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Symposium Paper

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Genetic studies at the Atomic Bomb Casualty Commission–Radiation Effects Research Foundation: 1946–1997

(genetic effects of atomic bombs/radiation genetics/genetic epidemiology/critique of Dubrova report/Hiroshima and Nagasaki)

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Beginnings

It is difficult, some 52 years later, to recreate the intensity of the concern about the delayed effects of exposure to the atomic bombs, as well as other radiation exposures, that surfaced in the first few months after the bombings. It is not generally appreciated that the survival in Japan of so many persons receiving exposures to ionizing radiation up to the amount compatible with survival was unexpected. The physicists on the Manhattan Project had assumed that anyone close enough to the hypocenter of the explosion to have received significant amounts of radiation would have been killed by the blast or thermal effects of the bombs (1). The survivors within 2 km of the hypocenter of the explosion, this being the radius of significant radiation, were, therefore, a group without parallel in human history, regardless of individual feelings about the use of the two bombs, and the significance of an intensive follow-up of this group was at that time immediately apparent to laypersons and scientists alike of all nationalities.

Dr. Putnam (2) has outlined the developments that led to the involvement of the Academy in the organization of the long-term studies of the atomic bomb survivors carried out by the Atomic Bomb Casualty Commission (ABCC). Elsewhere, I have described the somewhat unusual circumstances that resulted in then First Lieutenant Neel, Medical Corps, U.S. Army, being assigned to the small survey team that first touched down in Japan on November 25, 1946, charged with advising the Academy's new Committee on Atomic Casualties concerning both the potentialities and the problems inherent in any study the Academy might undertake (3).

The Genetic Challenge of Hiroshima and Nagasaki

Because my background at that time included a Ph.D. in genetics as well as my medical training, I covered the genetic beat for the group. It was obvious from the outset that the obstacles to a proper study were formidable. The task was clear: to ascertain all births occurring in the two cities and then examine every single one of those children. But the devastation in the two cities was daunting, all services badly disrupted and facilities in ruin; the vast majority of deliveries were at home—and in the Japanese culture, the birth of an abnormal child was considered a disgrace and concealed whenever possible. Human genetics as a discipline at that time was still a very fledgling science in the U.S., and almost nonexistent in Japan: there was no pool of expertise from which to recruit for the study, and the Academy, for all its well-deserved prestige as an advisory body, was not accustomed to operating field studies, let alone studies of that magnitude and difficulty. Finally, working out the appropriate relationship with the funding agencies, from the Atomic Energy Commission to the Department of Energy, presented issues that persist right down to the present. To say there was a certain amount of stumbling around in the beginning would be a kind appraisal of the situation. In particular, the resources necessary for a proper follow-up were grossly underestimated at first.

The Study

The key to the decision that a proper genetic study might be feasible materialized when, early on, Dr. I. Matsubayashi, chief of public health for Hiroshima City, informed me that during those difficult days, the Japanese still maintained their wartime rice-rationing system, with a special provision for pregnant women. A survey determined that the registration of pregnant women at the completion of the fifth lunar month of pregnancy was almost 100% complete, and, by coordinating the Atomic Bomb Casualty Commission effort with that registration, the basis for a prospective ascertainment of the total population of newborns-to-be in Hiroshima and Nagasaki was established. That procedure minimized the opportunities for the concealment of birth defects and other unfortunate pregnancy outcomes.

The initial battery of observations on each newborn included occurrence of major congenital defect/sentinel phenotype, stillbirth, survival of liveborn children through the neonatal period, sex of child, and birth weight. There was a further clinical examination of a subsample of these children at age 9 months (cf. ref. 4). In 1953, that major clinical program was discontinued, but births in the two cities were, as they were registered for civil purposes, screened for parental radiation history, and, where indicated, added to a growing cohort for future study. By 1984, there were very few births in the two cities to exposed parents, and the study cohort was closed out, with 31,150 children in the cohort of children one or both of whose parents had been within 2 km of the hypocenter of the bombings, the so-called proximally exposed. A suitably matched control cohort, which had been accumulating over the years, of 41,066 children, also was closed. In 1967, Dr. A. A. Awa and associates launched major cytogenetic studies of a subset of this cohort. In the 1970s, Dr. T. Furusho and Dr. M. Otake analyzed from school records the physical development of a subset of these children who were in middle and senior high school. In 1972, a search for mutational damage in a battery of serum proteins and erythrocyte enzymes was launched, using this cohort, which study came under the direction of Dr. C. Satoh. Finally, the children in these cohorts

