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Leukaemia and lymphoma among young people near Sellafield

SIR,—In a careful and detailed case-control study Professor Martin J Gardner and colleagues have produced strong evidence of a causal link between occupational radiation exposure of fathers at Sellafield and the subsequent occurrence of acute leukaemia in their children.[1] The authors suggest that this is most probably due to a germ cell mutation, but the alternative possibility is that fathers contaminate the home environment and this leads to irradiation of the fetus in utero or the infant in the early months of life. I have recently published a theoretical model of childhood leukaemogenesis based on spontaneous mutation in dividing cells that is relevant to this problem.[2]

I derived an equation that enables the calculation of the probability of a malignant clone arising as a result of a number of specific independent mutations (n) occurring in a population of dividing cells with a mutation rate per gene per cell generation of m. The epidemiological and kinetic data on childhood acute lymphoblastic leukaemia are best explained if $m \simeq 1 \times 10^{-6}$ and $n=4$. Furthermore, it can be shown that if the mutation rate is constant throughout all cell generations during intrauterine and early extrauterine life then the incidence of acute lymphoblastic leukaemia is proportional to m^4. Thus a 10-fold increase in the incidence, as seen in Seascale, would occur if the mutation rate was increased by a multiple of 1·8. Interestingly, if the increased mutation rate is confined to extrauterine life—that is, the last few cell generations—then the increase in incidence would be proportional to m. In other words a 10-fold increase in the mutation rate would be required to increase the incidence 10 times.

The model can also be used to calculate the effects of a germ cell mutation. If the fetus inherits one defective gene then only three subsequent mutations are required. The chance of acute lymphoblastic leukaemia arising in these circumstances is between 0·1 and 0·9 per affected child compared with the chance in the general population of 3×10^{-4} by age 15 years. A 10-fold increase in incidence due to germ cell mutation would require a mean frequency of mutation in spermatozoa of at least 3×10^{-3} if all affected infants develop acute lymphoblastic leukaemia and 3×10^{-2} if only 10% develop it. In fact these figures are underestimates because they ignore the possibility of selection against mutant spermatozoa. The most commonly quoted estimate of the mutant frequency of genes, which is based on in vitro measurement and the appearance of new mutants, is 2×10^{-5}.[2] Thus a 10-fold increase in the incidence of acute lymphoblastic leukaemia due to germ line mutation would require a 100-fold or 1000-fold increase in the mutation rate. It is difficult to believe that Sellafield workers could sustain this without a measurable effect on general health and a pronounced increase in the incidence of other cancers, particularly considering that smoking increases the mutant frequency by only 50%.[3]

Thus a 10-fold increase in the incidence of acute lymphoblastic leukaemia as a result of a radiation induced increase in the mutation rate would require a 100-fold or 1000-fold increase if acting on the germ cell; a 10-fold increase if acting on lymphocytes during early extrauterine life; but only a 1·8-fold increase if acting throughout intrauterine life, which seems the most plausible mechanism even though the pathways of exposure are unclear.

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1 Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of a case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J* 1990;**300**:423-9. (17 February.)
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SIR,—The results of Professor Martin J Gardner and colleagues,[1] which showed the high relative risk of leukaemia in children whose fathers had been exposed to external radiation in the period before conception, when contrasted with the absence of any similar tendency in the offspring of Japanese men who survived the atomic bomb explosions[2] suggest several mechanistic interpretations. One is the possibility of internal contamination by a radionuclide (as adumbrated in the leading article by Dr Valerie Beral).[3]

There are several reasons for serious consideration to be given to the possibility of such internal contamination, particularly in the light of the tissue distribution of metallic elements such as zinc.[4] Relatively high concentrations of zinc are found in semen[5] and there is a close association between zinc and DNA in the so called "zinc finger" domains of DNA binding proteins.[6] Jonas *et al*[7] proposed that substitution of zinc at these vulnerable sites by other cations, such as transition metals (for example, copper and iron), could lead to damage of DNA by the generation of reactive oxygen species of a type known to be produced by radiation,[8] and potentially mutagenic alterations in DNA bases by hydroxyl radical attack are known to occur.[9] Clearly, a similar substitution by relatively short lived radionuclides that are able to bind to thiols at zinc sites adjacent to the genome could be a source of local radiation induced metagenesis, and even the presence of unnatural non-radioactive derivatives might be expected to have a profound effect. If radionuclides were localised in spermatogonia any mutations induced would be amplified during spermatogenesis and could lead to a perceptibly higher incidence of genetic lesions in the offspring.

If such a mechanism were to be an important factor in the pathogenesis of childhood leukaemia found in the study of Professor Gardner and colleagues there might be a case for assessing the nutritional zinc state of workers in nuclear installations to ensure that those in contact with radionuclides are not deficient in this essential trace element. Zinc is known to alleviate the toxic effects of metals such as cadmium, either by the induction of increased concentrations of metallothionein or by binding to and masking vital sulphur containing moieties, and the absorption of metals such as iron, copper, and zinc is interdependent.[10]

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SIR,—Clusters of cases of childhood leukaemia have been shown to occur around the Sellafield and Dounreay nuclear reprocessing facilities in the United Kingdom.[1] Radiation exposure to the general population in the vicinity of these establishments cannot account for such excesses on current