Excerpt from

UNSCEAR 2001 REPORT

ANNEX

Hereditary effects of radiation

---

3. Possible genetic effects of radiation exposures resulting from the Chernobyl accident or from living in the vicinity of a nuclear power plant

(a) Down's syndrome and congenital abnormalities

(paragraph 362, given below as paragraph 1, and the following):

1. In the UNSCEAR 1993 Report [U4], it was mentioned that the results of Czeizel et al. [C23] had showed no increase in the prevalence of selected sentinel anomalies (predominantly autosomal dominant and X-linked diseases of childhood onset and Down's syndrome) in Hungary after the Chernobyl accident. Sperling et al. [S35], however, reported that in West Berlin, nine months after the Chernobyl accident (i.e. in January 1987), there was a significant increase in Down's syndrome; a cluster of 12 cases was found compared with two or three expected. (Note that the term cluster is used here in an epidemiological sense and not in the sense used in genetics to describe mutations originating from a single progenitor cell.) After excluding factors that might have explained the increase, including maternal age distribution, only exposure to radiation after the Chernobyl accident remained. In six of the seven cases that could be cytogenetically studied, the extra chromosome was found to be of maternal origin. The occurrence of the above cases coincided with the time of highest radiation exposure (when the conceptions should have occurred), particularly inhalation of ^{131}I, prompting the authors to suggest that exposure to ionizing radiation, especially ^{131}I, might be the causal factor. This interpretation is open to doubt, however, in view of the very low radiation doses.

2. In another study carried out in Germany, Burkart et al. [B26] recorded an increase in Down's syndrome births (10 observed vs. 4.4 expected) in northern Bavaria in December 1986, close in time to the occurrence of the Down's syndrome cluster in West Berlin. Further analysis revealed that the increase in northern Bavaria was due mainly to four diagnoses made in the urban areas of Nuremberg, Fuerth, and Erlangen. Chernobyl radiation exposure could be excluded as the cause, because the areas had received very little contamination and because the peak occurred in December 1986, one month before the occurrence of the Down's syndrome cluster in West Berlin.

3. In commenting on the Berlin cluster, Burkart et al. [B26] noted that (a) biological considerations argue against Chernobyl fallout as a plausible cause of the Berlin cluster; (b) the Chernobyl exposure cannot have been a common causal factor in northern Bavaria and West Berlin, since the higher rates in the former area can be traced to a time period shortly before fallout took place; and (c) in the absence of further clues, the close temporal relationship of the Berlin and the Bavarian clusters should be carefully analysed to generate hypotheses on a common factor influencing the incidence of Down's syndrome.

4. De Wals et al. [D26] reported on the results of a survey on the incidence of chromosomal syndromes (including Down's syndrome) in Europe registered in 19 birth defects registries from January 1986 to March 1987. The study population comprised 764 chromosomal syndrome cases, of which 621 were Down's syndrome cases in 482,193 total births. No evidence for any clustering was found in any of the registries for the period January to March 1987. Analysis of the frequency rates by month of conception also did not indicate any increase after May 1986.

5. Little [L30] provided a comprehensive review of studies undertaken in the wake of the Chernobyl accident with particular reference to those on congenital abnormalities and other adverse reproductive outcomes. The main points that emerge are the following: (a) an increased frequency of Down's syndrome in West Berlin in January 1987 and increases in the frequency of neural tube defects in several small hospital-based series in Turkey are not confirmed in larger and more representative series in Europe; (b) no clear changes are apparent in the birth prevalence of congenital anomalies in Belarus or the Ukraine (the republics with the highest exposures), although the data are difficult to interpret because the methods of acquisition were not described and were not reported in full; (c) the conclusion that there is no consistent evidence on congenital anomalies applies to other measured outcomes of pregnancy as well (miscarriages, perinatal mortality and low birth weight, sex ratio shifts, and multiple births); (d) there is evidence of indirect effects: an increase in induced abortions due to anxieties created, which is substantial enough to show up as a reduction in the total number of births; (e) no data are available on the reproductive outcomes of women pregnant at the time of the accident who were evacuated from the 30-km zone of contamination, of workers on site at the time of the accident, or of recovery operation workers; and (f) no data are available from several of the countries closest to the Chernobyl area (see also [B5, G9]).