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were followed for survival and malignancy, the studies on malignancy using the newly established Cancer Registries in Hiroshima and Nagasaki, with Dr. H. Kato playing a major role in those studies. It must be obvious that a study of this magnitude is the work of many more hands than those just mentioned. On the U.S. side, Dr. W. J. Schull, with whom I have been associated in these studies since 1949, played an especially prominent role. Altogether there were perhaps 100 professionals involved in these studies over the years, participants in the many scientific papers that have appeared.

In 1986, new estimates of the radiation exposures sustained by the survivors of the bombings became available, and the entire data set, which had been subject to numerous previous reports, was reanalyzed on the basis of these new dose schedules. The most relevant of the resulting papers were collected in a volume published by the National Academy Press in 1991 (5). There was no statistically significant effect of parental exposure on any of the indicators of possible genetic damage mentioned above, but, pooling the results of the analysis of all the indicators, where pooling was feasible, the net regression of the pooled indicators on parental exposure was slightly positive. Inasmuch as there seems no doubt some genetic damage resulted from the A-bomb exposures, we essayed to explore the implications of this small positive regression for the estimation of the genetic doubling dose of acute ionizing radiation for humans (6). The doubling dose is the exposure of a population to ionizing radiation that will produce the same amount of genetic damage as occurs spontaneously each generation. It can be expressed either as per haploid gamete or per diploid zygote (i.e., person); the studies in Japan yielded a zygotic estimate (7) whereas most of the experimental studies resulted in gametic estimates. The doubling dose is a convenient concept, but the many assumptions and practical difficulties in actually deriving a doubling dose were well enumerated by Muller (8). The situation has not changed materially in the ensuing 39 years (cf. ref. 9). Ideally, the concept embraces the whole spectrum of mutational morbidity, from mutations involving entire chromosomes to single nucleotide substitutions, thus requiring the study and integration of a wide range of genetic damage. In addition, for the Japanese data this calculation required specifying the contribution of spontaneous mutation in the preceding generation to such indicators as congenital defect and early death. Nevertheless, in an imperfect world, the doubling-dose concept supplies a perspective, if blurred, difficult to obtain by any other approach. Because of the mixed spectrum of radiation delivered by the atomic bombs, dose must be measured in sieverts (Sv).

The doubling-dose estimate suggested by these studies was an acute gonadal exposure of approximately 2.0 Sv equivalents, with a wide but, for several reasons, essentially indeterminate error (6). We believe that, as befits the situation, the assumptions in reaching this estimate have been very conservative. This estimate may be biased downward by the somewhat lower socioeconomic status of the proximally exposed parents than that of the control population in the decade after the bombing (10). For instance, if only 50% of the small increase in mortality among the children born to survivors of the bombing were socioeconomic in origin, the estimate of the doubling dose would become 4.0 Sv equivalents. This is a zygotic rather than gametic doubling dose. The calculations revealed that the doubling dose was unlikely to be less than 1.0 Sv equivalents, but in the absence of statistical significance an upper bound could not be assigned to the estimate. To be specific, the data do not exclude estimates of the zygotic doubling dose of acute radiation as high as 3 or 4 or even 5 Sv equivalents.

Most of the radiation human populations receive is in small dribbles, or even more or less continuously as from cosmic radiation or radon. In the mouse, at the experimental doses used, such chronic radiation is genetically only about ⅓ as effective in producing mutations as acutely delivered radiation, such as was involved in the Japanese exposures (11). For technical reasons discussed elsewhere (6), we have argued that with the radiation exposures in Japan, the appropriate conversion factor is ½. The zygotic doubling dose for chronic radiation thus becomes in the neighborhood of 4 Sv equivalents. For those for whom these radiation units are unfamiliar, some perspective to the numbers being used in this presentation is provided by the following: The average U.S. citizen is receiving about 0.004 Sv equivalents a year from all sources of radiation in the environment but especially from radon (12). This annual exposure is about 1/1,000 of a doubling dose. Otherwise stated, it would require some 1,000 years to accumulate a doubling dose of radiation in our industrialized society—and there is a long-running debate as to whether at these very low doses of radiation, the body's DNA repair mechanisms may be able to heal all the potential genetic damage caused by the radiation. In an additional effort to provide perspective, let me point out that in the decade after the atomic bombings, no less a scientific figure than the geneticist J. B. S. Haldane could speculate that the doubling dose of radiation for humans could be as low as 0.05 Sv equivalents (13); from this you can readily grasp the perspective brought to this issue by the studies in Japan.

