 1997 PNAS paper (Russell and Russell, 1997), results in the $CF_{G\ (7\ MM)}$ of 2.6. That CF was used to calculate the adjusted background mutation rate shown in Fig. 2. The following method was used to derive adjusted experimental mutation rates. The slope and Y-intercept described above by W. Russell and Kelly provide the portions of the adjusted experimental mutation rate related to radiation-induced mutations and "singleton" spontaneous mutations, respectively. The third portion required for such an estimate is the spontaneous mutation rate produced by masked mosaics, and that value is added to the Y-intercept shown on the Fig. 2, which results in the adjusted lines being parallel and higher than the solid black lines by the same amount as the value added to the Y-intercept. Once estimates of adjusted experimental mutation rates had been made, adjusted induced mutation rates for different doses were calculated by subtracting the adjusted background mutation rate from each adjusted experimental mutation rate. (Such an estimate could be improved if more precise information could be obtained on the number of masked mutants in the Russells' experiments.)

The estimate of the portion that results from masked mosaics, when expressed per locus (designated $P_{MM/L}$), was calculated using the following terms:

The only variable in the equation is:

S = sibship size, which is assumed to be the same for every H male in the experiment.

The constants used in the equations for $P_{MM/L}$ in this paper are as follows:

R = fraction of the H males that are masked mosaics, which is (7 ÷ 37,735)

T = Total number of offspring scored for mutations in the hypothetical SLT, which is 200,000.

U = Number of H males that sired the entire sample of T = (T ÷ S)

V = 0.25 (probability that an offspring of a masked mosaic male will be a mutant carrying the mutation for which its father is a masked mosaic, according to the mechanism proposed by L. Russell)

W = number of loci in SLT = 7

$$P_{MM/L} = \{[R \times U \times V \times S] \div (T \times W)\}$$

It is important to realize that when sibship size is held constant for all H males in an experiment (obviously only a hypothetical possibility), the above equation yields the same answer for extremely different values of S as demonstrated by the following three examples.

If S = 1, $P_{MM/L} = 6.63 \times 10^{-6}$

If S = 100, $P_{MM/L} = 6.63 \times 10^{-6}$

If S = 500, $P_{MM/L} = 6.63 \times 10^{-6}$

The variables U, T, and S in the equation all cancel out. They were only added above to demonstrate that if sibship size is held constant, those variables have no effect on the result. The simplified equation, which is $P_{MM/L} = [(R \times V) \div (W)]$, yields the same result as above of 6.63×10^{-6}. We used S of 1 in our calculation, but–as indicated–the result would be the same regardless of the sibship size used.

Since the mutation rate of 6.63×10^{-6} is specifically calculated for the frequency of masked mosaics of 7/37,735, it will henceforth be designated $P_{MM\ 7/L}$ and it is relevant to a sibship of 1 and appropriate for comparisons to the background mutation rate calculated for the $CF_{G\ (7\ MM)}$ of 2.6. The Russell-Kelly equation for the chronic slope shown in their 1982 paper is $Y = 8.10 \times 10^{-6} + (7.32 \times 10^{-8})D$, and we added 6.63×10^{-6} to that slope to derive the slope for the adjusted experimental mutation rates. Adjusted experimental mutation rates were then calculated for the doses of 4.3 … 90, 95, 100, 200 and 300 R. The background rate of 2.14×10^{-5} mutation per locus was subtracted from each adjusted experimental mutation rate to calculate the adjusted induced mutation rate for each dose. Because of the equations used in the conversions, both the adjusted spontaneous mutation rate per generation (i.e., background) and the adjusted experimental mutation rate relate to independent events. As noted earlier, singleton spontaneous mutations and induced mutations also are considered to be independent events.

Appendix 2

It is important to realize that the method that has been used in this paper (based on the Russells' suggested approach) to derive the $CF_{G\ (7\ MM)}$ of 2.6 is mathematically consistent with the approach used in Appendix 1 to derive the $P_{MM\ 7/L}$ of 6.63×10^{-6}. This is true even though the thought process used by the Russells to derive CFs for the spontaneous mutation rate per generation differs greatly from the thought process that we used to derive the $P_{MM\ (7/L)}$. Below we demonstrate that if our method of deriving $P_{MM\ (7/L)}$ is applied to derive $CF_{G\ (7\ MM)}$, the same result of 2.6 is achieved, which shows that the two methods are mathematically equivalent.

Those wanting to fully understand the Russells' approach, which is rather complicated, are referred to footnote 14 of this paper and pages 13,076 and 13,077 of the Russells' 1996 PNAS paper. Our approach is as follows: A mouse receives half of its chromosomes from its father and half from its mother. The singleton spontaneous specific-locus mutation rates per locus in male and female mice as taken from the Russells' 1996 PNAS paper are 6.64×10^{-6} and 1.60×10^{-6}, respectively, and they are based on SLT experiments on male and female mice, respectively. $P_{MM\ 7/L}$ must be counted twice when estimating the correction factor for the spontaneous mutation rate per generation because either the mother or the father of an H mouse could be a masked mosaic. According to L. Russell's hypothesis, the frequency of being a masked mosaic would be the same for both sexes. The only published data available for this calculation are for the male. Thus, by our approach, the calculation of the $CF_{G\ (7\ MM)}$ is as follows:

Numerator = male singleton rate + female singleton rate + $(2 \times P_{MM\ 7/L})$

Therefore the Numerator = $[6.64 \times 10^{-6} + 1.60 \times 10^{-6} + (2 \times 6.63 \times 10^{-6})]$

Denominator: $(6.64 \times 10^{-6} + 1.60 \times 10^{-6})$

$CF_{G\ (7\ MM)} = 2.6$

Because the $P_{MM\ 7/L}$ can be used to derive the same value for the $CF_{G\ (7\ MM)}$, it is completely reasonable to calculate the adjusted induced mutation rate for a particular dose by subtracting $CF_{G\ (7\ MM)}$ from an adjusted experimental mutation rate that is based on $P_{MM\ 7/L}$.

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