6. Siffel et al. [S34] studied the occurrence of sentinel anomalies (also including congenital abnormalities and Down's syndrome) in children (n=26,893) born within a 20-km radius of the Paks nuclear power plant in Hungary. Comparisons of the frequencies of sentinel anomalies, congenital abnormalities, unidentified multiple congenital abnormalities, and Down's syndrome before and after the operation of the power plant revealed no significant differences. It was concluded that the slightly elevated radiation background (0.2–0.4 $\mu Sv\ a^{-1}$) attributable to the operation of the power plant did not affect germinal and somatic mutation rates. Izhevsky et al. [I9], carried out a retrospective study on the pregnancy outcomes and pre-reproductive mortality of children of workers of the Mayak nuclear power plant. The workers were occupationally exposed to gamma radiation during 1948–1954, and data on doses and medical documents of the families were available. The authors found indications for a possible increase in pre-reproductive mortality of the children of exposed mothers.

(b) Mutations in human minisatellite loci

7. ***Background.*** As discussed in paragraph 52, a significant fraction of the eukaryotic (including the human) genome is composed of repetitive-sequence DNA. Much of this DNA has been grouped into various families based on sequence, organization, and size [S92]. In some of these families, variations in sequence and/or in the number of repeat units occur within and between species. One class of the repetitive DNA elements, simple tandem repeats, is characterized by a motif of short oligonucleotide core sequences reiterated in tandem arrays. These elements have been variously called minisatellites [J15], midisatellites [N17], and microsatellites [L34]. This repetitive DNA has been found to occur at many highly polymorphic (hypervariable) loci dispersed throughout the genome. The exceptionally high levels of polymorphic variation at these loci are due to variation in the number of tandem repeat cores. Family studies have demonstrated that simple tandem repeat loci are inherited in a co-dominant Mendelian fashion [K42] (see Jeffreys et al. [J5] for a recent review.)

8. The diversity of alleles at both human and mouse minisatellite loci is a result of mutation rates that are orders of magnitude higher than those of most protein-coding genes (e.g. [J5, J16, K42, K43, S63]). The principal advantage of these high mutation rates is that significant changes can be detected with smaller sample sizes. There is evidence to suggest that in somatic cells, the new length alleles may arise by mitotic recombination or unequal sister chromatid exchange; replication slippage does not appear to be a dominant process [J5, W22]. Analysis of minisatellite mutations in sperm suggests that they may arise by gene-conversion-like events, the reasonable candidate stage being meiosis [J5]. Worth noting here is that minisatellite variations very rarely have phenotypic effects (e.g. trinucleotide repeat expansions; see Table 8).

9. ***Radiation-induced minisatellite mutations.*** Dubrova et al. [D19] studied germ-line minisatellite mutations among children born between February and September 1994 to parents who were continuously resident in heavily polluted areas of the Mogilev region of Belarus after the Chernobyl accident. Blood samples were collected from 79 families (father, mother, and child) for DNA analysis. The control sample consisted of 105 non-irradiated Caucasian families from the United Kingdom, sex-matched to the offspring of the exposed group. DNA fingerprints were produced from all families by using the multi-locus minisatellite probe 33.15 and two hypervariable single-locus probes, MS1 and MS31. Additionally, most families were profiled with the minisatellite probes MS32 and CEB1. For the Mogilev families, the level of ^{137}Cs surface contamination was used as a dose measure, i.e. families were divided according to the median ^{137}Cs contamination levels into those inhabiting less contaminated areas (<250 kBq m^{-2}) and more contaminated areas (>250 kBq m^{-2}).