The Scientific Spin-Off of the Study

Although the dominating objective in the conduct of the genetic studies in Japan has been a comparison of the children born to A-bomb survivors exposed within 2 km of the hypocenter and the children of suitable controls, it was realized from the outset that the children of unexposed parents would provide data of interest in their own right. For instance, these studies have resulted in the first extensive normative data on the pattern of major congenital malformations in a mongoloid (Japanese) population and in similar data with respect to cytogenetic abnormalities in the general population and on inherited variation in a series of some 30 human proteins (14–16). However, the genetically most interesting data were on the effects of inbreeding. In the work preliminary to setting the design of the major program, it became clear that cousin marriage was by Western standards quite frequent in Japan, 6% of the newborns in Hiroshima and 8% in Nagasaki resulting from consanguineous marriages. Because if this difference in frequency between the two study groups of children was unequally distributed in the two cities it would be a confounding factor in the results, the consanguinity status of the parents of each child in the study was determined. In 1958–1960, a special study was undertaken of this extensive and unbiased sample of inbred children and suitable controls (17). This study, probably the most complete study of consanguinity effects ever performed, revealed smaller consanguinity effects than the prevailing opinion; the data have been extensively used not only in genetic counseling but also for insights into the biological significance of the surprising amount of variation encountered at the DNA level.

A Comparison with the Relevant Studies on Mice

When the atomic bomb project, the Manhattan Engineering District, was initiated during World War II, it was recognized that some increase in "occupational" exposures to radiation was inevitable, and studies to anticipate worker's health hazards were undertaken. At that time, most of the data available on the genetic effects of ionizing radiation were derived from experiments with *Drosophila*. The mouse met the obvious need for an experimental organism whose physiology was closer to the human, and although further experiments on *Drosophila* were sponsored by the District (and its successor agencies), major experiments on mice were initiated, experiments that after the war were amplified by additional efforts in many

countries. While the human data have been accumulating, the experimental data from mice have been the chief guide to human risks.

When the data from humans just summarized indicated less of a genetic radiation risk than the then-prevailing extrapolations to human from the mouse experiments, Susan Lewis and I (18) undertook a point-by-point comparison of the two data sets. This comparison emphasized those data from the mouse most nearly comparable to the human data. Unfortunately, for reasons discussed in some detail elsewhere (18), most notably the immaturity of the mouse fetus at birth and the intra-litter competition effect both before and after birth, although effects of paternal radiation on the frequency of congenital defects, stillbirths, and early survival were demonstrated in the offspring of radiated males, the data cannot be directly compared with the human data. A further reason for great care in extrapolating from mice to humans derives from all the differences between the exposure of a total population to instantaneous radiation, as in Japan, and the pattern of exposure usually used in the mouse experiments, namely, the exposure of members of a single inbred line at a predetermined age, followed by a controlled mating system in which a relatively few treated males father many offspring.

The most appropriate data for comparison with the human data would seem to be the results of the various specific locus-specific phenotype test systems. The results from eight different attempts to develop data from which such a radiation doubling dose for mice could be calculated, based on more or less specific locus (or specific phenotype) approaches, are shown in Table 1. (For present purposes, 1 Gy of radiation is for genetic purposes the same as 1 Sv equivalent.) Note the wide range in the various estimates, to which we found it impossible to attach errors in the usual statistical sense. Not shown there (because the data do not lend themselves to the calculation of a doubling dose) are the important results of Roderick (19), who estimated for mice a per locus recessive lethal mutation rate in postspermatogonial cells per locus from ionizing radiation of only 0.35×10^{-8}/0.01 Gy, whereas for the Russell 7-locus system, the corresponding rate for all postspermatogonial mutations was 45.32×10^{-8}/0.01 Gy, approximately 80% of these mutations being homozygous lethal. As Roderick pointed out, these results indicate about a 100-fold lesser sensitivity than the Russells' studies (20), although the error term to be attached to Roderick's estimate was large but difficult to calculate. The simple average of all the estimates in Table 1, unweighted because of the differing natures of the individual studies, was a male gametic doubling dose of 1.35 Gy, with an indeterminate error.

Table 1. A summary of the gametic doubling doses for acute, "high-dose" radiation of spermatogonia yielded by the various specific-locus/specific-phenotype systems developed in the laboratory mouse, after Neel and Lewis (17)

System	Doubling dose, Gy		Origin of treated males
Russell 7-locus	.44		101 × C3H
Dominant visibles	.16		Various
Dominant cataract	1.57		101/E1 × C3H/E1
Skeletal malformations	.26		101
Histocompatibility loci	>2.60		C57BL/6JN
Recessive lethals	.51		DBA
(3 studies)	.80	1.77	C3H/HeH × 101/H
	4.00		CBA, C3H
Loci encoding for proteins	.11		Various
Recessive visibles	3.89		C3H/HeH × 101/H
	Av. 1.35		

References to the sources of the data and the doubling-dose calculations will be found in Neel and Lewis (17).

There are several reasons to approach this estimate with caution. First, the data from many of the systems used in Table 1 are absolutely minimal for the generation of a doubling dose. Because of their magnitude, the data obtained by W. L. Russell at Oak Ridge (21, 22), yielding one of the lower estimates of the doubling dose, should have and did dominate the estimates, forcing us to look at them with great care. Second, Russell in his very first papers (23) recognized that the assumption that the loci he studied were representative of the genome was key. There are now data for the mouse indicating a 7-fold range in the rate per locus with which spontaneous mutation results in phenotypic effects (24, 25). In Russell's data (21), radiation produced 18 times more mutations at the s locus than at the a locus, surely a signal to extrapolate with caution (reviewed in ref. 21). Furthermore, in the test system developed by Lyon and Morris (26, 27) involving six different loci than those used in the Russell system, the radiation-induced rate was only about one-third of the rate in the Russell experiments. It is really not clear how best to treat these locus differences in spontaneous and induced mutation rates. The situation is further complicated in that the detailed analyses of L. B. Russell and colleagues (cf. refs. 28–30) reveals that the "specific locus system" is detecting events ranging from deletions of up to 11 cM, corresponding to physical lengths ranging to perhaps 20 nucleotide megabases, down to single nucleotide substitutions.

Third, the mouse doubling-dose estimates of Table 1 are male-based. The demonstration (31) that although in the first few litters posttreatment the offspring of radiated female mice exhibited about the same amount of genetic damage as the offspring of radiated male, there was no apparent damage in the later litters of these females, created a dilemma for risk setting. Was the human female similar to the mouse female in this respect? To be conservative, in extrapolating to the human situation, the mouse male-derived risks usually have been applied to both sexes. Thus, from Table 1 the zygotic doubling dose would become 2.7 Gy, but because of the lack of induced mutations in the late litters of females, this is almost certainly an underestimate of the mouse zygotic doubling dose. In the Japanese data, by contrast, radiated females contribute about half the dose on which the doubling dose estimate is based.

The fourth reason the murine-based estimate of 1.35 Gy may be conservative is the apparent omission of the observed "cluster" and "mosaic" mutations in the doubling-dose estimates derived from the Russell system. More than 30 years ago L. B. Russell (32) described some 40 specific locus mutations that in the course of the experiment at Oak Ridge occurred in the offspring of both irradiated and control mice as clusters of two or more. Of these, 21 had one irradiated parent and 19 came from a contemporary control population of slightly smaller size. It is not clear how many of these occurred in the basic 7-locus series that provided the mutation rates quoted above. More recently, Russell and Russell (20) also have described a series of some 37 mosaic mutants that appeared in the F_1 of both radiated and control mice, none of which apparently have been incorporated into the doubling-dose calculations of the past that used the Russell data. Selby (33) in a brief abstract has suggested that because of the failure to incorporate clusters into the calculations, "the size of the doubling dose has been underestimated by at least a factor of three." No similar estimate is yet available for the effect of noninclusion of the mosaic mutants, but it could be a factor of two. These clusters, apparently reflecting a relatively high mutation rate in the "perigametic—very early zygote" interval (see ref. 8), are well documented in humans and *Drosophila* and have been, by purpose or default, included in past doubling-dose estimates for these species (reviewed in ref. 34). The *Drosophila* data, however, suggest that only some 40% of all spontaneous mutations occur as clusters, so that although their omission from a calculation of the doubling dose for *Drosoph-*