10. The important findings are that (a) the frequency of minisatellite mutations is about twice as high in the children of the exposed families as in controls, and (b) the mutation frequencies show a correlation with the level of caesium contamination as demarcated above. The authors suggested that these findings are consistent with radiation induction of germ-line mutations but also noted that other non-radioactive contaminants from Chernobyl, such as heavy metals, could be responsible for the observed, apparently dose-dependent increase in the mutation rate.

11. In a subsequent extension of the above study, Dubrova et al. [D29] recruited 48 additional families from the affected region and used five additional minisatellite probes, including the multi-locus probe 33.6 and four hypervariable single-locus probes. These additional data confirmed the twofold higher mutation rate in children of exposed parents than in those of non-exposed. The spectra of mutations seen in the unexposed and exposed groups were indistinguishable, suggesting that the increased mutation frequency observed over multiple loci arise indirectly by some mechanism that enhances spontaneous minisatellite mutations. Obviously, further work is needed to clarify the structural basis of radiation-induced minisatellite mutations.

12. It has been argued [N19] that the use of control families from the United Kingdom introduces a significant confounding factor as well as possible ethnic/genetic differences from the population of Belarus. Secondly, the families in the United Kingdom may have experienced different patterns of environmental exposure to potentially mutagenic industrial and agricultural chemicals that might have contributed germ-line variation. Thirdly, it is not clear from the surface contamination maps of the region why control families receiving insignificant radiation doses were not obtained or why a second set of controls of children conceived prior to the accident could not be identified. Fourth, the trend in mutation frequency with likely dose received is also dependent on the division of families into just two groups on the basis of radiocaesium contamination; an analysis of trends based on individual assessment of contamination would be more revealing. Finally, from the data presented, it would seem that the germ-line doses in the whole region remain sufficiently uncertain to question the true significance of a less than twofold difference in mutation frequency between the two groups.

13. In a pilot feasibility study carried out on the children of survivors of the atomic bombings in Japan, Kodaira et al. [K44] (see also Neel [N18] for a commentary) screened 64 children from 50 exposed families and 60 from 50 control families for mutations at six minisatellite loci using the following probes: Pc-1, λTM-18, ChdTC-15, pλg3, λMS-1, and CEB-1. The cell lines chosen for this study were from the most heavily exposed parents, whose average parental combined gonadal equivalent dose was 1.9 Sv. A total of 28 mutations were found, but these were at the pλg3, λMS-1, and CEB-1 loci (there were no mutations at the other three loci). Twenty-two of these were in controls (of 1,098 alleles tested, i.e. 2%), six in the children derived from the irradiated gametes (among 390 alleles, i.e. 1.5%). Thus, there was no significant difference in mutation frequencies. Since they used different loci from Dubrova et al., the authors suggested that the use of the DNA fingerprint probes 33.16 and 33.15 may be worthwhile in studies of the children of survivors of the atomic bombings. However, the subsequent preliminary results of Kodaira and Satoh [K50] and Satoh and Kodaira [S44] using the above two probes showed no significant difference in mutation frequencies between the children of the exposed parents and the control children.

4. Summary

14. Two studies of the genetic effects of radiation in humans have recently been published. One of them involved the offspring of survivors of cancer who had received chemo- and/or radiotherapy treatments and the other involved females who had been exposed to radiation (from beta particles, gamma rays, and x rays) during infancy for the treatment of haemangiomas. Neither of these found significant effects attributable to parental exposure to chemical agents and/or radiation.

15. The results of studies of minisatellite mutations in the children of those exposed in areas contaminated by the Chernobyl accident and in the children of those exposed to the atomic bombings in Japan are not consistent: in children from Chernobyl areas, the mutation frequencies were increased, while in the Japanese children, there were no such increases. It should be noted that the control children for the Chernobyl study were from the United Kingdom.

16. The search for genetic effects associated with Chernobyl exposures in Belarus or Ukraine, which had the highest contamination, and in a number of European countries provide no unambiguous evidence for an increase in the frequencies of one or more of the following: Down's syndrome, congenital anomalies, miscarriages, perinatal mortality, etc.

(The full text of the UNSCEAR 2001 Report will be available on the internet shortly)