ila would have biased the estimate downward, it would not be by a factor of three. From the standpoint of the population geneticist, there are both theoretical and practical reasons cluster mutations must be properly incorporated into the doubling-dose issue. First, when Mother Nature views a newly fertilized egg carrying a mutant gene not present in either parent, she (or, more technically, the process of natural selection) does not ask exactly when and how that mutation originated. Selection must reckon with the totality of all the newly arisen mutations represented in the zygote, which is what we have in effect attempted to emulate in the study in Japan. Selection does not stop to ask whether the mutation occurred as a member of a cluster. Second, although the frequency of clusters may not be altered by radiation under the special circumstances of the design of the Russell study (23), with the radiation usually delivered at the 12th week of age, in the human experience, such as the exposures from the atomic bombs or the Chernobyl disaster, exposure is to both sexes at all ages and all stages of gametogenesis or fetal development, including the period particularly susceptible to the occurrence of what will become "clustered mutations." Unfortunately, because of aspects of the design of the mouse studies, namely, the repeated use of a relatively few radiated males to impregnate many females, and the resulting favorable circumstances for the detection of clusters, the proper comparison of the mouse with the human data must be approached with care. Nevertheless, it is of some importance that the mouse data be presented in such a way that this comparison can be undertaken.

At this point in time, then, given all the difficulties in the calculations and the wide errors to be attached to these calculations, the estimates of the doubling dose of radiation for humans and mice appear to be converging. There is no theoretical reason for this agreement between two animals as disparate as humans and mice, but some nevertheless may find this agreement somewhat reassuring with respect to the validity of the conclusions from the epidemiological studies in Japan. Furthermore, inasmuch as the suggested permissible population and occupational exposures for genetic reasons, set by the Academy's Committee on the Biological Effects of Atomic Radiation in 1956, were—quite properly at the time—highly influenced by W. L. Russell's early studies (23) on mice, the adjustments suggested, as well as the studies in Japan, imply that these guidelines are even more conservative than we committee members thought at the time.

Two Recent Challenges to the Validity of the Mouse/Human Data Just Reviewed

Within the past 7 years, there have been two very well-publicized challenges to the view of the genetic risks of radiation just developed. The first was the suggestion by Gardner *et al.* (35, 36), after an extensive epidemiological study, that the previously reported cluster of childhood leukemia in Seascale, West Cumbria, England, was associated with paternal employment in the nearby Sellafield Nuclear Reprocessing Plant, a finding given a genetic interpretation. Shortly thereafter, a suit claiming damages for personal injuries was initiated on behalf of two of the individuals who had developed leukemia. The suit was filed by a well-known British law firm, Leigh, Day, and Company, and directed against British Nuclear Fuels plc, the firm that operated the plant. The suit, heard before the Royal High Courts of Justice of England, was record-breaking in its estimated costs. A verdict for the plaintiffs would have challenged all of the present guidelines concerning occupational exposures. There is no time to lead you through the intricacies of the case (for reviews cf. refs. 37–40). After an extended trial, the judge found resoundingly for the defendant. The crucial evidence in reaching this verdict was supplied by the studies in Japan, which yielded results in flat contradiction with the possibility that the increase in leukemia in Seascale could be a genetic radiation effect.

The second of these challenges is still ongoing. In 1996, Dubrova *et al.* (41) reported that the rate of mutation involving a battery of DNA minisatellites was twice as high in children whose parents had been exposed in the Mogilev district of Belarus to fallout from the Chernobyl disaster than in controls. Minisatellites are regions of DNA characterized by identical tandem DNA repeats, the repeat unit usually varying between 5 and 45 bp in length. The function of this type of DNA is unknown; it has an extraordinarily high spontaneous mutation rate. The maximum cumulative exposures to these parents from fallout can be estimated at .08 Sv equivalents of chronic radiation, and the average may be half of that. Thus, the results suggest radiation sensitivities far, far greater than observed in the Japanese studies, and has been enthusiastically hailed by the press for the new insights they provide. Fortunately or unfortunately, depending on your viewpoint, the study is badly flawed (cf. refs. 9 and 42). First, the controls are drawn from England, a violation of all the canons of design for a study of this nature. Second, the alleged effect is several hundred times greater than would be anticipated from experimental studies on minisatellites in mice (43, 44). But third, and most convincingly, these results are flatly contradicted by a study by Kodaira *et al.* (45), at the Radiation Effects Research Foundation (RERF), successor agency to the Atomic Bomb Casualty Commission, a study even now being extended. H. Mohrenweiser (unpublished work), in a preliminary study, also finds no effect of parental radiation on minisatellite mutation rates in the children of the so-called Chernobyl liquidators, in whom the radiation dose was substantially higher than for the parents reported by Dubrova *et al.* (41). Again the role of RERF in establishing a sane view of radiation risks has been underlined.

These recent episodes underscore the wisdom of continuing, or even initiating, several types of genetic studies in Japan. Chief among these is the completion of a resource for genetic studies at the DNA level. This latter undertaking, initiated some 10 years ago, involves establishing Epstein–Barr virus-immortalized cell lines organized into mother/father/child trios, some 600 with respect to which one or both parents were proximally exposed to the bombs, another 600 in which neither parent received significant radiation at the time of the bombings. It was these cell lines that already have served as the basis for the above-quoted studies of Kodaira *et al.* (45). Establishing these cell lines has been a very major undertaking.

At the moment, a variety of approaches to the efficient use of these cell lines for mutation studies is being explored. Chief among them is the application of electrophoresis to produce two-dimensional agarose gels of enzyme-digested, isotope-labeled genomic DNA. In such gels, some 2,000 DNA fragments can be recognized (46, 47). Computer algorithms have been developed to assist in the analysis of these complex patterns (48–50). A mutation would be detected as a feature of the child's gel not present in either parent. The approach should be most efficient in the detection of mutations resulting in DNA insertions/deletions/inversions.

Should the pilot studies now underway at the Radiation Effects Research Foundation and the University of Michigan concerning the potential of this system be expanded into full-scale studies, and a definitive body of data begin to emerge, then, I suggest, the question arises of whether extensive parallel experimental studies involving the mouse should be undertaken. On the one hand, it can be argued that in this situation, the proper study of humans is humans, and at this level of genetic resolution, there is no need for animal experimentation. On the other hand, almost surely some will argue the need for parallel studies on mice and *Drosophila*. Then, for the first time, society would have homologous indicators across species, the resulting data of great theoretical and practical

value. Were such studies initiated, however, it would seem desirable that the circumstances of the radiation exposure in the animal work be made much more comparable to the human exposures in Hiroshima and Nagasaki than has been the case in the past. Specifically, it would seem highly desirable that the experimental radiation doses be lower than in the past, and that the experimental breeding pattern be better approximated to that of a human population. Finally, for cross-species comparisons, it would be highly desirable that in any further experiments the radiation exposures more equally involve both sexes and a variety of life stages, rather than being concentrated, as in the past, on one sex, the male, and exposure at one brief window during the life cycle, usually the 12th week.

This brief presentation attempts to summarize the most extensive and longest running study in genetic epidemiology ever undertaken. In retrospect, it seems clear that the data the study has yielded, together with the current revisions of the murine data, have resulted in a much more rational view of the genetic risks of exposure to ionizing radiation than existed in the first several decades after the bombings. Yes, there are genetic risks in exposure to ionizing radiation, but current national and international recommendations regarding permissible exposures now can be seen as incorporating an even wider margin of safety than appeared to be the case when they were promulgated. In closing, I reiterate that whatever success the study has enjoyed has been the result of an unparalleled collaboration between scientists of two nations and, on the U.S. side, a remarkable coordination between administrative support at the Academy and the field work in Japan. And isn't it a revealing commentary on the speed of scientific advance, that when these genetic studies began, the "gold standard" for an epidemiological study such as this was frequency of congenital defect and "sentinel" phenotypes resulting from single gene mutations, now it has become, damage to DNA.

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